Observational Study

Medicine®

OPEN

Metabolic syndrome predicts long-term mortality in subjects without established diabetes mellitus in asymptomatic Korean population

A propensity score matching analysis from the Korea Initiatives on Coronary Artery Calcification (KOICA) registry

Ki-Bum Won, MD[a,b], Hyuk-Jae Chang, MD, PhD[b,c,*], Donghee Han, MD[c], Jidong Sung, MD, PhD[d], Su-Yeon Choi, MD, PhD[e]

Abstract

Despite the different features of diabetes mellitus (DM) in Asian populations compared with Western populations, the impact of metabolic syndrome (MetS) on long-term mortality according to DM status has not yet been elucidated in the Asian population.

After performing 1:1 propensity score matching (PSM) using clinical variables including age, gender, smoking, and individual MetS components between DM and non-DM subjects from the data of the Korea Initiatives on Coronary Artery Calcification registry, mortality was evaluated according to DM and MetS in 14,956 asymptomatic Korean subjects.

The mean follow-up duration was 53.1 months (interquartile range: 33–80). The overall prevalence of MetS was 60%. DM subjects had higher mortality compared with non-DM subjects (1.2% vs 0.7%, respectively; $P=0.001$); the cumulative mortality by Kaplan–Meier analysis was higher in DM subjects than in non-DM subjects (log-rank $P=0.001$). DM increased the risk of mortality in PSM participants (hazard ratio [HR] 1.74; $P=0.001$). In non-DM subjects, MetS (HR 2.32) and one of its components, central obesity (HR 1.97), were associated with an increased risk of mortality (both $P<0.05$). In contrast, there was no significant difference in the risk of mortality according to MetS or its components in DM subjects. After adjusting for confounding risk factors, it was shown that MetS independently increased the risk of mortality in non-DM subjects.

Compared with non-DM subjects, DM subjects have an increased risk of long-term mortality among PSM participants. MetS appears to have an independent impact on mortality in subjects without established DM among the asymptomatic Korean population. Our results may not be applicable to the whole subjects with MetS because the PSM using MetS components was performed between subjects with and without DM which was very high risk for adverse clinical events.

Abbreviations: BP = blood pressure, CACS = coronary artery calcium score, CI = confidence interval, CKD = chronic kidney disease, DM = diabetes mellitus, FRS = Framingham risk score, GFR = glomerular filtration rate, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, HR = hazard ratio, LDL = low-density lipoprotein, MetS = metabolic syndrome, PSM = propensity score matching.

Keywords: diabetes mellitus, metabolic syndrome, mortality

1. Introduction

Diabetes mellitus (DM) increases the risk of all-cause and cardiovascular mortality.[1–4] It is well established that an aggravation of insulin resistance and a deterioration of insulin secretion are 2 central defects in DM pathogenesis.[5,6] However, the clinical features of DM in Asia are explicitly different from those in other parts of the world.[7] Several previous studies in a Korean population have reported that impaired insulin secretion is more prominent than insulin resistance, even in the status of impaired glucose tolerance and type 2 DM.[8,9]

Metabolic syndrome (MetS) is a concurrence of impaired glucose intolerance, abdominal obesity, dyslipidemia, and hypertension; insulin resistance is a major characteristic.[10,11] The prevalence of MetS is rapidly increasing worldwide and affects approximately 31% of Korean adults.[12,13] MetS has many characteristics in common with DM, and according to some classifications, has been identified as a risk factor for DM development. However, the numerous definitions of MetS have concurrently included established DM as part of the diagnostic criteria of MetS. The World Health Organization recently recommended that established DM should be excluded from the definition of MetS.[14] However, there is a paucity of data

Editor: Durga Tripathi.

This work was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI13C0715).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

[a] Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, [b] Severance Biomedical Science Institute, [c] Department of Internal Medicine, Yonsei Cardiovascular Center, Yonsei University College of Medicine, [d] Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, [e] Department of Internal Medicine, Seoul National University Healthcare System Gangnam Center, Seoul National University College of Medicine, Seoul, Republic of Korea.

[*] Correspondence: Hyuk-Jae Chang, Yonsei Cardiovascular Center, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea (e-mail: hjchang@yuhs.ac).

Medicine (2016) 95:49(e5421)

Received: 2 June 2016 / Received in final form: 18 September 2016 / Accepted: 27 October 2016

http://dx.doi.org/10.1097/MD.0000000000005421

supporting this recommendation, especially regarding the clinical significance of MetS concept for predicting adverse clinical outcomes in established DM status. This issue may be more important in the Asian population than in the worldwide population considering the different features of DM in Asia. In the present study, we investigated the impact of MetS on long-term mortality according to DM status within the concept of MetS using a large Korean multicenter registry.

