Original Article
Association of serum hepatocyte growth factor with pericardial fat volume in patients with coronary artery disease

Jingning Liu[1], Zhengxia Liu[1], Shikun Cai[1], Peng Lu[1], Xiang Lu[1], Gang Peng[2]

[1]Department of Geriatrics, The Second Affiliated Hospital, Nanjing Medical University, Jiangsu, China; [2]Department of Neurosurgery, The Second Affiliated Hospital, Nanjing Medical University, Jiangsu, China

Abstract: Hepatocyte growth factor (HGF), as a metabolic regulator, was shown to be secreted by adipose tissue and associated with metabolic syndrome (MS) and coronary artery disease (CAD). Pericardial fat, as a visceral fat, was found to be a significant predictor of CAD. We investigated the relationship between serum HGF levels and pericardial fat volume (PFV) in individuals aged between 40-65 years without liver or renal diseases, and also without medicine consumption. Serum HGF levels were found to be significantly higher in participants with CAD than those without CAD (P<0.001). In addition, the serum HGF levels had a significant positive correlation with the PFV in all the participants (r=0.485, P<0.001). Multivariate linear regression demonstrated that the serum HGF levels were significantly associated with PFV (β value=0.454, P<0.001) after adjustment for the metabolic parameters. Further regression assessment found that the serum HGF levels were significantly associated with PFV in participants with CAD (β value=0.586, P<0.001). The serum HGF levels were significant and independent predictors for determining the presence of CAD (OR=1.002, 95% CI: 1.000-1.004, P=0.011). This study therefore demonstrated that the serum HGF levels positively correlated with PFV in participants with CAD and can therefore be a significant predictor for the presence of CAD.

Keywords: Hepatocyte growth factor, pericardial fat volume, coronary artery disease, metabolic syndrome

Introduction

Hepatocyte growth factor (HGF) is mainly produced in mesenchymal cells and was firstly identified as a potent stimulator of hepatocyte growth [1]. The HGF binds to its receptor-cMet and exerts various biological functions, including mitogenic, motogenic, and morphogenic activities in cells of epithelial origin [2-4]. The HGF is preferentially expressed in the liver [2, 5] and has also been synthesized and secreted by the adipose tissue [6]. It has also been suggested that the HGF acts as a metabolic regulator in humans. Studies in human subjects have shown increased serum HGF levels in patients with obesity, hypertension, hyperlipidaemia, insulin resistance and metabolic syndrome (MS) [7]. Elevated serum HGF levels have also been associated with coronary artery disease (CAD) [8, 9].

Pericardial fat, an ectopic visceral fat, is present around epidardial coronary arteries and is considered as an important source of vaso-bioactive mediators in coronary artery atherogenesis [10-12]. Pericardial fat has also been reported to correlate with metabolic risk factors [13, 14], coronary artery stenosis [14], and coronary artery calcification [15]. Recent studies have found that pericardial fat volume (PFV) acts as an indicator for presence of coronary artery atherosclerosis [16, 17]. However, the relationship between the HGF levels and PFV in elderly population has not been investigated. The purpose of this study was therefore to investigate the association of serum HGF levels and PFV in participants with or without the CAD, in the presence or absence of MS.

Methods

Study participants

We screened 429 individuals aged between 40-65 years who had undergone cardiac evaluation with 64-slice multidirector computed

Table 1. Baseline characteristics of participants

Characteristics	No CAD	CAD	P
	N = 192	N = 93	
Age (years)	52.3±7.0	53.0±8.0	0.519
Male sex n (%)	94 (49)	48 (52)	0.674
BMI (kg/m^2)	26.5±2.5	27.0±2.1	0.047
Waist circumference (cm)	85.5±5.2	88.0±6.0	<0.001
Smoking n (%)	41 (21)	32 (34)	0.018
Systolic blood pressure (mmHg)	114.5±14.4	122.4±13.4	<0.001
Diastolic blood pressure (mmHg)	75.8±9.0	77.1±8.8	0.219
Fasting glucose (mg/dl)	104.3±16.6	109.0±16.3	0.024
Total cholesterol (mg/dl)	173.5±25.5	184.0±31.2	0.005
Triglycerides (mg/dl)	139.3±42.8	156.7±32.2	0.001
LDL-cholesterol (mg/dl)	98.8±21.1	102.3±25.1	0.240
HDL-cholesterol (mg/dl)	42.6±9.0	39.4±7.6	0.002
AST (U/L)	27.2±5.6	26.6±5.6	0.465
ALT (U/L)	27.3±7.6	27.9±7.0	0.510
HGF (pg/ml)	566.6±175.4	718.3±256.3	<0.001
Pericardial fat volume (cm^3)	150.4±24.7	181.9±44.6	<0.001

