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Medicine

IDENTIFYING CLINICALLY METABOLIC SIGNATURES OF OBESITY IN "NORMAL WEIGHT - OBESITY MIMICKERS

Dr Shiv Parshad Mittal* Associate Professor Dept of Medicine; MM Medical College & Hospital Kumarhatti (Solan) *Corresponding Author

Dr Kiranjeet Kaur Professor Dept of Biochemistry; MM Medical College & Hospital Kumarhatti (Solan)

ABSTRACT

Introduction: Sedentary life and altered dietary habits parallels with increase in normal weight but "lean mass" population. We attempt to study the prevalence of this problem.

Material and Method: 182 (male = 73 & female = 109) students with normal Body Mass Index (BMI) were studied.

Results: Mean age of either sex was 19 ± 1.23 years. Family history of diabetes mellitus was present in 47.46% and 45.83%; obesity in 2338.98% and 31.25%; hypertension in 18.64% and 12.5%; and coronary artery disease in 3 and 1 male and female students respectively.

13 male and 14 female students did not consent for waist and hip measurement. Students with normal BMI [N=145 (84.30%)], especially female [F=90 (52.33%)], performed mild exercises. Increased waist circumference (WC) and waist – hip ratio (WHR) were 4 & 12, and 12 & 26 found in these male and female students respectively.

In students with low birthweight (M=4 & F=9), WC was increased in 01 male and 01 female, and WHR in 02 male and 03 female students. In normal birthweight students (M=13 & F=23), increased WC and WHR were present in 4 and 3, and 2 and 5 male and female students respectively.

Conclusion: "Normal weight with Lean mass" students seem to be similar to metabolic active obese and we call them "*Normal Weight Obesity Mimickers*". Female students are at risk of developing DM & HTN, whereas male at risk of HTN and obesity later on.

KEYWORDS : Sarcopenic obesity, Normal weight with lean mass, Obesity mimickers.

INTRODUCTION:

India is in economic transition, adapting to western lifestyle and facing increase burden of obese population, especially affecting young population. Overweight and obesity are established risk factors for metabolic diseases such as diabetes mellitus (DM), hypertension (HTN), dyslipidemia, cardiovascular disease (CVD) and certain cancers. Obesogenic factors are multiple i.e. genetic susceptibility and environmental factors, ethnicity and racial factors, and sleep habits.

Indian population is observed to have a problem of "normal weight with lean mass". They being metabolically active, Incidence of CV mortality and morbidity in them is almost close to obese subjects. Obesity paradox formed the basis of this concept of *metabolic active normal weight people with lean-mass*. Initially, Obesity paradox was advocated in Chronic Kidney Diseases, now it is reported in other diseases e.g. metabolic diseases, cancer and elderly people. Since inception, existence of this concept remained under criticism. Though under criticism, we speculated the existence of "obesity paradox" in our participants with normal BMI.

MATERIAL & METHOD:

This non-interventional study was conducted in a MM Medical College Solan in students with normal BMI 182 (M=73 & F=109).

Duration of Study: About One Year
Inclusion criteria: All students.
Exclusion criteria: nil.

Study design:

Students were informed about the study. Those who consented were enrolled and evaluated clinically. History of symptoms suggestive of endocrine disorders, especially DM; hormonal / drugs therapy (those influencing weight), and F/H/O metabolic diseases, including obesity was recorded. Clinical examination also included measurement of Weight (Kg), Height (cm), BMI, waist circumference (WC) & hip circumference, and waist-hip ratio (WHR). Cut-off BMI for Indians for overweight (23Kg/m² and above), and WC (indicator of central obesity), was considered as ≥ 90 cm in male and ≥ 80 cm in female, and WHR ≥ 0.90 and ≥ 0.85 in male and female students respectively [1]. Important laboratory tests were done.

Ethical Issue:

Institution Ethical Committee approved the study and conducted accordingly.

RESULT:

421 students (M=182 & F=239) [182 students with normal BMI [M=73 & F= 109), 191 (M=91 & F=100) with BMI 23Kg/m² and above, and 48 with BMI less than 18.5 (M=19 & F=29)] completed this study. Mean age for either sex was 19 ± 1.23 years.

F/H/O Metabolic Diseases in Normal BMI Students (Table - 1 & 4): 27 students (M = 13 & F = 14) declined waist and hip measurement. F/H/O chronic metabolic diseases in remaining 155 students (M=60 & F=95) was:

(a) DM was prevalent in both paternal and maternal relatives, especially in female students.
(b) Obesity was prevalent in parental relatives in male students, whereas in female students it was prevalent in maternal and both paternal & maternal relatives.
(c) Prevalence of HTN was almost same in all relatives of male and female students.
(d) CAD was prevalent in paternal relatives of male students
(e) One male student had no F/H/O metabolic diseases.

