의학석사 학위논문

Characteristics of Stiffness According to Clinical Stages in Patients with Duchenne Muscular Dystrophy

뒤셴느근디스트로피 환자에서 임상적 단계에 따른 강직의 특징

2021년 10월

서울대학교 대학원

임상의과학과

원 준 희

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Abstract

Characteristics of Stiffness According to Clinical Stages in Patients with Duchenne Muscular Dystrophy

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Objective: Managing physical symptoms of Duchenne muscular dystrophy (DMD) is essential to improve quality of life (QoL). Stiffness is symptom that could affect QoL of individuals with DMD, but the data is scarce regarding stiffness as subjective physical symptom and the relation between stiffness and other physical symptoms. We aimed to evaluated characteristics of stiffness according to clinical stage of DMD and to investigate

the relationship of pain and contracture on stiffness.

Methods: We conducted cross-sectional study in single pediatric center. We recruited 148 participants with DMD with mean age of 14.5±5.3 years. We conducted a structured questionnaire to investigate location, frequency, severity and limitation of stiffness. The prevalence of stiffness characteristics were compared according to the clinical stage. The distribution of stiffness was compared with that of contracture and pain.

Results: Among 148 participants, 54 (36.5%) reported stiffness and the prevalence of stiffness was decreased as the stage of DMD progressed. The limitation was found in 36 participants (66.7%) among participants with stiffness. Participants of advanced clinical stage complained significantly more severe stiffness and patients with stiffness in upper extremity reported more frequent stiffness. The distribution of stiffness was different from those of contracture or pain.

Conclusion: Stiffness is a distinct symptom of individuals with DMD and the majority of participants with stiffness were limited their activity due to stiffness. Further study would be needed to evaluate subjective stiffness in DMD and to develop to proper method to manage stiffness in individuals with DMD.

Keyword : Duchenne muscular dystrophy, stiffness, contracture, pain

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List of Abbreviations

Amb Ambulatory

ENA Early non-ambulatory

LNA Late non-ambulatory

LE Lower extremity

P P-value

ROM Range of motion

UE Upper extremity

Chapter 1. Introduction

1.1. Study background

Duchenne muscular dystrophy (DMD) is one of the most severe inherited muscle diseases caused by dystrophin gene mutation. Muscle weakness induced by progressive muscle necrosis and degeneration occurs in skeletal, cardiac and respiratory muscles, resulting loss of ambulation, cardiac dysfunction and respiratory difficulty.[1] The leading cause of death is cardiac or respiratory failure due to weakness of muscles.[2] Recently, the life expectancy of individuals with DMD has been increasing by supportive device and comprehensive multidisciplinary care. Although novel treatment including dystrophin-target therapies was suggested for more fundamental management,[3,4] there is no cure for the disease to improve motor function and individuals with DMD should live with impaired muscle function. Conventionally, muscle weakness and medical comorbidities were considered important and managing quality of life was underestimated and underassessed in management strategy for DMD. Individuals with DMD could exhibit various symptoms that occur during the progression of disease or during treatment of DMD, including fatigue, pain, anxiety or depression.[5] In many cases, physical symptoms which could influence their quality of life are

taken for granted by medical staff or caregivers. It leads decrement of quality of life of individuals with DMD throughout their life. Recent guidelines for management of DMD emphasized the importance of enhancing quality of life in planning management strategy of individuals with DMD.[6] Therefore, it is essential to manage such physical symptoms to improve quality of life.

Stiffness can be candidate for physical symptom related with quality of life in individuals with DMD. Althou the patients with various myopathies could exhibit stiffness symptom, the data is scarce regarding stiffness as subjective physical symptom and whether stiffness is a separate symptom from other symptoms, such as contracture or pain. Objective stiffness was reported in previous study, known to be caused by the increase in connective tissue and decreased muscle extensibility coexisting with dysfunctions of the affected muscles in DMD.[6] Several studies reported that objective stiffness was increased in DMD group compared to healthy controls. Cornu et al assessed series elastic components of knee and elbow joints in individuals with DMD and reported stiffness index was higher in individuals with DMD than healthy controls.[7,8] Several studies evaluated the muscles by ultrasound elastography and reported muscle stiffness was higher in individuals with DMD than healthy controls.[9–11] However, these studies only reported objective stiffness and had several limitations. They investigated small size of participants less than 10 participants, used special equipment with poor accessibility in actual practice, and did not compare DMD

patients according to clinical stage.

There was little study regarding subjective stiffness. Janssen et al conducted web-based questionnaire including domains of stiffness to evaluate upper extremity (UE) function and reported that frequency, severity and limitation of stiffness were correlated with arm function of DMD patients.[12] However, their study had several limitations. They only evaluated stiffness in UE and did not evaluated stiffness in lower extremity (LE), that could be involved in early stage of disease and affect gait function. Because their study was conducted via internet, they could not perform face-to-face interview with precise information and conduct medical record review or physical examination. Previous study suggested that stiffness might occur due to loss of normal elasticity and plasticity, resulting joint contracture and the loss of range of motions.[7,13] There was no report investigating the relationship of stiffness and joint contracture. Moreover, pain is common physical symptom and could occur more than half of individuals with DMD.[14] There was no report comparing the involvement pattern of stiffness and pain, and investigating relationship of pain and contracture on stiffness.

1.2. Purpose of research

To establish management strategy for stiffness, more accurate information on stiffness than previously reported knowledges is necessary. Therefore, the aim of this study was to investigate the characteristics of stiffness according to clinical stages; location, frequency, severity, impact on QOL, and the relationship with pain and contracture in patients with DMD.