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; AST, glutamic-oxalacetic transaminase; ALT, glutamic-pyruvic transaminase.

tomography (MDCT) as a routine physical examination or for cardiac evaluation in high-risk participants with obesity, history of smoking or strong family history of CAD at the Second Affiliated Hospital of the Nanjing Medical University, from August 2013 to January 2015. All individuals were asked to fill out questionnaires on their medical history.

Subjects with acute coronary syndrome (ACS), previously documented CAD, suspected myocarditis or pericarditis, advanced renal and liver diseases, known malignant disease, systemic inflammatory disease, autoimmune disease or with medicine consumption were excluded from our study. We consequently identified 93 subjects firstly diagnosed with CAD and 192 subjects without CAD. A total of 285 individuals (male/female 142/143) were enrolled for analysis.

Ethics statement

This study was approved by the Scientific and Ethical Committee of the Second affiliated Hospital of the Nanjing Medical University. Written informed consents were obtained from all the participants.

Anthropometric and biochemical parameters

Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Waist circumference was measured to the nearest 0.1 cm at the narrowest point between the lower limit of the ribcage and the iliac crest. Blood pressure (BP) was measured by nurses in a standardized setting. Blinded BP measurements were repeated at least three times and the mean values from these repeated measurements were considered as individuals' BP values.

Serum glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, glutamic-oxalacetic transaminase (AST) and glutamic-pyruvic transaminase (ALT) concentrations were all measured after a minimum of 12-h fasting, using the Toshiba 200FR Neo chemistry auto-analyser (Toshiba Medical Systems, Tokyo, Japan). Serum HGF concentration was measured after fasting by the enzyme-linked immunosorbent assay (ELISA) (human HGF Instant ELISA 128 tests, eBiosciences, San Diego, CA, USA), using an automated microplate reader instrument (Thermo Multiskan MK3, Thermo Fisher Scientific, Waltham, MA, USA).

Multi-slice CT scan protocol

Cardiac MDCT was performed with a Brilliance 64 CT Scanner (Philip Medical System, Andover, MA, USA) using a standard scanning protocol: 64 × 0.625 mm section collimation, 420 ms of gantry rotation time, 120 kV tube voltage and 800 mA tube current with electrocardiographic-gated dose modulation. Subjects with heart rates over 65 beats per minute received 10-30 mg of intravenous esmolol (Qilu Pharmaceutical Co., Ltd., Jinan, China), before the MDCT imaging. The CT scan raw data were reconstructed at the 75% of the R-R interval to coincide with left ventricular diastasis. The CT reconstructed image data were transferred to a workstation
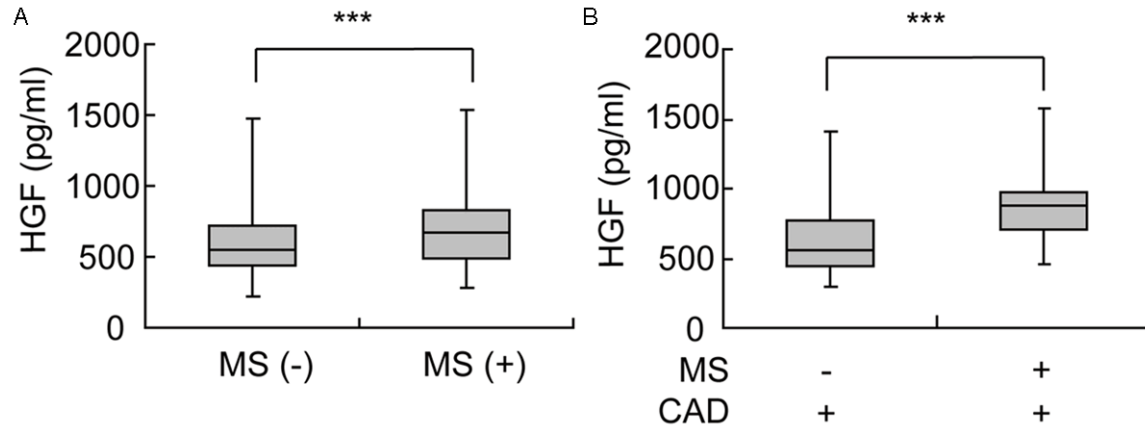
Figure 1. A: The differences in serum HGF levels between participants with and without metabolic syndrome (MS). B: The differences in serum HGF levels between CAD participants with MS and without MS. ***P<0.001. MS, metabolic syndrome; CAD, coronary artery disease.

