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Original Article

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Abstract

Objectives: To determine the frequency of metabolic syndrome in type 2 diabetes according to three commonly used operational definitions {World Health Organization(WHO), National Cholesterol Education Program Adult Treatment Panel(NCEP ATP III) and International Diabetes Federation(IDF)}. To evaluate the agreement between these classifications in the Pakistani cohort.

Methods: Data was collected retrospectively of 210 patients with type 2 diabetes visiting outpatient clinics of one of the large tertiary care hospitals at Karachi, Pakistan between June 2008 to November 2008.

Results: The prevalence of metabolic syndrome was found to be 81.4% (WHO), 86.7 %(IDF) and 91.9 %(NCEP ATPIII). The degree of agreement (kappa statistic) was found to be highest among IDF & NCEP ATPIII (0.728) as compared to (0.436 & 0.417) between WHO & ATP and WHO & IDF respectively. The most significant predictors for metabolic syndrome were found out to be female gender OR= 8.74 95% CI 1.51-50.53, low HDL cholesterol levels OR= 0.89 95% CI 0.84-0.94 and high systolic blood pressure OR= 1.06 95% CI 1.009-1.11.

Conclusion: Our study results suggested that NCEP ATPIII and IDF are the most reliable criteria for diagnosing metabolic syndrome in type 2 diabetic patients, with NECP capturing more patients in comparison to IDF definition. The alarmingly high frequency of metabolic syndrome in type 2 diabetes found in this study suggests that primary prevention strategies should be initiated earlier and early in this ethnic group and our health care system should be geared up to cope with this deadly quartet.

Keywords: Diabetes, Metabolic Syndrome, Obesity, Prevalence World Health Organization (JPMA 62: 569; 2012).

Introduction

Rapid urbanization, modernization and population growth in developing countries has led to an upsurge of non-communicable diseases[1] associated with significant morbidity and mortality along with certain cancers.[2] Metabolic Syndrome (MS) also described as "Deadly Quartet" and X syndrome[3,4] is one of these disease entities defined by cluster of cardiovascular risk factors which to a greater extent is influenced by ethnicity/race. This encompasses atherogenic dyslipidaemia, hypertension, dysglycaemia and visceral obesity and pro coagulant state.[5] Apart from increasing prevalence, the age of onset is also declining among South Asian (SA) population[6] due to genetic predisposition and consumption of easily available energy dense foods from an early age. This trend has got major health implications since South Asians constitute one fifth of world's population[7] and the health care system in majority of these countries is not very primed to deal with these medical conditions.

Five diagnostic criteria have been put forward since the inception of this syndrome MS which has created perplexity among practitioners. In 1998, World Health Organization (WHO) initially proposed a definition for MS metabolic syndrome[8] with main emphasis on gluco-centricity (Table-1). In 1999, the European Group for the study of Insulin Resistance (EGIR) recommended more or less similar criteria with lower cut offs for hypertension.[9]

Thereafter in 2001, NCEP ATP III National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) proposed another definition for the diagnosis of metabolic syndrome MS with less focus on insulin resistance as compared to WHO criteria but not addressing separate cut off points of waist circumference for Asian population initially.[10] In 2003, American Association of Clinical Endocrinologists (AACE) proposed another set of criteria for the diagnosis of MS metabolic syndrome. The main limitation of the above mentioned criteria is that the diagnosis is based on clinical judgment instead of presence of specific number of risk factors.[11]

Considering that SA have a higher percentage of body fat mainly in the form of abdominal adiposity at a lower Body Mass Index (BMI) in comparison with other population,[12] International Diabetes Federation (IDF) in 2005 suggested separate cutoff points of waist circumference for Asian population and defined central obesity as waist circumference of more than 80 cm for women and 90 cm in men based on local statistics from the corresponding area.[13] The revised NCEP ATPIII modified for SA South Asian population incorporated the same cut off points for Asian population as given by IDF. Apart from the cut off differences, NCEP ATP III gives equal weight to each component of metabolic syndrome MS as compared to IDF for which abdominal obesity remains a prerequisite for the diagnosis.[13] Moreover, microalbuminuria which is a controversial variable of WHO criteria is not included in other definitions. Among these definitions, WHO, NCEP ATPIII & IDF have been the main ones which are used most widely.

