
Research Article

Silent Ischemia in newly detected subjects of Diabetes mellitus with different Obesity phenotypes.

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Abstract:

Background: Obesity is the most challenging threat all across the globe. It is pandemic and is known to cause various complications, cardiovascular being the most common. Diabetes mellitus itself acts as an adjunct to increase the risk of incident cardiovascular diseases when associated with obesity. Metabolic Healthy Obesity (MHO), Metabolic Obesity Normal Weight (MONW) are some new parameters added to the current obesity variants which have added to further burden of risk stratification. This study was conducted to estimate the proportion of silent ischemia through exercise treadmill test (TMT) in newly detected cases of Diabetes Mellitus (DM) with different obesity phenotypes.

Aim: To estimate the proportion of silent ischemia through exercise treadmill test (TMT) in newly detected cases of Diabetes Mellitus (DM) with different obesity phenotypes. **Method:** The present study “ Proportion of silent ischemia through Treadmill test in newly detected cases of Diabetes Mellitus with different obesity phenotypes” was conducted in department of Medicine, Acharya Vinoba Bhave Rural Hospital and Jawaharlal Nehru Medical College, Sawangi (M), Wardha. Newly detected cases (within 6 months of diagnosis) of Diabetes Mellitus as per WHO criteria were divided into different obesity phenotypes as per definitions. Then all the cases were subjected to TMT and proportion of silent ischemia was detected in each category and compared with metabolic healthy normal weight controls.

Results: In cases of MetS(11.4%) showed positive TMT, in MHO group 13.89% had a positive TMT, in MONW group 17.51% had positive TMT. The Odds of having silent ischemia as compared to normal healthy subjects was 2.35%, 2.94%, and 3.82% in MetS, MHO, and MONW respectively.

Conclusion: So newly detected cases of DM should be given due importance for detection of silent ischemia according to their anthropometric status. Primary prevention in form of health education, exercise, dietary and life style modifications should be implemented once these cases are categorised either to be obese or having abnormal metabolic health.

Keywords: diabetes mellitus, MHO, MONW, MetS, TMT

Introduction:

Obesity is the most challenging threat all across the globe. It is pandemic and is known to cause various complications, cardiovascular being the most common. As far as Indian scenario is concerned, a recent study by Press Trust of India concluded that India, with 11% of adolescents, and 20% of all adults being overweight/Obese is the third-highest country after US and China.[1-3] Both obesity and diabetes mellitus are important independent risk factors for the development of cardiovascular disease. Obesity is the leading risk factor for type 2 diabetes. Diabetes mellitus itself acts as an adjunct to increase the risk of incident cardiovascular diseases when associated with obesity. Furthermore silent ischemia and myocardial infarctions are more common in diabetes.

Obesity shows great variability in different races when it comes down to define as per BMI cut-offs. Body Mass

Index (BMI) is still followed as a sole parameter for its definition, though; it has failed to show its correlation with the consequences of obesity related complications when other parameters like waist circumference, waist-hip ratio, visceral fat imaging etc are taken into account. Other terminologies like, Metabolic Healthy Obesity (MHO), Metabolic Obesity Normal Weight (MONW) are some new parameters added to the current obesity variants which have added to further burden of risk stratification. [4]

Many studies are now confirming that MHO and MONW variants are associated with increased cardiovascular morbidity and mortality. [5-15] MetS for Asian population is defined by using the NCEP Adult Treatment Panel III guideline with a modification, abdominal obesity being defined as a waist circumference 90 cm in men and 80 cm in women according to International Obesity Task Force central obesity criteria for Asia. [16] People with metabolic

syndrome (MetS) have a 2-fold risk of heart disease and heart attack (3-fold risk in women) compared to people without this condition. The risk of heart disease in people with METS is almost as high as those with diabetes and those who have both carry an exceptionally poor prognosis. [17-20]MS is a major determinant of presence and severity of clinical and subclinical inflammation, coronary atherosclerosis, acute coronary syndrome (ACS) and left ventricular dysfunction, heart failure and its complications. [21-23]This study was undertaken to assess the proportion of silent ischemia in newly detected cases of DM with different obesity phenotypes by exercise treadmill test as the tool.

Aim:

To estimate the proportion of silent ischemia through exercise treadmill test (TMT) in newly detected cases of Diabetes Mellitus (DM) with different obesity phenotypes.

Objectives:

- To detect proportion of silent ischemia in newly detected cases of Diabetes Mellitus.
- To estimate proportion of silent ischemia in different obesity phenotypes
- To correlate silent ischemia with Cardiovascular risk parameters in each group.

