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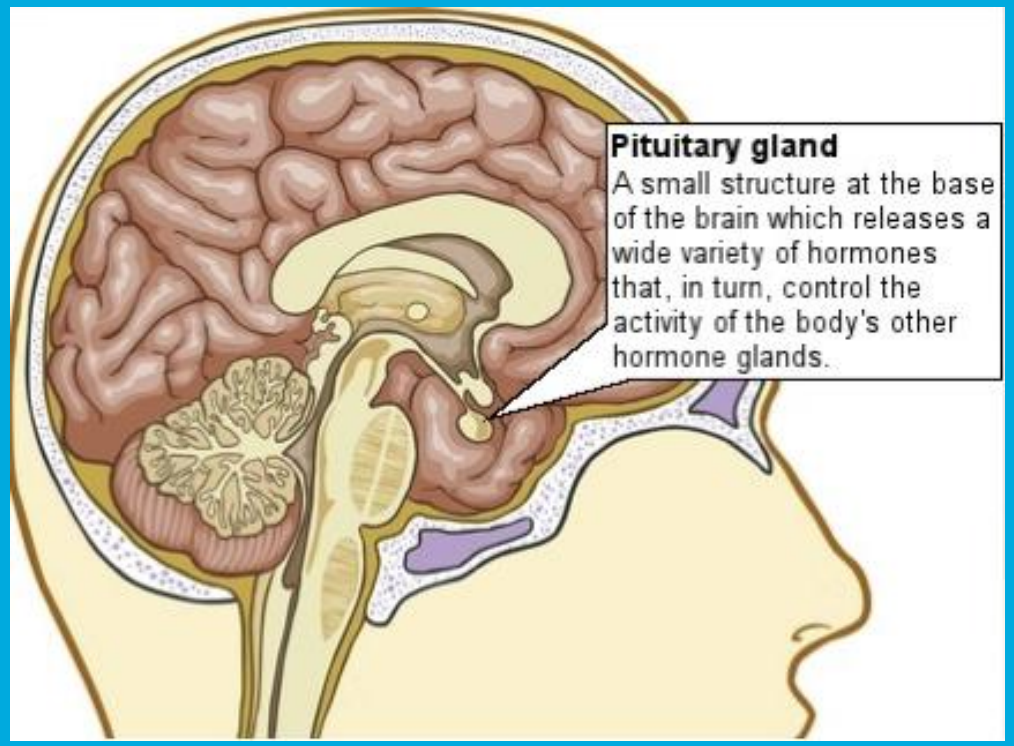
Endocrine care for DMD

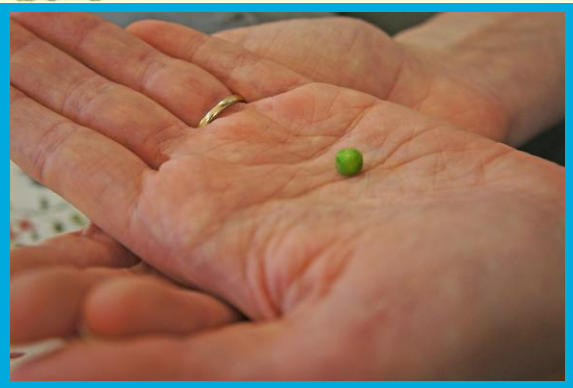
Sep 27, 2025

Prof. Dr. Anne Rochtus

SAMEN GRENZEN VERLEGGEN

Introduction to endocrinology





- Endocrinology = study of hormones
- What is a hormone?
  - Substances made by the body that keep you healthy
  - Growth, energy, mood, stress, blood sugar, and more

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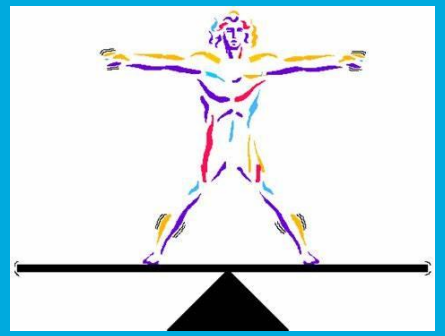
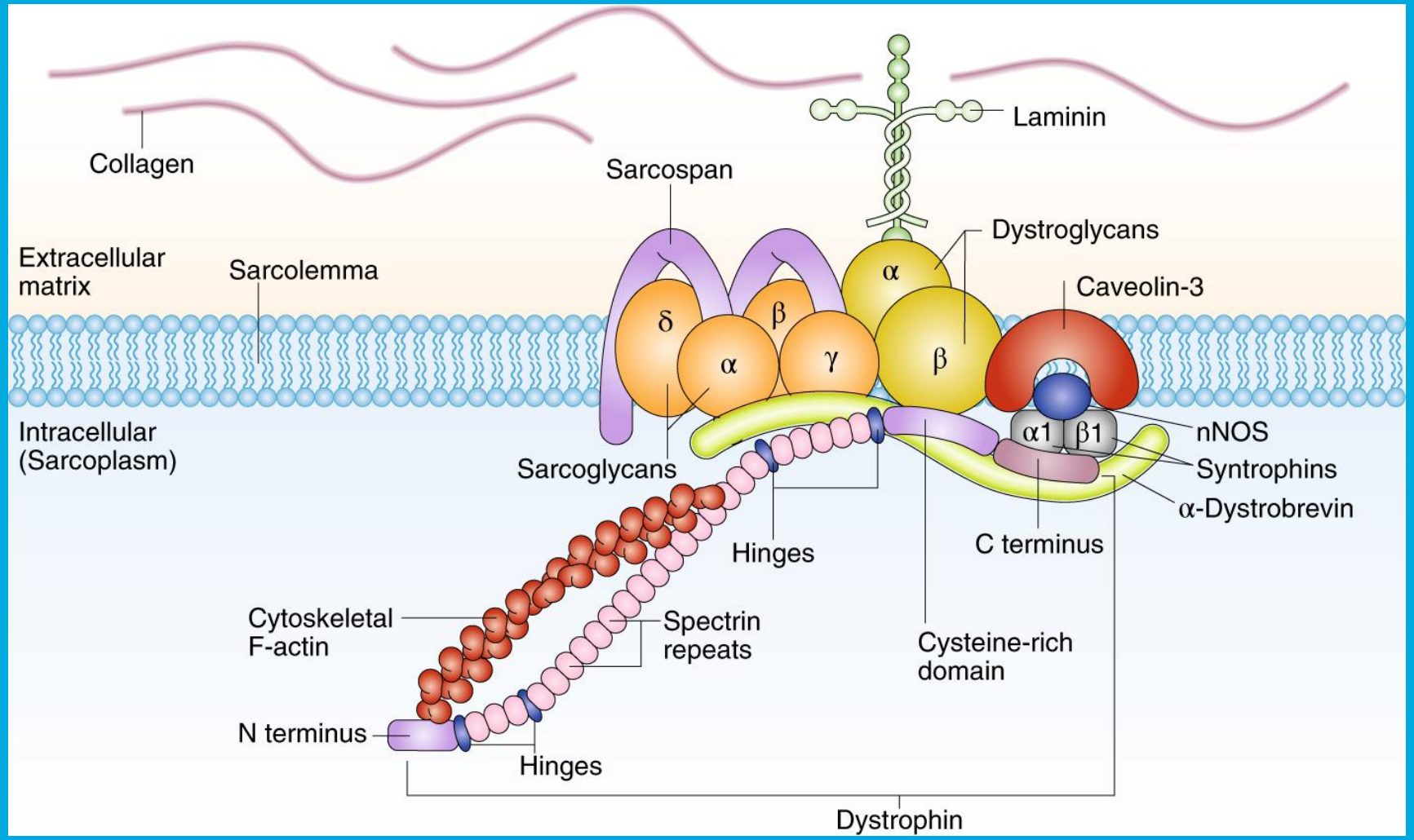
Homeostasis



Dystrophin

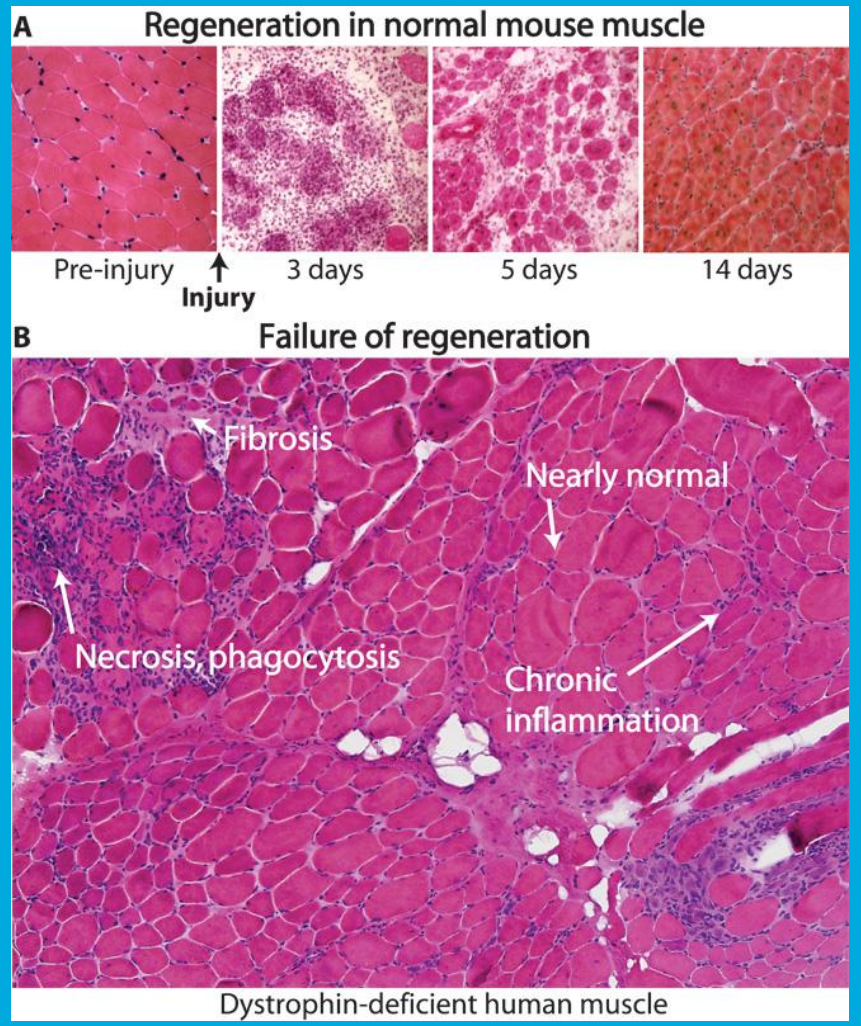


Davies et al. Nature 2006

Steroids in DMD

Inflammation plays a critical role in DMD progression

- DMD muscle consistently exhibit inflammatory changes and this is evident from birth
- Abnormal persistence of macrophages and infiltration of inflammatory cells



Benefits of corticosteroids in DMD

- Improve strength and timed **motor function** and delay the age at loss of ambulation
- Improve **upper limb function**
- Improve **pulmonary function**
- Reduce the need for **scoliosis surgery**
- Delay the onset of **cardiomyopathy**
- **Life expectancy**

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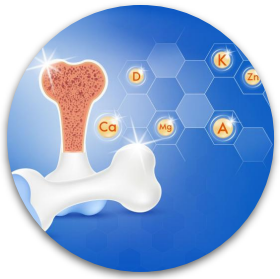
Endocrine side-effects of corticosteroids in DMD

Adrenal Insufficiency

Delayed Puberty

Growth delay



Bone Fragility

Metabolic Weight gain

Growth

- Short stature is common
- DMD patients are -1.08 SDS below population mean
- BMD patients are -0,27 SDS below population mean

