学　位　論　文

Association of high-sensitivity cardiac troponin, fibroblast growth factor 23 and left ventricular hypertrophy in Japanese patients with reduced renal function

（腎機能低下を有する日本人患者における高感度心筋トロポニン，線維芽細胞増殖因子 23，および左室肥大の関連）

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〔**Original**〕

Association of high-sensitivity cardiac troponin, fibroblast growth factor 23 and left ventricular hypertrophy in Japanese patients with reduced renal function

Running title: Cardiac troponin in renal dysfunction

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21 pages, 6 Tables, 1 Figure

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Chronic kidney disease is associated with elevation of high-sensitivity cardiac troponin I and T (hs-cTnI and hs-cTnT) and left ventricular hypertrophy (LVH). Elevation of fibroblast growth factor 23 (FGF23) at early stage of renal dysfunction is considered to be involved in LVH. Thus, the relationships among hs-cTnI, hs-cTnT, FGF23 and representative echocardiographic index of LVH were investigated. Serum hs-cTnI and hs-cTnT concentrations were measured in 212 patients with various renal functions. The positive occurrence frequency of hs-cTnI and hs-cTnT was compared and correlation of hs-cTnI, hs-cTnT and FGF23 was examined in relation to estimated glomerular filtration rate (eGFR, ml/min/1.73 m^2) categories (G1 $\geq$ 90, G2 60-89, G3a 45-59, G3b 30-44, G4 15-29, and G5 under 15). Association of hs-cTnI, hs-cTnT and FGF23 with representative echocardiographic index was examined. Hs-cTnI and hs-cTnT were involved in renal dysfunction and positive rates significantly differed in G3a, G3b, G4 and G5 (hs-cTnT > hs-cTnI). FGF23 was associated with both hs-cTnI and hs-cTnT. In multiple regression analysis FGF23 remained as a regulating factor for hs-cTnI and hs-cTnT. Left ventricular mass index (LVMI) correlated with hs-cTnI, hs-cTnT and FGF23. When adjusted with LVMI, correlation coefficients of hs-cTnI, hs-cTnT and FGF23 declined. Hs-cTnI was less affected

by renal dysfunction than hs-cTnT. Hs-cTnI and hs-cTnT were associated with FGF23 and LVH may be in part involved in these associations.

Key words: eGFR, Fibroblast growth factor 23, High-sensitivity cardiac troponin, Left ventricular hypertrophy

Introduction

Troponin has a trimeric structure of troponin I, C and T and regulates muscle contraction in myocyte and skeletal muscle [1]. Among them cardiac troponin I (cTnI) and T (cTnT) have clinical significance. Because cTnI and cTnT have different amino acid sequences from troponin in skeletal muscle [1], one can specifically detect cardiac troponin by immunoassay. High-sensitivity cTnI (hs-cTnI) and cTnT (hs-cTnT) are useful for diagnosing acute myocardial infarction (AMI) [2], especially non-ST elevation myocardial infarction within 2 hours from the onset [3]. However, the concentration of cardiac troponin, cTnT in particular, is persistently and modestly elevated in patients with renal dysfunction [4-6]. Therefore, at the time of diagnosing AMI in patients with renal dysfunction, one may overestimate the values of high-sensitivity cardiac troponins (hs-cTns). Thus, effects of renal function on hs-cTns were evaluated in relation to estimated glomerular filtration rate (eGFR).

In patients with renal dysfunction elevation of hs-cTns and left ventricular hypertrophy (LVH) often co-exist and high values of hs-cTns and LVH predict poor prognosis. Fibroblast growth factor 23 (FGF23) is the phosphorus regulating hormone. It is secreted from bone cells and acts on the proximal renal tubule. FGF23 suppresses renal reabsorption of phosphate and the absorption of phosphate in the intestinal tract [7],

suggesting that FGF23 may contribute to decreased serum phosphate concentration. The concentration of FGF23 is elevated from early stages of chronic kidney disease and may directly induce LVH, which is different from the original phosphorus regulating effect [8]. The precise relationships among hs-cTns and FGF23 have not been fully evaluated in Japanese patients with various renal function. In the present study, the relationships among hs-cTns, FGF23 and representative echocardiographic indexes of LVH were studied.