Material and Methods:

The present study “ Proportion of silent ischemia through Treadmill test in newly detected cases of Diabetes Mellitus with different obesity phenotypes” was conducted in department of Medicine, Acharya Vinoba Bhave Rural Hospital and Jawaharlal Nehru Medical College, Sawangi (M), Wardha. It is a 1200 bedded tertiary care centre and teaching Hospital.

This cross sectional study with comparison group was carried over a period of 6 months ;June 2018 to November 2018 after obtaining institutional ethical committee clearance.

SUBJECTS – The cases were newly detected cases (within 6 months of diagnosis) of Diabetes Mellitus as per WHO criteria for definition of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration more than or equal to 11.1 mmol/L (200 mg/d L) or
- Fasting plasma glucose more than or equal to 7.0 mmol/L (126 mg/dL) or Hemoglobin A1C more than or equal to 6.5% or
- 2-hour plasma glucose more than or equal to 11.1 mmol/L (200 mg/d L) during an oral glucose tolerance test

After selection of the cases, these cases were further categorized as the following:

Definition of Obesity variants

Metabolic syndrome (MetS) - was defined as per the Modified National cholesterol education programme adult treatment panel III (NCEP ATP III) criteria as proposed by the AHA/NHLB. [16,24-26]

The modified NCEP criteria require at least three of the

following components:

- (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 $\geq 130/85$ mmHg or receiving drug treatment
- (5) fasting plasma glucose ≥ 100 mg/dL.

Metabolic Healthy obese (MHO) was defined as;

BMI ≥ 25 Kg/m² (Cut off value in Asians), with ≤ 2 MeS criteria as per revised NCEP ATP III criteria . [27]

Metabolic obesity normal weight(MONW) was defined as ;

BMI ≤ 25 Kg/m², with ≥ 2 MeS criteria as per revised NCEP ATP III criteria.[28]

After dividing the cases into the following groups as mentioned above,

They were subjected to TMT

Informed consent

A written informed consent was taken from all the cases of study and control population after explaining the nature of test.

Study protocol

All the cases from study and control group were studied as per the proforma. A detailed medical history was taken with emphasis on any evidence of CAD and DM.

Drug history was taken to rule out use of any cardioactive drugs.

Detailed history was taken regarding duration and treatment of diabetes, hypertension, smoking or alcohol intake.Family history of CAD if any was recorded.

Clinical examination

A detailed clinical examination was carried out in all cases and included

Anthropometric measurements

Weight in kilograms was recorded with the subject standing motionless on the standard weighing machine, without footwear.

Height in centimetres was measured with patient standing without foot wear, against a wall mounted scale with the head positioned so that the top of the external auditory meatus was in level with the inferior margin of the bony orbit.

Body mass index (BMI) was calculated using the formula; BMI = weight in kg/ (height in meters)²

The cases were said to have normal BMI when it ranged Between 18.5 – 22.9kg/m²

Overweight when BMI ranged Between 23 – 24.9 kg/m²

And obese when BMI was 25 -29.9 kg/m²

Waist circumference: The waist circumference was measured at the midpoint between the lower margin of the last palpable

rib and the top of the iliac crest, using a stretch-resistant tape that provides a constant 100g tension.

Abdominal obesity was defined as waist circumference of

more than 90 cm in men and 80 cm in women as per the modified NCEP ATP III guidelines for Asian population.[16]

Laboratory investigations

All the cases were then subjected to a battery of investigation. Fasting and post meal.

Blood sugar was estimated in all cases by GOD/POD method using span kit. Lipid profile (Total cholesterol, HDL, triglycerides) was estimated by using the COD/POD method by Bayers kit. LDL was calculated using the Friedewald formula.

LDL cholesterol = (Total cholesterol – HDL cholesterol – Triglycerides/5)

The samples for fasting blood sugar and lipid profile were taken early morning after a fasting period of 8 hours and the post prandial blood sugar were collected two hours after major meal.

Exclusion Criteria:

- Known cases of CAD
- Chronic kidney disease
- Chronic liver disease
- COPD
- Were excluded from the study.

Treadmill Test

A written informed consent was taken after explaining the procedure as per the proforma. Subjects were asked to have a light meal two hours before the test. Subjects were asked to wear hospital loose gowns for proper attachment of the leads. Superficial cleansing was done. Non polarising silver chloride electrodes were used for electrical contact. The electrode positions were as per the standard recommendations. A stand by defibrillator (SCHILLER CARDIO PLUS TM MULTIPARA DEFIBRILLATOR) was kept ready for any eventualities. Emergency tray was available during procedure.

