

Prevalence of Coronary Heart Disease among Non-Smokers with Type 2 Diabetes Mellitus and Metabolic Syndrome Defined By NCEPATP 111 (National Cholesterol Education Programme Adult Treatment Panel 111)

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Abstract

Coronary Artery Disease (CAD) incidence varies according to certain risks; patients with pre-existing cardiovascular heart disease who later develop diabetes mellitus (DM) have the greatest risk, and non-diabetic patients with CAD, diabetic patients without CAD, and patients with metabolic syndrome (MetS) the next three high risk categories. Insulin resistance, a major feature in both DM and MetS probably causes atherogenic dyslipidaemia.

Objectives: (1) to determine the prevalence of MetS and DM in the study population, (2) to determine the prevalence of Coronary Artery Disease (CAD) in DM with MetS (DM+/MetS+), in DM alone (DM+/MetS-), MetS alone (MetS+/DM-) and in 'normal' group (DM-/MetS-), and (3) to determine the prevalence of MetS in DM patients.

Results: 62.1% of the study population had MetS, 44.7% had DM, 83.6% had both MetS and DM. 18.6% had CAD. CAD was seen in 25.2% of DM+/MetS+, 19.1% of MetS+/DM-, 14.3% of DM+/MetS-, and 11.6% of MetS-/DM- patients.

DM+/MetS+ group had the highest association with CAD OR= 2.19, CI (1.43-3.35), DM-/MetS- group the lowest association OR=0.45, CI (0.27-0.73), and DM+/MetS- (OR=0.69, CI (0.28-1.73) and MetS+/DM- (OR=0.94, CI (0.57-1.58) had no significant association with CAD.

Conclusion: Only DM+/MetS+ patients had a high risk of developing CAD. Risk of CAD in patients with MetS+/DM- and DM+/MetS- was not statistically significant in multivariate analysis, while the group with neither, MS-/DM-, had the lowest risk of developing CAD.

Keywords: NNCEPATP111-defined metabolic syndrome; Diabetes mellitus; Cardiovascular heart disease

Introduction

MetS is characterized clinically by a clustering of factors; abnormal blood lipids (low HDL-C and high triglycerides), impaired glucose tolerance, elevated blood pressure, and abdominal obesity [1-4]. It is associated with five-fold risk of type 2 DM and two-fold risk of cardiovascular disease [5,6]. DM developing with MetS, increases the macrovascular disease contributed by MetS as both confer a common factor of insulin resistance, an important cause of atherogenic dyslipidaemia [7-11]. The exact contributions of the elements comprising the metabolic syndrome are not fully known; the most important factors being weight, genetics, endocrine disorders (such as polycystic ovary syndrome in women of reproductive age), aging, and sedentary lifestyle, (i.e., low physical activity and excess caloric intake) [12-16].

Many studies have shown 65-85% of individuals with DM have MetS [17]. There is a controversy of the importance of MetS in diabetics as a separate factor for cardiovascular risk. The few studies that have examined the combined effect of MetS and DM on CAD risk found increased prevalence of atherosclerotic CAD in patients with either DM or MetS alone, and in individuals with concurrent DM and MetS, a significant greater prevalence compared than either factor alone. However, a small prospective study and the United Kingdom Prospective Diabetes Study reported that in individuals with DM, those with MetS had a higher risk of CAD mortality, but those with DM without MetS did not [18-22].

Strategies to activate the peroxisome proliferator activated receptor- α (PPAR- α) agonists such as exercise, omega 3 fatty acids and fibrates improve mitochondrial function and lipid metabolism in subjects with insulin resistance and prevent or reduce CAD and CAD

related deaths have been attempted. However, even though early studies with fibrate therapy seemed to be beneficial, the ACCORD and others studies showed that combination therapy with statins and fibrates had no additional benefit over statins alone [23-30]. At best, whether combination therapy may be beneficial in patients with low HDL-C and high triglycerides remains unanswered. A very recent study even questions the benefit of weight loss in DM type 2 for reducing CAD leaving in question the best methods of reducing CAD in this group of patients [31].

We performed a retrospective study of the prevalence and association of CAD in a population with and without DM and MetS in a rural Malaysian out-patient setting (OPD).