Chapter 2. Methods

2.1. Study population

We recruited the participants who were treated at pediatric rehabilitation clinic in Seoul National University Children's hospital between April 2020 and February 2021. Inclusion criteria were as follows: (1) confirmed diagnosis of DMD by genetic testing; (2) over than 7 years old; (3) no significant cognitive and physical impairments evaluated by the physician. To confirm DMD diagnosis, multiplex polymerase chain reaction and direct sequencing were initially conducted to detect mutations of the dystrophin gene. If the results of initial tests were negative, dystrophin gene sequencing was performed to detect point mutations, small deletions, or insertions. We excluded participants who had limitation to perform interview or physical examination because of medical condition. Because the research participants were children or adolescents, we explained the purpose and contents of this study to participants and their parents. The participants and their parents signed a written informed consent form. This study was approved by our Institutional Review Board (IRB No. 2004-193-1119).

2.2. Measures

A physician conducted face-to-face interviews using a structured questionnaire on stiffness, pain and functional ability. If the interviewee was unable to understand the questionnaire, a physician explained the contents to help complete the questionnaire. A physician measured range of motion(ROM) of major joints including bilateral shoulder, elbow, wrist, hip, knee and ankle, using goniometer. We recorded entire passive ROM according to the method of Norkin and White.[15] The presence of contracture in each joint was defined as the limitation of ROM compared to the reference range. The medical chart review was conducted to obtain demographic and medical information including year of diagnosis and year from wheelchair-bound status.

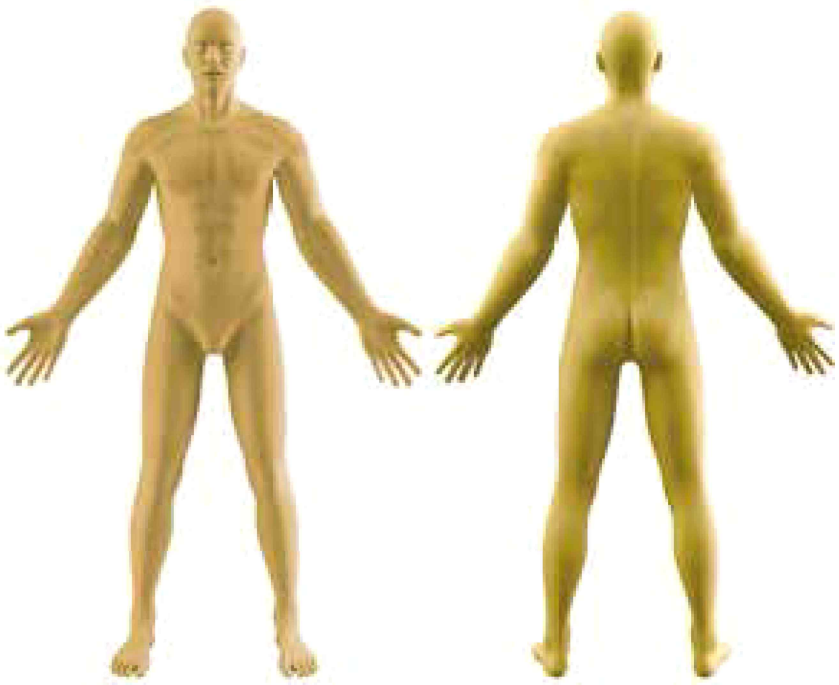
2.3. Characteristics of stiffness

The characteristics of stiffness was self-reported by the questionnaire. The stiffness questionnaire included contents from the stiffness domain in previous study conducted by Janssen et al.[16] The questionnaire includes three factors of stiffness: frequency, severity, and limitation. The frequency was measured by a Likert-type rating scale with seven response options ranging from '0=never' to

‘6=always’. The severity and limitations were measured by 11-point scale from 0 to 10: and ‘0=no stiffness’ to ‘10=worst stiffness imaginable’ for severity and ‘0=no limitations’ to ‘10=fully limited’ for limitation of daily activity due to stiffness. Each factor was classified into categories for statistical analysis. Frequency was classified into two categories: 1-3 for ‘not frequent’, 4-6 for ‘frequent’. Severity and limitation were classified into three categories: 1-3 for ‘mild’, 4-6 for ‘moderate’, and 7-10 for ‘severe’.[17]

The location of stiffness was marked by participants on a body map for children[18] and was coded as follows: UE (shoulder, arm, elbow, forearm, wrist, hand), LE (hip, thigh, knee, leg, ankle, foot) and trunk (head, cervical thoracic, lumbosacral). The body map used in this study was described in Figure 1. We classified location of stiffness by 4 categories: proximal UE, distal UE, proximal LE, and distal LE. The proximal UE included shoulder, arm and elbow region, distal UE included forearm, wrist and hand region. The proximal LE included hip, thigh and knee region and distal LE included leg, ankle and foot region. The prevalence of stiffness according to the clinical stage was investigated in each body region and each category.

Figure 1. The body map used for this study



2.4. Relation of stiffness with contracture and pain.

In each joint, we coded status of each joint by the presence of stiffness and contracture as follows: no stiffness nor contracture for ‘none’, stiffness without contracture for ‘stiffness only’, contracture without stiffness for ‘contracture only’, and coexisting stiffness and contracture in same joint for ‘coexist’. We initially investigated distribution of stiffness and contracture in entire participants. We classified the participants into 6 categories by presence of ‘stiffness only’, ‘contracture only’, and ‘coexist’ as follows: ’no stiffness nor contracture’, ‘stiffness’, ‘contracture’, ‘separate’, ′non-identical′, and ′identical′. ‘Stiffness’ and ‘contracture’ categories were composed of participants with only stiffness and only contracture in entire body, respectively. ‘Separate’ category consisted of participants with stiffness and contracture in different joints. ‘Non identical’ category included participants with overlapped stiffness and contracture in some joints. ‘Identical’ category contained participants with completely overlapped region of stiffness and contracture. If participant had “stiffness only” in ankle and “contracture only” in knee, he was classified as ‘separate’. If participants had ‘coexist’ in knee and ‘coexist’ in ankle, he was classified as ‘identical’. Subsequently, we investigated the change of distribution of stiffness and contracture in each joint by clinical stage. The prevalence of ‘stiffness only’,

‘contracture only’, and ‘coexist’ was investigated in each joint according to clinical stage group.

