



Frequent Unrecognized Vertebral Fractures Associated with Increased Body Fat Mass in Children and Adolescents with Duchenne Muscular Dystrophy

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Abstract

Objective Patients with Duchenne muscular dystrophy (DMD) have an increased risk of vertebral fractures (VFs). Ethnic variations may partly contribute to the fracture risk. This study aimed to demonstrate the VFs and body fat mass in Asian patients with DMD.

Methods Demographic data and DMD-related parameters of the enrolled patients were collected. Lateral thoracolumbar spine radiographs were performed for VF assessment. The Genant classification was applied for VF severity grading (mild, moderate, and severe). Body composition analysis using dual-energy X-ray absorptiometry was performed. Serum calcium, phosphate, intact parathyroid hormone, and 25-hydroxyvitamin D concentrations were determined.

Results There were 25 children and adolescents with DMD enrolled. The median (interquartile range [IQR]) age was 12.9 (9.6–19.3) years. Nine patients (36%) had VFs with a total of 31 sites of VFs (mild, $N = 10$; moderate, $N = 3$; and severe, $N = 18$). These VFs had never been recognized prior to this study. Comparing with the non-VF group, the VF group received a significantly greater cumulative prednisolone equivalent dose (1,258 [948–1,664] vs. 291 [17–823] mg/kg, $p = 0.003$). Body fat mass, represented by fat mass index and body fat percentage Z-scores, was greater in the VF group (2.46 [2.21–2.51] vs. 1.63 [0.36–2.07], $p = 0.011$ and 4.4 [3.1–5.5] vs. 1.8 [0.6–3.5], $p = 0.008$, respectively). No differences in serum calciotropic hormones and vitamin D status were demonstrated between patients with and without VFs.

Conclusions VFs were frequent in patients with DMD. Patients with VFs had greater cumulative glucocorticoid dose and body fat mass than those without VFs.

Keywords

- ▶ vertebral fracture
- ▶ osteoporosis
- ▶ Duchenne muscular dystrophy
- ▶ glucocorticoid
- ▶ body composition

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Introduction

Duchenne muscular dystrophy (DMD) is characterized by progressive muscular damage and degeneration. Increasing muscle weakness, loss of ambulation, respiratory impairment, and cardiomyopathy are evidenced in patients with increasing age.¹ Glucocorticoids are used for delaying the disease progression, and preserving respiratory and cardiac functions.^{1,2}

Patients with DMD frequently develop bone fragility as a result of several risk factors.³ Progressive muscle weakness, which leads to reduced weight-bearing activity, and the potent osteotoxicity of glucocorticoid treatment are the main risk factors for developing fractures. Additionally, prolonged use of glucocorticoid and DMD itself are associated with delayed puberty, vitamin D deficiency, obesity, and frequent falls, which further increase the already high risk of fractures.^{3,4}

Furthermore, body composition of patients with DMD undergoes changes secondary to prolonged glucocorticoid use and progressive degeneration of skeletal muscles, resulting in substitution of muscles with adipose and fibrous tissues.^{4,5} The changes lead to a decrease in lean mass and an increase in fat mass, which contribute to an elevated risk of fractures.^{4,6}

Vertebral fracture (VF) is one of the diagnostic criteria for defining osteoporosis in children.⁷ However, VFs in children are often asymptomatic and unrecognized, and if untreated, they can cause chronic back pain and aggravate future fracture risk.⁸ VFs in patients with DMD further impair the ambulation and quality of life.^{3,4}

Previous studies in Caucasians reported varied frequencies of VFs in patients with DMD, which have ranged from 9 to 53%.^{3,4,9–11} Data on VFs in Asians with DMD are relatively scarce, with reported frequencies of VFs at 5 and 33% in Indians and Hongkongers, respectively.^{12,13} Types of studies (surveillance study including both symptomatic and asymptomatic VFs or studies focusing only on symptomatic VFs), differences in glucocorticoid treatment, time points of VF assessment, and vitamin D status may contribute to the variations in frequencies of VFs.^{4,9–11} Moreover, ethnic variations in bone geometry, density, and microarchitecture have been demonstrated and may be one of the factors involved in the variations of VF frequencies.¹⁴ There have been reports that Asians carry lower fracture risks than Caucasians do.^{14–16} Studies of bone structure showed that Asians had smaller bones, more plate-like trabecular microarchitecture, and thicker and denser cortices as compared to Caucasians.^{14,15} Therefore, differences in bone strength and fracture risks between ethnic groups might exist. This study aimed to determine the frequency of VFs and body composition changes in Thai patients, an Asian in origin, with DMD and identify the factors associated with VFs.

