—Original—

Factors Associated with High-sensitivity Cardiac Troponin T in Patients with Type 2 Diabetes Mellitus

Takashi Hitsumoto

Hitsumoto Medical Clinic

Background: The blood concentration of high-sensitivity cardiac troponin T (hs-cTnT) is an established, useful biomarker for evaluating the pathogenesis of heart failure and predicting cardiovascular events. The aim of this study was to evaluate factors that are potentially associated with elevated blood hs-cTnT in patients with type 2 diabetes mellitus.

Patients and Methods: Patients with type 2 diabetes mellitus (N=280, 111 men and 169 women; mean ± SD age: 71 ± 9 years) with no history of cardiovascular events were enrolled. Relationships between hs-cTnT level and various clinical parameters were examined.

Results: Hs-cTnT was detected in 244 (87.1%) patients. There were no significant relationships between hs-cTnT and fasting blood glucose levels or insulin resistance. hs-cTnT was significantly correlated with advanced glycation end-product levels at the skin ($r=0.23$, $p<0.001$), blood concentrations of brain natriuretic peptide ($r=0.23$, $p<0.001$), reactive oxygen metabolites as markers of oxidative stress ($r=0.28$, $p<0.001$), and the augmentation index at the radial artery as marker of arterial reflection ($r=0.31$, $p<0.001$). Furthermore, multiple regression analysis revealed that these factors were also selected as independent variables, with hs-cTnT as a subordinate factor.

Conclusion: These results indicate that novel cardiovascular risk factors including advanced glycation end-products, in vivo oxidative stress, and high arterial reflection are closely associated with high concentrations of blood hs-cTnT in patients with type 2 diabetes mellitus.

(J Nippon Med Sch 2015; 82: 274–280)

Key words: troponin, type 2 diabetes mellitus, advanced glycation end products, oxidative stress, augmentation index

Introduction

Type 2 diabetes mellitus is closely associated with lifestyle and is an important risk factor for cardiovascular disease worldwide. However, the importance of type 2 diabetes mellitus as a risk factor for cardiovascular disease is not always explained by high blood glucose levels alone. Other classical cardiovascular risk factors, such as hypertension, dyslipidemia, and smoking habits, also affect the progression of atherosclerosis or the occurrence of cardiovascular events[1,2]. The significance of novel risk factors for cardiovascular disease, such as insulin resistance, inflammation, oxidative stress, advanced glycation end products (AGEs), and arterial dysfunction, in type 2 diabetes mellitus have recently been noted[3–5].

The blood concentration of cardiac troponin T (cTnT), a component of the troponin complex, is used clinically as a diagnostic marker for acute coronary syndrome because cTnT is rapidly released from the myocardium into the bloodstream following myocardial damage[6]. Furthermore, several clinical and epidemiological studies have demonstrated that the blood concentration of cTnT, i.e., high-sensitivity cTnT (hs-cTnT), measured with a highly sensitive assay, represents a useful biomarker for evaluating the pathogenesis of heart failure or predicting cardiovascular events[7,8]. A close relationship between diabetes mellitus and hs-cTnT elevation has been reported in the general population[9]. However, factors that are important for elevating hs-cTnT in patients with type 2 diabetes

Correspondence to Takashi Hitsumoto, MD, Hitsumoto Medical Clinic, 2–7–7 Takezakicyo, Shimonoseki City, Yamaguchi 750–0025, Japan
E-mail: web@hitsumoto.info
Journal Website (http://www.nms.ac.jp/jnms/)

mellitus are little known. Therefore, the present study was performed to clarify specific patient factors, including novel risk factors for cardiovascular disease, that affect hs-cTnT elevation in patients with type 2 diabetes mellitus as related to primary cardiovascular events.

Materials and Methods

1. Study Population

This study was conducted at the Hitsumoto Medical Clinic in Shimonoseki City from April 2013 through March 2014. The study population comprised 280 outpatients with type 2 diabetes mellitus undergoing antidiabetic treatment. No patients had a history of cardiovascular events, such as ischemic heart disease, stroke, and perivascular disease. The patients were 111 (39.6%) men and 169 (60.4%) women with a mean ± SD age of 71 ± 9 years. All participants provided informed consent, and the study protocol was approved by the Local Ethics Committee of the Hitsumoto Medical Clinic.