Methods

Study subjects

Serum samples (n=212) submitted to the medical laboratory of Asahikawa Medical University Hospital were utilized. Samples were obtained from heart disease patients with consistently positive urinary protein over past 3 months or with stable particular eGFR stage over past 3 months. Patients had no history of overt acute coronary syndrome in the past 3 years. Heart diseases included a history of AMI, angina pectoris, heart failure, atrial fibrillation, tachyarrhythmia, II degree atrioventricular block, cardiomyopathy (obstructive hypertrophic cardiomyopathy 1.4%, drug-induced cardiomyopathy 0.5%), aortic stenosis, aortic regurgitation, hypertensive heart disease, atrial thrombosis, atrial septal defect, and cardiac sarcoidosis. The prevalence of hypertension was 63.2%. The study protocol was approved by the institutional ethical committee (permission number 14CL002). All the participants gave informed consent to the secondary use of the samples.

Sample processing and measurement

Whole blood was collected into blood collection tube with serum separating agent and were centrifuged for 10 minutes at 1,180 x g. The serum was immediately collected into

sample tubes and stored at –80℃. ARCHITECT® ・high sensitive Troponin I *ST* (Abbott Laboratories, IL, USA) and Elecsys® reagent Troponin T hs STAT (Roche Diagnostics GmbH, Mannheim, Germany) were used for measurement of hs-cTnI and hs-cTnT, respectively. After dispensing the serum into the sample tube, the concentrations of hs-cTnI and hs-cTnT were measured with ARCHITECT i2000 SR (Abbott) and cobas 6000 (Roche), respectively. The minimum detection limits of hs-cTnI and hs-cTnT were 5 ng/L and 3 ng/L, respectively. These values were adopted when the measured values were below these values. The cut off values of hs-cTnI and hs-cTnT are 26.2 ng/L and 14 ng/L, respectively. FGF23 was measured using FGF23 ELISA kit (Kainos Laboratories, Inc., Tokyo, Japan), according to the manufacturer's instructions. The absorbance of FGF23 at 450 nm was measured using BEP III (Siemens Healthcare Diagnostics, Marburg, Germany). The FGF23 concentration was measured in duplicate

Echocardiography

The cardiac ultrasound examination was performed in 61 among 212 patients and echocardiographic index was calculated. Indexes included left atrial volume index (LAVI), interventricular septum thickness (IVST), posterior LV wall thickness (PWT), left ventricular end-diastolic dimension (LVDd), left ventricular mass index (LVMI),

early mitral inflow velocity (E), atrial filling velocity (A), the ratio between E and A (E/A), E wave deceleration time (DcT), average mitral annular early diastolic velocity of the ventricular septal and lateral walls (e'), the ratio between E and e' (E/e'), and ejection fraction (EF). Measurement of LVMI was performed using Devereux formula [9].

Statistical analysis

Samples from 212 patients were divided into 6 categories based on eGFR (mL/min/1.73m^2; eGFR= 194xCreatinin$^{-1.094}$xAge$^{-0.287}$ in male and eGFR= 194xCreatinin$^{-1.094}$xAge$^{-0.287}$x0.739 in female)[10]. Specifically, eGFR categories are as follows, G1 ≥ 90, G2 60-89, G3a 45-59, G3b 30-44, G4 15-29, and G5 under 15. Values of hs-cTns exceeding the cut off value were regarded as positive. Positive appearance frequencies of hs-cTns were calculated for each eGFR category and compared. Distribution widths of measured values of hs-cTns and FGF23 at each eGFR category were calculated. Scatter plots of hs-cTnI and FGF23, hs-cTnT and FGF23 were drawn. Because the data of hs-cTns and FGF23 were not normally distributed, the data were converted to natural logarithm. Multiple regression analysis was performed using hs-cTns as dependent variable, and gender, age, eGFR, history of heart diseases, blood

hemoglobin concentration (g/dL), serum calcium concentration (mg/dL), serum phosphate concentration (mg/dL) and FGF23 concentration (pg/mL) as independent variables. Pearson's correlation coefficient between hs-cTns and FGF23 and each echocardiographic index was calculated. In addition, the partial correlation coefficient between hs-cTns and FGF23 was calculated after adjusting as a correction variable for a specific cardiac ultrasound examination index. Correlation coefficient calculation, McNemar's test, multiple comparisons after the Kruskal Wallis test and multiple regression analysis were used for statistical analysis. Statistical analysis was carried out using statistical analysis software SPSS Statistics ver.22 (IBM Corp., NY, USA).

