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Cardiac Troponin Is Elevated in Patients with Thyrotoxicosis and Decreases as Thyroid Function Improves and Brain Natriuretic Peptide Levels Decrease

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Keywords
Thyrotoxicosis · Hyperthyroidism · Heart · Cardiac troponin · Brain natriuretic peptide

Abstract
Introduction: High-sensitive cardiac troponin reflects micromyocardial injury in the absence of overt myocardial infarction. ***Objective:*** This study aimed to clarify how thyrotoxicosis affects cardiac troponin. ***Methods:*** This was a prospective observational study in Japan. Untreated patients with thyrotoxicosis who visited Ito Hospital were enrolled, and medical treatment was initiated for hyperthyroidism. Thyroid function, high-sensitive troponin I (hsTnI), and brain natriuretic peptide (BNP) were measured at baseline and then every 3 months for 1 year. ***Results:*** Data from a total of 143 patients (median age, 42 years; 32 men and 111 women) were investigated. At baseline, median hsTnI was 1.9 pg/mL and ranged from 0 to 69.6 pg/mL. Five patients (3.5%) had a high hsTnI value that exceeded 26.2 pg/mL, which is used as the cutoff for diagnosis of myocardial infarction, and 22 patients (15.4%) had an intermediate value between 5.0 and 26.2 pg/mL. Multivariable regression analysis showed that significant predictors of the hsTnI value were age ($\beta = 0.20$, $p = 0.01$) and BNP ($\beta = 0.43$, $p < 0.0001$) ($R^2 = 0.27$, $F = 26.0$, $p < 0.0001$), and significant predictors of the BNP value were age ($\beta = 0.23$, $p = 0.001$), hemoglobin ($\beta = -0.43$, $p < 0.0001$), free T_4 (FT_4) ($\beta = 0.23$, $p = 0.001$), and hsTnI ($\beta = 0.27$, $p < 0.0001$) ($R^2 = 0.49$, $F = 33.8$, $p < 0.0001$). Correlations were found between a decrease in hsTnI and BNP in the first 3 months ($\rho = 0.49$, $p < 0.0001$). A decrease in FT_4 in the first 3 months was weakly correlated with decreases in hsTnI ($\rho = 0.32$, $p = 0.0004$) and BNP ($\rho = 0.32$; $p = 0.0003$). Of the 27 patients with elevated hsTnI (≥5.0 pg/mL), the hsTnI level was normalized in 20 patients within a year. ***Conclusions:*** In thyrotoxicosis, the myocardial biomarker hsTnI is elevated in about 20% of patients; hsTnI levels decrease as thyroid function improves and BNP decreases.

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Introduction

Thyrotoxicosis has a wide range of cardiac complications. Some typical ones are sinus tachycardia, atrial fibrillation, and cardiac failure [1]. Although clinicians rarely experience myocardial ischemia associated with thyrotoxicosis, coronary spastic angina and myocardial infarction in young patients with no abnormal coronary angiographic findings have been reported [2–5].

Troponin is a protein complex with high myocardial specificity used as a marker of myocardial damage. The greater sensitivity in determining cardiac troponin provided by high-sensitivity assays helps clinicians identify not only overt myocardial necrosis from myocardial infarction [6], but also micro-myocardial injury in the lower assay range [7, 8]. The Fourth Universal Definition of Myocardial Infarction (2018) defines elevations in cardiac troponin without clinical signs or symptoms as myocardial injury to distinguish this condition from myocardial infarction [9]. Minor elevations are useful for monitoring treatment and evaluating prognosis in patients with cardiac failure [10, 11] and are a risk factor for cardiovascular events and death in large cohort studies of the general population [12–15].

Patients with thyrotoxicosis have elevations in brain natriuretic peptide (BNP) in association with secondary cardiovascular complications such as cardiac failure or atrial fibrillation [16], but the effects on myocardial markers are unclear. Thyrotoxicosis affects cardiovascular prognosis negatively [17–19]. Determining how thyrotoxicosis affects levels of cardiac troponin, which are indicative of minor myocardial damage, is an informative pursuit. However, a small investigation that measured cardiac troponin levels in 15 patients with Graves' disease found no well-defined elevations [20]. We used high-sensitivity assays to evaluate cardiac troponin levels together with the cardiac failure marker BNP in larger numbers of thyrotoxic patients to better understand how often cardiac troponin levels are elevated and what the clinical features of this population are.