Materials and Methods

A cross-sectional retrospective study was conducted from January 2, 2011 to November 30, 2012. Data was obtained from patients' medical records who attended medical specialist OPD and OPD patients in a district hospital in Perak, Malaysia. Sample size (n = 398) was determined using the EpiInfo version 6 (CDC, Atlanta, GA, USA) for

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population surveys. Samples were selected using randomised clustered systematic sampling with four patients selected every week. Inclusion criterion was age ≥ 20 years, and exclusion criteria were patients with known pathological causes of obesity such as Cushing's and pseudo-Cushing's syndrome, known causes of dyslipidaemia such as chronic renal failure, nephrotic syndrome and hypothyroidism, HIV patients on antiviral drugs and smokers.

Body Mass Index (BMI) (body weight in kg/height in cm^2), Waist Circumference (WC) in cm. and Blood Pressure (BP) (mmHg) measurements (average of three readings one hour apart) were carried out by the same trained staff nurse. WC measurement was standardised at the midpoint between the lower costal cartilage and the highest point of the iliac crest with the patient exhaling completely. Samples for Fasting Plasma Glucose (FPG), serum Triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) were taken in early morning after overnight fast. Definitions were high WC: ≥ 90 cm for males and ≥ 80 cm for females; hypertension: systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg; high fasting plasma glucose: FPG 5.6-6.99 mmol/L; diabetes mellitus: FPG ≥ 7 mmol/L; low HDL-C: < 1.29 mmol/L in females and < 1.03 mmol/L in males; high TG: ≥ 1.7 mmol/L for both genders.

The research purpose was explained to each patients and the history and physical examination was done by the main investigator. Consent for blood tests from all the patients were obtained from all the patients.

The Harmonized NCEP criteria defined by lower cut-off points for waist circumference than the NCEP criteria was used to define MetS as more appropriate for South East Asians. CAD was defined by the patients' record: coronary angiography, angioplasty, CABG, symptoms of angina or unstable angina plus ECG changes, cardiac biomarkers with or without echocardiogram changes and response to coronary vasodilators. Patients were divided into two main groups: MetS+ and MetS-, and further sub-grouped according to DM: MetS+/DM+ and MetS+/DM-; and MetS-/DM+ and MetS-/DM- [32].

Statistical analyses were performed using the Statistical Package for the Social Sciences version 16 (SPSS Inc, Chicago, IL, USA). Student's *t*-test was used to compare the means. Pearson's chi-square test was used to identify the associations. P value less than 0.05 is defined as significant difference or association respectively.

Results

Prevalence of MetS was 83.6% in DM patients, 68.3% in patients with impaired fasting plasma glucose, and 34.6% in normal glucose tolerance group.

CAD prevalence was 11.6% in patients without either MetS or DM (MetS-/DM-); 14.3% in MetS-/DM+; 19.1% in MetS+/DM-, and 25.2% in the MetS+/DM+ groups.

The difference in prevalence of MetS found in groups with DM+, impaired FPG, and normal glucose tolerance was statistically significant ($\chi^2 = 86.9$).

Table 1 shows the frequency of demographic distribution of age, gender, ethnicity, prevalence of metabolic risk factors, MetS, DM, CAD, DM+/MetS+, MetS+/DM-, DM+/MetS- and DM-/MetS- in the study population.

Table 2 shows univariate analysis of age, BMI and WC cut-off, individual metabolic risk factors, DM, metabolic syndrome, DM+/MS+, MS+/DM-, DM+/MS- and DM-/MS- and their association with CAD (n= 398).

Variables	Number (%)	CAD + (n=74)	CAD - (n=324)
Age			
20-29	38 (9.5)	2 (5.3)	36 (11)
30-39	40 (10.1)	6 (15)	34 (10.5)
40-49	90 (22.6)	18 (20)	72 (22.2)
50-59	127 (31.9)	28 (22)	99 (30.6)
≥ 60	103 (25.9)	20 (19.4)	83 (25.6)
Gender			
Female	204 (51.3)	38 (18.6)	166 (18.4)
Male	194 (48.7)	38 (18.6)	158 (18.4)
Ethnicity			
Malay	162 (40.7)	38 (17.3)	124 (82.7)
Indian	144 (36.2)	28 (19.4)	116 (80.6)
Chinese	92 (23.1)	19 (19.6)	74 (80.4)

CAD showed no association with either gender or ethnicity.

Table 1: Distribution of demographic factors in the study population and association between CAD positive and negative subjects (n =398).

