SeCondary Osteoporosis & its Therapy
Duchenne Muscular Dystrophy

SCOT-DMD

Muscular Dystrophy UK
Fighting muscle-wasting conditions

Chief Scientist Office

Developmental Endocrinology Research Group
College & University

Scottish Muscle Network

ACTION DUCHENNE

University of Glasgow
NHS
Greater Glasgow and Clyde

NHS Scotland
BONE

Duchenne Care Conference
Amsterdam, 7 September 2018
Consequences of fragility fractures in DMD

Premature loss of ambulation (about 40% following first long bone fracture)

Fat embolism syndrome

Acute and chronic back pain

Progressive kyphosis, restrictive lung disease
Updated Standards Of Care- Bone

**Monitoring and diagnosis**
- At each clinical visit
  - Presence of back pain or fractures
- At baseline only (follow up as appropriate)
  - Serum calcium
  - Phosphate
  - Magnesium
  - Alkaline phosphatase
  - Parathyroid hormone
- At baseline and annually
  - Calcium/vitamin D intake
  - Spine BMD by DXA
  - Serum 25-hydroxyvitamin D₃
- At baseline and follow-up
  - Lateral thoracolumbar spine radiograph:
    - On steroids, every 1–2 years
    - Not on steroids, every 2–3 years
- If back pain or ≥0.5 SD decline in spine BMD Z score on serial measurements over 12-month period
  - Lateral thoracolumbar spine radiograph
- Continue monitoring until signs of bone fragility*

**Treatment: stabilisation phase**
- Before initiating intravenous bisphosphonate therapy
  - Treat calcium/vitamin D deficiency
  - Verify normal renal function
- When starting intravenous bisphosphonate therapy
  - Follow published regimen
  - Treat until clinically stable
- For monitoring of safety and efficacy of treatment
  - Obtain thoracolumbar spine radiograph annually and monitor the following every 6 months:
    - Spine BMD by DXA
    - Serum hydroxyvitamin D₃
    - Patient-reported back pain
    - Calcium/vitamin D intake
    - Biochemical markers of bone and mineral ion metabolism

**Treatment: maintenance phase**
- Once clinically stable
  - Consider continuing intravenous bisphosphonate therapy with titration to a lower dose, to preserve gains realised during stabilisation phase
- Vary duration of maintenance therapy depending on bone health status and whether steroid therapy is ongoing
- Monitor safety and efficacy of maintenance therapy

**Clinically significant bone fragility**

**Clinically stable†**

**No longer clinically stable†**
Lateral thoracolumbar spine x-ray
- At least every 2 years steroid treated
- At least every 3 years not on steroid

DXA
- Annually (but prioritise spine x-ray over DXA)

Vitamin D levels
- Annually
DXA in children

Adjusting for size in subjects with chronic disease

Z Score – Age and gender matched

T Score – 25 year old of same gender

T SCORE NOT APPROPRIATE IN GROWING CHILDREN

Adjusting for size in subjects with chronic disease
Diagnosis of osteoporosis in young people is not densitometry dependent.

Decision to commence bone protective therapy in young people is not densitometry dependent.

DXA results can vary by up to about 1 standard deviation depending on the method of size correction and normative data used (Ma J et al JCEM 2015).

A clear DXA fracture threshold based on BMC/BMD does not exist for children with chronic conditions (Wong et al Arch Dis Child 2008).

DXA or other bone monitoring modality is needed if bone protective therapy is used.
The diagnosis of osteoporosis should **NOT** be made solely on densitometry.

The finding of one or more vertebral compression (crush) fractures is indicative of osteoporosis.

In the absence of vertebral compression (crush) fractures, the diagnosis of osteoporosis is indicated by the presence of a clinically significant fracture and low BMC/BMD.

A clinically significant fracture history is one or more of the following:
- Two or more long bone fractures by age 10 years
- Three or more long bone fractures at any age up to 16 years
- Vertebral compression fractures
Vertebral fractures in chronic disease may often be asymptomatic
(Steroid-Associated Osteoporosis In The Paediatric Population)

In children with ALL, 16% have vertebral fractures at diagnosis prior to steroid
Another 25% will develop vertebral fractures after 4 years of chemotherapy/steroid
About 40% of these vertebral fractures are asymptomatic

Spontaneous and complete vertebral reshaping of vertebral fracture WITHOUT bone protective therapy is seen in other chronic childhood conditions but not in DMD

(Ma J et al 2017, Joseph S et al 2016)

- Insult to the skeleton may be minimised or removed in other conditions (eg ALL, IBD, JIA etc)
- Catch-up growth is possible

