Comparison of the Levels of Cardiac Troponin I in Patients with Duchenne and Becker Muscular Dystrophies to Assess Cardiac Dysfunction

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Abstract

Background: Cardiac troponin I (cTnI), uniquely expressed in the myocardium, is a marker for acute myocardial injury. Its clinical significance in Duchenne and Becker muscular dystrophy (DMD and BMD) and its relation to alpha-actinin-3 (*ACTN3*) genotype as a genetic modifier of cardiomyopathy are still unknown.

Methods and Results: Overall, 529 and 131 serum cTnI values of 127 DMD and 47 BMD patients, respectively, were reviewed. cTnI elevation was generally observed in the second decade of life. Both cTnI levels and the proportion of abnormal cTnI levels were significantly higher in DMD patients than in BMD patients (age range: 1< years ≤10 and 10< years ≤18 and 10< years ≤18, respectively). Decreased left ventricular ejection fraction was observed after cTnI elevation in both populations. cTnI levels by age in DMD patients with *ACTN3* null genotype tended to increase highly and early.

Conclusions: Myocardial injury indicated by cTnI was more common and severe in DMD patients than in BMD patients. cTnI elevation preceding cardiac dysfunction may represent an early phase of cardiomyopathy progression and may be a biomarker for early detection of cardiomyopathy in DMD and BMD patients. The *ACTN3* null genotype may be a risk factor for early myocardial injury.

Introduction

Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive muscular dystrophy caused by mutations in the *DMD* gene, resulting in the absence of dystrophin [1, 2]. Becker muscular dystrophy (BMD) is a milder allelic version of DMD, also caused by in-frame *DMD* gene mutations that allow for the synthesis of shortened and partially functional dystrophin [3, 4]. As dystrophin is expressed not only in skeletal but also in cardiac muscles, its absence or dysfunction affects the heart [5]. In fact, cardiomyopathy is common in patients with DMD or BMD [3, 6]. Long-term muscle deterioration, with significant implications for lung and heart dysfunction, is pathognomonic of DMD [7, 8]. Recently, improved respiratory management has contributed to better respiratory status in patients with DMD; therefore, end-stage heart failure (HF) following cardiomyopathy is increasingly becoming the main cause of death in these patients [9]. However, physicians encounter difficulties in the early detection of cardiac dysfunction, especially in DMD, because of the early loss of ambulation, which reduces the load on the heart, thereby reducing cardiac symptoms [10, 11]. Previous studies have shown that early diagnosis of cardiac involvement is important because timely initiation of cardioprotective medications relieves cardiac dysfunction and delays heart muscle remodeling [12, 13]. Echocardiography is a primary and standard modality to screen for cardiac dysfunction in patients with muscular dystrophy [11]. However, it is not always adequate for detecting the early, clinically asymptomatic phase of disease progression because body habitus or scoliosis renders the acoustic imaging windows inadequate [14]. Cardiovascular magnetic resonance imaging (cMRI) is a new noninvasive imaging modality for detecting early cardiac dysfunction [15]. However, it is costly, not globally available, and requires sedation in young patients [11]. Despite the increased awareness of cardiac dysfunction in DMD and BMD patients, an

average delay of 2.5 years between the onset of symptoms and the diagnosis of HF has been reported [16]. Therefore, accurate and low-cost biomarkers for early detection of cardiomyopathy are needed.

Cardiac troponin I (cTnI) is a member of the troponin complex and a major component of myofibrils [17]. cTnI is uniquely expressed in cardiac muscles [18], and because it appears in the blood following cardiac injury, it is used as a specific cardiac injury marker for acute myocardial infarction (AMI) in adults [19]. Although some studies have reported the utility of cTnI for evaluating cardiac function in muscular dystrophy, little is known about its characteristics and diagnostic value in these patients [18].

The alpha-actinin-3 (*ACTN3*) gene encodes alpha-actinin-3, one of the major structural components of sarcomeric Z-discs [20]. There is a common null variant—c.1729C > T (p.R577X) (rs1815739) (NM_001104.4)—of *ACTN3* that results in the replacement of arginine (R) with a premature stop codon (X) at amino acid 577 in the muscle protein alpha-actinin-3, leading to the deficiency of alpha-actinin-3 in the individuals with the homozygous p.577X genotype [21]. We have previously reported that the *ACTN3* homozygous p.577X genotype is associated with a lower left ventricular (LV) dilation-free survival rate in DMD [22], suggesting that *ACTN3* is a genetic modifier of cardiomyopathy.