-> Disease intrinsic effect

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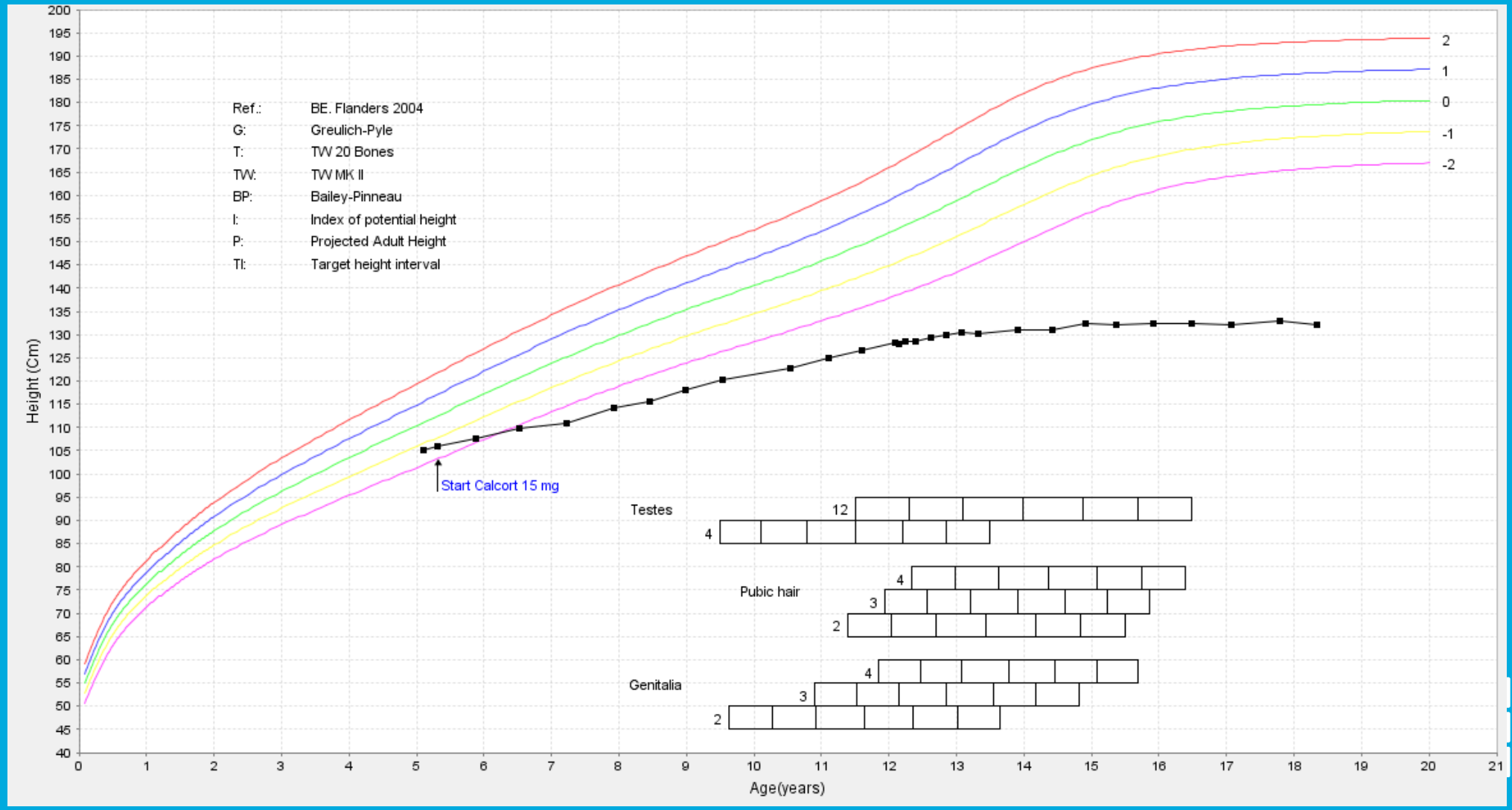
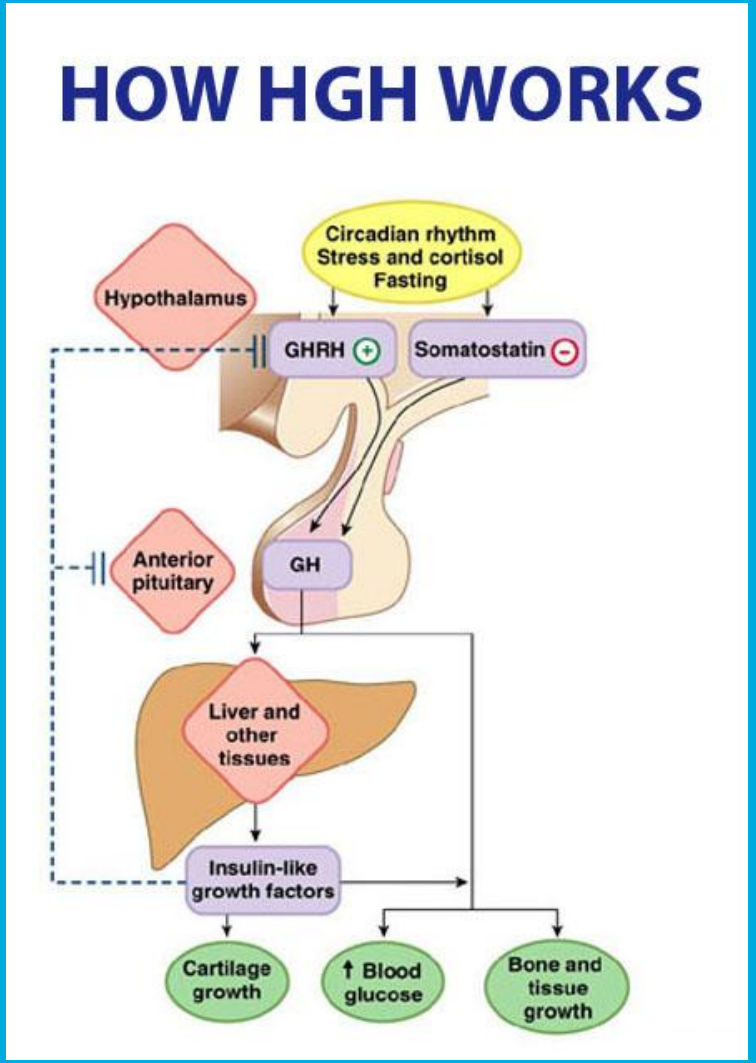
Steroids inhibit linear growth



Impaired linear growth

Mechanism

- Steroids impair chondrocyte differentiation, damages epiphyseal **growth plate**
- Steroids impair **GH secretion**
- Steroids make the body **less sensitive** for GH and IGF-1
- Chronic inflammation contributes to **hormonal resistance**



Puberty

- The time of life when a child experiences ***physical, mental & hormonal changes that mark a transition into adulthood.***
- The child ***develops secondary sexual characteristics and becomes able to have children.***
- Secondary sexual characteristics include:
  - ***Pubic, face, chest and armpit hair***
  - ***Voice changes***
  - ***Penis and testicle growth (boys)***
  - ***Breast growth (girls)***

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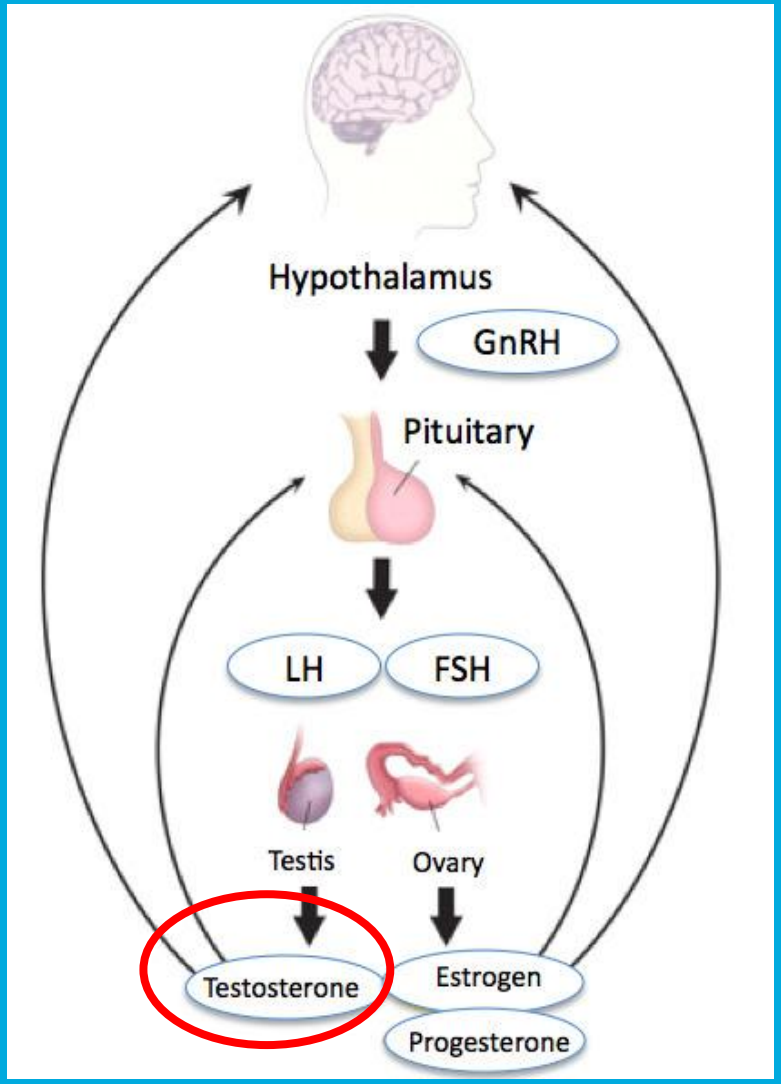
How does puberty work?

- Male puberty begins 9-14 yrs
- Hypothalamus
  - Gonadotropin releasing hormone (GnRH)
- Pituitary
  - Luteinizeing hormone (LH)
  - Follicular stimulating hormone (FSH)
- Testes
  - **Testosterone**
  - **Spermatogenesis**



Why is puberty important?

- Physical health
  - Strengthens bones
  - Supports muscle and heart health
  - Growth spurt
- Brain development
  - Necessary for last part of childhood brain development
- Functional considations
  - Make the penis grow
- Sexual and reproductive health
  - Sexual activity
  - Fertility

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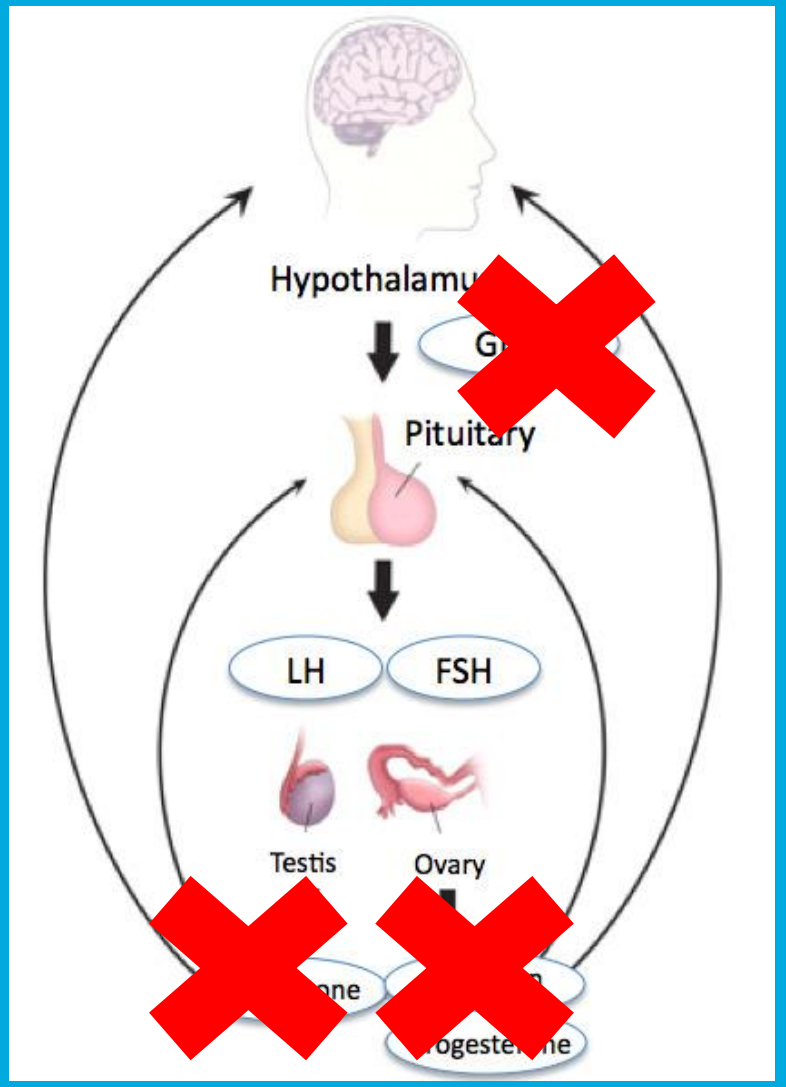
What happens to puberty in DMD?

- ***Puberty is not affected by DMD itself***
- Steroids delay/prevent puberty in most people
  - ***Block release of hormones*** (GnRH, LH, FSH) that stimulate ***testosterone***
- Puberty delay universal in boys on CS



How is delayed puberty diagnosed?

