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Original Article

Examination of Factors Affecting the Development of Osteoporosis in Children with Duchenne Muscular Dystrophy

Duchenne Musküler Distrofisi Olan Çocuklarda Osteoporoz Gelişimini Etkileyen Faktörlerin İncelenmesi

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ABSTRACT

Objective: Duchenne muscular dystrophy (DMD), which is primarily treated with glucocorticoids, is the most common genetic progressive neuromuscular disease in children, which can lead to osteoporosis and fractures. This study analyzed factors affecting osteoporosis before and after loss of ambulation and its relationship with fractures in DMD patients.

Method: This retrospective study included 40 DMD patients. Clinical and laboratory findings and bone mineral densitometry (BMD) values were analyzed.

Results: The median age at diagnosis was 3 years (Q1-Q3: 1-3.5). Osteoporosis was detected in 80% by femoral neck Z-score and 40% by vertebral Z-score, with all vertebral osteoporosis cases also meeting femoral neck osteoporosis criteria. Femoral neck Z-score worsened after loss of ambulation ($p<0.05$), while the lumbar Z-score remained stable. Fractures occurred in 35% of patients, with vertebral fractures in 17.5%. All vertebral fractures were associated with vertebral osteoporosis. No correlation was found between fractures and Dual-energy X-ray absorptiometry scores before loss of ambulation ($p>0.05$), and Z-scores were not significant predictors of fractures. The median age for glucocorticoid initiation was 48 months, with no significant difference between prednisolone and deflazacort regarding osteoporosis duration, scoliosis, or loss of ambulation ($p>0.05$). Scoliosis was present in 60% of patients before loss of ambulation, but no significant relationship was found between BMD and scoliosis.

Conclusion: The results of this study did not show a direct correlation between BMD before the loss of ambulation and the future risk of fractures. Therefore, BMD alone may not be a sufficient predictor of scoliosis progression in DMD patients.

Keywords: Duchenne muscular dystrophy, bone density, osteoporosis, fractures

ÖZ

Amaç: Duchenne musküler distrofisi (DMD), çocukluk çağında en sık görülen genetik ve ilerleyici nöromusküler hastalık olup, tedavisinde glukokortikoidler kullanılmaktadır. Hastalık, osteoporoz ve kırıklara yol açabilmektedir. Bu çalışmada, DMD hastalarında ambulasyon kaybı öncesi ve sonrası osteoporozu etkileyen faktörler ile kırıklarla olan ilişkiler değerlendirilmiştir.

Yöntem: Çalışmaya retrospektif olarak 40 DMD hastası dahil edilmiştir. Klinik ve laboratuvar veriler ile kemik mineral dansitometri (KMD) sonuçları analiz edilmiştir.

Bulgular: Hastaların tanı aldıkları medyan yaş 3 yıl (Ç1-Ç3:1-3,5) olarak bulunmuştur. Femur boynu Z-skoruna göre hastaların %80'inde, vertebra Z-skoruna göre ise %40'ında osteoporoz tespit edilmiştir. Vertebral osteoporoz saptanan tüm hastalarda femur boynu osteoporozu da bulunmuştur. Ambulasyon kaybı sonrasında femur boynu Z-skorlarında anlamlı bir kötüleşme gözlenirken ($p<0,05$), lomber Z-skorlarında değişiklik izlenmemiştir. Kırıklar hastaların %35'inde, vertebral kırıklar ise %17,5'inde görülmüştür. Tüm vertebral kırıkların, vertebral osteoporozla ilişkili olduğu belirlenmiştir. Ambulasyon kaybı öncesi çift enerji X-ışını absorbsiyometrisi skorları ile kırıklar arasında anlamlı bir ilişki saptanmamıştır ($p>0,05$) ve Z-skorlarının kırık riskini öngörmede anlamlı bir belirteç olmadığı gösterilmiştir. Glukokortikoid tedavisine başlanma medyan yaşı 48 ay olarak kaydedilmiş, prednizolon ve deflazakort grupları arasında osteoporoz süresi, skolyoz gelişimi ve ambulasyon kaybı açısından anlamlı bir fark bulunmamıştır ($p>0,05$). Ambulasyon kaybı öncesi hastaların %60'ında skolyoz tespit edilmiş, ancak KMD ile skolyoz arasında anlamlı bir ilişki gösterilememiştir.