Instrumentation

All the subjects had a treadmill test performed on a motor driven with tread mill software NASAN ST+ VERSION 6.0 analysed by computer.

Each case and control had a test exercise before starting the actual exercise.

The inclination and speed of treadmill was calibrated according to the standard Bruce protocol. All the cases and

control were made to run up to 9 minutes 3rd stage of standard bruce protocol.

Blood pressure recordings

Blood pressure was recorded by aneroid sphygmomanometer in the left arm, at the level of heart by auscultatory method in the supine position, standing position, after hyperventilation, during the last minute of each stage of treadmill testing and during peak exercise. The first and last korotkoffs sounds were taken as systolic and diastolic blood pressure respectively.

Peak exercise

The peak exercise on TMT was defined when the subject attained predetermined heart rate (220- age in years) or exhaustion, whatever had attained earlier. Ischemic response to exercise to treadmill was said to be present when there was flat or downsloping depression of the ST segment > 0.1 mV below baseline (i.e. the PR segment) and lasting longer than 0.08s. Upsloping or junctional ST segment changes are not considered characteristic of ischemia. Negative tests in which the target heart rate (85% of maximal predicted heart rate for age and sex) is not achieved are considered non diagnostic. The normal response to graded exercise included progressive increased in heart rate and blood pressure. Failure of blood pressure to increase or an actual decrease with the signs of ischemia during the test is an important adverse prognostic sign. The development of angina was said to be present when there was >0.2 mV ST depression and/ or that persisted for >5 min after the termination of exercise, i.e. during recovery.

Though not a part of this study, patients whose exercise stress test came out positive for asymptomatic CAD were subjected to coronary angiography, depending upon willingness and affordability of the patient, in order to provide maximum benefit to the patient.

Statistical analysis:

Statistical analysis was done by using descriptive and inferential statistics using chi square test, one way ANOVA, odd's ratio and multiple regression analysis and software used in the analysis were SPSS 22.0 version and Graph Pad Prism 6.0 version and p<0.05 is considered as level of significance.

Observation and Results:

Table 1: Baseline characteristics of the patients

	Metabolic Syndrome	Metabolic Healthy Obese	Normal wt metabolic obese	Normal	Total	p-value
Age(yrs)	47.31±11.70	46.36±13.50	47.95±12.53	44.28±11.27	46.14±12.11	0.23 NS
Gender						
Male	17(48.57%)	24(66.67%)	32(61.54%)	52(67.53%)		0.26

					125(62.50%)	NS
Female	18(51.43%)	12(33.33%)	20(38.46%)	25(32.47%)	75(37.50%)	
Clinical Parameters						
SBP	140.57±20.99	124.44±21.96	133.65±24.33	121.84±16.29	128.66±21.58	0.001 S
DBP	82.57±10.66	76.11±11.02	78.07±11.88	73.97±9.54	76.93±11.01	0.0001 S
BMI	26.65±0.99	26.69±1.36	22.77±2.19	22.44±2.25	24.03±2.74	0.0001 S
WC	81.62±3.54	78.44±4.43	80.19±5.52	76.88±5.49	79.03±5.31	0.007 S
FBS	155.85±32.92	141.22±27.25	164.01±41.93	145.14±34.67	151.22±36.12	0.001 S
PMBS	214.17±52.99	186.50±48.77	223.44±59.36	191.40±42.21	202.83±52.10	0.012 S
HDL	37.85±2.99	38.47±3.66	37.36±3.38	41.87±12.84	39.38±8.59	0.0001 S
LDL	150.20±7.54	146.69±8.35	147.82±16.04	135.40±18.64	143.25±16.14	0.698 NS
VLDL	25.22±10.34	24.25±10.52	27.78±11.83	26.42±18.83	26.18±14.51	0.001 S
TC	213.28±13.30	209.41±13.10	212.98±19.01	199.50±28.85	207.20±22.58	0.008 S
TG	163.34±12.87	161.36±25.82	166.88±33.91	152.62±19.14	159.78±24.82	0.0001 S

S – Significant

NS – Non Significant

There was significant difference in all the parameters except LDL

Mean SBP in the patients with metabolic syndrome was 140.57±20.99, in metabolic healthy obese it was 124.44±21.96, in normal wt metabolic obese it was 133.65±24.33 and in normal patients it was 121.84±16.29. Statistically significant difference was found mean SBP in patients of four groups(p=0.001).