- **Physical exam**
  - Testicular volume < 4 ml
- **Bloodwork**
  - Low morning levels of testosterone, LH, FSH
- **X-Ray**
  - Delayed **bone age** on a left hand X-ray

Treatment of delayed puberty

Testosterone replacement regimens

Injections into muscle every 4 weeks

Start low and go slow!

- Blood test – and adjust dose/6 months
- **Mimic normal puberty**
- Reduce side effects, mood swings

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Testosterone in DMD

Goals

- Promote physical changes of **puberty**
- **Muscle** strengthening
- Improve **growth** velocity
- Improve **bone** health, optimize **peak bone mass**
- Improve **self esteem**

Testosterone treatment should be standard in boys with DMD, undergoing long-term glucocorticoid treatment.

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Are there side effects?

- ***Well tolerated***
- ***Side effects of treatment***
  - Bleeding, bruising, pain at needle site
  - Skin rash to the shot
  - High blood counts (red cells, platelets)
- ***Signs of puberty***
  - Pimples
  - Hair growth, body odor
  - Mood swings
  - Increased libido
  - ***Testicles will remain small***

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How long will I need treatment?

- Great question!
- Limited information in people with DMD
- Some people can stop treatment after puberty is attained
  - "Positive feedback"
- Studies suggest about 50% will need to stay on testosterone as long as on high dose steroids
- ***Individualized discussion***

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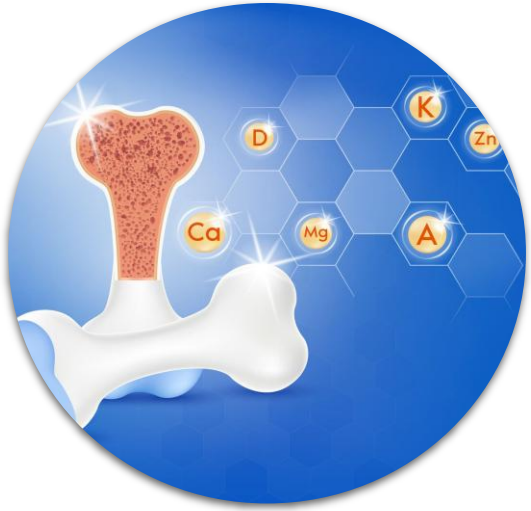
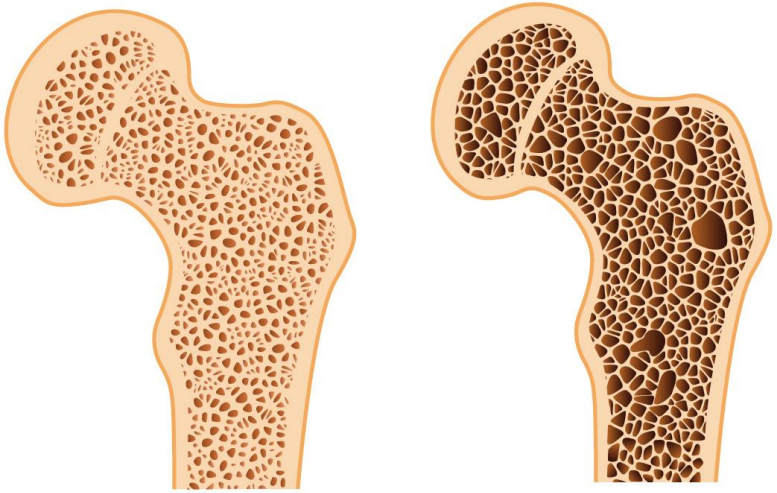
Conclusions puberty

- Puberty is a natural life-stage and is important **for physical, cognitive, and emotional health** into adulthood
- Most people with DMD on classic steroid regimens will need help **starting and maintaining puberty**
- Meet with your **pediatric endocrinologist at an early stage**

Bone fragility



- Predisposition for loss of bone strength
  - Nutrition & environment: vit D/calcium/sunlight
  - Myopathy - loss of ambulation
  - Prolonged glucocorticoid exposure
  - Delayed puberty
- Result
  - Fragility fractures
  - Vertebral fractures



Healthy bone

Osteoporosis

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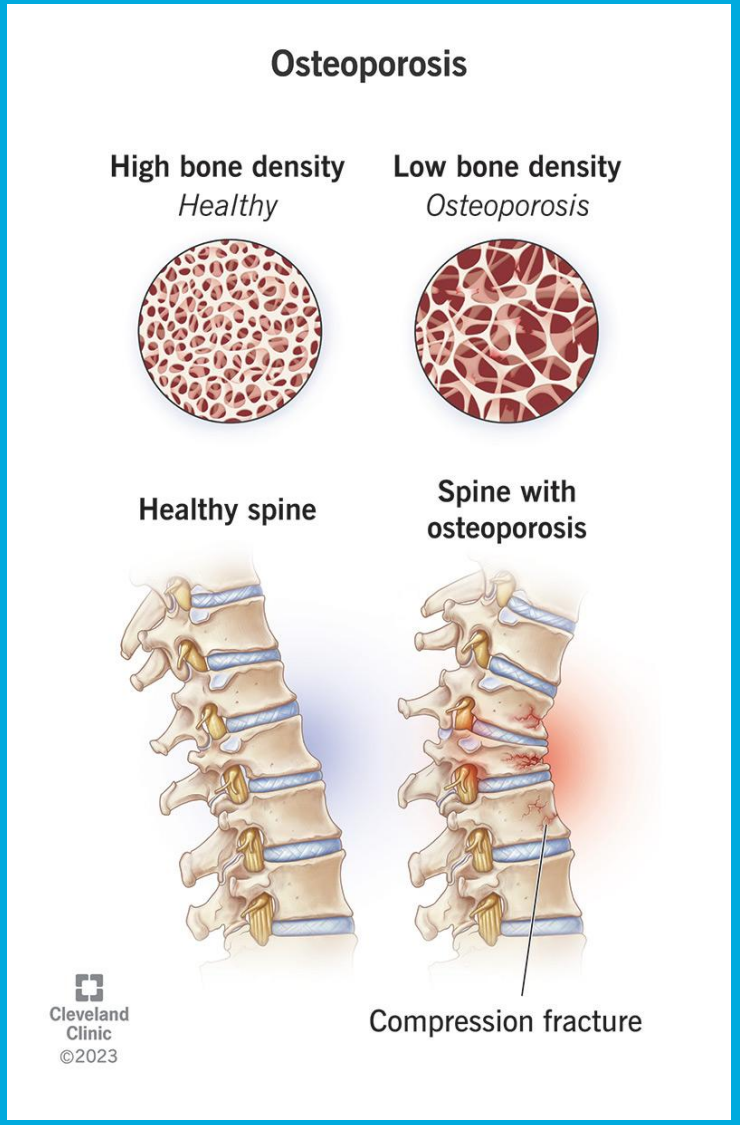
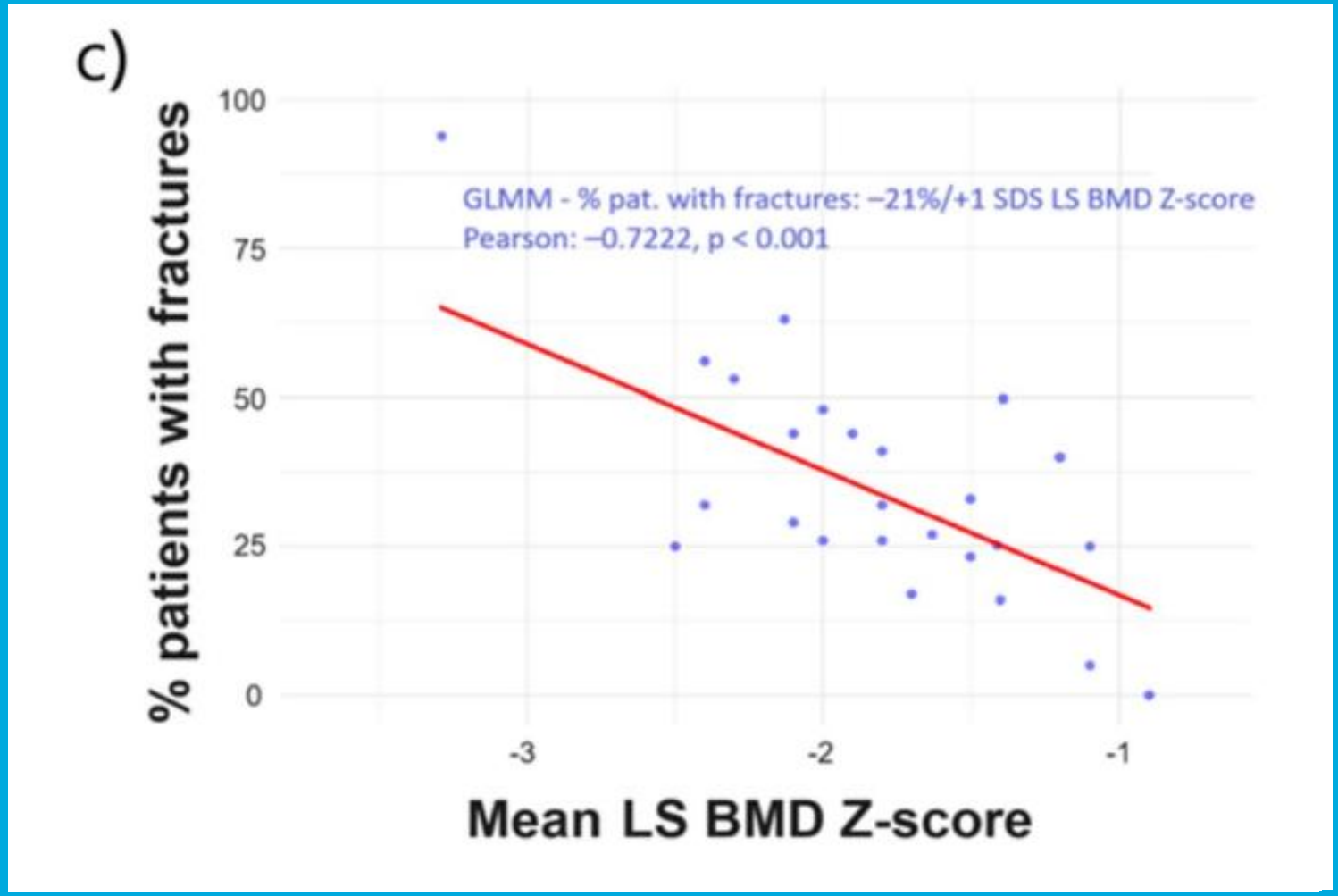
Fractures in DMD

- Disordered calcium homeostasis (immobilization)
- Inhibited bone formation, increased breakdown
- Types
  - Long bone fractures
    - » 20-25% by age 12
  - Vertebral fractures
    - » 58% at age 18 years



Risk factors for fractures



De Ford et al. Osteoporosis Int 2025

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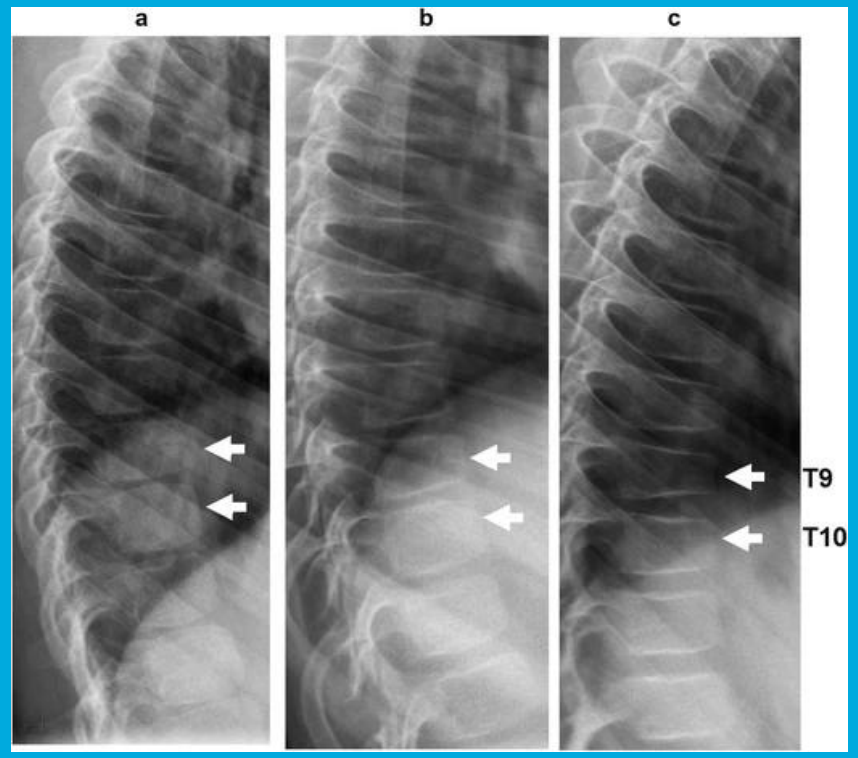
Timing of first vertebral fracture