2. Estimation of Cardiovascular Risk Factors

Cardiovascular risk factors evaluated included various clinical variables (such as markers of blood glucose levels and insulin resistance), classic coronary risk factors, kidney function, brain natriuretic peptide (BNP), inflammation, oxidative stress, arterial function, and hs-cTnT concentrations. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive agents. Dyslipidemia was defined as serum low-density lipoprotein cholesterol level ≥140 mg/dL, serum high-density lipoprotein cholesterol concentrations ≤40 mg/dL, triglyceride concentrations ≥150 mg/dL, or use of antidyslipidemic agents. The AGE levels were quantified with skin AGE levels, which were based on skin autofluorescence measured with a commercial instrument (AGE ReaderTM; DiagnOptics, Groningen, The Netherlands), as previously described[10,11]. Briefly, autofluorescence was defined as the average light intensity per nanometer in the range of 300 to 420 nm. Autofluorescence levels were expressed in arbitrary units (AUs). All patients were measured in a seated position at the volar side of the lower arm, 10 to 15 cm below the elbow hold. The validity and reliability of autofluorescence levels in a Japanese population measured with this method have been established[11].

Used as a marker of arterial function was the augmentation index (AIx) measured at the radial artery. The radial AIx was measured with an applanation tonometry-based device (HEM-9010AI; Omron Healthcare Co., Ltd., Kyoto, Japan) and the subject in a sitting position. This technique has been described in detail in previous studies[12]. Briefly, the tonometry sensor unit consists of a pressure sensor composed of an array of 40 microtransducer elements. When the unit is placed on a patient's wrist, 1 of the 40 sensor elements is automatically selected to obtain optimal radial pressure waveforms. The first and second systolic peaks are automatically detected and, consequently, the radial AIx is calculated. The validity and reliability of the radial AIx as measured with this method are well established, with several studies reporting a close linear correlation between the radial AIx and the central AIx[12]. In addition, right brachial blood pressure was automatically measured twice with the oscillometric method. The average of 2 readings was used to determine the systolic and diastolic blood pressures.

3. Blood Sampling

Blood samples were collected from the antecubital vein in the morning after the patient had fasted for 12 hours. Glucose and insulin concentrations were measured with the glucose oxidase method and an enzyme immunoassay, respectively. To measure insulin resistance, the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as follows[13]: HOMA-IR = fasting glucose concentration (mg/dL) × fasting insulin concentration (μg/mL)/405. Levels of hemoglobin A1c (HbA1c) were expressed as values with the National Glycohemoglobin Standardization Program. Total cholesterol and triglyceride concentrations were measured with standard enzymatic methods. Serum concentrations of high-density lipoprotein cholesterol were measured with selective inhibition. Serum concentrations of low-density lipoprotein cholesterol were calculated with the Friedewald equation[14]. The estimated glomerular filtration rate (eGFR) was calculated with the adjusted Modification of Diet in Renal Disease Study equation, which was proposed by the working group of the Japanese Chronic Kidney Disease Initiative[15]. The blood concentration of BNP was measured with a commercial kit (SHIONOSPOT Reader; Shionogi & Co., Ltd., Osaka, Japan). The concentration of high-sensitivity C-reactive protein (hs-CRP) was measured with high-sensitivity, latex-enhanced immunonephelometry. The derivatives of reactive oxygen metabolites (d-ROMs) test, which reflects blood hydroperoxide concentrations, was performed with a commercial kit (Diacron; Grosseto, Italy)[16]. The hs-cTnT concentration was also measured with a commercial kit (Roche Diagnostics, Basel, Switzerland)[17]. In the hs-cTnT assay, the lower limit of detection was 0.003 ng/mL.