2. Methods

2.1. Subjects and study design

We analyzed data from the Korea Initiatives on Coronary Artery Calcification (KOICA) multicenter registry. This is a retrospective, single ethnicity multicenter observational registry in a self-referral setting for subjects who underwent health check-ups at 3 healthcare centers in South Korea. Between December 2002 and July 2014, a total of 48,903 subjects were enrolled in this registry, and the median follow-up duration was 53.1 months (interquartile range: 33–80). Self-reported medical questionnaires were used for obtaining information about medical history. All data were acquired at the time of visit at each healthcare center. Of the 48,903 subjects from this registry, 6100 subjects were excluded from this analysis because of the lack of data for identifying the status of both MetS and DM. With the remaining subjects, we performed a 1:1 propensity score matching (PSM) between patients with and without DM using prespecified clinical variables, including age, gender, smoking, and individual MetS components. Finally, a total of 14,956 subjects composed of 7478 diabetics and 7478 nondiabetics were enrolled in the present study. The primary endpoint of this study was all-cause mortality. Ascertainment of mortality was determined by the Ministry of Security and Public Administration's query. Investigations were performed until December 20, 2014 in 2 centers and September 24, 2014 in the other center. The appropriate institutional review board committees approved the study protocol for the 3 healthcare centers.

Information on the medical history of hypertension, diabetes, and smoking status for each subject was systematically collected. Height, weight, and blood pressure (BP) were measured during healthcare center visits. All blood samples were obtained after a minimum 8-h fast and analyzed for triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and glucose levels. A subject's kidney function was assessed based on the estimated glomerular filtration rate (GFR) calculated using the formula validated in the Cockcroft-Gault formula.[15] Chronic kidney disease (CKD) was defined as an estimated GFR < 60 mL/min per 1.73 m^2. MetS was defined as the presence of $\geq$3 out of a list of 5 parameters: abdominal obesity based on waist circumference $\geq$90 cm in males or $\geq$80 cm in females; systolic BP $\geq$ 130 mm Hg or diastolic BP $\geq$ 85 mm Hg, a referral diagnosis of hypertension, or on antihypertensive treatment; HDL cholesterol level $<$40 mg/dL in men or $<$50 mg/dL in women; fasting triglycerides level $\geq$150 mg/dL; and impaired fasting glucose, defined as a fasting glucose level $\geq$100 mg/dL, a referral diagnosis of DM, or on DM treatment according to the National Cholesterol Education Program—Adult Treatment Panel III definition.[10] Diabetes was defined as a fasting glucose level $\geq$126 mg/dL, glycosylated hemoglobin (HbA1c) $\geq$6.5%, undergoing an antidiabetic treatment, or a referral diagnosis of diabetes.[16] In all of the centers, a coronary artery calcium scan was performed using a $>$16 slice multidetector computed tomography (CT) scanner. Specific CT scanner types used in each center included Philips Brilliance 256 iCT, Philips Brilliance 40 channel MDCT, Siemens 16-slice Sensation, and GE 64-slice Lightspeed. All 3 centers performed standard prospective or retrospective methods. The coronary artery calcium score (CACS) was evaluated on the basis of the scoring system from a previously described method.[17] In the present study, we used CACS $\geq$ 400 as the parameter for estimating severe coronary calcification in the present study.

2.2. Statistical analysis

Clinical and biochemical characteristics are shown according to the presence of DM and MetS. Continuous variables are expressed as the mean $\pm$ standard deviation, and categorical variables are presented as absolute counts and percentages. Differences between continuous variables were analyzed by Student t test, and those between categorical variables were analyzed by the χ^2 test or Fisher exact test, as appropriate. Kaplan–Meier survival analysis was performed for the cumulative incidence of all-cause death. Comparisons between groups were performed using the log-rank test. Cox hazard regression analysis was performed to identify the impact of DM, MetS, and individual MetS component for all-cause mortality. From the Cox model, hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. The forced entry method was used to enter independent variables into the multiple regression models for identifying the impact of MetS on mortality. SPSS statistical software version 20.0 (SPSS, Inc, Chicago, IL) was used for statistical analyses. Values of $P < 0.05$ were considered significant.

