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Musculoskeletal assessment in patients with Duchenne muscular dystrophy

뒤센느근디스트로피 환자에서의

근골격계 평가

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Musculoskeletal assessment in patients with Duchenne muscular dystrophy

By

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Abstract

Musculoskeletal assessment in patients with Duchenne muscular dystrophy

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Introduction: The aim of this study was to investigate systematic evaluation of limb and spinal musculoskeletal rehabilitation in accordance with the current clinical situation of early administration of steroids in patients with Duchenne muscular dystrophy (DMD). Three researches were conducted in this thesis. First, we investigated range of motion and contracture of lower extremity joints among male patients with DMD, based on the patients' ambulatory status. Differences in major joint contractures, based on passive stretching exercise participation, were also investigated. Second, patients with DMD often develop scoliosis that progresses rapidly after loss of ambulation. We attempted to examine the incidence of scoliosis, flexibility of scoliosis and pelvic tilt associated with scoliosis after two years of wheelchair-bound status to identify trends over time. Finally, in persons with DMD, weakness of the upper extremity (UE) muscles has a significant impact on daily activities and body function. This problem necessitates a screening tool that can be used quickly and easily in clinical situations, such as the Upper limb short questionnaire (ULSQ). However, its validity and reliability as a clinical measure have not yet been evaluated.

Methods: In the first research, total of 128 boys with DMD, followed at the DMD clinic of a tertiary care hospital, were included in this cross-sectional study. The passive ranges-of-motion of the hip, knee, and ankle joints were measured, in the sagittal plane, using a goniometer. The Vignos Scale was used to grade ambulatory function. Boys with DMD who performed stretching exercises for more than 5 min/session, >3 sessions/week, were classified into the stretching group. In the second research, we reviewed the medical records of 273 boys who were genetically identified as having DMD, and finally, 50 boys with serial records of radiographs after loss of ambulation were finally enrolled. And among them, only 31 patients developed scoliosis. Spine radiographs in sitting and supine positions were also reviewed to obtain Cobb angle, curve flexibility, and pelvic obliquity. Flexibilities (%) were calculated by the difference in angles between the sitting and supine positions divided by the angle at the sitting position, multiplied by 100. In the third research, face to face ULSQ interviews were held, and then repeated by telephone, at least four weeks later. Lower extremity and UE body function were measured by a physician using Vignos and a modified Brooke scale, respectively.

Results: In the first research, the hip flexion (23.5°), knee flexion (43.5°), and ankle plantarflexion (34.5°) contracture angles in the non-ambulatory group were more severe than those in the ambulatory group. Ankle plantarflexion contractures (41 patients, 52.6%) were more frequently observed early, even within the ambulatory period, than were hip (8 patients, 10.3%), and knee joint (17 patients, 21.8%) contractures. Passive stretching exercises >3 sessions/week were not associated with the degree of lower extremity joint contractures in the ambulatory or non-ambulatory group. In the second research, among 31 boys who had scoliosis, all but 2 boys with curves went through a sequential course of 1) no scoliosis, 2) nonstructural scoliosis, when scoliosis was only measurable in the sitting position, and 3) structural scoliosis, when scoliosis was also detectable in the supine position. Flexibility decreased each year after detection of scoliosis in those who developed scoliosis the first year, from 75.5 ± 5.0% to 57.1 ± 10.5% and to 49.1 ± 10.0% (mean ± standard deviation). Spinal flexibility was significantly correlated with curve magnitude of scoliosis in both sitting and supine position. In the third research, 160 subjects participated in the initial ULSQ interview among 167 participants, and 132 subjects completed follow-up interviews. Construct validity was confirmed by exploratory and subsequent confirmatory factor analysis. Sum scores of UE function correlated with the modified Brooke scale (Kendall's Tau 0.64, $p < .001$). Total and sum scores for each ULSQ component were higher in non-ambulators than in ambulators. Reliability was acceptable, determined by internal consistency and test-retest tools.

Conclusions: There have been few studies about the range of motion and the degree of contracture of the joints (hip, knee, and ankle) of the lower limb since the 2000s when steroids began to be widely used. Knowledge of lower extremity joint contracture profiles, based on ambulatory status, may be useful for developing appropriate strategies for joint management in this patient group. Regarding to scoliosis, our result suggests that in the early stage of scoliosis, wherein flexibility is maintained without structural scoliosis, interventions such as bracings should be considered in DMD scoliosis. Also, scoliosis curve in DMD patients should be evaluated dynamically to detect the scoliosis when the curve is fully reducible. This study could be a cornerstone for further studies involving application of spinal braces for neuromuscular scoliosis. Finally, ULSQ could be a valid and reliable measurement tool for persons with DMD to screen UE function, pain, and stiffness in clinical settings

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Keywords: Contracture; Duchenne muscular dystrophy; Function; Lower extremity; Pain; Scoliosis; Steroid; Stiffness; Upper extremity

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List of Abbreviations

AC 1 Gwet's first-order agreement coefficient

AFO Ankle-foot orthosis

ANOVA One-way analysis of variance

APF Ankle plantarflexion

CFI Comparative fit index

DMD Duchenne muscular dystrophy

EFA Exploratory factor analysis

GFI Goodness-of-fit index

HF Hip flexion

ICF International classification of functioning, disability and health

KF Knee flexion

KMO Kaiser-Meyer-Olkin

PUL Performance of upper limb assessment

RMR Root mean square residual

RMSEA Root-mean-square error of approximation

ROM Range of motion

UE Upper extremity

ULSQ Upper limb short questionnaire

WHO World Health Organization

1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder caused by a lack of dystrophin, and has an overall incidence of 1 in 4700 male births.[1, 2] Muscular dystrophy is characterized by progressive muscular weakness, from childhood, which eventually results in the loss of gait performance when patients are approximately 10–12-years-old.[3] In recent decades, the survival of patients with DMD has improved because of interdisciplinary care, such as the inclusion of noninvasive ventilation.[4] For a more fundamental therapeutic approach, novel treatments such as dystrophin-target gene therapies have been investigated in the past decade.[5,6] However, even if successful dystrophin protein restoration makes it possible to improve motor function in DMD, its effect may be limited in patients with advanced musculoskeletal complications. Furthermore, efforts to reduce musculoskeletal complications are important for maintaining function and have a close impact on quality of life.

1.1. Research I: Lower extremity joint contracture according to ambulatory status

In patients with neuromuscular conditions, contractures develop due to intrinsic myotendinous structural changes and extrinsic factors.[7] Specifically, in patients with DMD, joint contractures are associated with several factors, including loss of full joint range-of-motion (ROM), static positioning, muscle imbalance around a joint, and fibrotic changes (fatty tissue infiltration) within muscle tissues.[8] Lower extremity joint contractures negatively affect the gait of patients with ambulatory DMD.[9] For example, hip joint contractures can lead to pelvic obliquity, which is associated with scoliosis development.[10] In recent decades, the survival of patients with DMD has improved because of interdisciplinary care, such as the inclusion of noninvasive ventilation.[4] Hence, contracture prevention is essential for maintaining a patient's functional ability and an acceptable quality of life.

Although knowledge regarding lower extremity joint contracture profiles, based on disease progression, is necessary for the development of appropriate preventive strategies, studies is this area remain scarce. McDonald et al. reported that lower extremity contractures were rare in patients able to maintain an upright posture, but developed soon after the patients became confined to a wheelchair for the majority of the day.[11] However, these authors did not describe any differences between the major lower extremity joints, i.e., the hip, knee, and ankle. This study aimed to investigate the profile of hip, knee, and ankle joint contractures, based on the ambulatory status of patients with DMD. Furthermore, differences in major joint contractures were evaluated, based on the passive stretching exercises performed by ambulatory and non-ambulatory patients.

1.2. Research II: Scoliosis in Duchenne muscular dystrophy children

Scoliosis is a frequent complication of DMD that progresses rapidly, in the non-ambulatory stage of the disease.[12-17] Pelvic obliquity is also thought to be a mechanism of compensation for scoliosis.[18] These deformities in the musculoskeletal system together make sitting difficult, limiting the use of upper extremities and hampering activities of daily living. When scoliosis progresses, rib impingement onto the ilium may occur, causing pain and making hygiene difficult.[19] It is crucial to prevent scoliosis as it affects other organ systems.

After loss of ambulation, rapid progression of spinal deformity leads to a deterioration in pulmonary function.[14, 16, 17] Kurz et al. reported that with 10 degrees of thoracic curve progression, functional vital capacity decreased by 4%.[20] According to Hsu et al., in DMD patients whose spinal curves exceeded 40 degrees, vital capacity diminished by 12 to 16%.[21] Therefore, it is important to prevent, or delay spinal deformity as it leads to compromise of respiratory function.

Spinal orthosis attempts to prevent or delay scoliosis using spinal support at three points of the controlling mechanism; the lateral curve should be flattened by the pressure. Therefore, it is assumed that spine flexibility or reducibility is a significant influencing factor for the effectiveness of braces.[22, 23] Information regarding curve flexibility helps establish a strategy for brace application to manage scoliosis. If there is sufficient flexibility, the effectiveness of bracing therapy is expected.

Nevertheless, there have been only a few reports investigating spine flexibility in this patient group.[24] Therefore, this study is to investigate the curve flexibility of scoliosis for 2 years after loss of walking ability in children with DMD.

1.3. Research III: Upper limb short questionnaire for Duchenne muscular dystrophy

DMD is characterized by progressive muscular weakness. The function of the upper extremity (UE) decreases later than that of the lower extremity, usually after losing walking ability. The UE weakness appears first in the proximal and progresses to the distal region, which results in limitations performing daily activities.[4, 25] In recent decades, corticosteroid treatment can mitigate the progression of limb muscle weakness, and survival has improved because of interdisciplinary care, including noninvasive ventilation.[4, 25] With the current life expectancy and care techniques, men with DMD will live for longer than before with their impaired UE function. The weakness of the UE muscle will affect daily life functions in different ways to weakness in the lower extremity muscle because it is more difficult to compensate body functions with assistive devices, such as wheelchairs in the lower extremities.

Janssen et al. suggested that pain and stiffness could negatively affect the UE body function in people with DMD.[26] Therefore, a patient's UE function should be evaluated in the clinic, especially after losing ambulatory function. Existing UE evaluation tools record the observational findings[27-30] or use the patient's report[31-33] of their ability during UE activities.

In most cases, however, they include too many evaluation items, which can be challenging to complete in the clinical setting. For example, the Performance of Upper Limb assessment in DMD (PUL) includes 22 items subdivided into the shoulder, middle, and distal levels of the upper extremities.[34-36] For the PUL, scoring options varied across the scale between 0–1 and 0–6, according to performance and equipment such as weights, coins, and pencils, etc., which are required for the evaluation. Considering the progressive nature of the disease, rather than conducting detailed UE assessments at each clinic, the strategy of a simple screening assessment in each clinic and a detailed assessment when changes are detected may be more efficient. A screening assessment tool should be simple and closely related to the intervention plan.

Janssen et al. proposed the Upper limb short questionnaire (ULSQ) consisting of 14 items based on a review of existing relevant UE assessment tools for DMD.[37] The questionnaire consists of upper limb function (5 items), pain (6 items), and stiffness

(3 items) that require yes or no answers and can be used quickly and easily in clinical situations for screening purposes (Table 1).

However, the questionnaire is not a conventional clinical measure, and its validity and reliability have not been sufficiently demonstrated. This study aimed to evaluate the construct validity of ULSQ and its reliability to investigate whether the ULSQ can be used as a clinical measure when converted to a score with 1 point per item.

