

Association of Silent Myocardial Ischemia in Obese Patients with Metabolic Syndrome

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Abstract

Background: Egypt is among the first four countries suffering from obesity worldwide. The function of waist circumference [WC] as an independent indicator of silent myocardial ischemia [SMI] remains unknown in Egyptian obese patients. Thus, we aimed to detect SMI in a cohort of Egyptian obese individuals with metabolic syndrome [MS] and to examine its associations with various clinical and diagnostic results.

Methods: Fifty obese patients (G1) without overt coronary artery disease [“60 percent” females and “40 percent” males; mean age 40.2±4.5 years] and 50 ages & sex matched non-obese subjects who served as control group (G2) were enrolled in this study. Anthropometric tests were taken for both subjects. Laboratory evaluation included fasting blood sugar, serum triglycerides, high density lipoprotein cholesterol. Assay of serum uric acid, urea, creatinine and microalbuminuria. MS was established through the revised National Education Program on Cholesterol [NCEP-R]. Tc99 m SestaMIBI SPECT gated myocardial perfusion imaging [GSPECT] was used for SMI screening. Pearson Moment correlation equation was used to check correlation between different variables. The logistic regression analysis was performed univariate and multivariate and the linkages between SMI and significant variables were established.

Results: In (G1), 13/50 [26%] had SMI as compared to 2/50 [4%] among (G2) $p=0.0001$. GSPECT positivity significantly correlated with HDL ($r=0.4$; $p=0.02$); microalbuminuria [$r=-0.5$; $p=0.04$]; and WC [$r=0.6$; $p=0.04$]. Neither WC (OR 1.042; CI 0.8701.248; $p=0.654$) nor microalbuminuria (OR 1.794, CI 0.6734.784; $p=0.243$) were considered as independent predictor of SMI.

Conclusion: A significant association of SMI has been found among a cohort of Egyptian obese patients with MS using Tc99 m SestaMIBI GSPECT. Considering the fact, we believe that the latter has a place as a screening tool; whenever the diagnosis is made the better the result.

Key Words: Obesity – Ischemia – Metabolic syndrome – Silent myocardial ischemia.

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Introduction

IN the absence of angina or anginal equivalents, silent coronary artery disease [CAD] is characterized as the occurrence of myocardial ischemia or an infarction [1]. While silent CAD is the most frequent manifestation [2]. There are no screening guidelines for determining its burden in patients with traditional coronary atherosclerosis risk factors [3].

Over the years the prevalence of metabolic syndrome [MS] [4] and abdominal obesity has gradually increased [5]. Different organizations, such as the National Cholesterol Education Program (NCEP) [6,7] the International Diabetes Federation (IDF)[8] and the World Health Organization (WHO) [9] have published various criteria for defining metabolic syndromes. It was proposed that individual components be of MS were proposed to interact synergistically to cause or accelerate atherosclerosis [10].

However, several questions have been raised recently regarding the impact of MS on CAD or SMI risk compared with its components [11].

Recently it was reported that high waist circumference (WC) and therefore abdominal obesity was a higher risk factor for cardiovascular disease (CVD) than general obesity [12,15] with a clear correlation with MS [13,14,16]. Lakka et al., showed an increase in all cause mortality in men with metabolic syndrome using a given high WC of >102cm instead of ≥94cm [17].

However, there is still a large population segment with WC average of ≥94cm that remains at an increased risk of CVD [16,18-20]. In this way

we aimed to detect silent myocardial ischemia [SMI] in a cohort of obese Egyptians and to analyze its correlations with different clinical and diagnostic data.

Patients and Methods

Study population:

The research has been accepted by the scientific review board of Cairo University's local ethics committee. It was a cross-sectional analysis performed on 50 obese Egyptian patients [30 females and 20 males] without documented CAD. Patients with positive family history, diabetes [fasting blood sugar (FBS) > 126 mg/dl], hypertension [defined as blood pressure $> 140/90$ mmHg and/or antihypertensive drug use], elevated serum creatinine [> 1.2 mg/dl], abnormal renal sonography, urinary tract infection and other cardiovascular diseases have been excluded. Fifty Age and non-obese subjects matched by sex served as a control group.

