Is there any relationship between different phenotypes of metabolic syndrome and cardiovascular mortality rate?

Alireza Khosravi, Sareh Ahmadzadeh, Mojgan Gharipour, Jafar Golshahi, Masoumeh Sadeghi, Mahnaz Jozan, Nizal Sarrafzadegan

Department of Cardiology, Interventional Cardiology Research Center, Cardiovascular Research Institute, Hypertension Research Center, Cardiovascular Research Institute, Department of Cardiology, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

INTRODUCTION

Metabolic syndrome (MetS) is a clustering of several cardiovascular risk factors as hypertension (HTN), dyslipidemia, and diabetes. Retrospective studies have shown the positive effect of separate components of MetS on the mortality rate.

Abstract

Background: This study aimed to focus on different phenotypes of metabolic syndrome (MetS) and their impact on the cardiovascular disease (CVD) events among a sample of the Iranian population.

Materials and Methods: The Isfahan cohort study is a population-based, on-going longitudinal study of adults aged 35 years old or more, living in urban and rural areas of three counties in central Iran namely Isfahan, Najafabad and Arak. Participants were selected by multistage random sampling and were recruited to reflect the age, sex and urban/rural distribution of the community. The sample was restricted to subjects with MetS based on the National Cholesterol Education Program Adult Treatment Panel III criteria and no history of coronary heart disease, stroke, or cancer at the time of the baseline clinical examination.

Results: Among different phenotypes of MetS components, clustering of high triglycerides (TGs), low high-density lipoprotein (HDL) and abdominal obesity (ABO) was the most related to the all-cause mortality among women and followed in order by high TGs, hypertension (HTN) and ABO. In men, the highest rate of all-cause mortality was related to high TGs, low HDL, and HTN. Clustering of four components (high TGs, low HDL and HTN and obesity) is the most related to all-cause mortality in both sexes (12.1% in men, and 21.5% in women).

Conclusion: This study showed different phenotypes of MetS related with all-cause mortality rate and existing HTN in the phenotype of MetS increased the incidence of CVD mortality.

Key Words: All-cause mortality rate, Iran, metabolic, phenotype, syndrome
Nevertheless, studies using factor analysis of MetS components, including variables based on National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) and International Diabetes Federation criteria, have suggested that MetS is not a single disease entity and that MetS-related phenotypes comprise more than two underlying latent traits.\cite{3–6} If each MetS-related phenotype is a component of a clustered factor, identification of MetS phenotypes will improve our understanding of MetS. In doubt, genetic factors are related to the different phenotypes of MetS but it is important to increase our knowledge about the relationship between prevalence and rate of all-cause mortality due to MetS. Recent studies showed the common approach of a physician regarding the management of MetS is to treat individual components of MetS. While control of MetS has extremely importance because adverse effect between MetS and incidence of diabetes, cardiovascular disease (CVD) and premature mortality has evidenced.\cite{7–9} However, it is unclear how different phenotypes of MetS effects on all-cause mortality rate among the Iranian population. We believe finding a relation between different phenotypes of MetS in both sexes may give policy and health care decision makers some indications for better planning. Moreover, these findings will create new viewpoints for clinicians.

Hence, this study designed to focus on different phenotypes of MetS and their impact on the all-cause mortality among a sample of the Iranian population.

**MATERIALS AND METHODS**

**Study population**

The Isfahan cohort study (ICS) is a population-based, on-going longitudinal study of adults aged 35 years old or more, living in urban and rural areas of three counties in central Iran namely Isfahan, Najafabad and Arak.\cite{10} Baseline data collection for the ICS began in 2001. Participants were selected by multistage random sampling and were recruited to reflect the age, sex and urban/rural distribution of the community.\cite{11} The Ethics Committee of the Isfahan Cardiovascular Research Center approved the study. The sample included 6323 subjects 35–97 years of age (average 50.7 ± 11.6 years) who had complete data for body weight status, and the components of MetS. The sample was restricted to subjects with MetS based on the NCEP-ATP III\cite{11} criteria and no history of coronary heart disease, stroke, or cancer at the time of the baseline clinical examination. All participants provided their informed consent to participate in the clinical examination and follow-up study.