Incomplete vertebral reshaping of vertebral fracture may be possible with bisphosphonate therapy in DMD

(Sbrocchi AM et al 2012)
Grading Vertebral Fracture

MILD: Genant 1

MODERATE: Genant 2

SEVERE: Genant 3

Wedge fracture
Biconcave fracture
Crush fracture
Bisphosphonate Therapy In DMD

IV bisphosphonate (not oral)

Treat if:
- Painful vertebral fracture
- Moderate (ie Genant 2) vertebral fracture even without pain (Secondary prevention strategy)
- Fragility fracture / recurrent long bone fracture

Regular for a period of 2 years then ongoing till reach adult maturity but at lower dose or less frequent

Endocrine/bone clinician for monitoring
- DXA or other modality needed for safety monitoring
DXA may allow identification of VF

Newer generation DXA (i-DXA) may allow identification of VF similar to spine x-ray
Challenges for implementation: Bone

Getting the right x-rays
- Ensuring right x-rays done (Need lateral thoracolumbar)

Getting the right report
- Paediatric radiologists may still less experienced with reporting of VF
- Unfamiliar with genant staging
Scottish experience: 63% had a DXA at least in the previous 2 years

Weber DR et al J Neuromusc Dis 2018
Potential challenges in adult hospital

- Adult (post-menopausal osteoporosis) bone monitoring and treatment is densitometry based
- Difficulties in obtaining spine x-ray and DXA (Hoisting, positioning, scoliosis, rod)
- Interpreting DXA in the adult setting

Peripheral quantitative computed tomography
Osteoporosis in DMD is a low bone turnover state

Histomorphometry and Bone Matrix Mineralization Before and After Bisphosphonate Treatment in Boys With Duchenne Muscular Dystrophy: A Paired Transiliac Biopsy Study

Barbara M Misof,1 Paul Roschger,1 Hugh J McMillan,2 Jinhui Ma,3 Klaus Klaushofer,1 Frank Rauch,4 and Leanne M Ward2

Bone biopsy before and after IV bisphosphonates (Average 2.4 years)

- No change in bone volume/total volume and cortical thickness
- Mineralizing surface and cortical bone mineralization decreased
- Further reduction in bone turnover
1 - 3 June 2018
Workshop nr. 236
Bone protective therapy in Duchenne Muscular Dystrophy: Determining the feasibility and standards of clinical trials (BONE). Organisers: Prof Volker Straub, Dr. Jarod Wong, Prof Leanne Ward and Dr. Ros Quinlivan.
PUBERTY

DUCHENNE CARE CONFERENCE

AMSTERDAM, 7 SEPTEMBER 2018
91 boys managed in Scotland in paediatric service

29 boys (32%) aged 14 years or older

14/29 (48%) had puberty examined
15/29 (52%) never had puberty examined

11/14 (79%) had testes < 4ml
- 7 on testosterone therapy

3/14 (21%) had testes > 4ml
- None on testosterone therapy

Joseph S et al
Puberty assessment
- Challenging
- Local pathway needed
- Refer for assessment by paediatric endocrinologist by 12-13 years
**Treatment**

- Testosterone therapy from age 14 years building up over period of 2 ½ to 3 years (can consider from 12 years)
- Take off testosterone, perform biochemistry and review need for lifelong testosterone

- Testosterone open label trial (Newcastle)
- Need for randomised study: eg. earlier start vs conventional start

- Adults on steroid may have low or borderline testosterone levels (LH, FSH, testosterone—morning sample)
1. What is puberty?
Puberty is the period when a child’s body develops into an adult. This process often takes about 3 years. In a boy with no underlying chronic condition, the average age of developing puberty is approximately 11 years.

Changes that happen during puberty include:
(a) Growth of the penis and size of the testes
(b) Development of pubic and underarm hair
(c) Growth spurt
(d) Development of stronger bones and muscles

Puberty starts when the hypothalamus, a gland in the brain, releases a hormone called gonadotrophin releasing hormone (GnRH) which in turn tells the pituitary gland, a pea size gland that sits at the base of the skull, to release two other puberty initiating hormones: luteinizing hormone (LH) and follicular stimulating hormone (FSH). These two hormones (LH and FSH) tell your son’s testes to make the male hormone, testosterone. The hormones secreted from the pituitary gland leads to increased testes size, but testosterone causes pubic and underarm hair growth and an increase in the growth of the penis.

2. How is puberty affected in DMD?
If your son is taking steroid medicine (Prednisolone or Deflazacort), it is very likely that his puberty will be affected.

