Diabetes & Metabolic Syndrome: Clinical Research & Reviews 11S (2017) S721–S725

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

The association between ghrelin levels and markers of arterial stiffness and inflammatory markers in Saudi subjects with metabolic syndrome

Tarek Mohamed Ali[a,*], Osama Mahmoud Mehanna[b], Ahmad El Askary[c]

[a] Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Taif University, Saudi Arabia & Department of Medical Physiology, Faculty of medicine, Beni-Suef University, Egypt
[b] Department of Medical Physiology, Faculty of medicine, Taif University, Saudi Arabia & Department of Medical Physiology, Faculty of medicine, Al-Azhar University, Egypt
[c] Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Taif University, Saudi Arabia & Department of Medical Biochemistry, Faculty of Medicine, Al-Azhar University, Egypt

ARTICLE INFO

Keywords:
Ghrelin
Arterial stiffness
Metabolic syndrome
Saudi

ABSTRACT

Background: Arterial stiffness is a principal cardiovascular risk factor. Metabolic syndrome (MetS) is a predisposing factor to arterial stiffness and persistent MetS circumstances can deteriorate the arterial stiffness severity. Low concentrations of plasma ghrelin are meticulously connected to arterial stiffness. This work targeted to judge the relationship between plasma ghrelin levels and intima-media thickness (IMT) and brachial-ankle pulse wave velocity (baPWV) as markers of arterial stiffness and inflammatory markers and in Saudi subjects with MetS.
Patients and methods: Eighty-four young adults were recruited from the visitors of the outpatient clinics of Taif hospitals, and then they were divided into a control group that involves subjects without MetS and a study group involving those with MetS. Anthropometric measurements, blood pressure, plasma ghrelin levels, fasting plasma glucose levels (FPG) and lipid profile were assessed. baPWV was measured by a volume plethysmograph while IMT was evaluated by ultrasonography.
Results: Plasma ghrelin values were significantly ($P < 0.001$) decreased in the MetS group versus control group. Arterial stiffness was noticed in MetS group by significantly ($P < 0.01$) increased IMT and baPWV ($P < 0.001$) matched with control group. Plasma ghrelin concentrations were negatively associated with age, smoking, FPG, HbA1c, CRP, TNF-alpha, baPWV, and Lt Carotid IMT.
Conclusions: Depending on our outcomes showing the valuable properties of ghrelin in the cardiovascular system in patients with metabolic syndrome, it can be postulated that ghrelin may be associated with markers of atherosclerosis.

1. Introduction

Vascular disease is a unique principal reason of morbidity as well as mortality worldwide and it is viewed now as the primary cause of ischemia, myocardial infarction and stroke [1]. Structural and functional properties of the arterial wall can determine vascular functions. Arterial stiffness is a chief cardiovascular risk factor that reflects the degree of remodeling in large arteries, it is defined as hardening and reduction of arterial elasticity owing to pathological modifications of the blood vessel wall such as elastic lamina fragmentation, vascular smooth muscle cells (VSMC) hyperplasia and hypertrophy or loss of contractility, collagen deposition and arterial calcification [2,3]. Arterial stiffness, referred as arteriosclerosis, is a key mechanism in the progress of cardiovascular diseases (CVD), and the degree of arteriosclerosis is a strong surrogate indicator for determining the event of CVD [4]. Metabolic syndrome (MetS) is a worldwide pre-atherosclerotic health problem consisting of many risk factors as abdominal obesity, dyslipidemia, impaired glucose tolerance and hypertension. MetS is an adjunct to arterial stiffness and it is suggested that persistent MetS conditions can deteriorate the arterial stiffness severity also; the recovery of MetS status could lead to of postponement the existence of atherosclerosis [5–7]. Ghrelin is a peptide hormone that was initially identified from rat stomach regarded as an endogenous ligand that can bind to growth hormone secretagogue receptor It has multiple functions, including stimulating appetite and beginning food intake, controlling energy metabolism and controlling gastric motility [8]. Existing evidences propose that ghrelin could contribute to the event of

* Corresponding author.
E-mail address: tarek70ali@gmail.com (T.M. Ali).

http://dx.doi.org/10.1016/j.dsx.2017.05.005
1871-4021/

MetS in adults. Nearby a certain relationship between arterial stiffness and ghrelin as low plasma ghrelin concentrations are closely linked to coronary atherosclerosis severity and morphology in diabetic patients having coronary artery disease [9,10]. Brachial-ankle pulse wave velocity (baPWV) is a non-invasive unbiased effective index that reflects arterial stiffness in both aortic as well as peripheral arteries and reported as a dependable marker for the morbidity and mortality of cardio and cerebrovascular consequences [11]. Several studies have investigated the association between arterial stiffness assessed by baPWV and the constituents of MetS in different inhabitants worldwide.