Table 1. Upper limb short questionnaire (ULSQ) by Jenssen et al (2018)

Factor	Questions	Score options[a]
ULSQ-1 Heavy lifting	Do you experience problems in your arms when lifting heavy objects (>5 pounds)?	0: No 1: Yes
ULSQ-2 Light or no lifting	Do you experience problems in your arms when you reach for or lift light objects such as an empty can?	0: No 1: Yes
ULSQ-3 Basic hand function	Do you experience problems using your hands for basic functions like manipulating small objects or holding a key?	0: No 1: Yes
ULSQ-4 Gross hand function	Do you experience problems using your hands when performing daily activities that require gross hand function like washing your hands or eating with a spoon?	0: No 1: Yes
ULSQ-5 Fine hand function	Do you experience problems using your hands when performing daily activities that require fine hand function like buttoning up your shirt?	0: No 1: Yes
ULSQ-6 Pain limitations	Do you experience limitations performing daily activities due to pain in your upper limb?	0: No 1: Yes
ULSQ-7 Pain severity (not shoulder)	How severe is the pain you experience in your upper limb when performing daily activities?	0: No pain 1: Mild or severe pain
ULSQ-8 Distal pain frequency	How often do you have pain in your hands or fingers?	0: Not more than once a month 1: More than once a month
ULSQ-9 Shoulder pain	Do you experience pain in your shoulder(s)?	0: No 1: Yes
ULSQ-10 Proximal pain frequency (not shoulder)	How often do you experience pain in your upper or lower arm?	0: Not more than once a month 1: More than once a month
ULSQ-11 Elbow pain frequency	How often do you experience pain in your elbows?	0: Not more than once a month 1: More than once a month
ULSQ-12 Stiffness frequency	How often do you experience stiffness in your arms?	0: Not more than once a month 1: More than once a month
ULSQ-13 Stiffness limitations	Do you experience limitations performing daily activities due to stiffness in your upper limb?	0: No 1: Yes
ULSQ-14 Stiffness severity	How severe is the stiffness you experience in your upper limb when performing daily activities?	0: No stiffness 1: Mild or severe stiffness

2. Methods

2.1. Research I: Lower extremity joint contracture according to ambulatory status

2.1.1. Participants

Overall, 136 boys with DMD were included in this cross-sectional study conducted at the DMD clinic of Seoul National University Hospital (Seoul, Korea). DMD diagnoses were confirmed using a dystrophin gene study. The genetic test methods used to identify dystrophin mutations were multiplex polymerase chain reaction and direct sequencing (Xp21.2-p21.1, exons 1–79). If the deletion/duplication testing results were negative, dystrophin gene sequencing was performed to search for point mutations or small deletions/insertions. All children with DMD participating in the study were prescribed alternate-day deflazacort (0.9 mg/kg), according to the international consensus, after demonstrating a partial Gower sign.[38] Patients were excluded from the study due to the presence of co-morbidities (e.g., an acquired brain or spinal injury), absence of corticosteroid administration, use of ankle-foot orthosis (AFO), or use of therapeutic weight bearing (e.g., passive standing frame) to increase lower extremity ROM. The research was conducted in accordance with the Declaration of the World Medical Association, and was reviewed and approved by the Seoul National University Hospital Institutional Review Board (IRB no. 1605-028-760). Because of the study's retrospective design, the need for consent to participate was waived.

2.1.2. Measures

Demographic and medical data, including age, Gower sign results, and dystrophin gene study results, were collected. Clinical variables, such as lower extremity joint passive ROM and sagittal plane contracture angles (flexion/extension movements), were recorded. The contracture angles were measured bilaterally in the hip, knee, and ankle joints, using a goniometer, during clinical examinations performed by a physical therapist. Goniometry is the most commonly used technique for measuring joint motion limitations due to muscle contracture. With the patients in a supine position, the same physiotherapist measured and recorded all lower extremity joint passive ROMs, according to the method of Norkin and White.[39] Because the same physiotherapist performed all of the joint contracture measurements, the intra-tester measurement reliability is likely high, according to Pandya et al.[40] For each measurement, the protocol guided the reference points for the fulcrum and the proximal and distal arms of the goniometer. At each time point, duplicate passive ROM measurements were obtained and averaged.

A physician recorded the Vignos Scale score to grade lower limb function of the children with DMD.[41] The Vignos Scale classifies patients with DMD into 10 categories, based on their ability to walk. Patients with Vignos Scale scores of 1–7 were considered ambulatory, whereas patients with scores of 8–10 were considered non-ambulatory.

2.1.3. Procedure

The severities of hip flexion (HF), knee flexion (KF), and ankle plantarflexion (APF) contractures were classified, based on a previous study,[11] as mild (1°–19°), moderate

(20°–40°), and severe (>40°) for HF contractures; mild (1°–14°), moderate (15°–40°), and severe (>40°) for KF contractures; and mild (1°–14°), moderate (15°–30°), and severe (>30°) for APF contractures.

We investigated whether significant differences in passive stretching exercise participation existed between ambulatory and non-ambulatory patients. All patients with DMD who participated in the stretching exercises received help from their physical therapist at hospital. Children with DMD who performed stretching exercises for >5 min/session, for >3 sessions/week, were categorized into the stretching group; the others were classified into the non-stretching group.

2.1.4. Data analysis

Means and standard deviations (SD) were used to describe the basic patient characteristics. The mean values for right and left HF, KF, and APF angles were obtained for each patient, and the HF, KF, and APF contracture angles for both legs were averaged; t-tests confirmed the absence of significant differences between the left and right legs for all measurements. Data were also stratified according to patients categorized as ambulatory or non-ambulatory.

A generalized estimating equation was used to assess the extent of the differences in the degree of lower extremity joint contractures, depending on ambulatory status, and the degree of lower extremity joint contracture, between joint sites, depending on the patients' ambulatory status. The relationship among the HF, KF and APF contracture angles were assumed to be constant. The mean contracture angle of each lower extremity joint was compared to that of the hip joint. The p-values and 99.3% confidence intervals, including the Bonferroni correction, are presented for all seven tests.

Within each group, the mean HF, KF, and APF joint contracture angles were analyzed, using an independent samples t-test, to test for differences between the stretching and non-stretching groups.

Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). The level of statistical significance was set at 5% for 2-tailed tests.

2.2. Research II: Scoliosis in Duchenne muscular dystrophy children

2.2.1. Participants

Medical records and radiographs of 273 boys diagnosed with DMD who visited the pediatric rehabilitation department between March of 2017 and February of 2018 were reviewed. Ethical approval was obtained from the Institutional Review Board (IRB No. 1804-169-942). DMD diagnosis had been established using a dystrophin gene study. The genetic test methods used to identify dystrophin mutations included multiplex polymerase chain reaction and direct sequencing (Xp21.2-p21.1, exons 1–79). If deletion/duplication testing results were negative, then dystrophin gene sequencing was performed to search for point mutations or small deletions/insertions. All enrolled DMD pediatric patients were taking deflazacort (0.9 mg/kg) every other day, according to international consensus, at the pediatric department in the same hospital after a partial Gower sign had been observed.[15]

Inclusion criteria were as follows: (1) time points of the ambulation loss were charted; (2) 2-year records of whole spine radiographs both in supine and sitting positions were preserved with (3) the first follow-up radiography was performed less than 1 year after the onset of ambulation loss.

2.2.2. Review of medical records

Patients with DMD in our hospital had regular outpatient follow-up at 12-month intervals when ambulatory and 6 months after the loss of ambulation.[38] Whole spine radiographs were taken in the sitting and supine positions, and ambulatory functions were charted in Vignos scales at each outpatient follow-up. The onset of ambulation loss was defined when the charted scale value exceeded or equaled grade 8, when patients were able to stand with long leg braces, but were unable to walk even with assistance.[24]

2.2.3. Evaluation of scoliosis and pelvic obliquity

It was designated the patients who had no scoliosis both in sitting and supine positions as having “no scoliosis”; those who only had scoliosis in sitting position but not in supine position were designated as having “nonstructural scoliosis”; and those who had scoliosis both in sitting and supine positions were designated as having “structural scoliosis”.[22] Postero-anterior radiographs of selected patients were used in this study. To improve intraobserver reliability, the measurements were taken by a single well-trained physician.

The image field in the cranio-caudal direction ranged from the occiput to the acetabula. Cobb angle of more than 10° was considered significant.[14, 42, 43] Cobb angles were retrospectively measured by a single observer. The most oblique cranial and caudal end vertebrae were marked, and lines were drawn through the endplates of each vertebra, and the angles between them were measured.[44] As measurement error of Cobb angle results from errors in selecting the end vertebrae,[44, 45] initially selected end vertebrae were marked to be used for serial measurements to reduce measurement error.

The horizontal pelvic obliquity method measures angle between the line of most proximal iliac crests and the parallel line to the bottom of the radiograph. This angle is largely influenced by the patient's position.[46] Pelvic obliquity more than 5° was considered significant.[18, 47] This horizontal pelvic obliquity measurement is associated with the least interobserver and intraobserver variability.[46, 48] To minimize these errors, the patients were confirmed to be in the maximal and appropriate position and were well-fitted to the frame when taking images.

2.2.4. Evaluation of flexibility

Scoliosis curve flexibility was assessed by comparing the Cobb angle values in the supine position (gravity eliminated posture) and those in the sitting position (increase in the curve with gravity). Cobb angle and pelvic obliquity in each position and flexibility were analyzed at the time when scoliosis was first detected after ambulation loss, 1 year after scoliosis detection, and 2 years after scoliosis detection. The flexibility of the spine curve at each year was calculated as below.[23, 49]

$$Flexibility\ (\%) = \frac{Cobb\ angle\ at\ sitting - Cobb\ angle\ at\ supine\ position}{Cobb\ angle\ at\ sitting} \times 100$$

For the supine position, the hands were placed by the patient's side, and patients were instructed to lie down facing up on a scanning couch and then to straighten their trunk and legs maximally.[50] In the sitting position, patients were instructed to sit on a chair with a panel on the back, with the hip to be placed appropriately on the chair. They were asked to lie back maximally to eliminate tilts. The patients were instructed to hold handles on both sides during radiography. If they were unable to hold the handles, they were simply asked to lay their hands on the handles.

2.2.5. Statistical analysis

The demographic characteristics and measurements of the participants were classified by scoliosis development. To analyze changes in flexibilities in the series of radiographs, repeated measure analysis of variance was used. To evaluate the relationships among each index, Spearman's correlation tests were used. All data were statistically analyzed using the Statistical Package for Social Sciences for Windows ver. 17.0 (SPSS Inc., Chicago, IL, USA).

2.3. Research III: Upper limb short questionnaire for Duchenne muscular dystrophy

2.3.1. Participants

We recruited patients with DMD who were followed up at the DMD clinic of Seoul National University Children's Hospital from December 2018 to August 2019. The ULSQ was carried out with DMD patients over seven years old. All children with DMD included in the study were taking deflazacort (0.9 mg/kg) every other day, according to international consensus, at the neurologic division of the pediatric department in the same hospital after a partial Gower sign was observed.[38]

Exclusion criteria were the same as a previous study[37] : (a) patients who were diagnosed by at least age ten and (b) ambulatory status after age 14 in steroid-naïve DMD. DMD diagnosis was confirmed using a dystrophin gene study. The genetic test methods used to identify dystrophin mutations included multiplex polymerase chain reaction and direct sequencing (Xp21.2-p21.1, exons 1–79). If deletion or duplication testing results were negative, then dystrophin gene sequencing was performed to search for point mutations or small deletions or insertions. All the study participants provided their informed consent before completing the questionnaire. The research was conducted under the Declaration of the World Medical Association and was reviewed and approved by the Seoul National University Hospital Institutional Review Board (IRB no. 1810-120-982).

2.3.2. Procedure

2.3.2.1. Translation and re-translation

Before translating the questionnaire, we obtained permission from the original author of ULSQ to translate the original English version of ULSQ into Korean via e-mail. After a translator completed the translation into Korean, two Korean physiatrists in the pediatric division checked the Korean questionnaire. A different translator completed the backward-translation of the questionnaire into English. Afterward, both the Korean physiatrists in the pediatric division and the original author reviewed the expression and clarification of the backward-translated questionnaire compared with the original, marking the completion of the Korean version of ULSQ (Table 2).