Mean DBP in patients with metabolic syndrome was 82.57±10.66, in metabolic healthy obese it was 76.11±11.02, in normal weight metabolic obese it was 78.07±11.88 and in normal patients it was 73.97±9.54. Statistically significant difference was found mean DBP in patients of four groups (p=0.001).

Mean BMI in patients with metabolic syndrome was 26.65±0.99, in metabolic healthy obese it was 26.69±1.36, in normal weight metabolic obese it was 22.77±2.19 and in normal patients it was 22.44±2.25. Statistically significant difference was found mean BMI in patients of four groups (p=0.001).

Mean WC in patients with metabolic syndrome was 81.62±3.54, in metabolic healthy obese it was 78.44±4.43, in normal weight metabolic obese it was 80.19±5.52 and in normal patients it was 76.88±5.49. Statistically significant difference was found mean BMI in patients of four groups (p=0.007).

Mean FBS in patients with metabolic syndrome was 155.85±32.92, in metabolic healthy obese it was 141.22±27.25, in normal weight metabolic obese it was 164.01±41.93 and in normal patients it was 145.14±34.67. Statistically significant difference was found mean BMI in patients of four groups (p=0.001)

Mean PMBS in patients with metabolic syndrome was 214.17±52.99, in metabolic healthy obese it was 186.50±48.77, in normal weight metabolic obese it was 223.44±59.36 and in normal patients it was 191.40±42.21. Statistically significant difference was found mean BMI in patients of four groups (p=0.012)

Mean HDL in patients with metabolic syndrome was 37.85±2.99, in metabolic healthy obese it was 38.47±3.66, in normal weight metabolic obese it was 37.36±3.38 and in normal patients it was 41.87±12.84. Statistically significant difference was found mean BMI in patients of four groups (p=0.0001)

Mean VLDL in patients with metabolic syndrome was 25.22±10.34, in metabolic healthy obese it was 24.25±10.52, in normal weight metabolic obese it was 27.78±11.83 and in normal patients it was 26.42±18.83. Statistically significant difference was found mean BMI in patients of four groups (p=0.001)

Mean TC in patients with metabolic syndrome was 213.28±13.30, in metabolic healthy obese it was 209.41±13.10, in normal weight metabolic obese it was 212.98±19.01 and in normal patients it was 199.50±28.85. Statistically significant difference was found mean BMI in patients of four groups (p=0.008)

Mean TG in patients with metabolic syndrome was 163.34±12.87, in metabolic healthy obese it was 161.36±25.82, in normal weight metabolic obese it was 166.88±33.91 and in normal patients it was 152.62±19.14. Statistically significant difference was found mean BMI in patients of four groups (p=0.0001)

Table 2: Distribution of patients according to TMT

TMT	Metabolic Syndrome	Metabolic Healthy Obese	Normal wt metabolic obese	Normal	Total	p-value
Positive	4(11.43%)	5(13.89%)	9(17.51%)	4(5.19%)	22(11%)	0.16 NS
Negative	31(88.57%)	31(86.11%)	43(82.69%)	73(94.81%)	178(89%)	
Total	35(100%)	36(100%)	52(100%)	77(100%)	200(100%)	

Table 3: Odd's Ratio = 3.12 (95% confidence interval =1.01-9.62)

	Metabolic Syndrome	Metabolic Healthy Obese	Normal wt metabolic obese
Odd's Ratio	2.35	2.94	3.82
95% CI	0.55-10.02	0.74-11.71	1.10-13.16

Odds ratio between Metabolic Syndrome patients and normal patients was 2.35, which means that chances of TMT positive in Metabolic Syndrome patients was 2.35 times more as compared to normal patients.

Odds ratio between Metabolic Healthy Obese patients and normal patients was 2.94, which means that chances of TMT positive in Metabolic Healthy Obese patients was 2.94 times more as compared to normal patients

Odds ratio between Normal Weight Metabolic Obese patients and normal patients was 3.82, which means that chances of TMT positive in Normal Weight Metabolic Obese patients was 3.82 times more as compared to normal patients

Discussion:

Metabolic syndrome –

Out of the 200 cases of newly detected diabetes, 35 (17.5%) patients were having metabolic syndrome as described by the NCEP ATP 3 criteria. When these patients were further

subjected to TMT , 4 patients (11.4%) showed positive TMT, and after applying Odd's ratio it was concluded, that metabolic syndrome patients have 2.35 times higher probability of positive stress test than normal individuals.