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Sonuç: Elde edilen bulgular, ambulasyon kaybı öncesinde ölçülen kemik mineral yoğunluğunun ilerleyen dönemde kırık riskini öngörmede yeterli olmadığını göstermiştir. Bu nedenle BMD'nin tek başına skolyoz progresyonu için güvenilir bir prediktör olmayabileceği düşünülmektedir.

Anahtar kelimeler: Duchenne musküler distrofi, kemik dansitesi, osteoporoz, kırıklar

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common neuromuscular disorder caused by mutations in the dystrophin gene on the X chromosome, affecting one in 3600 male births[1]. These mutations in the dystrophin gene lead to progressive muscle fibre degeneration and weakness.This weakness may initially present as difficulty in walking, but gradually progresses to the point where affected patients are unable to perform activities of daily living and have to use a wheelchair[2].

Clinical signs usually appear in the first few years of life[3-5]. Muscle weakness is more pronounced, especially in proximal muscles. Although the clinical course of skeletal muscle and cardiac involvement can be variable, death usually occurs as a result of cardiac or respiratory failure[4-6].

Creatinine kinase is highly sensitive in the presence of physical examination findings that may be consistent with DMD[7]. DMD is an inherited X-linked recessive trait and the diagnosis should be confirmed by genetic testing[8,9]. Dystrophin immunocytochemistry can also be used to detect cases not identified with polymerase chain reaction testing[10,11]. The most important cause of osteoporosis in DMD patients is thought to be glucocorticoid use and decreased mechanical stimuli due to loss of ambulation[12]. In addition, nutritional deficiencies, hormonal imbalances, systemic inflammation, myokine release from dystrophic muscle, and vascular dysfunction also play a role in osteoporosis[12,13]. All these factors disrupt bone homeostasis by affecting the activity of osteoblasts and osteoclasts, and affect osteoporosis to varying degrees[12,13]. Glucocorticoids are the main treatment for DMD and early initiation has been shown to prolong ambulation[14]. Glucocorticoids improve muscle function, delay the development of respiratory complications and have been reported to delay scoliosis and even cardiomyopathy[15]. However, glucocorticoid therapy is associated with side-effects such as weight gain, cushingoid appearance, behavioral changes, delayed puberty, reduced growth, increased risk of fractures, cataracts, and hair growth[14,16]. Low-energy trauma vertebral fractures, long bone fractures, and osteoporosis are frequently seen in patients with DMD who are taking glucocorticoids[17]. It has been reported that 20-60% of boys with DMD have low-energy trauma extremity fractures (usually distal femur, tibia or fibula), while up to 30% develop symptomatic vertebral fractures[18,19]. The aim of this retrospective study was to analyse the clinical, demographic, and treatment-related factors associated with the development of osteoporosis before and after loss of ambulation in patients under the age of 18 years with genetically confirmed DMD, and to evaluate the relationship between osteoporosis and bone fractures based on Dual-energy X-ray absorptiometry (DXA) measurements, glucocorticoid use, and fracture history.

MATERIALS and METHODS

Patient data were obtained from hospital electronic medical records system. The study included patients under the age of 18 years with a diagnosis of muscular dystrophy, who were followed up at the Muscle Centre between 2013 and 2023, and who developed gait loss. Patients who were diagnosed with Becker muscular dystrophy, who did not continue follow-up in our centre, and who were not diagnosed with DMD by genetic tests were excluded from the study. Forty patients who attended regular follow-ups and had complete accessible records were included in the study

The diagnosis of DMD was based on clinical findings and genetic testing[20]. Clinical and demographic characteristics, laboratory tests and bone mineral densitometry values were analyzed before and after loss of ambulation. Body weight percentiles were calculated according to the Center for Disease Control and Prevention (CDC).