Table 2. Correlation between serum HGF levels and clinical parameters

	Correlation coefficient (r)	P
Age (years)	0.007	0.904
BMI (kg/m^2)	0.087	0.145
Waist circumference (cm)	0.197	0.001
Systolic blood pressure (mmHg)	0.192	0.001
Diastolic blood pressure (mmHg)	-0.010	0.803
Fasting glucose (mg/dl)	0.152	0.010
Total cholesterol (mg/dl)	0.086	0.146
Triglycerides (mg/dl)	0.031	0.600
LDL-cholesterol (mg/dl)	0.314	<0.001
HDL-cholesterol (mg/dl)	-0.176	0.003

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

for post processing (ZIO M900, Amin/ZIO, Tokyo).

Analysis of coronary artery disease

The scanned images were analyzed using a three-dimensional workstation by experienced radiologist specializing in cardiac MDCT. All 17 coronary artery segments (according to the American Heart Association classification) constituted the basis for detection of at least 50% diameter stenosis independent of reference vessel size. Coronary plaques were defined as structures > 1 mm^2 within and/or adjacent to the coronary artery lumen. We defined the CAD as having at least 50% luminal diameter stenosis and at least one major epicardial coronary artery with plaques.

Analysis of pericardial fat volume

The pericardial fat volume was measured by two observers blinded to the subject information and design of the study. Pericardial fat volume (PFV) was measured three-dimensionally using the contrast enhanced images. First, a predefined image display setting was used (window width 150 Hounsfield units (HU); window center -120 HU) to identify pixels that corresponded to adipose tissue [15]. The readers were then required to trim along the pericardial sac using axial, coronal, sagittal slice, and volume rendered image. PFV was defined as any adipose tissue located within the pericardial sac. A slice 1 cm above the most cranial slice, including the left anterior descending coronary artery, was defined as the superior border of pericardial fat.

Definition of metabolic syndrome

MS was defined according to the National Cholesterol Education Program guideline as the presence of at least three of the following traits: waist circumference ≥ 90 cm for men and ≥ 80 cm for women, triglyceride levels ≥ 150 mg/dl, HDL-cholesterol levels < 40 mg/dl for men and < 50 mg/dl for women, blood pressure ≥ 135/85 mmHg, and fasting blood glucose levels ≥ 110 mg/dl.

Statistical analysis

The Kolmogorov-Smirnov test was used to check normal distribution of all parameters. Continuous variables were presented as means

Table 3. Correlation between PFV and biochemical parameters

	Correlation coefficient (r)	P
BMI (kg/m^2)	0.356	<0.001
Waist circumference (cm)	0.341	<0.001
Systolic blood pressure (mmHg)	0.192	0.001
Diastolic blood pressure (mmHg)	-0.010	0.861
Fasting glucose (mg/dl)	0.262	<0.001
Total cholesterol (mg/dl)	0.209	<0.001
Triglycerides (mg/dl)	0.260	<0.001
LDL-cholesterol (mg/dl)	0.185	0.002
HDL-cholesterol (mg/dl)	-0.196	0.001
HGF (pg/ml)	0.485	<0.001

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HGF, hepatocyte growth factor.

