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NHS Greater Glasgow and Clyde

SeCondary Osteoporosis & its Therapy

Duchenne Muscular Dystrophy

SCOT-DMD

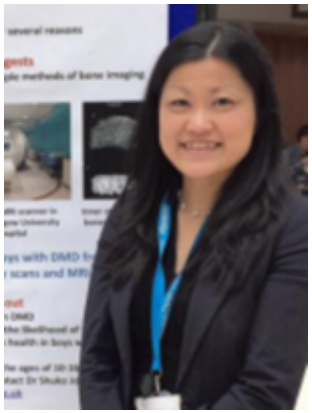
Muscular Dystrophy UK

Fighting muscle-wasting conditions

CHIEF SCIENTIST OFFICE

ACTION DUCHENNE

Acknowledgement



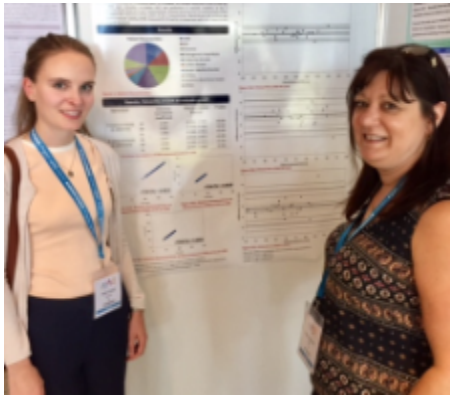
S Joseph

J Dunne

M DiMarco

C Duncanson

I Horrocks



S Shepherd and students

Research radiographers & MRI Physics

F Ahmed

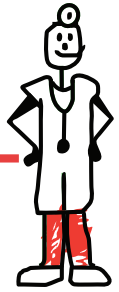
University of Glasgow

NHS Greater Glasgow and Clyde

BONE

DUCHENNE CARE CONFERENCE

AMSTERDAM, 7 SEPTEMBER 2018



Consequences of fragility fractures in DMD

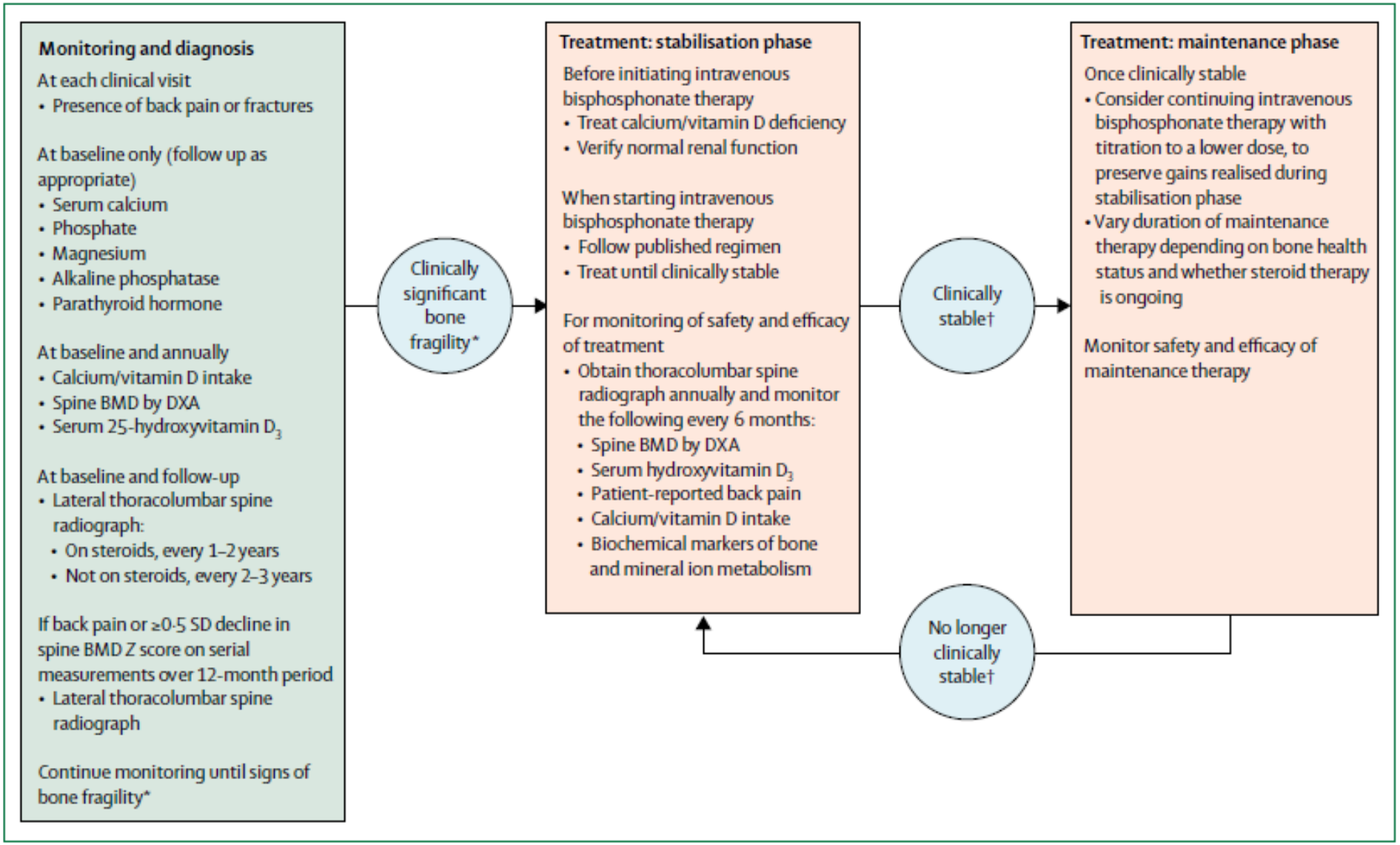
Premature loss of ambulation (about 40% following first long bone fracture)

Fat embolism syndrome

Acute and chronic back pain

Progressive kyphosis, restrictive lung disease

Updated Standards Of Care- Bone



Bone Monitoring (2018)

Lateral thoracolumbar spine x-ray

- At least every 2 years steroid treated
- At least every 3 years not on steroid

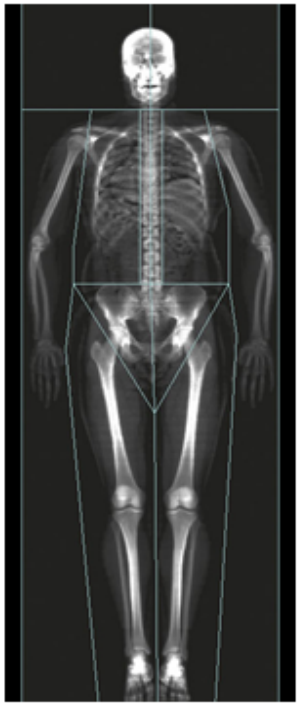
DXA

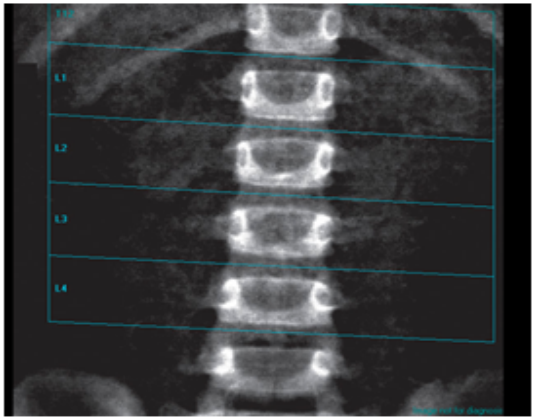
- Annually (but prioritise spine x-ray over DXA)

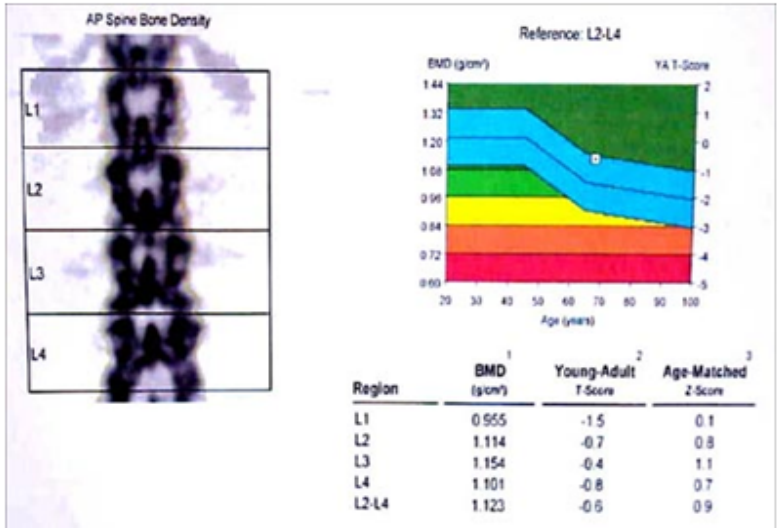
Vitamin D levels

- Annually

DXA in children







Region	BMD (g/cm²)	Young-Adult T-Score	Age-Matched Z-Score
L1	0.955	-1.5	0.1
L2	1.114	-0.7	0.8
L3	1.154	-0.4	1.1
L4	1.101	-0.8	0.7
L2-L4	1.123	-0.6	0.9

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

Osteoporosis In The Young

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.