3. Results

3.1. Baseline characteristics

Baseline characteristics of the PSM participants are presented in Table 1. Compared with non-DM subjects, DM subjects had significantly higher levels of fasting glucose and HbA1c. The

Table 1

Clinical characteristics of PSM participants.

Characteristics	Non-DM (n = 7478)	DM (n = 7478)	P
Age, y	56 ± 8	56 ± 9	0.180
Male, n (%)	6111 (81.7)	6052 (80.9)	0.216
Current smoking, n (%)	1761 (23.5)	1789 (23.9)	0.692
MetS, n (%)	4480 (59.9)	4458 (59.6)	0.714
MetS components, n (%)			
Central obesity	3860 (51.6)	3862 (51.6)	0.974
Increased BP	5414 (72.4)	5499 (73.5)	0.118
Increased triglyceride	2673 (35.7)	2669 (35.7)	0.946
Decreased HDL	1579 (21.1)	1626 (21.7)	0.349
Antihypertensive drugs, n (%)	2513 (39.0)	2957 (43.6)	<0.001
Lipid lowering drugs, n (%)	1436 (22.5)	2025 (30.0)	<0.001
Use of aspirin, n (%)	916 (15.7)	1341 (22.5)	<0.001
Total cholesterol, mg/dL	201 ± 35	191 ± 37	<0.001
LDL, mg/dL	127 ± 32	119 ± 33	<0.001
Fasting glucose, mg/dL	107 ± 6	121 ± 34	<0.001
GFR, mL/min per 1.73 m^2	87 ± 22	88 ± 23	0.226
HbA1c, %	5.7 ± 0.4	6.5 ± 1.2	<0001
CACS $\geq$ 400	316 (4.3)	445 (6.0)	<0.001

BP = blood pressure, CACS = coronary artery calcium score, DM = diabetes mellitus, GFR = glomerular filtration rate, HbA1c = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, MetS = metabolic syndrome, PSM = propensity score matching.

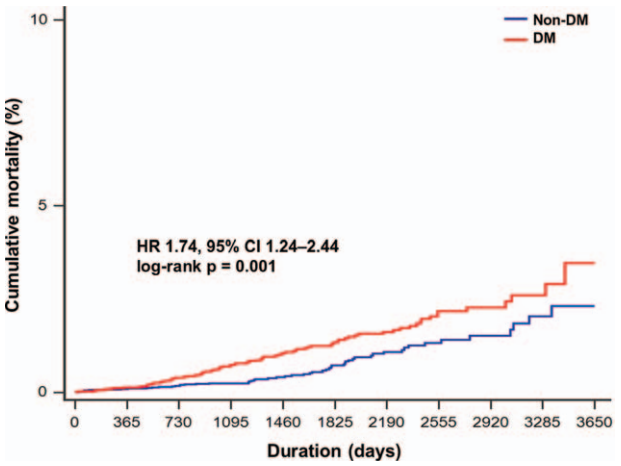

Figure 1. Kaplan–Meier survival analysis for the cumulative mortality according to DM in propensity score matching participants. DM = diabetes mellitus.

Table 2

Univariate Cox regression analysis for identifying the impact of MetS and its individual component on mortality according to DM in PSM participants.

Characteristics	HR	95% CI	*P*
Non-DM			
MetS	2.32	1.20–4.52	0.013
Central obesity	1.97	1.09–3.55	0.024
Increased BP	1.93	0.94–3.95	0.074
Increased triglycerides	1.14	0.65–1.98	0.651
Decreased HDL	1.08	0.57–2.06	0.819
DM			
MetS	1.14	0.74–1.73	0.556
Central obesity	0.91	0.60–1.36	0.635
Increased BP	1.07	0.67–1.71	0.771
Increased triglycerides	1.14	0.75–1.73	0.536
Decreased HDL	1.27	0.80–2.02	0.317

BP = blood pressure, CI = confidence interval, DM = diabetes mellitus, HDL = high-density lipoprotein, HR = hazard ratio, MetS = metabolic syndrome, PSM = propensity score matching.

levels of total cholesterol were significantly lower in DM subjects than in non-DM subjects. The incidence of CACS > 400 was significantly higher in DM subjects than in non-DM subjects (6.0% vs 4.3%, respectively; $P < 0.001$). Results of comparing metabolic abnormalities according to DM in the PSM participants that were described as continuous variables were presented in Supplementary Table 1, http://links.lww.com/MD/B435. Metabolic abnormalities that were described as continuous variables according to the number of MetS components in non-DM and DM participants were presented in Supplementary Table 2, http://links.lww.com/MD/B435.