All patients and controls were subject to full history and clinical examination including blood pressure measurement (BP), weight, height, WC, waist hip ratio (WHR), waist-height ratio (WHtR), and single photon emission gated myocardial perfusion [GSPECT] computed tomography using Tc99 m Sestamibi. WHR was considered to be increased if there were > 0.9 in men and > 0.85 in women [21] and the cut-off point for WHtR was 0.5 for both genders [22]. After overnight fasting, biochemical analyzes were performed including FBS, high density lipoprotein cholesterol (HDL), triglycerides (TG), urea, creatinine, and uric acid. Microalbuminuria assay was conducted using competitive immunoassay enzymes, using IMMULITE-2000 tools and albumin kits [23]. Microalbuminuria is characterized as a concentration of 20-200mg/l of urinary albumin, whereas macroalbuminuria is considered to be the concentration of urinary albumin > 200 mg/l [24]. Metabolic syndrome has been diagnosed with three or more of the following risk factors: WC > 88 cm in women and > 102 cm in men, TGs > 150 mg/dl in adults, HDL < 40 mg/dl in male and < 50 mg/dl in women, BP $> 130/85$ mmHg, FBS > 110 mg/dl based on the requirements of the National Plan for Cholesterol Education-Adult Care Panel III (NCEP-ATP III) [6,7,13].

Myocardial gated single photon emission computed tomography:

Dipyridamole was intravenously administered over 4-6min to cause pharmacological stress (0.56mg/kg body mass). A small rise in heart rate and a slight decrease in blood pressure support the

drug's pharmacological impact, with images taken 15min after infusion with dipyridamole. Tc-99 m Sesta-MIBI was injected with continuous ECG and blood pressure monitoring at a dosage of 22-25 mCi (814-925 mBq). Imaging was carried out over 2 days (within a period of 1 week) during the stress and rest phases using a dual head gamma camera (Philips Axis, Philips, The Netherlands) under the following conditions: Patient with elevated left arm (180o arc), counterclockwise rotation, 128x128 matrix, and 64 image/arc views (180°, 45°, anterior right oblique and 135° left oblique). A ramp filter and convection filter with oblique angle reformatting (short axis and long horizontal and vertical axis) (Butterworth filter; Texas Instruments, Texas, USA); For GSPECT, the processing of ECG-synchronized data was carried out using an R-wave trigger (8 frames/cardiac-cycle). Imaging was done 3060min after administration of SestaMIBI during the rest process. The GSPECT was analyzed in a joint session by three board-certified nuclear medicine physicians (two with 10 years of experience, and the other with 20 years' experience). Myocardial perfusion of the left ventricular (LV) walls was visually assessed for defects [myocardial perfusion defects (MPDs)]. The 17 myocardial segments were assigned to the territories of the left anterior descending artery [LAD], right coronary artery [RCA], and the left circumflex coronary artery [LCX] [25]. We classified patients as GSPECT negatives and GSPECT positives.

Statistical method:

All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows. Student *t*-test was used to analyze differences in numerical data and chi-squared test was used to determine the differences between proportions of categorical data. Correlation between different variables was tested using Pearson Moment correlation equation. Numerical data were tested for normality using Kolmogorov Smirnov test. Univariate logistic regression was performed to identify the associations between SMI and significant variables. Multivariate logistic regression analyses were performed using a stepwise forward selection approach. *p*-values < 0.05 were considered statistically significant.

Results

General characteristics of the study group [n. 50]:

This study included 50 obese patients [Group 1 (G1) 30 females "60%" and 20 males "40%"]

and 50 non-obese subjects as a control group (G2). G1 patients fulfilled the criteria for MS versus none in G2. Their different clinical and physical parameters are shown in Table (1) where significant statistical differences were elicited among all the parameters except for age and blood pressure measurements.