In this study, we compared cTnI levels in patients with DMD or BMD and assessed cTnI levels and cardiac function to determine whether cTnI is a biomarker of cardiac dysfunction in these patients. Furthermore, we evaluated the contribution of the *ACTN3* genotype to the serum levels of cTnI.

Results

Distribution of cTnI in patients with DMD and BMD by age

A total of 174 patients (127 DMD and 47 BMD patients) were enrolled. For patients with DMD or BMD, 529 and 131 serum cTnI values were collected, respectively. All data on serum cTnI levels, including multiple measurements for each person by age, for patients with DMD or BMD are shown in Fig. 1a and 1b, respectively. During the first decade of life, serum cTnI levels were rarely elevated, and abnormal values were generally found in the second decade in both groups. The cTnI levels stabilized at a low level after the third decade in both groups. Markedly high values (> 2.0 ng/mL) were observed in both patient groups during the second decade (Fig. 1a and b); these values were obtained from three DMD and two BMD patients. The three DMD patients who showed markedly high values had deletions of exons 56–62, small insertions in exon 8 (c.783dupT), and small deletion in exon 18 (c.2230_2231delAG). The mutations in the two BMD patients were small deletions in exon 27 (c.3613delG) [27] and deep intron mutation in intron 4 (c.265-463A > G). There was no specific predisposition to any mutation position or type. None of the patients showed symptoms such as chest pain or electrocardiogram (ECG) findings related to AMI at the time of cTnI measurement.

Comparison of serum cTnI levels and proportions of abnormal cTnI levels between DMD patients and BMD patients

To assess whether serum cTnI level or distribution differed between DMD and BMD, the highest serum cTnI value for each patient (only one value per patient over a lifetime) was adopted for statistical analysis. Thus, 127 and 47 values were collected for patients with DMD and BMD, respectively. Serum cTnI values and the proportions of patients with abnormal cTnI values were compared. The background data of the DMD (n = 127) and BMD (n = 47) patients at the time of serum cTnI assay are displayed in Table 1. There was no statistical difference in age between the DMD and BMD groups. Angiotensin-converting enzyme inhibitors, beta-blockers, steroids, non-invasive positive pressure ventilation were more commonly used in DMD patients. The comparison of the highest value of serum cTnI for each patient between DMD and BMD groups is shown in Table 2. The median (IQR) serum cTnI level in the DMD group was 0.06 ng/mL (0, 0.16), which was higher than that in the BMD group (0.01 ng/mL [0, 0.05]). When the data were divided into three patient age groups ($1 < \text{years} \leq 10$, $10 < \text{years} \leq 18$, and $18 < \text{years}$), the median serum cTnI ($1 < \text{years} \leq 10$, $10 < \text{years} \leq 18$) was statistically higher in patients with DMD than in those with BMD. In contrast, in patients > 18 years, there was no statistical difference. The proportion of patients with abnormal serum cTnI levels was statistically larger in patients with DMD within the age range of $10 < \text{years} \leq 18$ than in BMD patients.

Table 1
Patients' background characteristics

	DMD (n = 127)	BMD (n = 47)	P-value
Age, median (IQR), years	13 (8, 18)	15 (10, 18)	0.19
Medication, n (%)			
ACEI	42 (33.1)	7 (14.9)	0.022[$]
ARB	3 (2.4)	0 (0)	0.56
beta-blocker	42 (33.1)	5 (10.6)	0.004[$]
diuretic	3 (2.4)	0 (0)	0.56
Steroid	23 (18.1)	0 (0)	0.0006[$]
Motor, n (%)			
Gait	42 (33.1)	46 (97.9)	< 0.0001[$]
Walker	1 (0.8)	0 (0)	1.0000
wheelchair	84 (66.1)	1 (2.1)	< 0.0001[$]
Respiratory management, n (%)			
BiPAP or NPPV	13 (10.2)	0 (0)	0.021[$]
ventilator	0 (0)	0 (0)	-

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BiPAP, bi-level positive airway pressure; BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; NPPV, non-invasive positive pressure ventilation; IQR, interquartile range

[$]Values are statistically significant according to Fisher's exact test.