Table 2. Korean version of Upper limb short questionnaire (ULSQ)

요인	최초 항목	점수 평가
무거운 물건 들기	무거운 물체 (2 kg)를 들 때 팔에 어려움을 겪고 있습니까?	0: 아니오 1: 예
가벼운 물건 들기 혹은 아예 물건을 들 수 없음	빈 깡통과 같이 가벼운 물체를 손에 쥐고 드는데 있어 팔에 어려움을 겪고 있습니까?	0: 아니오 1: 예
기본적 손의 기능	작은 물체나 열쇠 잡기와 같이 기본적인 활동에 손을 사용하는 데에 어려움을 겪고 있습니까?	0: 아니오 1: 예
전반적 손의 기능	손을 씻거나 숟가락으로 음식을 먹는 등과 같은 전반적인 손기능을 요구하는 일상적 생활을 하는 데에 어려움이 있습니까?	0: 아니오 1: 예
정교한 손 기능	셔츠의 단추를 잠그는 등의 정교한 손기능이 필요한 일상적 활동을 하는 데에 어려움을 겪고 있습니까?	0: 아니오 1: 예
통증에 의한 제한 정도	상박 (팔꿈치 위의 팔)의 통증으로 인해 일상 생활을 하는 데에 제한 사항이 있습니까?	0: 아니오 1: 예
통증 정도 (어깨 통증 제외)	일상적 활동을 할 때 상박 (팔꿈치 위의 팔)에 겪는 통증의 심각도는 어느 정도입니까?	0: 통증 없음 1: 경증 또는 중증의 통증
말단부 통증 빈도	손이나 손가락 통증을 얼마나 자주 겪습니까?	0: 한달에 한번 이하 1: 한달에 한번 초과
어깨 통증	어깨 통증이 있습니까?	0: 아니오 1: 예
근위부 상지 통증 빈도 (어깨통증 제외)	팔의 통증을 얼마나 자주 겪습니까?	0: 한달에 한번 이하 1: 한달에 한번 초과
팔꿈치 통증 빈도	팔꿈치 통증을 얼마나 자주 겪습니까?	0: 한달에 한번 이하 1: 한달에 한번 초과

뻣뻣함 빈도	팔이 뻣뻣해지는 현상을 얼마나 자주 겪습니까?	0: 한달에 한번 이하 1: 한달에 한번 초과
뻣뻣함에 의한 제한 정도	팔의 뻣뻣함으로 인해 일상 생활을 하는 데에 있어 한계가 있습니까?	0: 아니오 1: 예
뻣뻣함 중증도	일상적 활동 시, 팔의 뻣뻣함의 정도가 얼마나 심각합니까?	0: 경직 증상 없음 1: 경증 혹은 중증의 경직

2.3.2.2. Survey and measure

The ULSQ consisted of three-dimension regarding UE function (5 items), pain (6 items), and stiffness (3 items). All questions required a binary answer (yes or no). The ULSQ was conducted during a face-to-face interview with the participants, their parents, and a research nurse. A physiatrist in the pediatric division recorded the Vignos scale and Brook scale in the clinic, which classifies these patients ten categories based on their walking ability. Grade 1 patients could walk and climb stairs without assistance, while grade 10 patients were confined to a bed.[41] Based on the Vignos scale, the ability of ambulation was classified into three categories: independent ambulation (Vignos scale 1-5), ambulation with assist or aids (Vignos scale 6-7), and loss of ambulation (Vignos scale 8-10). The original Brookes scales graded patients with DMD into six categories based on their ability to use their arms.[27] Grade 1 patients start with their arms at their sides and abduct them in a full circle until they reached above their head, while grade 6 patients had no functional ability to use their hands. We added an intermediate stage (grade 5.5) between grades 5 (cannot raise hands to the mouth, but can use hands to hold a pen or pick up pennies from the table) and grade 6 (Cannot raise hands to the mouth and has no useful function of hands). Grade 5.5 patients cannot hold a pen; however, they can move their fingers (e.g. press on a mobile or other electronic device), which modified the Brooke scale into a seven-step scale for this study. Landfeldt et al. also used an intermediate step in their DMD functional ability self-assessment tool in the same way as in our study to adjust for the information technology (IT) devices with a touchpad that were commonly used by DMD patients.[51] Four weeks after the initial interview, a physiotherapist conducted a second telephone ULSQ interview. ULSQ interview times, both by face to face and telephone, were within ten minutes. Demographic and medical data, including age, gender, prescribed medication, and dystrophin gene study results, were collected and tabulated.

2.3.3. Statistical Analysis

The mean and SD described essential patient characteristics. Exploratory factor analysis (EFA) of principal factors investigated the latent constructs of the questionnaires. For EFA, Bartlett's test of sphericity tested whether the correlation matrix of the sample was sufficient for factor analysis. The value of the Kaiser-Meyer-Olkin (KMO) measure of sampling was also measured to evaluate sample adequacy of the factor analysis. The eigenvalues-greater-than-one rule was applied to find common factors.[52] Factor rotation using orthogonal rotation (the varimax method) extracted the relevant factors. Confirmatory factor analysis using maximum likelihood estimation confirmed the factor structure obtained using EFA. Model for goodness of fit was evaluated using the Chi-square test, Goodness-of-Fit Index (GFI), Root Mean Square Residual (RMR), Comparative Fit Index (CFI), and Root-Mean-Square Error of Approximation (RMSEA). GFI and CFI values usually ranged from 0 to 1.0, with values of 0.90 or higher considered evidence of a good fit.[53] RMR and RMSEA values of less than 0.08 indicated an acceptable fit for the models.[53, 54] To measure internal consistency, we calculated the relevant Cronbach's α coefficients. Inter-rater reliability analysis employed the Gwet's AC1 (first-order agreement coefficient), which provided a reasonable chance-corrected coefficient in line with the percentage level of agreement.[55]

Furthermore, correlations between ULSQ and the Vignos/modified Brooke scale scores were calculated based on the Kendall rank correlation coefficient.[56] To evaluate the discriminative capability of the ULSQ, the total scores, as well as sum of each component on the ULSQ of patients with DMD, were compared according to the ambulatory disease stage using the Kruskal-Wallis one-way analysis of variance (ANOVA) by ranks.[57] If the difference between groups were significant, we conducted a post-hoc Tamhane's comparison. Descriptive statistics were expressed as means and SD. Statistical analysis was performed using SPSS version

23.0, and confirmatory factor analysis was performed with AMOS, ver. 6 (SPSS Science, Chicago, IL) to statistically confirm the hypothesized structures.

3. Results

3.1. Research I: Lower extremity joint contracture according to ambulatory status

3.1.1. Demographic and clinical information

A total of 136 boys with DMD were evaluated for inclusion in the study; eight were excluded due to not meeting the study criteria (Figure 1). Of the 128 eligible patients, 78 (61%) were included in the ambulatory group and 50 (39%) were in the non-ambulatory group. The mean age in the ambulatory group was 9.1 ± 2.2 years (range, 4–15 years) and that in the non-ambulatory group was 13.3 ± 3.0 years (range, 8–23 years); none of the patients withdrew from corticosteroid therapy. The number of patients based on ambulatory ability, is shown in Table 3.

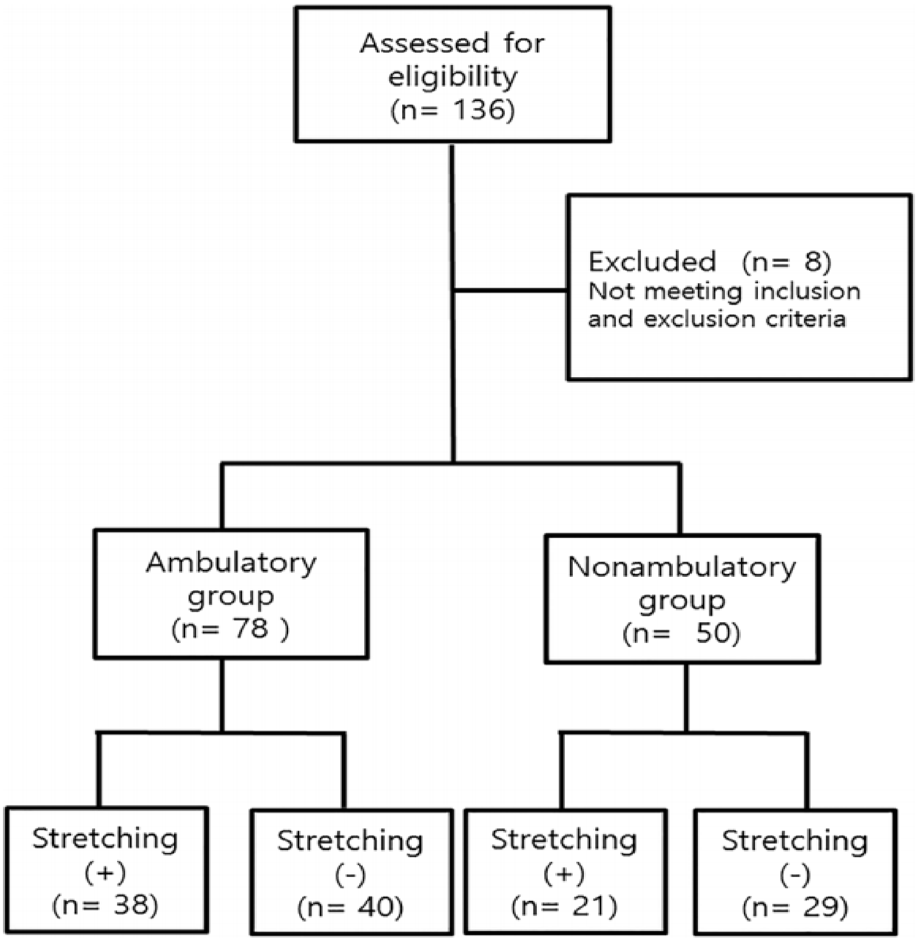

Figure 1. Subject flow diagram

Table 3. Patient Vignos scale score

Vignos	Number (%)
1	19 (14.8)
2	12 (9.4)
3	22 (17.2)
4	11 (8.6)
5	4 (3.1)
6	5 (3.9)
7	5 (3.9)
≥8	50 (39.1)
Total	128 (100)

3.1.2. Lower extremity joint contracture comparisons

Table 4 shows the number of patients exhibiting each lower extremity joint contracture angle severity. In the ambulatory group, HF and KF contractures were observed infrequently, whereas APF contractures were observed more frequently in ambulatory; 41 patients (52.6%) in the ambulatory group showed APF contractures

Table 4. Severity of lower limb joint contractures in patients with DMD, based on ambulatory status

	No contracture	Mild	Moderate	Severe	Total
Hip flexion					
Ambulatory	70 (89.7)	7 (9)	1 (1.3)	0 (0)	78 (100)
Non-ambulatory	7 (14.0)	17 (34.0)	24 (48.0)	2 (4.0)	50 (100)
Knee flexion					
Ambulatory	61 (78.2)	13 (16.7)	3 (3.8)	1 (1.3)	78 (100)
Non-ambulatory	2 (4.0)	3 (6.0)	19 (38.0)	26 (52.0)	50 (100)
Ankle plantarflexion					
Ambulatory	37 (47.4)	30 (38.5)	10 (12.8)	1 (1.3)	78 (100)
Non-ambulatory	1 (2.0)	8 (16.0)	14 (28.0)	27 (54.0)	50 (100)

DMD, Duchenne muscular dystrophy; values are presented as n (%).