Table (1): Clinical and physical parameters in obese patients and controls.

	Obese patients (G1)	Non-obese control (G2)	p-value
Age (ys)	40.2±4.5	41.2±4.1	0.6
<i>Sex distribution:</i>			
Females	30 (60%)	30 (60%)	-
Males	20 (40%)	20 (40%)	
WC (cm)	116.9±15	77±5.2	0.0001
WHR	1±0.1	0.7±0.1	0.0001
WHtR	0.7±0.1	0.5±0.02	0.0001
BMI	37.28±5.9	23.5±1.3	0.0001
SBP (mm Hg)	115.9±13.1	112.4±10.3	0.8
DBP (mm Hg)	74.4±11	71.8±9.3	0.9

G1: Group 1. G2: Group 2. BMI: Body mass index.
 WC : Waist circumference. SBP: Systolic blood pressure.
 WHR : Waist hip ratio. DBP:Diastolic blood pressure.
 WHtR : Waist-height ratio.
 Values are expressed as mean ± SD or no (%).

The laboratory data are detailed in Table (2). FBS, uric acid, TG and microalbuminuria were significantly higher in G1 while HDL was significantly lower in G1 with no difference in serum urea and creatinine.

Table (2): Laboratory data of obese patients and controls.

	Obese patients (G1)	Non-obese control (G2)	p-value
FBS (mg %)	102±12.7	93.7±12	0.004
Creatinine (mg/dl)	0.6±0.1	0.6±0.1	0.9
Urea (mg/dl)	11.4±3.6	12.5±4	0.9
Uric acid (mg/dl)	4.3±0.9	3.5±0.8	0.01
TG (mg/dl)	439.4±190.5	150±31	0.000
HDL (mg/dl)	33.3±7.7	48±0.8	0.000
Microalbuminuria (mg/l)	37.2±4	17±5	0.008
MS (No. %)	50/50 (100%)	0	0.000

FBS : Fasting blood sugar. HDL : High density lipoprotein.
 TG : Triglycerides. MS : Metabolic syndrome.
 Values are expressed as mean ± SD unless otherwise specified.

Myocardial perfusion GSPECT:

Of the 50 obese patients who were exposed to cardiac pharmacological stress monitoring [Dipyridamole] with subsequent GSPECT; 37 cases [74%] were negative and 13 cases [26%] were positive for SMI, 6/20 [30%] males and 7/30 females [23.3%]. Most lesions were of moderate grade [81.2 percent].

The vascular area most frequently affected was RCA with LCX and LAD similarly affected. Ischemia was found in a single vascular territory except in 3/13 [23%] where male cases resulted in the involvement of two vascular territories. Two patients in G2 demonstrated positive GSPECT [2/50; 4% vs. 26% in G1; p 0.001].

Associations and Cox-regression analysis:

- The Pearson correlation test revealed substantial statistical correlations between SMI and MS (*r* 0.7, *p* 0.02), WC (*r* 0.6, *p* 0.04), WHtR (*r* 0.6, *p* 0.03), HDL (*r* -0.5, *p* 0.02), and microalbuminuria (*r* 0.5, *p* 0.04). All other variables tested (age, sex, FBS, TG, and WHR, and BMI) showed no significant association (*p*>0.05) (Table 3).

Table (3): Associations of SMI and patients' data in obese patients (G1).

Variable	G1 [n. 50]
Age	<i>r</i> =0.3 <i>p</i> 0.5
Sex	<i>r</i> =0.2 <i>p</i> 0.6
FBS	<i>r</i> =0.2 <i>p</i> 0.5
TG	<i>r</i> =0.3 <i>p</i> 0.09
HDL	<i>r</i> =-0.5 <i>p</i> 0.02
Microalbuminuria	<i>r</i> =0.5 <i>p</i> 0.04
WC	<i>r</i> =0.6 <i>p</i> 0.04
WHR	<i>r</i> =0.2 <i>p</i> 0.9
WHtR	<i>r</i> =0.6 <i>p</i> 0.03
BMI	<i>r</i> =0.2 <i>p</i> 0.2
MS	<i>r</i> =0.7 <i>p</i> 0.02

SMI : Silent myocardial ischemia. BMI : Body mass index.
 G1 : Group 1. FBS : Fasting blood sugar.
 WC : Waist circumference. TG : Triglycerides.
 WHR : Waist hip ratio; HDL : High density lipoprotein.
 WHtR : Waist-height ratio. *p*-Value <0.05 is significant.