Puberty may:
(a) Start late (after 14 years old)
(b) Never start
(c) Start but then does not progress normally

Steroid medicines affect puberty in DMD mainly by affecting the release of the puberty initiating hormones from the hypothalamus and pituitary gland. As a result, this leads to a reduction in the production of testosterone by the testes. If your adolescent son does not have signs of puberty, he will have no pubic or underarm hair and have a smaller penis. Other people may assume he is much younger.
About 25% of boys with DMD are short before starting steroids.

Steroid cause growth failure

Need height measurement for interpretation of body mass index, lung function, blood pressure etc

**Height monitoring 6 monthly**

*Courtesy of C Wood & T Cheetham, Newcastle University*
Height prediction from ulna length

Leanne M. Gauld MBBS FRACP; Johanna Kappes BN, Department of Respiratory Medicine, Royal Children’s Hospital, Melbourne; John R Carlin PhD; Colin F Robertson MBBS FRACP MD, Department of Paediatrics, University of Melbourne, Melbourne, Australia.

*Correspondence to first author at Sleep Unit, Sydney Children’s Hospital, High Street, Randwick 2031, Sydney, Australia.
E-mail: gauldl1@sesahs.nsw.gov.au

**Height for boys = 4.605 (ulnar length) + 1.308 (age) + 28.003**

Courtesy of Zoe Davidson, Monash Uni, Melbourne
Retrospective study
N, 39
Mean age 11.5 years

1 year rhGH outcome
- HV 1.4 cm/yr vs 5.2 cm/year
- No change in motor function and cardiopulmonary outcomes

Adverse events
- Benign intracranial hypertension (n, 1)
- Impaired glucose tolerance (n, 2)
- Worsening of scoliosis (n, 2)


37% of juvenile arthritis treated with rhGH have impaired glucose tolerance
5% transient T2DM

Bismuth E et al Horm Res Pediatr 2010
Challenges for implementation: Growth & puberty

Accurate height measurement

Accurate pubertal assessment

Endocrine & bone expertise in specialist neuromuscular centres

Local dialogue & referral pathway
ADRENAL SUPPRESSION

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AMSTERDAM, 7 SEPTEMBER 2018
All patients who take steroids for longer than 6 months have adrenal suppression

Access to hydrocortisone as injections during severe illness (when unable to take steroids by mouth)

http://www.smn.scot.nhs.uk/patients-and-families/dmd/
Updated Standards of Care: Adrenal suppression

Need plan for severe illness especially vomiting illness
- Need for steroid to be given via other route
- Care with bisphosphonate infusion

Need plan for steroid during surgery/period when nil by mouth

Need plan for those on intermittent steroid

Need plan if discontinuing steroid

- PJ Nicholoff Steroid Protocol (Kinett K et al Plos Curr 2017)

- Local pathway
Challenges in implementation: Adrenal suppression

Lack of clarity of the issue of adrenal suppression

Work force issue
Who should do initial education/counselling?
- Neuromuscular doctor/nurse specialist
- Endocrine doctor/nurse specialist

Who should do ongoing education counselling?

Transition and adult care
Endocrine Consequences In DMD

Bone / osteoporosis

Puberty / hypogonadism

Growth failure / short stature

Secondary adrenal insufficiency

Obesity / metabolic consequences *

Nutrition in Duchenne muscular dystrophy 16–18 March 2018, Zaandam, the Netherlands

Ingrid E.C. Verhaart\textsuperscript{a,*}, Lenie van den Engel-Hoek\textsuperscript{b}, Marta L. Fiorotto\textsuperscript{c}, Mirjam Franken-Verbeek\textsuperscript{a}, Elizabeth Vroom\textsuperscript{a,d}, on behalf of the workshop participants

\textsuperscript{a} Duchenne Parent Project NL, the Netherlands
\textsuperscript{b} Department of Rehabilitation, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands
\textsuperscript{c} Department of Pediatrics, USDA/ARS Children’s Nutrition Research Center, Baylor College of Medicine, Houston, TX, US
\textsuperscript{d} World Duchenne Organisation (UPMMD), the Netherlands

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DISCUSSION POINTS
jarod.wong@glasgow.ac.uk
832 boys with DMD
520 more than 1 clinic visit

Time to first fracture is shortest in boys treated with daily Deflazacort

Joseph S et al Submitted
2 year longitudinal study of bone health (5-18 years DMD boys)

Visit 1:
- North Star Physiotherapy Assessment
- Spine X-ray
- Bone age
- DXA scan
- Annual blood test
  - Growth hormone axis
  - Bone Turnover
  - Gonadal Function