The interactions were significant, based on the use of the generalized estimating equation analysis. Consequently, the contracture angles of each lower extremity joint were compared based on ambulatory status. The mean KF and APF contracture angles were compared with the mean HF contracture angle in both the ambulatory and non-ambulatory groups. The mean APF contracture angle was 4.9° greater (99.7% confidence interval, 2.6–7.3) than the mean HF contracture angle (adjusted $p < .0001$), in the ambulatory group. Comparing the ambulatory and non-ambulatory groups, the mean HF angle was 22.0° (99.7% confidence interval, 17.5–26.5) greater, the mean KF contracture angle was 40.4° (99.7% confidence interval, 30.6–50.2) greater, and the mean APF contracture angle was 28.1° greater (99.7% confidence interval, 19.7–36.5) in the non-ambulatory group than in the ambulatory group (Table 5).

Table 5. Average lower extremity joint contracture angles, estimated using a generalized estimating equation

Ambulatory status	Joint	Estimated average values (confidence interval)	p-value*	p-value**
Ambulatory	Hip	1.5 (0.5–2.5)		<.0001
	Knee	3.1 (1.6–4.7)	.092	<.0001
	Ankle	6.4 (4.6–8.2)	<.0001	<.0001
Non-ambulatory	Hip	23.5 (20.4–26.6)		
	Knee	43.5 (36.5–50.4)	<.0001	
	Ankle	34.5 (28.6–40.3)	.001	

* Corrected p-values for comparisons of other ankle and knee joint contracture angles with that of the hip joint.

** Corrected p-value for comparisons of the joint contracture angles, depending on ambulatory status.

3.1.3. Differences in joint contracture angles, based on stretching participation

The mean age of the ambulatory boys with DMD in the stretching group was 8.8 ± 2.2 years and 9.4 ± 2.2 years in the non-stretching group. Among the non-ambulatory boys with DMD, the mean age was 13.6 ± 3.8 years in the stretching group and 13.1 ± 2.4 years in the non-stretching group. There were no significant differences in the mean ages of the boys, based on ambulatory ability, in the stretching and non-stretching groups. The mean duration of each stretching session was 16.2 ± 8.8 min (range, 5–30 min) for the ambulatory group and 16.8 ± 13.4 min (range, 5–60 min) in the non-ambulatory group; 31 (81.6%) patients in the ambulatory group and 17 (81.0%) in the non-ambulatory group had performed stretching exercises for >1 year. No differences were seen in the severities of the HF, KF, and APF joint contractures between the stretching and non-stretching groups, regardless of ambulatory status (Table 6).

Table 6. Independent-sample t-test results comparing the stretching and non-stretching groups

	Ambulatory group				Non-ambulatory group		
	Joint contracture				Joint contracture		
	HF	KF	APF		HF	KF	APF
Stretching (n = 38)	1.4 ± 4.3	2.4 ± 5.0	5.9 ± 6.4	Stretching (n = 21)	20.0 ± 1.5	37.4 ± 25.1	31.5 ± 22.1
No stretching (n = 40)	1.5 ± 4.9	3.8 ± 8.6	6.9 ± 9.6	No stretching (n = 29)	26.0 ± 10.8	47.9 ± 25.0	36.6 ± 20.9
p-value	.92	.39	.60	p-value	.06	.15	.41

Values are presented as means ± standard deviations.

HF: Hip flexion; KF: Knee flexion; APF: Ankle plantarflexion

3.2. Research II: Scoliosis in Duchenne muscular dystrophy children

3.2.1. Clinical Characteristics

Among 273 boys, 146 boys who were still ambulatory were excluded. In the remaining boys, 4 who had undergone spine surgeries during the follow-up period were also excluded. After excluding those without relevant medical information and radiologic records, 50 boys remained for analysis (Figure 2). There were 31 boys who developed scoliosis during follow up period. Characteristics of participants according to scoliosis development is shown in Table 7. Age of boys at ambulation loss was 13.1 ± 2.6 years. There were no significant difference between two groups except pulmonary function ($p < .05$). Among those who were included for analysis, no patient was prescribed for spinal orthosis.

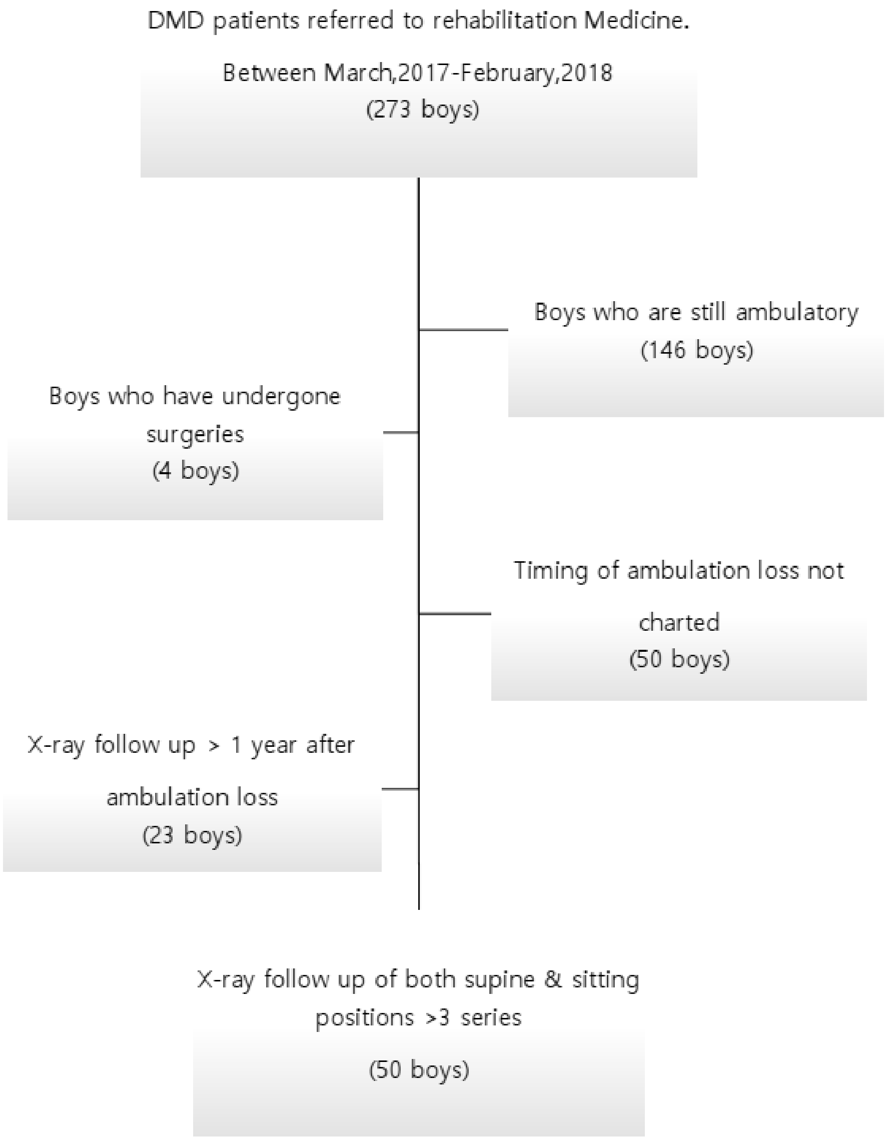

Figure 2. Flowchart of subject enrollment

Table 7. Demographic and clinical characteristics of participants

		Scoliosis development	No scoliosis	p-value	Total
Number of boys		31	19	-	50
Age (year)		13.6 ± 2.5	12.4 ± 2.6	.08	13.14 ± 2.6
Height (cm)		149.4 ± 25.5	142.9 ± 34.3	.66	146.9 ± 25.6
Body weight (kg)		49.1±16.5	45.9 ± 12.1	.36	47.9 ± 14.9
Functional assessment	Brooke scale	2.5 ± 1.7	2.0 ± 1.0	.31	2.3 ± 1.5
	Vignos scale	8.4 ± 0.6	8.3 ± 0.5	.43	8.3 ± 0.5
Pulmonary function	FVC % of predicted (%)	74.2 ± 12.5	84.5 ± 15.2	.03	78.2 ± 14.7

Values are presented as mean ± standard deviation. Comparison between groups was by Mann-Whitney test. FVC ; Functional vital capacity.

3.2.2. Development of scoliosis

The 50 boys had 2 years of annual follow-up radiographs available from the onset of ambulation loss. During this follow-up period, 19 boys fell under the category of no scoliosis, and 31 boys developed either nonstructural or structural scoliosis. At the first follow-up after ambulation loss, 12 boys developed scoliosis, and another 13 boys developed scoliosis the following year. At the last year of follow-up, 6 more patients were found to have scoliosis. Cobb angle increased each year after the ambulation loss both in sitting and supine positions (Table 8).

Table 8. Values are presented as mean ± standard deviation

Number of boys	Time 1			Time 2			Time 3		
	Cobb angle (°)		Flexibility (%)	Cobb angle (°)		Flexibility (%)	Cobb angle (°)		Flexibility (%)
	sitting	supine		sitting	supine		sitting	supine	
12	23.0±5.6	10.8±6.6	75.5±5.0	30.9 ± 5.9	18.2±6.6	57.1±10.5	34.4±4.4	22.2±6.3	49.1±10.0
25	11.1±3.5	5.2±3.3	60.7±6.5	27.2 ± 3.2	13.7±3.6	36.2±9.2			
31	22.4±2.8	8.2±3.0	86.2±5.0						

Time 1 represents the time when scoliosis was first detected after loss of walking ability

Time 2 represents the time 1 year after the detection of scoliosis

Time 3 represents the time 2 years after the detection of scoliosis

3.2.3. Scoliosis curve type changes

Among the 31 boys who developed scoliosis, except for the 6 boys who developed scoliosis at the last year of follow-up and the 4 boys who already had structural scoliosis at the first year of follow-up, only 2 boys had a course of "no scoliosis" that progressed directly to "structural scoliosis." The remaining 19 boys went through the sequence of (1) no scoliosis, (2) nonstructural scoliosis, and (3) structural scoliosis (Figure 3).

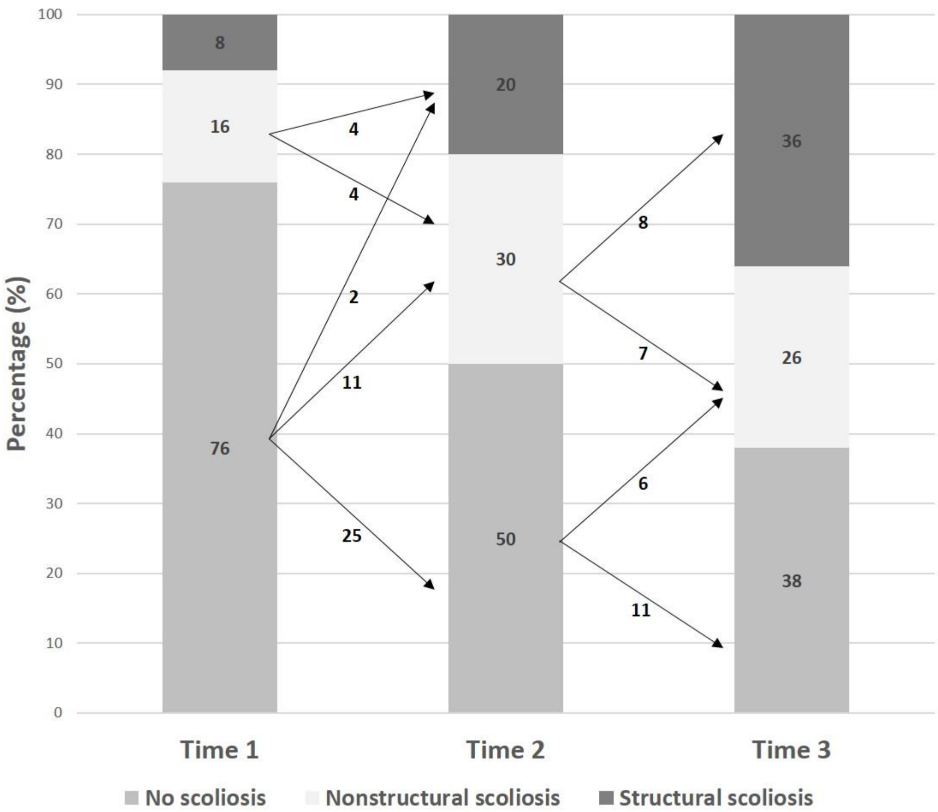

Figure 3. Curve type changes of subjects

Values are presented as number of patients. Note that only 2 boys at the first year had a course of no scoliosis to structural scoliosis

Time 1 represents the time when scoliosis was first detected after loss of walking ability

Time 2 represents the time 1 year after the detection of scoliosis

Time 3 represents the time 2 years after the detection of scoliosis

3.2.4. Changes in curve flexibility

Scoliosis was detected in the sitting position at the first visit after ambulation loss in 12 boys. In these 12 patients, consecutive follow-ups of supine and sitting radiographs were available for 2 years. Flexibility decreased over the follow-up period ($p = .011$). Mean values for flexibility were 75.5% at the first follow-up, 57.1% the next year, and 49.1% at the last follow-up. Cobb angle in this population increased over time. In the same context, for 25 patients whose scoliosis developed after 1 year follow up, consecutive follow-ups of supine and sitting radiographs were available for 2 time points. Flexibility decreased during follow-up period ($p = .02$). Mean values of flexibility were 60.7% at the first follow-up, 36.2% the next year. Cobb angle also increased over time in this group (Table 7).