Routine spine imaging	**No routine spine imaging**
Mean age 9.2 years	Mean age 12.3 years
Duration of GC 1.6 years	Duration of GC 5.3 years
Spine vBMD -0.3	Spine vBMD -2.5
No VF: 1.4 per person	No VF: 5.2 per person
Back pain in 40% (minimal)	Back pain 100% (significant)



Ma et al. Osteoporosis International 2017

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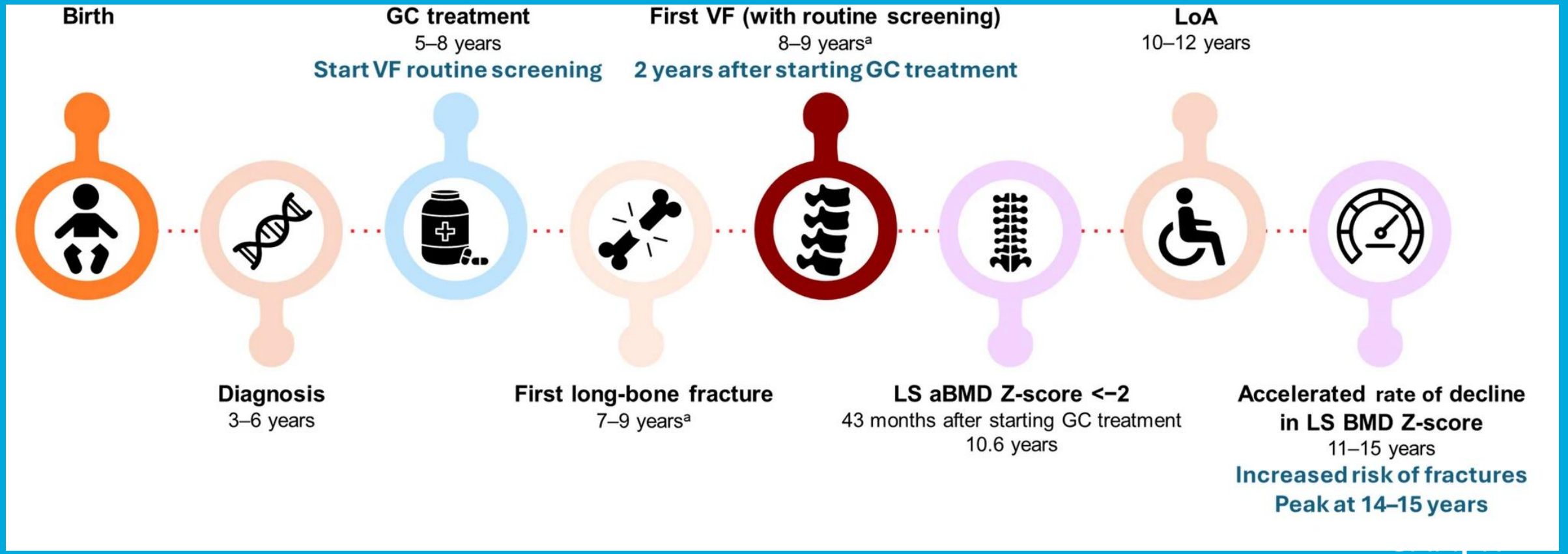


Ward et al. Osteroporosis Int. 2025

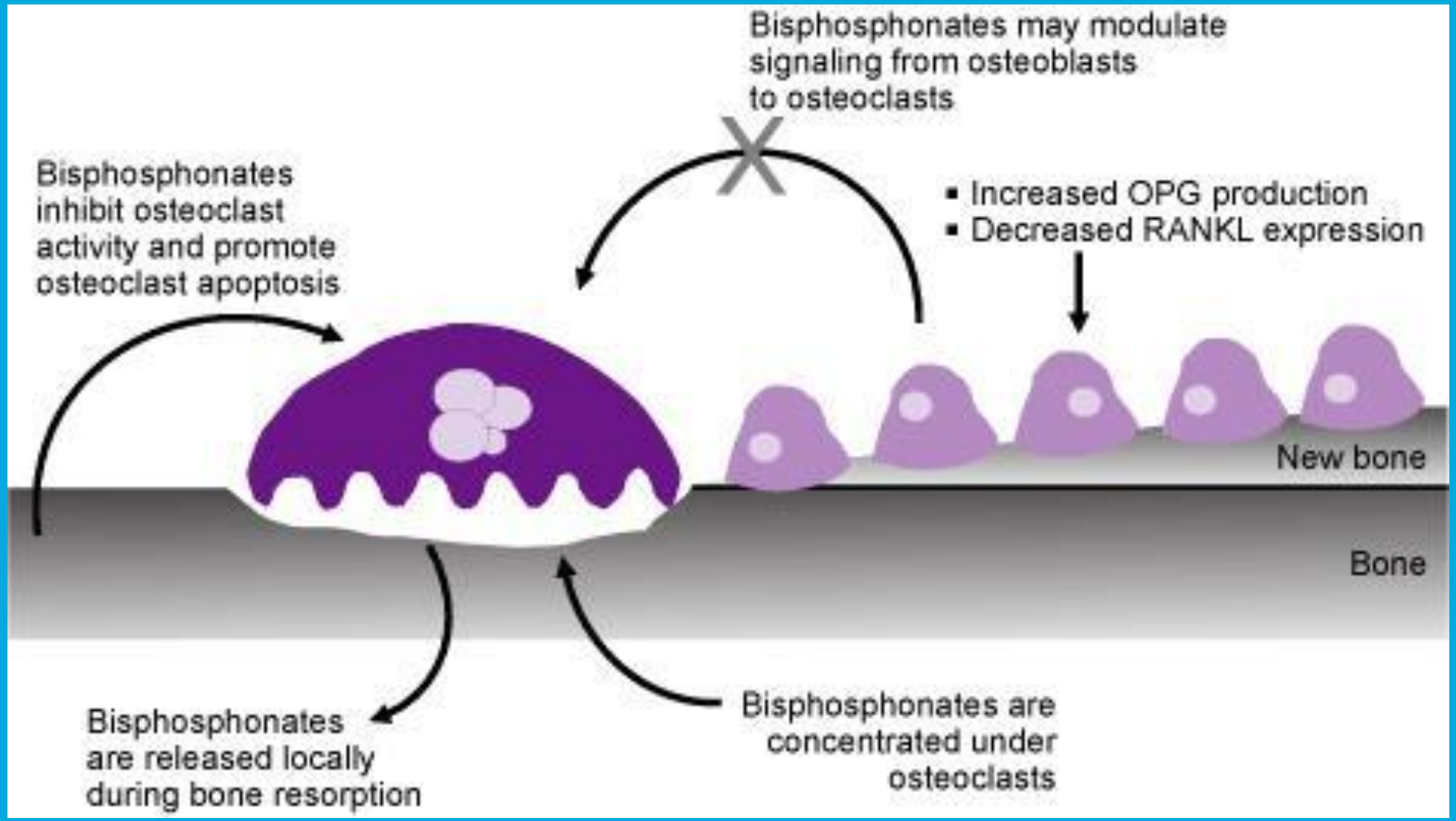
Calcium and vitamin D

- **Calcium**
  - Daily needs: adolescents typically need **1000–1300 mg/day**
  - Sources: **dairy products**, fortified foods, leafy greens
  - Supplements are needed if dietary intake or bone density is low
- **Vitamin D**
  - Recommended: **600-1000 IU/day**
  - Sunlight helps to produce vitamin D

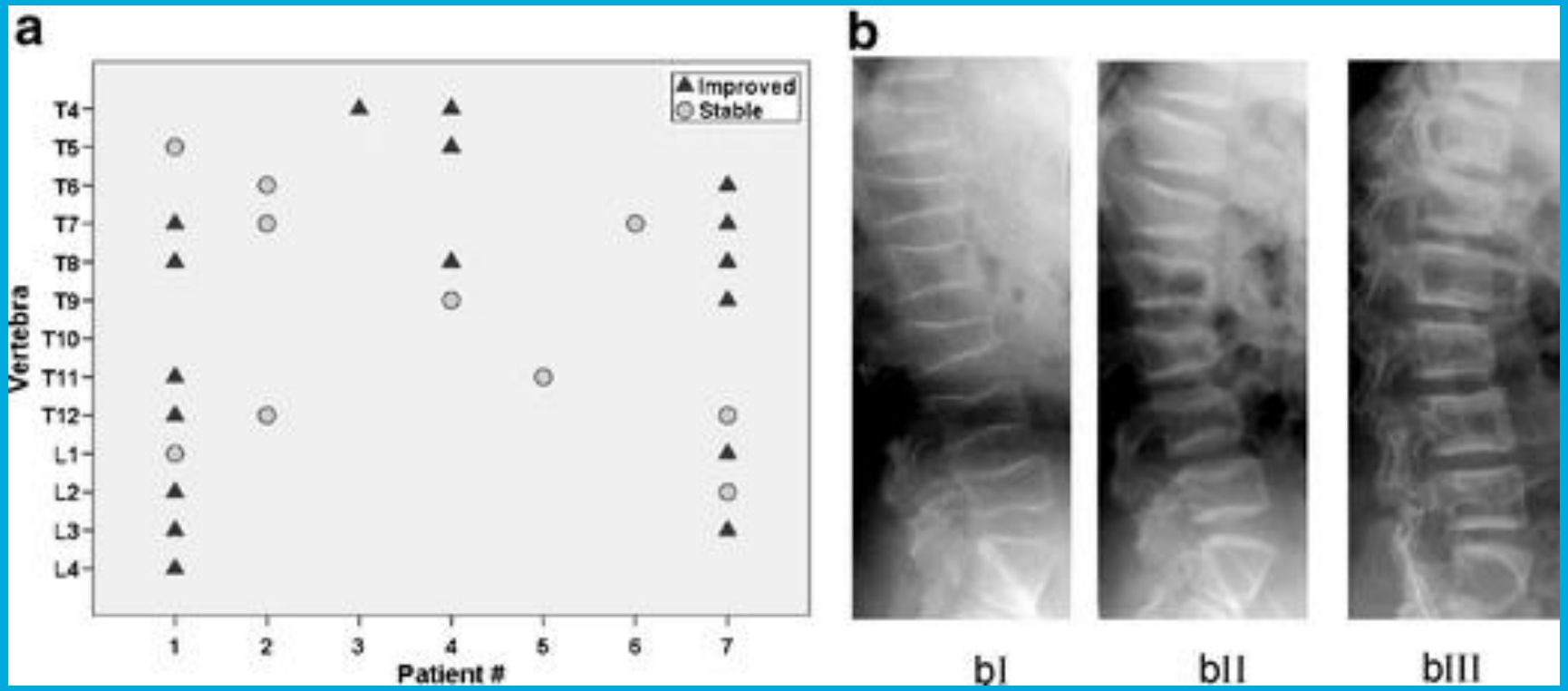
Zuivelproducten (per portie)	*Calcium*
50 g mozzarella	346 mg
1 sneetje harde kaas light (30 g)	279 mg
1 sneetje Belgische Gouda (30 g)	256 mg
1 glas melk (volle, halfvolle, magere) (150 ml)	180 mg
1 potje yoghurt (gemiddeld) (125 g)	178 mg
1 glas drinkyoghurt (magere) (150 ml)	176 mg
1 glas karnemelk (150 ml)	165 mg
1 glas chocolademelk (gemiddeld) (150 ml)	165 mg
30 g Belgische brie	135 mg
100 g plattekaas	116 mg
1 hoekje magere smeerkaas (20 g)	87 mg

Niet-zuivelproducten (per portie)	
200 g postelein (4 eetlepels, gekookt)	250 mg
200 g Chinese kool (5 eetlepels, gekookt)	250 mg
1 glas met calcium verrijkt fruitsap (150 ml)	219 mg
200 g broccoli (5 eetlepels)	200 mg
1 glas met calcium verrijkte sojadrink (150 ml)	165 mg
1 eetlepel tahin (sesampasta) (15 g)	134 mg
1 blikje zalm (85 g)	130 mg
150 g gekookte sojabonen (50 g gedroogd)	112 mg
200 g groene kool (gekookt)	106 mg
1 eetlepel sesamzaadjes (12 g)	94 mg
1 plakje tempeh (75 g)	83 mg