Table – 1 (Depiction of Metabolic diseases in Families of Normal BMI Students)

Family History of Diseases	Parental		Maternal		Paternal & Maternal		Total
	M	F	M	F	M	F	
Diabetes mellitus	9 (15%)	20 (21.05%)	8 (13.33%)	12 (12.63%)	11 (18.33%)	12 (12.63%)	72 (46.45%)
Obesity	11 (18.33%)	7 (7.37%)	6 (10%)	12 (12.63%)	6 (10%)	11 (11.58%)	53 (34.19%)
Hypertension	9 (15%)	8 (8.42%)	0	1 (1.05%)	2 (3.33%)	3 (3.16%)	23 (14.84%)
CAD	3 (5%)	0	0	1 (1.05%)	0	0	4 (2.58%)
Dyslipidemia	0	0	0	2 (2.11%)	0	0	2 (1.29%)

(N.B. M = male students, F = female students, CAD = coronary artery disease. Paternal family history= Father & paternal relatives, Maternal Family history = Mother & maternal relatives)

Birth weight**:** (Table-2): Only 59 (M= 23 & F=36) were aware of their birth weight. In 14 *low birthweight* students (M=3 & F=11): WC was increased in 01 male and 01 female and WHR in 02 male and 03 female students. In 41 *normal birthweight* (M=17 & F=24) students: WC and WHR were increased in 03 and 5 each of either sex respectively. In *high birthweight* category (M=3 & F=1), only one male had increased WHR.

Table – 2 (Correlation between Birth Weight and Waist & WHR Measurement)

Birth weight (Kg)	Male				Female				Total
	Waist (cm)		WHR		Waist (cm)		WHR		
	Up to 90	≥ 90	Up to 0.90	≥ 0.90	Up to 80	≥ 80	Up to 0.85	≥ 0.85	
≤ 2.5 Kg	2	1	1	2	10	1	8	3	14
2.5 – 3.5	14	3	12	5	21	3	19	5	41
≥ 3.5	3	0	2	1	1	0	1	0	4
Total	19	4	15	8	32	4	28	8	59

(N.B. Only 59 students with Normal BMI were aware of their birthweight)

Physical activities (Table-3): This Institution is located in hill. For most of the students walking over 750 feet between residential and teaching zones is the major mode of exercise. Thus, they perform mild exercise, few also use other modes to exercise.

After excluding the students (who denied WC and hip measurement), 155 students (M = 60 & F = 95) were analysed for physical activity. 145 (84.30%) students [M=55 (31.98%) & F=90 (52.33%)] perform mild exercises daily, 8 students (M= 3 & F=5) moderate exertion and 2 (M=2 & F=0) severe exertion. Parameters of WC and WHR in these students were:

- *Students Performing Mild exercise:* WC was normal in 51 (92.73%) and 78 (86.67%), and increased in 4 (7.27%) and 12 (13.33%) male and female students respectively. WHR was normal in 43 (78.18%) and 64 (71.11%), and increased in 12 (21.82%) and 26 (28.89%) male and female students respectively.
- *Students Performing Moderate exercise:* 2 male and 4 female students had normal WC, and increased in 1 male and 1 female. WHR was normal in 2 male and 3 female, and increased in 1 male and 2 female student.
- *Students Undertaking Severe Intensity exercise:* Both male had normal WC and WHR.

Table – 3 (Correlation between Physical Exertion, and WC & WHR in Students with Normal BMI)

Physical exertion	Male				Female				Total
	Waist (cm)		WHR		Waist (cm)		WHR		
	Up to 90	≥ 90	Up to 0.90	≥ 0.90	Up to 80	≥ 80	Up to 0.85	≥ 0.85	
Mild	51	4	43	12	78	12	64	26	145
Moderate	2	1	2	1	4	1	3	2	8
Severe	2	0	2	0	0	0	0	0	2

Correlating the intensity of exercise with WC and WHR (Table -3): Students engaged in *mild exercise*: female students were found to have appreciable increased in WC and WHR than male. But in male students WHR increased more than WC as compared to female.

In male students performing *moderate and severe exertion:* WC and WHR measurements were normal and in female, increase in WC and WHR was not appreciable.

Anthropometry and Relevant parameters of Students:

(i) We have compared the "*normal weight with lean mass*" students (Group -1) with those having BMI 23 and above (Group-2) to find out similarities, if any, and also to find for risk factors for the metabolic diseases in students of Group-1.

(a) Students of either sex had diabetic parental relatives predominantly and maternal relatives. In this subgroup, WC and WHR were increased in 14 male and 36 female students, and 17 male and 24 female respectively.

(b) 30 (37.5%) male and 38 (40%) female students had obese relatives. Obesity was prevalent in parental, and both paternal & maternal relatives of male students, whereas in female obesity was almost equally distributed in paternal & maternal relatives. In this subgroup, WC and WHR were increased in 16 male and 25 female students, and 13 male and 19 female respectively.