± standard deviation and analyzed using a student's t test. Categorical variables were expressed by n of subjects (%) and analyzed using a chi-square test. Person's correlation was performed to analyze the association between various metabolic parameters, serum HGF levels and PFV. The odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated by a multivariate logistic regression analysis and used to evaluate the risk factors related to CAD. All *P*-values were two sided and a *P*-value < 0.05 was considered statistically significant. Statistical analysis was conducted using SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the study participants

The baseline characteristics of the 285 participants with and without CAD (as assessed by coronary MDCT) are listed in **Table 1**. The mean age of the participants was 52.4 years and their mean BMI was 26.6 kg/m^2. The study group included 97 participants (34.1%) with MS. The participants with CAD had significantly higher BMI, WC, systolic blood pressure (SBP), fasting blood glucose, total cholesterol, triglycerides, HGF levels and PFV than those without CAD. The HDL- cholesterol levels were at the same time significantly lower in participants with CAD than in those without the CAD. Diastolic blood pressure (DBP), serum LDL- cholesterol, AST and ALT levels did not differ between the two groups.

Serum HGF levels

The mean serum HGF concentration was 616.1 pg/ml and there was no significant difference between the HGF levels in men (640.3±238.7 pg/ml) and women (592.2±190.8 pg/ml) p = 0.061). There was a significant difference in serum HGF levels in participants with and without the MS (706.0±237.1 pg/ml) vs 569.8±190.4 pg/ml, respectively, p<0.001, **Figure 1A**). In addition, the participants with CAD and MS had higher serum HGF levels when compared to those with CAD and without MS (825.7 pg/ml vs 603.8 pg/ml, p < 0.001, **Figure 1B**).

Association of serum HGF levels with clinical characteristics

The correlations between serum HGF levels and clinical parameters are shown in **Table 2**. The serum HGF levels showed a significant positive correlation with waist circumference, SBP, serum fasting glucose and LDL-cholesterol levels. The serum HGF levels also showed a significant negative correlation with HDL-cholesterol levels. There was no significant association between HGF, age, BMI, DBP, total cholesterol and triglycerides levels.

Association of PFV with serum HGF levels

The volume of pericardial fat, as measured by the cardiac MDCT, was analyzed in relation to metabolic parameters and serum HGF levels. The PFV correlated significantly and positively with metabolic parameters, such as BMI, waist circumference, SBP, serum fasting glucose, total cholesterol, triglycerides and LDL-cholesterol levels. There was a strong negative correlation between the PFV and HDL-cholesterol levels. Moreover, the PFV showed a significant positive correlation with serum HGF levels, as shown in **Table 3**.

The multivariate linear regression analysis, shown in **Table 4**, showed that the HGF had significant association with the PFV in participants after adjustments were made for BMI, waist circumference, SBP, serum fasting glucose and lipid levels. The association between the HGF and PFV in participants with and without the CAD was also investigated, respectively. There was no significant association between the HGF and PFV in participants without the CAD after adjustment for the metabolic parameters

Table 4. Multivariate linear regression model for variables in association with HGF levels

Variables	β-coefficient (95% CI)	P
PFV (cm^3)	0.454 (2.089-3.430)	<0.001
BMI (kg/m^2)	-0.165 (-25.498 to -4.091)	0.007
Waist circumference (cm)	0.080 (-1.446-7.669)	0.179
Systolic blood pressure (mmHg)	0.112 (0.144-3.188)	0.032
Glucose (mg/dl)	0.707 (-0.912-1.929)	0.481
Total cholesterol (mg/dl)	-0.016 (-0.900-0.646)	0.747
Triglycerides (mg/dl)	-0.087 (-1.003-0.072)	0.089
LDL- cholesterol (mg/dl)	0.262 (1.582-3.478)	<0.001
HDL- cholesterol (mg/dl)	-0.063 (-4.096-0.948)	0.220

PFV, pericardial fat volume; BMI, body mass index.

above (β value = 0.120, P = 0.133). However, the serum HGF levels were significantly associated with the PFV in the participants with CAD (β value = 0.586, P < 0.001). We further assessed the relationship between the HGF and PFV in the CAD participants with and without the MS, respectively. The serum HGF levels were found to be significantly correlated with the PFV in the CAD participants, independent of the MS (β value = 0.495, P = 0.002 vs β value = 0.445, respectively, P = 0.002).