The presence of pain was reported by questionnaire. The participants described average of pain intensity and maximal pain intensity during the past 4 weeks. Numeric rating scale was used for measuring pain intensity, indicating ‘0’ for no pain and ’10’ for pain as severe as could imaginable. Each participant marked the location of pain on the same body map for stiffness. The location of pain was coded in the same way as stiffness was coded. In each region, we classified the presence of stiffness and pain as follows: no stiffness or pain for ‘none’, stiffness without pain for ‘stiffness only’, pain without stiffness for ‘pain only’, and coexisting stiffness and pain in same joint for ‘coexist’. We investigated the distribution of stiffness and pain in entire participants and each joint in the same was as stiffness and contracture. We investigated distribution of stiffness and pain in entire participants by 6 categories: ’no stiffness nor pain’, “stiffness’, ‘pain’, ‘separate’, 'non-identical', and 'identical'.

2.5. Statistical analysis

Descriptive statistics using mean and standard deviation was used for demographic information of the study participants. We analyzed the stiffness by two different groups, group according to clinical stage and body site. Clinical stage group was classified as follows:

ambulatory (Amb), early non-ambulatory (ENA), and late non-ambulatory (LNA). Among non-ambulatory participants, we defined the ENA group as those with ≤15 years of age and the LNA group as those with >15 years of age.[19,20] In addition, the data was analyzed according to the subgroup by body site because stiffness characteristics might differ from stiffness involvement site. The group was classified as follows: UE, LE, and trunk. UE group, LE group, trunk group were composed of participants with stiffness in UE region, LE region, and trunk region, respectively.

We initially compared prevalence of stiffness in each region according to clinical stage. Subsequently, we compared prevalence of three characteristics of stiffness between clinical stage groups. We then compared prevalence between extremity groups. Lastly, we compared distribution of stiffness to those of contracture and pain. Non-parametric Kruskal-Wallis test was used to analyze difference of average between each group and a Bonferroni correction was utilized for post hoc analysis. Fisher's exact test was used to elucidate difference of prevalence between groups. The level of significance was set at p-value<0.05 for all analyses. All analyses were performed using SPSS (version 26.0 for Windows, IBM Corp., Armonk, NY, USA).

Chapter 3. Results

3.1. Baseline characteristics

We recruited 148 participants with DMD with mean age of 14.5±5.3 years (age range, 7-33 years). Among the participants, 62 (41.9%) were classified as Amb group, 35 (23.7%) were as ENA group, and 51 (34.4%) were as LNA group. The mean age in each group were 10.73±3.19 in Amb, 12.86±1.63 in ENA, and 20.33±3.68 in LNA. Contracture was found in 126 participants (85.1%) in at least one site and ankle contracture was most frequent contracture in entire group. Detailed characteristics of study population is described in table 1.

Table 1. Baseline characteristics of the study population

		Total (N = 148)	Ambulatory (N = 62)	Early non-ambulatory (N = 35)	Late non-ambulatory (N = 51)
Age		14.54±5.28	10.73±3.19	12.86±1.63	20.33±3.68
Age group	0-10	31 (21.0%)	29 (46.8%)	2 (5.7%)	0 (0.0%)
	10-20	91 (61.5%)	31 (50.0%)	33 (94.3%)	27 (52.9%)
	20-30	24 (16.2%)	2 (3.2%)	0 (0.0%)	22 (43.1%)
	30-	2 (1.4%)	0 (0.0%)	0 (0.0%)	2 (3.9%)
Year from diagnosis		9.41±4.28	7.23±3.26	8.46±2.32	12.73±4.33
Year from W/C bound		6.23±4.30	-	2.86±1.57	8.72±3.71
Contracture	Total	126 (85.1%)	43 (69.4%)	34 (97.1%)	49 (96.1%)
	Shoulder	2 (1.4%)	0 (0.0%)	0 (0.0%)	2 (3.9%)
	Elbow	6 (4.1%)	0 (0.0%)	0 (0.0%)	6 (11.8%)
	Wrist	13 (8.8%)	0 (0.0%)	0 (0.0%)	13 (25.5%)
	Hip	10 (6.8%)	1 (1.6%)	1 (2.9%)	8 (15.7%)
	Knee	62 (41.9%)	2 (3.2%)	21 (60.0%)	39 (76.5%)
	Ankle	121 (81.8%)	42 (67.7%)	32 (91.4%)	47 (92.2%)

W/C, wheelchair

3.2. Characteristics of stiffness

3.2.1. Prevalence and location of stiffness

Overall, 54 of 148 participants (36.5%) reported stiffness in their body. The prevalence of stiffness was not significantly different by the clinical stage of DMD (P = 0.51): Amb 41.9% (26/62), ENA 34.3% (12/35), LNA 31.4% (16/51). The number of participants presented stiffness in UE were 17 (11.5%) and those in LE were 37 (24%). The most frequently reported location was knee and leg, accounted for 12.8% and 10.8% of participants. The prevalence of stiffness in distal LE was significantly different between clinical stages and decreased by the advanced clinical stage (P=0.003). The proximal LE did not show significant difference. The stiffness in UE increased in LNA group. The prevalence of stiffness in proximal UE and distal UE were increased in the advanced clinical stage. However, there was no significant difference between groups in UE (Table 2).