**Assessments**

After obtaining informed written consent, medical interview, and physical examination were conducted. Measurements of blood pressure, anthropometric parameters as well as fasting blood tests were carried out following standard protocols and using calibrated instruments as has been described previously.\cite{12} WC was taken as the smallest circumference at or below the costal margin. HTN was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in men and women or treatment of previously diagnosed HTN. Subjects who smoked daily were considered as current smoker. In 2007 (the 7th year of follow-up), participants were invited for repeated laboratory measurements, physical examination and interview using the same protocol as baseline survey. Laboratory measurement methods were similar in 2001 and 2007, but the auto analyzer was different (Eppendorf, Hamburg, Germany in 2001 and Hitachi 902, Japan in 2007). Both instruments have been validated with an external standard laboratory center.

**Definition of metabolic syndrome**

The criteria of NCEP include: (1) Central obesity as the waist circumference >102 cm in men and >88 cm in women; (2) Fasting plasma triglycerides (TGs) ≥150 mg/dl; (3) low high-density lipoprotein (HDL) cholesterol with fasting HDL cholesterol <40 mg/dl in men and <50 mg/dl in women; (4) HTN with systolic blood pressure ≥130 mmHg and/or diastolic blood pressure 85 mmHg and/or antihypertensive agents\cite{6} hyperglycemia with fasting plasma glucose ≥100 mg/dl and/or hypoglycemic medications\cite{13} Abdominal obesity (ABO), high fasting glucose, HTN and hypertriglyceridemia were considered as ABO, high fasting blood glucose, HTN and high TG.

**Statistical analysis**

data were recorded and analyzed using SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA). Student’s t-test and Chi-square test were used to compare quantitative and qualitative data respectively.

**RESULTS**

The median follow-up for survivors was 108 years (range follow-up, 1–129 years). There were 331 deaths during follow-up. Of these, there were 118 CVD death, 31 of which due to CHD death. In total, 398 males and 848 females were studied.

The comparison of baseline data across different groups of participants based on the sex and CVD (Table 1).
Participants with CVD history have higher mean of age, and higher prevalence of HTN, HGLU, HTG and dyslipidemia. CVD patients are less educated (P < 0.001). Smoking status is more prevalent among CVD’s patients (P < 0.016). The pattern of distribution of different phenotypes of MetS differs between both sexes. The highest prevalence in a woman is related to clustering of high TG, low HDL and obesity (14.0%). Whereas, this figure is 3.3% in men. High TG, HTN and ABO have the highest prevalence among women and ABO have the highest prevalence among men (8.0%, 4.0%, respectively), which followed by low HDL and HTN, obesity (4.0%) in women [Table 2]. Table 2 shows the prevalence of all-cause mortality among subjects with different phenotypes of MetS based on sex. During 9 years of follow-up, 579 CVD deaths occurred, 314 among subjects with MetS (122 men and 194 women) and 265 among those with-out the syndrome (192 men and 71 women) (not weighted data). Among different phenotypes of MetS components, clustering of high TGs, low HDL and ABO was the most related to the all-cause mortality among women and followed in order by high TGs, HTN and ABO. In men, the highest rate of all-cause mortality was related to high TGs, low HDL and HTN [Table 2]. Clustering of four components (high TGs, low HDL and HTN and obesity) is the most related to all-cause mortality in the both sexes (12.1% in men, and 21.5% in women). Women with MetS consistently had a higher all-cause mortality rate than those without MetS, whereas no significant difference in mortality rate was observed among men (7.2 vs. 2.5) [Table 3].

Cox proportional hazards regression models confirmed the differential effect by sex in the association between MetS and CVD mortality and revealed a significant sex by MetS interaction (P ≥ 0.000); therefore, models were also stratified by sex [Table 4]. After adjustments for age and sex, the risk of all-cause mortality was higher among all subjects with MetS [Table 4] Confounding factors and diseases associated with increased mortality risk were sequentially included in the models, increasing the strength of the association between MetS and all-cause mortality. MetS was significantly associated with increased all-cause mortality after adjustments for age, sex, smoking, physical activity, major diseases, BMI, albumin, and LDL cholesterol levels in all subjects (HR 1.41 [95% CI 1.16–1.72], P ≥ 0.001).
**DISCUSSION**

To the best of our knowledge, no previous study has been conducted to establish the effect of different phenotypes of MetS associated with CVD events. Our results showed existing HTN in the phenotype of MetS increased the incidence of CVD mortality.