Variables	Number (%)	CAD (n= 74)	No CAD (n= 324)	P value, OR , (95% CI)
Age cut-off *	315 (85.2)	65 (20.6)	250 (79.4)	0.04, 2.14 (1.02-4.50)
BMI cut-off *	209 (52.5)	47 (22.5)	162 (77.5)	0.97, 1.60 (0.96-2.68)
WC cut-off *	173	35 (20.2)	138 (79.8)	0.62, 1.44 (0.85-2.44)
MetS Risks				
Hypertension	239 (60.1)	52 (21.8)	187 (78.2)	0.04, 1.73 (1.02-2.99)
Raised FPG	237 (59.5)	53 (22.4)	184 (77.6)	0.01, 1.92 (1.11-3.33)
Low HDL-C	224 (56.3)	42 (18.8)	182 (81.2)	0.18, 1.02 (0.62-1.71)
High TG	161 (40.5)	35 (21.7)	126 (78.3)	0.18, 1.41 (0.85-2.34)
High WC	268 (67.3)	54 (20.1)	214 (79.9)	0.25, 1.39 (0.79-2.44)
DM	161 (40.5)	38 (23.6)	123 (76.4)	0.03, 1.73 (1.04-2.87)
MetS	247 (62.1)	58 (23.5)	189 (76.5)	0.00, 2.25 (1.41-3.59)
DM+/MS+	151 (37.9)	38 (25.2)	113 (74.8)	0.00, 2.19 (1.43-3.35)
MS+/DM-	93 (23.6)	18 (19.1)	73 (80.9)	0.87, 0.94 (0.57-1.58)
DM+/MS-	28 (7)	4 (14.3)	24 (85.7)	0.53, 0.69 (0.28-1.73)
DM-/MS-	126 (31.6)	15 (11.6)	111 (78.4)	0.00, 0.45 (0.27-0.73)

*Age cut-off = 42.5 years old, BMI cut-off = 26.5 kg/cm^2 , WC cut-off = 94.5 cm for female and 96 cm for males, p value < 0.05 is significant

Table 2: Shows univariate analysis of individual components of MetS, full MetS and DM in association with CAD.

Variables	p value	OR (95% CI)
MetS	0.04	2.28 (1.04-5.03)
Hypertension	0.92	0.97 (0.48-1.96)
Raised fasting blood Glucose	0.52	1.23 (0.65-2.25)
High triglycerides	0.84	0.94 (0.53-1.68)
Low HDL-C	0.25	0.72 (0.41-1.27)
High WC	0.45	0.76 (0.37-1.55)

Table 3: Multivariate logistic regression analysis of association of risk factors of MetS and MetS with CAD.

Prevalence of CAD with MetS was higher than DM. Prevalence of CAD overall was 18.6%. Patients with DM+/MetS+ had the highest while those with DM+/MetS- and those with neither, MetS-/DM-, the lowest prevalence of CAD respectively. Patients with MetS + / DM- had an intermediate prevalence for CAD. Patients with MetS+/DM+, older age, hypertension, elevated FPG, MetS, DM and DM+/MetS+ were significantly associated with CAD by univariate analysis.

Table 3 shows CAD by multiple regression analysis. Only MetS+

was associated with CAD, indicating the combination of individual risk factors for MetS is more significant than any individual risk factors of MetS for developing CAD.

The analysis of association of CAD with DM, MetS and age by multiple regression analysis, showed only MetS is positive (Table 4).

Discussion

Our study showing the significant association of DM+/MetS+, but not Mets+/DM- or DM+/MetS- with CAD, (Table 2) is consistent with others [17-21]. This may be due to enhancement of macro and micro vascular diseases of MetS by hyperglycaemia of diabetes.

By univariate analysis, the prevalence of CAD in Mets+/DM- is

intermediate between DM overall and DM without MetS. This finding is consistent with finding of others [22,33] which demonstrated an increased prevalence, incidence, and risk of CAD mortality in subjects with metabolic syndrome, regardless of whether or not they had type 2 diabetes. This is also supported by studies from Quebec and Finland that showed even without hyperglycaemia, elevated levels of insulin (i.e., insulin resistance), were associated with risk of CAD [34,35].

While our study showing a higher prevalence of CAD in DM+/MetS- in univariate analysis than the cohort with neither is consistent with other reports, this was not significant by multivariate analysis [17-21].

Studies have shown that even small increases in fasting or postprandial glucose values (including impaired glucose tolerance or impaired fasting glucose) impart an increased risk for cardiovascular morbidity and mortality [36-41]. While again seen in our study by univariate analysis; with 11.4% (normal FPG), 14.5% (impaired FPG) and 22.9% (DM) patient groups having CAD respectively, this was not supported by multivariate analysis. Thus it appears; that FPG, if not in the DM range, may not be significantly associated with CAD as in our study MetS without DM was not significantly associated with CAD as opposed to DM+/Mets+.

