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Original article

Association of plasma thioredoxin-1 with renal tubular damage and cardiac prognosis in patients with chronic heart failure

Yoichiro Otaki (MD), Tetsu Watanabe (MD, PhD, FJCC)*, Hiroki Takahashi (MD, PhD), Shinpei Kadowaki (MD), Taro Narumi (MD), Yuki Honda (MD), Masahiro Wanezaki (MD), Shintaro Sasaki (MD, PhD), Harutoshi Tamura (MD, PhD), Satoshi Nishiyama (MD, PhD), Takanori Arimoto (MD, PhD), Tetsuro Shishido (MD, PhD), Takuya Miyamoto (MD, PhD), Isao Kubota (MD, PhD, FJCC)

Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan

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ABSTRACT

Background: Thioredoxin-1 (Trx-1) is an abundant 12.5 kDa redox protein expressed in almost all eukaryotic cells that protect against the development of heart failure and kidney dysfunction. Plasma Trx-1 levels are considered as a reliable marker for oxidative stress. However, it remains to be determined whether plasma Trx-1 levels can predict cardiac prognosis in patients with chronic heart failure (CHF).
Methods and results: We measured plasma Trx-1 levels and urinary β_2-microglobulin–creatinine ratio (UBCR), a marker for renal tubular damage, in 156 consecutive patients with CHF and 17 control subjects. The patients were prospectively followed for a median follow-up period of 627 days and 46 cardiac events were observed. The patients with cardiac events had significantly higher plasma Trx-1 levels and UBCR levels than the cardiac event-free patients. Multivariate Cox proportional hazard analysis revealed that an elevated Trx-1 level was independently associated with poor outcome in patients with CHF after adjustment for confounding factors (hazard ratio, 1.74; 95% confidence interval, 1.33–2.29; $p < 0.0001$). UBCR was increased with higher plasma Trx-1 levels. Kaplan–Meier analysis demonstrated that the highest Trx-1 tertile was associated with the highest risk of cardiac events.
Conclusion: Plasma Trx-1 level was associated with renal tubular damage and cardiac prognosis, suggesting that it could be a useful marker to identify patients at high risk for comorbid heart failure and renal tubular damage.

Introduction

Heart failure is a major health problem with high mortality that continues to increase in prevalence [1–4]. The development of heart failure is closely associated with progressive left ventricular remodeling in response to oxidative stress [5]. The major source of excessive oxidative stress in heart failure is considered to be increased intracellular levels of reactive oxygen species (ROS) [6].

Thioredoxin-1 (Trx-1) is an abundant 12.5 kDa cytosolic protein expressed in almost all eukaryotic cells and plays an important role in redox signaling. Trx-1 contains a dithiol/disulfide motif in the redox-active site and serves as an ROS scavenger [7,8]. Circulating Trx-1 was reported to be closely associated with systemic oxidative stress [9,10] and was used as a reliable oxidative stress marker. However, it is not known whether plasma Trx-1 is a useful prognostic marker of chronic heart failure (CHF).

Cardio-renal interaction was evaluated because kidney dysfunction is indicative of extremely poor prognosis in patients with CHF [11,12]. Notably, oxidative stress is a common pathophysiological factor in the development of cardiac and kidney dysfunction, and experimental studies have demonstrated that Trx-1 inhibits oxidative stress in both heart and kidney tissue [13,14]. We previously reported that renal tubular damage, as well as glomerular damage, is a risk factor for poor prognosis in patients with CHF [15]. Renal tubular cells are located in the renal medulla, which is affected by hypoxia. Thus, we hypothesized that plasma Trx-1 was associated with CHF-induced renal tubular damage.

* Corresponding author at: Department of Cardiology, Pulmonology and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan. Tel.: +81 23 628 5302; fax: +81 23 628 5305.
E-mail address: tewatana@med.id.yamagata-u.ac.jp (T. Watanabe).

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The purpose of the present study was to examine whether Trx-1 could predict cardiac prognosis in patients with CHF.

Methods

Study subjects

This was a prospective study of 156 consecutive patients who were admitted to our hospital for diagnosis or treatment of CHF. Seventeen age-matched control subjects who had no heart disease were also entered. The diagnoses of CHF were made by two cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, signs of pulmonary congestion, peripheral edema, and radiological or echocardiographic evidence of left ventricular enlargement or dysfunction.

Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data. The diagnoses of hypertension, diabetes mellitus, and hyperlipidemia were established on the basis of the patient's medical records or history of currently or previously received medical therapy. Ten patients were excluded from the study due to acute coronary syndrome within 3 months preceding the admission, active hepatic disease, pulmonary disease, or malignant disease. Demographic and clinical data including age, gender, New York Heart Association (NYHA) functional class, and medications at discharge were collected from hospital medical records and patient interviews.