The relationship between carotid artery intima media thickness (IMT) and cardiovascular disease has been well documented and ultra-sonographic measurement of carotid IMT is a non-invasive technique used for evaluation of vascular damage and there are some studies have assessed the effect of metabolic syndrome on carotid artery IMT [12,13].

It seems that assessment of the relationship between carotid IMT, baPWV, some inflammatory factors and ghrelin in MetS may predict asymptomatic vascular modifications in patients with MetS. The association between IMT and baPWV and MetS and its constituents may be dissimilar based on diverse populations, areas and traditional diet. Bearing in mind the recent increasing prevalence of MetS worldwide and focusing on the knowledge gap in the relation between ghrelin levels and early detection of atherosclerosis in Saudi adults with metabolic syndrome, we aimed in the current work to assess the association between IMT, baPWV, some inflammatory markers and ghrelin levels in Saudi subjects with MetS.

2. Patients and methods

According to the study protocols for human subjects, the current study was approved by the Ethics Committee, Taif University, Saudi Arabia. Patients were learned of the investigative nature of the research and a written informed consent was obtained before enrollment in the study.

2.1. Participants

Eighty-four individuals, 50male: 34 female aged from 54.49 ± 5.86 years recruited from the visitors of the outpatient clinics of Taif hospitals in the period from March 2016 and March 2017 and enrolled in this study then they were divided into a control group that involves subjects without MetS and a study group involving those with MetS in accordance with the 2005 Adult Treatment Panel III criteria. MetS was defined as the presence of at least three of the following five components: (1) central obesity [waist circumference >90 cm for men and >80 cm for women]; (2) triglycerides $\geq$150 mg/dL; (3) high density lipoprotein (HDL) cholesterol $<$40 mg/dL for men or $<$50 mg/dL for women; (4) blood pressure $\geq$130/85 mmHg; in addition (5) fasting plasma glucose >100 mg/dL [14].

2.2. Exclusion criteria

Patients receiving medication that could alter the metabolic profile (e.g., beta blocker, steroids and diuretics) and persons with a known history of primary hyperlipidemia, diabetes, secondary obesity, or individuals with previous gastric surgery were excluded from completing the study.

2.3. Anthropometric measurements

Body weight was taken in subjects dressed in light clothing with no shoes. Height was assessed in the standing position by means of a calibrated stadiometer. Body mass index (BMI) was estimated as weight/(height)^2 (kg/m2). Via a calibrated standardized tape, the waist circumference was assessed in centimeters in the standing position 1 inch above the umbilicus on the bare skin between the lower costal margin and the iliac crest (cm).It was measured by the same well-trained person. Blood pressure was determined in the brachial artery and ankles simultaneously as systolic (SBP), diastolic (DBP), mean (MAP) blood pressure, by automated oscillometric maneuvers (Omron HEM712C; Omron, Tokyo, Japan). Subjects were in a seated position after 10 min rest.

2.4. Biochemical assays

Morning overnight fast blood samples were assembled from the antecubital vein in the period between 08:30 and 09:30 a.m. The blood samples were collected directly into pyrogen-free anticoagulant EDTA-2Na tubes then centrifuged immediately at 1500*g* for 15 min at 4 °C. Multiple aliquots of the resulting plasma samples were stored frozen at −80 °C until use. Main circulating non-acylated ghrelin levels were assessed by means of the [Des-octanoyl]-Ghrelin (human) ELISA kit (Minneapolis, MN, USA) as stated by the manufacturer's instructions. Part of the collected blood samples was used to collect serum for assay of lipids.

Plasma glucose levels (FBG) were determined via an automated glucose oxidase technique. Serum levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein–cholesterol (HDL-C) and low-density lipoprotein–cholesterol (LDL-C) were established by enzymatic methods using an autoanalyser.