3.2.5. Correlation between spinal curve flexibility and other parameters

Spinal flexibility of 31 patients was inversely correlated with scoliosis curve angle in sitting and supine position ($r = -0.504$ and $r = -0.77$, respectively, $p < .05$ in both). Pulmonary function, forced vital capacity of % predicted was not correlated with spinal curve flexibility.

3.2.6. Development of pelvic obliquity

There was no pelvic obliquity in the 19 boys who had not developed scoliosis. In the remaining 31 boys with scoliosis, 18 developed pelvic obliquity. In these boys, pelvic obliquity had an increasing tendency after ambulation loss both in the sitting and supine positions (Table 9). The Cobb angle in the sitting position had a significant correlation with pelvic obliquity both in sitting ($r = 0.758$, $p < .001$) and supine positions ($r = 0.639$, $p < .001$). The Cobb angle in the supine position also significantly correlated with pelvic obliquity both in the sitting ($r = 0.844$, $p < .001$) and supine positions ($r = 0.810$, $p < .001$). Pelvic obliquity in sitting and supine position did not show correlations with spinal curve flexibility.

Table 9. Pelvic obliquity of subjects

Number of boys	Time 1			Time 2			Time 3		
	Pelvic obliquity (°)		Flexibility (%)	Pelvic obliquity (°)		Flexibility (%)	Pelvic obliquity (°)		Flexibility (%)
	sitting	supine		sitting	supine		sitting	supine	
4	12.0±8.0	5.3±4.1	100.0±40.0	11.4±3.7	9.1±3.5	27.3±18.7	18.4±7.3	12.6±5.8	32.5±12.7
10	9.1±3.5	4.2±4.9	61.5±42.5	11.4±1.1	6.9±1.5	42.4±10.7			
18	8.6±1.0	2.5±0.8	71.9±9.2						

Values are presented as mean ± standard deviation (SD).

Time 1 represents the time when scoliosis was first detected after loss of walking ability

Time 2 represents the time 1 year after the detection of scoliosis

Time 3 represents the time 2 years after the detection of scoliosis

3.3. Research III: Upper limb short questionnaire for Duchenne muscular dystrophy

3.3.1. Clinical characteristics

Among 167 participants, 160 subjects participated in face-to-face ULSQ interviews and 132 subjects completed follow-up telephone interviews. The mean age was 15.2 ± 4.4 years old (range 7-25 years). The number of patients with DMD by the Vignos scale and modified Brooke scale are represented in Figure 4. Forty-nine patients (30.6%), fifty-seven patients (35.6%), and fifty-four patients (33.8%) were independent ambulators, ambulators with assist or aids, and non-ambulators, respectively. The average age of diagnosis was 4.0 ± 2.8 years. All analyses included patients who used corticosteroid currently or in the past.

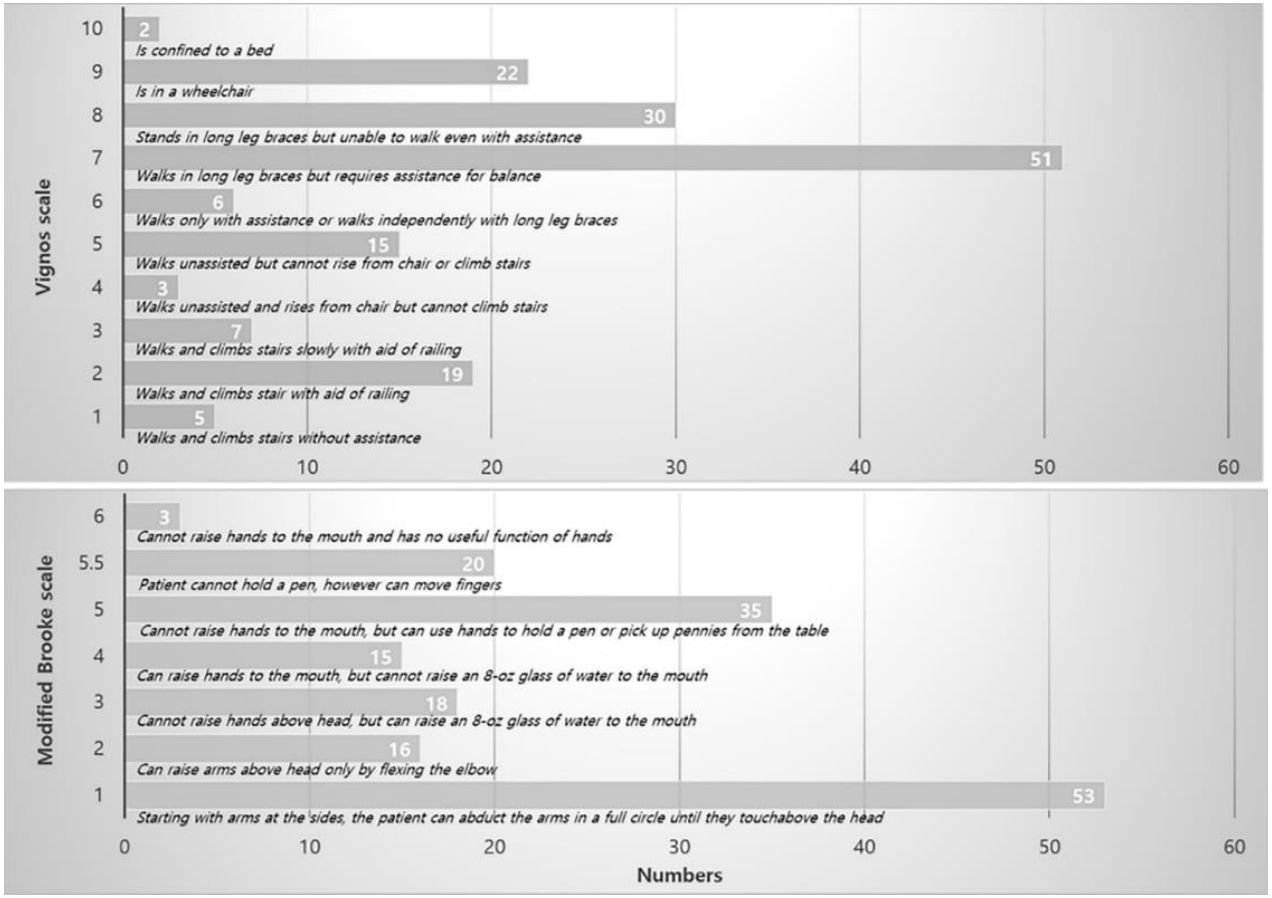

Figure 4. The numbers of individuals with DMD by Vignos Scale and modified Brooke scale

3.3.2. The result of Upper limb short questionnaire survey

The participants had answered either “yes” or “no” for fourteen items of ULSQ. The results for each question’s responses are found in Figure 5. Among the questionnaire regarding UE function, lifting heavy objects over 5 pounds was the most difficult UE function. Among the questionnaire related to UE pain, the most common pain area was the shoulder followed by proximal UE, elbow, and distal UE. For other questions, including ULSQ 3, 6, 8, and 10-14, less than 10% of respondents reported problems.

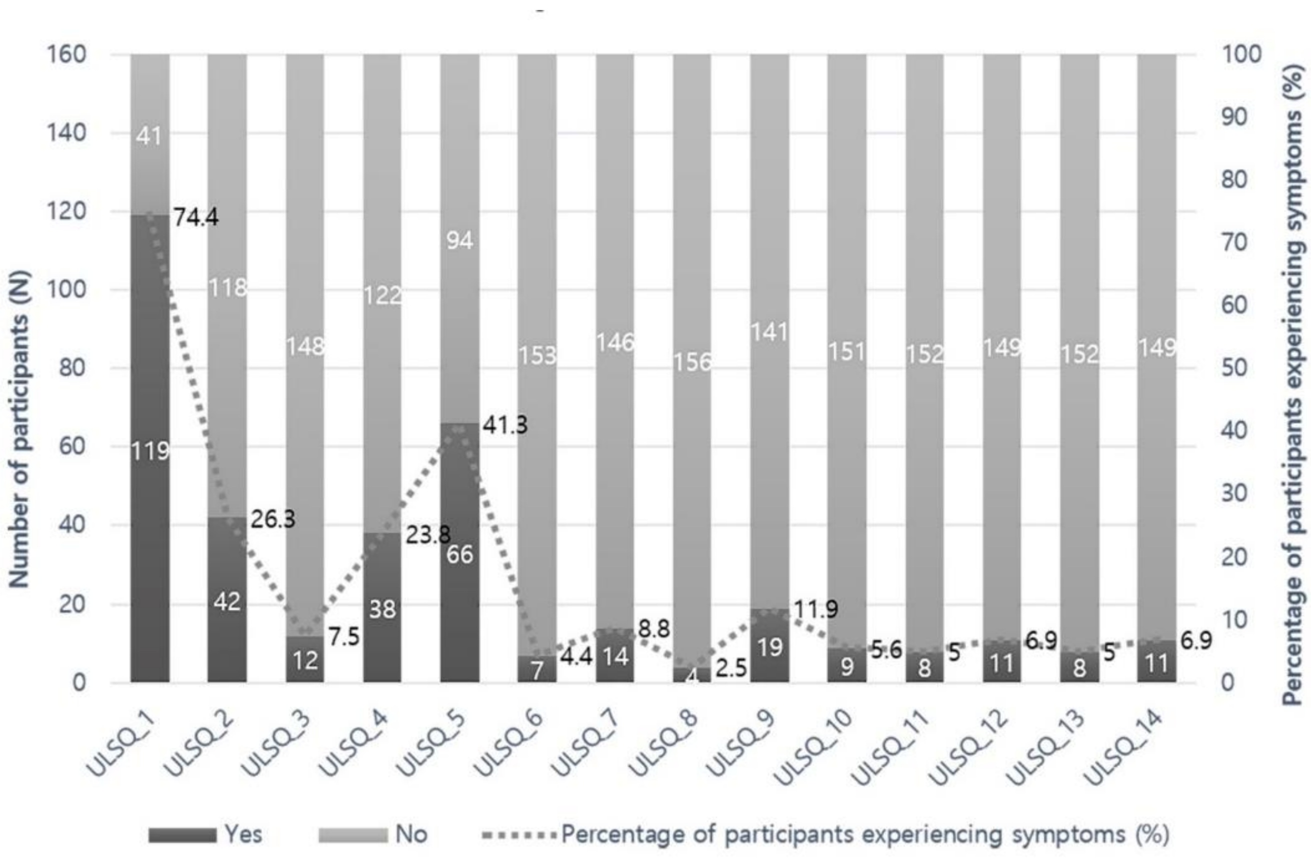

Figure 5. The result of Upper limb short questionnaire (ULSQ) survey

3.3.3. Factor analysis

The result of Bartlett's test of sphericity (df = 762.77, $p < .001$) indicated that the correlation matrix of the sample was worthy of factor analysis. The value of the KMO Measure of Sampling was 0.74, which was a middling value in sample adequacy. Three components had the possibility of an eigenvalue greater than 1.00. The eigenvalues of the first, second, and third components were 3.84, 2.19, and 1.87, respectively, and the first component explained 27.46% of the total variance. Factor rotation using orthogonal rotation was applied, and the result demonstrated three distinct factors comprised of UE function, pain, and stiffness in line with the previous study.[35] Subsequent confirmatory factor analysis showed that the sample size-dependent chi-square was significant ($\chi2$= 138.77, $p < .001$). The GFI value was 0.90, and the CFI value was 0.91. The RMSR value was 0.006, and the RMSEA value was 0.074. The confirmatory factor analysis indicated that the three-factor model could be acceptable in statistical terms as well as conceptual terms.