Table 2
Comparison of serum cTnI levels and proportion of abnormal cTnI levels in DMD and BMD patients

	DMD (n = 127)	BMD (n = 47)	P-value
cTnI, median (IQR), ng/mL			
Total	0.06 (0.00, 0.16)	0.01 (0.00, 0.05)	0.031*
(1 < years ≤ 10)	0.00 (0.00, 0.04)	0.00 (0.00, 0.00)	0.048*
(10 < years ≤ 18)	0.13 (0.07, 0.49)	0.04 (0.01, 0.15)	0.039*
(18 < years)	0.03 (0.00, 0.08)	0.02 (0.01, 0.04)	0.74
Abnormal cTnI levels, n/n (%)			
Total	71/127 (55.9%)	15/47 (31.9%)	0.006$
(1 < years ≤ 10)	8/44 (18.2%)	1/14 (7.1%)	0.43
(10 < years ≤ 18)	49/57 (86.0%)	10/22 (45.5%)	0.0005$
(18 < years)	14/26 (53.8%)	4/11 (36.4%)	0.48

Abbreviations: BMD, Becker muscular dystrophy; cTnI, cardiac troponin I; DMD, Duchenne muscular dystrophy; IQR, interquartile range

*Values are statistically significant according to Mann-Whitney's U test.

$Values are statistically significant according to Fisher's exact test.

Changes in serum cTnI levels, LVEF, and LVDd in the second decade of life

As shown in Fig. 1, abnormal cTnI values were generally found in the second decade of life in patients with DMD and BMD. Since the onset of cardiomyopathy was generally observed in the second decade of life among DMD patients [27, 28], we hypothesized that the elevation of serum cTnI was an initial abnormal finding suggesting cardiac involvement. To evaluate this, annual changes in serum cTnI levels and echocardiographic findings were described (Fig. 2). Only the first measurement of serum cTnI, LVEF, or LVDd was adopted for each individual if the parameters were measured multiple times at the same age. In DMD patients, the median serum cTnI level was elevated to the abnormal range (cTnI ≥ 0.05 ng/mL) at 11 years of age. It reached a maximum at 13 years, and thereafter, it decreased with age and returned to the normal range at 16 years of age (Fig. 2a). Median LVEF decreased with age and became abnormal (LVEF < 53%) at the age of 14 years—a year after the maximum cTnI level was observed. Cardiac dysfunction (LVEF < 53%) was observed three years after abnormal median serum cTnI levels (Fig. 2b). Median LVDd gradually increased but did not reach an abnormal value (LVDd > 55 mm; Fig. 2c). In BMD patients, serum cTnI value also increased with age and peaked at the age of 14 years. Thereafter, it decreased with age (Fig. 2d). In contrast to the finding in DMD patients, the median peak of serum cTnI

(0.04 ng/mL) in BMD patients did not exceed the upper limit of the standard value (≧ 0.05 ng/mL). LVEF decreased with age and became abnormal at the age of 17 years (Fig. 2e)—three years after the age at which cTnI peaked in BMD patients. LVDd gradually increased but did not reach an abnormal value; this finding was similar to the observation among DMD patients (Fig. 2f).

ACTN3 genotype and serum cTnI levels in patients with DMD

We have previously reported that the *ACTN3* XX null genotype is related to the early onset of dilated cardiomyopathy in DMD patients [26]. To evaluate the contribution of the *ACTN3* genotype to cTnI level, patients with DMD were grouped into three genotypes: the RR, RX, and XX genotypes. As the *ACTN3* genotype was analyzed only for patients whose genomes were conserved, the genotype was determined in 73 of the 127 DMD patients. Genotypes RR, RX, and XX were identified in 14 (19.18%), 38 (52.05%), and 21 (28.77%) of the 73 patients, respectively. Patients with the A*CTN3* XX genotype had maximum cTnI levels at the age of 11 years. On the other hand, in patients with RR and RX genotypes, cTnI peaked at the ages of 14 and 12 years, respectively (Fig. 3a). The highest median cTnI values were 0.16, 0.21, and 0.29 ng/mL in the RR, RX, and XX groups, respectively. Patients with the XX genotype had a higher cTnI peak value at an earlier stage of disease than those with other genotypes. To determine the impact of alpha-actinin-3 deficiency, patients were divided into two groups—XX group and RR and RX group—and we compared the annual change in cTnI levels between the two groups. The peak of cTnI in the XX group occurred three years earlier than in the RR and RX group (Fig. 3b).

Discussion

We confirmed that higher cTnI levels were generally found in the second decade of life in patients with DMD and BMD. Second, the median serum cTnI level by age was higher in DMD patients until the age of 18 years, and abnormal cTnI values were more common in the DMD group than in the BMD group. In addition, the median maximum cTnI levels were found one year before the median abnormal LVEF value in DMD patients and three years before in BMD patients. Finally, we found that the *ACTN3* XX genotype showed higher cTnI elevation earlier than the other two genotypes in DMD patients.