2.5. Measurement of pulse wave velocity

By means of a volume plethysmographic apparatus (model BP-203RPE, Colin, Co.Ltd. Komaki, Japan), baPWV was considered with an intra-observer (10.0%) and an inter-observer (8.4%) reproducibility [15]. In the present study, the baPWV was estimated as the mean of the left and right baPWV measures. After 15 min of rest, subjects were examined in the supine position on a different circumstance from the blood collection so that the contributor would be mentally comfortable. Waveform information were achieved from a volume plethysmographic sensor in cuffs on both brachiums and both ankles, then time intervals (T) between the wave forward-facing the brachiums and that of the ankles were computed. According to the subject's height, the distance (L) between the heart and selection points was considered automatically. baPWV = L/T (L = La- Lb) bearing in mind that La = the distance from the heart to ankle, then Lb = the distance from the heart to brachium [15].

2.6. Measurement of carotid IMT

The IMT of the common carotid artery was established consuming high-resolution B-mode ultrasonography (EnVisor; Philips Medical Systems, Andover, MA, USA) with a 5–12 MHz transducer and using IMT measurement software (Intima scope; Media Cross Co., Tokyo, Japan) at 3 levels of the lateral and medial walls of the carotid artery, 1–3 cm proximal to the carotid bifurcation. In the present study, the carotid IMT was computed as the mean of the left and right IMT values. All measurements were verified by a well-trained technician who was not aware of to the participant's anthropometric or laboratory data [13].

2.7. Statistical analysis

Continuous variables are stated as mean ± standard deviation. Each variable was checked for normality of distribution via the Kolmogorov–Smirnov test. Aimed at comparisons between MetS

(+) and MetS(−) groups, study variable parameters was analyzed using independent Student's *t*-test or the Mann–Whitney *U* test for numerical variables or the Chi-squared test or Fisher's exact test for categorical variables. All analyses were conducted using Statistical Package for Social Science (SPSS) statistical software ver. 20 (IBM Corp. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Pearson's correlation coefficient test or Spearman's correlation coefficient test was used to determine the relationship between plasma ghrelin, arterial stiffness and inflammatory markers in subjects with metabolic syndrome. This was depending on whether the variables were normally distributed. Statistical significance was agreed at $P < 0.05$.

3. Results

The clinical and biochemical features of the study groups were displayed in Table 1. There were 24 males and 18 females in the MetS group and 29 males and 13 females in the group without MetS group. No significant variations were detected in age, sex, current smoking category. Also, there were no significant disparities concerning the two groups regarding TC, LDL-C and hemoglobin A1C (%). Nevertheless, compared with the control group, MetS group had a significantly higher ($P < 0.01$) WC, BMI, SBP, DBP, TG, and FPG. Proinflammatory markers as TNF alpha, IL6 and CRP were significantly ($P < 0.01$) higher in MetS group than in control group. HDL-C was significantly ($P < 0.01$) lower in MetS group than in control group. Right and Left mean IMT were significantly ($P < 0.01$) higher in MetS group than in control group.

Fig. 1 revealed that plasma ghrelin concentrations were significantly ($P < 0.001$) decreased in the MetS group compared with control group. Arterial stiffness was measured by the non-invasive measurements and presented that baPWV was significantly ($P < 0.001$) increased in the MetS group compared with control group.

Table 2 shows that plasma ghrelin concentrations were negatively associated with age, smoking, baPWV, FPG, HbA1c, CRP, TNF-alpha and mean Lt IMT of carotid artery.