Type 2 diabetes is also emerging as a global epidemic with increasing prevalence in developing countries.[14] Pakistan is among top ten countries estimated to have the highest number of diabetics occupying sixth position on the diabetes prevalence listing currently[15,16] and it is estimated that prevalence would be doubled by 2025. MS Metabolic syndrome in combination with diabetes increases the risk of both macro vascular, micro vascular complications and atherosclerosis progression due to associated hypertension, lipoprotein abnormalities and visceral obesity.[17]

There are studies that have looked into the differences in most widely used definitions of metabolic syndrome MS in general,[18-21] but only few studies have compared these definitions in the diabetic population.[22-24] Therefore we decided to determine the frequency of MS metabolic syndrome in Type 2 diabetics according to NCEP ATPIII, IDF and WHO definitions and then to compare these traits within the Pakistani population.

Methods

This cross-sectional study was conducted in the out-patient clinics at a tertiary care hospital of Karachi, Pakistan. Data of 210 type 2 diabetes patients was collected retrospectively who were visiting the clinics between June and November 2008, by using a questionnaire which included demographic characteristics and individual components of MS i.e. weight, height, waist circumference and BMI etc. Both hip and waist circumference were recorded in centimeters and waist/hip ratio was calculated (WHR). BMI was calculated as a ratio of weight in kg to height in meters squared. Data was compiled between June and August 2009.

The sample size was calculated on an assumption that minimum 208 participants would be required to study the frequency of (MS) metabolic syndrome in type 2 diabetics of around 46-74% (2, 25) to achieve 80% power, 0.068 percentage point of true value and 5% significance level.

The laboratory tests which are routinely done for patients with type 2 diabetes including triglycerides and high density lipoprotein (HDL-C) were recorded. Patients already on anti-hypertensive and anti-lipid medications specifically in the form of fibric acid derivatives and niacin were taken as cases of hypertension and hypertriglyceridaemia respectively, irrespective of their blood pressure and lipid levels.

The data was analyzed separately according to NCEP ATP III, IDF and WHO definitions and the results were then compared. The frequency of MS was calculated with 95% CI based on three different criteria's. The data were presented as the mean ± SD and median [inter-quartile range (IQR)] for skewed variables, respectively. Categorical variables were presented as numbers and percentages; Continuous variables were compared using Student t test for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables and categorical variables were compared by chi-square or Fisher exact test. All analyses were conducted by using the statistical package for social sciences SPSS 14. A kappa test was done to determine the concurrence between three definitions. In univariate analysis, comparison between MS and without MS was done for each variable of interest. Multivariable logistic regression analysis was conducted to identify the factors associated with MS. All p values were two tailed and considered statistically significant if ≤ 0.05.

Results

Description of baseline, anthropometric and laboratory parameters of type 2 diabetics comparing patients fulfilling any one of the three definitions of metabolic syndrome MS with those not having MS syndrome are provided in Table-2.

Out of total 210 type 2 diabetic patients, 112 (53.3%) were males and 98 (46.7%) were females. Their mean age was 53.67 ± 11.17 years (Table-2). The mean duration of diabetes mellitus was 8.48 ± 7.18 years. Total 193 (91.9%) were found to have metabolic syndrome according to NCEP ATP III in comparison to 182 (86.7%) based on IDF criteria.

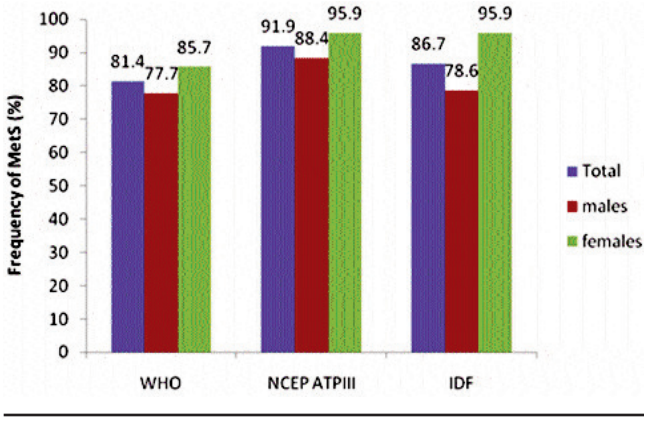

Figure-1: Frequency of Metabolic Syndrome according to three main diagnostic criteria.