Table 1 Patient characteristics

	Overall	hs-cTnT non-detection	hs-cTnT detection	p value
n (male/female)	280 (111/169)	36 (13/23)	244 (102/142)	0.521
Age (years)	71±9	69±6	72±9	0.048
Smoking n (%)	43 (15.4)	5 (13.9)	38 (15.6)	0.794
Body mass index (kg/m^2)	23.9±3.0	24.0±2.9	23.9±3.0	0.432
Hypertension (%)	246 (87.8)	27 (75.0)	219 (89.9)	0.017
Systolic BP (mm Hg)	141±18	137±16	142±18	0.057
Diastolic BP (mm Hg)	86±11	85±10	86±11	0.831
FBG (mg/dL)	138±16	137±15	138±16	0.636
IRI (μg/mL)	7.8±3.7	7.2±3.8	7.9±3.7	0.284
Log-HOMA-IR	0.4±0.2	0.3±0.3	0.4±0.2	0.169
HbA1c (%)	7.0±0.7	6.7±0.7	7.1±0.7	0.046
Skin autofluorescence (AU)	2.8±0.6	2.6±0.4	2.9±0.6	0.004
Dyslipidemia (%)	233 (83.2)	30 (83.3)	203 (83.2)	0.098
Total cholesterol (mg/dL)	220±38	224±43	220±38	0.620
LDL cholesterol (mg/dL)	139±36	140±41	139±35	0.879
Triglyceride (mg/dL)	147±61	139±67	148±60	0.427
HDL cholesterol (mg/dL)	53±15	56±24	52±13	0.119
Log-hs-CRP (mg/L)	–1.3±0.6	–1.3±0.6	–1.3±0.5	0.426
d-ROMs test (U. Carr)	364±97	321±71	371±98	0.004
Log-BNP (pg/mL)	1.7±0.4	1.4±0.3	1.7±0.4	<0.001
eGFR (mL/min/1.73 m^2)	57.6±21.3	65.9±22.9	56.3±20.8	0.012
r-AIx	86±12	81±9	87±12	0.003
Log-hs-cTnT (ng/mL)	–2.0±2.7	-	–2.0±2.7	-
Medication				
Insulin, n (%)	7 (2.5)	1 (2.8)	6 (2.5)	0.909
Statin, n (%)	94 (33.6)	15 (41.7)	79 (32.4)	0.272
RAS inhibitor, n (%)	136 (48.6)	14 (38.9)	122 (50.0)	0.215

Data are expressed mean±SD, hs-cTnT: high-sensitivity cardiac troponin T, BP: blood pressure, FBG: fasting blood glucose, IRI: immuno reactive insulin, HOMA-IR: homeostatic model assessment of insulin resistance, HbA1c: hemoglobin A1c, LDL: low-density lipoprotein, HDL: high-density lipoprotein, hs-CRP: high sensitivity C-reactive protein, d-ROMs: derivatives of reactive oxygen metabolites, BNP: brain natriuretic peptide, eGFR: estimated glomerular filtration rate, r-AIx: radial augmentation index RAS: renin-angiotensin system

4. Statistical Analysis

For all statistical analyses a commercially available statistical software program (StatView-J 5.0; HULINKS Inc., Tokyo, Japan) was used. Data are expressed as the mean ± SD. Between-group comparisons were performed with Student's *t*-test or the Mann-Whitney U-test, and the correlation coefficient was estimated with the Spearman rank-order correlation analysis. To clarify which, if any, independent factors contributed to hs-cTnT elevation, we performed a multiple regression analysis with hs-cTnT as a subordinate factor. A p-value of <0.05 was considered to be statistically significant.

Results

The hs-cTnT was detected in 244 (87.1%) patients (**Table 1**). Age, HbA1c, skin autofluorescence, d-ROMs test, BNP, and radial AIx were significantly higher and eGFR was significantly lower in patients in whom hs-cTnT was detected than in patients in whom it was not. However, neither fasting blood glucose levels nor HOMA-IR differed significantly between patients with or without detectable hs-cTnT. Correlations between hs-cTnT and various clinical parameters in the hs-cTnT detection cohort are presented in.

Age, HbA1c, skin autofluorescence, hs-CRP concentrations, d-ROMs test, BNP, eGFR, and radial AIx were all significantly correlated with hs-cTnT, but fasting blood glucose levels and HOMA-IR were not significantly correlated with hs-cTnT (**Table 2**).

