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Metabolic Syndrome Components and Long-Term Incidence of Cardiovascular Disease in Eastern Mediterranean Region: A 13-Year Population-Based Cohort Study

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Abstract

Background: The risk of cardiovascular events in individuals with metabolic syndrome (MetS) is higher than in general populations. We aimed at assessing the association between cardiovascular disease (CVD) and MetS and at identifying triple components that are the most predictive of future CVD events.
Methods: Data on 1387 CVD-free individuals recruited in an ongoing cohort in Isfahan, Iran (ICS) were analyzed. This included serum tests and health and lifestyle questionnaires measured at baseline in 2001, 2007, and 2013. The association between CVD and MetS, irrespective of composing components, was evaluated by using logistic regression. The hazard ratio (HR) of CVD events after MetS diagnosis was calculated for different combinations by using Cox PH regression.
Results: The prevalence of MetS was 34.4% at baseline, 19.5% of which was with diabetes. The prevalence of hypertension (blood pressure [BP]) and hyperglycemia (fasting plasma glucose [FPG]) increased over time. Irrespective of composing components, the odds of developing CVD in MetS individuals was higher than in those who did not develop MetS with adjusted odds ratio = 1.76; 95% confidence intervals (CI) = 1.22–2.55. Among the five most prevalent triple combinations, there was a significant association between CVD incidence and high-density lipoprotein + BP + waist circumference combination only with HR = 1.66; 95% CI = 1.04–2.67.
Conclusion: Some MetS components are more likely to result in CVD. Identifying the most predictive components could help in the timely initiation of proper interventions rather than waiting for all MetS components or symptoms of CVD.

Keywords: cardiovascular disease, metabolic syndrome components, risk, Iran

Background

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the world and the leading cause of death in the East Mediterranean Region (EMR) that accounts for 27.4% of total deaths in this region. Iran, with 46% of total deaths attributable to CVD, is among the high-risk countries in EMR.[1] Overweight, obesity, diabetes, dyslipidemia, hypertension, and a cluster of clinical symptoms of so-called metabolic syndrome (MetS) are the main contributors to CVD-related morbidity and mortality.

The report by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) defines MetS as a cluster of metabolic risk factors including central obesity, elevated triglycerides, hypertension, low levels of high-density lipoprotein (HDL), and elevated fasting plasma glucose (FPG).[2,3] MetS is common throughout the world, with an estimated prevalence of 10%–40% in different

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countries and even higher estimates as much as 85% in specific populations.[4–6] The prevalence of MetS in the United States has increased from 28% in the 1988–1994 survey to 34% in the 1999–2004 survey.[7] The interest in MetS increased after the definition of NCEP ATP III as it had an acceptable performance, compared with well-known measures such as body mass index (BMI), in assessment of amount and distribution of body fat and prediction of future conditions such as diabetes (T2D) and CVD.[8] MetS prevalence is age dependent and the reported prevalence in different age groups of the Iranian adult population ranges from 33.7% to 34.6% with higher rates in women.[9–11]

There is increasing evidence that MetS is a precursor to several conditions, mainly atherosclerotic CVD (ASCVD) and T2D, and increases both incidence and mortality.[3] The risk of CVD in individuals with MetS is twice that in general populations.[2,9] Several studies have shown that the mortality rate in ASCVD patients was higher in MetS individuals who are likely related to multiple metabolic risk factors of MetS, where meeting more of the five criteria increases the risk.[3,12] However, the components of MetS are inter-related and contribute synergistically to augmented risk of CVD and T2D.[13] Further, the role of each MetS component in later complications is not fixed and the amount of contribution depends on various factors such as ethnicity, race, sex, and the number of concomitant components.[3,8,13] The effect of such combinations, sometimes called trajectories, on subsequent CVD and mortality has been evaluated in The Framingham Offspring Study.[14] It considered the most prevalent triads of MetS components and assessed which combinations have associations with future CVD. The current research aimed at assessing the relationship between MetS and CVD and at evaluating the effect and predictive value of triads of MetS components on subsequent CVD in participants of an ongoing prospective study in Iran.

Materials and Methods

Participants

We retrieved data from the Isfahan Cohort Study (ICS), a population-based prospective study on participants of age >35 years living in urban and rural areas of three counties (Isfahan, Arak, and Najafabad) in central Iran.[15] After inclusion in the study in 2001, telephone interviews were conducted every 2 years as stated in the protocol. Full structured interviews and physical and biochemical measurements were performed only in three phases of 2001, 2007, and 2013 to determine whether and which MetS components were present.[15,16] In this study, we excluded participants CVD in 2001 and those who had none of the five components of MetS in the study period, and only data of individuals with measurements available in all three phases were analyzed.

