

# Endocrine & Bone Management In DMD: Impact on muscle function



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## **Potential conflict of interest:**

Previous research and fellowship funding by:

NovoNordisk UK

NovoNordisk Australia

# SeCondary Osteoporosis & its Therapy Duchenne Musclerary Dystrophy

## SCOT-DMD

**Muscular  
Dystrophy UK**  
Fighting muscle-wasting conditions



**CHIEF  
SCIENTIST  
OFFICE**



Scottish Muscle Network



**NorthStar**  
Clinical Network

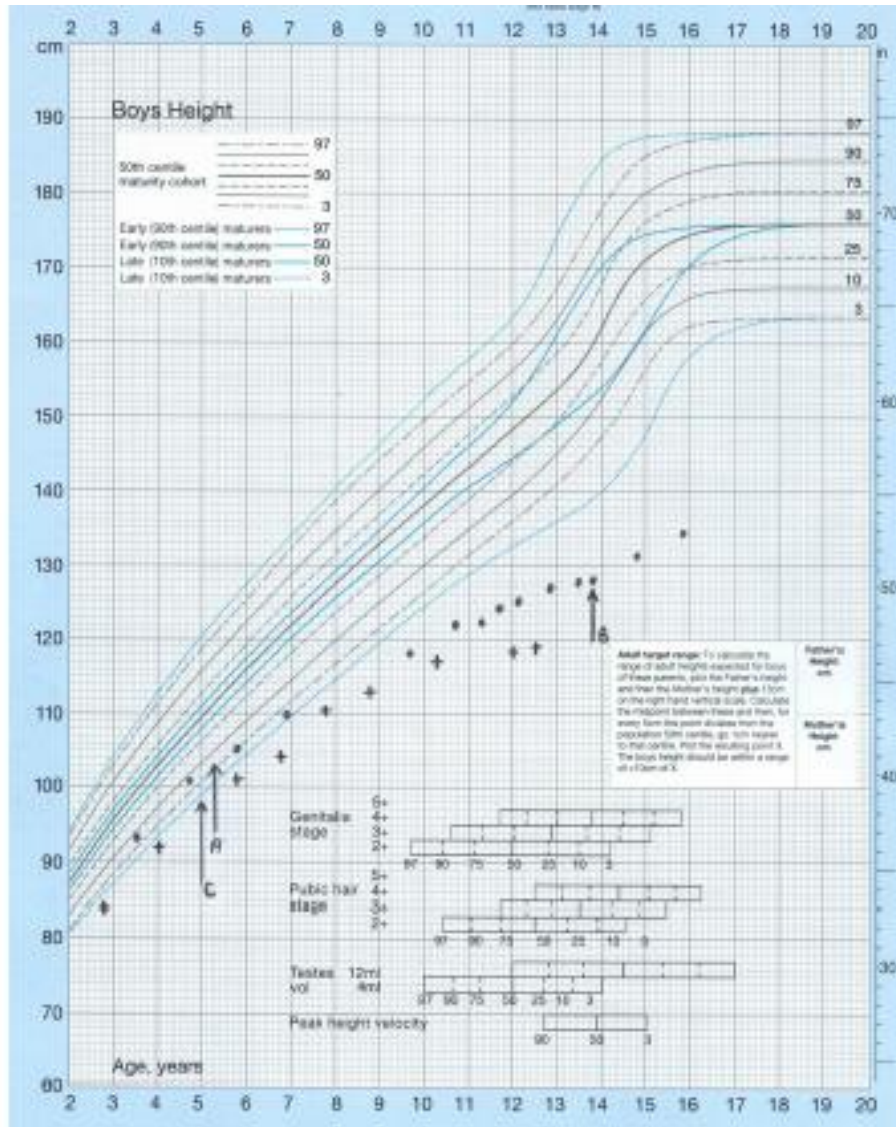


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# GROWTH ISSUES



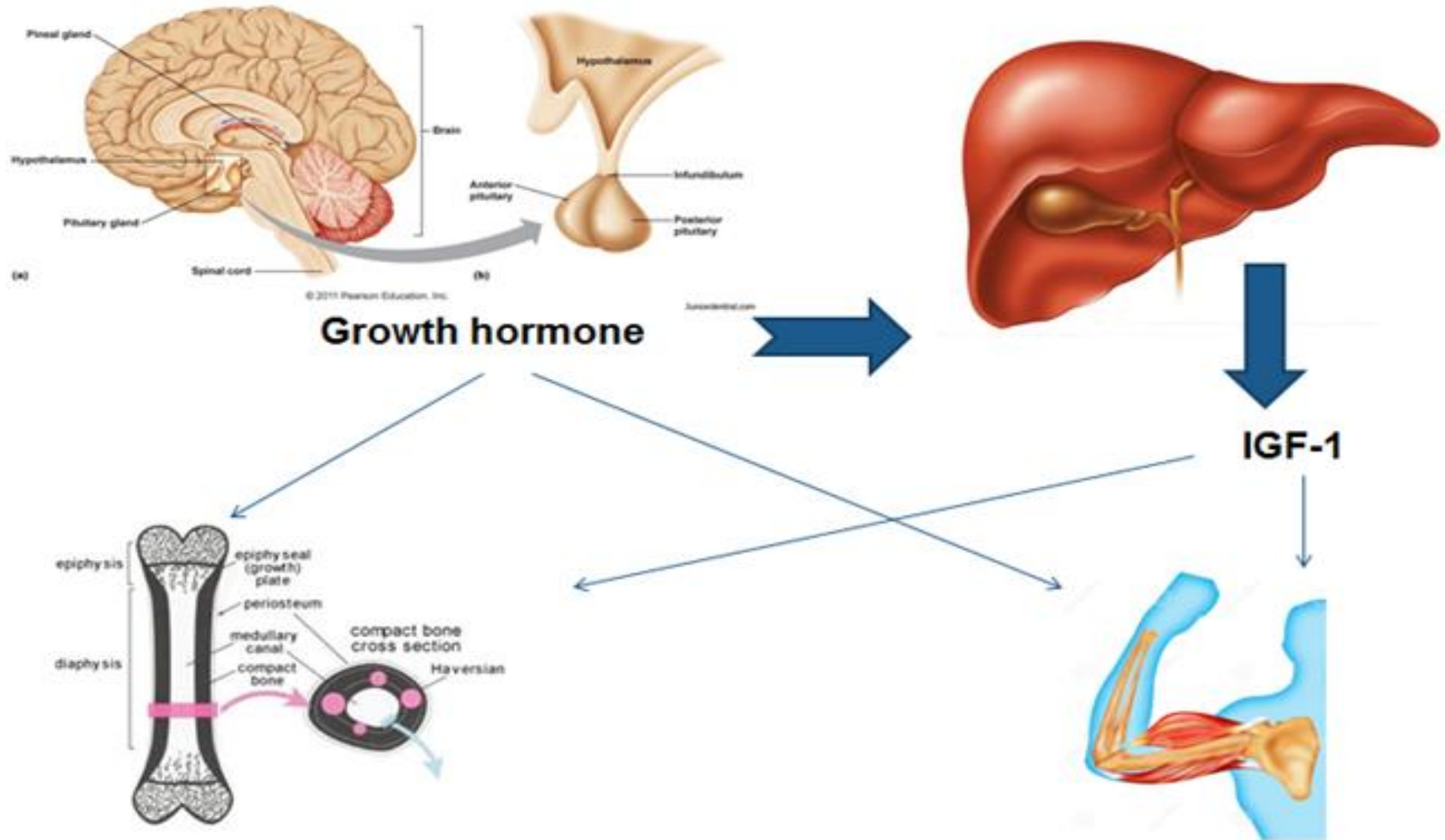
About 25% of boys with DMD are short before starting steroids