Table 2. Location of stiffness according to clinical stage

	Total	Amb	ENA	LNA	P
Upper extremity	17 (11.5%)	5 (8.1%)	3 (8.6%)	9 (17.7%)	0.287
Proximal	6 (4.1%)	1 (1.6%)	1 (2.9%)	4 (7.8%)	0.276
shoulder	3 (2.0%)	1 (1.6%)	1 (2.9%)	1 (2.0%)	1.000
arm	1 (0.7%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1.000
elbow	3 (2.0%)	0 (0.0%)	0 (0.0%)	3 (5.9%)	0.052
Distal	13 (8.8%)	4 (6.5%)	2 (5.7%)	7 (13.7%)	0.350
forearm	1 (0.7%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	0.581
wrist	6 (4.1%)	2 (3.2%)	1 (2.9%)	3 (5.9%)	0.763
hand	8 (5.4%)	3 (4.8%)	1 (2.9%)	4 (7.8%)	0.724
Lower extremity	37 (25.0%)	20 (32.3%)	8 (22.9%)	9 (17.7%)	0.190
Proximal	25 (16.9%)	11 (17.7%)	5 (14.3%)	9 (17.7%)	0.922
hip	5 (3.4%)	1 (1.6%)	0 (0.0%)	4 (7.8%)	0.131
thigh	8 (5.4%)	3 (4.8%)	2 (5.7%)	3 (5.9%)	1.000
knee	19 (12.8%)	8 (12.9%)	4 (11.4%)	7 (13.7%)	1.000
Distal*	25 (16.9%)	17 (27.4%)	6 (17.1%)	2 (3.9%)	0.003
leg	16 (10.8%)	10 (16.1%)	4 (11.4%)	2 (3.9%)	0.106
ankle	11 (7.4%)	7 (11.3%)	3 (8.6%)	1 (2.0%)	0.184
foot	4 (2.7%)	3 (4.8%)	0 (0.0%)	1 (2.0%)	0.554
Trunk	3 (2.0%)	1 (1.6%)	1 (2.9%)	1 (2.0%)	1.000
head	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
cervical	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
thoracic	3 (2.0%)	1 (1.6%)	1 (2.9%)	1 (2.0%)	1.000
lumbosacral	1 (0.7%)	1 (1.6%)	0 (0.0%)	0 (0.0%)	1.000

Amb, Ambulatory; ENA, Early non-ambulatory;

LNA, Late non-ambulatory; P, p-value.

* Significant difference

3.2.2. Characteristics of stiffness by clinical stage group

The most common frequency was ‘several times per week’ in entire participants. In the LNA group, ‘several times per week’ (25%) and ‘always’ (25%) were the most common frequency. The proportion of people who reported ‘frequent’ in frequency of stiffness was as follows: Amb 38.5%, ENA 75%, LNA 50%. There was no significant difference between clinical stages (Table 3).

Table 3. Stiffness frequency according to the clinical stage

	Total (N = 54)	Ambulatory (N = 26)	Early non-ambulatory (N = 12)	Late non-ambulatory (N = 16)	P-value
Not frequent	23 (42.6%)	16 (61.5%)	9 (75.0%)	8 (50.0%)	
Several times per year	5 (9.3%)	2 (7.7%)	0 (0.0%)	3 (18.8%)	
Several times per month	10 (18.5%)	6 (23.1%)	3 (25.0%)	1 (6.3%)	
Several times per week	18 (33.3%)	8 (30.8%)	6 (50.0%)	4 (25.0%)	
Frequent	21 (38.9%)	10 (38.5%)	3 (75.0%)	8 (50.0%)	0.416
Daily	9 (16.7%)	4 (15.4%)	2 (16.7%)	3 (18.8%)	
Half of the day	4 (7.4%)	3 (11.5%)	0 (0.0%)	1 (6.3%)	
Always	8 (14.8%)	3 (11.5%)	1 (8.3%)	4 (25.0%)	

Note: Frequency 3 or less, was classified as "not frequent", and 4 or more was classified as "frequent".

The most common severity was ‘mild’ stiffness in entire stage. ‘Severe’ stiffness was reported only in LNA group and the difference was significant by clinical stage (Amb 0%, ENA 0%, LNA 31.3%). The average of severity scale was higher in LNA stage, but the difference was not significant (Table 4).

Table 4. Stiffness severity according to the clinical stage

	Total (N = 54)	Ambulatory (N = 26)	Early non-ambulatory (N = 12)	Late non-ambulatory (N = 16)	P-value
Mild(1-3)	35 (64.8%)	18 (69.2%)	10 (83.3%)	7 (43.8%)	
Moderate(4-6)	14 (25.9%)	8 (30.8%)	2 (16.7%)	4 (25.0%)	0.014*
Severe(7-10)	5 (9.3%)	0 (0.0%)	0 (0.0%)	5 (31.3%)	
Average	3.3±2.12	2.88±1.51	2.5±1.31	4.56±2.87	0.102

* Significant difference

The limitation of daily activity was found in 36 participants (66.7%) among participants who complained stiffness. The most common limitation was 'mild' limitation in entire stage. Most participants with 'severe' limitation was found in LNA group. The average of limitation scale was not different between clinical stage groups (Table 5, Amb 3.56±2.04, ENA 3.00±1.41, LNA 4.08±3.50).

Table 5. Stiffness limitation according to the clinical stage

	Total (N = 54)	Ambulatory (N = 26)	Early non-ambulatory (N = 12)	Late non-ambulatory (N = 16)	P-value
None	18 (33.3%)	8 (30.8%)	6 (50.0%)	4 (25.0%)	
Present	36 (66.7%)	18 (69.2%)	6 (50.0%)	12 (75.0%)	
mild(1-3)	19 (35.2%)	9 (34.6%)	3 (25.0%)	7 (43.8%)	
moderate(4-6)	12 (22.2%)	8 (30.8%)	3 (25.0%)	1 (6.3%)	0.384
severe(7-10)	5 (9.3%)	1 (3.9%)	0 (0.0%)	4 (25.0%)	
Average	3.64±2.55	3.56±2.04	3.00±1.41	4.08±3.50	0.627

3.2.3. Characteristics of stiffness by body site group

The most common frequency was ‘daily’ in UE group and ‘several times per week’ in LE group. The prevalence of ‘frequent’ in UE showed significantly higher than that in LE, trunk group (70.6% in UE, 24.3% in LE, 0% in trunk group) (Table 6).