Cardiac dysfunction due to the progression of cardiomyopathy is the main cause of death in patients with DMD and BMD [29]. Therefore, international guidelines recommend early detection and therapy for cardiomyopathy in DMD and BMD patients [2, 30]. There are, however, some difficulties associated with diagnosing cardiomyopathy since the age of onset and severity can be variable [30], and symptoms due to deterioration of cardiac function, such as orthopnea and dyspnea on exertion or rest, are rare in DMD patients [10]. Nigro et al. reported that 61.5% of patients with DMD had preclinical cardiomyopathy without any symptom [6]. Perloff et al. reported that even asymptomatic DMD patients showed regional wall motion abnormalities after 10 years of age [31]. Early detection of cardiomyopathy in patients with DMD may, therefore, be relevant because timely initiation of medications or therapies will delay cardiac remodeling and relieve cardiac dysfunction. Biomarkers that can detect the onset of cardiomyopathy are thus required, and our study suggests that cTnI may be such a biomarker.

cTnI is a member of the troponin complex and a major component of myofibrils, and it is uniquely expressed in cardiac muscles [32]. It appears in the blood following cardiac injury and is a specific cardiac injury marker [15]. Its levels are elevated not only in acute but also in chronic pathogenic conditions. Recently, increasing cTnI levels have been shown in patients with cardiomyopathy or chronic HF in the general population [33, 34]. In the present study, 55.9% and 31.9% of the patients with DMD and BMD, respectively, had elevated cTnI levels. Although Kan et al. reported that DMD patients who had acute cardiomyopathy with acute chest pain had elevated cTnI levels and diffuse ST changes on ECG [35], none of the patients in our study complained of symptoms related to acute myocardial injury such as chest pain or dyspnea. Moreover, echocardiography and ECG did not show any sign of AMI. These results, therefore, indicated that chronic myocardial injury caused elevation of cTnI levels in patients with DMD and BMD in our study.

In the present study, we found higher serum cTnI levels with increasing age in DMD patients compared with BMD patients, and the proportion of patients with abnormal serum cTnI levels was larger in the DMD group at all ages and in the age range of $10 < \text{years} \leq 18$ when compared with the BMD group. In one study, cardiomyopathy was ubiquitously observed in patients with DMD (in more than 90% of patients over 18 years of age) [7]. On the other hand, the onset of cardiomyopathy was variable in patients with BMD. The onset of dilated cardiomyopathy, the typical end form of cardiomyopathy, occurs in the mid-teen years to 20s in DMD patients [7, 36] and 30s to 40s in BMD patients [37]. These results indicate that DMD generally has an earlier and more severe cardiac phenotype than BMD. In fact, DMD patients exhibited more severe LVEF decline compared to BMD patients. This difference in severity can be explained by the difference in dystrophin levels in the myocardium. In comparison with BMD patients who have an in-frame mutation that produces shortened and less functional dystrophin, DMD patients have a complete absence of dystrophin, resulting in myocardial disruption by mechanical stress [38]. The difference in the level of cTnI between the two groups of patients is considered to reflect the different degrees of myocardial damage in the two muscular disorders.

Previous studies have reported the utility of cTnI for evaluating the cardiac function, especially in patients with DMD. Matsumura et al. reported that most DMD patients showed higher levels of cTnI in the second decade of their lives; however, no obvious correlation between cTnI and LVEF or brain natriuretic peptide was observed [39]. Hammere-Lercher et al. reported that all patients with DMD, with a mean age of 7.5 years, had cTnI levels below the upper reference limit (URL), and there was no relation of cTnI level to clinical evidence of cardiac failure [18]. Castro-Cago et al. also reported no relationship between cTnI levels and cardiac function [40]. These reports suggest that cTnI cannot be used to evaluate cardiac function. However, as shown in our study, the cTnI level was transiently elevated in the second decade before the decline of LVEF. This indicated that the cTnI level was not associated with cardiac function at the time of measurement, but later, it was.