Association of serum HGF levels with CAD

Simple logistic regression analysis revealed that the waist circumference, SBP, serum fasting glucose, total cholesterol, triglycerides, HDL-cholesterol levels, HGF levels and PFV were associated with the presence of CAD. These variables were then entered into a backward, stepwise, multivariate logistic regression model. The multivariate logistic regression demonstrated that the serum HGF level was a significant and independent predictor for determining the presence of CAD in all the participants (**Table 5**).

Discussion

Results from our study demonstrated that the serum HGF levels were higher in the participants with CAD than those without CAD and the multivariate linear regression analysis confirmed the significant association between the HGF and PFV in the participants with CAD, independent of presence of metabolic parameters in a fully adjusted model. The multiple logistic regressions revealed that the HGF may be an independent predictor for determining the pres-

ence of CAD. To our knowledge, this is the first report to describe the association between the serum HGF levels with PFV, measured by computed tomography.

Previous studies have demonstrated that the HGF, an identified adipokine, is related to hypertension, glucose, lipid metabolism, and insulin resistance [18-21]. Studies also reported that serum HGF levels are increased in MS patients and correlated with the components of MS [7]. The correlation between the HGF and MS components, which are also CAD risk factors, actuates us to determine the relationship between HGF levels and the development of CAD.

Studies that have attempted to determine the relationship between serum HGF levels and development of coronary atherosclerosis have provided conflicting results. Previous studies demonstrated that serum HGF concentrations were increased in subjects with CAD compared to those with intact coronary arteries. It was reported that the increased HGF was involved in the pathogenesis of atherosclerosis and was a biochemical parameter for estimating the development of systemic arteriosclerosis [22, 23]. In addition, Suzuki et al. demonstrated that serum HGF levels were significantly higher in the unstable angina pectoris and acute myocardial infarction compared to the control group without CAD [24]. In our current study, we also found that the serum HGF levels were higher in the CAD participants than those without the CAD and highest in the CAD participants with MS. On the other hand, Daniel J et al. demonstrated that the HGF levels were similar in patients with and without CAD [25]. Several reasons can explain these conflicting results, such as the position of collected blood sample, enrollment of participants with different ethical backgrounds and basal characteristics. Variability could also arise when measuring total HGF levels, because the HGF ELISA kits could detect pro-HGF as well as proteolytically processed short forms of the HGF in our study.

Pericardial fat is an active adipokine-secreting tissue which was associated with the features of MS. Previous studies indicated that obesity seems to be a predisposing factor for accumu-

Table 5. Logistic regression analysis for presence of CAD in all participants

	Univariate Logistic Regression			Multivariate Logistic Regression		
	OR	95% CI	P Value	OR	95% CI	P Value
Age (years)	1.112	0.678-1.825	0.674			
Sex	1.287	0.784-2.114	0.318			
BMI (kg/m^2)	1.105	0.994-1.227	0.064			
WC (cm)	1.088	1.037-1.140	0.001	1.035	0.976-1.097	0.251
SBP (mmHg)	1.040	1.021-1.060	<0.001	1.028	1.006-1.050	0.012
DBP (mmHg)	1.018	0.990-1.047	0.219			
Glucose (mg/dl)	1.017	1.002-1.033	0.025	0.996	0.977-1.014	0.996
TC (mg/dl)	1.014	1.005-1.024	0.003	1.008	0.998-1.019	0.120
TG (mg/dl)	1.011	1.004-1.017	0.001	1.008	1.001-1.016	0.022
LDL-C (mg/dl)	1.007	0.996-1.018	0.212			
HDL-C (mg/dl)	0.956	0.928-0.986	0.004	0.985	0.951-1.020	0.401
HGF (pg/ml)	1.002	1.000-1.004	<0.001	1.002	1.000-1.004	0.011
PFV (cm^3)	1.031	1.021-1.041	<0.001	1.022	1.011-1.034	<0.001

BMI, body mass index; WC, Waist circumference; SBP, systolic blood pressure; DBP, TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; HGF, hepatocyte growth factor; PFV, pericardial fat volume.

lation of excess epicardial fat [13] and body fat, particularly the abdominal fat tissue is strongly correlated to epicardial fat [14-16]. Studies demonstrated that the PFV were correlated with arterial blood pressure, fasting glucose levels, and lipid metabolism [13, 26-28]. In accordance with previous investigations, this study has also shown a positive correlation between the PFV, BMI, waist circumference, SBP and metabolic parameters.