Bisphosphonate therapy



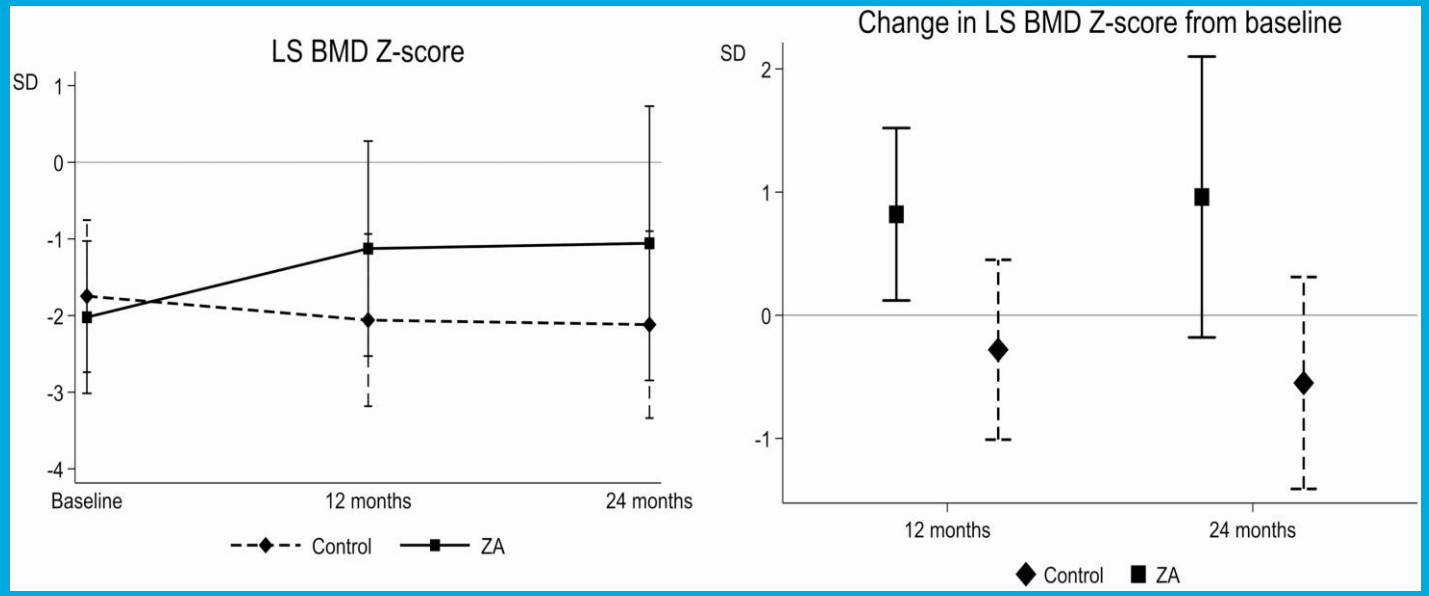
Bisphosphonate therapy in DMD



Back pain resolved in ALL patients
Improvement in DXA bone density
Stabilisation of structural parameters on bone histomorphometry
Reduction of bone formation markers
Incident vertebral fractures in previously normal vertebra

Sbrocchi et al. Osteoporos Int 2012.

Bisphosphonate therapy in DMD



Prophylactic IV bisphosphonates (ZA) **improve BMD** & **reduce fracture rates** in boys with DMD.

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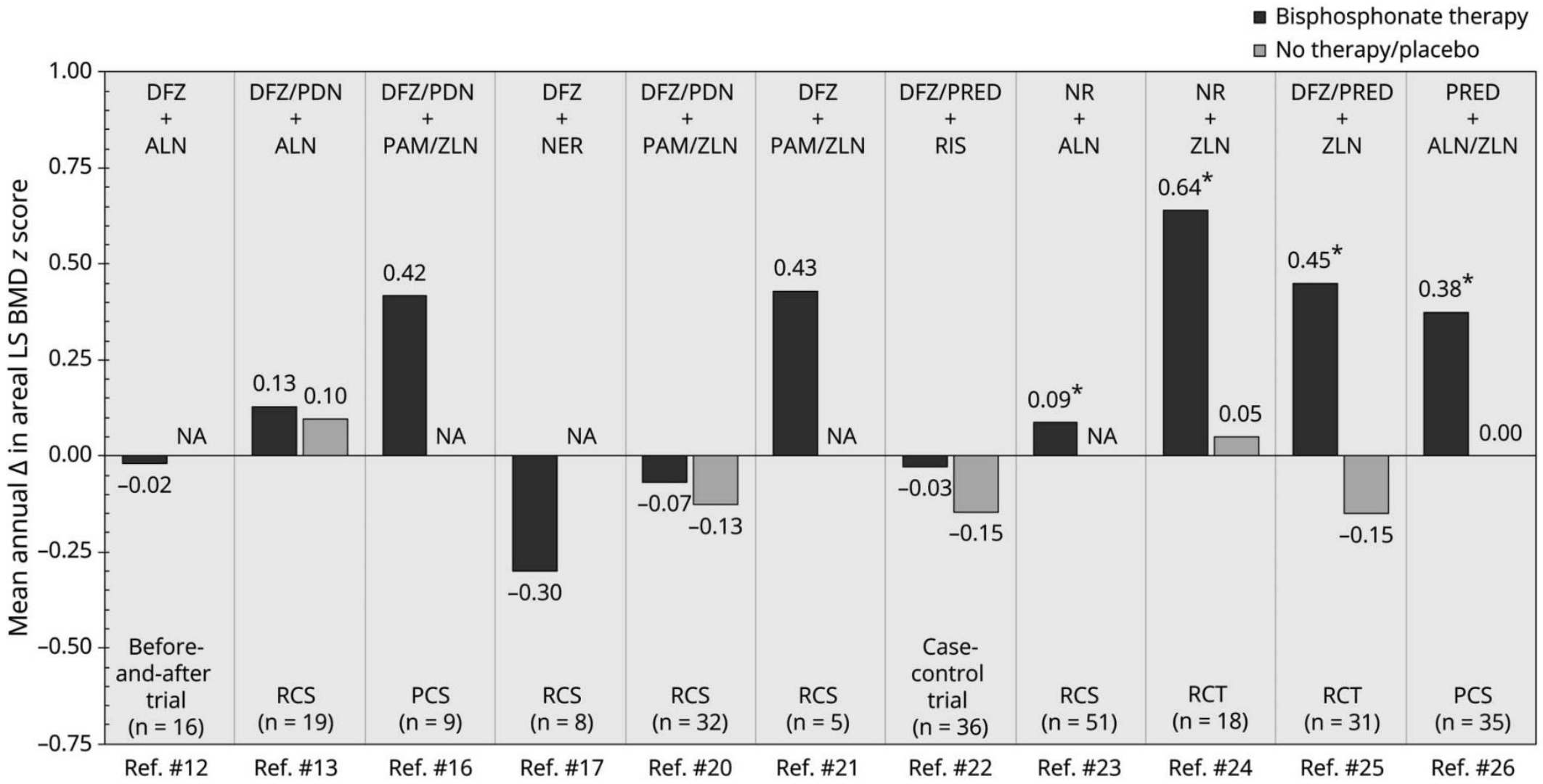
Zacharin et al. JCEM 2021

Figure 2 Mean Annual Change in Areal LS BMD Z Score in Glucocorticoid-Exposed Patients With DMD Treated With Bisphosphonates



ALN = Alendronate; BMD = Bone mineral density; DFZ = Deflazacort; DMD = Duchenne muscular dystrophy; LS = Lumbar spine; NA = Not applicable; NER = Neridronate; NR = Not reported; PAM = Pamidronate; PCS = Prospective cohort study; PDN = Prednisone; PRED = Prednisolone; RCS = Retrospective cohort study; RCT = Randomized controlled trial; RIS = Risedronate; ZLN = Zoledronate. * Statistically significant change.

Side-effects of bisphosphonates

SIGNS and **SYMPTOMS**

- Fever and **flu-like symptoms**
- Low levels of calcium in your blood (hypocalcaemia)
- Bone and joint pain
- **Diarrhoea**
- Lack of energy and strength
- **Feeling sick** (nausea)
- Irritation of the food pipe (oesophagus)

WHAT YOU CAN DO:

- **Drink** enough (>1.5L) **water**
- **Calcium** supplementation
- **Pain killer**
- **Rest**
- **Increase** the dose of **corticosteroids**
  - Calcort x2 (after 12h)
  - Solucortef IV (during hospitalization)

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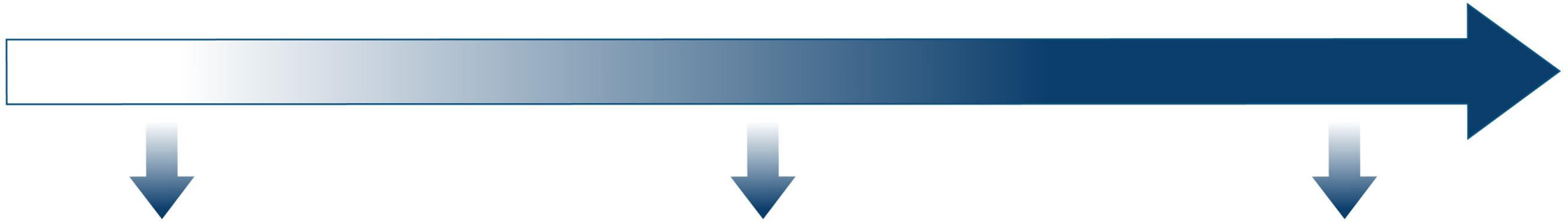
The Shifting Standard of Care for Osteoporosis Management in DMD



2010

- Spine x-ray if back pain or kypho-scoliosis
- Treat symptomatic vertebral fractures with IV BP therapy

Tertiary prevention

Bushby K, et al. *Lancet Neurol*. 2010; 9(2): 177-89

2018

- Monitor from the time of diagnosis or GC initiation with periodic spine x-rays
- Treat vertebral fractures with IV BP therapy
- Treat a first long bone fracture with IV BP therapy (no need for multiple fractures)

Secondary prevention

Birnkrant DJ, et al. *Lancet Neurol*. 2018; 17(4): 347-61.

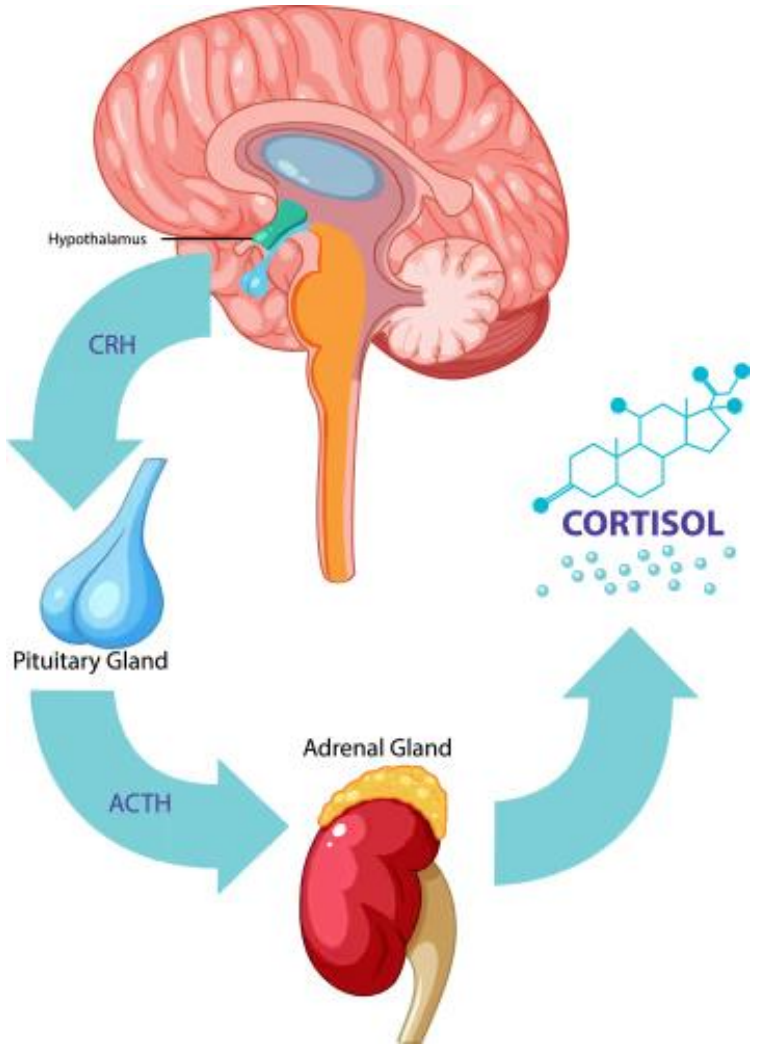
2024

- Determine how to prioritize *boys not already on bone protection therapy* and intervene prior to first fractures

Primary prevention

Adrenal insufficiency

- Glucocorticoids (< adrenal gland): carbohydrate metabolism, immune response and inflammation.
- Prolonged corticosteroid use inhibits the body's natural cortisol secretion.
- Cortisol levels may be insufficient during times of physiological stress.