Table 6. Stiffness frequency according to body site group

	Upper extremity (N = 17)	Lower extremity (N = 37)	Trunk (N = 3)	P-value
Not frequent	5 (29.4%)	26 (70.3%)	3 (100.0%)	
Several times per year	1 (5.9%)	4 (10.8%)	0 (0%)	
Several times per month	1 (5.9%)	7 (18.9%)	2 (66.7%)	
Several times per week	3 (17.7%)	15 (40.5%)	1 (33.3%)	
Frequent	12 (70.6%)	11 (29.7%)	0 (0%)	0.003*
Daily	5 (29.4%)	5 (13.5%)	0 (0%)	
Half of the day	2 (11.8%)	2 (5.4%)	0 (0%)	
Always	5 (29.4%)	4 (10.8%)	0 (0%)	

Note: Frequency 3 or less, was classified as "not frequent", and 4 or more was classified as "frequent".

* Significant difference

The most common severity was ‘mild’ stiffness in entire group. The proportion of severe stiffness was not significantly different between groups (UE 17.7%, LE 8.1%, Trunk 0%). The average of severity scale was not differ significantly (Table 7).

Table 7. Stiffness severity according to body site group

	Upper extremity (N = 17)	Lower extremity (N = 37)	Trunk (N = 3)	p-value
Mild(1-3)	11 (64.7%)	23 (62.2%)	2 (66.7%)	
Moderate(4-6)	3 (17.7%)	11 (29.7%)	1 (33.3%)	0.658
Severe(7-10)	3 (17.7%)	3 (8.1%)	0 (0.0%)	
Average	3.65±2.74	3.27±1.85	2.67±2.35	0.633

The limitation was found in majority of participants in entire group. The 'mild' limitation was most commonly found in UE, LE and trunk group. The prevalence of 'severe' limitation was not different between body site groups (Table 8, UE 17.7%, LE 8.1%, trunk 0%).

Table 8. Stiffness limitation according to body site group

	Upper extremity (N = 17)	Lower extremity (N = 37)	Trunk (N = 3)	p-value
None	6 (35.3%)	12 (32.4%)	1 (33.3%)	
Present	11 (64.7%)	25(67.6%)	2 (66.7%)	
mild(1-3)	6 (35.3%)	13 (35.1%)	1 (33.3%)	
moderate(4-6)	2 (11.8%)	9 (24.3%)	1 (33.3%)	0.535
severe(7-10)	3 (17.7%)	3 (8.1%)	0 (0.0%)	
Average	4.18±3.09	3.39±2.35	3.50±2.50	0.414

3.3. Relation between location of stiffness, contracture, and pain

For stiffness and contracture, participants in 'identical' category were 8 of 148 participants (5.4%). There were 16 participants in 'non-identical' category (10.8%). Majority of participants had either stiffness or contracture (56.1%). There were 23 participants (15.5%) in 'separate' category. Detailed distribution of stiffness and contracture is described in Table 9. Figure 2 demonstrates the prevalence of stiffness and contracture in each joint and Figure 3 shows the prevalence by each clinical stage. In knee and ankle, 'coexist' account for 48% and 76.9% of participants with stiffness. Participants with 'contracture only' increased with advanced clinical stage in every joint. The number of participants with 'stiffness only' and 'coexist' decreased with clinical stage in knee and ankle, while increasing in shoulder, elbow, wrist joint.

Table 9. Distribution of stiffness and contracture in entire participants

	Number	Percentage
No stiffness nor contracture	18	12.2%
Stiffness or contracture only		
Stiffness	4	2.7%
Contracture	79	53.4%
Stiffness and contracture		
Separate	23	15.5%
Non-identical	16	10.8%
Identical	8	5.4%

Stiffness: individuals with only stiffness

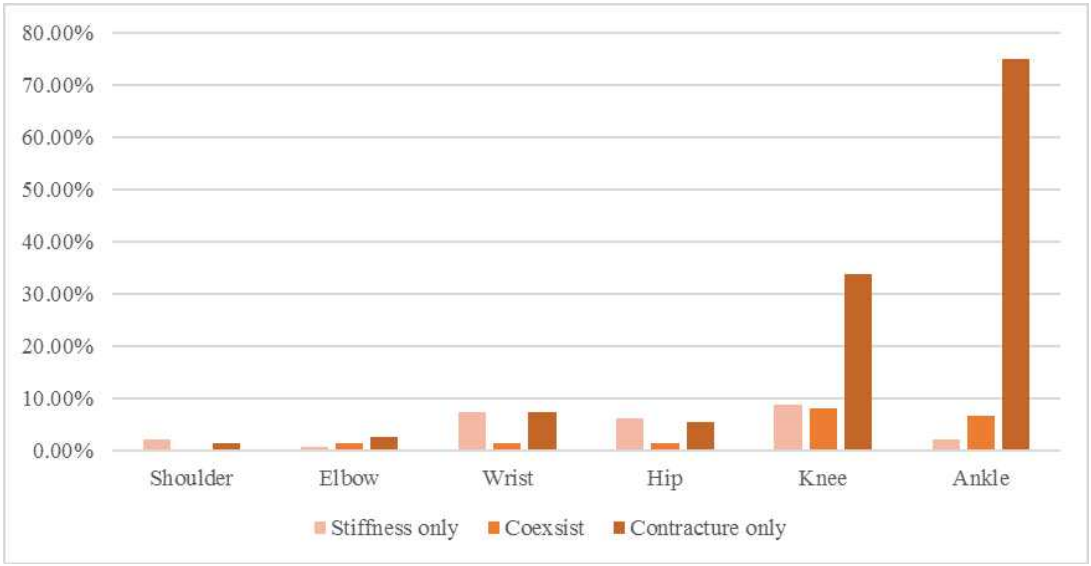
Contracture: individuals with only contracture

Separate: individuals with stiffness and contracture in different joints

Non-identical: individuals with overlapped stiffness and contracture in some joints and stiffness or contracture in other joints.