A very recent meta-analysis which done by Mottillo et al. suggested about an emerge need to do prospective studies, which investigate the risk associated with the MetS independent of the risk of its individual components in order to establish whether or not the MetS adds any prognostic significance. Their results showed MetS without considering it is individual components is associated with a 2-fold increasing in the CVD outcomes and increasing in all-cause mortality by 1.5-fold.

In the previous study which done in the ICS data showed MetS increased the risk of Ischemic heart disease 1.58 (1.06–2.35) in men and 1.72 (1.08–2.74) in women.

Our results also suggested that clustering TG, HDL and HTN has greater prognostic value for cardiovascular outcomes in Iranian men, whereas in women with clustering of TG, HDL and ABO has superior predictive value for CVD events. Our results showed a woman with the phenotype of high TG, low HDL and ABO had the greatest risk for CVD events (37.6%). Although the exact mechanisms which explaining the role of MetS in increasing the risk of CVD women are unclear; however, numerous theories have been hypothesized. First of all, central adiposity tends to be more pronounced in women post-menopause than in men, and thus may be linked to a higher risk of CVD. Second, the lipid profile is different in women compared to men. HDL decreases post menopause and low-density lipoprotein (LDL) cholesterol increases compared to men. HDL decreases post menopause and therefore, more atherogenic. Third, there is evidence that elevated TG are more highly associated with coronary artery disease in women than in men.

**Table 3: CVD mortality on various MetS phenotype**

| Phenotype                  | CVD events |
|----------------------------|------------|
|                            | Total      | Men        | Women      |
| None                       | 192 (61.1) | 71 (26.8)  |
| HTG + HDL + ABO            | 43 (7.4)   | 10 (3.2)   | 33 (12.5)  |
| HTG + HDL + HGLU           | 6 (1.0)    | 6 (1.9)    | *          |
| HTG + HDL + HTN            | 28 (4.8)   | 22 (7.0)   | 6 (2.3)    |
| HTG + HTN + ABO            | 52 (9.0)   | 21 (6.7)   | 31 (11.7)  |
| HTG + HTN + HGLU           | 12 (2.1)   | 11 (3.5)   | 1 (0.4)    |
| HTG + ABO + HGLU           | 5 (0.9)    | 1 (0.3)    | 4 (1.5)    |
| HDL + HTN + ABO            | 14 (2.4)   | 4 (1.3)    | 10 (3.8)   |
| HDL + ABO + HGLU           | *          | *          | *          |
| HDL + HTN + HGLU           | 4 (0.7)    | 3 (1.0)    | 1 (0.4)    |
| HTN + ABO + HGLU           | 3 (0.5)    | 2 (0.6)    | 1 (0.4)    |
| HTG + HDL + ABO + HDL      | 11 (1.9)   | 3 (1.0)    | 8 (2.3)    |
| HTG + HDL + ABO + HTN      | 70 (12.1)  | 13 (4.1)   | 57 (21.5)  |
| HDL + HTN + ABO + HTG      | *          | *          | *          |
| HDL + ABO + HGLU + HDL     | 28 (4.8)   | 8 (2.5)    | 20 (7.2)   |
| Total                      | 167 (100)  | 314 (100)  | 265 (100)  |

ABO: Abdominal obesity, GLU: High fasting glucose, HDL: High-density lipoprotein, HTN: Hypertension, MetS: Metabolic syndrome, HTG: Hypertriglyceridemia, HGLU: Fasting blood sugar, *: Number was lower 5 person in each group

