Neuromuscular Disorders 17 (2007) 919–928

www.elsevier.com/locate/nmd

Low bone mineral density and decreased bone turnover in Duchenne muscular dystrophy

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Received 27 March 2007; received in revised form 27 March 2007; accepted 25 May 2007

Abstract

This cross-sectional study examined bone mineral density, bone turnover, body composition and calciotropic hormones in 24 boys with Duchenne muscular dystrophy (DMD) (2.3–19.7 years), most of whom were being treated with prednisolone, and 24 age-matched healthy boys. Our study demonstrated lower bone mineral density in the DMD group for total body, spine, hip, heel and forearm measurements. These differences between DMD patients and controls increased with increasing age. Biochemical markers of both bone formation and resorption revealed reduced bone turnover in DMD patients. The fracture rate was not higher in DMD patients. The DMD group had low vitamin D levels but high leptin levels in comparison with the control group. Muscle strength correlated with bone mineral density assessed at the hip and heel in the DMD group. Interventions that increase bone formation should be considered, as DMD patients have reduced bone turnover in addition to their low bone mineral density.

Keywords: Children; Skeleton; Steroids; DXA; Bone markers; Calciotropic hormones

1. Introduction

Skeletal development depends on hereditary and dietary factors, as well as the mechanical forces applied to the bones over the years. Several hormones and growth factors also affect the skeleton. Bone strength is determined by its geometry, size, micro-architecture and mineral density. Inactivity and immobilisation lead to the loss of mineral from the skeleton [1]. Peak bone mass achieved during early adulthood serves as "the bone bank" for the remainder of life [2,3] and it has recently been indicated that a higher peak bone mass reduces the risk of osteoporotic fractures later in life [4]. Low bone mass is associated with an increased risk of fractures in children [5] and conditions that reduce mobility during childhood are associated with osteopenia and an increased fracture risk [6].

Duchenne muscular dystrophy (DMD) is an inherited X-linked recessive disorder and is the most common type of muscular dystrophy in childhood [7], with an incidence of 1:3500 male births [8]. The onset of DMD occurs at approximately three years of age. The disease progresses during childhood, with increasing difficulty walking, and, between 7 and 13 years of age, the boys are often dependent on a wheelchair. At the present time, there is no specific causal treatment, but glucocorticoids (GC) have been shown to slow the progression of the disease and improve muscle strength and motor function [9–13]. Pharmacological doses of oral GC do, however, suppress bone formation, due to increased osteoblastic apoptosis, and increase bone resorption, due to increased osteoclastogenesis [14]. The combined actions of GC on bone remodelling can

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doi:10.1016/j.nmd.2007.05.008

therefore evidently cause osteoporosis, which is known to increase the fracture risk in adults [15,16]. In addition, it has been reported that children treated with oral GC have lower bone mass [17]. The extent to which GC contribute to increased fracture risk in children is, however, unclear [18] and neither osteoporosis in children nor the risk of fracture in relation to bone density has been defined.

Bone remodelling, the continuous process of bone formation and resorption, can be assessed and monitored by biochemical markers of bone turnover. These markers are able to detect subtle changes in formation and resorption earlier than any X-ray method [19]. Relatively few studies of bone health in DMD have been published [20,21]. It was recently reported that DMD patients, with or without GC therapy, have a marked reduction in bone mineral density, increased bone turnover and low 25-hydroxyvitamin D (25(OH) D) levels in a GC-treated group [22]. The reduced mobility of DMD patients, together with the increasing use of GC, suggests that these boys run an increased risk of fractures. Recent studies have shown that boys with DMD are more prone to fractures than the normal population [23]. Further knowledge of the skeletal conditions in boys with DMD is needed, as recently summarised in two DMD workshop reports [20,21].

This study was designed to investigate bone mineral density, biochemical markers of bone turnover and key regulators of bone mass in boys with DMD treated with prednisolone in comparison with healthy age-matched controls. In addition, we investigated body composition and the effect of muscle strength and motor function on bone mass in the DMD group.