Materials and Methods

This cross-sectional study enrolled patients with DMD who attended the Pediatric Neurology Clinic at the Faculty of Medicine Ramathibodi Hospital, a tertiary medical school hospital, between March 2023 and January 2024. All patients

had the diagnosis of DMD confirmed by either multiplex ligation-dependent probe amplification for dystrophin gene analysis or immunohistochemistry study of muscle tissue obtained from biopsy for dystrophin protein identification. Glucocorticoid treatment with either prednisolone (0.75 mg/kg/d) or deflazacort (0.9 mg/kg/d) was initiated when patients were ≥ 5 years old and began to walk with an abnormal gait pattern. Glucocorticoid dosage adjustment was performed according to the ambulation status. Demographic data, including age, auxological data, and DMD-related parameters, were collected. Weight, height, and body mass index (BMI) Z-scores were calculated using Thai National Growth References.¹⁷ Overweight and obesity were defined as BMI Z-scores of greater than +1 to +2 and greater than +2, respectively.¹⁷ Pubertal stage was assessed according to Tanner staging. Ambulatory status was determined using the Ambulatory Function Classification System for DMD (AFCS), which consists of five levels: level 1, walking at normal speed and with normal postural alignment; level 2, walking independently without an assistive device or brace, but with evidence of abnormal gait patterns (tiptoeing or waddling) and with impaired postural alignment (excessive trunk lordosis); level 3, walking across short distances with the use of a handheld mobility device (a walker or crutch); level 4, inability to walk with the use of a powered wheelchair; and level 5, the need for transportation in a manual wheelchair.¹⁸ Glucocorticoid treatment, including types, dose, and duration, was recorded. Cumulative doses of glucocorticoids were determined by summation of the doses received during the course of treatment until enrollment, and expressed in prednisolone equivalent doses as milligram per kilogram.¹⁹ Calcium and vitamin D intakes at enrollment were estimated from daily amount of milk and dairy product intakes, and calcium and/or vitamin D supplements. Vitamin D supplementation was not routinely prescribed, but rather was prescribed according to each doctor's practice.

Blood samples were collected for determination of serum calcium, phosphate, albumin, parathyroid hormone (PTH), and 25-hydroxyvitamin D (25-OHD). Serum PTH and 25-OHD concentrations were measured by chemiluminescence assay (Roche Diagnostics GmbH, Mannheim, Germany). Vitamin D status was categorized into three groups according to serum 25-OHD concentrations, sufficiency (≥ 75 –250 nmol/L), insufficiency (50–74 nmol/L), and deficiency (< 50 nmol/L).²⁰

All patients underwent lateral thoracolumbar spine radiographs for VF assessment and dual-energy X-ray absorptiometry (DXA) scan for body composition assessment. VF was assessed by a musculoskeletal radiologist (P.F.) who was blinded from the patients' clinical data, using Genant's classification.²¹ The severity of VF was defined in accordance with the percentages of vertebral height loss: 20 to 25% as mild, 26 to 40% as moderate, and greater than 40% as severe.

DXA was performed using Hologic Discovery W DXA scanner (Hologic, Bedford, MA, United States) and the measurement procedures were operated in the fast array mode. Lumbar spines (L1–L4) and total body less head (TBLH) bone mineral content and areal bone mineral density (BMD) were assessed. The BMD Z-scores were calculated using the mean