ISCD Consensus 2013

ISCD The International Society For Clinical Densitometry

Skeletal Health Assessment In Children and Adolescents (Males and Females ages 5-19)

The diagnosis of osteoporosis should NOT be made solely on densitometry

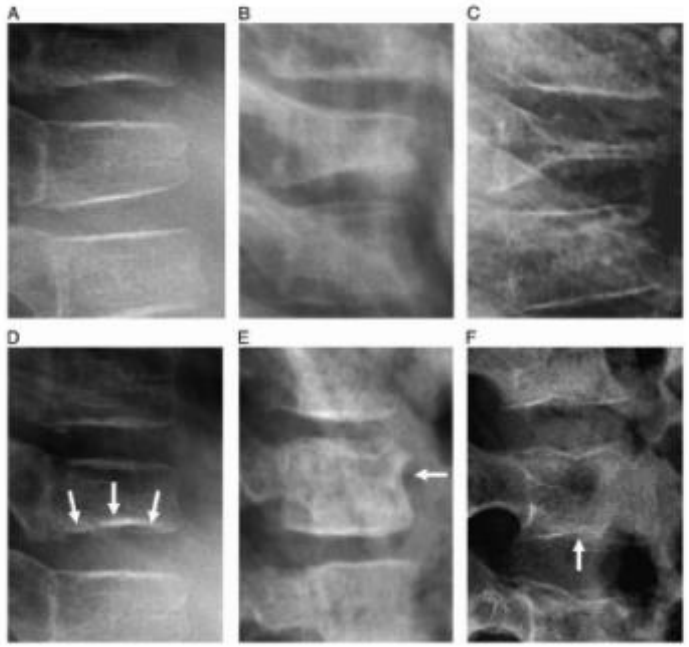
The finding of one or more vertebral compression (crush) fractures is indicative of osteoporosis

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 Fracture In Childhood Chronic Conditions



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

Halton J et al JBMR 2009, Huber AM et al Arthritis Care Res 2010, Rodd C et al Arthritis Care Res 2011, feber J et al Osteoporos Int 2012, Alos N et al, J Clin Oncol 2012, Phan V et al, Osteoporos Int 2014, Le Blanc et al, JBMR 2015, Cummings EA et al JCEM 2015

Rationale for VF screening in DMD

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

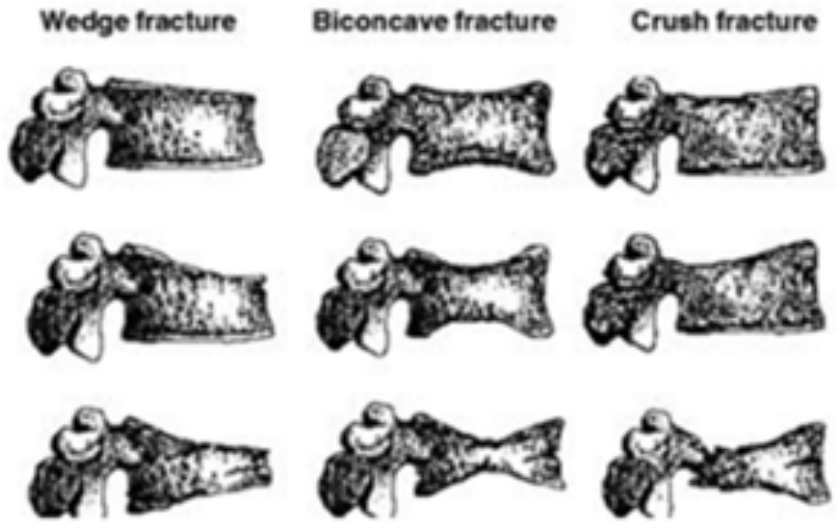
Incomplete vertebral reshaping of vertebral fracture may be possible with bisphosphonate therapy in DMD
(Sbrocchi AM et al 2012)

Grading Vertebral Fracture

MILD: Genant 1

MODERATE: Genant 2

SEVERE: Genant 3



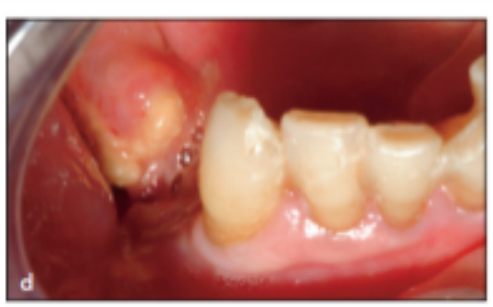
Bisphosphonate Therapy In DMD

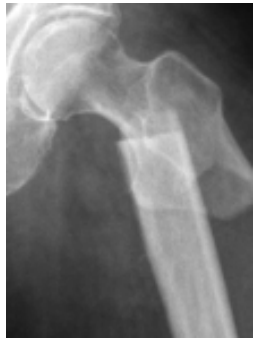
IV bisphosphonate (not oral)

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





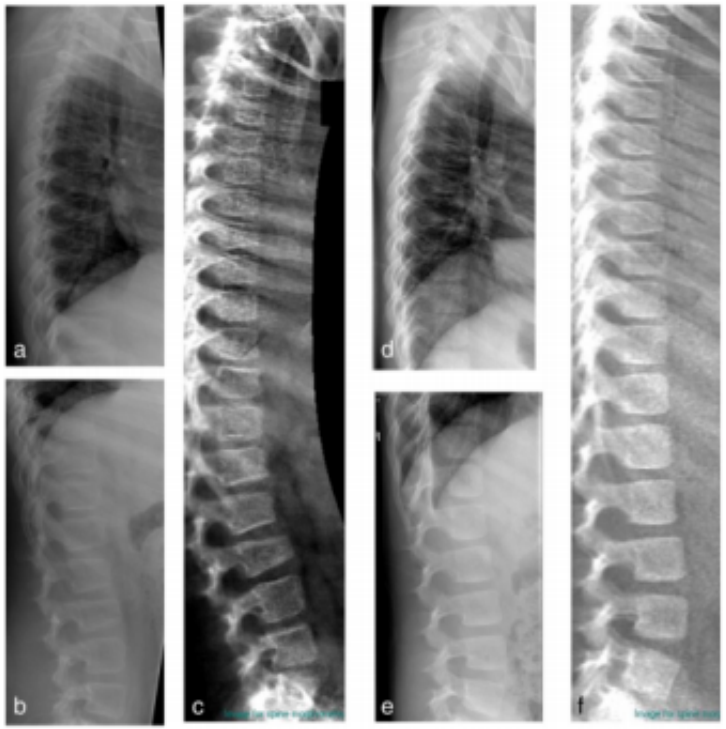
DXA may allow identification of VF

Original Full Length Article

A critical appraisal of vertebral fracture assessment in paediatrics☆

Andreas Kyriakou, Sheila Shepherd, Avril Mason, S. Faisal Ahmed *

Developmental Endocrinology Research Group, School of Medicine, University of Glasgow, Royal Hospital for Sick Children (RHSC), 1345 Govan Road, Glasgow G51 4TF, United Kingdom



Newer generation DXA (i-DXA) may allow identification of VF similar to spine x-ray