Variables	p value	OR (95% CI)
MetS	0.02	2.05 (1.09-3.85)
DM	0.44	1.24 (0.72-2.16)
Age ≥ 42.5	0.15	1.74 (0.81-3.73)

Table 4: Multivariate logistic regression analysis of association of MetS, DM and Age 43 and above with CAD.

		with CAD	without CAD	P-value		with CAD	without CAD	P-value
Age	DM+/MS+	(n=38) 53.5 ± 11.6	(n=113) 53.6 ± 11.1	0.91	FPG	(n=38) 9.33 ± 2.83	(n=113) 9.13 ± 2.51	0.69
	DM+/MetS-	(n=4) 52.1 ± 12.9	(n=24) 56.7 ± 10.0	0.30		(n=4) 9.25 ± 1.88	(n=24) 9.39 ± 3.39	0.67
	MetS+/DM-	(n=18) 50.2 ± 13.9	(n=60) 51.3 ± 13.5	0.25		(n=18) 5.17 ± 0.73	(n=60) 5.36 ± 0.67	0.32
	MetS-/DM-	(n=14) 44 ± 17.7	(n=127) 45.5 ± 16.5	0.49		(n=14) 4.69 ± 0.71	(n=127) 4.84 ± 0.53	0.44
BMI	DM+/MS+	(n=38) 30.1 ± 7.16	(n=113) 30.2 ± 7.04	0.78	Triglycerides	(n=38) 2.24 ± 2.03	(n=113) 2.14 ± 1.74	0.46
	DM+/MetS-	(n=4) 23.3 ± 3.23	(n=24) 23.5 ± 3.70	0.49		(n=4) 1.29 ± 0.43	(n=24) 1.35 ± 0.42	0.19
	MetS+/DM-	(n=18) 28.5 ± 5.10	(n=60) 29.3 ± 5.50	0.13		(n=18) 2.12 ± 1.15	(n=60) 1.99 ± 0.98	0.48
	MetS-/DM-	(n=14) 25.0 ± 6.83	(n=127) 25.1 ± 7.12	0.88		(n=14) 1.20 ± 0.55	(n=127) 1.37 ± 0.60	0.48
WC	DM+/MS+	(n=38) 99.1 ± 12.6	(n=113) 98.4 ± 11.4	0.63	HDL-C	(n=38) 1.04 ± 0.34	(n=113) 1.03 ± 0.35	0.27
	DM+/MetS-	(n=4) 84.1 ± 11.5	(n=24) 83.3 ± 12.5	0.09		(n=4) 1.32 ± 0.49	(n=24) 1.27 ± 0.45	0.62
	MetS+/DM-	(n=18) 98.1 ± 10.4	(n=60) 98.3 ± 10.4	0.47		(n=18) 1.03 ± 0.31	(n=60) 1.02 ± 0.31	0.80
	MetS-/DM-	(n=14) 83.7 ± 14.1	(n=127) 83.5 ± 14.9	0.88		(n=14) 1.34 ± 0.57	(n=127) 1.37 ± 0.60	0.69
Systolic BP	DM+/MS+	(n=38) 143 ± 17.2	(n=113) 143 ± 16.40	0.58	Total CHO	(n=38) 5.18 ± 1.42	(n=113) 5.14 ± 1.46	0.05
	DM+/MetS-	(n=4) 112 ± 15.9	(n=24) 120 ± 13.8	0.71		(n=4) 5.32 ± 1.89	(n=24) 5.44 ± 1.65	0.55
	MetS+/DM-	(n=18) 142 ± 18.3	(n=60) 142 ± 18.0	0.91		(n=18) 5.13 ± 1.53	(n=60) 5.18 ± 1.55	0.43
	MetS-/DM-	(n=14) 122 ± 17.8	(n=127) 123 ± 17.6	0.96		(n=14) 4.74 ± 1.35	(n=127) 4.84 ± 1.38	0.15
Diastolic BP	DM+/MS+	(n=38) 85.7 ± 10.4	(n=113) 85.6 ± 10.3	0.79	LDL-C	(n=38) 3.37 ± 1.50	(n=113) 3.43 ± 1.46	0.92
	DM+/MetS-	(n=4) 77.7 ± 10.7	(n=24) 78.1 ± 10.2	0.51		(n=4) 3.20 ± 1.21	(n=24) 3.09 ± 0.86	0.59
	MetS+/DM-	(n=18) 86.0 ± 10.1	(n=60) 85.0 ± 10.0	0.36		(n=18) 3.17 ± 1.13	(n=60) 3.28 ± 1.11	0.12
	MetS-/DM-	(n=14) 77.0 ± 10.4	(n=127) 78.4 ± 9.32	0.33		(n=14) 3.18 ± 1.12	(n=127) 3.28 ± 1.15	0.16

Only the DM+/MetS+ with CAD is found to be different from that of CAD negative by having p value 0.05 although it is not less than 0.05

Table 5: Mean of age, BMI, metabolic risk factors, total cholesterol and low density lipoprotein in subjects with DM+/MetS+, MetS+/DM-, DM+/MetS- and MetS-/DM- with and without CAD.