Table 1 Clinical characteristics of all enrolled patients

| Parameters | Patients | | | p-value ^a |
|--|---------------------|---------------------|---------------------|----------------------|
| | All (N = 25) | VFs (N = 9) | Non-VFs (N = 16) | |
| Age at diagnosis of DMD (y) | 7.5 (5.8–10.4) | 7.8 (7.0–12.1) | 7.1 (5.2–10.1) | 0.251 |
| Duration of disease (y) | 5.7 (1.9–9.0) | 7.0 (4.8–9.0) | 3.9 (0.4–10.8) | 0.468 |
| Age at enrollment (y) | 12.9 (9.6–19.3) | 15.4 (12.3–18.7) | 10.2 (8.5–19.7) | 0.208 |
| Weight Z-score | −0.1 (−1.8 to 0.8) | 0.3 (−2.0 to 0.8) | −0.3 (−1.9 to 0.7) | 0.834 |
| Height Z-score | −2.4 (−3.5 to −0.9) | −2.9 (−4.8 to −2.5) | −1.1 (−3.4 to −0.2) | 0.050 |
| BMI Z-score | 1.4 (−1.1 to 2.5) | 2.2 (1.0–2.5) | 0.4 (−1.7 to 2.5) | 0.117 |
| BMI status^b | | | | |
| Overweight | 3 (12%) | 1 (11%) | 2 (13%) | 0.127 |
| Obesity | 11 (44%) | 6 (67%) | 5 (31%) | |
| Genital Tanner stage^b | | | | |
| I | 13 (52%) | 4 (45%) | 9 (56%) | 0.469 |
| II | 3 (12%) | 2 (22%) | 1 (6%) | |
| III | 1 (4%) | 1 (11%) | 0 (0%) | |
| IV | 2 (8%) | 0 (0%) | 2 (13%) | |
| V | 6 (24%) | 2 (22%) | 4 (25%) | |
| Level of ambulatory status (AFCSD)^b | | | | |
| 1 | 1 (4%) | 0 (0%) | 1 (6%) | 0.541 |
| 2 | 11 (44%) | 3 (33%) | 8 (50%) | |
| 3 | 4 (16%) | 3 (33%) | 1 (6%) | |
| 4 | 6 (24%) | 2 (23%) | 4 (25%) | |
| 5 | 3 (12%) | 1 (11%) | 2 (13%) | |
| Type of glucocorticoid used^b | | | | |
| Prednisolone | 20 (80%) | 8 (89%) | 12 (75%) | 0.369 |
| Deflazacort | 2 (8%) | 1 (11%) | 1 (6%) | |
| None | 3 (12%) | 0 (0%) | 3 (19%) | |
| Total duration of glucocorticoid treatment until the enrollment (y) | 4.7 (2.0–8.1) | 7.0 (4.6–8.9) | 1.7 (0.3–6.1) | 0.057 |
| Glucocorticoid dose at enrollment (mg/kg/d) ^c | 0.6 (0.4–0.7) | 0.6 (0.4–0.6) | 0.5 (0.4–0.8) | 0.680 |
| Cumulative glucocorticoid dose until the enrollment (mg/kg) ^c | 869 (300–1,606) | 1,258 (948–1,664) | 291 (17–823) | 0.003 |
| Calcium intake (mg/d) | 540 (390–665) | 500 (390–730) | 540 (375–688) | 0.955 |
| Vitamin D supplement (IU/d) | 2,857 (2,500–5,714) | 5,714 (2,500–5,714) | 2,857 (1,786–5,714) | 0.281 |

Abbreviations: AFCSD, Ambulatory Function Classification System for Duchenne muscular dystrophy; BMI, body mass index; DMD, Duchenne muscular dystrophy; VFs, vertebral fractures.

^aComparing between patients with VFs and non-VFs.

^bData are presented in median (interquartile range, IQR) or N (%).

^cExpressed as prednisolone equivalent dose.

and standard deviation (SD) of white male population from the National Health and Nutrition Examination Survey (NHANES) 2012 for the TBLH region and the mean and SD of Asian male population from native Japanese reference data for the L1–L4 regions. A BMD Z-score of ≤ 2 was defined as low BMD for age. Body fat percentage (%BF) was calculated from the percentage of total body fat mass (kg) divided by total body mass (kg). The %BF Z-score was calculated using the reference ranges for total body fat determined by DXA.²² Fat mass index (FMI) and lean mass index (LMI) were determined using the formulas of body fat mass/height² (kg/m²) and body lean mass/height² (kg/m²) respectively.

The FMI and LMI Z-scores were calculated using the reference ranges for body composition indices determined by DXA.²³

The study protocol was approved by the Ethics Committee on Human Research of the Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand (MURA2023/103). The study conformed with the Declaration of Helsinki. Written informed consent was obtained from the patients or their legal guardians.

Data analyses were performed using SPSS version 27.0 (IBM, Armonk, NY, United States). Data were presented as percentage and median with interquartile range (IQR), where appropriate. Comparisons between two groups were

performed using the Mann–Whitney *U* test for continuous data and chi-squared test for categorical data.

Results

There were 25 patients enrolled. Clinical characteristics of the patients are presented in ►Table 1. Their median (IQR) age at enrollment was 12.9 (9.6–19.3) years, and median (IQR) duration of disease was 5.7 (1.9–9.0) years. Based on their BMI Z-score, there were three overweight patients (12%) and 11 patients (44%) with obesity. At enrollment, 16 patients (64%) ambulated independently with and without mobility devices (AFCS levels 1–3), while 9 patients

(36%) were wheelchair bound (AFCS levels 4–5). Six patients reported occasional nonspecific back pain.