Challenges for implementation: Bone

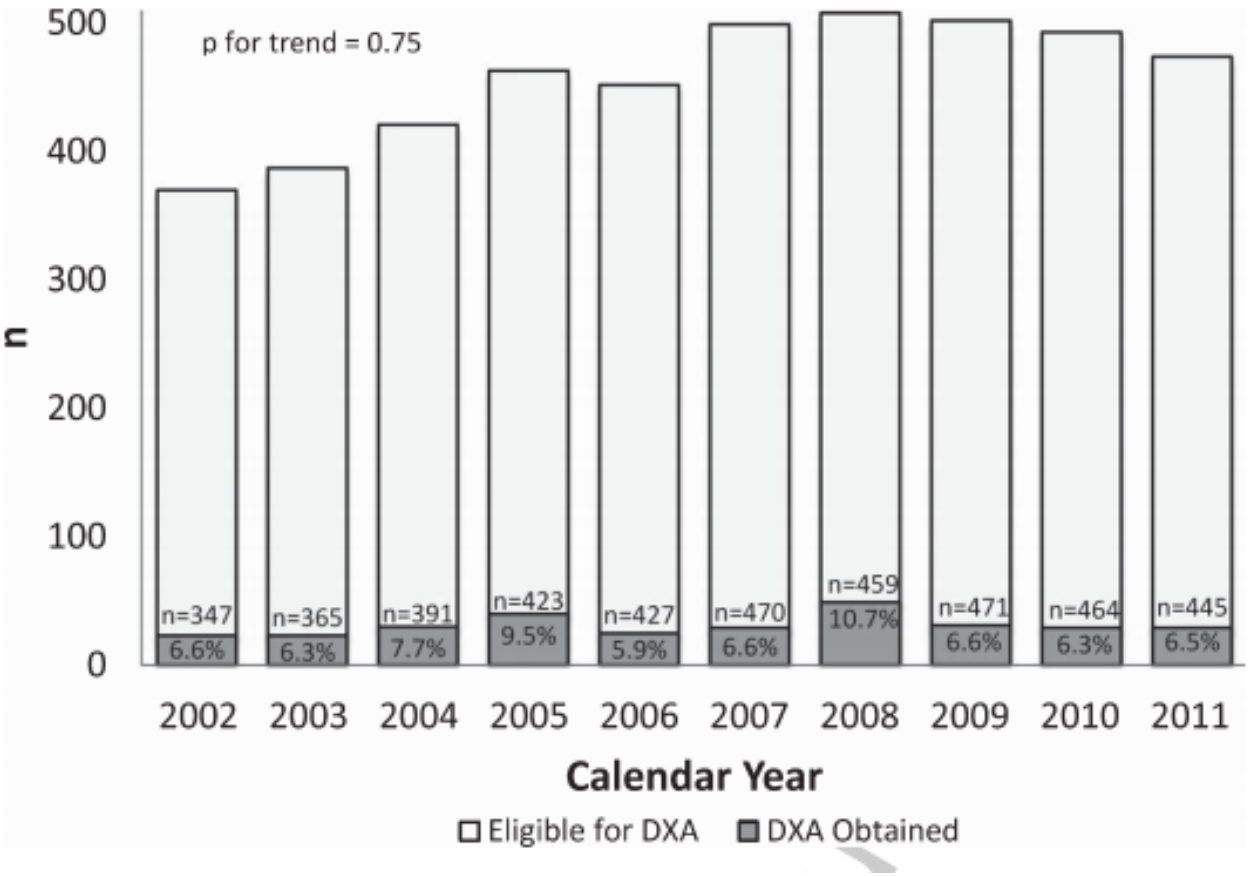
Getting the right x-rays

- 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

Inconsistent bone monitoring in DMD



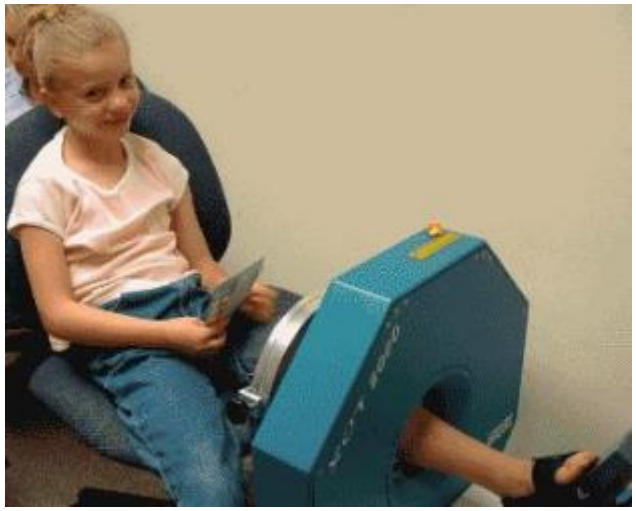
Weber DR et al J Neuromusc Dis 2018

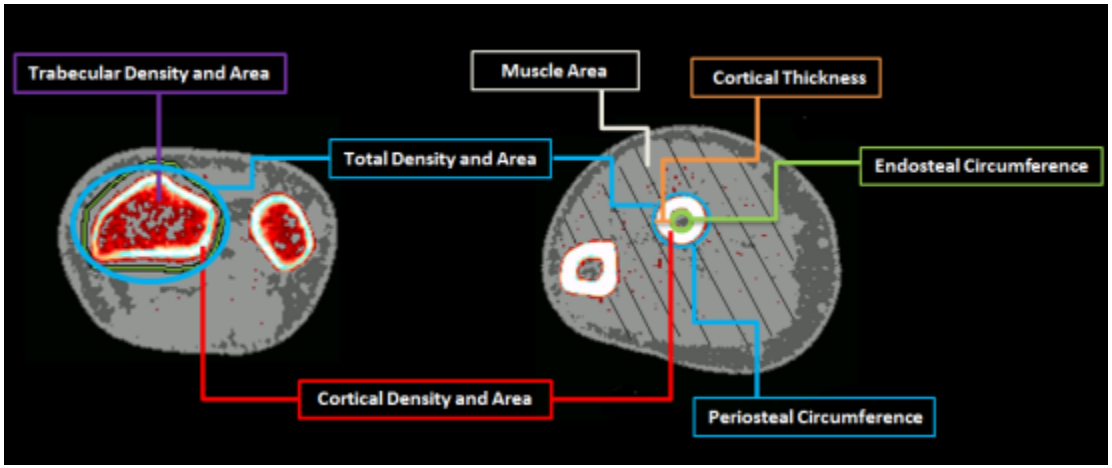
Scottish experience: 63% had a DXA at least in the previous 2 years

What about adult bone monitoring?

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 Ward[2]

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

ENMC Workshop On Osteoporosis Trials In DMD

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.

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PUBERTY

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AMSTERDAM, 7 SEPTEMBER 2018

Puberty In DMD- Scottish Experience

91 boys managed in Scotland in paediatric service

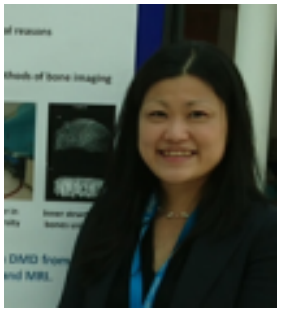
29 boys (32%) aged 14 years or older

14/29 **(48%)** had puberty examined

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

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

15/29 (52%) never had puberty examined



Joseph S et al

Updated Standards Of Care- Puberty

Puberty
Physical assessment of pubertal status by Tanner staging every 6 months starting by age 9 years

→

Delayed puberty
Testicular volume <4 cm^3 at age 14 years or older

→

Refer to endocrinologist

→

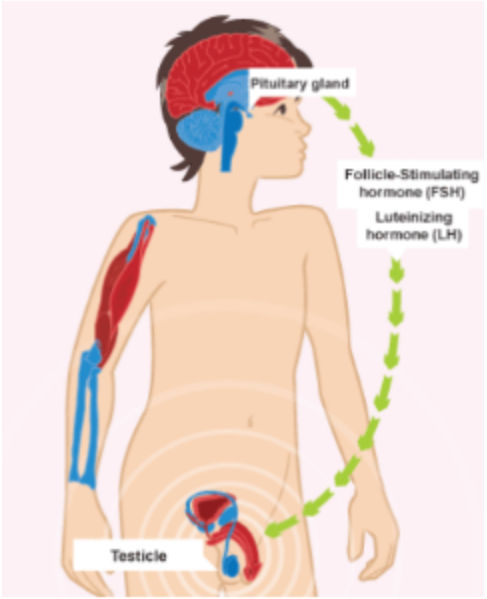
Recommended
Laboratory assays:
- Luteinising hormone
- Follicle-stimulating hormone
- Testosterone

Treatment for confirmed hypogonadism:
- Initiate testosterone replacment at low dose and gradually increase over time
- Recommended for age ≥14 years; can be considered from aged 12 years

To be considered
Assessment of bone age with left-hand x-ray

Puberty assessment

- Challenging
- Local pathway needed
- Refer for assessment by paediatric endocrinologist by 12-13 years



Updated Standards of Care- Puberty

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 life long 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)

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Information about

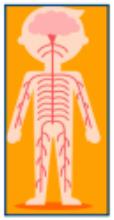
Puberty and Hormones in Duchenne Muscular Dystrophy (DMD)

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

Available on Scottish Muscle Network website

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GROWTH

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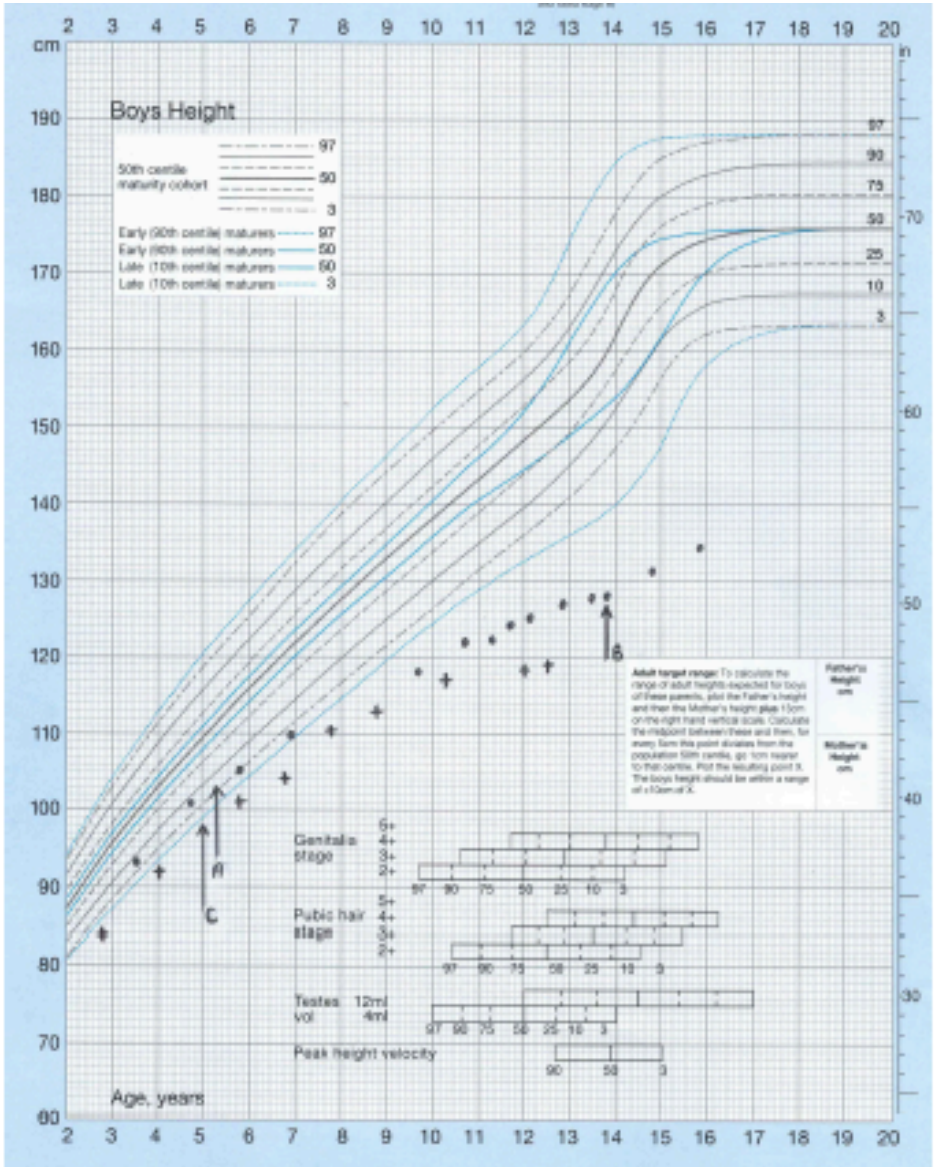
Updated Standards of Care: Growth



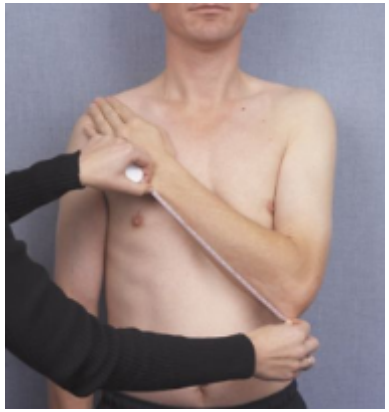
Courtesy of C Wood & T Cheetham, Newcastle University

About 25% of boys with DMD are short before starting steroids.