Lower frequency was documented with WHO criteria of 171 (81.4%) Figure-1. The frequency increased to 179 (85.2%) by WHO, using the new cut offs for defining overweight (BMI of 23 vs. 30).

The degree of agreement (kappa statistic) between WHO, ATP III and WHO, IDF definitions were 0.436 95% CI 0.26-0.60 and 0.417 95%CI 0.25-0.57respectively. In contrast kappa statistic between IDF and ATP III definitions was found to be 0.728 95%CI 0.57-0.87.The overall agreement between three definitions was 0.37 (95% CI 0.26-0.51) Figure-2.

Central obesity was present in 162 (77%) patients by WHO criteria followed by 197 (90.5%) based on IDF and NCEP ATP III. Hypertension was found in 116 (55.2%) patients according to WHO in comparison to 147 (70%) by NCEP & IDF cut off of blood pressure. Presence of low HDL

Table-1: Diagnostic Criteria for the Metabolic Syndrome from WHO, NCEP (ATPIII) and IDF definitions.

WHO	NCEP(ATPIII)	IDF
Diabetes or impaired glucose or insulin resistance (obligatory) plus two or more of the following Obesity: BMI > 30kg/m² or WHR >0.9 (M) >0.85 (F)	Any three of the five criteria below constitute a diagnosis of Metabolic Syndrome Central Obesity * (Waist circumference ethnicity specific. For South Asians ≥90 cm in Men ≥80 cm in women	Central Obesity (pre requisite) plus any two of the four other criteria constitute a diagnosis of Metabolic Syndrome Central Obesity * (Waist circumference ethnicity specific. For South Asians ≥90 cm in Men ≥80 cm in women
Dyslipidaemia: Triglycerides ≥150 mg/dl (1.7mmol/l)	Dyslipidaemia: Raised Triglycerides >150mg/dl (1.7mmol/l) Or on specific treatment for this lipid disorder.	Dyslipidaemia: Raised Triglycerides >150mg/dl (1.7mmol/l) Or on specific treatment for this lipid disorder.
Reduced HDL-C < 35 mg/dl (0.9mmol/l) (M) < 39mg/dl (1.0mmol/l) (F) or on specific treatment for this lipid disorder	Reduced HDL <40mg/dl (1.03mmol/l) in M <50mg/dl (1.29 mmol/l) in Women Or on specific treatment for this lipid disorder.	Reduced HDL <40mg/dl (1.03mmol/l) in M <50mg/dl (1.29 mmol/l) in Women Or on specific treatment for this lipid disorder.
Hypertension: Blood Pressure ≥ 140/90 mm Hg or medication	Hypertension: Blood Pressure ≥130 Systolic ≥85 diastolic or on treatment for hypertension	Hypertension: Blood Pressure ≥130 Systolic ≥85 diastolic or on treatment for hypertension
Microalbuminuria: Albumin excretion ≥ 20 µg/min or albumin: creatinine ratio ≥ 30mg/g	Raised Fasting Glucose ≥100 mg/dl (5.6mmol/l) or previously diagnosed type 2 diabetes	Raised Fasting Glucose ≥100 mg/dl (5.6mmol/l) or previously diagnosed type 2 diabetes

Table-2: Basic anthropometric and Laboratory Characteristics of Patients with Type 2 Diabetes with and without MS Metabolic Syndrome.

	Patients with Metabolic Syndrome N=196	Patients without Metabolic Syndrome N=14	P value
Age, years	53.67 ± 11.17	48.86 ± 14.64	0.12
Sex			0.050
Male	101(51.5)	11(78.6)	
Female	95(48.5)	3(21.4)	
BMI kg/m^2, median (IQR)	26.60 (6.57)	24.76 (7)	0.10
Waist circumference	100.69 ± 10.44	93.67 ± 8.55	0.01
Triglycerides (mg/dl), median (IQR)	137 (87.5)	109 (55.25)	0.005
HDL cholesterol (mg/dl), median (IQR)	39 (13)	48.50 (18)	<0.001
Blood Pressure (mmHg)			
Systolic B.P	126.62 ± 17.46	113.57 ± 8.41	<0.001
Diastolic B.P	76.07 ± 10.11	72.14 ± 8.01	0.15
Microalbuminuria, median (IQR)	8.34 (21)	4.57 (8.13)	0.06

Data shown as mean ± SD (Standard Deviation)
Gender distribution is shown as no & percentages.