Our study, which in agreement with others, found no significant association of MetS+/DM- and DM+/MetS- with CAD, is also consistent with recent findings that patients with obesity alone, without associated morbid conditions, do not appear to have an increased incidence of CAD [42].

Our finding of association of CAD prevalence with MetS (Tables 2-4) is also consistent with other studies [5,32,43,44]. Our study is unable to answer whether the presence of more risk elements of MetS contribute to a higher risk of CAD [16]. In multivariate analysis only MetS is significantly associated with CAD although elevated FPG and hypertension are significantly associated with CAD in univariate analysis (Table 2). It indicates that perhaps elevated FPG and hypertension are the more important driving factors for CAD risk in MetS. While not in agreement with some studies [18] where low HDL-C was the most predictive risk of CAD, our finding support yet other studies as well as the recent analysis of metabolic syndrome in the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study [45,46] that BP elevation is the most common component (95.4%) of the metabolic syndrome. The contribution of metabolic syndrome components to CAD and all-cause mortality was mainly related to BP and glucose abnormalities. It also supports that MetS, irrespective of its definition, is an independent clinical indicator of macro and micro vascular complications in diabetes [21,22,47,48]. Therefore, metabolic syndrome appears not to be just a pre-diabetes syndrome, but by itself, a very high-risk state [43].

We showed that LDL-C levels were comparable in CAD and non-CAD groups (Table 5 a-e), (although many of our patients were on statins), CAD may be caused by triglycerides rich arthrogenic lipids, a component of LDL-C which was not measured. It is supported by our finding in table 5 that TG alone is noted to be in association with CAD. Our findings support the Heart Protection Study that asserted treatment of CAD with statins alone is insufficient therapy of CAD [25].

45.4 percent and 10 percent of our study cohort were on statins and fibrates respectively. Our finding are thus in agreement with other studies that showed raising HDL-C by drug means does not improve risk of CAD above lowering of LDL-C with statins [31]. However, this may depend on which component of the MetS is the most dominant. If it is low HDL-C, combined therapy might have additional benefit, but if, for example, it is hypertension and elevated FPG, combined therapy may not have any additional benefit.

This study has several limitations. Firstly, 54% of patients enrolled

were already on treatment for hypertension, diabetes mellitus and hypercholesterolemia. We tried to overcome these by obtaining the necessary sample size and by using pre-therapy data. Secondly, most of the patients in this study already had MetS with DM simultaneously at presentation. The cross-sectional study employed here is unable to answer whether DM+/MetS- or DM-/MetS+ progressing to DM+/MetS+ is more predisposing to CAD (Table 6), for which a prospective study of isolated DM and MetS is necessary. Finally, as this was a hospital-based study, the findings do not represent the whole Malaysian population or the local community. Further larger population-based studies are necessary to support our findings.

In conclusion, our study showed that only DM patients with MetS+ are significantly associated with CAD morbidity.

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Variable	CHD +	CHD -	p-value
	Mean ± SD	Mean ± SD	
Age	53.5 ± 11.6	53.6 ± 11.1	.09
BMI	30.1 ± 7.16	30.2 ± 7.04	.45
WC	99.1 ± 12.6	98.4 ± 11.4	.15
Systolic BP	143 ± 17.2	143 ± 16.4	.26
Diastolic BP	85.7 ± 10.4	85.6 ± 10.3	.75
FPG	9.33 ± 2.83	9.13 ± 2.51	.08
Triglycerides	2.24 ± 2.03	2.14 ± 1.74	.04
HDL-C	1.04 ± 0.34	1.03 ± 0.35	.43
Total CHO	5.18 ± 1.42	5.14 ± 1.46	.31
LDL-C	3.37 ± 1.50	3.43 ± 1.46	.33

Triglycerides only is noted to be significantly different among CAD positive and negative

Table 6: Mean of age, BMI, metabolic risk factors, total cholesterol and low density lipoprotein in subjects with DM+/MetS+ in the whole study population with and without CAD.

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