Patients and Methods

Patient Selection and Clinical Records

This was a prospective observational study. Untreated patients with thyrotoxicosis who visited Ito Hospital between March 2015 and May 2016 were enrolled. Of these, patients who did not provide written consent, those who were pregnant or undergoing infertility treatment, and those who had subacute thyroiditis or ischemic heart disease were excluded. Assessments on the first visit included an electrocardiogram, thyroid ultrasonography, and blood tests: serum free T_4 (FT_4), free T_3 (FT_3), thyroid-stimulating hormone (TSH), TSH-binding inhibitory immunoglobulin (TBII), BNP, and high-sensitive troponin I (hsTnI). Basically, antithyroid drugs (ATDs) were initiated for patients with hyperthyroidism. Potassium iodide was administrated in combination with ATDs for patients with severe Graves' disease [21] and as monotherapy for patients with mild Graves' disease [22]. Assessments at 3, 6, 9, and 12 months included FT_4, FT_3, TSH, BNP, and hsTnI.

A high hsTnI value (H-hsTnI) was defined as an hsTnI level ≥26.2 pg/mL, which is the cutoff value for the diagnosis of myocardial infarction [23]. Concerning the cutoff values (7.0 pg/mL for men and 4.7 pg/mL for women) for a potential risk of future cardiovascular events in a general population cohort study [14], in our study, 5 pg/mL was set as the lower limit of intermediate elevation of the hsTnI level. Thus, an intermediate value (I-hsTnI) was defined as an hsTnI level ≥5.0 and <26.2 pg/mL. Normal was defined as values <5.0 pg/mL (N-hsTnI). A high BNP value (H-BNP) was defined as a BNP level ≥100 pg/mL with the possibility of heart failure according to the cutoff value shown in the Japanese Heart Failure Society (JHFS) statement [24]. A mild high BNP value (mild H-BNP) was defined as a BNP level ≥40 pg/mL with the possibility of mild heart failure according to the cutoff value shown in the JHFS statement [24]. Normal was defined as values <40 pg/mL (N-BNP).

Assays

FT_3, FT_4, TSH, and TBII were measured with a commercial rapid electrochemiluminescence immunoassay kit (ECLusys FT_3, FT_4, TSH, and TRAb; Roche Diagnostics GmbH, Mannheim, Germany). The reference ranges for the normal values used in Ito Hospital were 2.2–4.3 pg/mL, 0.80–1.60 ng/dL, 0.20–4.50 μU/mL, and <2.0 IU/L, respectively.

Both hsTnI and BNP assays were based on a commercial chemiluminescent microparticle immunoassay. The hsTnI assay (STAT high-sensitive troponin I; Abbott Laboratories, Abbott Park, IL, USA) was performed for the measurement of cardiac troponin I on Architect i2000 (Abbott Laboratories). According to the manufacture's instruction, the limit of detection of the assay was 1.9 pg/mL. The BNP assay (BNP-JP; Abbott Laboratories) was performed for the measurement of BNP on Architect i2000 (Abbott Laboratories). According to the manufacture's instruction, the limit of detection of the assay was 0.8 pg/mL [25].

Electrocardiogram

Electrocardiographic diagnosis was performed by a cardiologist (G.T.) blinded to other information. The patterns were divided into 7 categories: (1) tachycardia; (2) arrhythmia; (3) loading abnormality, with left and right atrial wave abnormalities; (4) myocardial damage, with an abnormal ST segment; (5) left ventricular hypertrophy, with high voltage; (6) block; and (7) normal.

Thyroid Volume

Thyroid volume was measured by ultrasonography [26].