- Analysis of univariate regression revealed that MS (OR 1.011; CI 0.971-1.156; $p=0.02$), WC (OR 2.006; CI 0.913-2.950; $p=0.01$), WHtR (OR 1.012; CI 1.427-2.078; $p=0.02$), HDL (OR 2.009; CI 0.903-2.050; $p=0.01$) and micro-albuminuria (OR 1.011; CI 0.931-1.186; $p=0.02$) were significant SMI predictors (Table 4).
- All relevant variables from the univariate analysis have been included in a stepwise multivariate regression. Accordingly, checking for the beneficial effect of micro-albuminuria and WC on the existence of silent MI was selected.

The analysis however showed that neither WC (OR 1.042; CI 0.8701-1.248; $p=0.654$) nor micro-albuminuria (OR 1.794, CI 0.673-4.784; $p=0.243$) were considered to be independent predictors of SMI (Table 5).

Table (4): Significant predictors of silent myocardial ischemia in obese patients (G1) by Univariate regression analysis [n. 50].

Variate	Odds ratio	95% Confidence interval	p-value
WC	2.006	0.913-2.950	0.01
WHtR	1.012	1.427-2.078	0.02
HDL	2.009	0.903-2.050	0.01
MS	1.001	0.971-1.156	0.02
Microalbuminuria	1.011	0.931-1.186	0.02

p-Value <0.05 is significant.
 G1 : Group 1.
 WC: Waist circumference.
 WHtR : Waist-height ratio.
 HDL : High density lipoprotein.
 MS : Metabolic syndrome.

Table (5): Significant predictors of silent myocardial ischemia in obese patients (G1) by Multivariate regression analysis [n. 50].

Variate	Odds ratio	95% Confidence interval	p-value
WC	1.042	0.870-1.248	0.654
Microalbuminuria	1.794	0.673-4.784	0.243

p-Value <0.05 is significant.
 G1 : Group 1.
 WC: Waist circumference.

Discussion

Metabolic syndrome (MetS) is a cluster of risk factors linked to insulin resistance, subclinical inflammation, increased future risk of diabetes and coronary artery disease (CAD) [10]. Because of its high percentage of body fat, abdominal obesity and insulin resistance, South Asians are more likely to develop MetS [26]. Despite some debate, most experts seem to agree that the elevated cardiovascular risk seen in these subjects is possibly due to a clustering of risk factors [27]. The correlation

between MetS and increased risk CAD has been verified in several epidemiological and clinical studies [28]. Which is the leading cause of death globally. CAD morbidity and mortality are higher in MetS patients; thus, early evaluation of the risk of CAD in MetS patients is important because it may lead to improved adherence of patients or physicians to risk reducing behaviors or treatments and improve clinical outcomes.

The prevalence of SMI in obese subjects versus control group based on GSPECT was 26 per cent and 4 per cent in the present study.

No previous studies have, to our knowledge, focused on the value of G-SPECT using Tc-99 m SestaMIBI for SMI detection in obese Egyptian patients regarding the fact that Egypt is now among the top four countries with the highest incidence of obesity worldwide.

This research used GSPECT as a noninvasive and reproducible method for screening nonovert SMI and to ensure optimum target heart rates; pharmacological stress test [Dipyridamole] was used [29]. Our cases were also positive for MS by meeting 3/5 of the required criteria [WC >88cm in females and >102cm in males, TGs \geq 150mg/dl in males and HDL <40mg/dl in female]. According to NCEP-ATP III criteria [13].