(c) HTN was common in parental relatives of 11 (13.75%) male and 22 (23.16%) female students. In this subgroup, WHR was also found to be increased in male (45.45%) and female (42.11%) students.

Table – 4 BMI measurement

BMI (Kg/m²)	Male	Female	Total
≤ 18.5	19 (10.38%)	29 (12.18%)	48 (11.40%)
18.5 – 22.9	73 (39.89%)	109 (45.80%)	182 (43.23%)
23 – 24.9	35 (19.13%)	38 (15.97%)	73 (17.34%)
25 and above	56 (30.60%)	62 (26.05%)	118 (28.03%)
Total	183	238	421

Table – 5 (Waist Circumference in Students with Normal BMI)

	Waist Circumference (cm)				
Male	Up to 90 cm	91 – 94 cm	95 – 99 cm	100 cm & above	Total
	55 (91.67%)	3 (5%)	2 (3.33%)	-	60
Female	Up to 80 cm	81 – 84 cm	85 – 89 cm	90 – 95 cm	
	82 (86.32%)	8 (8.42%)	4 (4.21%)	1 (1.05%)	95

(ii) Waist Circumference and WHR measurement**:** Students with normal BMI were 182 [M = 73 (39.89%) & F=109 (45.80%)]. 13 male and 14 female students denied waist and hip measurement. Of the remaining participants 155 [M = 60 (38.71%) & F = 95 (61.29%). WC and WHR were normal in 55 (91.67%) and 47 (78.33%) and increased in 5 (8.33%) and 13 (21.67%) *male* students respectively, and in *female* WC and WHR normal in 82 (86.34%) and 67 (70.53%), and increased in 13 (13.68%) and 28 (30.21%) respectively (Table – 5).

DISCUSSION:

The global prevalence of both overweight and obesity is increasing continuously [1]. India is rapidly transitioning into western lifestyle and also facing these problems of overweight and obesity. These are established risk factors for metabolic diseases such as DM, HTN, cardiovascular disease (CVD), dyslipidemia, and certain cancers [2]. Obesogenic risk factors, apart from strong genetic susceptibility and environmental factor are multifactorial, like, ethnicity and racial groups, "toxic environment - obsogens", sleep habits [3-4], and processed foods.

Under genetic influence, Indians have propensity to develop "*normal weight with lean mass*". Being metabolically active, incidence of CVD mortality and morbidity in them approaches almost close to those in obese and overweight people. It is termed as "*Obese paradox*" - extra fat is added to maintain normal weight in lieu of muscle loss i.e. sarcopenic obesity [5-6]. BMI parameters are generally used to classify body health, but it is considered as an indicator of obesity and not of muscle mass, and it does not define potential harmful effects of adiposity. There is category of obese people who are metabolically inactive, they may survive longer than their metabolically active counterparts [7-8] or with people with normal BMI. These later are the "*normal weight with lean mass"* persons.

Genetic with inheritable modifications play an important role in central adiposity even in people with normal weight. They are covertly protected because of normal weight, but adverse metabolic effects seem to be almost similar to those present in obese metabolically inactive persons. Many studies have questioned the existence of "Obesity paradox" i.e. people with overweight may live longer. Their criticism based on the observation that irrespective of metabolic activity, overweight people have significantly increased risk of CV morbidity and mortality compared with those with normal BMI and hence shorter longevity. They also have metabolic adverse effects and greater risk of CAD in relationship of abdominal adiposity (indicated by WHR) [9-10].

Our main discussion will be focused on *normal weight students of either sex*. We may like to identify some risk factors in these normal weight students:

(i) Waist Circumference (WC) and Waist – Hip ratio (WHR): Significant students of either sex, especially female, with normal BMI, had increased WHR and WC than male counterpart (Table – 5). One study has compared, normal weight middle-aged men and women competing hazard ratios for incident CVD were: for overweight (BMI, 25.0-29.9) 1.21 (95% CI, 1.14-1.28) and 1.32 (95% CI, 1.24-1.40) respectively, for obesity (BMI, 30.0-39.9) 1.67 (95% CI, 1.55-1.79) and 1.85 (95% CI, 1.72-1.99), and for morbid obesity (BMI, ≥40.0) 3.14 (95% CI, 2.48-3.97) and 2.53 (95% CI, 2.20-2.91) [9]. Though this study involved middle aged individuals, yet based on these parameters some extrapolation can be speculated in our students. That is, if corrective measures are not ensured at this young age, present parameters may likely to worsen till middle age and may also get complicated by other risk factors for metabolic diseases. As WHR is a reliable indicator for abdominal adiposity and insulin resistance [12, 14]. These normal weight students with increased WHR / WC seem to be prone to metabolic diseases, especially the DM and CVD in future [11-12, 15]. Some have observed that WC is predictor of DM and not CVD [13]. WHR (Central obesity) has stronger association for CAD / CVD than BMI because of adverse metabolic effects of visceral fat [16-18]. These risk prone students must modify their lifestyle and prevent or delay any comorbid condition in future.