3.3.4. Construct validity

Kendall rank correlation coefficient (Kendall's Tau) and the p-value are summarized in Table 10. Among the three components, the sum scores of the first component, UE function was the most highly related to Brook scale (Kendall's Tau 0.64, $p < .001$) (Figure 6). Although the sum scores of the second component regarding pain and the third component regarding stiffness also showed that it statistically significantly correlated with the modified Brooke scale (Kendall's Tau 0.17, $p = .013$; Kendall's Tau 0.18, $p = .011$), the strength of the relationship was very weak. The total scores of fourteen items of ULSQ had a significant correlation with the modified Brooke scale (Kendall's Tau 0.61, $p < .001$), respectively. The total scores and sum scores of each component of differences between ambulatory groups were compared to assess the discriminative capability of ULSQ using the Kruskal-Wallis test (Table 11). For total scores and each sum score regarding upper limb dysfunction, pain, and stiffness, there was a significant difference between ambulatory groups. Post-hoc Tamhane's test revealed a significant difference in total scores and sum scores of upper limb function between the independent ambulatory and assisted ambulatory groups ($p < .001$) as well as between the independent ambulatory and non-ambulatory group ($p < .001$). However, in the case of pain and stiffness, the difference of sum scores were only between the independent ambulatory and the non-ambulatory groups (pain: $p = .028$, stiffness: $p = .019$).

Table 10. Correlation between scores of Upper limb short questionnaire (ULSQ) and modified Brooke scale

		Sum of Component 1 (Upper limb function)	Sum of Component 2 (Pain)	Sum of Component 3 (Stiffness)	Total scores of ULSQ
Brooke	Kendall's Tau[a]	.64	.17	.18	.61
scale	p-value	<.001	.013	.011	<.001

a: Kendall Rank Correlation Coefficient

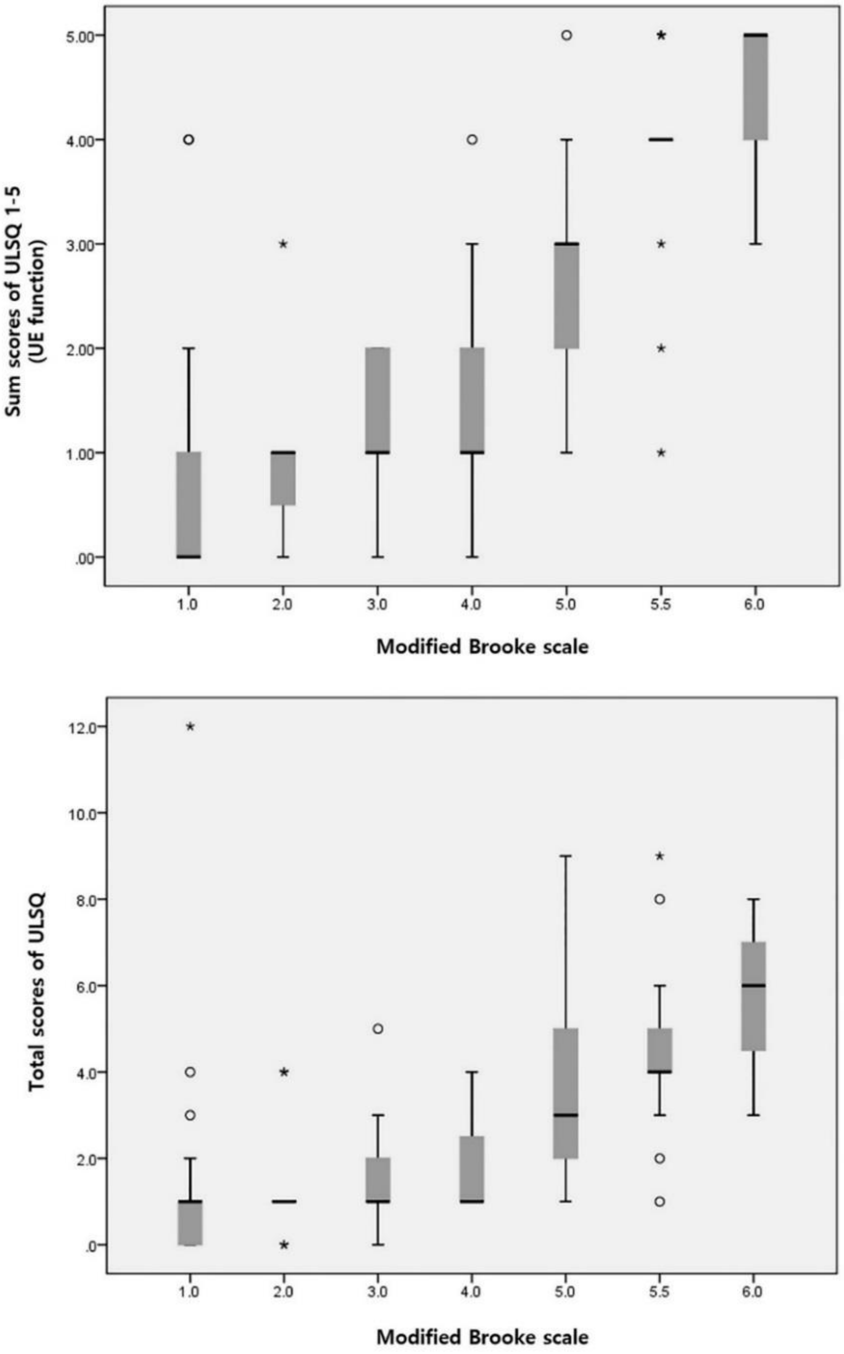

Figure 6. The box plot for sum scores of Upper limb short questionnaire (ULSQ) from 1 to 5 items (Above) and total scores of ULSQ (Below) according to the modified Brooke scale. UE: upper extremity

Table 11. Results from Kruskal-Wallis tests and post-hoc pairwise comparisons for total scores and sum scores of each component between different ambulatory stages

	Ambulatory Group	N	Mean Rank	Chi-Square	p-value	Tamhane post hoc		
						Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
Sum of Component 1 (Upper limb function)	Group 1	49	47.29	39.926	<.001	<.001	<.001	.283
	Group 2	57	90.58					
	Group 3	54	100.00					
Sum of Component 2 (Pain)	Group 1	49	72.61	7.384	.025	.484	.028	.619
	Group 2	57	78.25					
	Group 3	54	90.04					
Sum of Component 3 (Stiffness)	Group 1	49	73.00	8.304	.016	.054	.019*	0.980
	Group 2	57	81.58					
	Group 3	54	86.17					
Total scores of ULSQ	Group 1	49	46.32	42.734	<.001	<.001	<.001	.263
	Group 2	57	89.11					
	Group 3	54	102.43					

N: number; Group 1: independent ambulator; Group 2: ambulator with assist or aid; Group 3: non-ambulator.

3.3.5. Reliability

Cronbach's alpha values were 0.71, 0.72, and 0.86 for UE function, pain, and stiffness, respectively, indicating adequate internal consistency for all factors. The test-retest reliability of the ULSQ using mean Gwet's AC1 coefficients and their 95% confidence intervals with the percentage level of agreement summarized in Table 12. The first and second-rater tend to conduct the ULSQ consistently, as all measured items lie within the 95% confidence interval.

Table 12. Test-retest reliability

Items	Agreement (%)	AC1 (95% CI)
ULSQ_1	73.74	0.63 (0.48, 0.78)
ULSQ_2	85.86	0.78 (0.66, 0.9)
ULSQ_3	78.79	0.69 (0.55, 0.83)
ULSQ_4	90.91	0.86 (0.76, 0.95)
ULSQ_5	81.82	0.64 (0.49, 0.79)
ULSQ_6	94.95	0.94 (0.9, 0.99)
ULSQ_7	89.9	0.88 (0.8, 0.96)
ULSQ_8	97.98	0.98 (0.95, 1)
ULSQ_9	90.91	0.89 (0.82, 0.96)
ULSQ_10	92.93	0.92 (0.86, 0.98)
ULSQ_11	94.95	0.94 (0.9, 0.99)
ULSQ_12	98.99	0.99 (0.96, 1)
ULSQ_13	100	NA
ULSQ_14	100	NA

AC1: Gwet's first-order agreement coefficient

NA: Not applicable

4. Discussion

4.1. Research I: Lower extremity joint contracture according to ambulatory status

This study examined HF, KF, and APF contractures among male patients with DMD, based on the patients' ambulatory status, and investigated the differences in major joint contractures, based on passive stretching exercise participation. Our findings indicated that HF, KF, and APF contractures are more common and severe when there is deterioration of ambulatory function. Moreover, stretching exercises alone are unlikely to prevent lower extremity joint contractures.

The frequency and severity of lower extremity joint contractures rapidly increases after the loss of ambulatory function in children with DMD. This finding is consistent with the results of a previous study by McDonald et al.[11] However, unlike their results, lower extremity contractures were common in the ambulatory patients in our study, especially those involving the ankle joint. In ambulatory patients, APF contractures may be associated with a compensatory mechanism. Gaudreault et al. reported that, in children with DMD, the APF moments caused by early APF contractures contribute to the production of the net APF moment during the stance phase of gait.[58] An alternative hypothesis, suggested by Sutherland et al., is that as weakness progresses, ambulatory DMD patients exert APF moments during the stance phase of gait to oppose KF moments, allowing movement of the force line in front of the knee joint's center. They suggested that this compensatory gastrocnemius-soleus muscle group activity assists with knee stability as well as the muscle imbalance contributed by the APF contracture.[59] However, when APF contracture proceeds further, knee joint compensation and increased HF angle during the stance phase may decrease gait stability.[60, 61] Additionally, excessive APF contractures often make the wearing of regular shoes and passive standing difficult for patients with DMD, after the loss of ambulatory function. Because this study was a cross-sectional study, a demonstration of the interplay between APF contracture and muscle weakness that occurs during disease progression was not possible.