Multiple regression analysis was performed with explanatory variables with p<0.10 in univariate analysis. From the analysis, radial AIx, skin autofluorescence, d-

Table 2 Correlation between hs-cTnT and clinical parameters in hs-cTnT detectable patients

	r	p value
Sex (female=0, male=1)	0.01	0.947
Age	0.13	0.045
Smoking (no=0, yes=1)	0.08	0.198
Body mass index	–0.11	0.053
Hypertension (no=0, yes=1)	0.05	0.455
Systolic BP	0.10	0.059
Diastolic BP	0.11	0.051
FBG	0.10	0.062
IRI	0.10	0.071
Log-HOMA-IR	0.09	0.107
HbA1c	0.12	0.049
Skin autofluorescence	0.23	<0.001
Dyslipidemia (no=0, yes=1)	0.09	0.173
Total cholesterol	0.08	0.240
LDL cholesterol	0.06	0.359
Triglyceride	–0.02	0.722
HDL cholesterol	0.08	0.219
Log-hsCRP	0.18	0.004
d-ROMs test	0.28	<0.001
Log-BNP	0.23	<0.001
eGFR	–0.17	0.008
r-AIx	0.31	<0.001
Insulin (no=0, yes=1)	0.02	0.744
Statin (no=0, yes=1)	0.02	0.789
RAS inhibitor (no=0, yes=1)	0.03	0.666

(n=244)
Abbreviation as in Table 1

Table 3 Multiple regression analysis for the association between hs-cTnT and clinical parameters

	Correlation coefficient	p value
Explanatory factor		
r-AIx	0.23	0.002
Skin autofluorescence	0.17	0.005
d-ROMs test	0.14	0.040
Log-BNP	0.13	0.047
Log-hs-CRP	0.11	0.105
Age	0.08	0.287
Systolic BP	0.08	0.311
Diastolic BP	0.05	0.474
Body mass index	–0.04	0.607
eGFR	–0.04	0.612
FBG	0.03	0.658
IRI	0.03	0.661
HbA1c	0.03	0.685

R^2=0.22, F value=12.9, p<0.001
Abbreviation as in Table 1

ROMs test, and BNP were selected as independent variables when hs-cTnT was a subordinate factor (**Table 3**).

Discussion

Otsuka et al.[18] reported that the prevalence of detectable elevation of hs-cTnT in a healthy population was 80.9% at a cut-off level of 0.002 ng/mL and 67.7% at a cut-off level of 0.003 ng/mL. The results of this study indicated that up to 87.1% of the population was detected with an elevation of hs-cTnT at a cut-off level of 0.003 ng/mL. Although the mean age of the population in the present study was higher than that in the study by Otsuka et al., the results of this study indicated that hs-cTnT were highly detected in persons with type 2 diabetes mellitus, suggesting that the myocardial damage of type 2 diabetes mellitus was progressive in the subclinical stage of cardiovascular disease. Otsuka et al. also concluded that age, blood pressure, eGFR, and left ventricular hypertension were independent determinations of hs-cTnT level in multivariate analysis. Moreover, this study also indicates that age and eGFR had significant relations with hs-cTnT in single regression analysis, although blood pressure levels showed no significant relations with hs-cTnT. However, the abovementioned factors were not selected as independent variables for hs-cTnT by multivariate analysis. Discrepancy between the results of the studies by Otsuka et al. and those of the present study may be partly explained by differences between the healthy population and the patients having type 2 diabetes mellitus or those under the influence of medication. From the results of this study, we can interpret that in patients with type 2 diabetes mellitus, novel risk factors including skin autofluorescence, d-ROMs test, and AIx are more important factors for hs-cTnT elevation than age, blood pressure levels, and kidney function.

In basic studies, high blood glucose concentrations have been reported to cause myocardial damage via dysfunction of the microcirculation, increased oxidative stress, or other pathways[19,20]. In clinical studies, furthermore, relationships among markers of blood glucose concentrations and cTnT blood concentrations have been reported[21,22]. Zheng et al.[21] reported that fasting blood glucose level was an independent predictor of blood hs-cTnT in an overt cardiovascular disease-free community-based study. Selvin et al.[22] also reported a significant relationship between hs-cTnT elevation and HbA1c levels. In the present study, however, fasting blood glucose levels showed no statistically significant relationship with hs-