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Deflazacort (Calcort)

A derivative of prednisolone with similar anti-inflammatory and muscle preserving effects but:

- Better preservation of bone mass
- Less weight gain
- Better lipid profiles
- Less glucose intolerance
- Less scoliosis
- More cataracts

6 mg Deflazacort = 5 mg Prednisone

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Risk factors for adrenal crisis include:

- Dehydration
- Infection and other physical stress
- Injury to the adrenal or pituitary gland
- Not taking exogenous steroids
- Surgery
- Trauma

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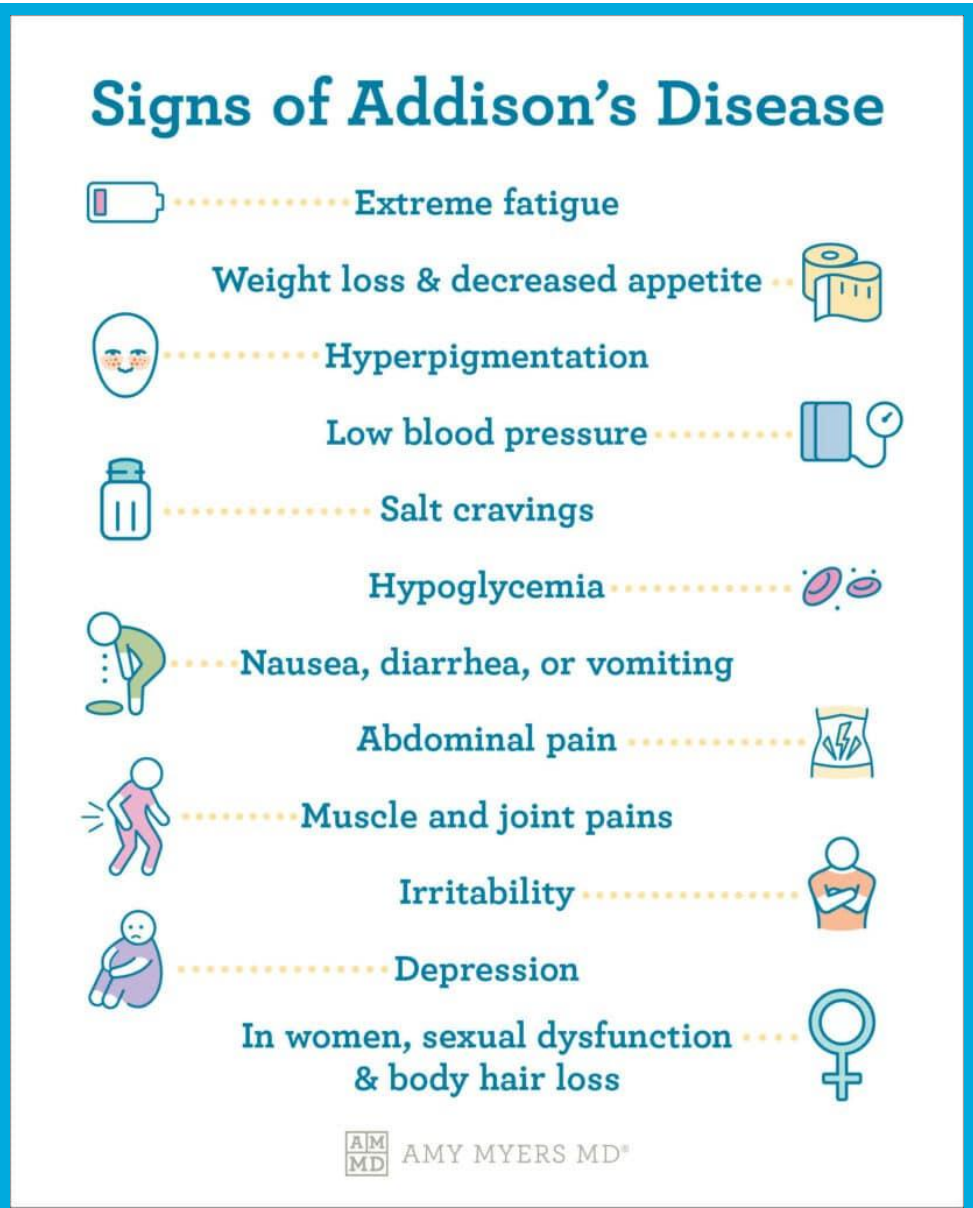

EXTRA STRESS-STEROIDS

- **Deflazacort (Calcort) extra**
  - Double dose
  - Triple dose

  Best spread out over time
  E.g. 8 a.m. – 8 p.m.
- **Drink plenty of fluids**
- If it doesn't work: vomiting/drowsiness → **hospital** → Solucortef IV

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Metabolic consequences

Obesity

- **Reduced mobility**: as muscle weakness progresses, physical activity declines, leading to lower energy expenditure
- **Steroid therapy**: glucocorticoids, while beneficial for slowing disease progression, increase appetite and promote fat accumulation
- **Altered body composition**: even with normal or low BMI, patients may have increased fat mass and reduced lean muscle

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Metabolic consequences

Insulin resistance

- **Steroid-induced insulin resistance**: long-term corticosteroid use impairs insulin signaling and glucose uptake
- **Reduced muscle mass**: skeletal muscle is a major site of glucose disposal; its loss contributes to impaired glucose metabolism
- **Fat accumulation**: visceral fat promotes systemic inflammation and worsens insulin sensitivity

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Strategies

Nutritional counseling: Tailored diets to manage weight and support bone and muscle health.

Physical therapy: Even passive movement and stretching can help maintain metabolic function.

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Vamorolone clinical data

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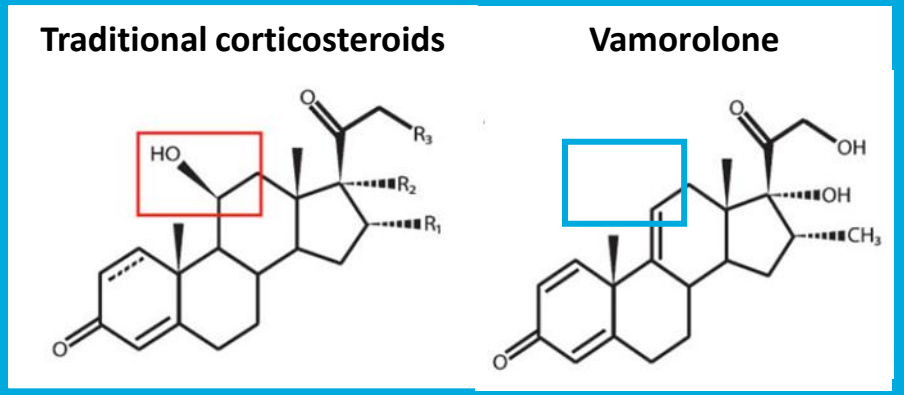
Vamorolone

- Lacks hydroxyl group at C11 → prevents key hydrogen bonds with glucocorticoid (Asn564) and mineralocorticoid (N770) receptors.
- **Weak transactivation** → reduced gene transcription and fewer side effects.
- **Preserved transrepression** → maintains anti-inflammatory efficacy.



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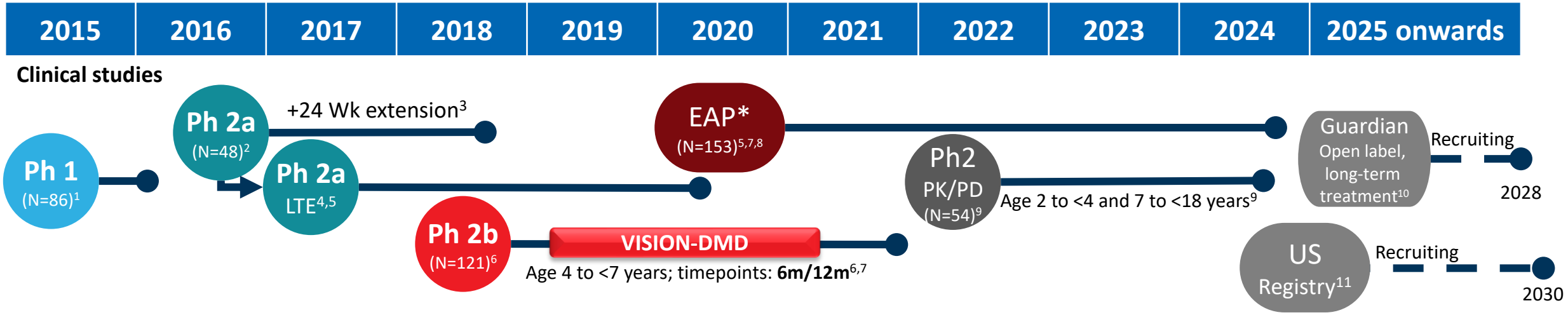
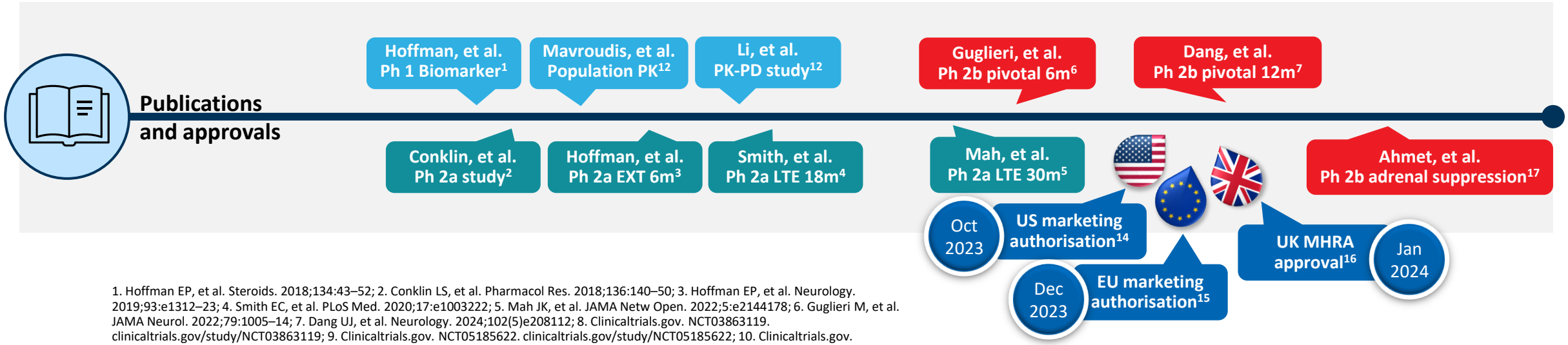
Vamorolone clinical studies and publications in DMD





1. Hoffman EP, et al. Steroids. 2018;134:43–52; 2. Conklin LS, et al. Pharmacol Res. 2018;136:140–50; 3. Hoffman EP, et al. Neurology. 2019;93:e1312–23; 4. Smith EC, et al. PLoS Med. 2020;17:e1003222; 5. Mah JK, et al. JAMA Netw Open. 2022;5:e2144178; 6. Guglieri M, et al. JAMA Neurol. 2022;79:1005–14; 7. Dang UJ, et al. Neurology. 2024;102(5)e208112; 8. Clinicaltrials.gov. NCT03863119. clinicaltrials.gov/study/NCT03863119; 9. Clinicaltrials.gov. NCT05185622. clinicaltrials.gov/study/NCT05185622; 10. Clinicaltrials.gov. NCT06713135. clinicaltrials.gov/study/NCT06713135; 11. Clinicaltrials.gov. NCT06564974. clinicaltrials.gov/study/NCT06564974. 12. Mavroudis PD, et al. J Clin Pharmacol. 2019;59:979–88; 13. Li X, et al. J Clin Pharmacol. 2020;60:1385–9610; 14. FDA. New drug approvals 2023. Available at: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2023; 15. Vamorolone EPAR Product Information. Available at: https://www.ema.europa.eu/en/documents/product-information/agamree-epar-product-information_en.pdf; 16. Vamorolone. MHRA Summary of Product Characteristics version April 2025; 17. Ahmet A, et al. J Clin Endocrinol Metabol. 2024; 110(2):334–44 (all accessed January 2025).