Glucocorticoid (prednisolone or deflazacort) treatment was started in all patients after an average age of 4 years. The choice of deflazacort or prednisolone was based on availability of treatment. Prednisolone treatment was started at 0.5-0.75 mg/kg/day and deflazacort at 0.5-0.9 mg/kg/day. Dose adjustment was made according to the clinical follow-up of the patients. All patients were referred to a dietician at least once and were recommended a calcium-rich diet. Annual height and weight follow-up was performed, and body weight percentiles were calculated according to the CDC. Vitamin D supplementation was adjusted according to annual blood calcium and vitamin D values.

Ambulation loss was classified according to the Ambulatory Functional Classification System for DMD (AFCSD). The AFCSD consists of 5 levels, defined as follows: level 1, walking at normal speed and with normal postural alignment; level 2, walking independently without an assistive device or support, with abnormal walking patterns such as tiptoeing or waddling and impaired postural alignment such as excessive trunk lordosis; level 3, walking only short distances using a hand-held mobility device such as a walker or crutches; level 4, unable to walk and using a battery powered wheelchair; and level 5, needing manual wheelchair transportation[21]. According to the AFCSD classification, levels 4-5 were considered immobilized (non-ambulant).

Regular bone mineral density (BMD) measurements are recommended after the initiation of glucorticoid therapy for the monitoring of bone health and early diagnosis of osteoporosis in patients with DMD[22,23]. DXA is used for this purpose. All DXA scans were performed using a DMS Group IMD device (model: HF1 F/12; X-ray tube: OX/110-5). Device calibration was conducted routinely in accordance with the manufacturer's guidelines to ensure measurement accuracy and reliability. The DXA scans taken before and after loss of ambulation were analyzed to examine BMD. PA lumbar vertebral and femoral (femoral neck) imaging was performed[24]. The age- and height-adjusted Z scores were used in the evaluation of DXA scans[25]. The patients were separated into two groups as those with a BMD Z-score of ≤-2 standard deviation score (SDS) or >-2 SDS. The parameters affecting BMD were analyzed.

The diagnosis of osteoporosis is established based on the criteria outlined in the 2019 Pediatric Position Statement of the International Society of Clinical Densitometry. The presence of one or more vertebral compression fractures, in the absence of local pathology or high-energy trauma, is considered indicative of osteoporosis. In cases where vertebral compression fractures are not present, the diagnosis requires both a clinically significant fracture history and a BMD Z-score of ≤-2.0. A clinically significant fracture history is defined by at least one of the following: (1) two or more long bone fractures occurring by the age of 10 years or (2) three or more long bone fractures at any age up to 19 years[26].

The study was approved by the Ethics Board of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval number: 2023/06-41, dated: 13.07.2023).

Statistical Analysis

The analyses were conducted using SPSS software. Normality of data distribution was evaluated with the Shapiro-Wilk test. Quantitative variables were expressed as mean and standard deviation values for normally distributed data, and as median and interquartile range values for non-normally distributed data. Categorical data were assessed using chi-square tests or Fisher's exact tests. Comparisons of continuous variables between two groups were performed with the Independent Samples t-test or the Mann-Whitney U test, and for more than two groups, ANOVA or Kruskal-Wallis tests were utilized. Post-hoc analyses were conducted to determine specific group differences. The level of statistical significance was set at $p<0.05$