4. Discussion

MetS is a gathering of obesity, impaired glucose metabolism, hypertension, and dyslipidemia, and it is considered now as a predictive for the occurrence of diabetes and cardiovascular diseases young population, principally in the overweight or obese [5]. In the present study, there were significant increases in WC, BMI, SBP, DBP, and FPG in Mets groups contrasted to control group. This outcome was in accordance with Yoon et al. [22], report which revealed that MetS was positively associated with body weight, waist circumference, blood pressure and blood glucose levels. With reference to lipid profile, there was a significant increase in serum TG, moreover, total cholesterol and LDL cholesterol were not significantly changed in MetS groups compared to control group. There was a significant decrease in HDL cholesterol in MetS group ($P < 0.0001$) compared to control group. This was in accordance with a previous study found that MetS was positively associated with TG and negatively associated with the HDL-cholesterol level [16]. Also, we observed a significant decrease in plasma ghrelin concentration and a negative association between plasma ghrelin concentrations and FPG and HbA1c in MetS patients, indicating that ghrelin acting a role in regulating the levels of plasma glucose in MetS patients The cause of hyperglycemia associated with low ghrelin level may be attributed to the fact that ghrelin endorses the preadipocytes proliferation and differentiation and enhances adipocytes sensitivity to insulin [11]. The precise mechanism of reducing ghrelin secretion is not fully recognized. Some authors suggested that low ghrelin may be associated with the incidence of hypertension [17]. Another option suggested that the cause may be due to hyperglycemia [18]. The most important outcome of the present study is the association of increased arterial stiffness, revealed by increased baPWV and IMT values, markers of arterial stiffness, with significantly decreased plasma ghrelin concentrations in MetS subjects compared with control patients after adjustments for the major frequently documented risk factors for atherosclerosis. Furthermore, the mean velocity of baPWV had a 1.5 times faster and ITM was 1.2 thicker in subjects with MetS than individuals with no MetS. Previous reports indicated that circulating ghrelin concentrations are an independent determining factor of arterial stiffness, even after modification for confusing cardiovascular risk factors. These results endorse that ghrelin actively contributes in the arterial stiffness pathophysiology in subjects with MetS [11]. To our knowledge, this is the first study characterizing the association of plasma ghrelin concentrations with early atherosclerosis in Taif populations of Saudi Arabia. baPWV are closely allied to the severity of arterial stiffness [11]. Though, the mechanism by which MetS may perhaps increase baPWV remains ambiguous. One possible clarification for our results is that elevated blood pressure can increase baPWV through direct action on the arterial wall [11]. A previous study [19]

Table 1
General characteristics, pro-inflammatory markers and intima-media thickness of the study groups.

Variable	Group without MetS (n = 42)	Group with MetS (n = 42)	p- value
Age (yr)	55.85 ± 4.27	56.23 ± 4.12	0.20
Waist circumference (cm)	85.4 ± 5.2	95.6 ± 7.5	0.04
BMI	24.6 ± 2.8	27.3 ± 2.7	0.04
SBP (mmHg)	124.6 ± 20.7	133.3 ± 14.3	0.02
DBP (mmHg)	76.3 ± 7.5	82.9 ± 12.5	0.04
MAP (mmHg)	91.51 ± 12.60	95.51 ± 8.92	0.03
Total cholesterol(mg/dL)	179.23 ± 38.45	182.56 ± 44.21	0.76
Triglyceride(mg/dL)	103.43 ± 37.22	184.71 ± 113.12	<0.01
High density lipoprotein cholesterol (HDL) (mg/dL)	49.14 ± 13.11	42.23 ± 11.63	0.02
Low density lipoprotein cholesterol (mg/dL)	111.23 ± 34.11	108.65 ± 31.54	0.78
Fasting plasma glucose (mg/dL)	100.46 ± 8.34	120.54 ± 23.67	<0.01
CRP (mg/L)	3.43 ± 1.76	6.43 ± 3.12	0.025
TNF alpha (pg/ml)	4.56 ± 2.11	8.45 ± 3.1	0.013
IL6 (pg/ml)	5.23 ± 1.89	10.58 ± 2.57	0.023
Hemoglobin A1c (%)	5.83 ± 0.52	6.45 ± 1.37	0.405
Right mean IMT (mm)	0.81 ± 0.20	0.94 ± 0.20	0.013
Left mean IMT (mm)	0.79 ± 0.20	0.93 ± 0.20	0.003

Values are represented as mean ± standard deviation.
SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, IMT: intima-media thickness.

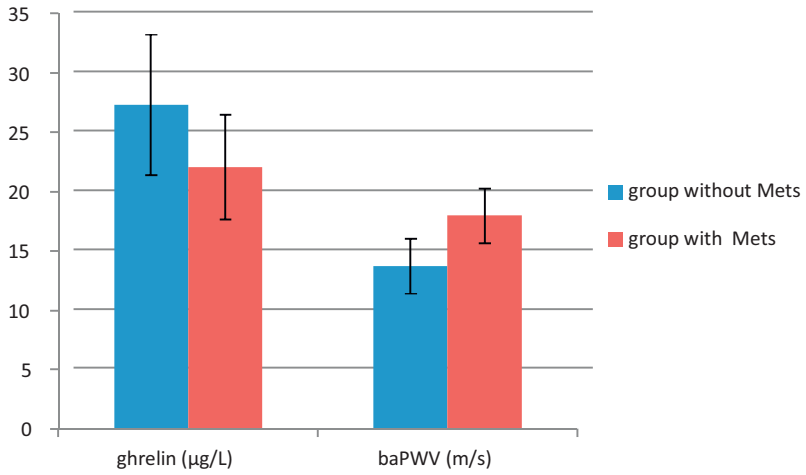

Fig. 1. The ghrelin concentrations and brachial – ankle pulse wave velocity (baPWV) in study groups. Values are given as Mean ± SD. Plasma ghrelin level is significantly lower in MetS group than in non- MetS group. on the other hand, ba-PWV is significantly higher in MetS group than in non- MetS group.