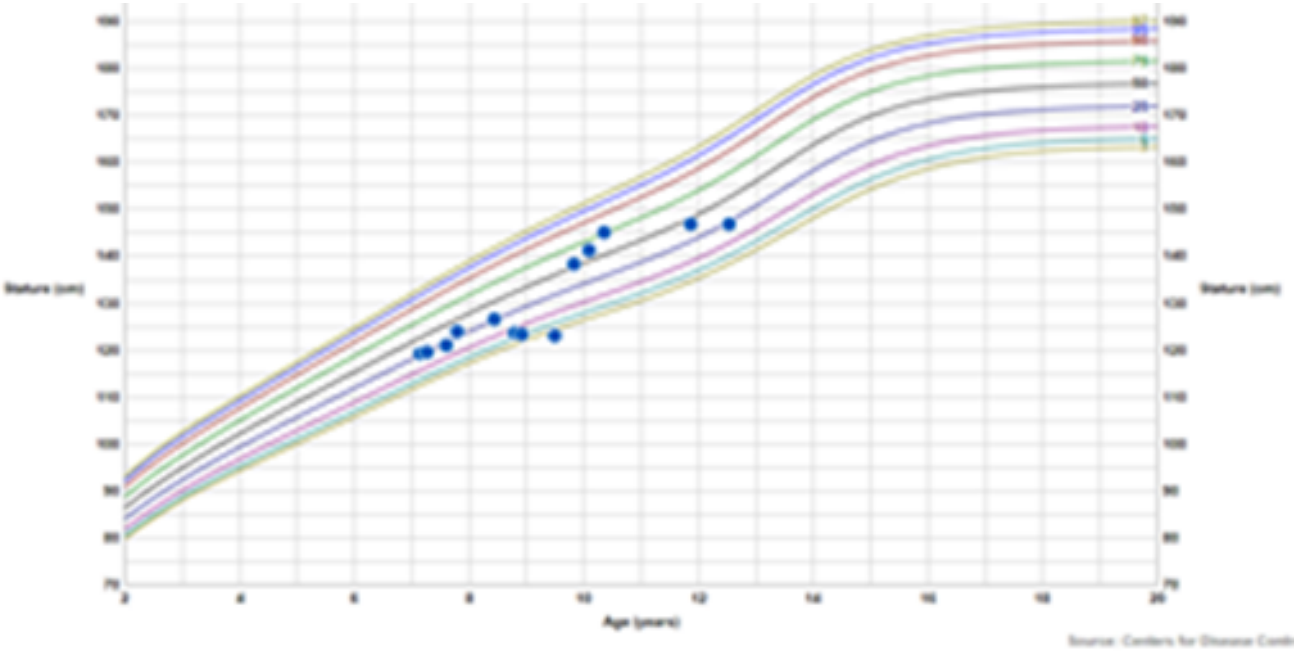
Steroid cause growth failure

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

Height monitoring 6 monthly



Ulnar length in DMD



Height prediction from ulna length

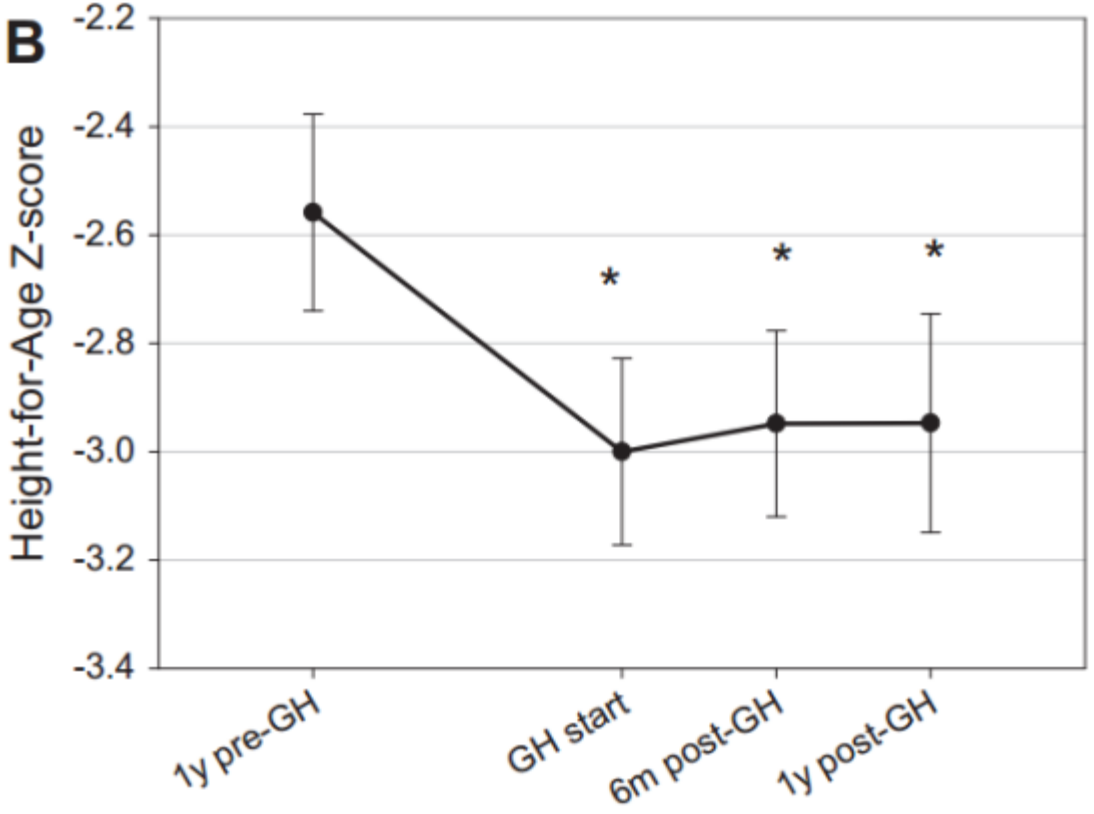
Leanne M Gauld* MBBS FRACP;
Johanna Kappers BN, Department of Respiratory Medicine, Royal Children's Hospital, Melbourne;
John B Carlin PhD;
Colin F Robertson MBBS FRACP MD, Department of Paediatrics, University of Melbourne, Melbourne, Australia.

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

Courtesy of Zoe Davidson, Monash Uni, Melbourne

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

rhGH In DMD- Growth Outcomes



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)

Rutter M, et al Neuromuscl Disor 2012

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

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ADRENAL SUPPRESSION

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Updated Standards of Care: Adrenal suppression

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)

Information about

Adrenal Suppression from Long Term Use of Steroid in Duchenne Muscular Dystrophy (DMD)

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

The PJ Nicholoff Steroid Protocol for Duchenne and Becker Muscular Dystrophy and Adrenal Suppression

June 27, 2017 · Advanced Diagnostics and Biomarkers

Citation

Kinnett K, Noritz G. The PJ Nicholoff Steroid Protocol for Duchenne and Becker Muscular Dystrophy and Adrenal Suppression. PLOS Currents Muscular Dystrophy. 2017 Jun 27 . Edition 1. doi: 10.1371/currents.md.d18deef7dac96ed135e0dc8739917b6e.

Scottish Muscle Network

Scottish Muscle Network Protocol 2016

Secondary adrenal insufficiency and long-term steroid use in DMD

ALL boys with DMD on current treatment regime of steroid have secondary adrenal insufficiency and will need an emergency plan during acute illness.

Physiological cortisol production is equivalent to 10 mg/m^2/day Hydrocortisone. ALL current steroid regime used exceeds this and therefore endogenous steroid production will be suppressed. The amount is however much higher than endogenous stress dose of steroid production and therefore there is no need to increase oral steroid during mild illness. However, emergency plan during severe illness especially when unable to tolerate oral steroid or during surgical procedure is crucial.

Steroid equivalence for glucocorticoid activity

1 mg Prednisolone = 4 mg hydrocortisone
1 mg Deflazacort = 6 mg hydrocortisone

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[a,*], Lenie van den Engel-Hoek[b], Marta L. Fiorotto[c], Mirjam Franken-Verbeek[a], Elizabeth Vroom[a,d], on behalf of the workshop participants

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

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DUCHENNE AWARENESS DAY 7 sept

DISCUSSION POINTS

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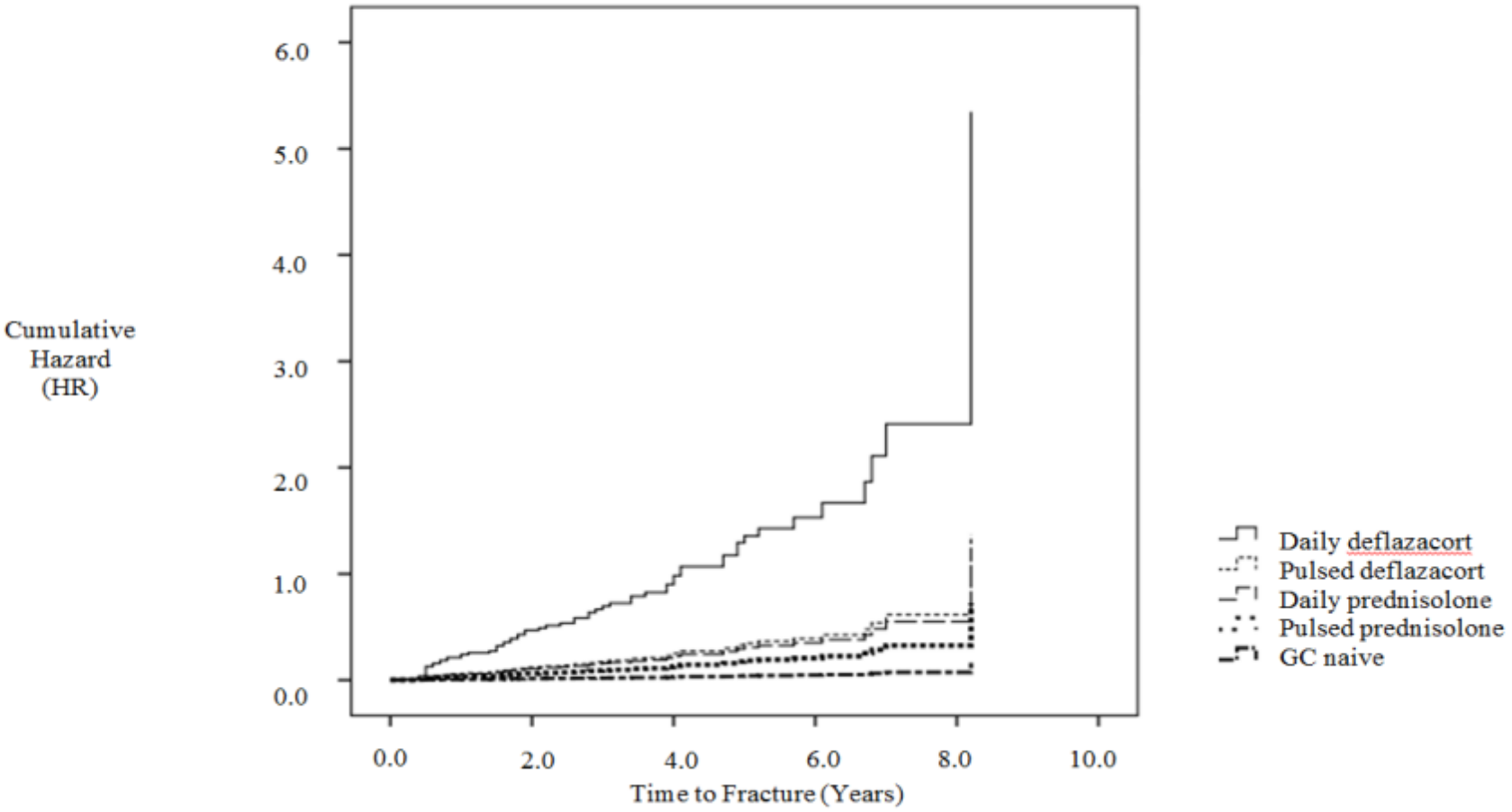
Fracture In DMD (NorthStar UK)