Results

Clinical characteristics of study subjects and correlations among evaluated variables

Table 1 shows clinical characteristics of patients. Gender, age, Cys-C and NT-proBNP positively correlated with hs-cTns. The correlation between NT-proBNP and hs-cTnI was observed in G2, G3b, and G5. The correlation coefficients were 0.455 (p = 0.004), 0.549 (p = 0.001) and 0.625 (p = 0.002), respectively. The correlation between NT-proBNP and hs-cTnT was observed in G1, G2, G3a, G3b and G5. Correlation coefficients were 0.401 (p = 0.017), 0.401 (p = 0.011), 0.308 (p = 0.035), 0.430 (p = 0.008) and 0.639 (p <0.001), respectively. eGFR, hemoglobin and calcium negatively correlated with hs-cTns. Phosphate showed no correlation with hs-cTns. Cys-C, phosphate and NT-proBNP positively correlated with FGF23. eGFR and hemoglobin negatively correlated with FGF23.

Values of hs-cTns and FGF23 for each eGFR category

Positive rate and concordance rate of hs-cTns are summarized in Table 2. The positive rate of hs-cTns significantly differed at G3a-G5. Median values, first quartile and third quartile of hs-cTns and FGF23 for each eGFR category are shown in Figure 1 (a), (b), and (c), respectively. Hs-cTns and FGF23 were increased with eGFR reduction. Table 3

shows all P values when multiple comparisons were performed for each eGFR category for hs-cTns and FGF23. Hs-cTnT and FGF23 exhibited highly variable values among different eGFR categories. Scatter plots and approximated curve of hs-cTns and FGF23 in all patients are shown in Figure 1 (d) and (e). The Pearson's correlation coefficients between FGF23 and hs-cTnI, and between FGF23 and hs-cTnT were 0.354 (p= 0.005) and 0.655 (p< 0.001), respectively and both showed positive correlation.

Multiple regression analysis of hs-cTns and FGF23

Using gender (male), age, eGFR, history of heart disease, hemoglobin, calcium, phosphate and FGF23 as an independent variable, regulatory factors of hs-cTns were defined (Table 4). Gender and history of heart diseases were defined as factors regulating hs-cTnI. Hemoglobin, eGFR and calcium were defined as factors regulating hs-cTnT. Age and FGF23 were defined as factors regulating both hs-cTnI and hs-cTnT. Using FGF23 as dependent variable, and eGFR, hemoglobin, phosphate and hs-cTns as independent variable, eGFR, phosphate, hs-cTns were defined as regulatory factors of FGF23.

Correlations of hs-cTns and FGF23 with echocardiographic indexes

Correlation of hs-cTns and FGF23 and representative echocardiographic index were evaluated (Table 5). The indicators correlated with hs-cTns were IVST, PWT, e’ and E/e'. The indicators correlated with hs-cTnT were A and E/A. On the other hand, LVMI correlated with hs-cTns and FGF23. In addition, the partial correlation coefficient between hs-cTns and FGF23 when adjusted with each echocardiographic index was calculated (Table 6). When adjusted by LVMI, partial correlation coefficient between hs-cTnI and FGF23 and between hs-cTnT and FGF23 were decreased.