Montazerifar F Et al; [29] studied the prevalence of CAD in metabolic syndrome cases and concluded that MetS was the most prevalent risk factor in CAD patients. The prevalence increased with age. The risk was higher by 84.8% in low HDL, 77.8% higher in high FB, 75.8% higher in high WC.

Mahalle N Et al; [30] in his study found that south asians were more prone to develop MetS and 64% patients presented with MetS. He also stated that there was a strong correlation between MetS and its components with severity of CAD.

In another cohort study , Seo et al. [31] investigated the association of MetS and components of MetS with coronary artery calcium (CAC), a marker of coronary atherosclerosis,

and evaluated differences in the effect according to different definitions of MetS. MetS was significantly associated with the presence of CAC. Moreover, a higher number of MetS components was significantly associated with a higher risk of CAC.

Metabolic healthy obese - Out of the 200 cases of newly detected diabetes 36 (18%) patients had metabolic healthy obesity (MHO). When these patients were further subjected to TMT, 5 (13.8%) patients showed positive TMT. When the data was analysed and odds ratio was applied, it was concluded that newly detected cases of DM with MHO had 2.94 times higher chances of positive stress test as compared to control.

Twig G et al;[32]studied incident CAD in young MHO population. Participants were categorized by BMI and the number of metabolic abnormalities (based on the Adult Treatment Panel-III). The incidence of CAD among MH lean, overweight, and obese participants was 0.23, 0.45, and 1.0/1000 person-years respectively. This risk persisted when BMI was treated as a time-dependent variable, or when fasting glucose, HDL-c, triglycerides, or BP were added to the model. Similar results were also obtained when a more permissive definition of MH was used. The study concluded that, obesity may continue to contribute to increased risk for incident CAD in young men even in the presence of a healthy metabolic profile. **Roberson LL Et al; [33] in a similar study** concluded that MHO patients had 30% association with all-cause mortality, 14% CVD mortality, and 33% higher chances of CVD as compared to MHNW. **Fan J Et al; [34] in his study** found that MHO individuals had high risk of CVD events compared to MHNW individuals. **Kuk JL Et al ; [35]study also** concluded that obesity, even in the absence of observable metabolic abnormality is associated with higher risk of all-cause CVD mortality. **Brant LC Et al, [36] in a study concluded that,** metabolically healthy obese individuals had more impaired vascular function than metabolically healthy normal-weight individuals.

Ogorodnikova A Det al; [37] Using pooled data from the Atherosclerosis Risk in Communities and Cardiovascular Health Studies, assessed incident CVD using three definitions of the metabolically healthy obesity. The CVD incidence rates, after a mean follow-up 11.8 years were 7.1, 5.8, and 8.4 per 1,000 person-years in metabolically benign obese via the three definitions suggesting MHO is not a benign condition.

Normal weight metabolic obese: In our study, out of the 200 cases of newly detected DM, 43 (21.5%) patients were in metabolic obese normal weight (MONW) category. When these patients were further subjected to TMT, 9 (20.93%) patients had positive TMT. When the data was analysed and odds ratio was applied, it was concluded that newly detected cases of DM with MONW phenotype had 3.82 times higher chances of positive stress test as compared to normal population.

Oliveros E Et al; [38] in a study concluded that individuals with normal weight but metabolically obese had higher risk of

developing MetS, cardiometabolic dysfunction, and mortality. **Sohee Kim et al; [39] in a study** concluded that compared to MHNW individuals, NWO showed higher inclination to words subclinical atherosclerosis (higher prevalence of soft plaque in coronary artery).

Nowak M et al; [40] found that, MONW individuals exert an effect on increased risk of cardiovascular diseases and non insulin dependent diabetes mellitus. Identification of individuals at risk is difficult not only because no clear definition of MONW is established but also due to common belief that the cardiovascular risk in nonobese is low. The awareness of association of metabolic abnormalities in MONW with atherosclerosis should argue physicians into early screening and modification of cardiovascular risk factors in nonobese individuals. **Sharma S et al. [41]** found that older individuals with CAD and altered WHR or WC were at higher mortality risk. A normal BMI with higher WHR or WC also showed higher risk of mortality

Conclusion:

The study concluded that in newly detected diabetes mellitus silent ischemia was prevalent on all the different obesity phenotypes. Metabolic obesity normal weight subjects had maximum percentage of silent ischemia, followed by MHO category. MetS was also associated with increased proportion of silent ischemia. So newly detected cases of DM should be given due importance for detection of silent ischemia according to their anthropometric status. Primary prevention in form of health education, exercise, dietary and life style modifications should be implemented once these cases are categorised either to be obese or having abnormal metabolic health.

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