Glucocorticoid treatment was prescribed in 22 patients (88%), prednisolone in 20 of them and deflazacort in 2 of them. Three patients did not receive glucocorticoid treatment (one patient was diagnosed early in the course of the disease and had AFCS level 1, and two patients had totally dependent ambulation with AFCS level 5 at the time of diagnosis). The median (IQR) prednisolone equivalent dose at enrollment was 0.6 (0.4–0.7) mg/kg/d with the cumulative prednisolone equivalent dose of 869 (300–1,606) mg/kg. The median (IQR) duration of glucocorticoid treatment was 4.7 (2.0–8.1) years.

Table 2 Calcitropic blood chemistries and dual-energy X-ray absorptiometry (DXA) results of all enrolled patients

| Parameters | Patients | | | p-value ^a |
|---|---------------------|---------------------|---------------------|----------------------|
| | All (N = 25) | VFs (N = 9) | Non-VFs (N = 16) | |
| Blood chemistries | | | | |
| Calcium (mmol/L) ^b | 2.4 (2.3–2.5) | 2.4 (2.3–2.5) | 2.4 (2.3–2.6) | 0.419 |
| Phosphate (mmol/L) ^b | 1.5 (1.3–1.6) | 1.4 (1.2–1.5) | 1.5 (1.4–1.7) | 0.221 |
| PTH (pmol/L) ^b | 2.9 (2.2–4.4) | 3.4 (2.6–4.5) | 2.4 (2.0–4.1) | 0.219 |
| 25-OHD (nmol/L) | 85 (58–101) | 96 (85–115) | 77 (48–95) | 0.123 |
| 25-OHD status^c | | | | |
| Sufficiency | 15 (60%) | 8 (89%) | 7 (44%) | 0.108 |
| Insufficiency | 5 (20%) | 1 (11%) | 4 (25%) | |
| Deficiency | 5 (20%) | 0 (0%) | 5 (31%) | |
| TBLH BMD (g/cm ²) | 0.5 (0.5–0.6) | 0.6 (0.5–0.7) | 0.5 (0.5–0.6) | 0.381 |
| TBLH BMD Z-score | −3.7 (−5.1 to −2.2) | −4.6 (−7.7 to −3.5) | −2.9 (−4.1 to −1.5) | 0.027 |
| Low BMD for age (Z-score ≤ −2) ^c | 18 (72%) | 9 (100%) | 9 (56%) | 0.057 |
| L1–L4 BMD (g/cm ²) | 0.5 (0.4–0.6) | 0.5 (0.4–0.6) | 0.5 (0.4–0.6) | 1.000 |
| L1–L4 BMD Z-score | −2.1 (−3.8 to −1.3) | −2.9 (−3.8 to −2.1) | −1.9 (−3.7 to −1.2) | 0.156 |
| Low BMD for age (Z-score ≤ −2) ^c | 14 (56%) | 8 (89%) | 6 (38%) | 0.033 |
| LMI (kg/m ²) | 10.6 (9.0–13.2) | 13.0 (8.7–13.6) | 9.8 (8.8–11.9) | 0.121 |
| LMI Z-score ^d | −3.7 (−5.4 to −0.8) | −3.7 (−5.9 to −0.5) | −3.6 (−4.9 to −1.0) | 0.646 |
| FMI (kg/m ²) | 9.8 (5.7–14.0) | 14.2 (11.5–15.0) | 6.9 (3.9–11.1) | 0.006 |
| FMI Z-score ^d | 1.96 (1.15–2.48) | 2.46 (2.21–2.51) | 1.63 (0.36–2.07) | 0.011 |
| %BF (%) | 45 (34–55) | 50 (49–58) | 39 (31–47) | 0.005 |
| %BF Z-score ^e | 3.1 (1.3–4.3) | 4.4 (3.1–5.5) | 1.8 (0.6–3.5) | 0.008 |

Abbreviations: 25-OHD, 25-hydroxyvitamin D; %BF, body fat percentage; BMD, areal bone mineral density; FMI, fat mass index; L1–L4, first to fourth lumbar vertebral levels; LMI, lean mass index; PTH, parathyroid hormone; TBLH, total body less head; VFs, vertebral fractures.

^aComparing between patients with VFs and non-VFs.