Discussion

In this study hs-cTns correlated with age, male gender, heart disease history, NT-proBNP, eGFR, Cys-C, hemoglobin and calcium. Hemoglobin and calcium are affected by renal function, suggesting that hs-cTns are increased with renal dysfunction. With multiple regression analysis eGFR, hemoglobin and calcium remained with hs-cTnT but not with hs-cTnI, suggesting that hs-cTnT is more likely to be affected by renal function in comparison to hs-cTnI. The molecular weight of hs-cTnI (24kDa) is smaller than that of hs-cTnT (37kDa)[11]. Thus, hs-cTnT is more likely to be affected by decreased renal clearance. Hs-cTnT positive rate increased with reduction of eGFR. With G3a, G3b, G4, G5 categories positive rate of hs-cTnT was significantly higher than that of hs-cTnI. Positive rate of hs-cTnI exceeded 10% only in G5. Therefore, in emergency department hs-cTnI would make a meaningful measurement in comparison to hs-cTnT. One needs caution when using hs-cTnT in patients with eGFR categories G3a-G5 and serum creatinine concentrations are always taken into consideration. In diagnosing non-ST elevation myocardial infarction cut-off values of hs-cTns need to be elevated with renal impairment. In patients with eGFR<60 hs-cTnT cut-off values of 35.8 ng/L increased sensitivity and specificity [12]. Conversely, hs-cTnT may be more sensitive than hs-cTnI in reflecting small myocardial damage. In addition, several

studies have investigated the utility of hs-cTns in renal dysfunction. Hs-cTnT is indeed a predictor of cardiovascular events in dialysis patients [13]. In renal dysfunction and chronic heart failure hs-cTn is previously reported to predict prognosis [14].

On dialysis high values of FGF23 were correlated with mortality even after correction with serum phosphate [15]. Furthermore, correlation of FGF23 with cardiovascular adverse events is reported in general population [16]. However, there are only a few studies that evaluated the relationships among hs-cTns and FGF23 in renal dysfunction. In this study FGF23 concentrations were increased with renal dysfunction and correlated with hs-cTns. With multiple regression analysis hs-cTns correlated with FGF23. eGFR, phosphate and hs-cTns were defining factors of FGF23. LVMI was correlated with hs-cTns and FGF23. On adjustment with LVMI correlations of FGF23 with hs-cTns attenuated, suggesting that at least in part the relationship between hs-cTns and FGF-23 may be mediated by LVH.

The exact mechanism responsible for the relationship between hs-cTns and FGF23 remains speculative. In chronic kidney disease animal model anti-FGF23 antibody did not affect expression of genes related to myocardial hypertrophy [17]. Thus, it is likely that high values of FGF23 and myocardial damage are provoked by common factors. Inflammation and oxidative stress induce FGF23 production [18], [19]. Inflammation

and oxidative stress may cause both FGF23 increase and cardiovascular adverse events. These potential mechanisms may be enhanced in renal dysfunction. Our results validate a previous study, in which hs-cTns associated with FGF-23 [20] and showed that hs-cTnI was less affected by renal dysfunction than hs-cTnT. Further studies will clarify if routinely measuring hs-cTns and FGF-23 in patients with reduced renal function may help identify high risk subjects for cardiovascular diseases and if reducing FGF-23 may ameliorate myocardial damage in these patients.

This study has certain limitations. The ultrasound study was performed in 61 among 212 patients. The correlation with hs-cTns and FGF23 for LVMI needs further investigation because gender difference in LVMI was not taken into consideration.

In conclusion, this study is the first report that highlighted the precise relationship among hs-cTns and FGF23 in Japanese patients with various renal function. Hs-cTnI was less affected by renal dysfunction than hs-cTnT. One must pay attention to creatinine concentration in evaluating troponin concentrations in renal dysfunction. Hs-cTns are related to FGF23 and LVH may be involved in these associations.

Acknowledgements

The secretarial assistance of Ms. Noriko Saito is greatly appreciated.

Conflict of Interest

None declared.

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Table 1. Characteristics of Patients and Correlation Between all Variables, hs-cTns and FGF23

The number of patients, median values, Spearman's correlation coefficient and P value of all variables, hs-cTns and FGF23 are shown.

Table 2. The Positive Rate and Concordance Rate of hs-cTns for Each eGFR Category

The corresponding numbers for each eGFR category in 212 cases, the positive rate (%) of hs-cTns in each eGFR category, and concordance rate (%) of hs-cTns are shown. The difference in the positive rate of hs-cTns at each eGFR category was verified using McNemar 's test. * $P < 0.001$.