Statistical Analysis

Data are expressed as medians and range for continuous variables, and the numbers with frequencies are shown for dichotomous variables. Clinical and biochemical variables were compared using the Wilcoxon test for continuous variables without a normal distribution, whereas Student's *t* test was used for continuous vari-

ables with a normal distribution. Statistical significance was calculated with the χ^2 test or Fisher's exact test. Spearman's rank correlation analysis was performed to assess the relationship between 2 variables. Multivariable regression analysis was performed to analyze the predictors for hsTnI and BNP values. The baseline variables were included in the multivariable regression analysis. Box-Cox transformation was performed for variables without normal distribution. We used the variables significant at the level of $p < 0.10$ on univariable regression models and constructed the final multivariable regression models based on stepwise regression. Assumptions for linear regression models (e.g., normality, linearity, and homoscedasticity) were confirmed using the normal quantile plot and the residual plot for each outcome. A p value <0.05 was considered significant. JMP version 14.0.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patients' Characteristics

The baseline characteristics of the 143 included patients with untreated thyrotoxicosis are shown in Table 1. The median age of the patients was 42 years, and 111 patients (78%) were females. The patients included 129 with Graves' disease, 12 with painless thyroiditis (PT), and 2 with an autonomously functioning thyroid nodule. Atrial fibrillation was found in only 4 cases (2.8%). None had renal dysfunction that could affect the hsTnI level; the median estimated glomerular filtration rate was 129.2 (interquartile range, 104.1–155.7) mL/min/1.73 m^2.

Table 1. Baseline characteristics

Variables	
Patients, *n*	143
Age (median [IQR]), years	42 [32–51]
Sex (male/female), *n* (%)	32/111 (22/78)
Smoking habit (smoker), *n* (%)	34 (23.8)
Weight (median [IQR]), kg	53 [49–60]
BMI (median [IQR]), kg/m^2	20.7 [19.0–23.0]
Diagnosis, *n* (%)	
Graves' disease	129 (90.2)
PT	12 (8.4)
AFTN	2 (1.4)
Symptoms at diagnosis, *n* (%)	
Palpitations	104 (73)
Chest discomfort	13 (9)
Dyspnea	23 (16)
Edema	40 (28)
SBP (median [IQR]), mm Hg	134 [125–151]
DBP (median [IQR]), mm Hg	83 [76–94]
HR (median [IQR]), beats/min	90 [80–106]
Atrial fibrillation, *n* (%)	4 (2.8)
Laboratory tests at diagnosis	
eGFR (median [IQR]), mL/min/1.73 m^2	129.2 [104.1–155.7]
Hb (median [IQR]), g/dL	13.2 [12.1–14.0]
FT_3 (median [IQR]), pg/mL	16.6 [11.6–24.6]
FT_4 (median [IQR]), ng/dL	4.58 [3.5–7.11]
TSH (median [IQR]), μU/mL	0.01 [0.01–0.01]
TBII (median [IQR]), IU/L	9.1 [3.2–21.6]
Electrocardiogram (N/R/M/H/L/B/A/NA), *n* (%)	62/45/6/5/9/4/11/1 (43.4/31.5/4.2/3.5/6.3/2.8/7.7/0.7)
Thyroid volume (median [IQR]), mL	31 [21–42]

IQR, interquartile range; BMI, body mass index; PT, painless thyroiditis; AFTN, autonomously functioning thyroid nodule; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; FT_3, free T_3; FT_4, free T_4; TSH, thyroid-stimulating hormone; TBII, TSH-binding inhibitory immunoglobulin. Electrocardiogram interpretations are summarized as follows: N, normal; R, tachycardia; M, myocardial damage; H, left ventricular hypertrophy; L, atrial load; B, block; A, arrhythmia including atrial fibrillation; NA, not available.

hsTnI Levels in Thyrotoxic Patients

The distribution of hsTnI levels is shown in Figure 1a. The median hsTnI value was 1.9 pg/mL, and hsTnI was distributed widely, ranging from 0 to 69.6 (interquartile range, 0.8–3.6) pg/mL. Five patients (3.5%) had high values exceeding 26.2 pg/mL (H-hsTnI group). Out of the 5 patients, 1 patient showed slight chest discomfort; however, none of the patients showed significant ST elevation at the initial examination, and the electrocardiographic category revealed tachycardia ($n = 3$), atrial fibrillation ($n = 1$), and atrial load ($n = 1$). Echocardiography was performed in 3 of the 5 patients, but no wall motion abnormalities suggesting ischemic heart disease were found.