^bReference ranges for blood chemistries:

- Calcium: 2.1–2.6 mmol/L.
- Phosphate: 1.1–1.7 mmol/L.
- PTH: 2.0–6.9 pmol/L.

^cData are presented in median (interquartile range, IQR) or *N* (%).

^dLMI and FMI Z-scores were calculated using reference ranges for body composition indices assessed by DXA.²³ The median (IQR) LMI and FMI of age-matched healthy boys from a previous report²³ were as follows:

- 10.0–10.9 years: 13.2 (12.4–14.1) and 3.8 (3.0–5.1) kg/m², respectively.
- 12.0–12.9 years: 14.4 (13.1–15.5) and 3.7 (2.9–5.1) kg/m², respectively.
- 15.0–15.9 years: 16.7 (15.0–18.0) and 3.2 (2.5–4.6) kg/m², respectively.

^e%BF Z-score was calculated using reference ranges for total body fat assessed by DXA.²² The median (IQR) %BF of age-matched healthy boys from a previous report²² were as follows:

- 10.0–10.9 years: 28% (24–34%).
- 12.0–12.9 years: 24% (20–29%).
- 15.0–15.9 years: 21% (17–25%).

The median (IQR) estimated calcium intake was 540 (390–665) mg/d. Vitamin D supplementation was prescribed in 22 of 25 patients (88%) at the dose of 2,857 (2,500–5,714) IU/d with once a week or once every 2 weeks of 20,000 IU/capsule of ergocalciferol. Calcitropic blood chemistries are shown in ►Table 2. Five patients (20%) had vitamin D deficiency (two of them had no vitamin D supplementation). None of the patients with VFs had vitamin D deficiency.

Body composition and BMD data are summarized in ►Table 2. Patients with DMD had greater FMI and %BF than the age-matched healthy boys from previous reports^{22,23} (9.8 [5.7–14.0] vs. 3.7 [2.9–5.1] kg/m², $p < 0.001$ and 45% [34–55%] vs. 24% [20–29%], $p < 0.001$, respectively).

VFs were identified in 9 of 25 patients (36%). Among nine patients with VFs, four (44%) reported an occasional nonspecific back pain. Six patients with VFs (67%) ambulated independently with and without mobility devices (AFCS levels 1–3), while three patients (33%) were wheelchair bound (AFCS levels 4–5). All patients with VFs had been treated with glucocorticoids for the median (IQR) duration of 7.0 (4.6–8.9) years. The characteristics of each patient with VFs are presented in ►Table 3.

A total of 31 VFs were identified in nine patients (►Fig. 1; mild: 10 [32%]; moderate: 3 [10%]; and severe: 18 [58%]). The most frequently affected site was the first lumbar (L1) level. Five out of nine patients had multiple sites of VFs. One patient (patient 4, ►Table 3) who was a 13.3-year-old

Table 3 Characteristics of nine patients with vertebral fractures (VFs)