Table 3. The P Values of Multiple Comparison Test Between Each eGFR Category of hs-cTns and FGF23

The difference in measured values between eGFR categories was verified by multiple comparison test. The P values between each category of hs-cTns and FGF 23 are shown.

Table 4. Multiple Regression Analysis in hs-cTns and FGF23

Multiple regression analysis was performed using hs-cTns as dependent variables, and

gender, age, eGFR, history of heart disease, hemoglobin, calcium, phosphate and FGF23 as independent variables. β means normalized partial regression coefficient.

Table 5. Correlation of hs-cTns and FGF23 With Echocardiographic Index

Pearson's correlation coefficient between indices for cardiac ultrasound examination, hs-cTns and FGF23 was calculated. LAVI, left atrial volume index; IVST, interventricular septum thickness; PWT, posterior LV wall thickness; LVDd, left ventricular end-diastolic dimension; LVMI, left ventricular mass index; E, early mitral inflow velocity; A, atrial filling velocity; E/A, the ratio between E and A; DcT, E wave deceleration time; e', average mitral annular early diastolic velocity of the ventricular septal and lateral walls; E/e', the ratio between E and e'; EF, ejection fraction.

Table 6. Partial Correlation Between hs-cTns and FGF23 in the Case Where Echocardiographic Index is Used as an Adjusted Variable

The partial correlation coefficient between hs-cTns and FGF23 was calculated. LAVI, IVST, PWT, LVDd, LVMI, E, A, E/A, DcT, e', E/e', and EF were used as adjusted variables as indicators of cardiac ultrasound examination.

Figure legends

Fig. 1 Concentrations of hs-cTns and FGF23 of Each eGFR Category and Correlation Between hs-cTns and FGF23

(a), (b), (c) The vertical axis shows hs-cTnI (a), hs-cTnT (b) and FGF23 (c). The horizontal axis shows eGFR categories. Dotted line indicates the cut off value of hs-cTnI (26.2 ng/L) and hs-cTnT (14 ng/L). The lower end of the box for each stage is 25th percentile value, and the upper end is 75th percentile value. The middle line shows the median value and the upper end of bar shows the maximum value. In G1 of panel (a), values of hs-cTnI were below the detection limit (<5.0 ng/L) up to 75th percentile of all data. **(d), (e)** Scatter plots of FGF23 and hs-cTnI (d) and hs-cTnT (e) are shown. Because the data of hs-cTns and FGF23 were abnormally distributed, natural log-transformed data was used. Dotted line indicates an approximated curve.

Table 1.

Variable	n	Median (25th percentile-75th percentile)	Spearman's Correlation coefficient					
			hs-cTnI		hs-cTnT		FGF23	
			r	P	*r*	P	*r*	P
Gender (male)	120	−	0.201	0.003	0.137	0.046	0.090	0.193
Age	212	69 (58－76)	0.363	<0.001	0.451	<0.001	0.063	0.361
eGFR (mL/min/1.73m^2)	212	48.6 (29.5－75.5)	-0.408	<0.001	-0.702	<0.001	-0.660	<0.001
Cys-C (μg/mL)	212	1.18 (0.85－1.78)	0.414	<0.001	0.765	<0.001	0.681	<0.001
Blood Hemoglobin (g/dL)	212	12.4 (10.6－13.6)	-0.245	<0.001	-0.533	<0.001	-0.383	<0.001
Serum Calcium (mg/dL)	212	9.2 (8.8－9.6)	-0.145	0.035	-0.306	<0.001	-0.083	0.231
Serum Phosphate (mg/dL)	212	3.4 (3.0－3.8)	-0.056	0.417	0.082	0.233	0.233	0.001
NT-proBNP (pg/mL)	212	155.3 (66.9－617.0)	0.490	<0.001	0.670	<0.001	0.426	<0.001

Table 1, Atsushi Ito

Table 2.

eGFR categories	G1	G2	G3a*	G3b*	G4*	G5*
n	35	39	47	37	26	28
Positive rate of hs-cTnI, %	5.7 (2/35)	2.6 (1/39)	2.1 (1/47)	5.4 (2/37)	7.7 (2/26)	25.0 (7/28)
Positive rate of hs-cTnT, %	20.0 (7/35)	17.9 (7/39)	55.3 (26/47)	64.9 (24/37)	73.1 (19/26)	96.4 (27/28)
Concordance rate, %	80.0 (28/35)	79.5 (31/39)	46.8 (22/47)	40.5 (15/37)	34.6 (9/26)	25.0 (7/28)

Table 2, Atsushi Ito

Table 3.