Steroids further reduce growth

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

**Height monitoring 6 monthly**





Not recommended routinely

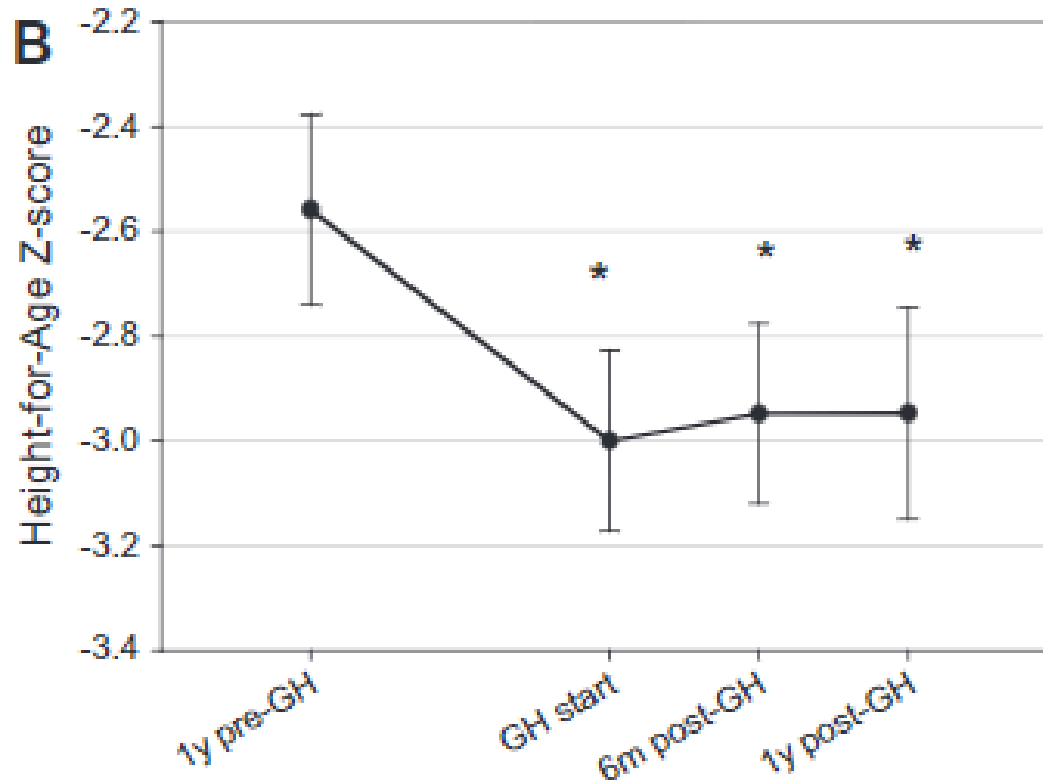
Not licenced indication

May improve growth rate but remain short

Daily injections

Side effects: high blood sugar (diabetes), raised pressure behind the eyes



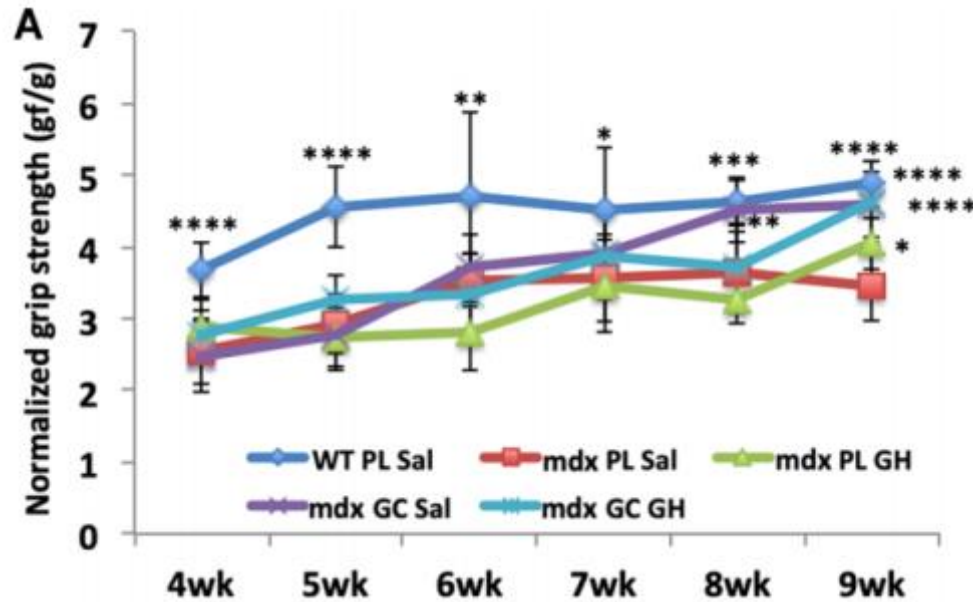


39 boys with DMD treated with growth hormone  
Daily injections

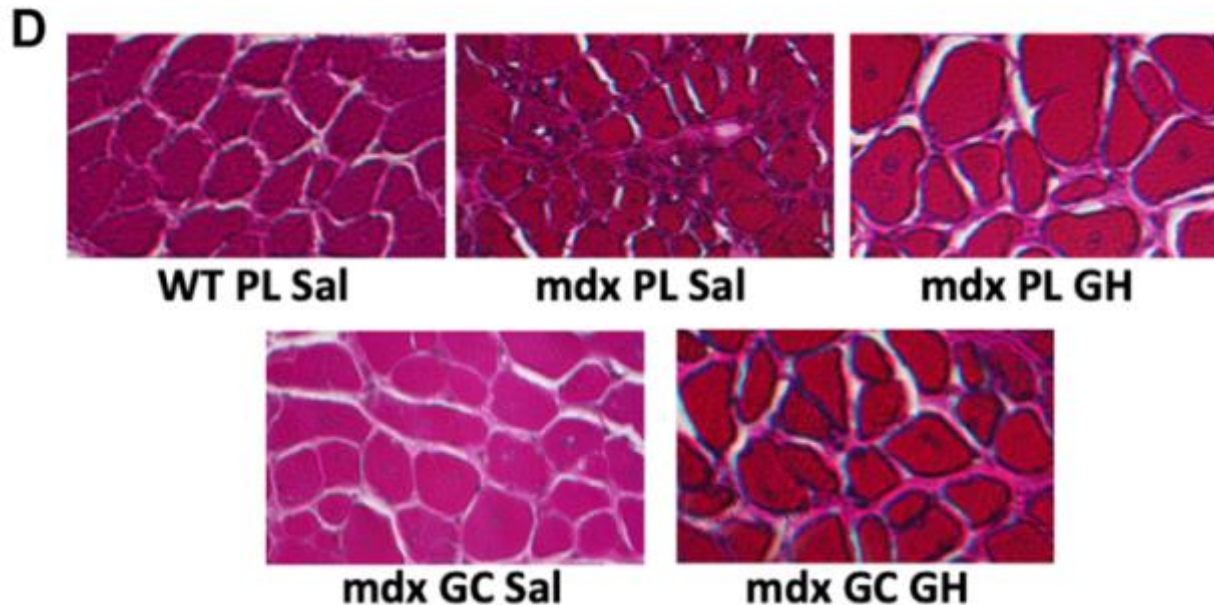
No change in muscle function

Side effects: insulin resistance/glucose abnormalities, benign intracranial hypertension





Growth hormone improve bone strength with little improvement in muscle





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# PUBERTY

Information about

## Puberty and Hormones in Duchenne Muscular Dystrophy (DMD)



Almost all boys on daily steroid treatment will not show signs of puberty

- Important for psychological well-being
- Bone / muscle effect

Average age of boys showing signs of puberty about 10-11 years

**Puberty to be examined from age 12-13 years**



Injections  
Creams/gel  
Tablets

Treatment from age 14 years if no signs of puberty  
(Can be considered from age 12 years)

Build up dose slowly over about 3 years



Lead to physical changes of puberty

Improvement in growth rate

- Approximately 5 ½ inches (*Wood et al, Neuropaediatrics 2015*)
- Glasgow experience approximately 2 inches
- Average growth rate in adolescent boys approximately 8-10 inches