cTnT. The HbA1c levels also showed no significant relationships with hs-cTnT by multivariate analysis, even though the result from single regression analysis was significant. On the other hand, skin autofluorescence level as a marker of AGE in vivo was an independent factor related to hs-cTnT elevation as a subordinate factor. Basic studies report several pathways by which AGE could influence diabetic cardiomyopathy or cardiac remodeling[23,24], and results of the present study also indicated the importance of AGE to clinical myocardial damage. Yamagishi et al. reported that AGE is a marker that is compatible with the theory of "hyperglycemic memory"[25]. Therefore, we should be intervening at an early stage of blood glucose elevation and adequately controlling blood glucose levels over the long term to prevent the progression of myocardial damage in patients with type 2 diabetes mellitus. Insulin resistance has been considered to have an important role in the pathogenesis of type 2 diabetes mellitus. Furthermore, some clinical studies have reported a correlation between insulin resistance and myocardial damage[26,27]. In the present study, however, HOMA-IR as a marker of insulin resistance was not significantly correlated with hs-cTnT. The HOMA-IR has limitations as a marker of insulin resistance, especially in patients with high blood glucose levels[28]. This study included a substantial number of patients with a high fasting blood glucose level. Therefore, additional studies using another accurate insulin resistance marker, such as a glucose clamp test, are warranted to evaluate putative relationships between insulin resistance and hs-cTnT in patients with type 2 diabetes mellitus.

Oxidative stress is closely associated with the progression of heart failure. Several pathways have been identified by which oxidative stress leads to myocardial damage, including dysfunction of the mitochondrial electron transport complex, activity of nicotinamide adenine dinucleotide phosphate oxidase, and apoptosis of myocardial cells[29,30]. Furthermore, this study revealed the importance of oxidative stress in the myocardial damage that occurs with type 2 diabetes mellitus and subclinical heart failure. Among a number of markers of oxidative stress, the d-ROMs test is considered to be clinically useful for evaluating oxidative stress in vivo, because the measurement of serum hydroperoxide concentrations is accurate, simple, and can be performed rapidly[16,31]. Recent clinical studies have reported a relationship between d-ROMs test results and atherosclerosis or atherosclerotic risk factors in patients with type 2 diabetes mellitus[32,33]. Furthermore, the results of this study indicated that the d-ROMs test results are expected to predict not only atherosclerosis, but also the degree of subclinical myocardial damage in patients with type 2 diabetes mellitus.

The AIx communicates arterial wave reflection[12], and some clinical studies have reported that AIx is elevated with an increase in arterial wall stiffness[34]. In recent years, several studies have indicated the importance of left ventricular dysfunction in heart failure or the progression of myocardial damage; furthermore, increases in aortic artery stiffness are known to cause left ventricular dysfunction[35]. Therefore, the relationship between hs-cTnT and radial AIx identified in this study was considered to reflect myocardial damage via left ventricular dysfunction resulting from an increase in vascular resistance or afterload. Endothelial dysfunction is one of the crucial factors in the development of heart failure, and some clinical studies have reported that AIx is indicative of endothelial dysfunction[36,37]. Endothelial dysfunction has also been known to cause left ventricular dysfunction or myocardial damage[38,39]; therefore, the significant correlation of hs-cTnT with radial AIx in patients with type 2 diabetes mellitus may be partly explained by the presence of endothelial dysfunction.

This study had several limitations. First, ultrasonic echocardiography, coronary angiography, and multidetector computed tomography angiography were not performed; therefore, cardiovascular diseases, such as heart failure or coronary artery disease, may have remained undetected in the study patients. Second, the medical treatments for diabetes mellitus, hypertension, and/or dyslipidemia may have influenced the study results. Third, further studies using radioimmunoassay, magnetic resonance imaging, Doppler echocardiography, or other medical devices are required to clarify the relationship between hs-cTnT elevation and degree of subclinical myocardial damage or left ventricular dysfunction. Fourth, this study was cross-sectional in a single unit and the sample size was relatively small. Additional prospective studies, including evaluations of interventional therapy, are required to clarify the clinical significance of hs-cTnT, AGE, d-ROMs test, and AIx in patients with type 2 diabetes mellitus.

In conclusion, the study findings indicate that novel cardiovascular risk factors including AGE, in vivo oxidative stress, and high arterial reflection are closely associated with high concentrations of blood hs-cTnT in patients with type 2 diabetes mellitus.

Acknowledgement: The author thanks Dr. Kohji Shirai for his

important contributions.

Conflict of Interest: The author has no conflicts of interest to declare.