| Parameters | Patients | | | | | | | | |
|--|-----------|-----------|--------------|----------------|-----------|---------------------------|-------------|-------------------------|---------------------------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| At diagnosis | | | | | | | | | |
| Age (y) | 11.1 | 14.2 | 7.2 | 8.0 | 13.0 | 7.5 | 4.4 | 7.8 | 7.2 |
| 25-OHD concentration (nmol/L) | 48 | ND | ND | 34 | 58 | 52 | 61 | ND | ND |
| At enrollment | | | | | | | | | |
| Age (y) | 20.5 | 21.2 | 12.9 | 13.3 | 15.4 | 11.7 | 11.6 | 16.4 | 9.9 |
| Duration of disease (y) | 9.4 | 7.0 | 5.7 | 5.3 | 2.4 | 4.2 | 7.2 | 8.6 | 2.7 |
| Weight Z-score | 0.8 | 0.4 | –2.7 | 0.3 | –1.2 | 2.6 | 0.9 | –0.8 | 0.8 |
| Height Z-score | –2.5 | –3.3 | –3.7 | –3.4 | –2.9 | –1.7 | –2.4 | –6.0 | –1.0 |
| BMI Z-score | 2.2 | 2.2 | –1.3 | 2.3 | 0.3 | 3.7 | 2.6 | 2.5 | 1.6 |
| Genital Tanner stage | V | V | I | I | II | I | I | III | II |
| AFCS level | 2 | 4 | 2 | 3 | 4 | 3 | 2 | 5 | 3 |
| History of occasional back pain | Yes | No | No | Yes | No | No | No | Yes | Yes |
| Type of glucocorticoid used | Pred. | Pred. | Pred. | Pred. | Pred. | Pred. | Deflazacort | Pred. | Pred. |
| Total duration of glucocorticoid treatment until the enrollment (y) | 9.4 | 7.0 | 5.7 | 5.1 | 2.4 | 4.1 | 7.2 | 8.6 | 2.7 |
| Cumulative glucocorticoid dose until the enrollment (mg/kg) ^a | 1,681 | 1,595 | 1,004 | 1,065 | 484 | 893 | 1,258 | 2,241 | 591 |
| Blood chemistries | | | | | | | | | |
| Calcium (mmol/L) ^b | 2.3 | 2.4 | 2.5 | 2.4 | 2.5 | 2.6 | 2.5 | 2.3 | 2.4 |
| Phosphate (mmol/L) ^b | 1.2 | 1.1 | 1.5 | 1.5 | 1.1 | 1.4 | 1.7 | 1.5 | 1.5 |
| PTH (pmol/L) ^b | 4.4 | 5.0 | 3.4 | 4.6 | 4.5 | 2.3 | 2.1 | 2.9 | 2.4 |
| 25-OHD (nmol/L) | 84 | 102 | 132 | 96 | 85 | 64 | 127 | 87 | 84 |
| BMD and body composition | | | | | | | | | |
| TBLH BMD Z-score | –2.5 | –4.6 | –6.7 | –5.4 | –8.8 | –3.8 | –3.5 | –11.6 | –3.6 |
| L1–L4 BMD Z-score | –1.3 | –2.9 | –2.1 | –3.8 | –3.8 | –2.1 | –2.2 | –4.6 | –3.3 |
| LMI Z-score | –3.7 | –6.8 | –6.3 | –0.1 | –5.5 | –0.3 | –0.7 | –2.0 | –4.7 |
| FMI Z-score | 2.4 | 2.5 | 1.1 | 2.3 | 2.2 | 3.0 | 2.5 | 2.5 | 2.5 |
| %BF Z-score | 5.2 | 6.8 | 1.3 | 3.3 | 4.8 | 3.9 | 2.9 | 4.4 | 5.7 |
| Number of VFs | 1 | 1 | 3 | 17 | 1 | 2 | 1 | 2 | 3 |
| Sites of VFs (severity) | L1 (mild) | L1 (mild) | T7–T9 (mild) | T1–L5 (severe) | L1 (mild) | L4 (moderate) L1 (severe) | L2 (mild) | L5 (mild) T9 (moderate) | T12 (mild) T4 and L1 (moderate) |

Abbreviations: 25-OHD, 25-hydroxyvitamin D; %BF, body fat percentage; AFCS, Ambulatory Function Classification System for Duchenne muscular dystrophy; BMD, areal bone mineral density; BMI, body mass index; FMI, fat mass index; L, lumbar vertebral level; LMI, lean mass index; ND, no data; Pred., prednisolone; PTH, parathyroid hormone; T, thoracic vertebral level; TBLH, total body less head.

^aExpressed as prednisolone equivalent dose.

^bReference ranges for blood chemistries: calcium 2.1–2.6 mmol/L; phosphate 1.1–1.7 mmol/L; and PTH 2.0–6.9 pmol/L.