Side effects

- Generally well tolerated
- Acne

Wood et al. *BMC Pediatrics* (2019) 19:131  
<https://doi.org/10.1186/s12887-019-1503-x>

BMC Pediatrics

STUDY PROTOCOL

Open Access

## Observational study of clinical outcomes for testosterone treatment of pubertal delay in Duchenne muscular dystrophy



C. L. Wood<sup>1\*</sup>, T. D. Cheetham<sup>2</sup>, K. G. Hollingsworth<sup>3</sup>, M. Guglieri<sup>1</sup>, Y. Ailins-Sahun<sup>4</sup>, S. Punniyakodi<sup>5</sup>, A. Mayhew<sup>1</sup> and V. Straub<sup>1</sup>

Impact of testosterone on muscle function in DMD  
Impact of earlier start of testosterone on clinical outcomes



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# **BONE HEALTH / OSTEOPOROSIS**

Muscle weakness

Steroids

Vitamin D and nutritional deficiencies

Poor growth

Delayed or absent puberty





## Fractures are very common

- At least 50% of boys with DMD will have a fracture
- Compression fracture of the back common and underestimated if diagnosed based just on back pain

**Spine x-rays: Baseline then 1-2 yearly (steroid); 2-3 yearly not on steroid**

**Vitamin D levels: Baseline then annually**

**DXA (bone density scan): Baseline then annually**

## Prioritise spine x-ray above DXA scan

- Bone density results should not be used as a guide to start bone protective medicine
- Presence of vertebral fracture is indication for consideration of bone protective medicine



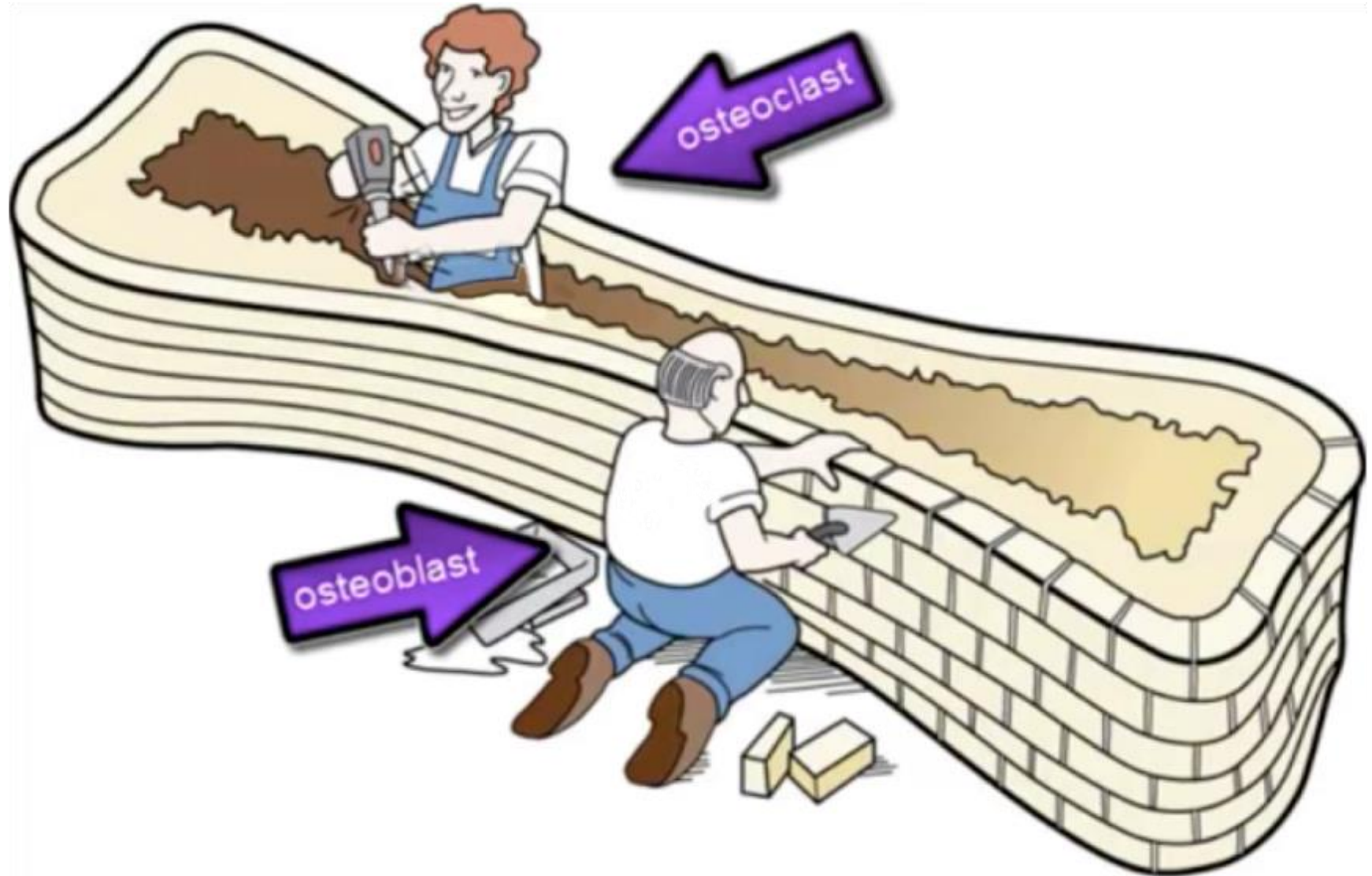
Normal spine



Mild vertebral fractures



Multiple severe vertebral fractures



Improve bone by reducing bone breakdown

Useful in post-menopausal osteoporosis as problem is due to increase breakdown of bone