RESULTS

Evaluation was made of 40 male patients diagnosed with DMD, with a median age of 12 (Q1-Q3:11-14) years. A history of DMD in siblings was present in 3 patients and 3 patients had a history of DMD in uncles. The median age at diagnosis of DMD was 3 years (Q1-Q3:1-3.5). The diagnosis of 6 patients was made during screening because of a family history of DMD, and 34 patients (85%) were diagnosed incidentally in further investigations due to elevated liver function tests. The median age of onset of walking was 12 months (min 11- max 30 months). The median age at which gait deterioration began was 4 years and the median age at loss of ambulation was 10 years. Scoliosis was found in 24 patients (60%). According to the femoral neck Z score, 32 (80%) patients met the definition of osteoporosis, while only 16 (40%) patients met the definition of osteoporosis according to the vertebral Z score. All patients with osteoporosis according to the vertebral Z-score also met the definition of osteoporosis according to the femoral neck Z score. In 14 patients there was a history of low-energy trauma bone fracture during the mobilized period. Six patients (15%) had long bone fractures. The distribution of these fractures was as follows: three patients (7.5%) had humerus fractures, two patients (5%) had femur fractures, and one patient (2.5%) had a tibia fracture. Treatment was started of deflazacort in 17 (42.5%) patients, and prednisolone in 23 (57.5%) (Table 1).

The laboratory parameters before and after loss of ambulation showed a significant decrease in the creatinine kinase value after loss of ambulation. Lumbar spine Z-score values were similar, but femoral neck Z-score values worsened after loss of ambulation (Table 2).

Patients who did not have vertebral osteoporosis before loss of ambulation had a similar age at diagnosis and onset of walking, but a younger age at immobilisation [9.5 (9-10), p=0.046)]. These patients had higher vitamin D levels [15.5 (10.4-21.1) vs. 11.9 (8.9-14.9) (p=0.051)]. The rates of long bone fractures and scoliosis were similar in other patients, but all vertebral fractures were observed in these patients (Table 3). There was no difference between the Ca, P, vitamin D, ALP, PTH and CK values of patients with lumbar spine Z osteporosis and other patients after loss of ambulation.

Table 1. The clinical and demographic characteristics of the patients with DMD	
Current age (years) (Median Q1-Q3)	12 (11-14)
Age at diagnosis (years) (Median Q1-Q3)	3 (1-3.5)
Family history of DMD	6 (15%)
Brother	3 (7.5%)
Uncle	3 (7.5%)
Diagnostic sign	
Incidental liver function test elevation	29 (72.5%)
Family screening	6 (15%)
Gait impairment	5 (12.5%)
Independent walking age (months) (median; min-max)	12 (12-36)
Age of gait impairment (years) (median; min-max)	4 (3-5)
Age of immobilization (years) (median; min-max)	10 (7-15)
Vertebral osteoporosis before loss of ambulation, n (%)	16 (40)
Femoral neck osteoporosis before loss of ambulation, n (%)	32 (80)
Scoliosis, n (%)	24 (60)
Bone fracture n (%)	14 (35)
Vertebral	7 (17.5)
Non-vertebral	7 (17.5)
Steroid preference, n (%)	
Deflazacort	17 (42.5%)
Prednisolone	23 (57.5%)
Daily dose of vitamin D supplements (IU)	2000 (min 750-max 3000)
IU: International units, DMD: Duchenne muscular dystrophy	

Table 2. Laboratory findings and bone mineral densitometry values of the patients with DMD before and after loss of ambulation			
	Before loss of ambulation	**After loss of ambulation**	**p-value**
Ca (mg/dL)	9.72±0.31	9.79±0.38	0.379
P (mg/dL)	4.94±0.53	4.74±0.65	0.107
Alp (U/L)	108.2±33.6	104.2±40.3	0.356
TSH (ng/dL)	2.69±1.31	2.74±1.67	0.859
T4 (ng/dL)	1.16±0.42	1.14±0.48	0.772
Vit D (µg/L)	14.99±5.97	16.83±6.46	0.07
PTH (µg/L)	39.56±14.39	42.31±35.6	0.653
CK (U/L)	7218±3880	4422±2659	**0.001**
Weight SDS	0.16±1.31	0.34±1.44	0.114
Femoral neck Z score	-2.64±1.03	-2.87±1.04	**0.03**
Lumbar spine Z score	-1.21±1.69	-1.63±1.72	0.09
Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, TSH: Thyroid stimulating hormone, T4: Thyroxine, VitD: Vitamin D, PTH: Parathyroid hormone, CK: Creatinin kinase, SDS: Standard deviation score, DMD: Duchenne muscular dystrophy			

There was no difference between the Ca, P, ALP, vitamin D, PTH and CK levels of the patients with femoral neck osteoporosis before loss of ambulation and the other patients (p>0.05). There was no difference between the Ca, P, ALP, PTH and CK values of patients with femoral neck osteoporosis and other patients after loss of ambulation, but vitamin D levels were higher in patients with osteoporosis (Table 4).