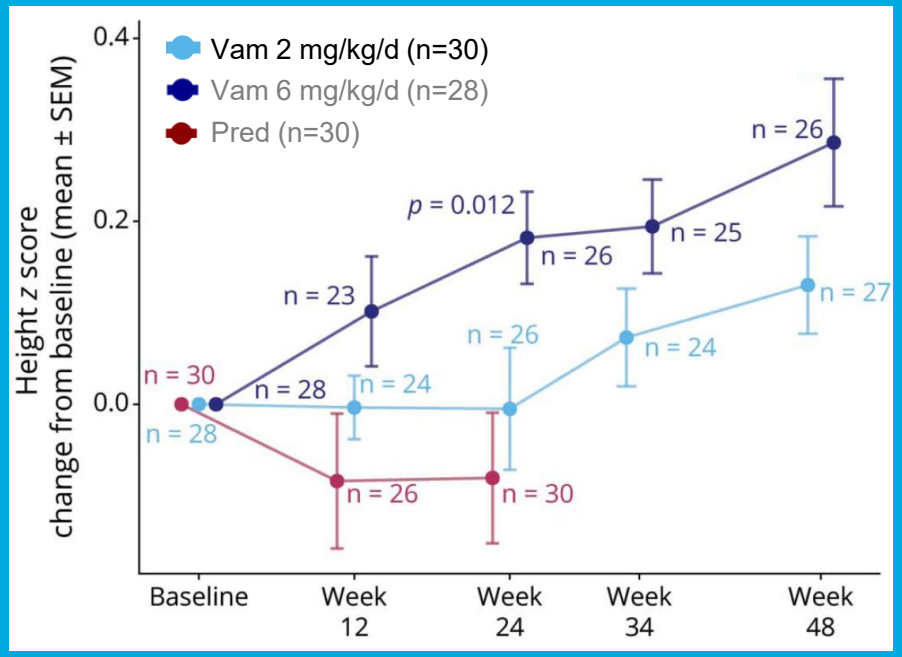
*EAP included patients from the Phase 2a and VISION-DMD trials.
DMD, Duchenne muscular dystrophy; EAP, expanded access protocol; Est, estimated; EU, European Union; m, month; MHRA, Medicines and Healthcare products Regulator Agency; PD, pharmacodynamic; PK, pharmacokinetic; Ph, phase; UK, United Kingdom; US, United States.

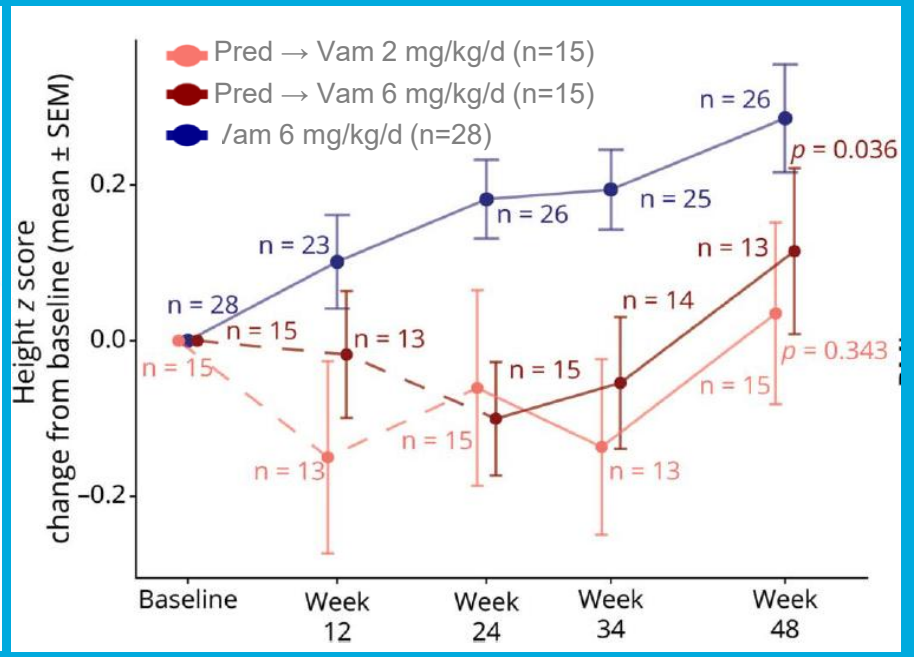
santhera
THEIR FUTURE - OUR FOCUS

NP-ALL-DMD-VAM-0019; date of preparation: July 2025

Vamorolone: continued growth

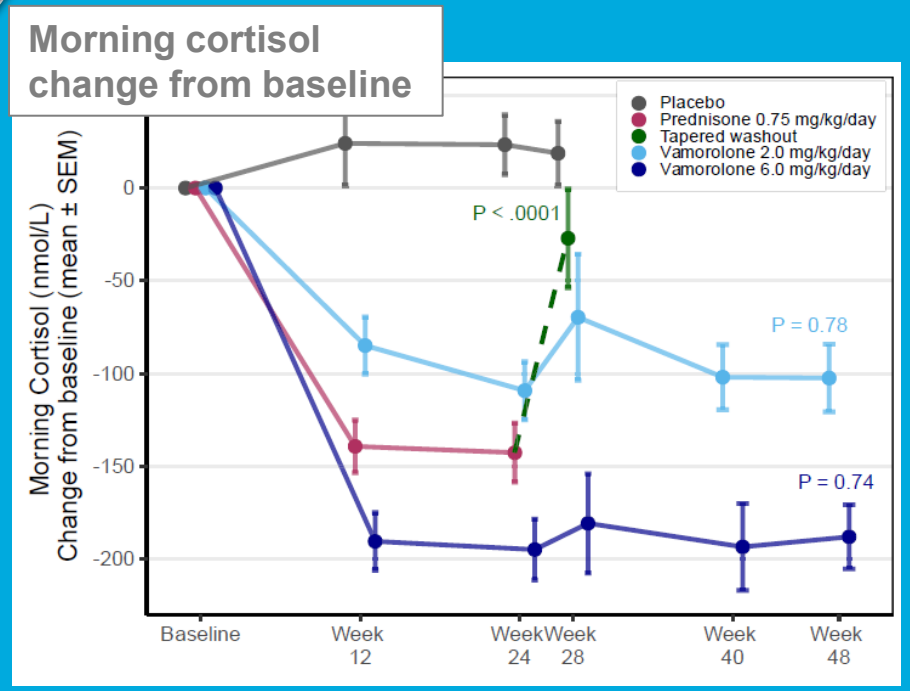
Change in height z-score from baseline*

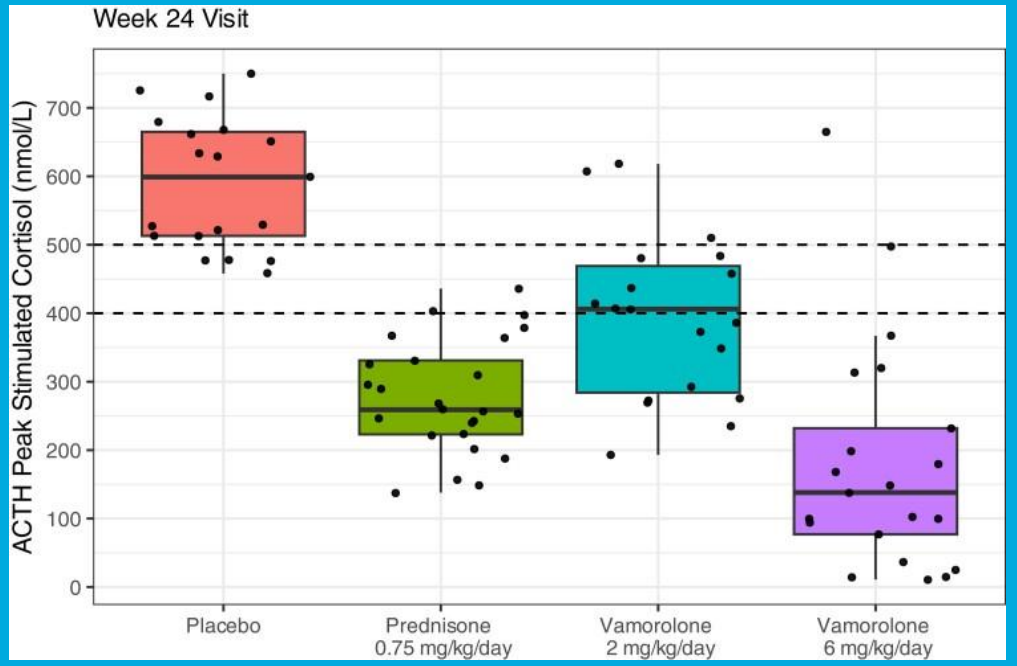




Dang et al. Neurology 2024.

Vamorolone: adrenal insufficiency



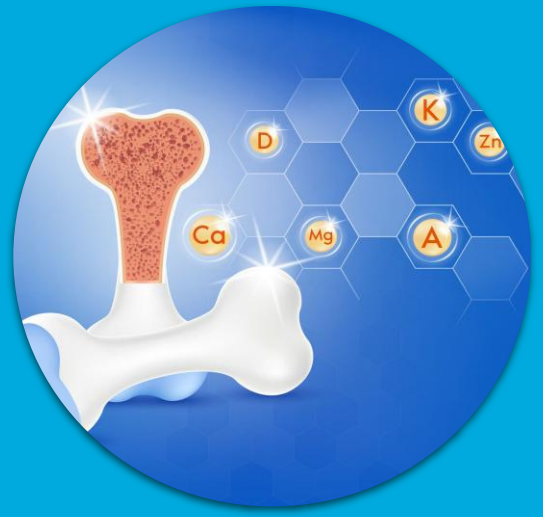


Vamorolone causes adrenal suppression

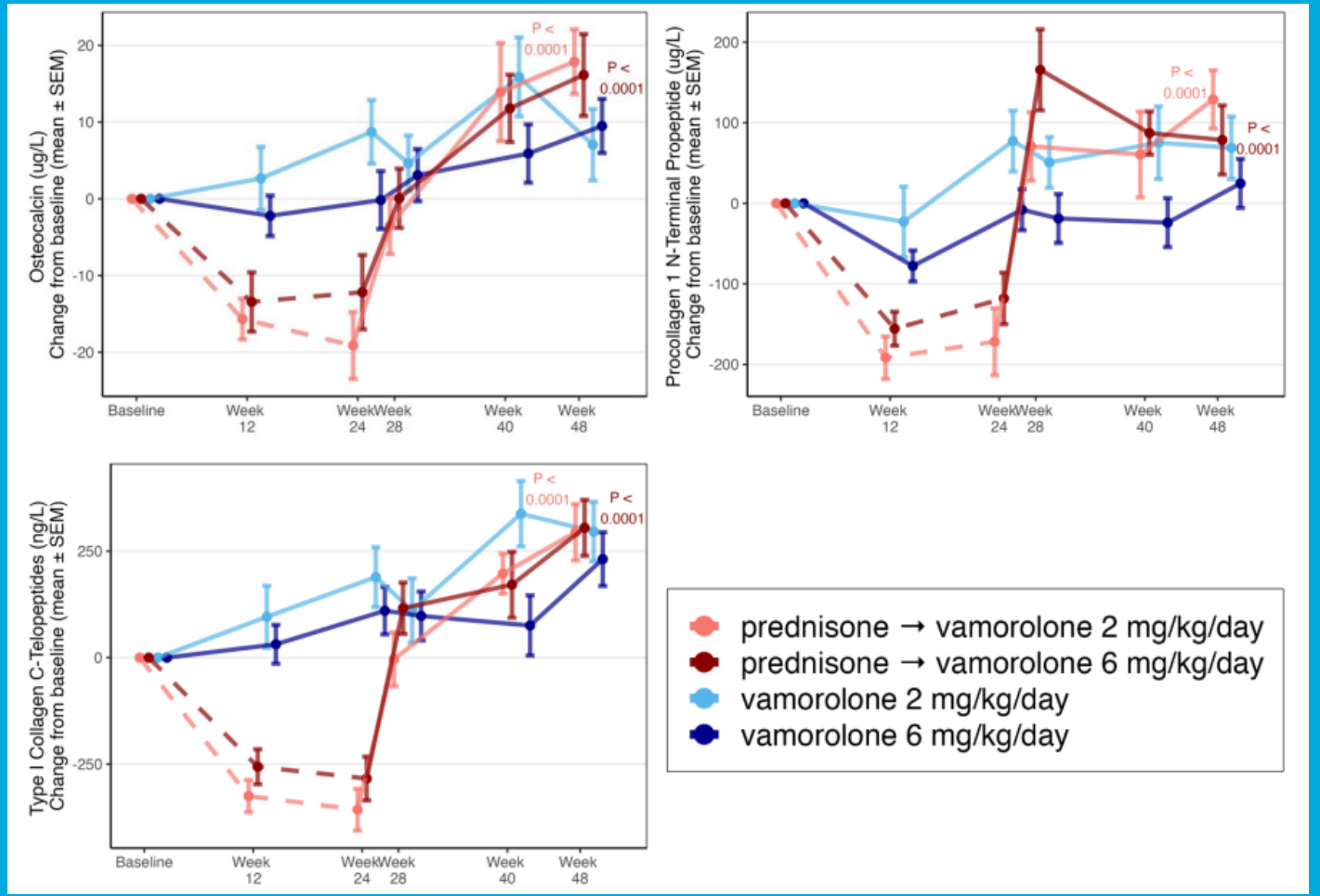
Adrenal insufficiency education and hydrocortisone stress dosing guidelines are essential