Biochemical assays

Venous blood and urine samples were obtained in the early morning within 24 h of admission. Plasma Trx-1 was measured with human thioredoxin-1 enzyme-linked immunosorbent assay (ELISA) kits (Japan Institute for the Control of Aging, Nikken Seil Co., Ltd., Shizuoka, Japan). Brain natriuretic peptide (BNP) concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi Co., Ltd., Tokyo, Japan) [16]. The estimated glomerular filtration rate (GFR) was calculated using the modification of diet in renal disease (MDRD) equation with the Japanese coefficient as previously reported [17]. We quantitatively measured urinary albumin by immunoturbidimetry in a single spot urine specimen collected in the early morning. Urinary albumin levels were corrected for urinary creatinine in a single manner to urinary microalbumin–creatinine ratio (UACR). Urinary β_2-microglobulin concentration to creatinine ratio (UBCR), a marker for renal tubular damage, was determined by the latex agglutination method (BML, Inc., Tokyo, Japan) [18]. N-acetyl-β-D-glucosaminidase (NAG), a marker of early renal tubular damage, was measured in single spot urine specimens. Because BNP, UACR, UBCR, NAG, and Trx-1 were not normally distributed, we performed all analyses using log-transformed values.

End-points and follow-up

The patients were prospectively followed for a median period of 627 days (interquartile range, 406–896 days). All the patients were followed by telephone interview or medical record review twice a year for 1250 days. The end points were cardiac death (defined as death from progressive heart failure, acute coronary syndrome, or sudden cardiac death) and progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs and was established by the attending physician.

The study was approved by the institutional ethics committee, and all the patients provided informed consent.

Statistics

All values are expressed as the mean ± standard deviation (SD). We employed *t*-tests, chi-square tests, and linear analysis to compare continuous and categorical variables, respectively. Kruskal–Wallis test was used to compare Trx-1 with NYHA functional class. A Cox proportional hazard analysis was performed to determine independent predictors for cardiac events. Significant predictors selected in the univariate analysis were entered into the multivariate analysis. The receiver operating characteristics curve of Trx-1 was constructed to determine the area under the curve (AUC), sensitivity, and specificity. The AUC for cardiac events was calculated by the trapezoidal rule. Proportionality in the Cox model was evaluated with log-minus-log survival plots. A cardiac event-free curve was constructed according to the Kaplan–Meier method and compared using a log-rank test. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with a standard program package (JMP version 8; SAS Institute Inc., Cary, NC, USA).

Results

Baseline patient characteristics

The subjects' baseline characteristics are presented in Table 1. There were 96 patients with NYHA functional class II and 60 patients with class III or IV. Hypertension, diabetes mellitus, and hyperlipidemia were identified in 101 (65%), 43 (28%), and 53

Table 1
Clinical characteristics of patients with chronic heart failure and control subjects.

Variables	Control $n=17$	All patients $n=156$	p value
Age, years	69 ± 5	72 ± 10	0.1638
Gender (men/women)	7/10	100/56	0.0646
NYHA functional class (II/III, IV)		96/60	
Hypertension, *n* (%)	12 (71%)	101 (65%)	0.4240
Diabetes mellitus, *n* (%)	2 (17%)	43 (28%)	0.2778
Hyperlipidemia, *n* (%)	6 (35%)	53 (34%)	0.9685
Etiology			
Ischemic heart disease, *n* (%)		41 (26%)	
Nonischemic heart disease, *n* (%)		115 (74%)	
Blood examination			
Log_{10} BNP (pg/mL)	1.4 ± 0.3	2.6 ± 0.5	<0.0001
Log_{10} Trx-1 (ng/mL)	1.7 ± 0.4	2.1 ± 0.8	0.0445
Kidney function			
eGFR (mL/min/1.73 m^2)	72 ± 8	67 ± 26	0.5411
Log_{10} UACR (mg/g)	1.2 ± 0.9	1.5 ± 0.6	0.1823
Log_{10} UBCR (μg/g)	1.6 ± 0.7	2.2 ± 0.9	0.0445
Log_{10} NAG (U/g)	0.77 ± 0.12	1.01 ± 0.29	0.0139
Echocardiography			
LVEDD (mm)	47 ± 6	56 ± 10	0.0155
LVEF (%)	70 ± 6	49 ± 17	0.0004
Medication			
ACEIs and/or ARBs, *n* (%)		117 (75%)	
β-Blockers, *n* (%)		117 (75%)	
Statin, *n* (%)		61 (39%)	
Aldosterone blockers, *n* (%)		44 (28%)	
Loop diuretics, *n* (%)		104 (67%)	

Data are expressed as mean ± SD, number (percentage).
ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II recepter blockers; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; NAG, N-acetyl-β-D-glucosaminidase; NYHA, New York Heart Association; Trx-1, thioredoxin 1; UACR, urinary albumin to creatinine ratio; UBCR, urinary β_2-microglobulin to creatinine ratio.