BMI defines grades of body weight. Normal BMI means individual is a "*normal weight healthy person*". BMI, also an indicator of obesity, but it does not provide information regarding the type, location and severity of adiposity [7]. Obesity is always cited as risk for metabolic diseases, but some obese persons are considered healthy with respect to their metabolic and cardiorespiratory fitness as they lack notable metabolic abnormalities / activity [19]. Metabolic active students, at any BMI (normal or low) with increased WC and WHR, and genetic propensity for metabolic diseases are at increased risk of developing DM and obesity-related morbidities. We have observed that, at any BMI, F/H/O parental DM seems to influence both male and female students. But, at any BMI, F/H/O obesity seems to influence the male and not the female (with *normal BMI*) students. These students of either sex seem to be at risk of developing DM and male students at risk of obesity and related morbidities in future.

It is the type of adiposity, its location, function and degree of inflammation that determine the deleterious consequences on CV health, at any BMI. A normal BMI individual, with sarcopenic obesity (decreased lean mass but with extra fat), cannot be compared with another individual with normal or more lean mass and less fat. Thus, metabolically active normal BMI (low lean mass with extra fat) students may be compared with obese person far obesity and CV related morbidities. We call them "*normal weight Obesity mimickers*". Increased WC, especially WHR, is a fairly reliable indicator of central adiposity, reflecting DM and CVD health.

(ii) Physical activities: 93.55% students [M=55 & F=90], with normal BMI, performed daily mild exercise. Our findings have shown worsening in physical activities since "2016 - Indian Report Card on the physical activity of children and youth", where India *fared pretty poorly in the worldwide survey,* securing 'D- grade' (60-80%) for not meeting physical activity guidelines [20].

In this subgroup (performing mild activities), WHR, especially the WC (13.33% vs 7.27%), was significantly increased in female students than in male. It is widely accepted that inadequate daily physical exercise is in itself an independent risk factor for chronic metabolic diseases, certain cancers, sarcopenia and decreased bone health, depression and anxiety [21-22]. Therefore, students with increased WC and WHR, especially the female, compounded by genetic propensity are at increased risk of these disabilities as they age.

(iii) HTN and DM: We have found systolic HTN (systolic blood pressure >135 mm Hg) in 2 male students only, and diastolic HTN (diastolic blood pressure 85 mm Hg and above) was present in 9 (M = 6 & F = 3). One male student with normal BMI also had 'random glucose intolerance'. Various studies have established that overweight / obesity, especially the central adiposity, are known risk factors for HTN and insulin resistance [23 – 27]. It seems "*Normal Weight Obesity Mimickers*" also inherit insulin resistance (IR) similar to other metabolic diseases. Both IR and HTN are documented to have a cause-effect relationship (IR a cause for HTN or vice versa) or may have non-causal association. Insulin increases blood pressure via several mechanisms: increases sodium absorption, sympathetic activation, altered transmembrane ion transport, and hypertrophy of resistance blood vessels [27]. Conversely, HTN can cause IR by altering insulin delivery to the skeletal muscles, especially the type 2b fibres (fast twitch fibres). It has been also hypothesized, that, HTN and IR are the independent consequences of same metabolic disorder or IR is a genetic marker and/or a pathogenetic mechanism of multiple metabolic abnormalities frequently associated with HTN [27].

Students with increased WC, especially the WHR, are at risk of hyperinsulinemia, because central adiposity is a pathogenic factor for IR. Hyperinsulinemia is an independent risk factor for HTN [26]. Increased WHR found in 13 male and 28 female students, making them prone to risk of future development of HTN and IR/ DM, metabolic diseases, and CV morbidity and mortality.

CONCLUSION:

We concluded that most of normal weight students are at risk of developing metabolic and cardiovascular diseases in future. These "normal weight lean mass" students being metabolic active seem to be similar to obese people, and we call them "*Normal Weight Obesity Mimickers*". Female are at higher risk for DM & HTN, whereas male for HTN and obesity, as they age.

Limitations:

1. Less participants and no long follow up.
2. We have measured anthropological parameters to the nearest degree of unit - cm or Kg.
3. F/H/O relevant diseases and birthweight were based on students' statement.
4. Due to operational reasons, investigations: Fasting Blood Glucose and Lipids. Measurement of the fat content and muscle mass could not be done.

Conflict of Interest: None to disclose.

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Authors' contribution: All authors participated in study design, collection and collating relevant medical literature, preparation of manuscript, editing and final revision.

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