References

1. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383–393.
2. Kamimura M, Moroi M, Isobe M, Hiroe M: Role of coronary CT angiography in asymptomatic patients with type 2 diabetes mellitus. Int Heart J 2012; 53: 23–28.
3. Shinozaki K, Kashiwagi A, Nishio Y, Okamura T, Yoshida Y, Masada M, Toda N, Kikkawa R: Abnormal biopterin metabolism is a major cause of impaired endothelium-dependent relaxation through nitric oxide/O2-imbalance in insulin-resistant rat aorta. Diabetes 1999; 48: 2437–2445.
4. Lutgers HL, Graaff R, Links TP, Ubink-Veltmaat LJ, Bilo HJ, Gans RO, Smit AJ: Skin autofluorescence as a noninvasive marker of vascular damage in patients with type 2 diabetes. Diabetes Care 2006; 29: 2654–2659.
5. Kulkarni NB, Ganu MU, Godbole SG, Deo SS: Effect of age and Blood Pressure on Surrogate Markers of Atherosclerosis in Patients with Type 2 Diabetes Mellitus. J Clin Diagn Res 2014; 8: BC08–11.
6. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C: Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Eng J Med 2009; 361: 858–867.
7. Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, Angelici L, Barlera S, Parrinello G, Maggioni AP, Tognoni G, Cohn JN; Val-HeFT Investigators: Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007; 116: 1242–1249.
8. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM: Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011; 123: 1367–1376.
9. Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, Wians F, Sabatine MS, Morrow DA, de Lemos JA: Prevalence and determinants of troponin T elevation in the general population. Circulation 2006; 113: 1958–1965.
10. Meerwaldt R, Hartog JW, Graaff R, Huisman RJ, Links TP, den Hollander NC, Thorpe SR, Baynes JW, Navis G, Gans RO, Smit AJ: Increased accumulation of skin advanced glycation end products precedes and correlates with clinical manifestation of diabetic neuropathy. J Am Soc Nephrol 2005; 16: 3687–3693.
11. Nomoto K, Yagi M, Arita S, Hamada U, Yonei Y: A survey of fluorescence derived from advanced glycation end products in the skin of Japanese: differences with age and measurement location. Anti-Aging Medicine 2012; 9: 119–124.
12. Takazawa K, Kobayashi H, Shindo N, Tanaka N, Yamashina A: Relationship between radial and central arterial pulse wave and evaluation of central aortic pressure using the radial arterial pulse wave. Hypertens Res 2007; 30: 219–228.
13. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412–419.
14. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499–502.
15. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S: Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 2007; 11: 41–50.
16. Cesarone MR, Belcaro G, Carratelli M, Cornelli U, De Sanctis MT, Incandela L, Barsotti A, Terranova R, Nicolaides A: A simple test to monitor oxidative stress. Int Angiol 1999; 18: 127–130.
17. Mingels A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, van Dieijen-Visser M: Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. Clin Chem 2009; 55: 101–108.
18. Otsuka T, Kawada T, Ibuki C, Seino Y: Association between high-sensitivity cardiac troponin T levels and the predicted cardiovascular risk in middle-aged men without overt cardiovascular disease. Am Heart J 2010; 159: 972–978.
19. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. Nature 2001; 414: 813–820.
20. Cai L, Wang Y, Zhou G, Chen T, Song Y, Li X, Kang YJ: Attenuation by metallothionein of early cardiac cell death via suppression of mitochondrial oxidative stress results in a prevention of diabetic cardiomyopathy. J Am Coll Cardiol 2006; 48: 1688–1697.
21. Zheng J, Ye P, Luo L, Xiao W, Xu R, Wu H: Association between blood glucose levels and high-sensitivity cardiac troponin T in an overt cardiovascular disease-free community-based study. Diabetes Res Clin Pract 2012; 97: 139–145.
22. Selvin E, Lazo M, Chen Y, Shen L, Rubin J, McEvoy JW, Hoogeveen RC, Sharrett AR, Ballantyne CM, Coresh J: Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. Circulation 2014; 130: 1374–1382.
23. Umadevi S, Gopi V, Elangovan V: Regulatory mechanism of gallic acid against advanced glycation end products induced cardiac remodeling in experimental rats. Chem Biol Interact 2014; 208: 28–36.
24. Bodiga VL, Eda SR, Bodiga S: Advanced glycation end products: role in pathology of diabetic cardiomyopathy. Heart Fail Rev 2014; 19: 49–63.
25. Yamagishi S, Nakamura K, Imaizumi T: Advanced glycation end products (AGEs) and diabetic vascular complications. Curr Diabetes Rev 2005; 1: 93–106.
26. Narumi T, Shishido T, Kiribayashi N, Kadowaki S, Nishiyama S, Takahashi H, Arimoto T, Miyashita T, Miyamoto T, Watanabe T, Shibata Y, Konta T, Ueno Y, Kato T, Kayama T, Kubota I: Impact of insulin resistance on silent and ongoing myocardial damage in normal subjects: the Takahata study. Exp Diabetes Res 2012; 2012: 815098.
27. Uetani T, Amano T, Harada K, Kitagawa K, Kunimura A, Shimbo Y, Harada K, Yoshida T, Kato B, Kato M, Marui

