Testosterone treatment of pubertal delay in Duchenne muscular dystrophy

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How does DMD affect bone health?

- Mutations of the *DMD* gene on Xp21, encoding dystrophin, expressed in muscle sarcolemma
- Lack of dystrophin leads to destabilization of muscle membrane, calcium influx, protease & pro inflammatory cytokine activation via T cell, mast cell and macrophage recruitment , with mitochondrial dysfunction
- → progressive muscle fibre necrosis, muscle weakness, loss of independent ambulation , cardiorespiratory disorder

Current standard of care

Current treatments aimed to prolong mobility, delay /reduce complications and need for surgery and increase lifespan have adverse effects on bone health

Corticosteroid effects on bone?

Pro-inflammatory cytokines IL-1b, TNF a, IL-6 may affect longitudinal growth via inhibition of growth plate chondrogenesis and altered IGF1

MacRae 2017

Fracture prevalence ?

408 boys aged 3–19 years : Retrospective study DMD
Fracture prevalence progressively with age
+ worsening motor function
Prevalence of total fractures
16.5%, 37.4%, and 83.3% at ages 5, 10 & 18
Prevalence of vertebral compression # 4.4%, 19.1%, and 58.3% at same ages

Tian 2014

Risks to Bone Health ?

- Immobility
- Poor muscle function
- High cytokines
- Osteoclastogenesis
- Weight gain
- Corticosteroid
- Poor osteoblast function
- Ca & Vit D intake & malabsorption
- **Delayed puberty**

Principles of care

Early detection of signs of bone fragility:
Active screening for vertebral fracture :
TL spine XR,
? DEXA lateral vertebral morphometry
?prophylactic treatments
anti-resorptive agents
growth-promotion – GH,IGF1

- **Anabolic agents: androgens**

Joseph S 2016

What do we know?

- Severely delayed puberty is near universal in DMD
- Corticosteroids suppress DHEAS & HPG axis
- Most young adults with DMD cannot maintain androgens

What is the use of puberty

- Puberty increases bone mass accrual ↑40-50%
- ↑ cortical thickness + trabecular mineralization
- Improved psycho social and emotional outlook

What did we do?

Aims: to evaluate impact of pubertal induction with testosterone on bone mass accrual, QoL, motor function, progression of vertebral fracture in boys with DMD taking long-term corticosteroid treatment

Retrospective review of boys aged > 14 years with DMD on long-term corticosteroids, regardless of bisphosphonate treatment status, treated at RCH from 2012-18

- To **identify boys with delayed puberty**, testes <4ml who had been treated with testosterone for pubertal induction.
- To compare **mean % ΔBMD** before and after pubertal induction by DXA
- To identify **progression/new onset vertebral fracture** >20% ***after*** pubertal induction
- To assess **body composition** before and after pubertal induction
- To assess **motor function** before and after pubertal induction
- To assess **post-treatment QoL** by WHOQOL-BREF & Kessler K-10 questionnaires.
- To assess **ability to maintain adult Testosterone** levels in boys who had ceased treatment after achieving full adult virilization

Results

IM Testosterone undecanoate group (N = 11)

Median age (At start)	Median age (To Reandron)	Mean % Δ LS BMD pre-treatment *^	Mean % Δ LS BMD 1 year post-treatment	Mean % Δ LS BMD at least 2 post-treatment #
14.5 years	16.3 years	- 1.52 %	+ 11.7%	+ 24.65 %

* 3 patients with 2nd baseline scan taken at 5 – 8 months after start of Andriol.
^ 10 out of 11 patients had received prior Zoledronic acid treatment before androgen treatment
# Only 10 out of 11 patients included because one patient had undergone spinal surgery and no longer able to use LS spine BMD for assessment. For this particular patient, there was 6.9% increase in forearm BMD from 2nd to 4th year post-treatment.

Oral Testosterone undecanoate group (N = 6)

Median age (At start)	Mean current dose of Andriol	Mean % Δ LS BMD pre-treatment Δ	Mean % Δ LS BMD 6-24 months post-treatment
14.2 years	107 mg per day	- 0.83 %	+ 14.2 %

Δ 5 out of 6 patients had received prior Zoledronic acid treatment before androgen treatment.

IM Testosterone undecanoate group (N = 11)