**Table 4: Association between MetS and CVD mortality**

| MetS component          | Male          | Female        | Total          |
|-------------------------|---------------|---------------|----------------|
|                         | OR (95% CI)   | P             | OR (95% CI)    | P             | OR (95% CI) | P       |
| HTG + HDL + ABO         | 1.16 (0.59-2.27) | 0.666         | 1.61 (1.05-2.47) | 0.028         | 1.09 (0.78-1.53) | 0.579 |
| HTG + HDL + HGLU        | 3.15 (1.23-8.08) | 0.078         | *              | *             | 2.71 (1.12-6.85) | 0.026 |
| HTG + HDL + HTN         | 2.90 (1.81-4.65) | 0.000         | 3.40 (1.46-7.90) | 0.004         | 3.15 (2.09-4.74) | 0.000 |
| HTG + ABO + HGLU        | 1.12 (0.25-4.89) | 0.884         | 2.44 (1.01-5.92) | 0.048         | 1.51 (0.71-3.18) | 0.282 |
| HTG + HTN + ABO         | 2.43 (1.53-3.86) | 0.000         | 3.27 (2.15-4.98) | 0.000         | 2.38 (1.76-3.20) | 0.000 |
| HTG + HTN + HGLU        | 4.84 (2.43-9.64) | 0.000         | 8.75 (0.78-97.55) | 0.078         | 5.99 (3.09-11.59) | 0.000 |
| HDL + AB + HGLU         | *              | *             | *              | *             | *              | *       |
| HDL + HTN + ABO         | 3.25 (1.03-10.29) | 0.045         | 1.92 (0.99-3.74) | 0.054         | 1.50 (0.86-2.61) | 0.148 |
| HDL + HGLU              | 26.71 (7.29-258.70) | 0.004         | 4.50 (0.40-30.33) | 0.256         | 7.42 (2.08-26.42) | 0.002 |
| HTN + ABO + HGLU        | 2.23 (0.47-10.58) | 0.312         | 1.75 (0.22-13.85) | 0.596         | 1.85 (0.54-6.33) | 0.325 |
| TG + HDL + ABO + HGLU   | *              | *             | *              | *             | *              | *       |
| TG + HDL + ABO + HTN    | 2.58 (1.37-4.86) | 0.003         | 3.68 (2.57-5.27) | 0.000         | 2.45 (1.86-3.23) | 0.000 |
| TG + HDL + HGLU + HTN   | 7.56 (3.34-17.07) | 0.000         | 10.50 (2.46-44.73) | 0.001         | 8.65 (4.25-17.57) | 0.000 |
| HTN + ABO + HGLU + HTG  | 3.15 (1.61-6.18) | 0.001         | 8.25 (4.86-14.01) | 0.000         | 4.73 (3.16-7.07) | 0.000 |
| HDL + HTN + ABO + HGLU  | *              | *             | *              | *             | *              | *       |
| HTN + ABO + HGLU + HDL  | 7.31 (2.99-17.83) | 0.000         | 6.02 (3.48-10.41) | 0.000         | 4.63 (2.98-7.21) | 0.000 |

ABO: Abdominal obesity, GLU: High fasting glucose, HDL: High-density lipoprotein, HTN: Hypertension, MetS: Metabolic syndrome, HTG: Hypertriglyceridemia, HGLU: Fasting blood sugar, OR: Odds ratio, CI: Confidence interval, TG: Triglyceride, BMI: Body mass index, HR: Heart rate, LDL: Low-density lipoprotein, *: Numbers was lower 5 person in each group
In a meta-analysis, it was shown that an increase in TG of 18 mg/dl was associated with a 76% increased CVD risk in women compared with a 32% increased risk in men. A number of other unique risk factors such as polycystic ovary syndrome, hormonal contraceptive use, and gestational diabetes may be responsible for greater relationship between the MetS and CVD risk in women.

**Study limitations**

Our study has a number of potential limitations. First of all, the length of follow-up was limited to 7 years, which limited the number of events associated with the MetS in our population study.

**CONCLUSION**

This study showed different phenotypes of MetS related with all-cause mortality rate and existing HTN in the phenotype of MetS increased the incidence of CVD mortality.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**

1. De Simone G, Devereux RB, Chiniali M, Best LG, Lee ET, Galloway JM, et al. Prognostic impact of metabolic syndrome by different definitions in a population with high prevalence of obesity and diabetes. The Strong Heart Study. Diabetes Care 2007;30:1851-6.

2. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. Diabetes Care 2007;30:8-13.

3. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – A new worldwide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469-80.

4. Austin MA, Edwards KL, McNeely MJ, Chandler WL, Leonetti DL, Talmud PJ, et al. Heritability of multivariate factors of the metabolic syndrome in nondiabetic Japanese Americans. Diabetes 2004;53:1166-9.

5. Huang P, Kraja AT, Tang W, Hunt SC, North KE, Lewis CE, et al. Factor relationships of metabolic syndrome and echocardiographic phenotypes in the HyperGEN study. J Hypertens 2008;26:1360-6.

6. Lin HF, Boden-Albala B, Juo SH, Park N, Rundek T, Sacco RL. Heritabilities of the metabolic syndrome and its components in the Northern Manhattan Family Study. Diabetologia 2005;48:1197-205.

7. Franklin BA, Cushman M. Recent advances in preventive cardiology and lifestyle medicine: A themed series. Circulation 2011;123:2274-83.

8. Ghaem Maralani H, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, et al. Metabolic syndrome and mortality in the elderly: A time-dependent association. Diabetes Res Clin Pract 2013;99:205-16.

9. Saito I, Iso H, Kokubo Y, Inoue M, Tsugane S. Metabolic syndrome and all-cause and cardiovascular disease mortality: Japan Public Health Center-based Prospective (JPHC) Study. Circ J 2009;73:879-84.

10. Sarrafzadegan N, Talaei M, Sadeghi M, Kelishadi R, Oveisgharan S, Mohammadiard N, et al. The Isfahan cohort study: Rationale, methods and main findings. J Hum Hypertens 2011;25:545-53.

11. Sarrafzadegan N, Talaei M, Kelishadi R, Toghanianfar N, Sadeghi M, Oveisgharan S, et al. The influence of gender and place of residence on cardiovascular diseases and their risk factors. The Isfahan cohort study. Saudi Med J 2012;33:533-40.

12. O’Donnell CJ, Ridker PM, Glynn RJ, Berger K, Ajanu U, Manson JE, et al. Hypertension and borderline isolated systolic hypertension increase risks of cardiovascular disease and mortality in male physicians. Circulation 1997;95:1132-7.

13. Gharipour M, Sarrafzadegan N, Sadeghi M, Andalib E, Talaei M, Shafie D, et al. Predictors of metabolic syndrome in the Iranian population: Waist circumference, body mass index, or waist to hip ratio? Cholesterol 2013;2013:198384.

14. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk in a systematic review and meta-analysis. J Am Coll Cardio 2010;55:1113-32.

15. Malik S, Wong ND, Franklin SS, Kamath TV, L’Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all-causes in United States adults. Circulation 2004;110:1245-50.

16. Suzuki T, Hirata K, Elkind MS, Jin Z, Rundek T, Miyake Y, et al. Metabolic syndrome, endothelial dysfunction, and risk of cardiovascular events: The Northern Manhattan Study (NOMAS). Am Heart J 2008;156:405-10.

17. Donato GB, Fuchs SC, Oppermann K, Bastos C, Spritzer PM. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause 2006;13:280-5.

18. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation 2002;106:1930-7.

19. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213-9.

20. Williams K, Tchernof A, Hunt KJ, Wagenknecht LE, Haffner SM, Sniderman AD. Diabetes, abdominal adiposity, and atherogenic dyslipoproteinemia in women compared with men. Diabetes 2008;57:3289-96.

21. Legro RS. Polycystic ovary syndrome and cardiovascular disease: A premature association? Endocr Rev 2003;24:302-12.

22. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The women’s health initiative randomized controlled trial. JAMA 2004;291:1701-12.

23. Hsia J, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, et al. Conjugated equine estrogens and coronary heart disease: The women’s health initiative. Arch Intern Med 2006;166:357-65.

24. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349:523-34.

25. Carr DB, Utschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care 2006;29:2078-83.