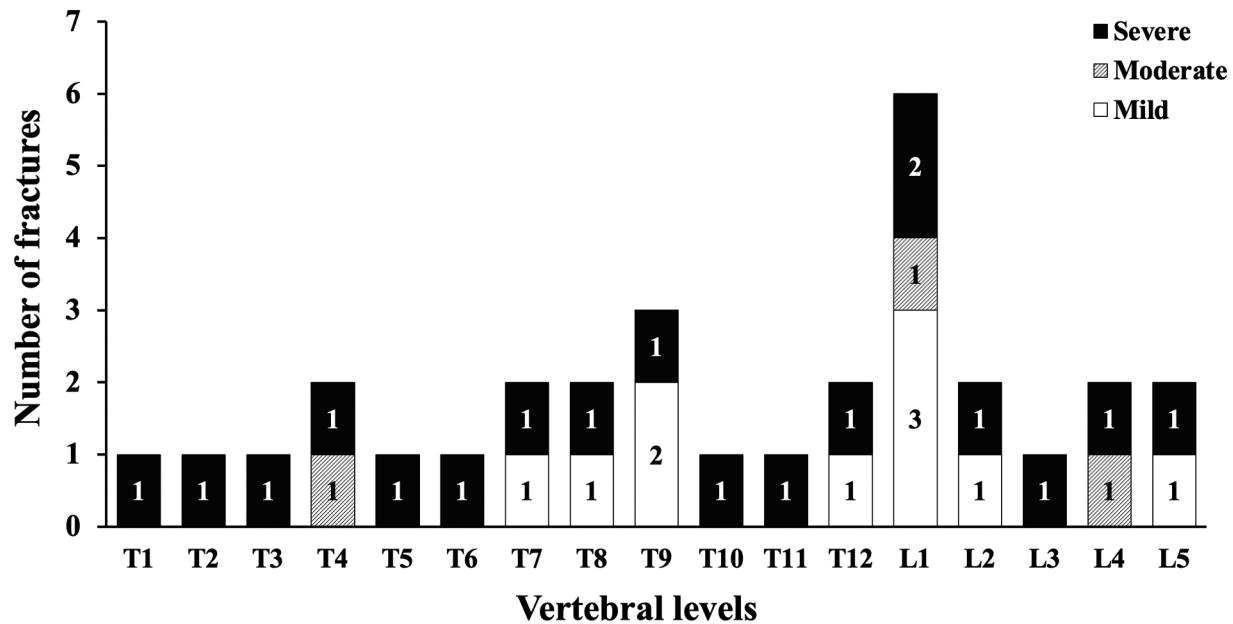


Fig. 1 The sites of 31 vertebral fractures and their severity in nine patients.

prepubertal boy with AFCS level 3, who had been diagnosed with DMD for 5.3 years and had received prednisolone treatment for 5.1 years with a cumulative dose of 1,065 mg/kg, suffered up to 17 sites of severe VFs (► **Fig. 2**).

Patients with VFs received greater cumulative prednisolone equivalent doses than patients without VFs (1,258 [948–1,664] vs. 291 [17–823] mg/kg, $p = 0.003$; ► **Table 1**). Additionally, TBLH BMD Z-score of the VF group was lower than

that of the non-VF group ($-4.6 [-7.7 \text{ to } -3.5]$ vs. $-2.9 [-4.1 \text{ to } -1.5]$, $p = 0.027$). Total body fat represented by FMI and %BF Z-scores of the VF group was greater than that of the non-VF group (► **Table 2**).

Discussion

Previous studies reported the prevalences of VFs at approximately 5 to 60% among patients with DMD from different ethnicities.^{3,4,9–13} Regarding ethnic variations in bone geometry and microarchitecture, this study's findings did not support the protective effect of being Asians on the occurrence of VFs. This could be explained by the fact that there were other more potent factors causing VFs, which included glucocorticoid therapy, reduced muscle mass, increased fat mass, and immobilization. The discrepancy of VF occurrence among studies could be contributed by several factors. The present study included asymptomatic VFs, and a relatively high frequency of VFs at 36% was demonstrated. In contrast, some of the previous studies that focused only on symptomatic patients had reported lower frequencies of VFs at 5 and 23%.^{3,12} Status of ambulation, which reflects the severity of DMD, might affect the rate of VFs. A previous study performed lateral spine radiographs only on patients who were wheelchair bound (AFCS levels 4–5) and showed the frequency of VFs at 9%,¹¹ while this study included only 36% of patients with AFCS levels 4 to 5. Several patients who suffered VFs had AFCS levels 2 to 3 (► **Table 3**). The findings suggested that VFs could develop in the less severe patients without recognized symptoms.

The finding of this study was consistent with that of the most previous studies that demonstrated that VFs occurred exclusively in patients treated with glucocorticoids, mainly prednisolone.^{3,9–12} This study's patients with VFs received