Identical: individuals with coexisting stiffness and contracture

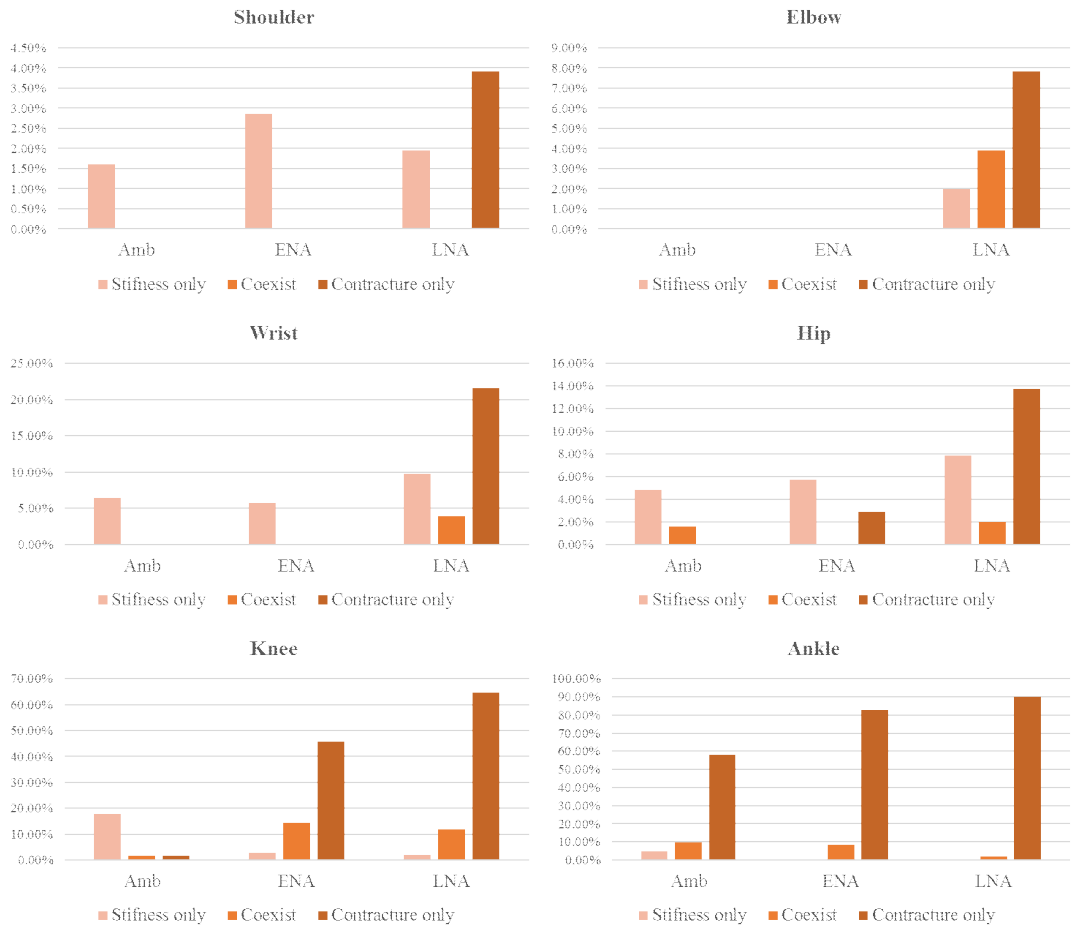
Figure 2. Correlation of stiffness and contracture in each joint.



Coexist: coexisting stiffness and contracture.

The participants without stiffness and contracture were not shown.

Figure 3. Correlation of stiffness and contracture in each joint according to clinical stage



Coexist: coexisting stiffness and contracture

The participants without stiffness and contracture were not shown.

For stiffness and pain, 6 participants were classified as 'identical' category (4.1%). There were 10 participants in 'non-identical' category (6.8%). Most participants had either stiffness or pain (43.3%). There were 19 participants (12.8%) in 'separate' category. Detailed distribution of stiffness and pain is described in Table 10. In each region, coexist group was accounted for less than 6%. Detailed information regarding pain and stiffness in each region is shown in Figure 4.

Table 10. Distribution of stiffness and pain in entire participants

	Number	Percentage
No stiffness nor pain	49	33.1%
Stiffness or pain only		
Stiffness	45	30.4%
Pain	19	12.8%
Stiffness and pain		
Separate	19	12.8%
Non-identical	10	6.8%
Identical	6	4.1%