There was no correlation between bone fracture and femoral neck and vertebral DXA scores before the loss of ambulation. Before the loss of ambulation, the vertebral Z-score was -1.06±1.62 SDS (n=33) in patients without vertebral compression fractures, compared to -1.87±1.97 SDS (n=7) in patients with fractures, with no significant difference determined between the two groups (p=0.346).

Glucocorticoid therapy was initiated for the patients at a median age of 48 months (minimum 44 months, maximum 54 months). Steroid preference (prednisolone or deflazacort) had no effect on the development of osteoporosis and no effect on the development of scoliosis according to the vertebral Z-score of the laboratory parameters. No significant difference was determined between patients on prednisolone and patients on deflazacort in respect of the incidence of bone fractures, scoliosis and osteoporosis (p=0.792). The delay in loss of ambulation was similar in both groups (p=0.71).

Table 3. The relationship between the parameters of the patients and the presence of vertebral osteoporosis before loss of ambulation

	Vertebral osteoporosis before loss of ambulation		
Parameter	**No (n=24)**	**Yes (n=16)**	**p-value**
Age of immobilization (years) (median), IQR	9.5 (9-10)	10 (10-11.5)	**0.046**
Independent walking age (month) (median), IQR	12 (12-16.5)	12(12-12)	0.071
Age at diagnosis (years)	3(1-4)	2(1.5-3)	0.308
Vit D (µg/L), IQR	15.5 (10.4-21.1)	11.9 (8.9-14.9)	**0.051**
TSH (ng/dL), IQR	2.7(1.0-4.2)	2.3(1.2-2.7)	**0.020**
T4 (ng/dL), IQR	1.1(0.9-1.2)	1.1(1-1.2)	0.841
Ca (mg/dL), IQR	9.7(9.4-9.9)	9.7(9.6-10.1)	0.442
P (mg/dL), IQR	4.9 (4.5-5.3)	5.1(4.5-5.3)	0.981
CK (U/L), IQR	7028 (4823-9040)	7396(3239-8413)	0.420
Alp (U/L), IQR	109 (79-136)	100(81-131)	0.625
Bone fracture	6(25%)	8(50%)	0.104
Vertebral compression fracture	-	7(43.8%)	**0.001**
Non-vertebral fracture	6(25%)	1(6.3%)	0.210
Scoliosis	14(58.3)	10(62.5)	0.792

Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, TSH: Thyroid stimulating hormone, T4: Thyroxine, VitD: Vitamin D, PTH: Parathyroid hormone, CK: Creatinin kinase, SDS: Standard deviation score, IQR: Interquantile range

Table 4. Relationships between femoral neck Z scores and laboratory findings before and after loss of ambulation

Femoral neck Z scores						
Before loss of ambulation osteporosis				**After loss of ambulation osteporosis**		
	No n=8	**Yes n=32**	**p**	**No n=6**	**Yes n =34**	**p-value**
Ca (mg/dL)	9.6±0.3	9.7±0.3	0.461	9.9±0.29	9.8±0.4	0.519
P (mg/dL)	4.7±0.6	5±0.5	0.214	4.8±0.7	4.7±0.6	0.793
Alp (U/L)	130±40.5	103±30.5	0.139	127±37	100±40	0.152
VitD (µg/L)	16.3±4.1	14.7±6.4	0.376	14±2	17.3±6.8	0.029
PTH (µg/L)	45.2±9.7	38.1±15.1	0.121	73.5±84.1	36.8 ±14.7	0.335
CK (U/L)	7939±2529	7037±4163	0.446	4269±2568	4450±2712	0.879

Ca: Calcium, P: Phosphate, ALP: Alkaline phosphatase, TSH: Thyroid stimulating hormone, T4: Thyroxine, VitD: Vitamin D, PTH: Parathyroid hormone, CK: Creatinin kinase, SDS: Standard deviation score, IQR: Interquantile range

The weight percentile of 3 patients was >2 SDS before loss of ambulation, and only 1 patient had body weight percentile >2 SDS after loss of ambulation. When patients with and without bone fracture were compared, the vertebral and femoral Z scores before and after loss of ambulation were not determined to predict bone fracture (p=0.104).