3.2. Clinical outcomes according to DM and MetS

A total of 144 all-cause deaths occurred during the follow-up period. The incidence of all-cause death was higher in DM subjects than in non-DM subjects (0.7% vs 1.2%, respectively; $P = 0.001$). In the Kaplan–Meier analysis, DM subjects had higher cumulative mortality compared with nondiabetic subjects (log-rank $P = 0.001$). Additionally, DM increased the risk of mortality in PMS participants (HR 1.74; 95% CI 1.24–2.44; $P = 0.001$) (Fig. 1). In non-DM subjects, MetS subjects had significantly higher cumulative mortality compared with non-MetS subjects (log-rank $P = 0.011$). However, as shown in Fig. 2, there was no significant difference in the cumulative mortality according to MetS in DM subjects (log-rank $P = 0.556$).

3.3. Impact of individual MetS component on the mortality according to DM

The results of univariate Cox hazard regression analyses to identify the impact of MetS and its individual components on mortality according to DM status are presented in Table 2. In non-DM subjects, MetS (HR 2.32; 95% CI 1.20–4.52; $P = 0.013$) and central obesity (HR 1.97; 95% CI 1.09–3.55; $P = 0.024$) among its individual component were significantly associated with an increased risk of mortality. In contrast, there was no significant difference in the risk of mortality according to MetS and its individual components in DM subjects. In the multivariate Cox hazard regression analyses after adjusting individual MetS components as continuous variables also showed consistent results (Supplementary Table 3, http://links.lww.com/MD/B435).

3.4. Independent impact of MetS on mortality in non-DM subjects

Multiple Cox hazard regression models were analyzed to identify the impact of MetS on mortality in non-DM subjects. After adjusting consecutive variables including age, gender, CKD, smoking, and CACS > 400, MetS was independently associated with the increased risk of mortality in non-DM subjects (Table 3). In addition, the number of MetS components was independently associated with the increased risk of mortality

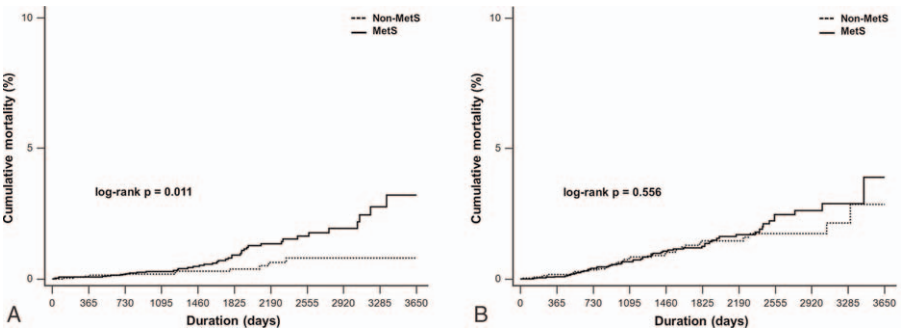

Figure 2. Kaplan–Meier survival analysis for the cumulative mortality according to MetS in (A) non-DM and (B) DM subjects. DM = diabetes mellitus, MetS = metabolic syndrome.

Table 3

Cox regression models for the impact of MetS on mortality in non-DM participants.

	Univariate		
MetS	**HR**	**95% CI**	***P***
Model 1*	2.09	1.07–4.07	0.031
Model 2†	2.31	1.18–4.50	0.014
Model 3‡	2.34	1.19–4.59	0.013
Model 4§	2.34	1.19–4.59	0.013
Model 5‖	2.44	1.20–4.94	0.013

CI = confidence interval, CACS = coronary artery calcium score, CKD = chronic kidney disease, DM = diabetes mellitus, HR = hazard ratio, MetS = metabolic syndrome.

* Adjusted for age.

† Adjusted for age and gender.

‡ Adjusted for age, gender, and CKD.

§ Adjusted for age, gender, CKD, and smoking.

‖ Adjusted for age, gender, CKD, smoking, and CACS > 400.

in non-DM subjects (Supplementary Table 4, http://links.lww.com/MD/B435).

4. Discussion

To the best of our knowledge, this PSM study provides the first information on the differential association between MetS and long-term mortality according to DM status in the asymptomatic Asian population. There were 2 major findings: DM subjects had the increased risk of long-term mortality compared with non-DM subjects after PSM with abnormal metabolic components and MetS was independently associated with the increased mortality only in subjects without established DM.

