Testosterone treatment of pubertal delay in Duchenne muscular dystrophy

Zacharia M, Lee S. Dept of Endocrinology, Murdoch Children’s Research Institute, Royal Children’s Hospital, Parkville, Victoria 3052, Australia

How does DMD affect bone health?
- Mutations of the DMD gene on Xp21, encoding dystrophin, expressed in muscle sarcolemna
- Lack of dystrophin leads to destabilization of muscle membrane, calcium influx, protease & pro-inflammatory cytokine activation via T cell, mat 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

Corticosteroids effects on bone?
Pro-inflammatory cytokines IL-1b, TNFα, IL-6 may affect longitudinal growth via inhibition of growth plate chondrogenesis and altered IGF1

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

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, 7 DXA lateral vertebral morphometry
- ?Prophylactic treatments anti-resorptive agents growth-promotion – GH, IGFI
- Anabolic agents: androgens

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 bisphosphate 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

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

Results

IM Testosterone undecanoate group (N = 11)

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<th>Mean % ΔA BMD (yr)</th>
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Vertebral fracture status
- Improved
- No progression

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 C1 related to sexual health were not addressed
- Domain 4: Environment (Population norm 75.1 +/- 120)
- 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

BMD increased more rapidly after pubertal induction

Ventral # stabilized with no progression after pubertal induction

Measures of physical and psychological 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

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

Poster presented at: Poster Session Online - Osteoporosis, Osteopenia and Bone Health - Tuesday, November 1, 2016 - Bone, growth plate and mineral metabolism - Margarita zachariah