Measurements and outcomes

All participants were interviewed by trained health professionals using a standard questionnaire on demographic information, lifestyle, and other health aspects. All physical examinations, including waist circumference (WC), blood pressure (BP), serum tests of HDL, FPG, and triglyceride (TG), were conducted by using calibrated instruments and methods specified in the ICS protocol.

According to the NCEP ATP III, participants with at least three of the following criteria were classified as MetS in each examination: (i) FPG ≥110 mg/dL, (ii) WC >102 cm in males and >88 cm in females, (iii) TG ≥150 mg/dL, (iv) HDL of <40 mg/dL in males and <50 mg/dL in females, and (v) BP as systolic/diastolic BP of ≥130/≥85 or treated or under treatment for hypertension.[17] CVDs were defined as a combination of ischemic heart disease (including definite or probable myocardial infarction, unstable angina, and sudden cardiac death) and stroke. Details on ICS protocol and procedures could be found elsewhere.[15]

The protocol of ICS received approval from the Ethics Committee of Isfahan Cardiovascular Research Center that collaborates with the World Health Organization and was financially supported by grant number 31309304. All participants signed written consent before inclusion in the ICS.

Statistical analysis

Descriptive statistics were calculated as *n* (%) and mean ± standard deviation and compared between groups by using chi-square and independent-samples *t*-test. The association between MetS and CVD incidence was assessed by using logistic regression, and odds ratios and 95% confidence intervals (CI) were calculated. To evaluate the impact of different combinations of MetS components on CVD, we selected five most frequent triple patterns at baseline out of all possible triple combinations in the Cox proportional hazards regression model to obtain hazard ratios (HR) and corresponding 95% CIs. Here, those participants classified as MetS subject by more than three criteria were considered in all triple combinations of existing criteria (e.g., a person identified as MetS subject by four criteria of BP, WC, HDL, and FPG was enumerated in the following four triple combinations: BP + WC + HDL, BP + WC + FPG, WC + HDL + FPG, and BP + HDL + FPG). All analyses were conducted in R software version 3.4.1 at a significance level of 0.05 by adjusting for sex, age, BMI, diabetes, and smoking status.

Results

The sample included 1387 adults, 51.3% of whom were female, with age of 47.4 ± 9.2 years (48.2 ± 9.6 for males and 46.6 ± 8.7 for females) in 2001. The prevalence of MetS and T2D was 34.4% (19.5% of which were diabetic) and 9.7%, respectively. Other descriptive statistics of participants at baseline are shown in Table 1. We assessed the association between MetS and future CVD by using logistic regression

Table 1. Characteristics of Participants in 2001 Described as Mean ± Standard Deviation and *N* (%)

Variable	*All* (n = *1387*)	*Female* (n = *714*)	*Male* (n = *673*)	P
Age	47.42 ± 9.18	46.63 ± 8.72	48.26 ± 9.59	<0.001
BMI	27.47 ± 4.49	28.71 ± 4.67	26.15 ± 3.89	<0.001
Diabetes (yes)	135 (9.7)	77 (10.8)	58 (8.6)	<0.001
Smoking (yes)	292 (21.1)	13 (1.8)	279 (41.6)	<0.001
Level of education				
Illiterate	259 (18.7)	154 (21.5)	106 (15.8)	<0.001
Primary school	262 (40.5)	332 (46.6)	230 (34.2)	
>Primary school	265 (40.8)	228 (32)	337 (50.1)	

Table 2. Association Between Metabolic Syndrome and Cardiovascular Disease Incidence (Logistic Regression)

Variable	*Odds ratio*[a]	P
Diabetes mellitus (yes)	1.91 (1.20, 3.04)	<0.001
Smoking (yes)	1.85 (1.20, 2.84)	<0.001
MetS (yes)	1.76 (1.22, 2.55)	<0.001
Age	1.04 (1.02, 1.06)	<0.001
Sex (male)	1.29 (0.86, 1.93)	0.22

[a]Adjusted for BMI.
MetS, metabolic syndrome.

in Table 2. The adjusted results indicated that the odds of developing CVD in MetS cases, irrespective of its composing components, was 1.76; 95% CI = 1.22–2.55 times that in MetS-free cases.