Most previous studies on joint contractures in patients with DMD were reported before universal steroid use. In some studies, those who received steroid medications were excluded from the analysis. Unlike previous studies, all of the patients in the present study were prescribed deflazacort. However, our results are similar to those obtained when steroids were not widely used.[11] Mendell et al. also suggested that although prednisone treatment improves the strength and functioning of patients with DMD, it has no significant effect on major joint ROM.[62]

No differences were observed in the contracture angles between the stretching and non-stretching groups, regardless of ambulatory status. These results are comparable with the results of Brooke et al.,[8] who reported no correlation between patients performing passive joint stretching exercises and joint contractures. A few authors have suggested that joint angles should be managed in parallel with orthotic management, rather than solely through stretching. Hyde et al. demonstrated that patients undergoing passive stretching combined with the use of nighttime splints demonstrated 23% less annual change in APF contracture angles than did the patients managed with stretching only.[63] Others performed a longitudinal analysis that suggested early and continuous use of daytime articulated AFOs promoted positive changes in the kinematic parameters of gait when used before the functional deficit became too advanced, alleviating the increase in pelvic tilt and decrease in hip extension angles during the stance phase of gait.[64] Standing devices might also be considered for use, with or without AFO application, because they allow maintenance of an upright position and provide leg joint stretching.[65]

Because of the limited evidence available regarding the optimal frequency of stretching exercises in children with DMD, we arbitrarily set the criteria for the stretching exercise group as >3 sessions/week; in clinical situations, daily stretching exercises may not be realistic. Further, the current stretching recommendations from the American College of Sports Medicine apply only to healthy adults. To maintain long-term flexibility and ROM, stretching exercises are recommended at least 2–3 days per week, and the same recommendations for stretching exercises are usually applied to pediatric populations, based on these recommendations.[66] Based on a systematic review on ankle dorsiflexion stretching,[67] calf muscle stretching provides increased ankle dorsiflexion, particularly after 5–30 min of stretching in healthy individuals. Therefore, children who stretched >5 min/session were included in the stretching group, in this study.

We acknowledge that this study has several limitations. First, the cross-sectional design may effect selection and institutional biases. Second, the duration and technical appropriateness of the stretching exercises were not controlled. Although the patients and their parents received stretching technique education from the institution where the study was conducted, the stretching techniques were not monitored or evaluated. Future prospective studies that control the quality and quantity of this type of intervention could help better understand its benefits for delaying the progression of joint contractures.

4.2. Research II: Scoliosis in Duchenne muscular dystrophy children

Curve flexibility has not been much investigated in neuromuscular patients due to relatively low incidence of the disease itself, and difficulties of regular visits due to physical disabilities of patients. However, the authors managed to gather information of DMD patients with regular follow ups with strict intervals, and adequate information of physical function and the timing of ambulation loss. We found that there is a period of fully reducible scoliosis curve soon after loss of walking ability in neuromuscular scoliosis of DMD patients. This is a period when spinal curve could be effectively reduced by spinal orthosis. Therefore, with early detection of scoliosis, and during the period when the curve is fully reducible, application of spinal braces should be considered.

Historically, bracing in neuromuscular scoliosis has been known to be ineffective.[68-71] Nevertheless, the beneficial effects of spinal bracing should be reconsidered in DMD patients for the following reasons: First, the exact timing of bracing was not indicated in existing studies[68, 70-72]; the subjects were those with scoliosis who rejected surgery, or who had low lung capacity and could not tolerate the surgery; this is thought to occur after rigid and structural scoliosis develop.[71] Second, studies on the effect of spinal bracing on scoliosis were written in the non-steroid era. Clearly, there has been a change in the course of scoliosis development in DMD patients who use steroids.[15, 73, 74] A number of studies have reported that glucocorticoids slowed the rate of curve progression.[15, 73, 75] Use of spinal braces in DMD patients who are taking glucocorticoids might further decrease the necessity for scoliosis surgery.

Etiology of spinal curve progression in neuromuscular conditions remains still only incompletely understood.[76, 77] Asymmetrically decreased tone of the paraspinal muscles is known to result in scoliotic curve formation, and it is expected to worsen in wheel chair bound patients. Loss of ambulation indicates that DMD has been already progressed to a certain degree that trunk muscles are also fairly impaired by then.[72] After loss of ambulation, spinal curvature rapidly progresses, and as it was shown in our study, flexibility also decreases almost simultaneously. It was contemplated that as the mechanical forces on the weaker side of spine are maintained, compensation builds on the skeletal system. As this condition continues, as long as the patients maintain sitting position in daily living, deformity of the musculoskeletal system may further progress, resulting in decreased spinal curve flexibility.

Within 2 years after loss of ambulation, scoliosis rapidly progressed that as many as half of patients who did not have rigid component of scoliosis eventually fell into the category of partially reducible scoliosis. Therefore, to detect scoliosis before rigid component of the curve develops, regular interval follow ups of at least within 1 year should be necessary. This is in line with guidelines of Birnkrant et al., that neuromuscular assessment and management should start in the early stage after loss of ambulation at least every 6 months.[14, 16, 17] Once the spinal curve becomes rigid, it is generally accepted that correction cannot be accomplished with orthotics. In such cases, surgical treatment might be needed. Nevertheless, surgery itself could be a burden for DMD patients because of progressive cardiomyopathy and respiratory muscle weakness.[78]

In this study, authors evaluated scoliosis by assessing spine radiographs in two different positions; sitting and supine. There was a substantial difference in the Cobb angles based on the position. Therefore, it should be noted that scoliosis should be evaluated dynamically, and a single supine radiograph is not sufficient to diagnose the early phase of scoliosis development.

In the future, prospective studies of applying spinal orthosis, beginning orthotic management at very early phase of scoliosis development, should be helpful in preventing further progression of curve in this patient group.

Neuromuscular scoliosis, unlike idiopathic scoliosis, is thought to be flaccid type and result in C-shaped curves.[79] This type of scoliosis extends its curve distally, causing pelvic obliquity.[47] Pelvic obliquity impairs sitting balance, hampering activities of daily living. Causes of pelvic obliquity are thought to include spinal deformities, hip contractures, leg-length discrepancy, or any combination of these factors.[80] Numerous studies reported that pelvic obliquity was more closely-related with spine deformity than with muscular imbalance below the pelvis.[81] Moreover, hip surgeries should have no effect on the correction of pelvic obliquity.[81, 82] The results of the present study are in line with those of previous studies. The subjects without scoliosis had no pelvic obliquity; in other words, only those with scoliosis developed pelvic obliquity. There was also a high correlation between Cobb angle and pelvic obliquity.

This study has several limitations. First, data collection was attempted with strict follow-up interval of 1 year, without missing radiographs. Therefore, the data were highly-refined, but there was a rather short follow-up of 2 years. More details regarding eventual courses of scoliosis curve and flexibility may be obtained with longer follow-up times and similar study designs. Second, Scoliosis consists of two components: lateral deviation and rotation. It is known that the apical vertebra is most deeply rotated.[81] In the present study, however, only lateral deviation was considered for evaluation. We evaluated the lateral deviation because the participants in were in the early stage of scoliosis, only 2 years after ambulation loss. Because the degree of rotation increases according to the severity of coronary curves, we assumed that the rotative degree would not have a serious impact.[83, 84] Lastly, the participants are grouped according to the yearly time-frame after loss of ambulation, not according to the magnitude of the spinal curve. Flexibilities of curves are largely influenced by the degree of the curve. However, in our study, as it is shown in table 1, Cobb angle of standard deviation of each group is around 5 degrees, which means that within each group, the degree of Cobb angle is relatively homogenous. Also, Cheung et al. reported that in adolescent idiopathic scoliosis, curve flexibility is the only parameter that significantly influences in-brace correction in adolescent idiopathic scoliosis, regardless of curve size or age.[85]

4.3. Research III: Upper limb short questionnaire for Duchenne muscular dystrophy

Our study confirmed the construct validity and test-retest reliability of ULSQ. Furthermore, it was expected that the sum scores of the items related to the UE function component (ULSQ 1 to 5) could be a clinical measure of UE function for screening purposes.

The difference between ULSQ and other UE assessment tools is that ULSQ briefly assesses pain and stiffness in addition to UE function. The pain experienced by boys with DMD has rarely been reported. For example, Duchenne muscular dystrophy Functional Ability Self-Assessment Tool (DMDSAT) designed to measure functional ability in patients with DMD consists of 6 levels of upper limb function, 5 levels of mobility, 5 levels of transfer, and 3 levels of ventilator use.[51] The lowest level of upper limb function on this scale is 0, meaning that ‘cannot move fingers’ and the 5 levels above it correspond to each level of upper limb function module of ULSQ, from 5 to 1. Despite this similarity, DMDSAT is a tool for evaluating and monitoring overall functional activity, including the lower extremities, so it does not include assessment of pain or stiffness.

Hunt et al. surveyed pain experiences in 12 young people (from 11 to 21 years) with DMD, and the authors reported that 9 persons had pain in their lower extremity and 8 persons in their back.[86] However, there were no patients with UE pain in the study. On the contrary, Janssen et al. reported that UE pain occurred from the early ambulatory period and that the incidence and severity increased as the disease progressed. In the study, shoulder pain was in 60% of patients in the late ambulatory period.[87]

In our study, 35 DMD patients (21.9% of participants) reported UE pain, and among patients who reported UE pain experience, 19 patients (54.3%) reported shoulder region pain. In non-ambulator, 18 patients (33.3%) and 9 patients (16.7%) reported pain and stiffness respectively. Higher Brooke scale scores (severe UE impairment) tended to increase the incidence of pain and stiffness. The mechanisms of UE pain in DMD patients are not yet known. Bergsma et al. suggested that people with DMD might tend towards the disuse of the UE due to more severe proximal weakness.[88] Consequently, they cannot use the full capacity of their hands because they cannot be manipulated in 3D space. Jansen et al. also argued that assisted bicycle exercise in the UE could delay functional deterioration by avoiding no use.[87] It is unknown whether disuse or no use caused by using the UE less than capacity is associated with pain. Almost all of the UE pain in DMD patients that we authors observed through this study was muscle origin pain rather than joint or ligament origin pain. For example, in the shoulder region, the pain was localized in the shoulder girdle muscles, such as the rhomboid, trapezius, and supraspinatus infraspinatus muscle, rather than the shoulder joint. In the future, it is necessary to study the characteristics of UE pain, including the regions, features, and trigger and relief factors in DMD patients.

Janssen et al. reported in their web-based questionnaire study that more frequent stiffness complaints, more limitations due to stiffness, more frequent elbow pain were the variables negatively correlated with UE function.[26] In the present study, more frequent stiffness complaints, more limitations due to stiffness, more severe stiffness complaints have a correlation with impaired UE function such as primary hand function, gross hand function, and fine hand function. Pain limitations seemed to be correlated with impaired primary hand function. Contrary to the results of research by Janssen et al., whole UE pain except elbow pain was correlated with gross hand function. For the correlation between pain and stiffness, more severe pain complaints and proximal UE pain, including shoulder also positively correlated with more frequent stiffness complaints, more limitations due to stiffness, and more severe stiffness complaints.

Future research on clinical significance is also needed, including whether upper extremity pain and stiffness may limit activity, and how it affects the quality of life.[26] These studies will provide the basis for establishing an intervention strategy for UE pain and stiffness in this patient group.

In our study, 17 (16%) independent or assisted ambulatory patients reported pain in their UE. Bergsma et al. observed that patients with facioscapulohumeral dystrophy mainly showed symptoms of UE pain although there were few activity limitations associated with upper limbs, and suggested that these results may be related to overuse rather than no use.[88] In the same way, UE pain in ambulatory DMD patients may have occurred from a different mechanism than that of non-ambulatory DMD patients.