Twenty-two patients (15.4%) had an intermediate hsTnI value between 5.0 and 26.2 pg/mL (I-hsTnI group). When the H-hsTnI group and the I-hsTnI group were combined ($n = 27$) and compared with a normal group (N-hsTnI group; $n = 116$), their age tended to be older, their hemoglobin (Hb) was significantly lower, and their BNP was significantly higher (see online suppl. Table 1; see online Supplementary Materials). None of the 27 patients with elevated hsTnl levels was diagnosed as myocardial infarction with ST elevation neither at the first visit nor during the follow-up.

BNP Levels in Thyrotoxic Patients

The distribution of BNP is shown in Figure 1b. The median BNP value was 24 pg/mL, ranging from 2.0 to 508.3 pg/mL (interquartile range, 13–46 pg/mL). Eight patients (5.6%) had a high BNP value exceeding 100 pg/mL (H-BNP group). Thirty-one patients (21.7%) had a

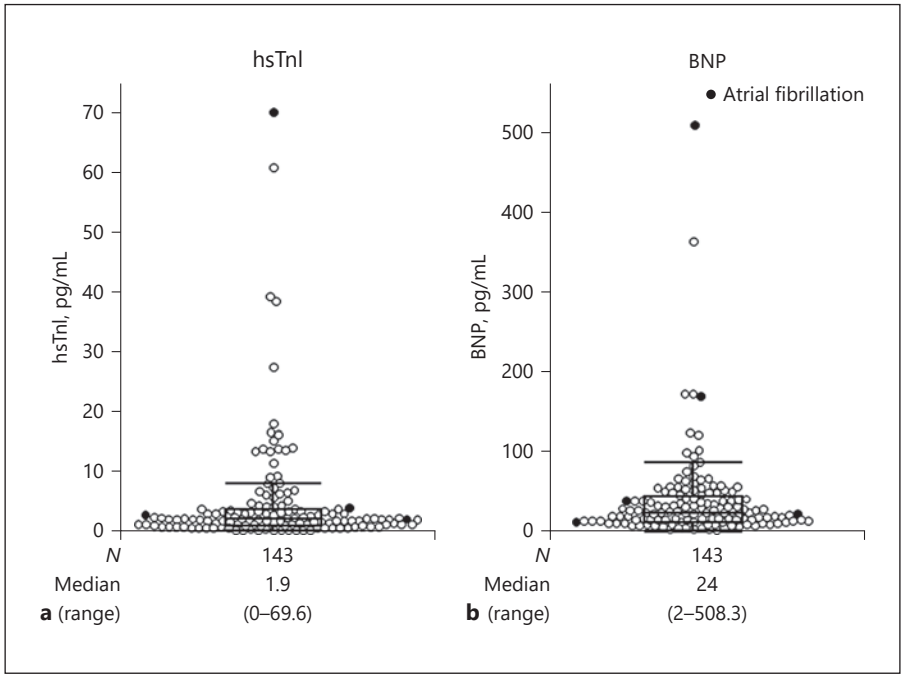

Fig. 1. Distribution of cardiac markers in thyrotoxic patients. Distribution of hsTnI in thyrotoxic patients (**a**). Distribution of BNP in thyrotoxic patients (**b**). hsTnI, high-sensitive troponin I; BNP, brain natriuretic peptide.

mild high value between 40 and 100 pg/mL (mild H-BNP group). When the H-BNP group and the mild H-BNP group were combined ($n = 39$) and compared with a normal group (N-BNP group; $n = 104$), their age, FT_4, TBII, and hsTnI were significantly higher, and their Hb was significantly lower (online suppl. Table 1).