Table 2
The relationship between plasma ghrelin levels and indicators of arterial stiffness in subjects with metabolic syndrome.

	OR	95% CI	P value
Age	−1.725	−1.467,−2.145	<0.01
Smoking	−1.248	−1.038,−1.785	0.032
FPG	−1.199	−1.015, −1.705	0.043
HbA1c	−1.212	−1.220,−1.441	0.025
baPWV	−1.462	−1.205, 2.015	<0.01
Mean IMT. Rt	1.165	1.115, 1.507	0.053
Mean IMT. Lt	−1.217	−1.322,−1.091	0.035
CRP	−1.316	−1.336, −1.552	0.015
TNF alpha	−1.290	−1.110, −1.472	0.014
IL6	1.010	1.010, 1.172	0.064

Every data was adjusted by gender and age. OR: Odd ratio, CI: confidence interval, FPG: fasting plasma glucose, ITM: intima media thickness, CRP: C- reactive protein, TNF: tumor necrosis factor. IL6: interleukin 6.

proposed that the "risky" gathering of central obesity, triglyceridemia, hypertension, hyperglycemia, was significantly related to exceedingly stiff arteries. Arterial stiffness is connected to hypertension and obesity [20]. Ghrelin seems to be associated with these circumstances. It is postulated that there is a certain relationship between circulating ghrelin concentrations and arterial stiffness in MetS subjects [4]. Arterial stiffness, as measured by IMT was negatively associated with ghrelin in our study which was in agreement with the results of Ukkola et al. who reported positive correlation between ghrelin and IMT in subjects with MetS [21]. However, Hajmohammadi T et al., [10] didn't find any significant relationship between IMT and ghrelin in subjects with Mets. However, evidence from animal models directed that ghrelin improves vasodilation and regulation of blood pressure. This effect was chiefly performed through the endothelial system by means of adjusting the balance between endothelin (ET)-1and NO by increasing NO bioactivity [10]. In addition, ghrelin suppresses hyperglycemia-induced apoptosis and inhibits the inflammatory response in vascular endothelial cell [22–24]. It was evidenced in our study that there is a significant increase in TNF, IL6 and CRP and a negative correlation of ghrelin to TNF and CRP ($P < 0.05$) in MetS patients versus control group. The positive effects of ghrelin in cardiovascular system might also be accompanying the attenuation of sympathetic nerve activity. Then, insulin resistance, type 2 diabetes, and metabolic syndrome which all are considered as risk factors for atherosclerosis usually accompany low ghrelin concentrations [9]. It is postulated that the inverse relationship between the level of low circulating ghrelin and the enhanced arterial stiffness detected in the present study may be attributable to disorder of endothelial function owing to reduced ghrelin [9]. There is an alternative line of recent suggestion showing vasoconstrictive properties physiological doses of ghrelin and vasodilator influences using pharmacological doses on coronary arterioles [12]. Consequently, the roles of ghrelin in the cardiovascular system have not yet been decidedly recognized [9].

5. Conclusion

Depending on our outcomes and the previous reports showing the valuable properties of ghrelin in cardiovascular system in patients with metabolic syndrome, it can be postulated that ghrelin may be associated with markers of atherosclerosis.