While MetS is a somewhat reversible condition because its diagnosis depends on the number of clustering components, DM is a chronic and progressive illness that is strongly associated with the increased risk of mortality.[1–4] It is well known that the clinical features of DM in Asia (when compared with other parts of the world) are explicitly different in DM developed at a younger age and in a much shorter time than in subjects with much lower body mass index.[7] In clinical practice, MetS has been promoted as a means of identifying the risk of DM development because of its major characteristics.[18] However, established DM has been concurrently included in the diagnostic criteria for MetS as a component of impaired fasting glucose. Despite the recent recommendation that established DM be excluded from the definition of MetS,[14] data supporting this recommendation are limited.

A previous study from Aerobics Center Longitudinal Study, which was performed in a Western population, reported that the presence of DM is associated with the increased risk of cardiovascular mortality and that MetS status does not have an effect on this risk in men.[19] In Korea, a recent cross-sectional cohort study reported that MetS had an incremental impact on subclinical atherosclerosis in patients without established DM.[20] However, a paucity of data on the association between DM, MetS, and clinical outcomes in Asian populations exists. In the present study, in an asymptomatic Korean population, DM subjects had higher long-term mortality compared with non-DM subjects after 1:1 PSM with individual components of MetS. Thus, all participants had basically the component of impaired fasting glucose and might be relatively higher-risk patients compared with general population.

Interestingly, MetS independently increased the risk of mortality only in subjects without established DM. Central obesity was associated with the increased risk of mortality in non-DM subjects. Previous studies have indicated that adverse clinical events might be directly dependent on hyperglycemia in DM subjects but might be influenced by multiple traditional risk factors in patients without established DM.[21–23] Moreover, recent evidence has suggested a close relationship between glucose fluctuations and adverse clinical outcomes in DM subjects because of increased oxidative stress responses and inflammatory factors.[24–26] These effects might offset the impact of MetS and/or its individual components on long-term mortality in subjects with established DM. Additionally, considering that central obesity is strongly associated with insulin resistance, newly developed DM might be associated with increased mortality in non-DM subjects with central obesity during follow-up periods. Given the controversy over the definition of MetS, the present results indicate that diabetes strongly impacts long-term mortality irrespective of MetS and presents proper evidence arguing against the inclusion of established DM in the classification of MetS. Further prospective studies should be conducted to address these issues in clinical practice.

The International Diabetes Federation (IDF) emphasizes that central obesity is essential for the diagnosis of MetS.[27] Furthermore, despite the recent argument on the predictive value of MetS for mortality over the Framingham risk score (FRS), waist circumference appears to have a significant role as part of the FRS provided their cut-off points are optimized.[28] In clinical practice, there is a paucity of data on the predictive value of the levels of triglyceride and HDL for adverse clinical outcomes at the era of statin which is improved to reduce mortality across a wide range of cholesterol levels in high-risk patients. In our study, patients with DM had significantly higher mortality compared with patients with non-DM despite significantly lower LDL levels in the PSM participants of present study. We could identify that only central obesity was significantly associated with the increased risk of mortality among all MetS components and the number of MetS components independently impacted on the increased mortality in non-DM subjects. These results might strongly support the IDF definition that central obesity has a pivotal role in the pathogenesis of MetS and is a prerequisite for the diagnosis of MetS.

The present study has some limitations. First, the incidence of all-cause death, the primary endpoint, was very small despite the large sample size of this study. Because the KOICA registry data are based on the generally healthy population who received health check-ups in healthcare centers; the number of clinical events at follow-up was limited. Second, the present study was retrospective and might have been influenced by unobserved confounders. However, we attempted to minimize the bias effects or confounding factors using the 1:1 PSM analysis. Despite the limitations of this study, it appears to be unique in that we first identified the different association between MetS and long-term mortality according to DM in the asymptomatic Korean population. Furthermore, to our knowledge, the population size in this study is the largest to date reporting the impact of MetS on mortality according to DM status in an Asian population. Considering the explicitly different clinical features of DM in Asians compared with Western populations, the results of our study might provide useful information for applying the concept of MetS for predicting adverse clinical outcomes in an Asian population.

5. Conclusion

In conclusion, DM subjects have an increased risk of long-term mortality compared with non-DM subjects after PSM with metabolic abnormalities. MetS appears to have an independent

impact on mortality only in subjects without established DM among the asymptomatic Korean population. Our results may not be applicable to the whole subjects with MetS because the PSM using MetS components was performed between subjects with and without DM which was very high risk for adverse clinical events.