Patient	Age at start of androgen (yr)	Age at switch to Reandron (yr)	Mean % Δ LS BMD pre-treatment	Mean % Δ LS BMD 1 year post-treatment	Mean % Δ LS BMD at least 2 post-treatment	Vertebral fracture status	Motor function
1	16.7	17.2	-10.00 %	+3.40%	+37.00%	No progression	Insufficient data
2	17.7	18.9	-10.08%	+16.3%	+12.70%	Progression of compression fracture on L5	Ambulatory Improved
3	14.2	15.7	-0.50%	+24.4%	+11.90%	No progression	Ambulatory Deteriorated
4	14.3	16.3	+4.00%	+9.70%	+18.80%	No progression	Non-ambulatory Improved
5	14.4	16.3	+4.80%	+4.00%	+25.79%	No progression	Ambulatory to non-ambulatory
6	16.3	17.7	-2.00%	+7.30%	+38.90%	No progression	Non-ambulatory Improved
7	14.0	16.3	+1.90%	+8.20%	+41.07%	No progression	Non-ambulatory Improved
8	15.3	16.8	+0.10%	+23.78%	+1.50%	No progression	Ambulatory to non-ambulatory
9	15.1	17.0	-5.00%	+17.60%	+32.70%	No progression	Non-ambulatory Improved
10	14.5	16.3	+6.30%	+4.50%	+26.11%	No post X-ray for comparison	Ambulatory to non-ambulatory
11	13.8	16.0	-5.50%	+9.55%	Only forearm BMD feasible due to spinal surgery	Post-spinal surgery for scoliosis	Non-ambulatory Improved

Oral Testosterone undecanoate group (N = 6)

Patient	Age at start of androgen (yr)	Current dose of Andriol (mg per day)	Mean % Δ LS BMD pre-treatment	Mean % Δ LS BMD 6-24 months post-treatment	Vertebral fracture status	Motor function
1	14.0	120	-3.00%	+18.20%	Improved	Non-ambulatory Improved
2	16.0	160	-11.80%	+16.40%	New crush fracture, but improved backpain after stepping up Andriol	Non-ambulatory Improved
3	14.2	120	-10.20%	+27.20%	No progression	Non-ambulatory Improved
4	14.2	80	+10.60%	+16.10%	No post-treatment X-ray for comparison	Ambulatory Deteriorated
5	14.1	80	+8.35%	+8.10%	Andriol started for one year	Ambulatory to non-ambulatory
6	15.6	80	+1.07%	-0.8%	Andriol started for one year	Non-ambulatory Improved

Mean WHOQOL-BREF score

- **Domain 1 : Physical Health (Population norm 73.5 +/- 18.1) 58**
- **Domain 2: Psychological wellbeing (Population norm 70.6 +/- 14.0) 63**
- **Domain 3: not done as Q's related to sexual health were not addressed**
- **Domain 4: Environment (Population norm 75.1 +/- 13.0) 71**

Kessler K-10 scale for psychological distress 15

- **Score under 20 – likely to be well**
- **Score 20-24 – likely to have mild mental disorder**
- **Score 25-29 – likely to have moderate mental disorder**
- **Score 30 and over – likely to have severe mental disorder**

IM Testosterone undecanoate group (N = 11)

Patient	Testosterone level 2-6 months after cessation of Reandron
1	28.9 nmol/l
2	7.3 nmol/l
3	Still on Reandron
4	5.3 nmol/l
5	15.7 nmol/l
6	11.1 nmol/l
7	10.5 nmol/l
8	Still on Reandron
9	Still on Reandron
10	Still on Reandron
11	14.4 nmol/l

IM Testosterone undecanoate group – Change of Individual body composition (N = 8)

Patient	% Change of lean mass/Ht² per year		% Change of fat mass/Ht² per year	
	Before androgen	After androgen	Before androgen	After androgen
1	-22.29%	+6.92%	+21.02%	+1.68%
2	-2.95%	-1.77%	-3.98%	-2.62%
3	-3.19%	+0.57%	+9.89%	-4.52%
4	-18.31%	+3.59%	+3.15%	+4.25%
6	+6.33%	+3.44%	+37.24%	+1.66%
8	+5.97%	+2.01%	-2.39%	+1.32%
10	+6.18%	-3.84%	+9.12%	+4.17%
11	-6.95%	+1.51%	+5.77%	-5.42%

3 out of 11 patients excluded from analysis as insufficient baseline data to compare with post androgen changes.

IM Testosterone undecanoate group – Mean change in body composition(N = 8)

Mean % Change of lean mass/Ht² per year		Mean % Change of fat mass/Ht² per year	
Before androgen	After androgen	Before androgen	After androgen
-4.40%	+1.55%	+9.98%	+0.07%

3 out of 11 patients excluded from analysis as insufficient baseline data to compare with post androgen changes.

What does this mean?

A normal rate of change of aBMD accrual in the normal child is 3-5% pa
During puberty this increases to 10-15% pa

For our cohort we have

- Normalized rate of adolescent pubertal bone mass accrual despite all other adverse events that contribute to bone loss in DMD
- Provided a physiologic intervention aimed to increase cortical thickness and trabecular mineralization
- Aiming to reduce future fracture risk (unproven here)
- Increased successful transition to a more adult psycho-social & emotional state

BMD increased more rapidly after pubertal induction

Vertebral # stabilized with no progression after pubertal induction

Measures of physical and psychologic well being were similar to a normal population

Ability to maintain Testosterone levels after cessation of supplementation varied

Body composition measures improved after androgen treatment , with less fat and increased lean mass

Our conclusion: Pubertal induction should be advocated as part of standard practice for all boys with DMD using corticosteroids who have pubertal delay

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Bone, growth plate and mineral metabolism
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