Factors Associated with hsTnI and BNP Levels in Thyrotoxic Patients

The relationships of baseline variables to baseline hsTnI and BNP levels are shown in Table 2. Weak positive correlations were found between hsTnI and age and between BNP and age, FT_4, FT_3, TBII, and atrial fibrillation. A weak negative relationship was found between hsTnI and Hb, and a negative relationship was found between BNP and Hb. A positive relationship was found between hsTnI and BNP. FT_4 and FT_3 had a strong correlation ($\rho = 0.94$, $p < 0.0001$); therefore, either FT_4 or FT_3 was included in the multivariable regression model. The significant predictors of the hsTnI value at baseline were found to be age and BNP, and the predictors of the BNP value were age, Hb, hsTnI, and FT_4 or FT_3 (Table 3). Figure 2 shows the distribution of hsTnI and BNP, with the electrocardiogram category. Among the patients with elevated hsTnI (H- and I-hsTnI groups), no findings of ischemic change or myocardial damage were apparent on the electrocardiograms.

Table 2. Univariable regression analysis for hsTnI and BNP levels

Independent variables	Dependent variables			
	hsTnI		BNP	
	β	*p* value	β	*p* value
Age	0.32	0.0001	0.28	0.0007
Smoker	0.04	0.61	−0.07	0.40
Female	−0.08	0.31	0.20	0.02
Weight	0.12	0.17	−0.12	0.16
BMI	0.12	0.17	−0.06	0.52
SBP	0.11	0.19	0.01	0.87
DBP	0.04	0.61	−0.16	0.07
HR	0.10	0.24	0.15	0.08
Atrial fibrillation	0.17	0.04	0.23	0.005
eGFR	−0.04	0.66	0.15	0.08
Hb	−0.29	0.001	−0.56	<0.0001
FT_3	0.10	0.22	0.23	0.006
FT_4	0.11	0.18	0.35	0.003
TBII	0.17	0.08	0.30	0.0003
hsTnI	–	–	0.49	<0.0001
BNP	0.49	<0.0001	–	–
Thyroid volume	0.05	0.53	0.07	0.42

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; FT_3, free T_3; FT_4, free T_4; TBII, TSH-binding inhibitory immunoglobulin; hsTnI, high-sensitive troponin I; BNP, brain natriuretic peptide.

Table 3. Predictors of hsTnI and BNP levels

Independent variables	Dependent variables	Unstanderdized coefficients		Standerdized coefficients β	*t* value	*p* value	VIF
		B	SE				
hsTnI	Age	0.03	0.01	0.20	2.60	0.01	1.09
	BNP	0.04	0.01	0.43	5.72	<0.0001	1.09
BNP (model 1)	Age	0.39	0.12	0.23	3.28	0.001	1.30
	Hb	−7.03	1.03	−0.43	−6.83	<0.0001	1.10
	FT_4	2.59	0.79	0.23	3.28	0.001	1.21
	hsTnI	3.02	0.75	0.27	4.05	<0.0001	1.24
BNP (model 2)	Age	0.38	0.12	0.22	3.18	0.002	1.29
	Hb	−7.11	1.03	−0.44	−6.90	<0.0001	1.10
	FT_3	0.58	0.19	0.21	3.12	0.002	1.19
	hsTnI	3.07	0.75	0.28	4.11	<0.0001	1.23

Multivariable regression analysis was performed for predictors of hsTnI ($R^2 = 0.27$, $F = 26.0$, $p < 0.0001$), BNP (model 1) ($R^2 = 0.49$, $F = 33.8$, $p < 0.0001$), and BNP (model 2) ($R^2 = 0.49$, $F = 33.3$, $p < 0.0001$). Atrial fibrillation was not included in the final multivariable regression model because only 4 patients experienced atrial fibrillation in our data. Hb, hemoglobin; FT_3, free T_3; FT_4, free T_4; hsTnI, high-sensitive troponin I; BNP, brain natriuretic peptide, VIF; variance inflation factor; SE, standard error.