Combination between eGFR categories	hs-cTnI	hs-cTnT	FGF23
G1 − G2	3.133	0.195	0.409
G1 − G3a	0.128	<0.001	<0.001
G1 − G3b	0.011	<0.001	<0.001
G1 − G4	0.024	<0.001	<0.001
G1 − G5	<0.001	<0.001	<0.001
G2 − G3a	0.743	<0.001	0.107
G2 − G3b	0.071	<0.001	<0.001
G2 − G4	0.059	<0.001	<0.001
G2 − G5	<0.001	<0.001	<0.001
G3a − G3b	0.859	0.727	0.738
G3a − G4	0.617	0.016	0.040
G3a − G5	<0.001	<0.001	<0.001
G3b − G4	3.402	0.727	0.811
G3b − G5	0.004	<0.001	<0.001
G4 − G5	0.040	<0.001	<0.001

Table 3, Atsushi Ito

Table 4.

Dependent variable	ln(hs-cTnI)		ln(hs-cTnT)	
Independent variable	***β***	**P**	***β***	**P**
Gender (male)	0.155	0.021	0.083	0.097
Age	0.202	0.004	0.265	<0.001
eGFR	-0.031	0.721	-0.153	0.017
Heart Diseases	0.149	0.019	0.087	0.065
Blood Hemoglobin	-0.095	0.227	-0.164	0.005
Serum Calcium	-0.065	0.333	-0.162	0.001
Serum Phosphate	0.004	0.953	0.024	0.640
ln(FGF23)	0.222	0.010	0.386	<0.001

Table 4, Atsushi Ito

Table 5.

Echocardiographic index	Correlation with ln (hs-cTnI)		Correlation with ln (hs-cTnT)		Correlation with ln (FGF23)	
	r	P	*r*	P	*r*	P
LAVI	0.188	0.151	0.188	0.149	0.078	0.555
IVST	0.317	0.013	0.348	0.006	0.176	0.176
PWT	0.357	0.005	0.476	<0.001	0.176	0.175
LVDd	0.076	0.562	-0.041	0.755	0.022	0.866
LVMI	0.407	0.001	0.474	<0.001	0.288	0.025
E	-0.066	0.611	0.011	0.934	0.027	0.838
A	0.213	0.125	0.442	0.001	0.270	0.050
E/A	-0.232	0.094	-0.296	0.032	-0.142	0.310
DcT	-0.037	0.783	-0.063	0.636	-0.125	0.346
e’	-0.294	0.022	-0.272	0.034	-0.097	0.458
E/e’	0.264	0.039	0.274	0.032	0.097	0.457
EF	-0.210	0.104	-0.077	0.555	-0.191	0.141

Table 5, Atsushi Ito

Table 6.

Adjusted variable	Correlation between ln (hs-cTnI) and ln (FGF23)		Correlation between ln (hs-cTnT) and ln (FGF23)	
	r	P	*r*	P
-	0.354	0.005	0.655	<0.001
LAVI	0.338	0.009	0.644	<0.001
IVST	0.320	0.013	0.644	<0.001
PWT	0.317	0.014	0.660	<0.001
LVDd	0.354	0.006	0.657	<0.001
LVMI	0.271	0.036	0.615	<0.001
E	0.357	0.005	0.655	<0.001
A	0.342	0.013	0.613	<0.001
E/A	0.360	0.009	0.641	<0.001
DcT	0.352	0.007	0.658	<0.001
e’	0.343	0.007	0.657	<0.001
E/e’	0.342	0.007	0.657	<0.001
EF	0.327	0.011	0.654	<0.001