Ahmet et al. J. Clin Endocrinol Metab 2024

Vamorolone: effect on bone



- Serum bone markers were maintained
- After 2.5 years of treatment with vamorolone, the burden of vertebral fractures **appeared** to be reduced compared to daily prednisone and deflazacort

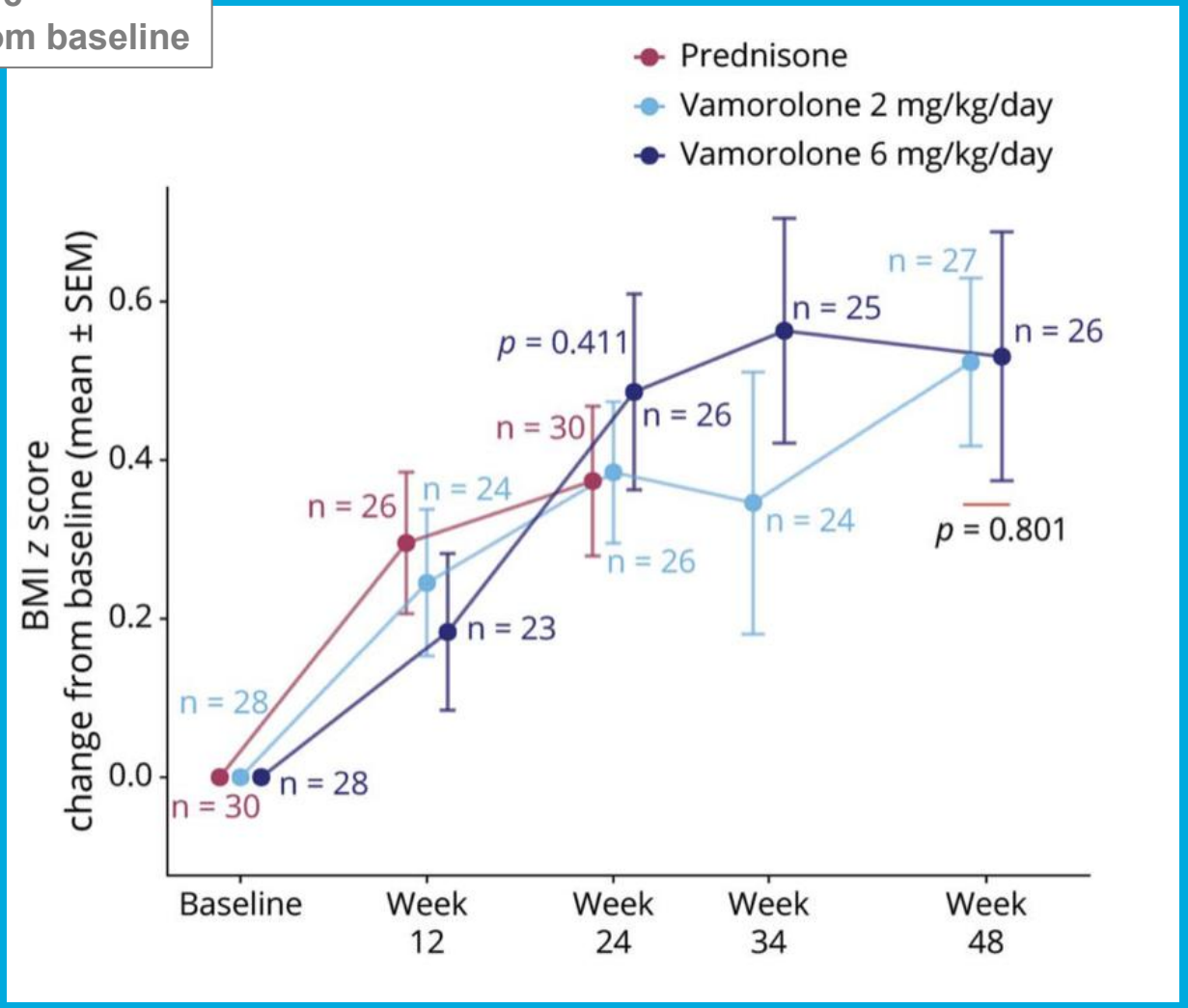


Dang et al. Neurology 2024.

Vamorolone: effect on BMI

BMI increased up to week 24 in both vamorolone dose groups and in the prednisone group

BMI z-score change from baseline



Dang et al. Neurology 2024.

Clinical trials with vamorolone

- Similar motor efficacy
- Less impact on growth and bone markers
- Well tolerated

- Adrenal suppression still present, even more severe
- Long-term bone and puberty effects still under investigation

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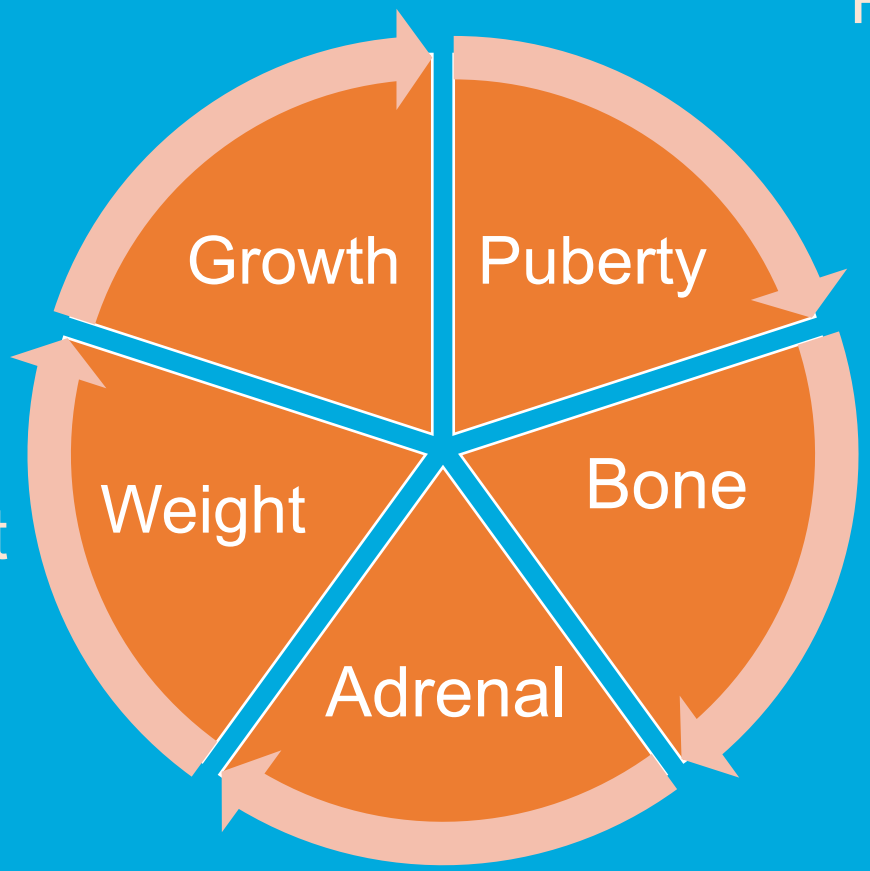
Endocrine care for DMD



Testosteron

Psychological care

Calcium
Vitamin D
Zoledronic Acid

Alertness
Stress dose

Healthy diet
Metformin?

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UZ LEUVEN

Thank you for your attention!

Questions?

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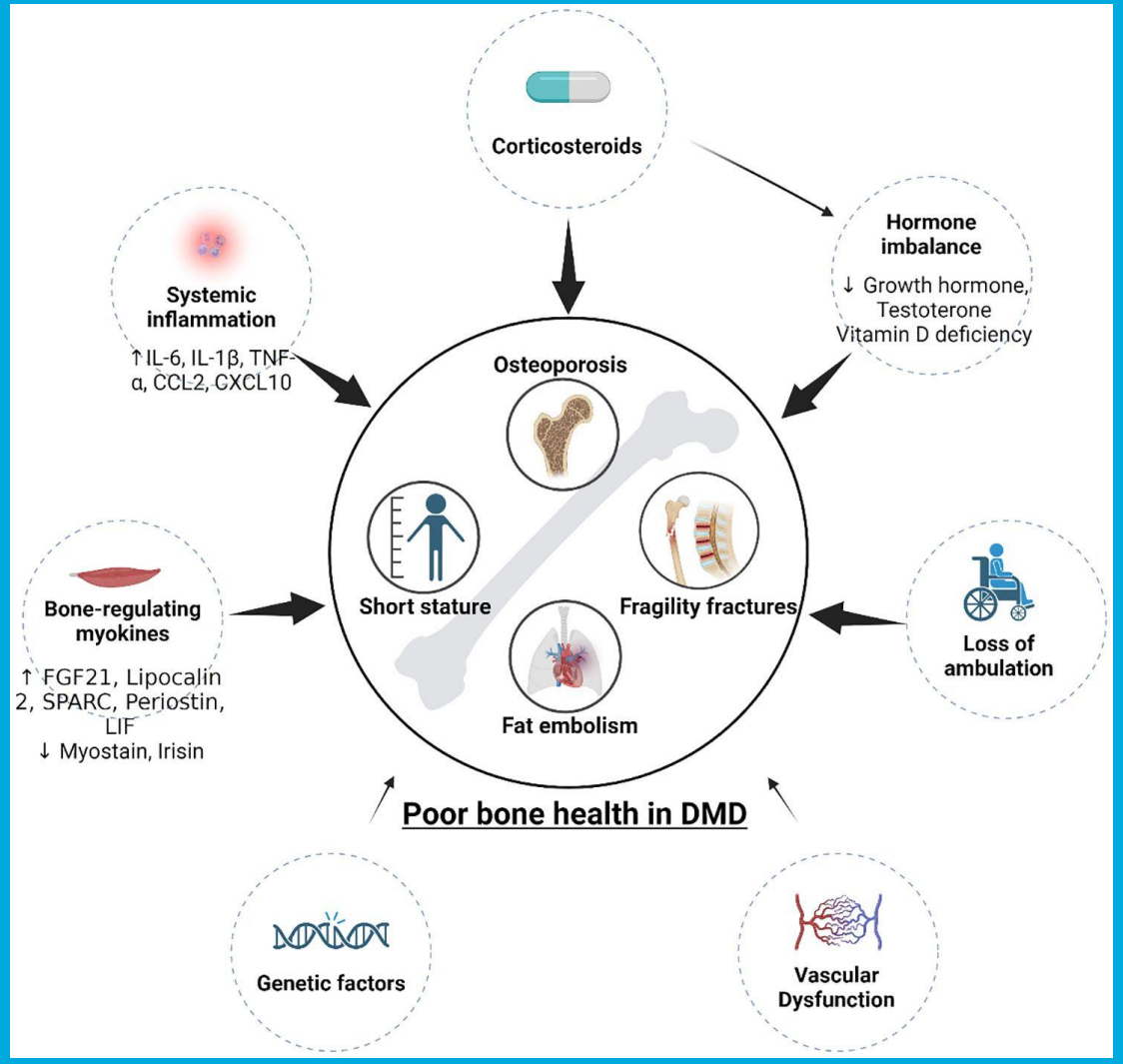
Short stature and osteoporosis



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