832 boys with DMD
520 more than 1 clinic visit

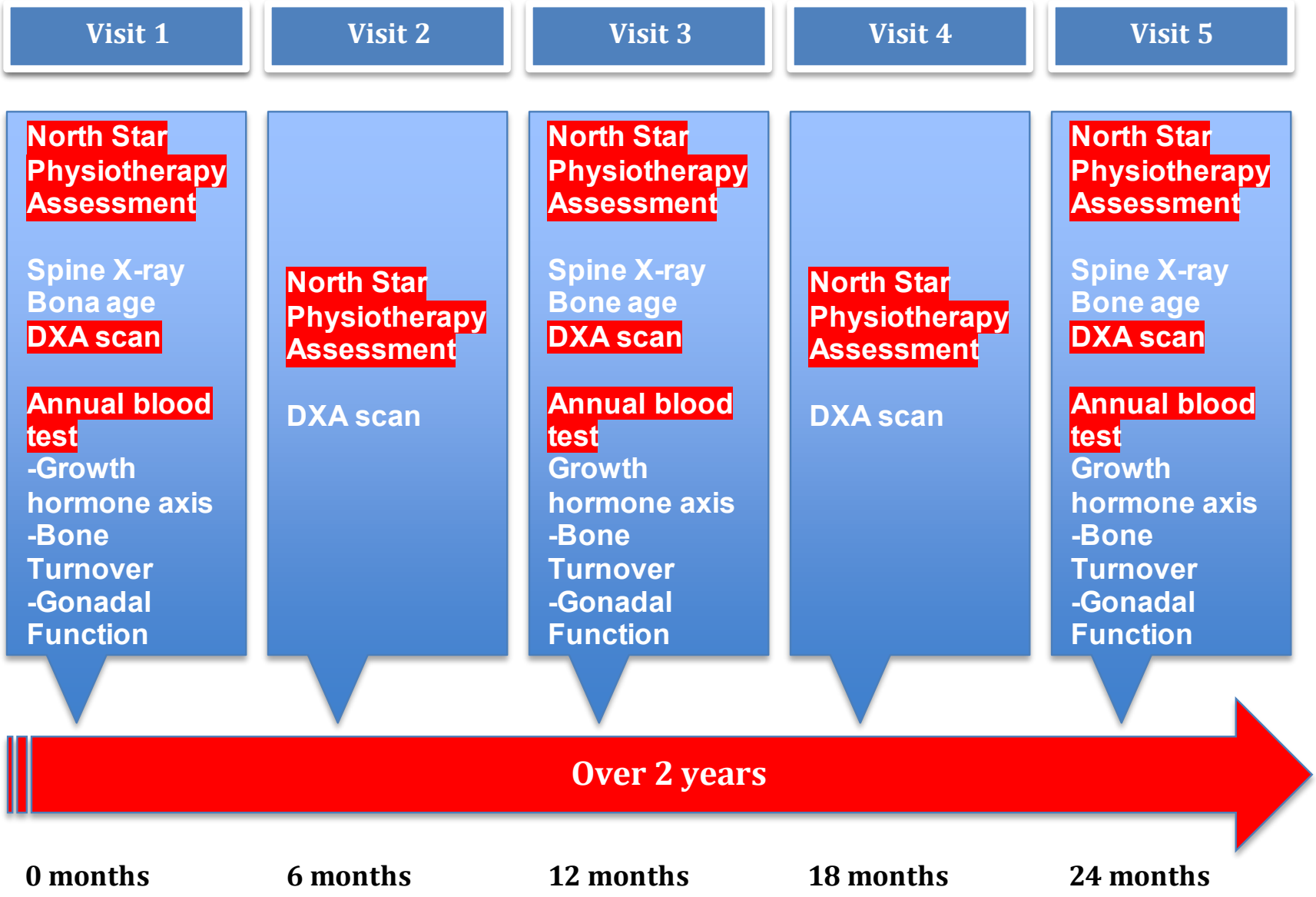


Time to first fracture is shortest in boys treated with daily Deflazacort

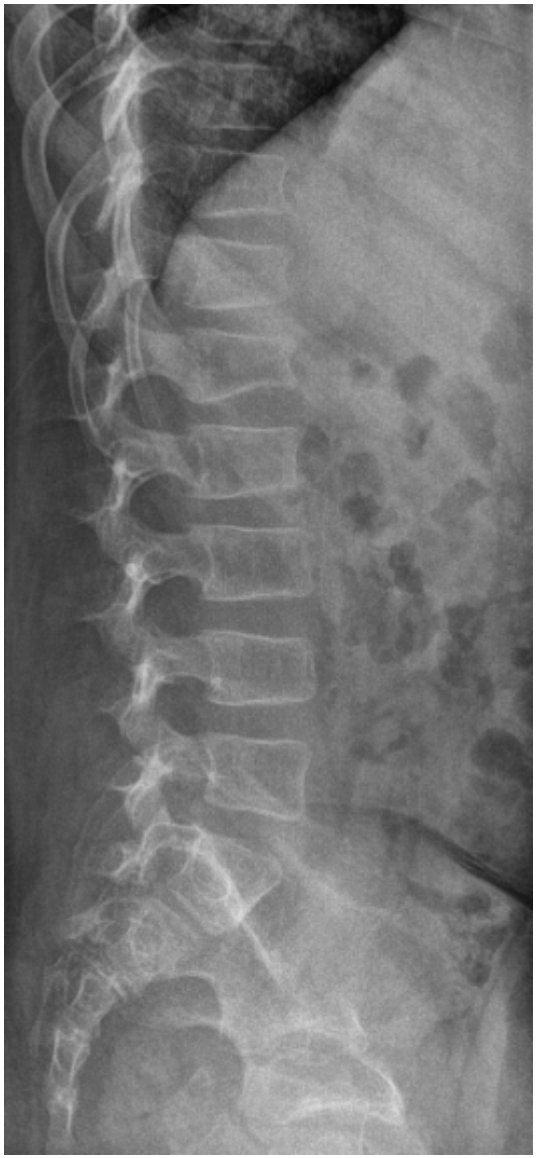
Joseph S et al Submitted

Prospective Study

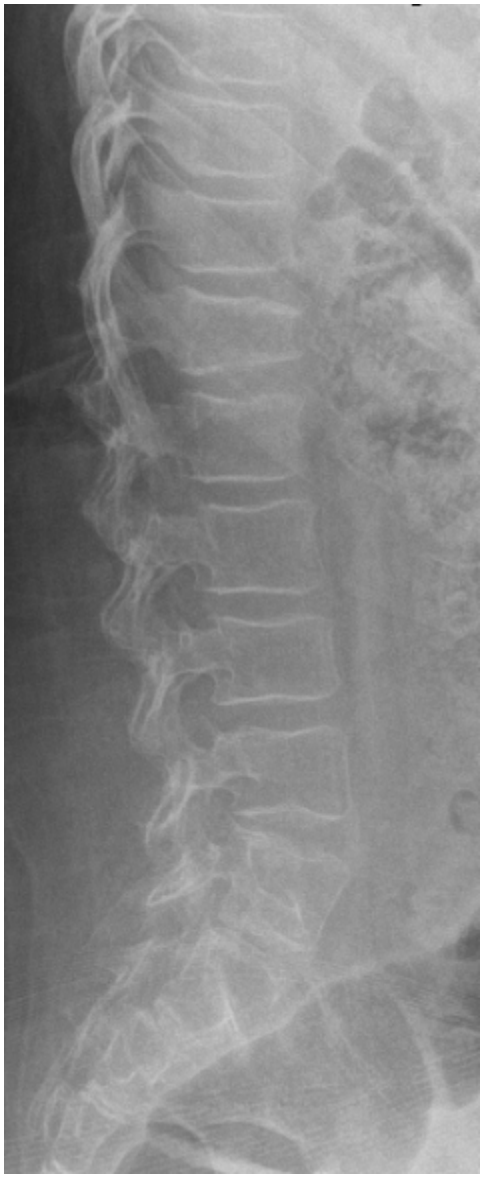
2 year longitudinal study of bone health (5-18 years DMD boys)