Table-3: Frequency of 95% CI of MS Metabolic Syndrome using WHO, NCEP (ATPIII) and IDF Criteria by Age and Gender.

	n	WHO n (%)	ATPIII n (%)	IDF n (%)
Total	210	171 (81.4)	193 (91.9)	182 (86.7)
		(75.61-86.09)	(87.41-94.86)	(81.3-90.59)
Male				
≤ 45	32	24 (75)	28 (87.5)	23 (71.87)
		(57.74-86.70)	(71.79-94.89)	(54.47-84.40)
46-55	36	29 (80.55)	32 (88.88)	31 (86.11)
		(64.84-90.17)	(74.58-95.46)	(71.22-93.80)
56-65	25	19 (76)	22 (88)	19 (76)
		(56.35-88.42)	(69.84-95.64)	(56.35-91.34)
≥ 66	19	15 (78.94)	17 (89.47)	15 (78.94)
		(56.33-91.34)	(68.30-96.79)	(56.33-91.34)
Total	112	87 (77.67)	99 (88.39)	88 (78.57)
		(69.09-84.38)	(81.13-93.05)	(70.06-85.14)
Female				
≤ 45	17	13 (76.47)	17	17
		(52.36-90.30)	(81.46-99.85)	(81.46-99.85)
46-55	31	25 (80.64)	29 (93.54)	29 (93.54)
		(63.56-90.72)	(79.19-98.02)	(79.19-98.02)
56-65	40	37 (92.5)	38 (95)	38 (95)
		(80.07-97.27)	(83.46-98.46)	(83.46-98.46)
≥ 66	10	9 (90)	10	10
		(58.72-97.71)	(71.50-99.77)	(71.50-99.77)
Total	98	84 (85.71)	94 (95.91)	94 (95.91)
		(77.41-91.26)	(89.99-98.73)	(89.99-98.73)

Table-4: Risk factor predicting prevalence of metabolic syndrome.

	Odd ratio [95% CI)
Sex	
Male	1.0
Female	8.74[1.51,50.53]
HDL cholesterol (mg/dl)	0.89[0.84,0.94]
Systolic B.P	1.06[1.009,1.11]

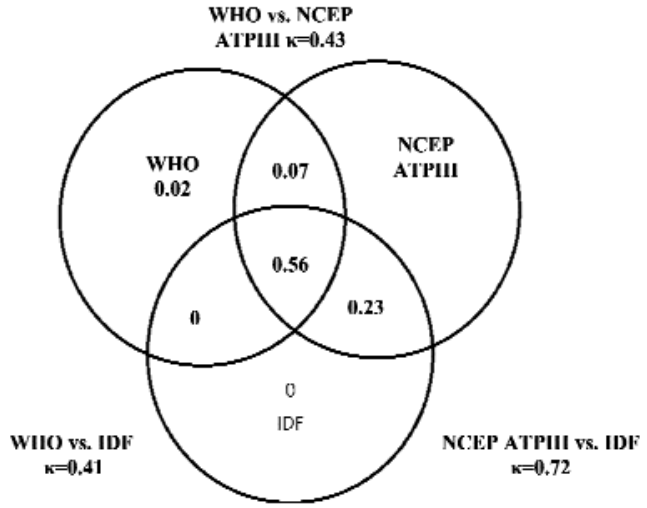

Figure-2: Degree of agreement (kappa statistic) between three definitions of Metabolic Syndrome.

cholesterol again differed being present in 77 (36.7%) when WHO definition was applied and 144 (68.6%) by ATP III and IDF.

Furthermore, gender wise breakdown of frequency of MS by WHO showed that 84 (85.7%) females suffered from MS as compared to 87 (77.7%) males, a difference not statistically significant (p=0.13). However, by all other criteria MS was significantly more common among females as compared to males, 95.9% vs. 88.4% (p=0.04) by ATP III and 95.9% vs. 78.6% (p<0.001) by IDF (Table-3).