N, Nanki M, Hotta N, Ishii H, Matsubara T, Murohara T: Impact of insulin resistance on post-procedural myocardial injury and clinical outcomes in patients who underwent elective coronary interventions with drug-eluting stents. JACC Cardiovasc Interv 2012; 5: 1159–1167.
28. Kang ES, Yun YS, Park SW, Kim HJ, Ahn CW, Song YD, Cha BS, Lim SK, Kim KR, Lee HC: Limitation of the validity of the homeostasis model assessment as an index of insulin resistance in Korea. Metabolism 2005; 54: 206–211.
29. Li SY, Yang X, Ceylan-Isik AF, Du M, Sreejayan N, Ren J: Cardiac contractile dysfunction in *Lep/Lep* obesity is accompanied by NADPH oxidase activation, oxidative modification of sarco(endo)plasmic reticulum Ca^{2+}-ATPase and myosin heavy chain isozyme switch. Diabetologia 2006; 49: 1434–1446.
30. Boudina S, Abel ED: Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord 2010; 11: 31–39.
31. Fukui T, Yamauchi K, Maruyama M, Yasuda T, Kohno M, Abe Y: Significance of measuring oxidative stress in lifestyle-related diseases from the viewpoint of correlation between d-ROMs and BAP in Japanese subjects. Hypertens Res 2011; 34: 1041–1045.
32. Kotani K, Tsuzaki K, Taniguchi N, Sakane N: Correlation between reactive oxygen metabolites & atherosclerotic risk factors in patients with type 2 diabetes mellitus. Indian J Med Res 2013; 137: 742–748.
33. Watanabe K, Ohara M, Suzuki T, Ouchi M, Suzuki K, Hashimoto M, Saigusa T, Aoyama J, Nakano H, Oba K: Aortic arch calcification detectable on chest X-ray films is associated with plasma diacron-reactive oxygen metabolites in patients with type 2 diabetes but without cardiovascular disease. J Nippon Med Sch 2013; 80: 410–419.
34. Oliver JJ, Webb DJ: Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler Thrombs Vasc Biol 2003; 23: 554–566.
35. Jaroch J, Łoboz Grudzień K, Bociąga Z, Kowalska A, Kruszyńska E, Wilczyńska M, Dudek K: The relationship of carotid arterial stiffness to left ventricular diastolic dysfunction in untreated hypertension. Kardiol Pol 2012; 70: 223–231.
36. Soga J, Nakamura S, Nishioka K, Umemura T, Jitsuiki D, Hidaka T, Teragawa H, Takemoto H, Goto C, Yoshizumi M, Chayama K, Higashi Y: Relationship between augmentation index and flow-mediated vasodilation in the brachial artery. Hypertens Res 2008; 31: 1293–1298.
37. Hitsumoto T: Clinical significance of the augmentation index in patients with preserved kidney function. J Nippon Med Sch 2012; 79: 422–429.
38. Zizek B, Poredos P: Increased left ventricular mass and diastolic dysfunction are associated with endothelial dysfunction in normotensive offspring of subjects with essential hypertension. Blood Press 2007; 16: 36–44.
39. Martí V, Aymat R, Ballester M, García J, Carrió I, Augé JM: Coronary endothelial dysfunction and myocardial cell damage in chronic stable idiopathic dilated cardiomyopathy. Int J Cardiol 2002; 82: 237–245.

(Received, July 7, 2015)
(Accepted, October 29, 2015)