DISCUSSION

DMD is a progressive disease diagnosed at an early age in children, causing muscle weakness, severe disability and early death with pulmonary and cardiac complications in addition to neuromuscular symptoms[5]. The disease was first described by the French electrophysiologist and neurologist Guillaume-Benjamin-Amand Duchenne (de Boulogne) in 1868 and can cause neuromuscular disease as well as cognitive impairment, learning and behavioural problems[4]. The mean age at diagnosis ranges from 4.3-4.11 years, and there has been significant progress in recent years[3]. In this study, the median age at diagnosis was 3 (1-3.5) years. Patients with DMD usually become wheelchair-dependent before the age of 12 years. The average age at which patients lose the ability to walk has been reported to be 9.4±2.4 years[27]. In this study, the age at diagnosis appears to be better than in the current literature, with the median age at which loss of ambulation occurred being 10 years, which is similar to the literature.

DMD is a serious, progressive muscle disease that can result in death at a young age. Although there is currently no definitive cure, glucocorticoids are the main treatment[28]. However, long-term use of glucocorticoids in DMD patients and progressive loss of muscle strength due to the nature of the disease lead to adverse effects on bone such as osteoporosis[29].

Low BMD is often underestimated despite causing significant morbidity. Osteoporosis/osteopenia is common, especially in patients receiving glucocorticoid therapy, and this condition poses a significant risk for pathological fractures[12]. Mechanical stress is important in maintaining bone volume and structure. Motor paralysis, long-term bed rest, and situations that may cause immobilization (such as putting a cast on the fractured area) cause rapid bone loss. It is known that bone resorption is accelerated and bone formation is suppressed due to bone remodeling disorder that occurs after immobilization. Therefore, it is important to prevent disuse osteoporosis[30,31]. Loss of ambulation can cause further demineralization of bone, further altering bone health and increasing the fracture risk[32].

In this study, vertebral osteoporosis was found in 40% and femoral neck osteoporosis in 80% of patients before loss of ambulation. It was also observed that BMD decreased after loss of ambulation, especially in the femoral neck. This was consistent with the findings of Larson and Henderson[17], who reported that in children with DMD, lumbar spine bone density decreases only slightly in ambulatory individuals, but drops significantly with the loss of mobility. These results support the mechanical stress theory, which posits that mechanical load plays a critical role in preventing bone resorption.

DXA is the most widely used technique for the assessment of BMD in children[33]. In patients with DMD, DXA should be performed before starting glucocorticoids, every 1-2 years if glucocorticoids are used, and annually if bisphosphonate therapy is used[24]. In children, posteroanterior lumbar vertebral and femoral neck measurements are performed[24]. A difference of approximately 0.5 SDS can be seen between the femoral neck Z-score and the lumbar vertebral Z score. This difference increases further below Z-score -3 SDS. Immobile children such as those with DMD may have preserved lumbar DXA but low femoral neck DXA[34].

In this study, femoral neck measurements were found to be lower than the lumbar vertebral BMD measurements. A difference of approximately 1 SDS was determined between the lumbar and femoral neck Z-scores, consistent with the literature. This was attributed to the fact that DXA measurements of the hip region (total hip or femoral neck) in children are less reliable due to the difficulties in determining the area to be measured[25]. In addition, the measurement differences detected in this study may lead to differences in the diagnosis of osteoporosis. Although DXA is a routinely recommended method for BMD monitoring in DMD patients, it has some disadvantages[35,36]. It is known that DXA may give inaccurate results due to spinal deformities or anatomical changes[36]. Therefore, quantitative computed tomography (QCT) is one of the methods that has been recommended for the diagnosis of osteoporosis in DMD patients in recent years[35]. QCT has the advantage of being able to directly measure trabecular bone density in the vertebrae, which shows greater changes than cortical bones in osteoporosis and responds rapidly to treatment[35,36]. It can be considered that QCT will be used more widely in the future and provide better predictions.