Recently, myocardial fibrosis (MF) in DMD patients has been demonstrated using cMRI with late gadolinium enhancement (LGE), which revealed that subepicardial fibrosis was the main characteristic of DMD patients [41]. When the myocardium is injured, damaged cardiomyocytes are repaired by

recruitment, proliferation, and activation of cardiac fibroblasts, which produce extracellular matrix components, resulting in the formation of fibrotic scars [42]. Remarkably, MF has been reported in DMD cardiomyopathy before the onset of myocardial dysfunction in young patients with DMD [43]. We hypothesize that serum cTnI levels may increase with the progression of MF because the observed timings of fibrosis and cTnI rise are the same (early second decade of life). Recently, Sonia et al. reported that cTnI values correlated with cMRI findings in patients with DMD cardiomyopathy [44]. They showed that cTnI levels in DMD patients with mild LGE were significantly increased compared to those in patients without LGE. These studies and the present study indicate that cTnI, a standard marker for AMI, may have the potential to become an alternative, cost-effective, and noninvasive biomarker for detecting early signs of cardiac injury. In fact, cTnI has gained popularity as a biomarker in the diagnosis of HF [45], and the cost of cTnI assay has been reported to be 10—100 times less than that of cardiac imaging [46].

As measurable plasma cTnI is found in the healthy population [24, 47], the abnormal value of cTnI is recommended to exceed the 99th percentile URL [48]. However, there is no internationally accepted standard for the 99th percentile URL of cTnI, although a wide range of variables has been used as the 99th percentile URL [49]. Caselli et al. recently reported plasma cTnI levels in healthy neonates, children, and adolescents; 357 participants had a high sensitive immunoassay similar to that used in our study. In their study, the cTnI showed the highest value in the first weeks of life, and it decreased progressively up to adulthood. Therefore, the 99th percentile URL needs to be defined according to age. They reported that the 99th percentile URL was age dependent; it was 61.3 ng/L for the whole population minus neonates and infants ($1 < \text{years} \leq 18$) and 41.3 ng/L for the group of adolescents ($10 < \text{years} \leq 18$) [24]. Unfortunately, they did not report the 99th percentile URL for toddlers ($1 < \text{years} \leq 10$). Therefore, we decided to define the 99th percentile URL according to the patient's age as follows: $\geq$0.07 ng/mL, $1 < \text{years} \leq 10$; $\geq$0.05 ng/mL, $10 < \text{years} \leq 18$; and $\geq$ 0.03 ng/mL, > 18 years (manufacturer's recommendation).

In the present study, we also examined the relationship between the *ACTN3* genotype and cTnI levels in patients with DMD and found that the maximum cTnI level in patients with *ACTN3* XX genotype was observed a few years earlier compared with the other two genotypes. These results suggest that patients with the XX genotype may have a higher risk for myocardial injury. Interestingly, the existence of alpha-actinin-3 has been reported not only in skeletal muscles but also in human fetal and adult hearts [50]. We recently reported that the XX genotype is related to a lower LV dilation-free survival rate in patients with DMD [22]. The impact of alpha-actinin-3 deficiency on cardiomyopathy progression was not elucidated in this study. Our results, however, indicate that alpha-actinin-3-deficient myocardium can be sensitive to mechanical and/or hypoxic damage that induces elevation of cTnI levels.

This study has some limitations. First, it was a retrospective observational study and was subject to selection bias. Second, although we evaluated a relatively large number of patients with DMD and BMD compared to previous studies, the number of participants may not be enough to allow generalization of our results to larger cohorts. However, the rarity of these muscular disorders may make it difficult to conduct studies on larger samples. Third, no patient had cTnI level measured over a long follow-up

period; therefore, we could not elucidate precise changes in serum cTnI level for each patient by age. Finally, we did not assess the effects of cardioprotective medications that might affect cTnI levels. In addition, since we measured cTnI level only once at assessment for each patient, we do not know whether the value is reproducible or not. Despite these limitations, our study is unique in that it is a longitudinal study with a large number of DMD or BMD patients. Our findings may positively impact cardiac care by supporting the use of cTnI as a biomarker for cardiomyopathy.

In conclusion, we evaluated and compared serum cTnI levels and cardiac function in patients with DMD or BMD in a large cohort. cTnI levels were higher in DMD patients compared with BMD patients of each age group until the second decade of life, suggesting myocardial injury indicated was more severe in DMD patients. The *ACTN3* null genotype may be a risk factor for early myocardial injury.

Methods

Study design and subjects

This retrospective, clinical observational study was conducted with the approval of the Ethics Committee of Kobe University (Approval No. 1534). Informed consent was obtained from the patients or their parents. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

We reviewed the electronic charts of patients with DMD or BMD at Kobe University Hospital. Between August 1, 1991 and May 15, 2019, 459 DMD and 104 BMD patients were followed up. Of these, patients whose cTnI was measured at least once were enrolled in this study. The clinical diagnoses of DMD or BMD were confirmed by the identification of mutations in the *DMD* gene. Gene mutations were analyzed in both genomic DNA and mRNA extracted from muscle or lymphocytes, as described previously [23].