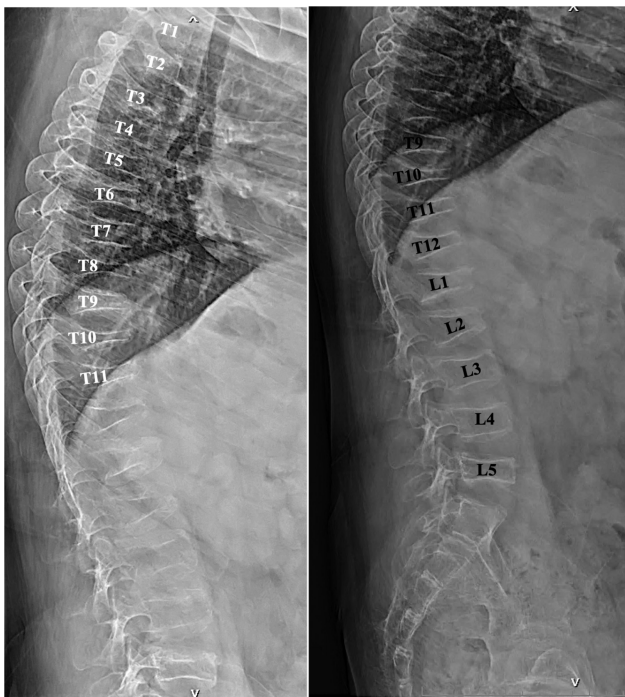


Fig. 2 Lateral thoracolumbar spine radiographs of patient 4 who had the most severe vertebral fractures. L, lumbar vertebral level; T, thoracic vertebral level.

greater cumulative dose of glucocorticoid therapy than those without VFs. Greater cumulative glucocorticoid dose and longer duration of glucocorticoid treatment were reported to be associated with high prevalence of VFs.^{9,10} The findings emphasized the potent osteotoxic effect of glucocorticoids. Most of the patients in this study were treated with prednisolone. One of the two patients who received deflazacort had VFs (patient 7, **Table 3**). Previous studies of deflazacort-treated patients reported the frequencies of VFs at 19 and 53%.^{9,11} A previous study comparing between patients who were treated with deflazacort for approximately 5.5 years and untreated patients showed that VFs occurred exclusively in deflazacort-treated patients.¹¹ Therefore, both prednisolone and deflazacort had significant detrimental effects on the bones.

None of the patients with VFs in this study had vitamin D deficiency, which was in contrast with a previous study that reported vitamin D deficiency in 67% of their patients with VFs detected during the spinal fracture surveillance.¹⁰ Although their patients had less glucocorticoid exposure and shorter duration of disease than this study's patients with VFs, asymptomatic and mildly painful VFs were detected. Therefore, optimization of vitamin D status would at least in part lessen the risk of VFs in patients with DMD.

The present study identified the most frequently affected site of VFs at the vertebral L1 level. The finding was consistent with the findings of previous studies in glucocorticoid-treated patients with DMD and acute lymphoblastic leukemia.^{10,24,25} Mechanical or compression stress on the thoracolumbar junction, which serves as a site of transition from being fixed by ribs to being freely mobile, has been proposed as the mechanism for the most vulnerable site for fracture at the vertebral L1 level.²⁴

Concerning patients with VFs, patient 4 who was the most severely affected patient experienced 17 sites of severe VFs (**Fig. 2**). Despite having the most severe VFs among nine patients with VFs, his TBLH BMD Z-score was not the lowest, suggesting that BMD was not a good predictor for VFs. Additionally, his L1–L4 BMD Z-score might not be reliable because there were fractures along these vertebrae, which could cause overestimation of the areal BMD assessed by DXA. Short stature (height Z-score of -3.4), obesity (BMI Z-score of $+2.3$), and relative pubertal delay (genital Tanner stage I at 13.3 years of age) might have contributed to his severe VFs.^{4,25} Moreover, vitamin D deficiency at the time of diagnosis was noted, which could be an additional factor contributing to the susceptibility to VFs. Furthermore, unrecognized VFs might have contributed to the progression of his VFs.²⁵

Regarding body composition, this study demonstrated that patients with DMD exhibited greater total body fat, expressed as FMI and %BF, than age-matched healthy boys, particularly in the VF group (**Table 2**). Increased body fat in these patients could be a result of muscle degeneration from the disease progression and prolonged glucocorticoid treatment.^{4,5} As a result, LMI was reduced in patients with DMD as compared with the age-matched healthy boys. An increase in body fat mass could potentiate the risk of VFs, which was supported by the association of greater %BF with an

increased risk of osteoporosis found in a previous study of Chinese adults.⁶

This study's findings of low BMD among patients with DMD, especially those with VFs, were consistent with other studies.^{10–12} Decreases in muscle strength and physical activity compromised the bone–muscle unit, thus causing low BMD.

This study adds data on VFs and body composition in patients with DMD of Asian ethnicity for whom data have been relatively scarce. However, this study acknowledges the limitation of its small sample size of this rare disease from a single center. Owing to the nature of cross-sectional study, longitudinal data on VF development have been lacking.

Bisphosphonate therapy (intravenous zoledronic acid) is planned for the treatment of VFs in all patients.

Conclusion

In conclusion, VFs were frequent in patients with DMD. Patients with VFs had greater cumulative glucocorticoid dose and body fat mass than those without VFs.

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Conflict of Interest

None declared.

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