Recent studies have demonstrated that PFV, assessed by MDCT, was independently and significantly associated with the presence of coronary plaques, especially uncalcified plaques [29-31]. These results suggested that the PFV correlated significantly with the presence of coronary atherogenesis, particularly the early stage of pathological process [12, 29]. In our study, the PFVs from the participants with CAD were higher than in those subjects without the CAD. In accordance with previous studies, the assessed PFV in our study included the fat around all three coronary artery. However, Djaberi et al. showed a smaller volume than our results. The possible reason may be that they did not include the fat around the left coronary proximal section [32].

In this study, the association between the HGF and PFV was significant after adjustments were made for BMI, waist circumference, SBP and metabolic parameters. We further found the significant positive association between the HGF and PFV in the CAD participants, and the HGF was also a predictor for determining the presence of CAD in the participants. Previous study demonstrated that the pericardial fat is a source of proinflammatory cytokines [33] and it secrets tumor necrosis factor-alpha (TNF-alpha), Interleukin 1 (IL1), IL6, monocyte chemoattractive protein-1 (MCP-1) and free fatty acids [34]. In addition, the pericardial fat was believed to contribute to the pathogenesis of CAD by local paracrine interactions with coronary artery [35, 36].

Moreover, investigations reported that the HGF exerts anti-inflammatory action and also inhibits neutrophil infiltration via the down-regulation of adhesion molecules (such as intercellular adhesion molecule-1/E-selectin) on the endothelial cell surface [37]. The HGF can also suppress the production of the proinflammatory cytokines (such as IL1, IL6 and IL 18) via recruitment of anti-inflammatory regulators, such as heme oxygenase-1 [38]. The higher HGF levels in the participants with larger PFV may be viewed as a compensatory mechanism in response to local or systemic metabolic and inflammatory disequilibrium. Further studies are thus needed in order to understand the role of the HGF in coronary atherosclerotic process and to determine the underlying mechanisms of interaction between the HGF and PFV in the pathogenesis of CAD.

The main limitation in our study was the low participants' number. We also lacked data on the amount of calcified, non calcified and mixed coronary artery plaques to assess the association between the HGF and PFV on plaque stability and clinical events.

In summary, this study demonstrated that the serum HGF levels were higher in the subjects with CAD than those without CAD. The study

also showed a significant positive correlation between the serum HGF levels and PFV in the CAD subjects, independent of the MS. The HGF can thus be used as a biomarker for evaluating the visceral fat volume, especially PFV and the risk of CAD in subjects with high risk factors, such as obesity or MS who could develop atherosclerotic heart disease.

Disclosure of conflict of interest

None.

Address correspondence to: Xiang Lu, Department of Geriatrics, The Second Affiliated Hospital, Zhongshan North Road 262#, Nanjing, Jiangsu, China. Tel: +862558509900; Fax: +862558509900; E-mail: luxiang66@njmu.edu.cn; Gang Peng, Department of Neurosurgery, The Second Affiliated Hospital, Zhongshan North Road 262#, Nanjing, Jiangsu, China. Tel: +862558509823; Fax: +862558509823; E-mail: pg1502@njmu.edu.cn

References

[1] Nakamura T, Nawa K and Ichihara A. Partial purification and characterization of hepatocyte growth factor from serum of hepatectomized rats. Biochem Biophys Res Commun 1984; 122: 1450-1459.

[2] Nakamura T, Nishizawa T, Hagiya M, Seki T, Shimonishi M, Sugimura A, Tashiro K and Shimizu S. Molecular cloning and expression of human hepatocyte growth factor. Nature 1989; 342: 440-443.

[3] Rubin JS, Bottaro DP and Aaronson SA. Hepatocyte growth factor/scatter factor and its receptor, the c-met proto-oncogene product. Biochim Biophys Acta 1993; 1155: 357-371.

[4] Zarnegar R and Michalopoulos GK. The many faces of hepatocyte growth factor: from hepatopoiesis to hematopoiesis. J Cell Biol 1995; 129: 1177-1180.