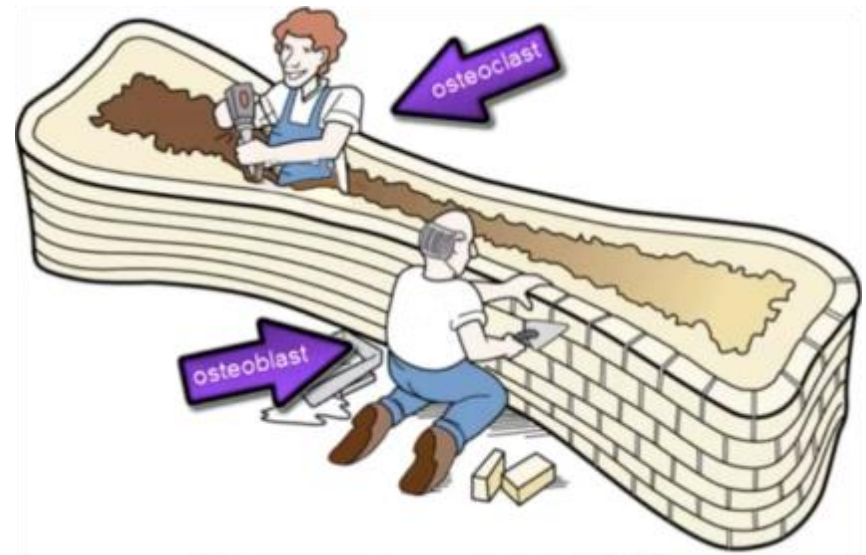
In steroid treated patients like DMD, bone problem is due to reduction in amount of bone formed

Can be given as tablets

- Indigestion

Can be given as medicines into drip

- Pamidronate or zoledronate
- Fever, nausea, flu like reaction



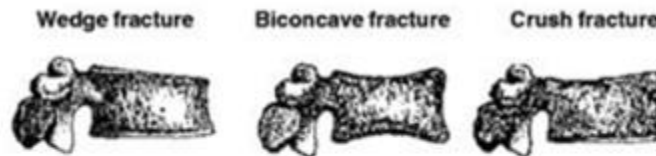
Currently not recommended as preventative medicine

## Indication are:

Painful vertebral fractures

Moderate or severe vertebral fractures (even without pain)

MILD: Genant 1



MODERATE: Genant 2



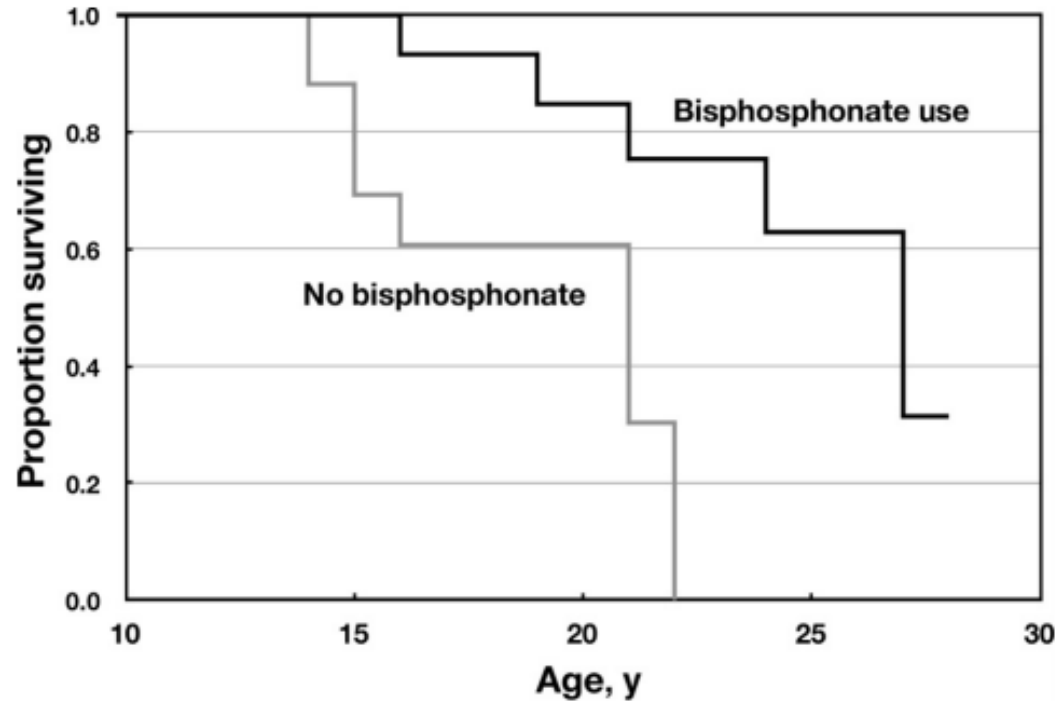
SEVERE: Genant 3



Long bone fracture with minimal trauma

## **IV bisphosphonate**

- Very effective in relieving bone pain from vertebral fracture
- Improve bone density
- Stabilize degree of vertebral fracture
- Unclear if will completely stop new vertebral fracture
- Unclear if will prevent long bone fracture in the future