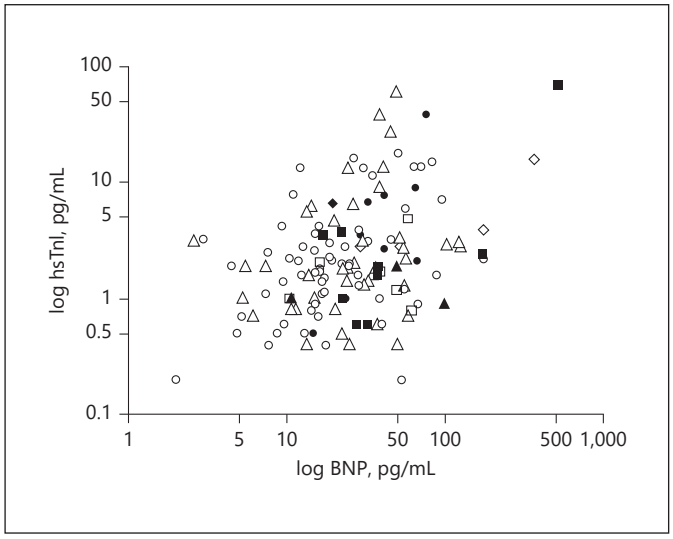

Fig. 2. Distribution of hsTnI and BNP at baseline. The distribution of hsTnl (logarithmic transformation) and BNP (logarithmic transformation) is displayed using markers reflecting the following electrocardiogram categories. ○: normal; △: tachycardia; □: myocardial damage; ◇: left ventricular hypertrophy; ●: loading abnormality; ▲: block; ■: arrhythmia; ◆: not available. The ECG categories of the case with a hsTnl value of 0 pg/mL ($n = 9$) are as follows: tachycardia ($n = 5$), left ventricular hypertrophy ($n = 1$), arrhythmia ($n = 1$), and normal ($n = 2$). hsTnI, high-sensitive troponin I; BNP, brain natriuretic peptide.

Clinical Course and Changes in Variables

As the initial treatment for hyperthyroidism, ATDs were administered to 123 patients (methimazole: $n = 107$, propylthiouracil: $n = 16$), and potassium iodide was administered to 98 patients (in combination with ATDs: $n = 90$, as monotherapy: $n = 8$). The PT patients were followed up without ATDs. For tachycardia, a β-blocker was used in 66 patients, and a calcium channel blocker was selected when a β-blocker was contraindicated; a calcium channel blocker was administered in 8 patients. The changes after 3 months compared to baseline were evaluated. The change in hsTnI (ΔhsTnI) was weakly correlated with the changes in FT_4 (ΔFT_4) ($\rho = 0.32$, $p = 0.0004$) and FT_3 (ΔFT_3) ($\rho = 0.30$, $p = 0.0008$). The change in BNP (ΔBNP) was weakly correlated with ΔFT_4 ($\rho = 0.32$, $p = 0.0003$) and ΔFT_3 ($\rho = 0.28$, $p = 0.002$). ΔBNP and ΔhsTnI were correlated ($\rho = 0.49$, $p < 0.0001$). Figure 3 shows the change in the hsTnI value in 27 cases whose hsTnI value was ≥5 pg/mL (H- and I-hsTnI groups). In the H-hsTnI group ($n = 5$), the hsTnI level was normalized in 3 months in 2 patients and 9 months in 1 patient. In the remaining 2 patients, the hsTnI remained high. In the I-hsTnI group ($n = 22$), the hsTnI level was normalized in 3 months in 14 patients, 6 months in 1 patient, and 12 months in 2 patients, and 2 patients dropped out in the early study period. In the remaining 3 patients, hsTnI remained elevated. In total, except for the 2 patients who