Detection and prevention of osteoporosis in patients with DMD is crucial to reduce complications such as

vertebral fractures, long bone fractures and scoliosis. In a two-year follow-up study of 6,213 children by Clark et al.[37], a weak inverse association was identified between BMD and subsequent fracture risk. The study also suggested that childhood fracture risk is associated with volumetric BMD and that cortical thickness, as one of the determinants of volumetric BMD, has a significant impact on skeletal fragility. While bone size was not found to have a direct relationship with fracture risk, children who sustained fractures tended to have relatively smaller skeletal structures compared to their overall body size[37]. Corticosteroids are thought to delay the loss of muscle strength through anti-inflammatory action. Despite the beneficial effects, corticosteroids have negative side-effects on bone health, resulting in low bone mass and increased bone fragility[38,39]. King et al.[19] reported that long bone fractures were 2.6-fold more common in DMD patients treated with steroids compared to patients who did not use steroids. In addition, vertebral compression fractures were reported in 32% of the steroid-treated group, while vertebral fractures were not seen in the steroid-naive group.[19] According to a study by Tian et al.[40], the prevalence of fractures in DMD patients increases with age. The prevalence of vertebral fractures was reported as 4.4%, 19.1%, and 58.3% at ages 5, 10, and 18 years, respectively. In addition, no significant association was determined between vertebral Z-scores and vertebral compression fractures in the current study, which was consistent with the literature[41]. The prevalence of vertebral compression fracture was 17.5% in the current study. Although this rate is a relatively low rate compared to the literature, it is thought that this rate may increase during the follow-up of the patients. The data in the current study do not support the value of Z scores as predictors of future fractures. However, fractures were observed in 35% of the patients and vertebral fractures were observed in 17.5% of the patients (all of these patients had vertebral osteoporosis). This suggests that it is difficult to use the bone health status of the patients for fracture prediction, or that different methods such as QCT should be tried for prediction. As Z-scores are limited in fracture prediction, it is thought that fracture risk assessment should be supported by advanced imaging methods such as QCT, especially in clinically high-risk patients. Long bone fractures also occur in patients with DMD. In a study of 378 patients with DMD from 4 neuromuscular centres, McDonald et al.[18] reported that 79 patients had long bone fractures, and most fractures were reported in mobile patients (47%). Lower limb fractures can significantly reduce a patient's function and accelerate the decline in walking ability due to prolonged immobilization and/or restriction of activities[42]. In a 2020 study of 287 patients, Yıldız et al.[43] reported that bone fractures were identified in 51 patients, and 36.4% of those with fractures subsequently lost the ability to walk. In a study by King et al.[19], it was reported that humerus fracture was more common in the non-steroid group and femur fracture was more common in the steroid group. In this study, all patients were on long-term steroid therapy and humerus fracture was observed more frequently than in the literature. This finding may be due to the small sample size. In the current study, bone fracture was seen in all the patients during the mobile period, but no patient was immobilized due to fracture.

The development of scoliosis in DMD is thought to be related to decreased mobility and paraspinal muscle weakness[44,45]. Prolonged ambulation and corticosteroid use may delay scoliosis onset and reduce the need for surgery[46-50]. Although low BMD is common in idiopathic scoliosis, Tsaknakis et al.[51] found no correlation between BMD and scoliosis severity in DMD. In this study, 60% of patients developed scoliosis before ambulation loss, despite early steroid use. No significant association was found between BMD and scoliosis or osteoporosis, suggesting that BMD alone may not predict scoliosis severity or osteoporosis risk in these patients.