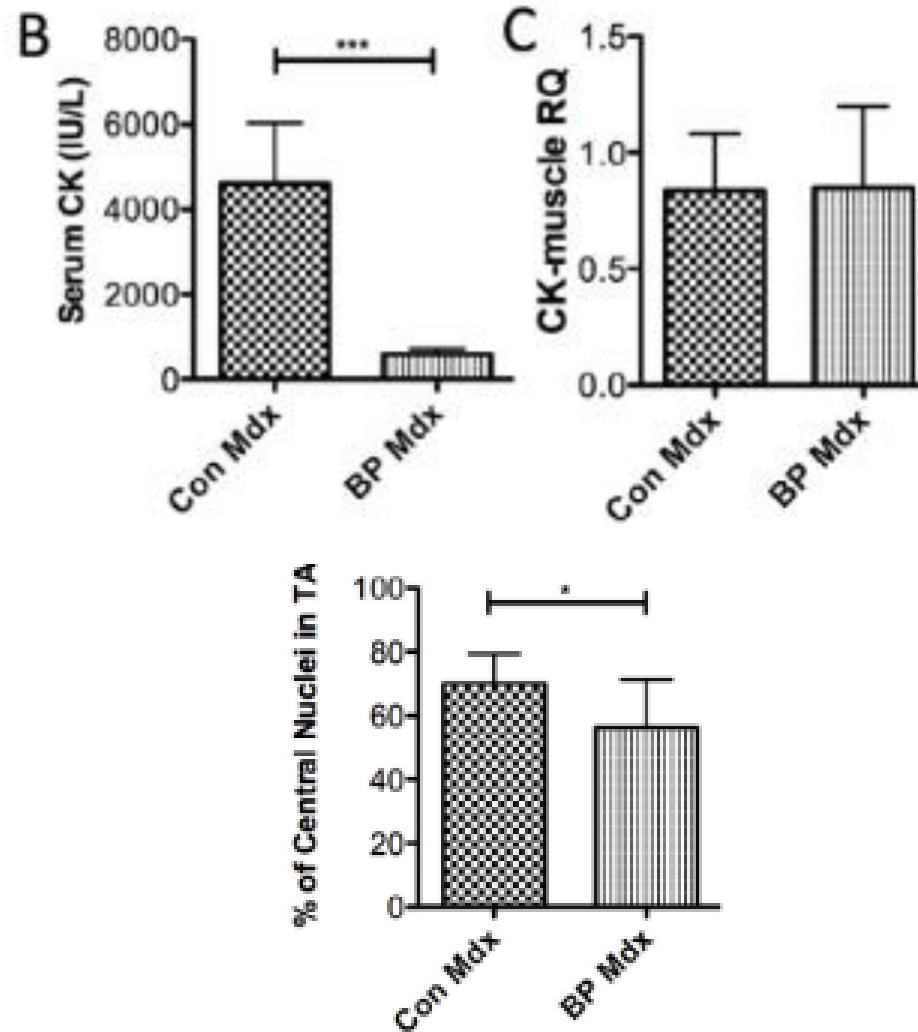


60% survivors age 20 years in non-bisphosphonate treated  
85% survivors age 20 years in bisphosphonate treated

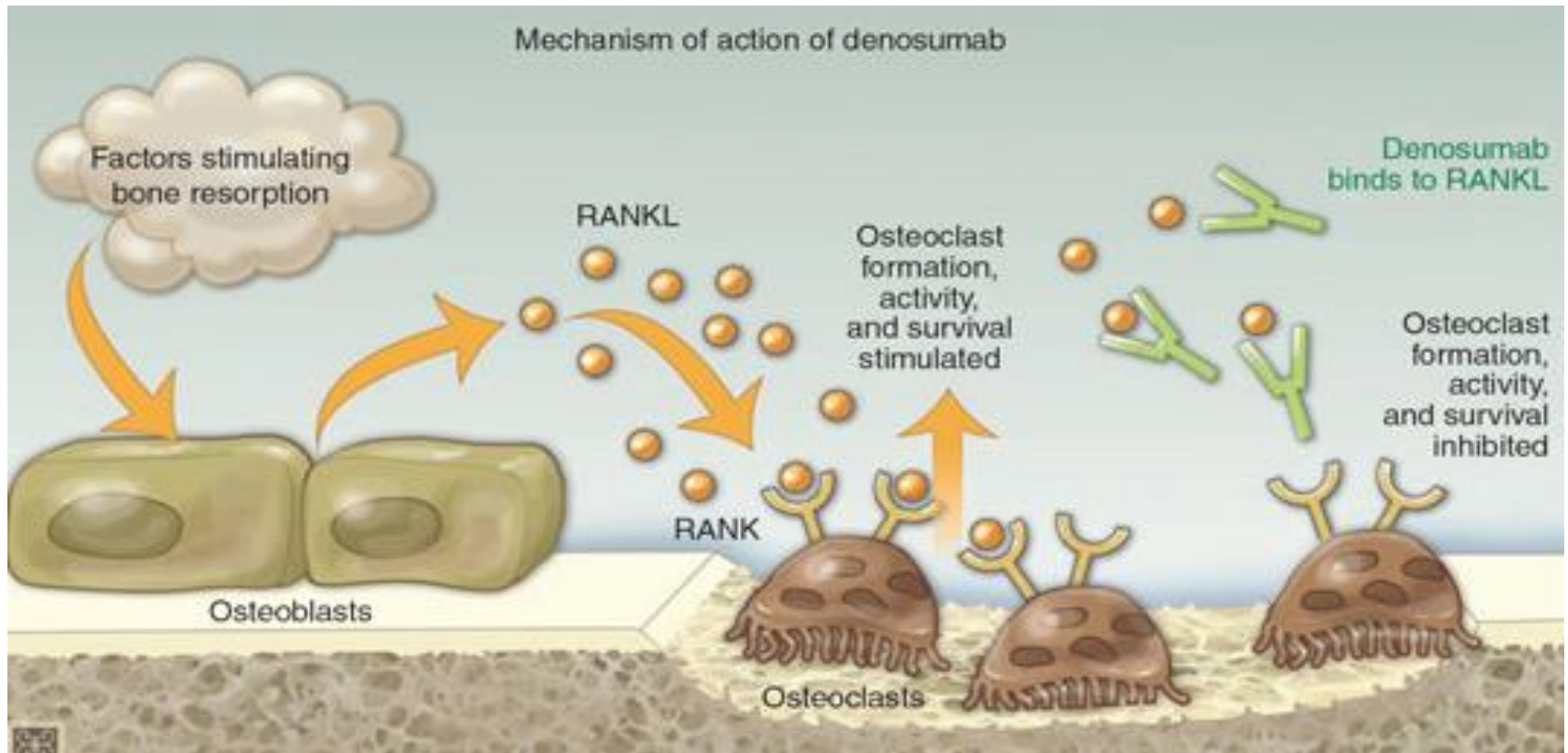
Small study: 44 boys and only 17 treated with bisphosphonate  
Cardiac meds and respiratory support not studied