None of our subjects have been positive for diabetes or hypertension, as such diseases are known as CAD predictors [13]. A large retrospective study was conducted by Vakil et al. [11] on male veterans [n. 1071; >40 percent with MS] for GSPECT detection of SMI and two-dimensional stress echocardiography but lacked controls and female sex in their study.

They found that 21.7 percent met stress imaging criteria for SMI, which was raised to 30 percent in high cases of WC [>102cm] comparable to our results [26 per cent]. Low HDL and high TG have traditionally been associated with increased prevalence of SMI [30,31]; Vakil et al. [11] have shown that they have not significantly increased the prevalence of SMI which is consistent with our data as regard the absence of significant association between SMI and TG. While low HDL has shown significant association with SMI in the present study, it was not among the significant predictors using multivariate regression analysis.

Microalbuminuria reflects widespread vascular damage and generalized vascular endothelial dysfunction [32]. The association between microalbuminuria and cardiovascular damage is independent

of renal function [33]. Besides, it might express the interaction between components of MS [32]. However, in the present study, Multivariate analysis showed that neither WC nor microalbuminuria is significant predictor of SMI in G1. This may be attributed to the small sample size of the study groups and the lack of information regarding the duration of exposure to each individual component of MS which are considered the main limitations of our study.

Finally, previous clinical trials have shown that the presence of SMI predicted an increased risk of future cardiac events [34,35]; hence, it remains of paramount importance to screen high risk patients like those with high WC using a non-invasive tool as GSPECT.

Conclusion:

A substantial association of SMI has been identified among a group of Egyptian obese patients using Tc99 m Sesta-MIBI GSPECT. Given the fact, we assume that the latter has a position as a screening tool; once the diagnosis is made, the better the result is.

Conflicts of interest:

The authors declare no conflicts of interest.

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رابطة نقص تروية عضلة القلب الصامت في مرضى السمنة ويعانون من متلازمة التمثيل الغذائي

مصر من بين الدول الأربع الأولى التي تعاني من السمنة في جميع أنحاء العالم. وكان هدف الدراسة هو دور محيط الخصر WC كمتنبئ مستقل لنقص تروية عضلة القلب الصامت SMI لا يزال غير معروف لدى مرضى السمنة المصريين. وهكذا هدفنا إلى الكشف عن SMI في مجموعة من الأفراد المصريين الذين يعانون من السمنة المفرطة المصاحبة لمتلازمة التمثيل الغذائي وتحليل ارتباطاتها بالبيانات السريرية والتشخيصية المختلفة. خمسون مريض يعانون من السمنة المفرطة (G1) بدون مرض الشريان التاجي العلني إناث ٦٠٪ و ٤٠٪ ذكور يتراوح أعمارهم بين ٤٠.٢ ± ٤.٥ سنوات و ٥٠ فرد من الذين يعانون من السمنة المفرطة الذين خدموا في المجموعة الضابطة (G2). وقد اتخذت تدابير القياسات تدابير القياسات البشرية لجميع الموضوعات. شمل التقييم المختبري نسبة السكر في الدم الصيام، الدهون الثلاثية في الدم، الكوليسترول، حمض اليوريك في الدم، اليوريا، الكرياتينين ومقاييس الزلال في البول. تم تعريف مرض تصلب العصبى المتعدد عن طريق استخدام GSPECT myocardial perfusion imaging Tc-99m SestaMIBI gated SPECT myocardiogram لتحديد الارتباطات بين SMI والمتغيرات الهامة. وقد وجد أن المجموعة الأولى ١٣/٥٠ عندهم SMI مقارنة بـ ٢/٥٠ (G2) إيجابية GSPECT ترتبط بشكل كبير مع HDL والزلزال في البول ومحيط الخصر. ولم نجد أن محيط الخصر والزلزال في البول له علاقة في التنبؤ SMI. ويمكن اعتبار GSPECT عامل مساعد للكشف على SMI.