The prevalence of MetS components in each examination is shown in Table 3. Among single components, the prevalence of hypertension (BP) and hyperglycemia (FPG) increased over time whereas the prevalence of the other components decreased. In MetS-free participants at baseline who developed MetS in the study course ($n = 366$), HDL (6.3%), TG (83.6%), BP (81.4%), WC (71.0%), and FPG (41.6%) were the most frequent MetS components. The five most frequent triple combinations of MetS components in all individuals diagnosed with MetS in the study were HDL + WC + TG (480 cases), HDL + WC + BP (470 cases), HDL + BP + TG (469 cases), WC + BP + TG (463 cases), and HDL + FPG + TG (233 cases). Table 4 shows the adjusted results of Cox regression on these combinations. HDL + BP + WC was the only triple combination that showed a significant association with CVD incidence with HR = 1.66; 95% CI = 1.04–2.67.

Discussion

This study was conducted to evaluate the association between CVD and MetS and to examine the ability of triple MetS components in prediction of future CVD events in individuals with MetS. Besides the contribution of MetS to increased risk of CVD, we observed that combinations of MetS components have implications for risk modification and prognosis. Our findings showed that, among the most frequent triple combinations of MetS components, diagnosis of MetS based on HDL + WC + BP leads to the highest risk of CVD incidence with HR = 1.66.

Despite controversies on the definition of MetS, it has value in identifying individuals at higher risk of diabetes and CVD who may be considered at low risk by single criteria or fall below the threshold needed for initiation of drug therapy.[8,18,19] The results of a cohort study on the 30–75-year-old population showed that MetS is a more powerful tool in predicting coronary heart disease, CVD, and total mortality than its every single component.[8] In a large sample prospective cohort, the presence of one to two MetS components was associated with increased risk of mortality from CHD and CVD and MetS was a stronger predictor of CHD, CVD, and total mortality than its single components, where HR of CVD mortality was 1.10 for individuals with one or two components and 1.47 for MetS individuals.[20] A systematic review and meta-analysis of 87 studies concluded that the risk of cardiovascular outcomes in MetS individuals is twice that in the MetS-free population.[21]

A large number of studies have argued for physiological and pathophysiological mechanisms for each MetS component in subsequent CVD incidence.[22,23] Among the other components, hypertension and hyperglycemia have been shown to have specific importance in acute ischemic noncardioembolic stroke, myocardial infarction, and cardiovascular death.[24,25]

In The Framingham Offspring Study, WC and BP along with hyperglycemia were the most predictive of CVD risk among triple components of MetS with estimated HR of 2.36; 95% CI = 1.54–3.61. HDL, BP, and TG were the second triple with HR of 1.94; 95% CI = 1.19–3.16. As expected, hypertension is likely the most important feature in MetS to be controlled to prevent subsequent CVD incidence. It seems

Table 3. Prevalence (%) of Metabolic Syndrome and Its Components in All Participants Diagnosed with Metabolic Syndrome in Study Course

	All			*Females*			*Males*		
Variable	*2001 (n = 477)*	*2007 (n = 462)*	*2013 (n = 628)*	*2001 (n = 346)*	*2007 (n = 296)*	*2013 (n = 390)*	*2001 (n = 131)*	*2007 (n = 166)*	*2013 (n = 238)*
WC	436 (91.4)	352 (76.1)	517 (82.3)	338 (97.6)	284 (95.9)	369 (94.6)	98 (74.8)	29 (17.4)	148 (62.1)
HDL	355 (74.4)	360 (77.9)	367 (58.5)	272 (78.6)	230 (77.7)	331 (84.8)	81 (62.1)	55 (33.3)	206 (86.5)
TG	436 (91.4)	392 (84.8)	455 (72.4)	309 (89.3)	238 (80.4)	268 (68.7)	127 (96.9)	66 (39.4)	187 (78.5)
BP	285 (59.7)	315 (68.1)	471 (75.0)	196 (56.6)	186 (62.8)	291 (74.6)	91 (69.4)	55 (33.0)	180 (75.6)
FPG	87 (18.2)	182 (39.4)	286 (45.5)	60 (17.3)	110 (37.1)	182 (46.6)	27 (20.6)	31 (18.7)	103 (43.2)
Most prevalent triple combinations									
WC + BP + TG	214 (44.8)	165 (35.7)	246 (39.1)	158 (45.6)	130 (43.9)	177 (45.3)	56 (24.7)	35 (21.0)	69 (29.0)
HDL + WC + TG	151 (31.6)	215 (46.5)	290 (46.1)	126 (36.4)	173 (58.4)	206 (52.8)	25 (19.0)	42 (25.3)	84 (35.2)
HDL + WC + BP	151 (31.6)	153 (33.1)	311 (49.5)	126 (36.4)	126 (42.5)	226 (57.9)	25 (19.0)	27(16.2)	85 (35.7)
HDL + BP + TG	149 (31.2)	186 (40.2)	265 (42.1)	104 (30.05)	99(33.4)	152 (38.9)	45 (34.3)	87 (52.4)	113 (47.7)
WC + FPG + TG	62 (13.0)	91 (19.7)	145 (23.0)	50 (14.4)	73 (24.6)	104 (26.6)	12 (9.1)	18 (10.8)	41 (17.2)
HDL + FPG + TG	39 (8.1)	95 (20.5)	157 (25.0)	27 (7.8)	55 (18.5)	92 (23.5)	12 (9.1)	40 (24.0)	65 (27.3)
BP + FPG + TG	42 (8.8)	86 (18.6)	126 (20.0)	25 (8.0)	41 (13.8)	86 (22.0)	17 (12.9)	45 (27.1)	40 (16.8)
HDL + WC + FPG	39 (8.1)	76 (16.4)	174 (27.7)	33 (9.5)	67 (22.6)	132 (33.8)	6 (4.5)	9 (5.4)	42 (17.6)
HDL + BP + FPG	20 (4.1)	65 (14.0)	150 (23.8)	13 (3.7)	39 (13.1)	102 (26.1)	7 (5.3)	26 (15.6)	48 (20.1)
WC + BP + FPG	30 (6.2)	68 (14.71)	165 (26.2)	24 (6.93)	54 (18.2)	27 (6.9)	6 (4.5)	14 (8.4)	38 (15.9)

BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; MetS, metabolic syndrome; TG, triglyceride; WC, waist circumference.

Table 4. Association Between Cardiovascular Disease Incidence and the Most Prevalent Triple Combinations of Metabolic Syndrome Components

Variable	*HR*[a] *(95% CI)*	P
HDL + BP + WC	1.66 (1.04–2.67)	0.04
HDL + BP + TG	1.21 (0.73–2.02)	0.44
HDL + WC + TG	0.99 (0.66–1.50)	0.99
WC + BP + TG	1.22 (0.78–1.89)	0.37
HDL + FPG + TG	0.66 (0.22–1.94)	0.45

CI, confidence intervals; HR, hazard ratio.
[a]Adjusted for age, sex, smoking status, type 2 diabetes, and BMI.

that aging, less activity, and increase in overweight prevalence will increase MetS prevalence and both short- and long-term risk of CVD worldwide.[7]

Lipid profiles are core components of MetS that contribute to cardiovascular incidence and mortality. Low HDL cholesterol levels are associated with increased risk of cardiovascular events, independently from low-density lipoprotein (LDL) cholesterol.[26,27] Results of a large prospective study in the CVD-free Japanese population suggested an inverse association between HDL cholesterol and coronary heart disease.[27]

A large number of studies have concluded that cardiovascular events increase with serum TG levels.[27–29] Both low HDL cholesterol and high TG levels are in direct association with small dense LDL cholesterol, the most atherogenic portion of LDL cholesterol.[7] However, whether raising HDL cholesterol by intervention could reduce cardiovascular risk remains disputable.[30,31]

WC was found to be one of the three factors most strongly associated with CVD risk. The mechanism is unclear and was not sought in this study. It is possible, however, that WC is associated with CVD risk through disturbed adipose tissue function. The imbalances in various adipokines released by excess accumulated visceral fat could result in metabolic disorders and subsequent conditions.[7] The role of leptin and adiponectin, an adipose tissue-specific hormone, in cardiovascular events is conflicting.[32] Regardless of weight and BMI, leptin has direct association with MetS and is positively associated with hypertension and obesity indices, with stronger association with abdominal adiposity mainly measured by WC.[33–39] Also, adiponectin has reverse association with metabolic disorders and obesity anthropometrics such as WC and its concentration is low in obese subjects.[6,40]

WC has better performance in risk prediction than other indices of general obesity such as BMI. After some age, especially in old age, BMI becomes constant as a result of muscle volume loss. However, abdominal fat mass measured by WC continues to increase.[7] The increase in WC is not reflected properly by BMI and therefore, the predictive ability of BMI is decreased. Even though weight management is the cornerstone in CVD risk reduction, WC should be monitored as another key component.[41]

Conclusion

MetS prevalence is increasing and individuals enter MetS with different trajectories, some of which are more likely to result in CVD. Proper and punctual preventive measures could help in controlling MetS prevalence and subsequent risk of diabetes and cardiovascular events. It would be useful to identify the most predictive factors to initiate such interventions, rather than waiting for all MetS components or symptoms of CVD in this population.

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Authors' Contribution

M.M. and N.S. conceptualized the study and participated in discussion. M.M. and M.B. analyzed the data and prepared the initial draft. H.R.R. and M.S. participated in data collection, literature review, and draft preparation. T.J.-K. participated in study design, literature review, and data analysis and revised the article. All authors approved the final article.

Author Disclosure Statement

No conflicting financial interests exist.

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