Results unclear

# Bisphosphonate in DMD mouse models







## Denosumab (Prolia)

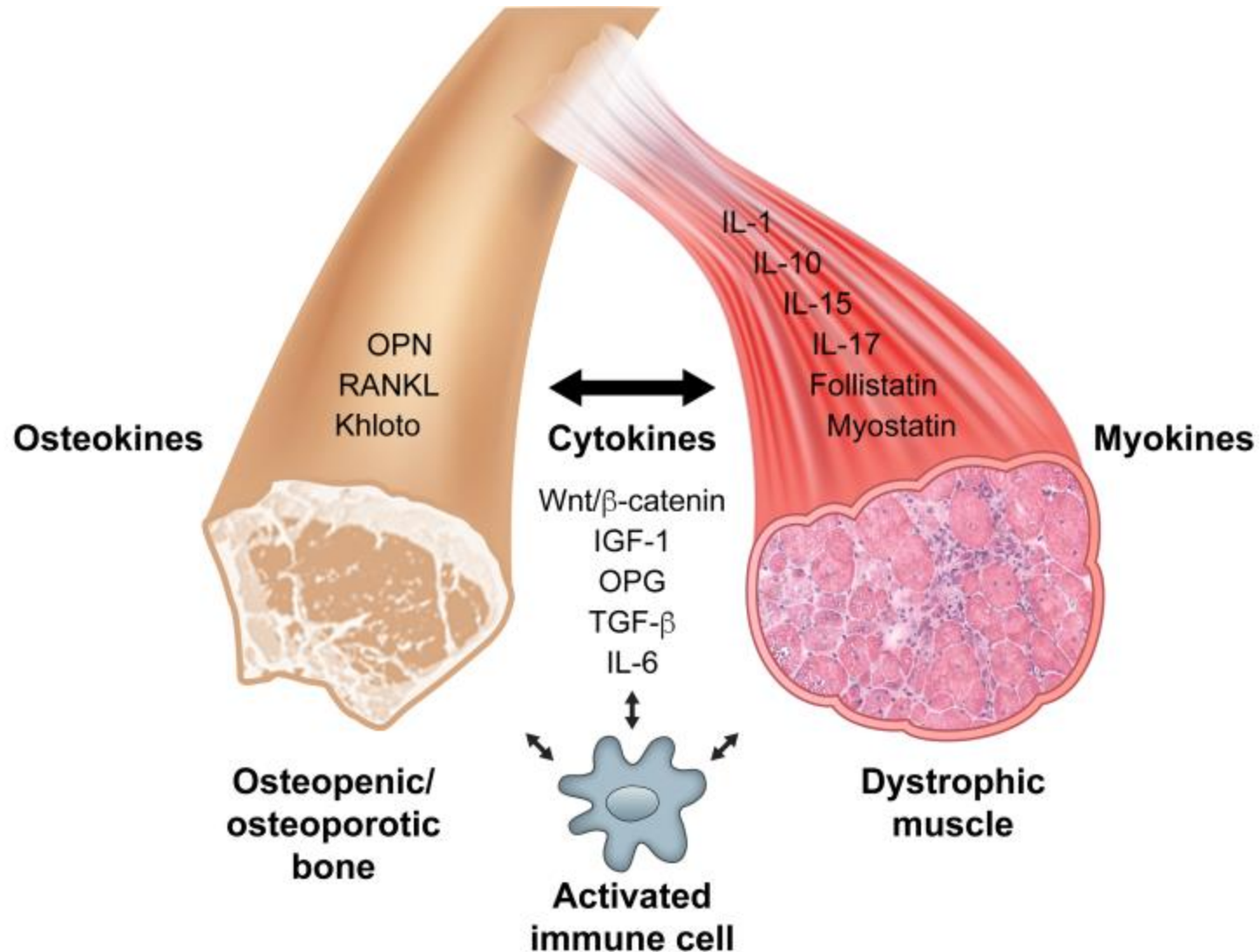
SC mode of administration

May be more potent than (oral) bisphosphonate

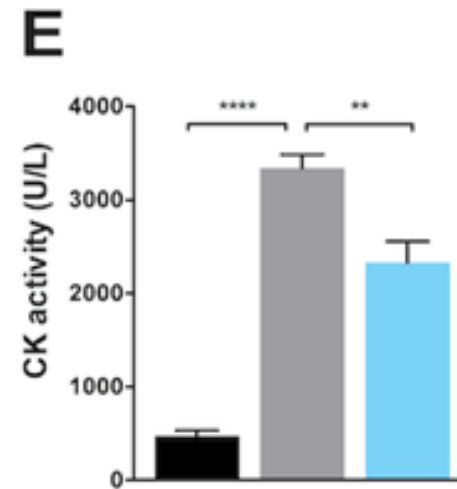
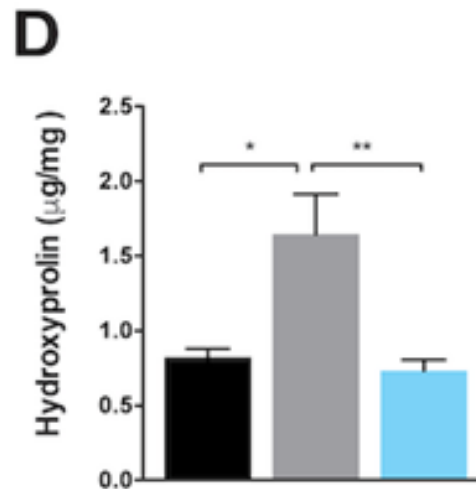
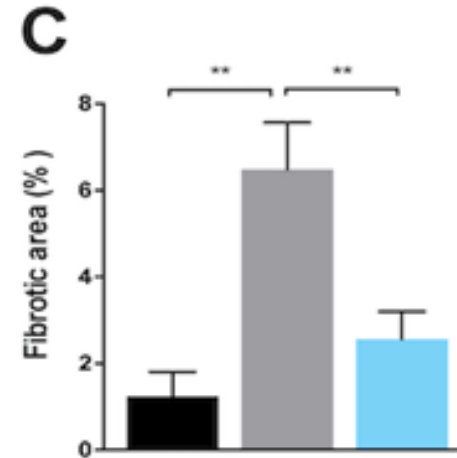
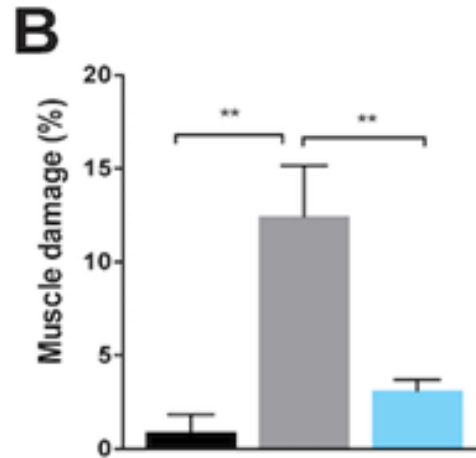
May have a direct impact on muscle in animal models of DMD

May have increased risk of fracture on discontinuation

# Cross talk between muscle and bone



WT   
  *mdx/utrn*+/- PBS   
  *mdx/utrn*+/- anti-RANKL [4mg/kg/3d]



## **Growth promoting agents**

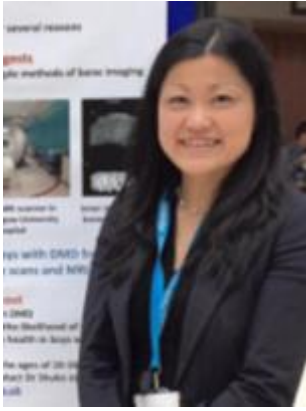
- Growth hormone is not routinely recommended for growth promotion in DMD
- Impact of growth hormone and IGF-1 to improve muscle function in DMD is unclear

## **Testosterone**

- Testosterone therapy in DMD leads to physical changes of puberty and some improvement in growth rate
- Testosterone improves bone development in DMD and may increase gain in muscle mass (but need more detailed study)

## **Bone protective therapy**

- Bisphosphonate therapy is currently indicated if there is evidence of fractures
- Targeting the RANKL pathway may be an opportunity to address bone and muscle for people with DMD.



S Joseph



J Dunne



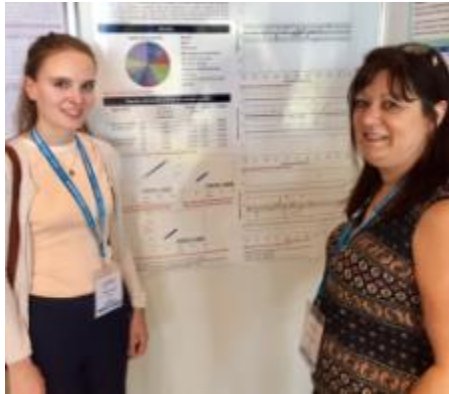
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