Serum cTnI measurements and reference values

Serum cTnI levels were measured with Architect STAT cardiac troponin I assay (Abbott Diagnostics) until April 14, 2015. Thereafter, the assay method was changed to Architect STAT highly sensitive TnI assay (Abbott Diagnostics) using the Architect *i*2000$_{SR}$ platform in our hospital. The limit of detection was < 10 pg/mL and 1.1—1.9 pg/mL, and the 99th percentile values were 28 and 26 pg/mL, respectively, for the former and latter assay methods, as reported by the manufacturer. When the acquired data was less than a minimum reference value, we defined the value as zero. Abnormal serum cTnI levels were defined as follows: ≥0.07 ng/mL (patient's age: 1 < years ≤ 10), ≥ 0.05 ng/mL (patient's age: 10 < years ≤ 18), and ≥ 0.03 ng/mL (patient's age: >18 years), according to previous literature and the manufacturer's recommendations [24, 25].

Echocardiography

A detailed echocardiogram method has been previously described [23]. Briefly, all

echocardiograms were performed by T. Yamamoto. Echocardiographic evaluation of patients with DMD or BMD was scheduled annually until the age of 12 years and biannually thereafter. All patients were placed in the supine position during the investigation. Cardiac dysfunction was defined as left ventricular ejection fraction (LVEF) < 53% [23]. LV dilation was defined as LV end-diastolic dimension (LVDd) > 55 mm [23].

ACTN3**genotyping**

The *ACTN3* genotype was determined only in DMD patients whose genomic DNA was conserved in our laboratory. Genomic DNA was isolated using standard phenol-chloroform extraction methods. *ACTN3* exon 15 was amplified by polymerase chain reaction (PCR) as previously described [26]. The purified PCR-amplified products were sequenced using the Premix sequencing system (Fasmac Co., Ltd., Kanagawa, Japan). If patients had a variant in two alleles of c.1729C (p.577R), the *ACTN3* genotype was defined as 577RR (RR). If patients had a single nucleotide variant of c.1729C > T (p. R577X) in one allele, the *ACTN3* genotype was defined as 577RX (RX), and in two alleles, as 577XX (XX).

Statistical analysis

Data were expressed as numbers and percentages or medians and interquartile ranges (IQR). Mann-Whitney's U test or Fisher's exact test was used, as appropriate, for statistical analysis of the results. A difference was considered statistically significant when the p-value was < 0.05. Analyses were performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA).

Abbreviations

ACTN3
alpha-actinin-3; AMI:acute myocardial infarction; BMD:Becker muscular dystrophy; cMRI:cardiovascular magnetic resonance imaging; cTnI:cardiac troponin I; DMD:Duchenne muscular dystrophy; ECG:electrocardiogram; HF:heart failure; IQR:interquartile range; LGE:late gadolinium enhancement; LV:left ventricular; LVEF:left ventricular ejection fraction; LVDd:left ventricular end-diastolic dimension; MF:myocardial fibrosis; PCR:polymerase chain reaction; URL:upper reference limit

Declarations

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Competing interests

The authors declare no competing interests.

Author contributions

H.Y.: Conceptualization, Methodology, Formal Analysis, Investigation, Writing—Original Draft. **H.A.:** Conceptualization, Methodology, Investigation, Writing—Review & Editing, Supervision, Project Administration, Funding Acquisition. **T.Y.:** Resources, Writing—Review & Editing, Supervision. **M.M.:** Writing—Review & Editing, Supervision. **K.I.:** Writing—Review & Editing, Supervision.