Visit 2:
- North Star Physiotherapy Assessment
- Spine X-ray
- Bone age
- DXA scan
- Annual blood test
  - Growth hormone axis
  - Bone Turnover
  - Gonadal Function

Visit 3:
- North Star Physiotherapy Assessment
- Spine X-ray
- Bone age
- DXA scan
- Annual blood test
  - Growth hormone axis
  - Bone Turnover
  - Gonadal Function

Visit 4:
- North Star Physiotherapy Assessment
- Spine X-ray
- Bone age
- DXA scan
- Annual blood test
  - Growth hormone axis
  - Bone Turnover
  - Gonadal Function

Visit 5:
- North Star Physiotherapy Assessment
- Spine X-ray
- Bone age
- DXA scan
- Annual blood test
  - Growth hormone axis
  - Bone Turnover
  - Gonadal Function

Over 2 years:
- 0 months
- 6 months
- 12 months
- 18 months
- 24 months
VF in DMD

VF no back pain  VF chronic intermittent mild back pain
Vertebral abnormality in a steroid naive boy with DMD
Severe VF and no back pain
Progression of VF
Vertebral abnormality in a steroid naive boy with DMD
3T MRI imaging of muscle and bone

Figure 1: T1 weighted image for cortical analysis

a) 11-year old healthy control
b) 11-year old boy with DMD

Figure 2: Binarised trabecular microarchitecture

a) Healthy 11-year old control
b) 11-year old subject with DMD
Testosterone In DMD

14 DMD treated with testosterone for delayed puberty

8 treated till attained adult secondary sexual characteristics (Mean 3.1 years)

6 still undergoing treatment

5/8 had testosterone measurements at adult maturity
- 4/5 (80%) low testosterone level at adult maturity (off testosterone)

6/8 testes examined at adult maturity
- 6/6 (100%) testes small (< 5 ml) at adult maturity

PERSISTENT HYPOGONADOTROPHIC HYPOGONADISM

Woods CL et al Neuropaediatrics 2015
Feasibility of Dual Energy X-Ray Absorptiometry Based Images for Measurement of Height, Sitting Height, and Leg Length in Children

N Capaldi,¹,²,⁷ KT Kao,²,⁷ R MacDonald,¹,² KC Grainger,³ S Joseph,²,⁴ S Shepherd,² A Mason,² and SC Wong²,⁸

¹ School of Medicine, University of Glasgow, Glasgow, United Kingdom; ² Developmental Endocrinology Research Group, Royal Hospital for Children, Glasgow; ³ Department of Sports Science, London Metropolitan University, London; and ⁴ Paediatric Neurosciences Research Group, Royal Hospital for Children, Glasgow, United Kingdom
rhGH In JIA-Growth Outcome

Prospective, uncontrolled study
N, 13 rhGH and n, 18 no rhGH
rhGH 0.047 mg/kg/day

37% of JIA treated with rhGH have impaired glucose tolerance
5% transient T2DM

Bechtold S et al J Clin Endocrinol Metab 2007
Bismuth E et al Horm Res Pediatr 2010

Fig. 1. Synchronized mean growth curves during GH treatment in 13 children and adolescents (solid line) with JIA in comparison with 18 control patients (dashed line) not treated with GH, according to sex; reference lines are for 97th, 50th, and 3rd percentiles, respectively.
Discharge diagnosis was viral illness in 4/6; pneumonia in 1/6 and rotavirus gastroenteritis in 1/6.

Intravenous hydrocortisone was only administered in 4/6 (66.7%) of acute admissions despite management with IV fluids.
Bolus intravenous IV hydrocortisone was only administered at induction in 6/12 (50%) of elective surgical admissions.
Physiological replacement of steroid
- 10 mg/m² Hydrocortisone
- 3.8 mg/m² Deflazacort
- 2.5 mg/m² Prednisolone or Prednisone

Steroid for mild illness
- 20 mg/m² Hydrocortisone
- 6.8 mg/m² Deflazacort
- 5 mg/m² Prednisolone or Prednisone
33 boys with DMD steroid treated and only Glasgow address (up to Dec 2015)
- **4/33 (12%)** had emergency steroid plans in place

- Currently, **entire clinic** has had emergency plans in place including:
  1. All educated to inject hydrocortisone
  2. School visit and hydrocortisone in school
  3. Formal steroid plan & DMD adrenal insufficiency leaflet given out
  4. All track care alerts in place
  5. Discussed at every neuromuscular clinic
  6. Home visit for training within the first 6 months of starting steroid
Every single adrenal crisis is preventable