For prevalence of hypertriglyceridaemia, no statistically significant difference between both genders were found. However, for low HDL cholesterol, prevalence was higher in males, 44 (57.14%) than in females 33 (43%) by WHO criteria (p<0.001). In contrast on the basis of ATP III

and IDF definitions, prevalence of low HDL cholesterol levels were higher (p=0.009) in females 77(57.46%) than in males 57(42.53%). Likewise, central obesity was found to be more common among female patients based on IDF and NCEP (ATPIII) cutoffs 64.8% females vs. 35.2% males (<0.001) but showing reverse pattern with WHO criteria, 57.14% males vs. 43% females (p <0.001).

To find out the independent predictors of MS, a multivariable logistic regression was performed. Female gender, low HDL cholesterol and high systolic blood pressure were found to be the most important predictors for MS (Table-4).

Discussion

Our study showed a considerably high frequency of MS in people with type 2 diabetes based on NECP (ATPIII) and IDF criteria. The frequency was quite high in comparison to 46-76% found in other hospital based studies from Pakistan.[25-27] This is very interesting keeping in view that all of these studies were done in the same region. The disparity could be attributed to lower frequency of obesity (30-74%) found in the above mentioned studies in comparison to our study (90.5%). It is speculated that this intra-regional difference could be due to the fact that certain communities have high tendency to develop obesity and MS despite of belonging to the same region due to differences in life style, eating habits and level of physical activity.[28] On the other hand, another hospital based study from Pakistan revealed comparable frequency of MS according to NCEP criteria.[29]

One of the hospital based studies in Iran, showed the prevalence of MS in type 2 diabetics according to the NCEP (ATPIII) criteria, to be 65%.[30] In this study instead of BMI, waist circumference was used highlighting the importance of abdominal adiposity, a better marker of MS as compared to BMI. A multicenter hospital based study in Brazil and Finland showed a close frequency of central obesity and MS (85 & 91.5%) was observed in type 2 diabetics[31] although the study population comprised of people of European descent. Our data was also consistent with an Indian study showing prevalence of 91.1% MS[20] using the same NCEP (ATPIII) definition. However, separate components of MS were found to be more common in our population as compared to South Indians.[20] The higher frequency of MS in diabetic population found in our study is a source of major concern since diabetes itself is an important risk factor for atherosclerotic cardiovascular disease (ASCVD) and the presence of the components of the MS in type 2 diabetics are associated with both micro and macro vascular complications as well as distal neuropathy.[31]

All type 2 diabetic patients should therefore be screened for MS and offered intensive management to avoid complications as coronary heart disease which is closely linked with central obesity and insulin resistance.[32]

The higher frequency of MS in women according to all criteria is also consistent with other studies from South Asian countries.[33,34] This could be attributed to less physical activity in women due to ethnic and cultural restrictions. This also highlights the importance of education of our women in terms of prevention of MS with life style changes which would indirectly influence the eating habits of the whole family.

Regarding the selection of criteria for diagnosing MS the slightly higher prevalence of MS by ATP III definition in comparison to IDF (91.9% vs. 86.7%) could be attributed to the relative flexibility of the ATP III in which abdominal obesity is not considered as a prerequisite for the diagnosis.

Except for this difference the ATP III and IDF definitions are essentially identical as seen by the degree of agreement (kappa statistic= -0.728). According to this, NCEP (ATPIII) and IDF are the most reliable criteria's for diagnosing MS in type 2 diabetic patients, with NECP capturing more patients in comparison to IDF. In contrast WHO showed lower frequency of MS due to different cutoffs used for HDL levels and obesity. This difference remained significant even after adjusting it with BMI cutoffs for Asian population of 23 vs.30 endorsed by WHO expert consultation[35] pointing towards the fact that waist circumference or central obesity is a more valuable tool for detection of MS in Asian population.

Conclusion

On the basis of these findings NCEP (ATPIII) modified criteria should preferably be used in the Pakistani population. Using waist circumference an obligatory criterion still missed out 5.2% cases of MS in our study. To further validate these recommendations, more studies are required to estimate the predictive power for micro and macro vascular complications and to establish the most appropriate definition of MS for South Asian population with type 2 diabetes. The alarmingly high frequency of MS in type 2 diabetes found in our study, indicates that our health care system should to take emergent steps in implementing life style intervention programmes.

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