Many treatment methods are used to prevent osteoporosis and fractures and improve bone health in patients with DMD. Regular monitoring of bone health and early diagnosis, exercise therapies, alternative treatments to corticosteroids, anti-resorptive agents, vitamin D supplements and hormone therapies are among these methods. Vitamin D deficiency affects approximately 50% of the global population. Since vitamin D is synthesized in the skin through sunlight exposure, its deficiency is primarily attributed to lifestyle changes that limit ultraviolet B-induced production[52]. Patients with DMD tend to be less exposed to sunlight, especially after immobilization. Periodic monitoring of calcium intake and serum 25-hydroxyvitamin D concentrations is recommended for patients with DMD. If calcium intake is below the recommended age-appropriate amount or if serum 25-hydroxyvitamin D levels fall below 30 ng/mL, patients should be fed a calcium-rich diet and supplemented with vitamin D[23]. All the patients in our centre were checked annually for blood calcium, phosphorus, and vitamin D values. The blood calcium and phosphorus values of all the current study patients were found to be within normal limits.

Nevertheless, nutritional recommendations were made for all the patients whether or not a deficit was detected. Patients without osteoporosis before loss of ambulation had higher vitamin D values [15.5 (10.4-21.1) versus 11.9 (8.9-14.9) p=0.051]. This finding is very valuable in terms of emphasizing the protective effect of vitamin D.

Physical therapy is an important part of DMD treatment, but there is no standard physiotherapy protocol[42]. Bisphosphonates are one of the options used in the treatment of osteoporosis, but there is not enough evidence for young DMD patients[34,53]. Denosumab and Tocilizumab have shown promising results as monoclonal antibodies that regulate osteoclastic activity and reduce bone mineral loss[34,54]. The effects of growth hormone and testosterone on bone density have been investigated within the scope of hormone treatments, but definitive results have not been reached[34]. Teriparatide (PTH analog) has the potential to improve bone quality, but there is not enough data on its use in DMD patients[55].

Study Limitations

The limited number of patients and the retrospective design can be considered limitations of the study.

CONCLUSION

This study focuses on bone problems developing in DMD patients, such as osteoporosis, fractures, and scoliosis. The median age of the patients at the time of diagnosis was 3 years, and the median age for starting to walk was 12 months. These findings indicate that the symptoms began early and were also recognized early in our clinic. In 80% of the patients, there was femoral neck osteoporosis, and in 40%, there was vertebral osteoporosis. In all patients with vertebral osteoporosis, femoral neck osteoporosis was also present. The study also found that, particularly in the femoral neck, BMD decreased after the loss of ambulation, but no change in Z scores was observed in the vertebrae after the loss of ambulation. Fractures were observed in 35% of the patients, and vertebral fractures were seen in half of these patients (17.5% of all patients). In particular, all patients with vertebral fractures had vertebral osteoporosis. The study results did not show a direct correlation between BMD before the loss of ambulation and the future risk of fractures. Scoliosis was present in 60% of the patients before the loss of ambulation, but no significant relationship was found between BMD and the severity of scoliosis. This suggests that BMD alone may not be a sufficient predictor of scoliosis progression in DMD patients. Patients who did not develop osteoporosis before loss of ambulation had higher vitamin D levels.

An important contribution of this study to the literature is the high rate of osteoporosis in the femoral neck region in the pre-ambulatory period. A unique aspect of this study is that it is one of the first series to show a high rate of femoral neck osteoporosis in the pre-ambulatory period. This finding shows the need for closer monitoring of bone health, especially in the phase before the immobility period begins, and for early preventive approaches to be planned. In addition, these data may guide the timing of treatment protocols to be applied in the future.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Board of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval no: 2023/06-41, dated: 13/07/2023).

Informed Consent: Retrospective study.

Footnotes

Author Contributions

Concept: Y.G., F.B., B.N.D., N.O.D., Design: Y.G., P.G., F.B., B.N.D., N.O.D., Data Collection or Processing: Y.G.,S.M.D.,Ö.A.Y., A.Ö.Y., B.T., H.B., Analysis or Interpretation: Y.G., Ö.Al., B.T, Literature Search: Y.G., Writing: Y.G.

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