Stiffness: individuals with only stiffness

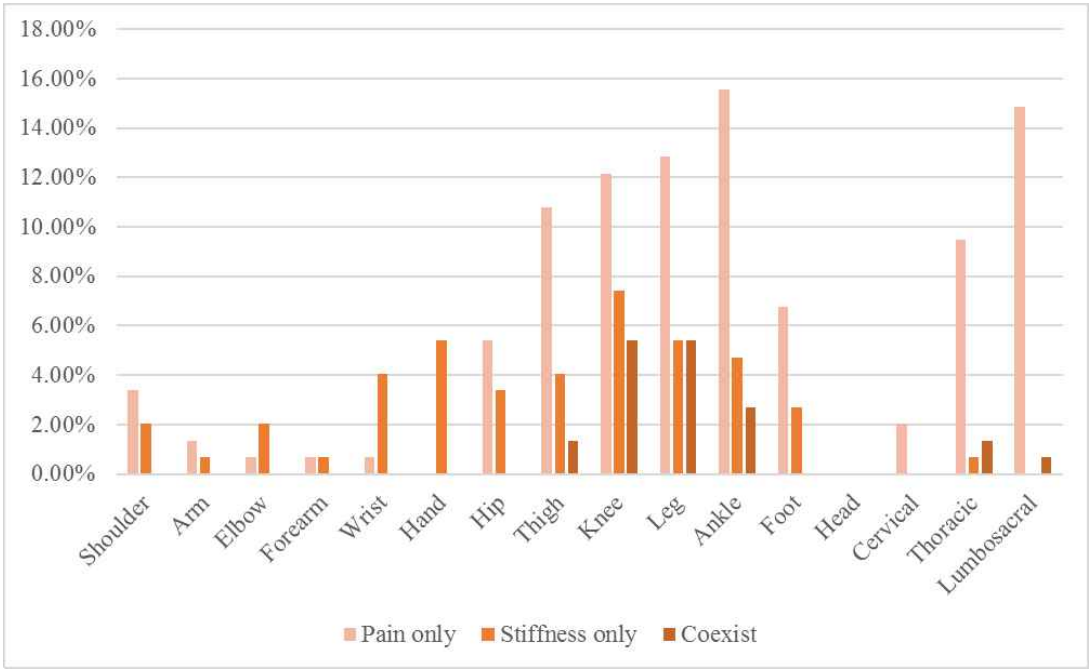
Pain: individuals with only pain

Separate: individuals with stiffness and pain in different joints

Non-identical: individuals with overlapped stiffness and pain in some joints and stiffness or pain in other joints.

Identical: individuals with coexisting stiffness and pain

Figure 4. Distribution of stiffness and pain in each joint.



Coexist: coexisting stiffness and pain.

The participants without stiffness and pain were not shown.

Chapter 4. Discussion

4.1. Summary of study findings

This was the first study investigating subjective stiffness of entire body in individuals with DMD and characteristics of stiffness. We recruited 148 participants with DMD in single center and revealed that about one third of participants complained stiffness in their body. Approximately, two third of participants with stiffness complained the limitation of their activity due to stiffness. Participants of advanced clinical stage complained significantly more severe stiffness and patients with UE stiffness reported more frequent stiffness. Also, the distribution of stiffness was different from those of contracture or pain.

4.2. Comparison with other symptoms

Muscle stiffness is a term commonly used to describe discomfort with movement of a joint.[21] Patients could describe various medical conditions as stiffness including rigidity, spasticity. contracture and pain. Participants in this study had no other comorbidities, such as movement disorder or upper motor neuron disease. Therefore, the

stiffness in this study could not be rigidity or spasticity. Furthermore, the distribution pattern of stiffness was not matched with those of pain and contracture. The location of contracture and stiffness were not overlapped in more than one half of participants and more than 10% of participants answered the locations of stiffness separately from the locations of contracture. About half of the 148 participants did not have pain and stiffness in same region and two third of participants with stiffness did not have overlapped pain site. In each joint, participants with coexisting stiffness and pain was not accounted for more than 10%. This results imply that participants with DMD recognize stiffness as different entity from pain or contracture. To our best knowledge, subjective stiffness was reported in only one study in individuals with DMD.[16] We could suggest that stiffness is distinct symptom from other physical symptoms in patients with DMD.

4.3. Comparison with objective stiffness

The stiffness symptom in this study could be the reflection of objective stiffness in participants with DMD. Subjective stiffness in this study showed consistent results with previous studies investigating objective stiffness. In early stage of disease, 40% of participants complained stiffness and most frequent region of stiffness were knee and lower leg. In the late stage of DMD, the proportion of

participants with stiffness was decreased, especially in distal LE. Stiffness in UE was increased in late stage of DMD.

The pathophysiology of objective stiffness was explained by progression of fibrosis in DMD. It was previously reported that endomysial tissues were increased in early stage of DMD, even if there was no obvious muscle degeneration.[22] Because the lack of dystrophin constantly induce myofiber breakdown in DMD, fibroblast and myofibroblasts are persistently activated in myofibers. It alters the extracellular matrix production and results extracellular matrix with much denser ultrastructure. As the disease progress, recovery potential of muscle tissue is limited and not able to compensate myofiber breakdown, resulting fatty cell replacement.[23]

Pichiecchio et al.[9] compared muscle tissue elasticity of DMD children (age range 38-59 months) and age matched controls by shear-wave elastography. They reported that muscle stiffness of DMD group was higher than that of controls in thigh muscles, not in lower leg muscles. Other study including older participants (age range 5-22 years) reported stiffness of DMD participants was significantly higher than those of control group in thigh, leg, biceps, and triceps, except abductor digiti minimi muscles.[24] After 12 months, stiffness was significantly increased in every muscle except abductor digiti minimi.[11] Lin et al.[10] compared stiffness value of different stage of DMD by shear-wave elastography. The stiffness value of lower leg in non-ambulatory stage was lower than that of ambulatory stage. The muscle necrosis and muscle volume decrease were suggested for the

explanation of decreased stiffness in lower leg. The lower leg muscles might prone to muscle necrosis caused by overuse.[23] The loss of ambulation might result decreased muscle volume of lower leg. In summary, the objective stiffness is first found in proximal LE. As the disease progress, the stiffness gradually progresses and spread to distal LE and proximal UE. The stiffness progression of distal UE is the slowest. After muscle necrosis is done and muscle loses its activity, stiffness value tends to decrease.

Since the measured subjects are different, it is difficult to directly compare the results of this study with those of previous studies. However, the subjective stiffness in this study showed similar progression patten with previous studies. The prevalent LE stiffness in Amb group could be explained by presence of fibrosis in early stage of disease. Increased UE stiffness in LNA group might reflect the progression of fibrosis in late stage. The decreased prevalence of LE stiffness in LNA group can be explained by decreased stiffness value due to muscle necrosis and disuse atrophy. However, the data is scarce regarding correlation of subjective and objective stiffness. A few studies investigated the patients with chronic neck pain to reveal the correlation between neck and shoulder stiffness measured by shear-wave elastography and chronic neck pain symptom, but the results were inconsistent.[25,26] Therefore, the study investigating the relationship between stiffness symptom and objective stiffness in DMD patients would be necessary.