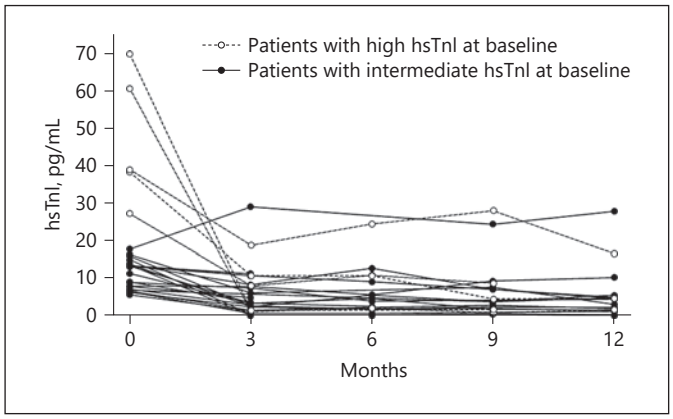

Fig. 3. Changes in hsTnI levels during the follow-up. Changes in hsTnI levels of the 27 cases with elevated hsTnI (≥5 pg/mL) at baseline are shown. As the initial treatment, antithyroid drugs (ATDs) were administered to 26 patients (methimazole: n = 23, propylthiouracil: n = 3), and potassium iodide was administered to 20 patients (in combination with ATDs: n = 19, as monotherapy: n = 1). For 1 patient with incidental micropapillary carcinoma, surgical treatment was performed on the 128th day after the initial visit. In this case, the data before the surgery were plotted. hsTnI, high-sensitive troponin I.

dropped out, in 25 of the 27 patients with elevated hsTnI (H- and I-hsTnI groups), the hsTnI level was normalized in 20 patients (80%), whereas in 5 patients (20%), the hsTnI level remained elevated despite normal thyroid function. A 53-year-old woman with Graves' disease showed re-elevation of hsTnI and BNP levels, along with re-elevation of thyroid function tests, due to noncompliance with treatment for hyperthyroidism (online suppl. Fig. 1). No patient had new signs of heart disease up to the final confirmation date (May 27, 2020).

Discussion

This study is the first of its kind to show, in a large population, that the myocardial biomarker hsTnI was elevated in thyrotoxicosis. The hsTnI levels decreased as thyroid function improved and BNP decreased, and minor myocardial injury might have contributed to the pathophysiology of thyrotoxicosis.

Five (3.5%) of the patients in the present study had a high hsTnI level exceeding the 26.2 pg/mL cutoff value used to diagnose ischemic heart disease, and 22 patients (15.4%) had mild elevations. The cutoff value of hsTnI for the diagnosis of ischemic heart disease is internationally recommended by guidelines to be the 99th percentile of the distribution in the general population [9]. Therefore, the measurement kit in the present study used 26.2 pg/mL, which is widely used in clinical practice [21]. Meanwhile, the different distribution of hsTnI across age and sex has been reported (i.e., greater in the older population than the younger population, and in males than females) [9]. In a recent study of the hsTnI levels in the Japanese general population, Abe et al. [27] reported that the distribution of hsTnI showed a sex difference in the 99th percentile values, at 17.7 pg/mL for women and 30.6 pg/mL for men. According to this cutoff value, the frequency of hsTnI exceeding the 99th percentile was estimated to be 3.5% in the present study (5 cases). The present study cases were younger (median age 43 years for women and 40 years for men) than Abe's study population (median age 48 years for women and 51 years for men). Considering the younger age composition, the result that 3.5% of patients with thyrotoxicosis had a hsTnI level above the 99th percentile value is higher than in the general population. These percentages, which cardiologists and internists who care for patients with ischemic heart disease should find noteworthy, call attention to the fact that patients with thyrotoxicosis may have elevated hsTnI levels.

In patients with thyrotoxicosis, hsTnI and BNP were correlated. The hsTnI levels decreased and normalized in 80% within 12 months as thyroid function improved and BNP decreased. Multivariable regression analysis suggested that, in patients with thyrotoxicosis, high levels of thyroid hormone cause cardiac volume/pressure load resulting in increased BNP values, and they cause micromyocardial injury resulting in elevation of hsTnI values. Since thyroid hormone levels were not correlated with high hsTnI levels, myocardial damage is presumed to be an indirect effect mediated by cardiac volume/pressure load reflected in elevated BNP levels. The electrocardiograms of the 27 patients with elevated hsTnI levels showed no definitive evidence of myocardial ischemia, which indicates that hsTnI levels are elevated in thyrotoxicosis even when no overt myocardial infarction is present. The hsTnI elevations seen in the present study suggest thyrotoxicosis be a factor underlying myocardial injury.