Figure 1

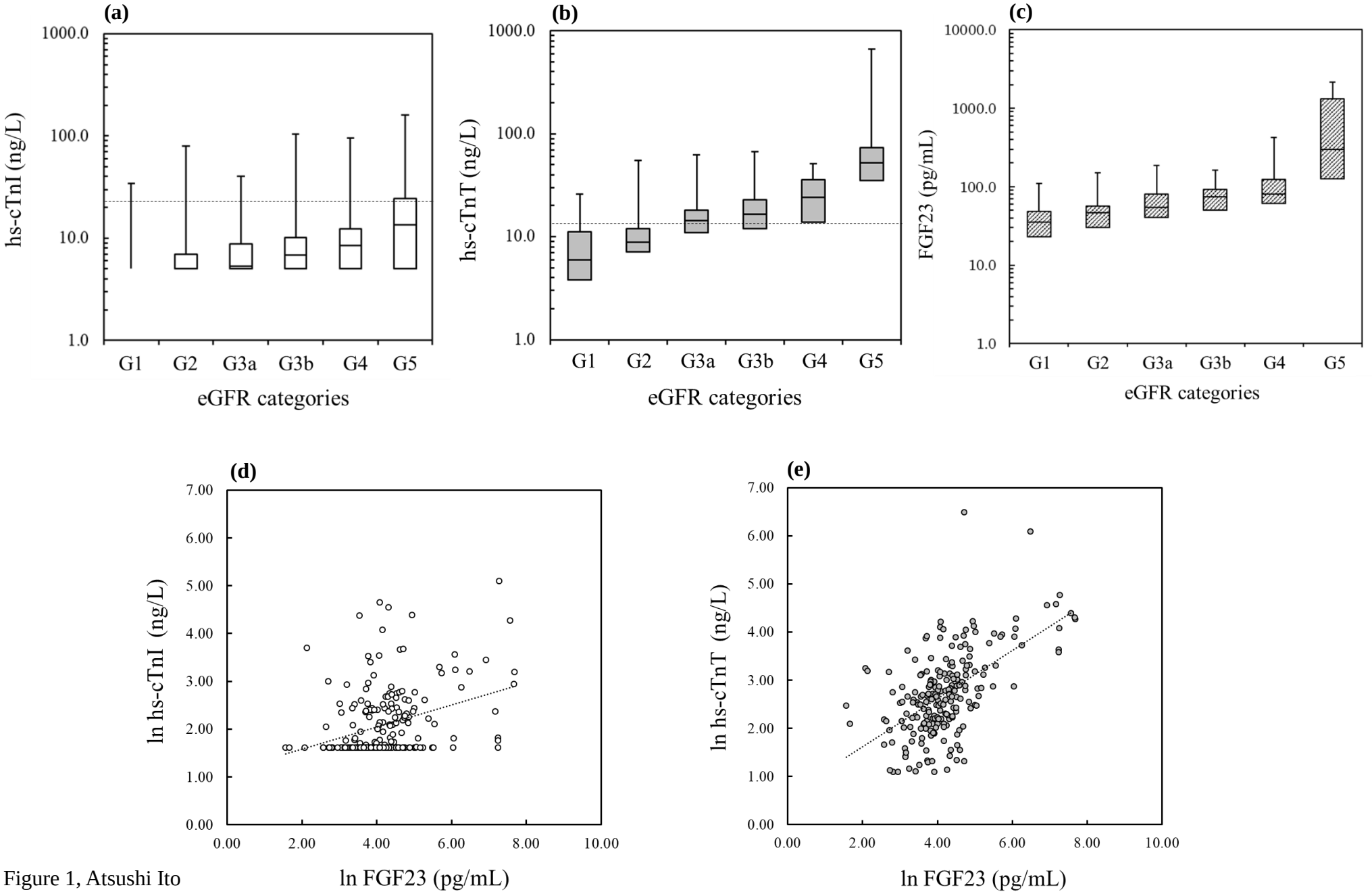

Figure 1, Atsushi Ito