[5] Tashiro K, Hagiya M, Nishizawa T, Seki T, Shimonishi M, Shimizu S and Nakamura T. Deduced primary structure of rat hepatocyte growth factor and expression of the mRNA in rat tissues. Proc Natl Acad Sci U S A 1990; 87: 3200-3204.

[6] Rahimi N, Saulnier R, Nakamura T, Park M and Elliott B. Role of hepatocyte growth factor in breast cancer: a novel mitogenic factor secreted by adipocytes. DNA Cell Biol 1994; 13: 1189-1197.

[7] Eckel RH, Grundy SM and Zimmet PZ. The metabolic syndrome. Lancet 2005; 365: 1415-1428.

[8] Nishimura M, Ushiyama M, Nanbu A, Ohtsuka K and Yoshimura M. Vascular endothelium-re-
lated factors and atherosclerosis/arteriosclerosis: serum hepatocyte growth factor as a possible indicator of vascular lesions. Rinsho Byori 1998; 46: 671-677.

[9] Konya H, Miuchi M, Satani K, Matsutani S, Tsunoda T, Yano Y, Katsuno T, Hamaguchi T, Miyagawa J and Namba M. Hepatocyte growth factor, a biomarker of macroangiopathy in diabetes mellitus. World J Diabetes 2014; 5: 678-688.

[10] Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, Sarov-Blat L, O'Brien S, Keiper EA, Johnson AG, Martin J, Goldstein BJ and Shi Y. Human epicardial adipose tissue is a source of inflammatory mediators. Circulation 2003; 108: 2460-2466.

[11] Sacks HS and Fain JN. Human epicardial adipose tissue: a review. Am Heart J 2007; 153: 907-917.

[12] Vela D, Buja LM, Madjid M, Burke A, Naghavi M, Willerson JT, Casscells SW and Litovsky S. The role of periadventitial fat in atherosclerosis. Arch Pathol Lab Med 2007; 131: 481-487.

[13] Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, Di Mario U and Leonetti F. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003; 88: 5163-5168.

[14] Taguchi R, Takasu J, Itani Y, Yamamoto R, Yokoyama K, Watanabe S and Masuda Y. Pericardial fat accumulation in men as a risk factor for coronary artery disease. Atherosclerosis 2001; 157: 203-209.

[15] Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabadi AA, Vasan RS, O'Donnell CJ and Fox CS. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. Circulation 2008; 117: 605-613.

[16] Leber AW, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, Wintersperger B, Reiser M, Becker CR, Steinbeck G and Boekstegers P. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. J Am Coll Cardiol 2005; 46: 147-154.

[17] Fayad ZA, Fuster V, Nikolaou K and Becker C. Computed tomography and magnetic resonance imaging for noninvasive coronary angiography and plaque imaging: current and potential future concepts. Circulation 2002; 106: 2026-2034.

[18] Hu ZP, Wang BN, Qian HY, Zhou Q, Wei W and Wang Y. Fixed-dose telmisartan/hydrochloro-

thiazide in comparison with losartan/hydrochlorothiazide in decreasing serum hepatocyte growth factor and improving endothelial dysfunction in hypertensive patients. Int Heart J 2010; 51: 252-258.

[19] Morishita R, Moriguchi A, Higaki J and Ogihara T. Hepatocyte growth factor (HGF) as a potential index of severity of hypertension. Hypertens Res 1999; 22: 161-167.

[20] Tsukagawa E, Adachi H, Hirai Y, Enomoto M, Fukami A, Ogata K, Kasahara A, Yokoi K and Imaizumi T. Independent association of elevated serum hepatocyte growth factor levels with development of insulin resistance in a 10-year prospective study. Clin Endocrinol (Oxf) 2013; 79: 43-48.

[21] Hiratsuka A, Adachi H, Fujiura Y, Yamagishi S, Hirai Y, Enomoto M, Satoh A, Hino A, Furuki K and Imaizumi T. Strong association between serum hepatocyte growth factor and metabolic syndrome. J Clin Endocrinol Metab 2005; 90: 2927-2931.

[22] Morishita R, Aoki M, Yo Y and Ogihara T. Hepatocyte growth factor as cardiovascular hormone: role of HGF in the pathogenesis of cardiovascular disease. Endocr J 2002; 49: 273-284.