References

[1] Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318–27.
[2] Laurent S, Alivon M, Beaussier H, Boutouyrie P. Aortic stiffness as a tissue biomarker for predicting future cardiovascular events in asymptomatic hypertensive subjects. Ann Med 2012;44(Suppl. (1)):S93–7.
[3] Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: the framingham heart study. Circulation 2010;121(4):505–11.
[4] Zhao YT, Yang HB, Li L, Gao K, Li PF, Xie WW. Reciprocal relationship between plasma ghrelin level and arterial stiffness in hypertensive subjects. Clin Exp Pharmacol Physiol 2013;40(November (11)):735–9, doi:http://dx.doi.org/10.1111/1440-1681.12165.
[5] Zhou F, Zhang H, Yao W, Mei H, Xu D, Sheng Y, et al. Relationship between brachial-ankle pulse wave velocity and metabolic syndrome components in a Chinese population. J Biomed Res 2014;28(4):262–8.
[6] Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 2009;120(16):1640–5.
[7] 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(5):469–80.
[8] Soares JB, Leite-Moreira AF. Ghrelin, des-acyl ghrelin and obestatin: three pieces of the same puzzle. Peptides 2008;29:1255–70.
[9] Pöykkö SM, Kellokoski E, Ukkola O, Kauma H, Päivänsalo M, Kesäniemi YA, et al. Plasma ghrelin concentrations are positively associated with carotid artery atherosclerosis in males. J Intern Med 2006 Jul;260(1):43–52.
[10] Hajmohammadi T, Sadeghi M, Dashti M, Hashemi M, Saadatnia M, Soghrati M, et al. Relationship between carotid intima-Media thickness with some inflammatory biomarkers, ghrelin and adiponectin in iranians with and

without metabolic syndrome in isfahan cohort study. ARYA Atheroscler 2010;6 (2)56–61 Summer.
[11] Wang A, Su Z, Liu X, Yang Y, Chen S, Wang S, et al. Brachial- ankle pulse wave velocity and metabolic syndrome in general population: the APAC study. BMC Cardiovasc Disord 2016;16(1)228 Nov 18.
[12] Pöykkö SM, Kellokoski E, Ukkola O, Kauma H, Päivänsalo M, et al. Plasma ghrelin concentrations are positively associated with carotid artery atherosclerosis inmales. J Intern Med 2006;260(July (1)):43–52.
[13] Ren D, Wang J, Li H, Li Y, Li Z. Red blood cell distribution width and carotid intima-media thickness in patients with metabolic syndrome. BMC Cardiovasc Disord 2017;17(1)44 28.
[14] Saely CH, Koch L, Schmid F, Marte T, Aczel S, Langer P, et al. Adult Treatment Panel III 2001 but not International Diabetes Federation 2005 criteria of the metabolic syndrome predict clinical cardiovascular events in subjects who underwent coronary angiography. Diabetes Care 2006.
[15] Tomiyama H, Matsumoto C, Shiina K, Yamashina A. Brachial-Ankle PWV: current status and future directions as a useful marker in the management of cardiovascular disease and/or cardiovascular risk factors. J Atheroscler Thromb 2016;23(2):128–46.
[16] Yoon SE, Ahn SG, Kim JY, Park JS, Shin JH, Tahk SJ, et al. Differential relationship between metabolic syndrome score and severity of coronary atherosclerosis as assessed by angiography in a non-diabetic and diabetic Korean population. J Korean Med Sci 2011;26:900–5.
[17] Pöykkö SM, Kellokoski E, Hörkkö S, Kauma H, Kesäniemi YA, Ukkola O. Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes 2003;52:2546–53.
[18] Wang A, Su Z, Liu X, Yang Y, Chen S, Wang S, et al. Brachial-ankle pulse wave velocity and metabolic syndrome in general population: the APAC study. BMC Cardiovasc Disord 2016;16(1)228 Nov 18.
[19] Scuteri A, Cunha PG, Rosei EA, Badariere J, Bekaert S, Cockcroft JR, et al. Arterial stiffness and influences of the metabolic syndrome: a cross-countries study. Atherosclerosis 2014;233(2):654–60.
[20] Kim YK. Impact of the metabolic syndrome and its components on pulse wave velocity. Korean J Intern Med 2006;21(2):109–15.
[21] Ukkola O, Poykko S, Paivansalo M, Kesaniemi YA. Interactions between ghrelin, leptin and IGF-I affect metabolic syndrome and early atherosclerosis. Ann Med 2008;1–9.
[22] Zhao H, Liu G, Wang Q, Ding L, Cai H, Jiang H, et al. Effect of ghrelin on human endothelial cells apoptosis induced by high glucose. Biochem Biophys Res Commun 2007;362:677–81.
[23] Li WG, Gavrila D, Liu X, Wang L, Gunnlaugsson S, Stoll LL, et al. Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. Circulation 2004;109:2221–6.
[24] Rossi F, Bertone C, Petricca S, Santiemma V. Ghrelin inhibits angiotensin II-induced migration of human aortic endothelial cells. Atherosclerosis 2007;192:291–7.