VF in DMD



VF no back pain



VF chronic intermittent mild back pain

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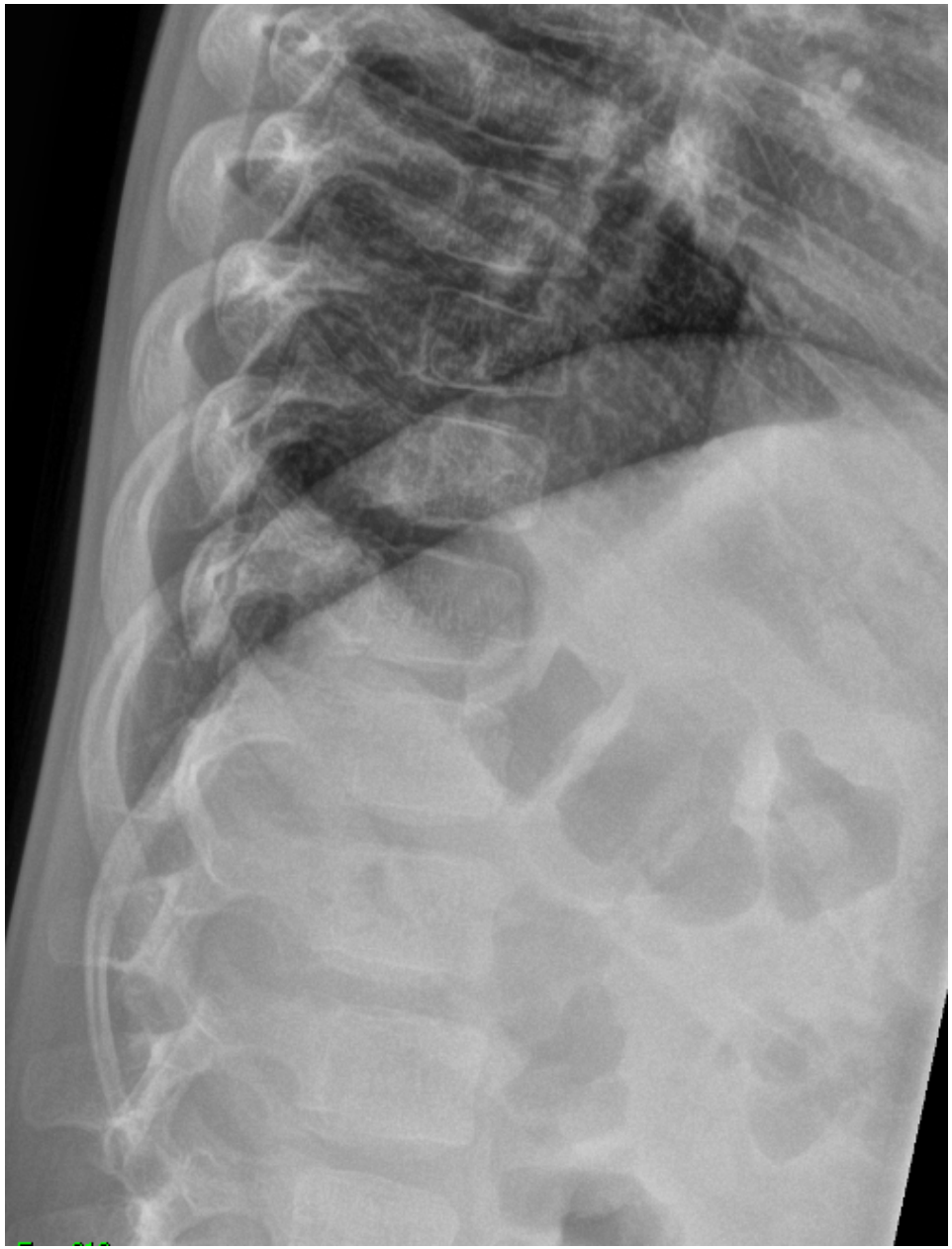
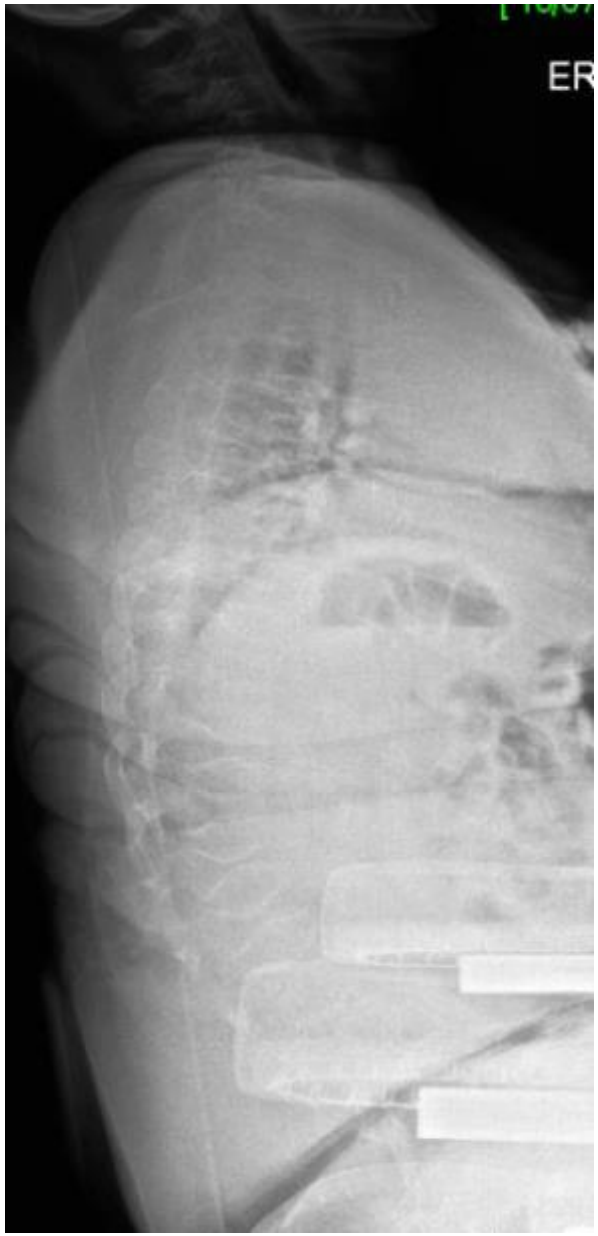
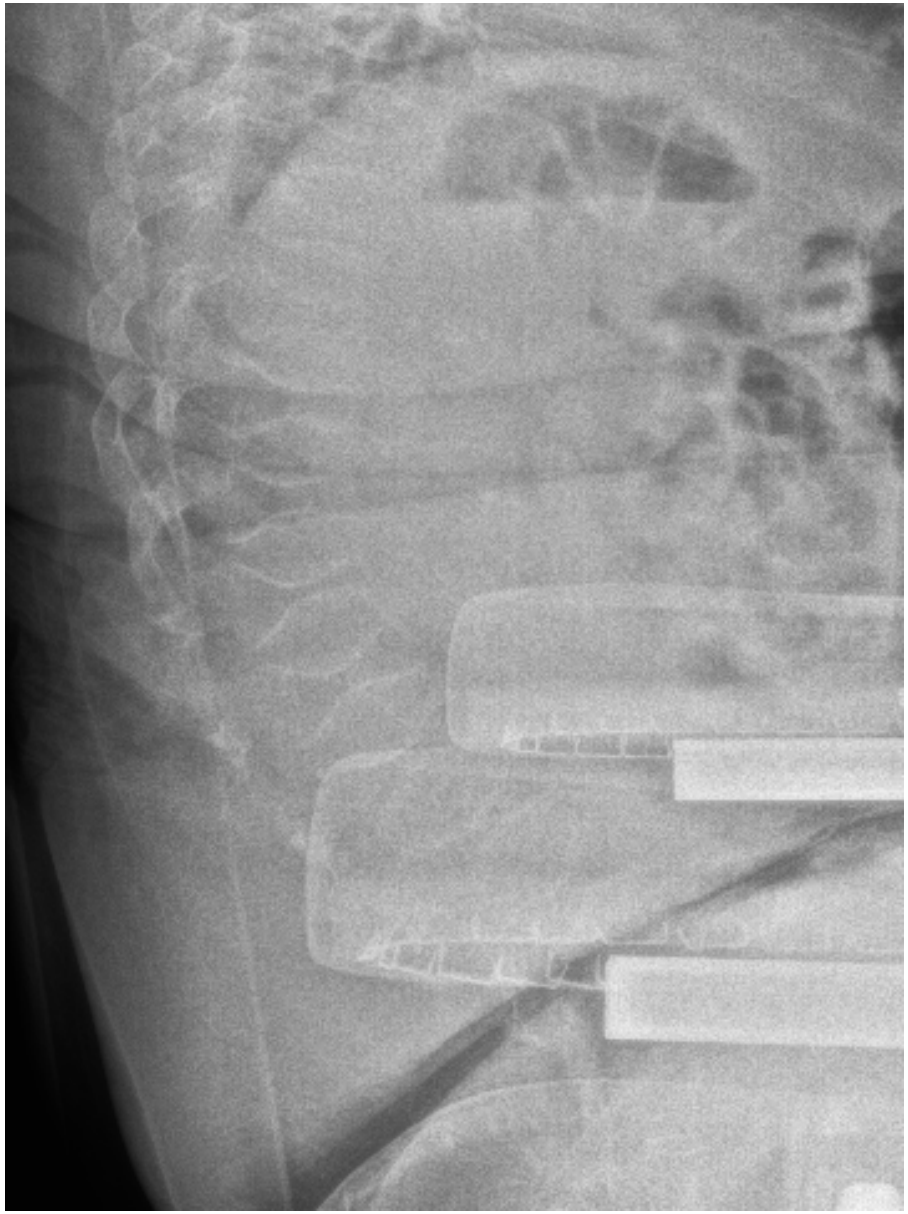
Vertebral abnormality in a steroid naive boy with DMD



Severe VF and no back pain





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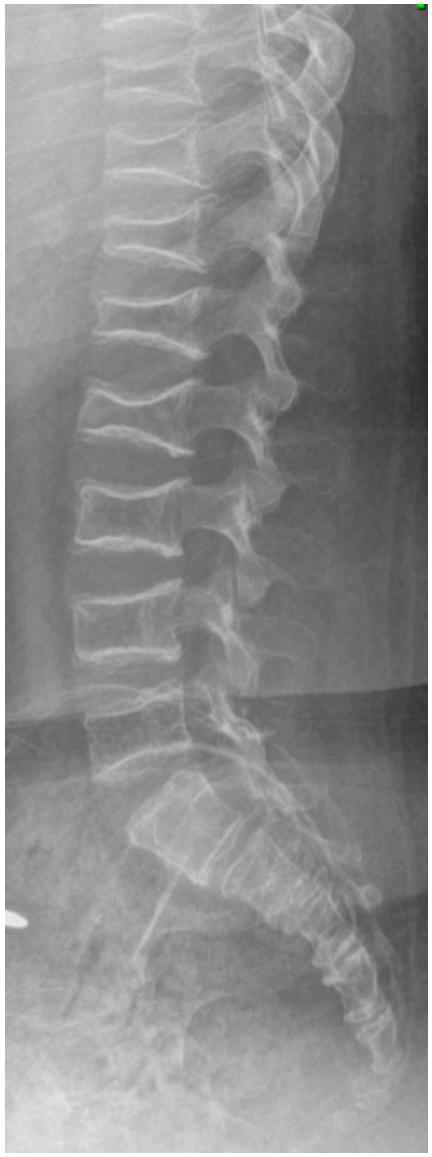
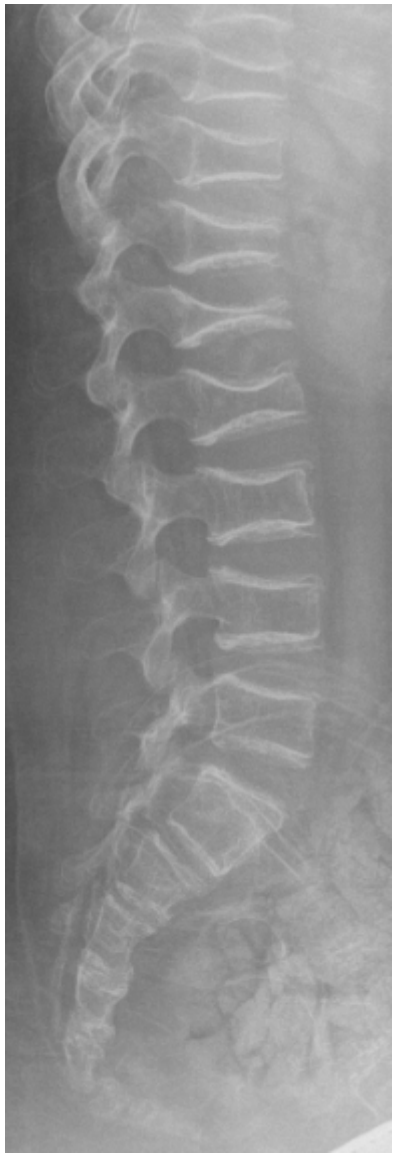
Progression of VF