In the process of conducting this study, the following practical problems were encountered. First, concerning the ULSQ1, many participants were unaware of whether they could lift objects more substantial than 5 pounds. Although ULSQ uses a self-report method, in these cases, we asked the patients to lift a book that weighed approximately 5 pounds above their shoulder level. ABILHAND-plus has the option 'I don't know' among 4 answer options.[32] When Janssen used this evaluation tool, 28.5% of respondents chose the option in at least one of the items.[37] It could be suggested to make the self-report as the default method in ULSQ, but to allow performing the activities of ULSQ when the patients do not know their capacities. Second, there are various types of keys, such as electronic or card keys, so it could be appropriate to add another example of small object manipulation such as holding and using a pencil in ULSQ 3. Third, when asked about the hand function of ULSQ 3 and 4, patients with DMD often answered that they could not do it. However, they could do it when their hands were on the table. It would be helpful for an accurate assessment to specify that the activities of ULSQ 3 and 4 are those with the arms on the table. Fourth, in the case of ULSQ 5, which evaluates fine hand function, it might be better to replace the example such as "unwrapping a small piece of candy" rather than "buttoning up the shirts." Most of the respondents in our study did not wear shirts with buttons as they had difficulty in buttoning up their shirts. Finally, for the younger patients to be questioned, including a simple human UE figure designating each region in the questionnaire could enhance the understanding of the questions.

This study had some limitations. To investigate construct validity, we compared ULSQ only with the Brooke scale, which evaluates UE body function. Further comparisons are needed to confirm the construct validity. For example, PUL,[36] Capabilities of upper extremity instrument (CUE),[89] ACTIVILIM,[90] and ABILHAND,[32] which evaluate UE function at the activity level and DMDSAT,[51] a screening tool for functional status of persons with DMD could be candidates for additional validation.

4.4. Implication for clinical trial in Duchenne muscular dystrophy

Clinical trials for novel disease-modifying treatments aiming at dystrophin restoration or improvements in muscle quality have progressed during the past decade.[5,6] The validated outcome measure for DMD to evaluate treatment efficacy is important for investigating clinically meaningful effects in patients with DMD.[91] As efficacy endpoint, measures of strength, timed motor performance and pulmonary function have been well studied[92] and most therapeutic trials using these endpoints usually target ambulatory patients. Although the efficacy endpoint should be used in a wide spectrum of disease stages considering the increased life expectancy for patients with DMD, consensus has not been established regarding what measures are most sensitive to change in disease progression and are reliable in the non-ambulatory stage. The measurement of muscle strength of lower extremity and timed motor function may show limited utility in the non-ambulatory stage. Rather, occurrence and progression of lower limb joint contracture and scoliosis should be continuously monitored from the early ambulatory stage to the late non-ambulatory stage, including the transition phase across the loss of ambulation. The results of these studies, such as lower extremity joint contractures and scoliosis along with spinal curve flexibility, may complement as supplementary outcomes in the future clinical trial. Furthermore, during the non-ambulatory stage of the disease, the natural history of UL and respiratory function is important clinical information that captures disease progression.[93] ULSQ using as an outcome measure may comprehensively evaluate pain and stiffness which may have an impact on UE function, as well as UE function in the non-ambulatory stage.

The International Classification of Functioning, Disability, and Health (ICF) developed by the World Health Organization (WHO) consists of body function, body structures, activity limitations and participation restriction, and environment factors, [94] and it provides a standardized approach to evaluation of primary problems and degree of impairment.[95] Disability in body structure and function results in problems with activity and participation in neuromuscular disorders including DMD. Most outcome measures in clinical trial for DMD assess body function and activity limitation. However, it is necessary to assess not only functional ability but also whether candidate drugs targeting dystrophin-related pathologies can reduce musculoskeletal complications of body structure because variable degrees of impaired contracture may affect body structure functional capacity.[91] In order to make up for this, we provide information about body structure such as lower extremity joint contracture and scoliosis with spinal curve flexibility. In summary, knowledge for the contemporary dataset of musculoskeletal complications in our research is expected to make additional contributions to the field of “new” natural history in the steroid era and may help to improve clinical trial methodology.

5. Concluding Remarks

In patients with DMD, HF, KF, and APF contractures were more common and more severe in non-ambulatory patients. APF contractures were observed more frequently, even early in the ambulatory period. Prevention of lower extremity joint contractures solely through stretching exercises is unlikely. Knowledge of lower extremity joint contracture profiles, based on ambulatory status, may be useful for developing appropriate strategies for joint management in this patient group. After loss of ambulation when scoliosis starts to develop, there is a period of fully reducible curve in DMD scoliosis patients. This result suggests that in the early stage of scoliosis, wherein flexibility is maintained without structural scoliosis, interventions such as bracings should be considered in DMD scoliosis. Also, scoliosis curve in DMD patients should be evaluated dynamically to detect the scoliosis when the curve is fully reducible. This study could be a cornerstone for further studies involving application of spinal braces for neuromuscular scoliosis. Finally, the ULSQ consisting of 14 items that assessed UE function, pain, and stiffness in patients with DMD is a valid and reliable assessment tool for screening purposes. Furthermore, it is expected that the sum scores of the items related to the UE function component (ULSQ 1 to 5) could measure the activity limitation related to UE in clinical practice.

Finally, we proposed to change the details of the question to make the application of ULSQ more accurate and useful.

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Appendix

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Lower extremity joint contracture according to ambulatory status in children with Duchenne muscular dystrophy

Young-Ah Choi, Seong-Min Chun, Yale Kim & Hyung-Ik Shin

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Scoliosis in Duchenne muscular dystrophy children is fully reducible in the initial stage, and becomes structural over time

Young-Ah Choi, Hyung-Ik Shin & Hyun Iee Shin

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국문 초록

뒤셴느근디스트로피 환자에서의 근골격계 평가

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서론: 뒤셴느근디스트로피에서 스테로이드 치료와 비침습적 환기 보조 등의 보조적인 치료 방법으로 인해 평균 생존 기간이 크게 증가하였다. 따라서 기능을 최대한 유지하고 합병증을 최소한으로 줄이기 위한 체계적인 사지 및 척추의 근골격계 평가가 필요하다. 첫 번째 연구에서는 하지의 주요 관절 별 가동범위 및 구축 정도 그리고 보행 능력에 따른 스트레칭 중재 효과를 평가하였다. 보행 능력을 소실한 이후에 가장 흔히 발생하는 근골격계 합병증은 척주측만증으로 두 번째 연구에서는 척주측만증의 발생과 척주측만증의 유연성, 그리고 척주측만증과 연관 있는 골반 기울임을 평가하여 서로 간의 연관성 및 시간에 따른 추이를 확인하였다. 마지막으로 휠체어 의존 시기에 독립적인 일상생활 동작 영위하기 위해서는 상지 기능이 가장 중요하므로 한국의 임상적 상황에 맞는 뒤셴느근디스트로피의 상지 평가도구를 마련하고자 하였다.

방법: 첫 번째 연구에서는 과거 스테로이드 치료를 받았거나, 지속해서 치료받고 있는 128명의 뒤셴느근디스트로피 환자를 대상으로 Vginos 척도로 평가한 보행 능력 감소에 따른 관절 가동범위 및 구축 정도의 변화와 주 3회 스트레칭 중재를 시행한 경우와 그렇지 않은 군으로

나누어 각 보행 능력에 따른 스트레칭 중재의 효과를 단면적으로 조사하였다. 두 번째 연구에서는 뒤셴느근디스트로피 환자 273명을 대상으로 휠체어에 완전히 의존하게 된 시점에서부터 2년 동안 Cobb 각도 및 골반 기울임을 측정하였으며, 앉은 자세와 앙와위 자세의 Cobb 각도의 차이를 통해 척추의 유연성을 측정하였다. 더불어 각 자세에서의 Cobb 각도와 척주측만증의 유연성, 그리고 골반 기울임의 연관성을 확인하였다. 마지막으로 상지 기능 평가도구를 개발하기 위해 2018년도에 발표된 영문으로 된 상지 간단 설문지를 번역, 역번역 및 원저자 확인 후 한국어판 상지 간단 설문지를 완성하였으며, 160명의 뒤셴느근디스트로피 환자들을 대상으로 신뢰도 및 타당도를 평가하였다.

결과: 첫 번째 연구에서 보행 가능한 그룹에서는 고관절과 슬관절 굴곡 구축이 드물게 관찰되었으나 족저굴곡 구축은 보행 가능 시기에서도 52.6%에서 관찰되어, 보행 가능 시기에서도 발목의 경우 족저굴국 구축이 빈번하게 발생함을 확인하였다. 보행 가능한 그룹에서는 평균 고관절 굴곡 구축 각도와 비교하였을 때 평균 족저굴곡 구축은 4.9도 정도 더 있는 것으로 나타났다. 보행 가능한 그룹과 보행 불가능한 그룹 간의 구축 정도를 비교하였을 때 보행 불가능한 그룹에서 보행이 가능한 그룹에 비해 평균적으로 고관절 굴곡 구축은 22도, 슬관절 굴곡 구축은 40.4도, 족저굴곡 구축은 28.1도 더 구축된 것으로 나타났다. 보행 가능한 그룹과 보행 불가능한 그룹에서 각각 주 3회 스트레칭 중재를 시행한 군과 시행하지 않은 군 간에 고관절 굴곡, 슬관절 굴곡, 족저굴곡의 구축 각도를 비교하였으나, 모두 유의한 차이가 없었다. 두 번째 연구에서 뒤셴느근디스트로피 환자 273명 중 50명이 2년간 추적관찰 기간 동안의 평가를 모두 완료하였으며, 그 중 31명에서 척주측만증이 발생하였다.

2명을 제외하고 모두 척주측만증이 없는 상태에서 비구조적 척주측만증, 구조적 척주측만증 순서로 단계별로 진행하는 것을 확인하였다. 척주측만증의 유연성은 매년 추적 관찰 시 마다 감소하는 경향을 보였는데 척주측만증이 발생한 첫해는 75.5 ± 5.0 % (평균 ± 표준 편차), 그 다음 1년 후 관찰 시에는 57.1 ± 10.5 %, 마지막 추적 관찰 시 49.1 ± 10.0 % 순으로 나타났다. 또한 앉은 자세와 앙와위 자세에서 측정한 척주측만증의 유연성은 각 자세에서의 Cobb 각도와 유의한 상관관계가 관찰되었다. 마지막으로 뒤센느근디스트로피 환자 167명 중에서 160명이 첫 번째 설문조사에 응답하였으며, 두 번째 설문조사는 132명이 응답하였다. 탐색적 요인분석 및 확인적 요인분석을 통해 구성 타당도를 검증하였으며, 상지 기능에 관련한 설문 문항들의 총합은 Brooke 척도와 높은 정도의 상관관계를 보였다. 상지 간단 설문지의 총합과 상지 기능, 통증, 뻣뻣함과 관련된 각 세부 문항들의 합 역시 보행 불가능한 그룹에서 보행 가능한 그룹에 비해 유의하게 높았다. 또한 내적 일관성과 검사-재검사 신뢰도를 통해 신뢰도를 검증하였으며, 신뢰도는 적절하였다.

결론: 뒤센느근디스트로피에서 보행 능력을 소실할수록 고관절 굴곡 구축, 슬관절 굴곡 구축, 족저굴곡 구축의 빈도와 심각성이 높아진다. 스트레칭 중재 단독으로는 하지 관절 구축을 예방 할 수 없어 향후 스트레칭 중재 이외에 다른 중재 치료를 함께 적용 고려해야 할 것으로 사료된다. 또한, 뒤센느근디스트로피에서 척주측만증 발생 초기에는 유연성이 있어 척주측만증의 정도를 감소시킬 수 있는 기간이 존재한다. 그러나 척주측만증 각도가 증가하면서 유연성은 저하된다. 척주측만증의 유연성을 확인하기 위해서는 적어도 앉은 자세와 앙와위 자세에서 각각

측정하여 동적으로 평가할 필요가 있다. 마지막으로 한국판 상지 간단 설문지는 타당도와 신뢰도가 검증되어 임상적으로 한국의 뒤센느근디스트로피 환자의 상지 평가도구로 사용될 수 있을 것으로 기대된다.

주요어: 구축, 기능, 뒤센느근디스트로피, 뻣뻣함, 상지, 스테로이드, 척주측만증, 통증, 하지

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