Acknowledgments

The authors thank Hyo-Eun Kim, MS (Keimyung University Dongsan Medical Center) and Ji-Min Sung, PhD (Severance Biomedical Science Institute) for their contributions for the statistical analyses in this study.

These persons gave permission to be named in the Acknowledgements of the present study.

References

[1] Lowe LP, Liu K, Greenland P, et al. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in Black and White men: the Chicago Heart Association Detection Project in Industry Study. Diabetes Care 1997;20:163–9.
[2] Wei M, Gaskill SP, Haffner SM, et al. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio Heart Study. Diabetes Care 1998;21:1167–72.
[3] Morgan CL, Currie CJ, Peters JR. Relationship between diabetes and mortality: a population study using record linkage. Diabetes Care 2000;23:1103–7.
[4] Saydah SH, Eberhardt MS, Loria CM, et al. Age and the burden of death attributable to diabetes in the United States. Am J Epidemiol 2002;156:714–9.
[5] Welsh M, Mares J, Oberg C, et al. Genetic factors of importance for beta-cell proliferation. Diabetes Metab Rev 1993;9:25–36.
[6] DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am 2004;88:787–835.
[7] Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006;368:1681–8.
[8] Shin CS, Lee HK, Koh CS, et al. Risk factors for the development of NIDDM in Yonchon County, Korea. Diabetes Care 1997;20:1842–6.
[9] Kim DJ, Lee MS, Kim KW, et al. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001;50:590–3.
[10] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in AdultsExecutive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.
[11] Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Circulation 2005;112:2735–52.
[12] Mozumdar A, Liguori G. Persistent increase of prevalence of metabolic syndrome among U.S. adults: NHANES III to NHANES 1999–2006. Diabetes Care 2011;34:216–9.
[13] Lim S, Shin H, Song JH, et al. Increasing prevalence of metabolic syndrome in Korea: the Korean National Health and Nutrition Examination Survey for 1998–2007. Diabetes Care 2011;34:1323–8.
[14] Simmons RK, Alberti KG, Gale EA, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO expert consultation. Diabetologia 2010;53:600–5.
[15] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[16] American Diabetes AssociationStandards of medical care in diabetes—2013. Diabetes Care 2013;36:S11–66.
[17] Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32.
[18] Gupta AK, Prieto-Merino D, Dahlöf B, et al. Metabolic syndrome, impaired fasting glucose and obesity, as predictors of incident diabetes in 14120 hypertensive patients of ASCOT-BPLA: comparison of their relative predictability using a novel approach. Diabet Med 2011;28:941–7.
[19] Church TS, Thompson AM, Katzmarzyk PT, et al. Metabolic syndrome and diabetes, alone and in combination, as predictors of cardiovascular disease mortality among men. Diabetes Care 2009;32:1289–94.
[20] Won KB, Chang HJ, Kim HC, et al. Differential impact of metabolic syndrome on subclinical atherosclerosis according to the presence of diabetes. Cardiovasc Diabetol 2013;12:41.
[21] Larsen JR, Brekke M, Bergengen L, et al. Mean HbA1c over 18 years predicts carotid intima media thickness in women with type 1 diabetes. Diabetologia 2005;48:776–9.
[22] Czernichow S, Bertrais S, Blacher J, et al. Metabolic syndrome in relation to structure and function of large arteries: a predominant effect of blood pressure. A report from the SU.VI.MAX. Vascular study. Am J Hypertens 2005;18:1154–60.
[23] Sander D, Schulze-Horn C, Bickel H, et al. Combined effects of hemoglobin A1c and C-reactive protein on the progression of subclinical carotid atherosclerosis: the INVADE study. Stroke 2006;37:351–7.
[24] Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008;57:1349–54.
[25] Kurtz P, Claassen J, Helbok R, et al. Systemic glucose variability predicts cerebral metabolic distress and mortality after subarachnoid hemorrhage: a retrospective observational study. Crit Care 2014;18:R89.
[26] Meng X, Gong C, Cao B, et al. Glucose fluctuations in association with oxidative stress among children with type 1 diabetes mellitus: comparison of different phases. J Clin Endocrinol Metab 2015;100:1828–36.
[27] Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469–80.
[28] López-Suárez A, Bascuñana-Quirell A, Beltrán-Robles M, et al. Metabolic syndrome does not improve the prediction of 5-year cardiovascular disease and total mortality over standard risk markers. Prospective population based study. Medicine (Baltimore) 2014;93:e212.