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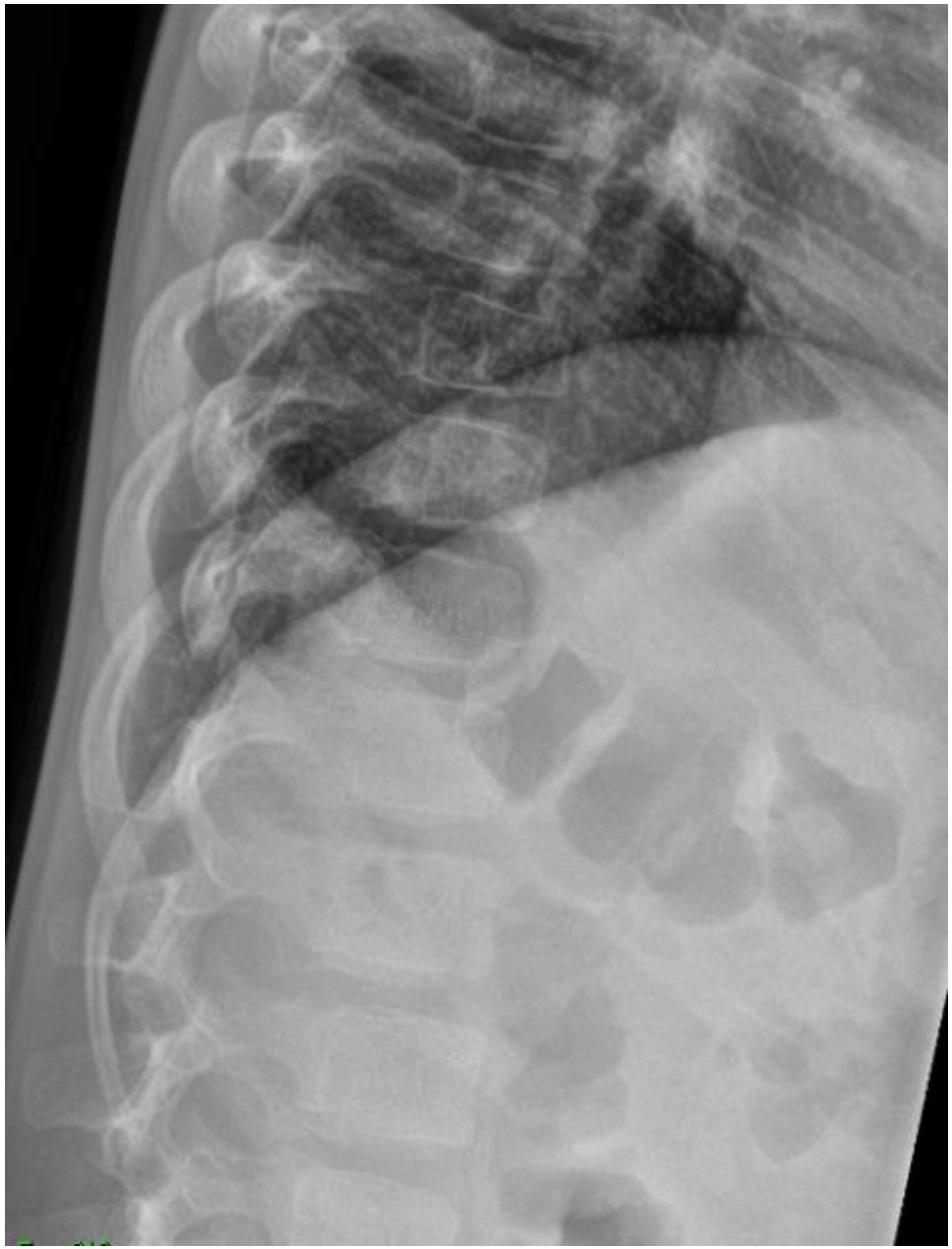
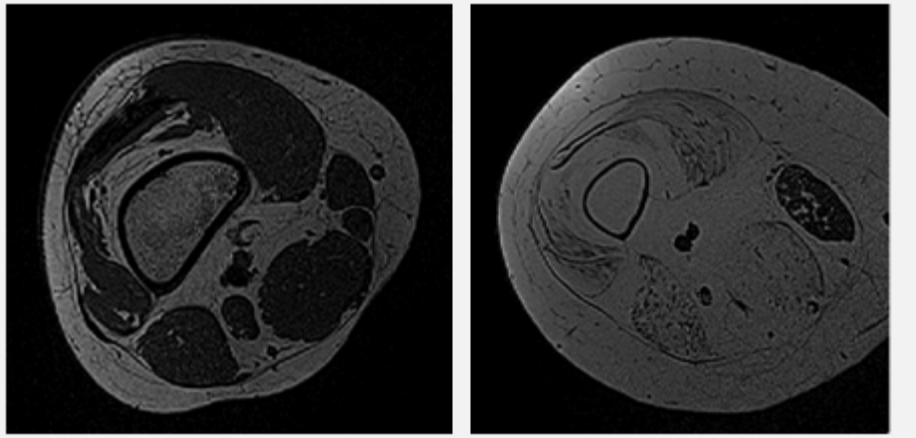
Vertebral abnormality in a steroid naive boy with DMD

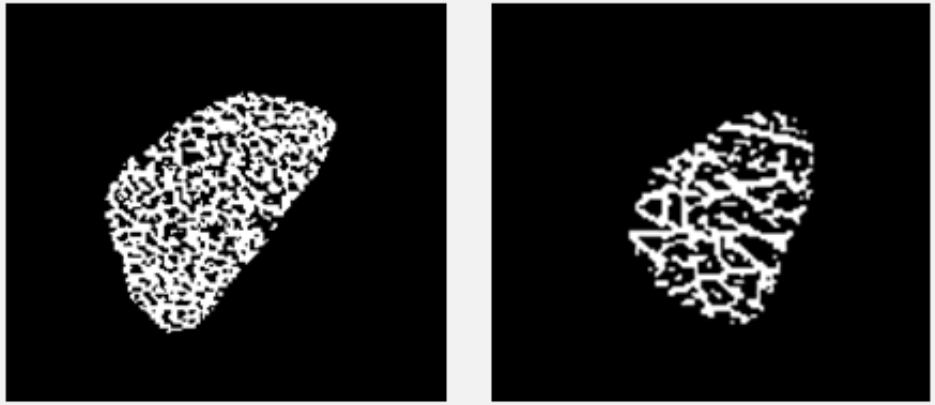


3T MRI imaging of muscle and bone



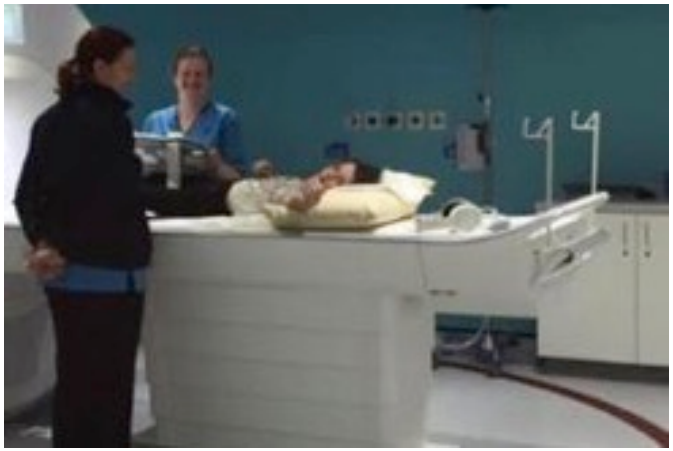
a)11-year old healthy control b)11-year old boy with DMD

Figure 1: T1 weighted image for cortical analysis



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

Figure2: Binarised trabecular microarchitecture



Testosterone In DMD

14 DMD treated with testosterone for delayed puberty

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

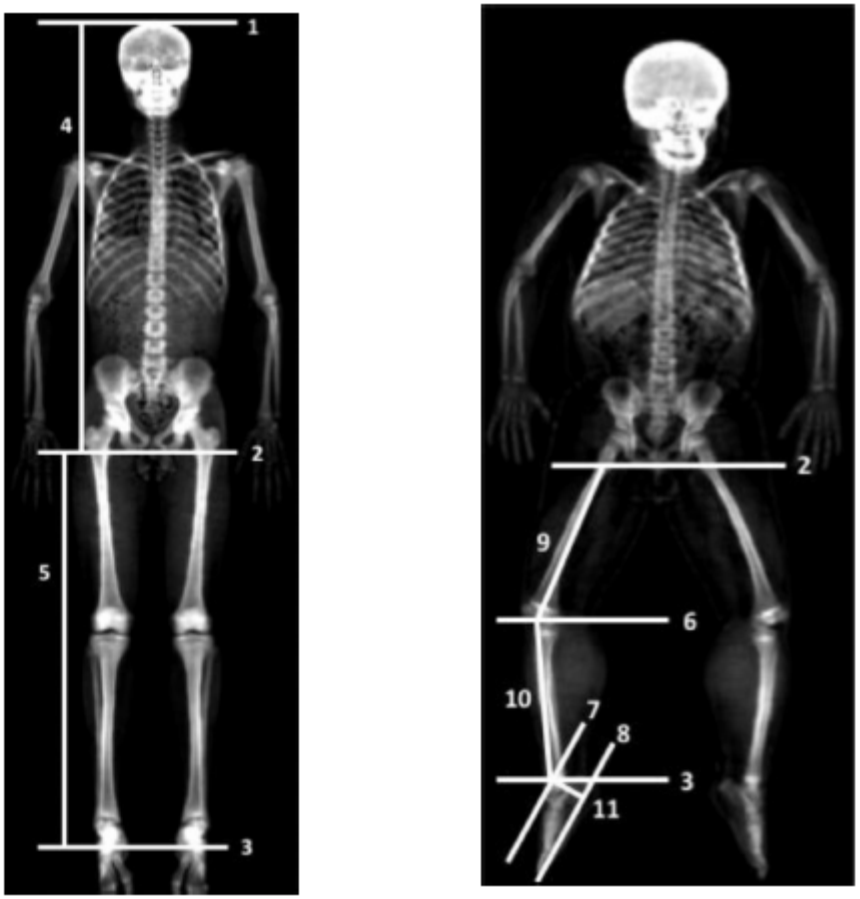
6 still undergoing treatment

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,†] KT Kao,[2,†] R MacDonald,[1,2] KC Grainger,[3] S Joseph,[2,4] S Shepherd,[2] A Mason,[2] and SC Wong[2,]*