2. Materials and methods

2.1. Patients and controls

Twenty-four boys, 2.3–19.7 years of age (11.9 ± 5.2), with immunohistochemically verified DMD, were included in the present study. At the time of inclusion, 16 patients were being treated with between 0.22 and 0.35 mg/kg/day of prednisolone (duration 0.1–11.5 years, median 6 years; cumulative lifetime dose 13–1495 mg/kg, median 766 mg/kg). Prior to this study (3.5–10.5 years before inclusion), four patients had received prednisolone treatment (duration 1.3–3.2 years, median 2.2 years; cumulative lifetime dose 166–409 mg/kg, median 281 mg/kg). The medication was withdrawn in these patients because of weight gain or because the patients and their parents chose to terminate this treatment. One patient had declined treatment and three newly diagnosed patients had not yet received their first dose of prednisolone when the study was initiated. Each DMD boy was matched with a control as closely as possible with respect to age (±6.7 months). The control group comprised 24 boys, 2.7–19.6 years of age (11.8 ± 5.1), who were recruited randomly from healthy boys known by the patients' families or known by the hospital staff. Height was measured using a wall-mounted ruler to the nearest 0.1 cm. Weight was measured on analogue scales to the nearest 0.1 kg. It was not possible to measure standing height in six of the DMD boys due to muscle weakness. In these patients, the arm span was measured [24]. Descriptive auxological data are presented in Table 1. A questionnaire concerning general health and earlier fractures was designed for the participating children and parents to complete at inclusion. Information on previous fractures was also collected from clinical files and previously performed spinal radiographs. Dietary records were also kept for four days. Pubertal staging was performed according to the Tanner scale [25] and by a self-assessment of testis size made by the participants or by a parent [26]. Informed consent was obtained from all the children and their parents. This study was approved by the Human Ethics Committee at the Medical Faculty, Sahlgrenska Academy at Göteborg University. The study started in November 2003 and sampling was completed in April 2006.

2.2. Assessment of motor function and muscle strength

Motor function and muscle strength tests were performed in the patient group. Motor function was classified according to the Vignos scale (grades 1–9) (Table 2) [27]. Isometric muscle strength was measured using an electronic hand-held myometer, according to Scott and co-workers [28]. Values from the knee extensor measurements were used for further analysis. In order to determine muscle

Table 1
The study groups are broken down by age into four groups – 0–6.0, 6.1–10.0, 10.1–15.0 and 15.1–20 years of age

	0–6.0 years ($n = 4$)		6.1–10.0 years ($n = 5$)		10.1–15.0 years ($n = 9$)		15.1–20 years ($n = 6$)	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Age (yr)	4.4 ± 1.6	4.6 ± 1.4	8.2 ± 1.2	8.0 ± 1.2	12.7 ± 1.6	12.7 ± 1.7	18.6 ± 1.0	18.7 ± 1.1
Weight (kg)	18.8 ± 2.3	21.4 ± 4.8	29.4 ± 7.2	32.2 ± 6.8	40.8 ± 8.0	49.0 ± 9.6	57.4 ± 12.4	74.6 ± 10.4
Weight SD	0.3 ± 1.2	1.0 ± 0.6	0.4 ± 1.1	1.4 ± 1.1	−0.9 ± 2.1	0.5 ± 2.0	−1.7 ± 1.7	0.3 ± 1.1
Height (cm)	100.9 ± 5.9	111.4 ± 14.3	121.2 ± 5.7	130.5 ± 8.6	140.5 ± 14.4	159.8 ± 8.9	166.4 ± 11.7	179.5 ± 5.5
Height SD	−1.2 ± 1.4	0.58 ± 1.2	−1.8 ± 0.6	0.07 ± 0.7	−2.7 ± 1.6	0.4 ± 1.2	−2.1 ± 1.8	−0.1 ± 0.8
BMI (kg/m^2)	18.5 ± 1.2	17.2 ± 1.6	19.9 ± 3.9	18.8 ± 2.8	20.8 ± 4.7	19.2 ± 3.3	20.9 ± 4.8	23.2 ± 3.6
BMI SD	1.7 ± 0.8	0.9 ± 1.2	1.8 ± 1.3	1.5 ± 1.1	0.7 ± 2.0	0.2 ± 1.7	−1.2 ± 3.0	0.2 ± 1.5

The numbers of patients and age-matched controls, respectively, are expressed as (n). The values are the means ± SD. Body mass index is expressed as (BMI).