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Figures

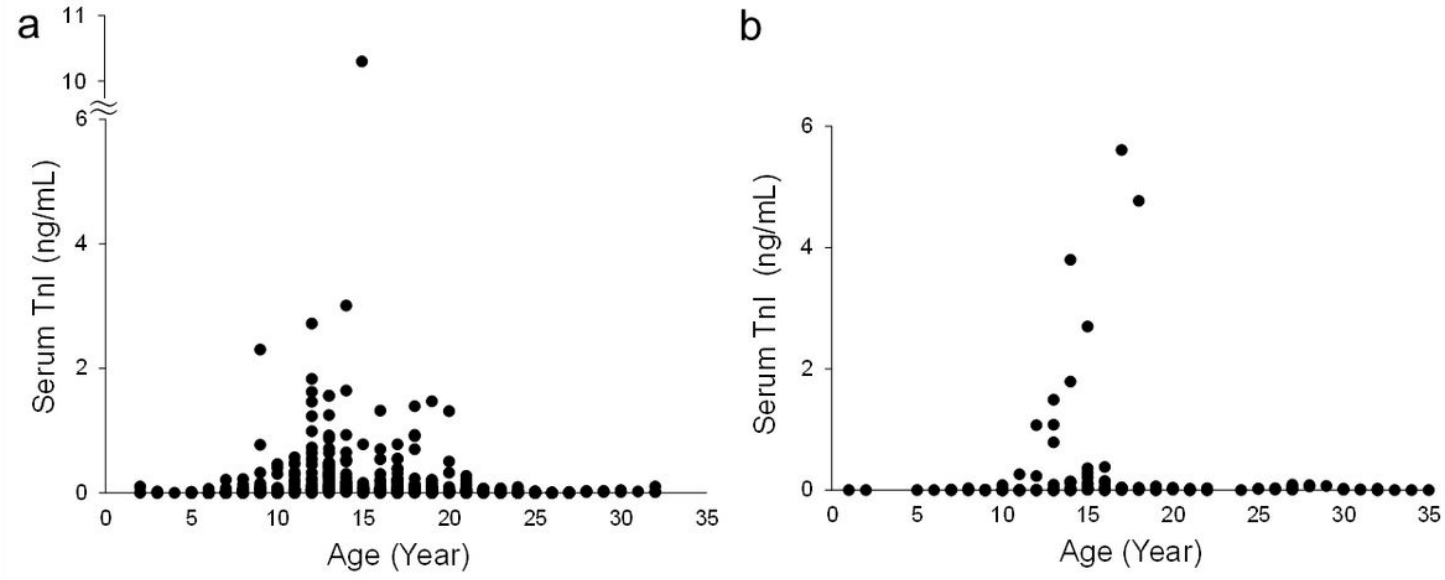

Figure 1

Serum cTnI levels in patients with DMD (a) and BMD (b) by age In all, 529 and 131 serum cTnI values were obtained from 127 DMD and 47 BMD patients, respectively. cTnI, cardiac troponin I; BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy

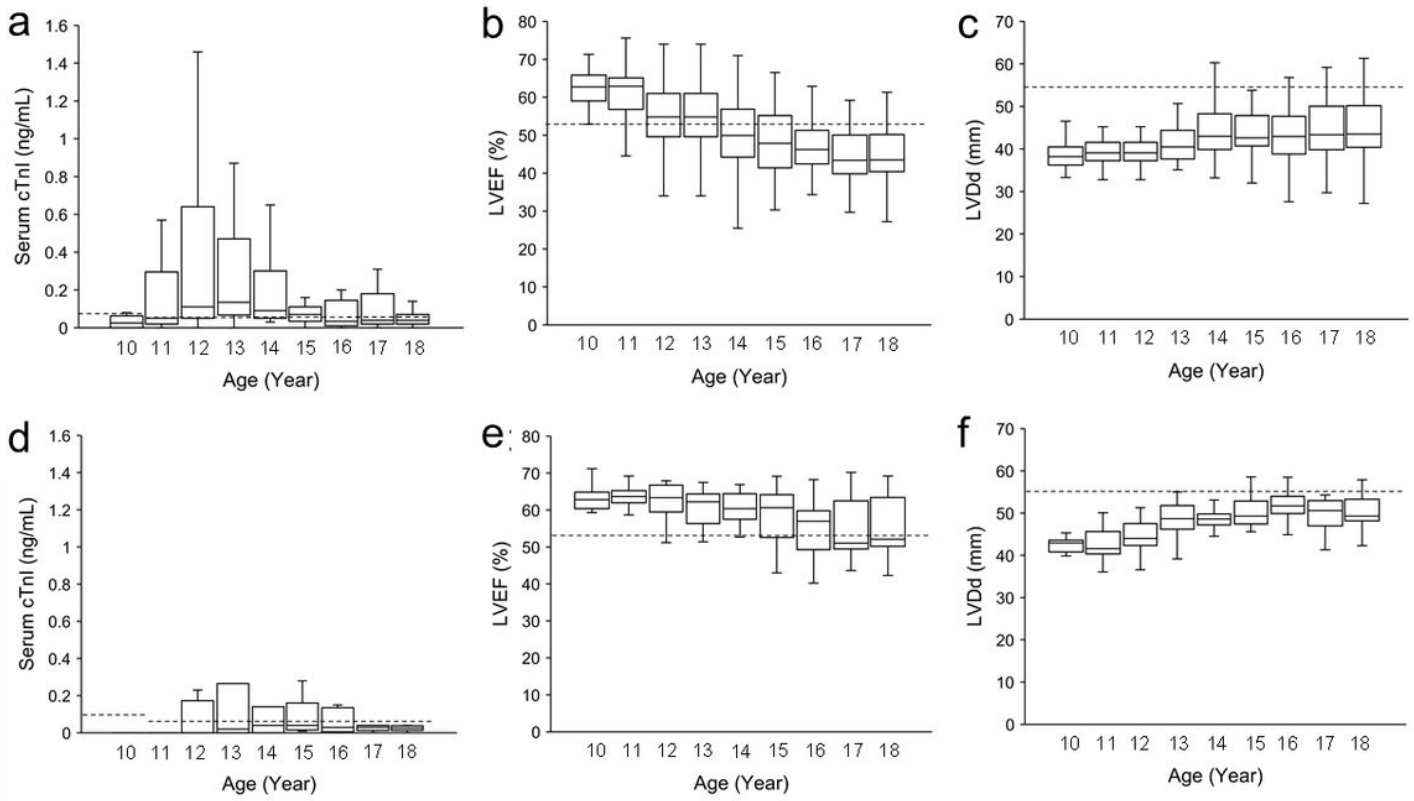

Figure 2

Serum cTnI levels, LVEF, and LVDd in the second decade of life in patients with DMD and BMD Dotted lines in a and d show upper limits of reference values. Dotted lines in b and e, and C and F indicate the assessment of cardiac dysfunction (LVEF <53%) and left ventricular dilation (LVDd >55 mm), respectively. A box and whisker plot show the first quartile to the third quartile. A vertical line goes through the box at the median. The upper and lower whiskers represent scores outside the middle 50%. cTnI, cardiac troponin I; BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic dimension

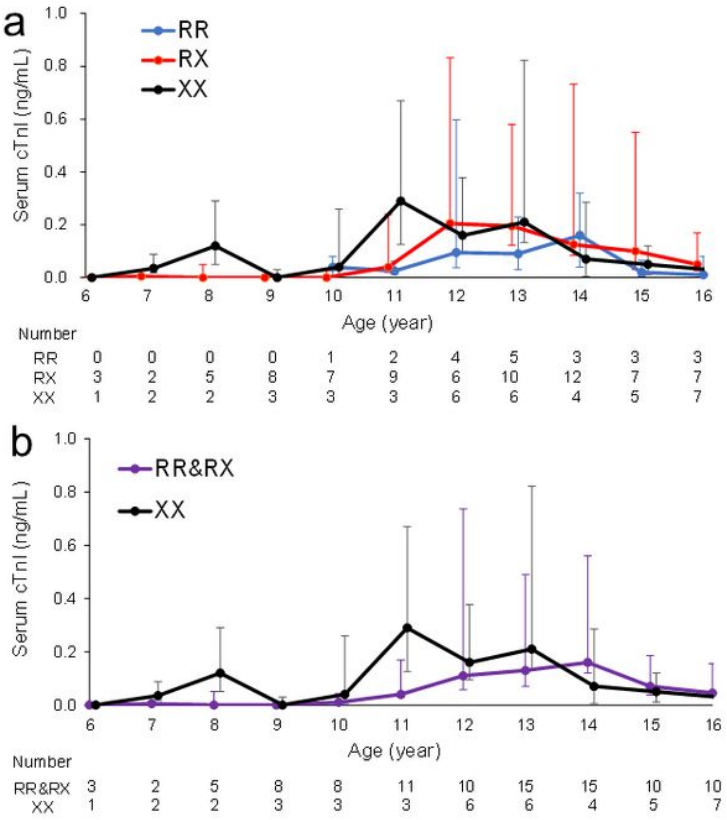

Figure 3

Changes in serum cTnI levels in patients with different ACTN3 genotypes The XX genotype showed an early onset of cTnI elevation (a). When compared between the XX genotype group and the RR and RX genotype groups, serum cTnI in the XX group peaked three years earlier (b). Data are represented as median, the positive vertical bar represents 75th percentile, and the negative vertical bar represents 25th percentile. RR, RX, and XX represent the ACTN3 577RR, 577RX, and 577XX genotypes, respectively. cTnI, cardiac troponin I