4.4. Relation of stiffness and contracture

As muscle necrosis and fibrosis progress in DMD, the weakness gradually progress resulting loss of muscle function. The loss of function could cause failure to fully mobilize the joint. Immobilization and fibrosis of muscle and tendon lead to joint contracture.[13] In our study, it is assumed that participants feels stiffness when fibrosis progress, and contracture develops later. After muscle necrosis and fatty degeneration is done, subjective stiffness is presumed to diminish and only contracture last. In UE, 'stiffness only' was found in Amb, ENA group. 'Coexist' and 'contracture only' were found only in LNA. Because fibrosis progression in UE occurs later than that of LE, it is assumed that progressive fibrosis result increase of both stiffness and contracture in LNA group. LE stiffness showed different pattern. In knee and ankle joint, participants with 'stiffness only' decreased in ENA and LNA group. Participants with 'coexist' was highest in ENA group in knee joint and was decreased in ankle joint. Stiffness in hip joint showed increased 'stiffness only' and 'contracture only' in LNA group. In ankle, lower proportion of participants feels stiffness could be explained by nearly complete fibrosis and necrosis in ambulatory stage. In knee joint, fibrosis is assumed to progressive between Amb and ENA group. Therefore, we suggest that stiffness symptom could be seen as an indicator for progression of contracture, and it can suggest a preventive strategy

that provides more intensive and selective rehabilitation management for each patient. The pattern of developing contracture was consistent with previous studies. McDonald et al reported severity of LE joint contractures rapidly increased after the loss of ambulatory function in children with DMD.[27] Choi et al reported that the moderate to severe contracture was frequent in ankle joint of ambulatory DMD group, whereas mild contractures were frequent in hip and knee.[28]

4.5. Limitation of activity due to stiffness

Among 54 participants with stiffness, 36 participants complained limitation of daily activity due to stiffness. The participants with late stage of disease and with UE stiffness showed higher frequency of severe limitation, but the difference was not significant. In previous study, frequency, severity, and limitation of stiffness were reported significantly correlated with UE functions assessed by the Capabilities of Upper Extremity questionnaire and the ABILHAND questionnaire.[29] Therefore, providing proper management to stiffness would be required to improve function and quality of life of patients with DMD. Klinger et al suggested moderate, adequately tailored exercise and potential antifibrotic drugs to manage stiffness.[23] Other study suggested that 10 minute of calf massage was effective for stiffness in calf muscles in DMD.[30] Further study will be needed to improve stiffness in individuals with DMD.

4.6. Limitation of the study

There are several limitations in our study. First, we could not classify participants in detail. As we could not collect detailed data regarding functional status of the participants, we only could classify participants by age and ambulatory status. Ambulatory patient might have different functional status range from normal walking to walking only short distance with assist.[31] Detailed classification, such as classification used by Birnkrant et al[6] or ambulation function classification system for DMD[31], might show more comprehensive data of stiffness. Because participants had to understand and answer the questionnaire, we could not obtain data from young children and evaluate very early stage of DMD. Lastly, we conducted cross-sectional study and we could not track the change of subjective stiffness of participants.

4.7. Conclusion

In conclusion, stiffness was distinct symptom in participants with DMD. It was identified one of third participants with DMD and the majority of participants with stiffness were limited their activity due to stiffness. Participants of advanced clinical stage complained

significantly more severe stiffness and patients with UE stiffness reported more frequent stiffness. Further study would be needed to evaluate subjective stiffness in DMD and to develop to proper method to manage stiffness in individuals with DMD.

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요약 (국문 초록)

목적: 뒤셴느근디스트로피(Duchenne muscular dystrophy) 환자에서 삶의 질을 향상시키기 위해서는 다양한 신체증상을 관리하는 것이 필수적이다. 강직(stiffness)은 뒤셴느근디스트로피 환자의 삶의 질에 영향을 줄 수 있는 증상 중 하나이지만, 강직을 주관적 신체증상으로 다룬 연구와, 강직과 다른 신체증상을 비교한 연구는 거의 이루어지지 않았다. 이에 본 연구는 뒤셴느근디스트로피 환자에게서 강직의 임상양상과 특성을 연구하고, 강직이 통증과 관절의 구축과 관련이 있는지 연구하고자 하였다.

방법: 서울대학교어린이병원 재활의학과에 내원한 뒤셴느근디스트로피 환자를 대상으로 단면연구를 시행하여. 평균 연령은 14.5±5.3세의 148명의 환자를 모집하였다. 연구자가 설문지를 통하여 강직의 빈도, 강도, 일상생활의 제한, 부위를 조사하였다. 임상 단계에 따른 강직의 특성의 변화를 비교하였고, 강직의 분포를 관절의 구축과 통증의 분포와 일치하는지 비교하였다.

결과: 148명의 참가자 중 54명(36.5%)가 경직을 호소하였다. 임상 단계가 진행됨에 따라 강직의 유병률은 감소하였다. 강직이 있는 참가자 중 36명(66.7%)이 강직으로 인하여 일상생활에 제한이 있다고 호소하였다. 임상 단계가 진행될수록 환자는 강직의 강도를 심하게 호소하였으며, 강직이 상지에 있는 환자가 더 잦은 강직을 호소하였다. 강직의 분포는 관절의 구축과 통증의 분포와 차이를 보였다.

결론: 강직은 뒤셴느근디스트로피 환자가 호소하는 증상 중 하나이며, 강직을 호소하는 환자의 대부분은 강직으로 인하여 일상생활이 제한된다고 호소하였다. 추후 연구를 통하여 뒤셴느근디스트로피의 환자에서 강직을 평가하고 관리하는 방법의 개발이 필요하다.

색인 : 뒤셴느근디스트로피, 강직, 구축, 통증

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