[23] Nishimura M, Ushiyama M, Nanbu A, Ohtsuka K, Takahashi H and Yoshimura M. Serum hepatocyte growth factor as a possible indicator of arteriosclerosis. J Hypertens 1997; 15: 1137-1142.

[24] Suzuki H, Murakami M, Kondo T, Shibata M, Ezumi H, Okabayashi H, Yorozuya M, Makishima N, Hamazaki Y, Nakatani M, Namiki A and Katagiri T. [Changes of serum hepatocyte growth factor in coronary artery disease]. J Cardiol 2000; 35: 319-324.

[25] Lenihan DJ, Osman A, Sriram V, Aitsebaomo J and Patterson C. Evidence for association of coronary sinus levels of hepatocyte growth factor and collateralization in human coronary disease. Am J Physiol Heart Circ Physiol 2003; 284: H1507-1512.

[26] Wang CP, Hsu HL, Hung WC, Yu TH, Chen YH, Chiu CA, Lu LF, Chung FM, Shin SJ and Lee YJ. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol (Oxf) 2009; 70: 876-882.

[27] Iacobellis G, Corradi D and Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med 2005; 2: 536-543.

[28] Gaborit B, Kober F, Jacquier A, Moro PJ, Cuisset T, Boullu S, Dadoun F, Alessi MC, Morange P, Clement K, Bernard M and Dutour A. Assessment of epicardial fat volume and myocardial triglyceride content in severely obese subjects: relationship to metabolic profile, cardiac function and visceral fat. Int J Obes (Lond) 2012; 36: 422-430.

[29] Konishi M, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Matsubara J, Matsuzawa Y, Sumida H, Nagayoshi Y, Nakaura T, Awai K, Yamashita Y, Jinnouchi H, Matsui K, Kimura K, Umemura S and Ogawa H. Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease. Atherosclerosis 2010; 209: 573-578.

[30] Aslanabadi N, Salehi R, Javadrashid A, Tarzamni M, Khodadad B, Enamzadeh E and Montazerghaem H. Epicardial and pericardial fat volume correlate with the severity of coronary artery stenosis. J Cardiovasc Thorac Res 2014; 6: 235-239.

[31] Nafakhi H, Al-Mosawi A, Al-Nafakh H and Tawfeeq N. Association of pericardial fat volume with coronary atherosclerotic disease assessed by CT angiography. Br J Radiol 2014; 87: 20130713.

[32] Djaberi R, Schuijf JD, van Werkhoven JM, Nucifora G, Jukema JW and Bax JJ. Relation of epicardial adipose tissue to coronary atherosclerosis. Am J Cardiol 2008; 102: 1602-1607.

[33] Tadros TM, Massaro JM, Rosito GA, Hoffmann U, Vasan RS, Larson MG, Keaney JF Jr, Lipinska I, Meigs JB, Kathiresan S, O'Donnell CJ, Fox CS and Benjamin EJ. Pericardial fat volume correlates with inflammatory markers: the Framingham Heart Study. Obesity (Silver Spring) 2010; 18: 1039-1045.

[34] Iacobellis G and Barbaro G. The double role of epicardial adipose tissue as pro- and anti-inflammatory organ. Horm Metab Res 2008; 40: 442-445.

[35] Iacobellis G, Leonetti F, Singh N, M Sharma A. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. Int J Cardiol 2007; 115: 272-3.

[36] Malavazos AE, Ermetici F, Coman C, Corsi MM, Morricone L and Ambrosi B. Influence of epicardial adipose tissue and adipocytokine levels on cardiac abnormalities in visceral obesity. Int J Cardiol 2007; 121: 132-134.

[37] Mizuno S and Nakamura T. Prevention of neutrophil extravasation by hepatocyte growth factor leads to attenuations of tubular apoptosis and renal dysfunction in mouse ischemic kidneys. Am J Pathol 2005; 166: 1895-1905.

[38] Kamimoto M, Mizuno S, Matsumoto K and Nakamura T. Hepatocyte growth factor prevents multiple organ injuries in endotoxemic mice through a heme oxygenase-1-dependent mechanism. Biochem Biophys Res Commun 2009; 380: 333-337.