The hsTnI levels were weakly positively correlated with age and weakly negatively correlated with Hb. A study of patients with severe cardiac failure showed that anemia compounded with elevated hsTnI and BNP levels may worsen outcomes and that the relative local myocardial ischemia and impaired oxygenation associated with anemia may worsen cardiac failure [28]. In patients with Hb dilution from increased body fluid levels associated with cardiac failure or anemia associated with thyrotoxicosis,

the increased contractile force caused by thyrotoxicosis may produce impaired oxygenation and relative ischemia in the myocardium taxed by high cardiac output.

As with hsTnI, elevated BNP was weakly positively correlated with age and weakly negatively correlated with Hb. This correlation with age agrees with the general trend of decreased cardiac reserve and greater susceptibility to cardiac failure associated with aging. BNP was also weakly positively correlated with FT_4, FT_3, and TBII and thus more indicative than hsTnI of the extent of thyrotoxicosis and Graves' disease. Since a thyroid hormone response element is present in the BNP promoter [29], to some extent, high BNP levels may be due to the direct action of thyroid hormones via a thyroid hormone response element.

Cohort studies in the general population and studies of chronic cardiac failure have shown that small elevations in hsTnI are a risk factor for a poor cardiovascular prognosis [10–16]. Why small elevations have cardiovascular consequences is poorly understood [30]. A meta-analysis of the association between thyrotoxicosis and mortality found a relative risk of death from cardiovascular disease of 1.13 [17]. Recent reports also indicate that poor control of thyrotoxicosis results in a poor cardiovascular prognosis [18, 19]. Because patients whose thyroid function has worsened experience a resurgence in hsTnI levels, inadequate or unstable control of thyroid function could lead to repeated micro-myocardial damage in thyrotoxicosis and a poor cardiovascular prognosis. This makes controlling and maintaining thyroid function all the more important from the perspective of cardiac protection.

The results of the present study that hsTnI was elevated in patients with thyrotoxicosis are clinically very important, and they may lead to the elucidation of the mechanism of the poor cardiovascular prognosis and prediction of cardiovascular prognosis in thyrotoxicosis patients. It will be interesting to see whether myocardial damage as indicated by small hsTnI elevations at the first visit and follow-up reflects increases in the risk of death from the cardiovascular complications of thyrotoxicosis.

Several issues remain for the future. First, it would be very important to verify how the differences in duration, cause, and treatment of thyrotoxicosis and the presence of atrial fibrillation have an impact on hsTnI levels. Given the small number of patients with PT, autonomously functioning thyroid nodule, and atrial fibrillation in the present study, it was difficult to compare clinical features and laboratory parameters. Second, the evaluation with echocardiography also requires further study. Echocardiography was not a routine examination of our daily clinical practice. It would be important to estimate the volume/pressure overload that may be related with the elevation of hsTnl levels and the left ventricular systolic dysfunction caused by thyrotoxicosis-induced tachycardia that may be involved in the observed association. Third, severe cases need further study. Ito Hospital is a thyroid disease-specific medical institute. Usually, severe cases are admitted to hospitals dealing emergency cases and referred to our hospital after initiation of treatments. Theretofore, this study targeting untreated patients did not include patients with severe heart failure.

Conclusion

The myocardial biomarker hsTnI is elevated in patients with thyrotoxicosis, and hsTnI levels decrease as thyroid function improves and BNP decreases.

Acknowledgements

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Institutional Review Board Committee of Ito Hospital (No. 125). The written informed consent of all patients was obtained.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work: N.W., N.H., K.I.,N.S., A.Y., H.O., M.S., M.M., K.E., G.T., and J.Y.N. Drafting the work or revising it critically for important intellectual content: N.W., G.T., and J.Y.N. Final approval of the version to be published: N.W., K.S., and K.I. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: N.W.

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