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rhGH In JIA-Growth Outcome

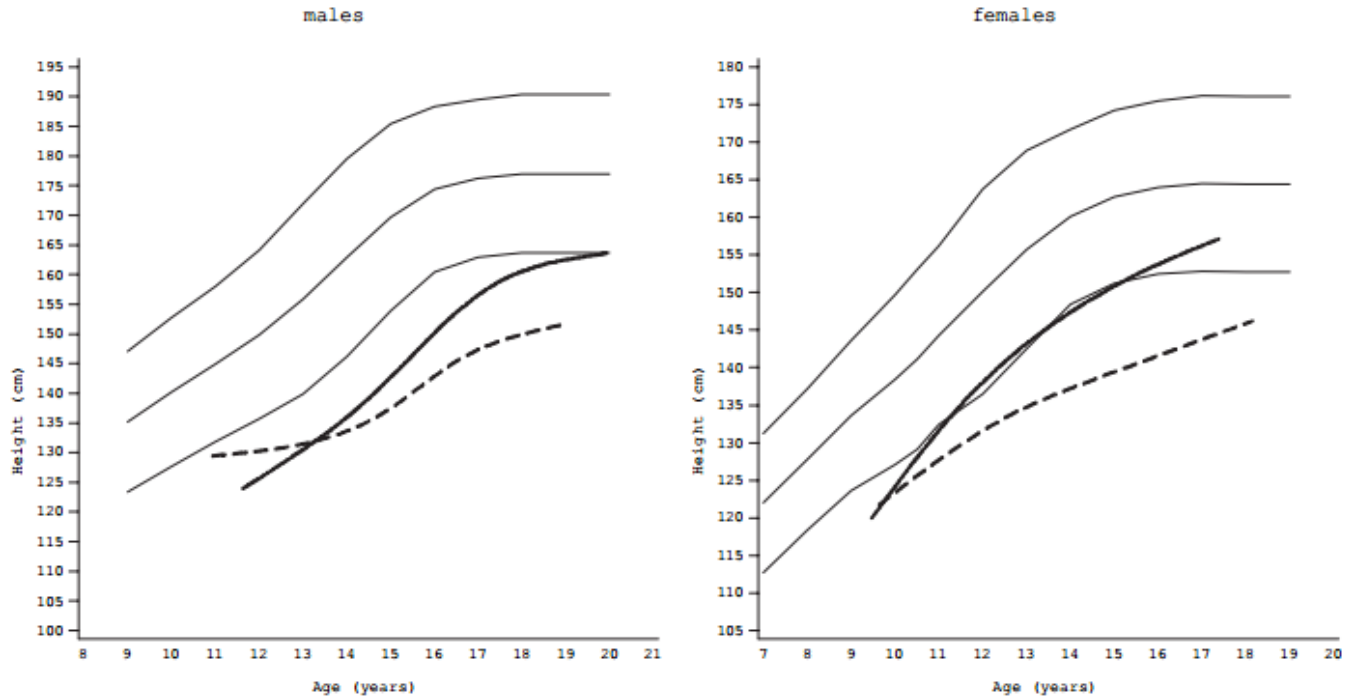
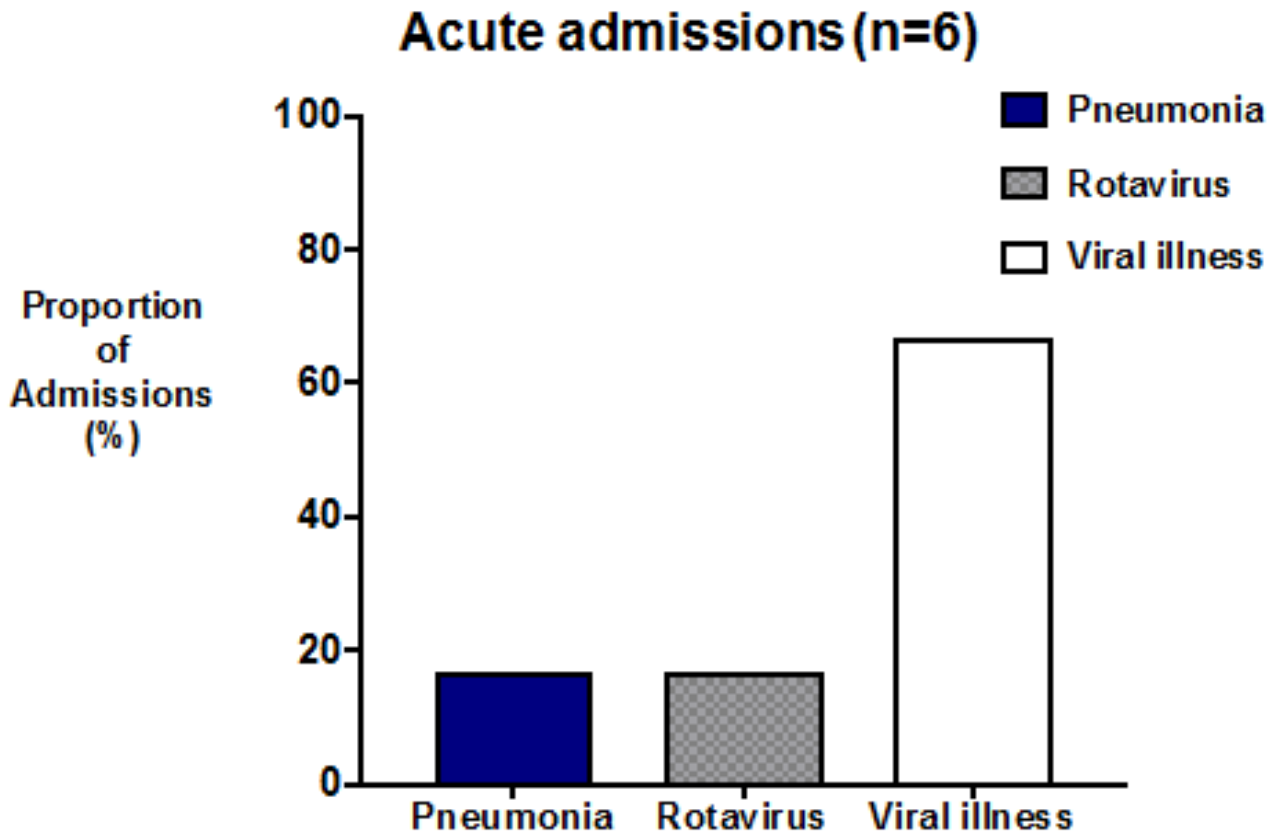


FIG. 1. Synchronized mean growth curves during GH treatment in 13 children and adolescents (*solid line*) with JIA in comparison with 18 control patients (*dashed line*) not treated with GH, according to sex; reference lines are for 97th, 50th, and 3rd percentiles, respectively.

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

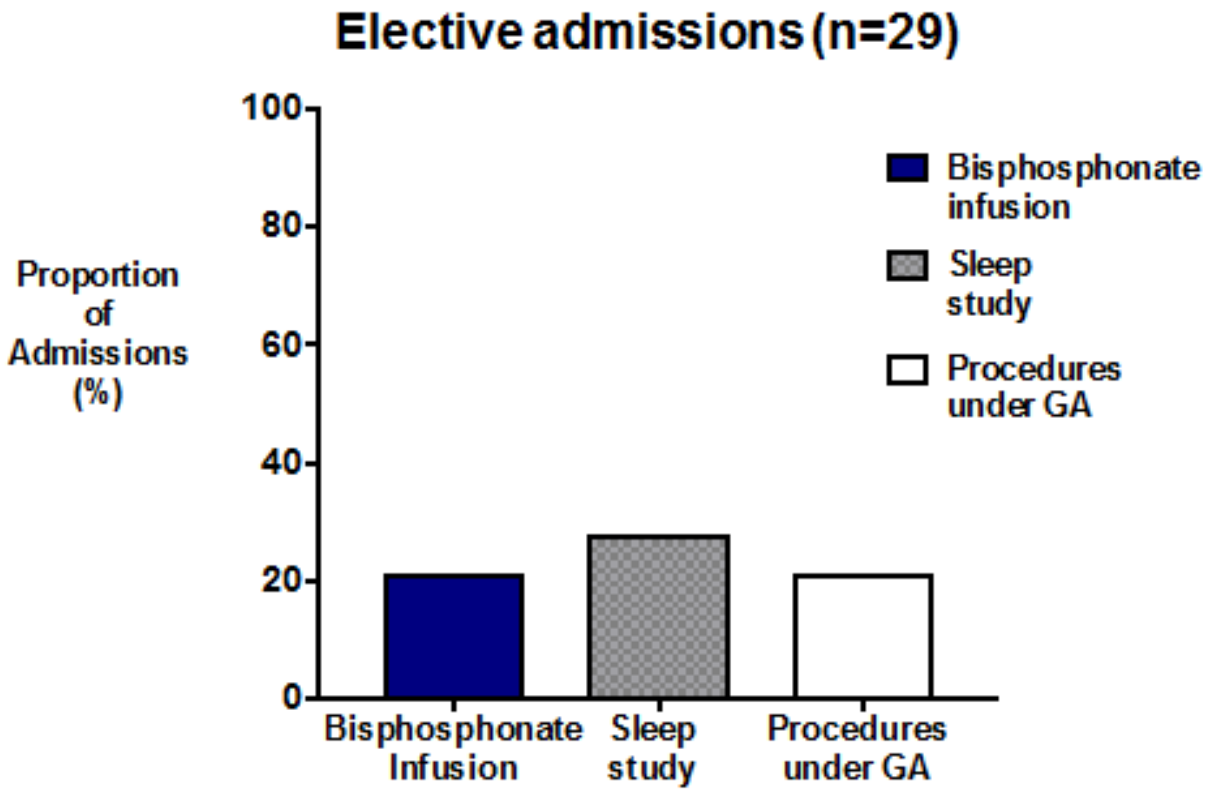
37% of JIA treated with rhGH have impaired glucose tolerance
5% transient T2DM

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



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.

Who is at risk of adrenal suppression?

Physiological replacement of steroid

- 10 mg/m^2 Hydrocortisone
- 3.8 mg/m^2 Deflazacort
- 2.5 mg/m^2 Prednisolone or Prednisone

Steroid for mild illness

- 20 mg/m^2 Hydrocortisone
- 6.8 mg/m^2 Deflazacort
- 5 mg/m^2 Prednisolone or Prednisone

Audit of steroid sick day training & inpatient management

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

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Why are some patients with Duchenne muscular dystrophy dying young: An analysis of causes of death in North East England

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[b] The John Walton Muscular Dystrophy Research Centre, Newcastle University, Institute of Genetic Medicine, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK

Pointers that can potentially minimise the risk of a premature death in DMD
Be aware of indications for starting non-invasive ventilation and refer appropriately
Ensure clinics are equipped to measure weight and closely monitor nutritional status at each visit
Be aware of the side-effect profile of corticosteroids, including adrenal insufficiency and immunosuppression
Find out why patients are failing to attend appointments
Ensure early cardiac screening and close surveillance of cardiomyopathy
Ensure multidisciplinary coordination of care among the different specialists
Consider early referral for psychological support

Every single adrenal crisis is preventable