Bone metabolism in Classical Galactosemia

Bianca Panis

Maastricht UMC+

Content

- Introduction of myself
- Bone growth and bone mineral density (BMD) explained
- Bone Mineral Density – what can go wrong?
- How is BMD measured?
- BMD and Classical Galactosemia – literature
- BMD and Classical Galactosemia - recommendations

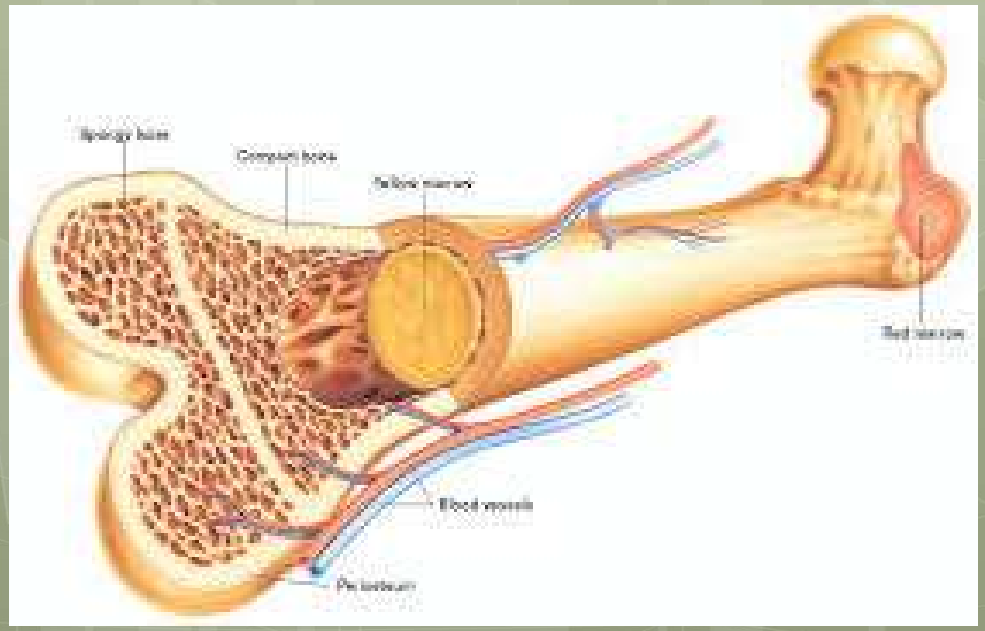
Bianca Panis

Paediatrician and child neurologist

Maastricht Universital Hospital Maastricht, MUMC+ the Netherlands

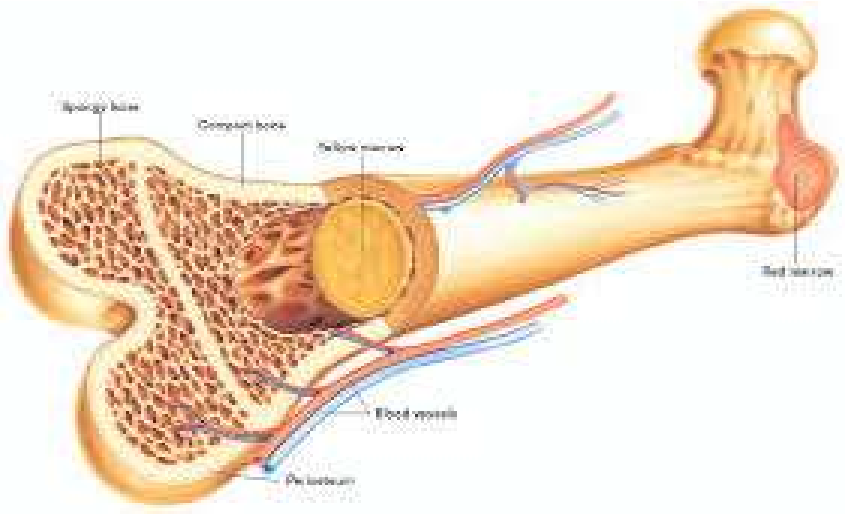
2006 PhD on bone metabolism in classical galactosemia (prof. Estela Rubio Gozalbo)

Per 2021: fellow in Genetic Metabolic Diseases (MUMC+)



Bone growth and bone mineral density explained

Normal bone


Spongy bone
Compact bone
Yellow marrow
Red marrow
Blood vessels
Periosteum

Normal bone

Bone = living tissue: constantly being broken down and replaced.

Two major cells important

- Osteoblast ↑
- Osteoclast ↓

Balance determines bone mineral density (BMD)

Normal bone

Childhood:

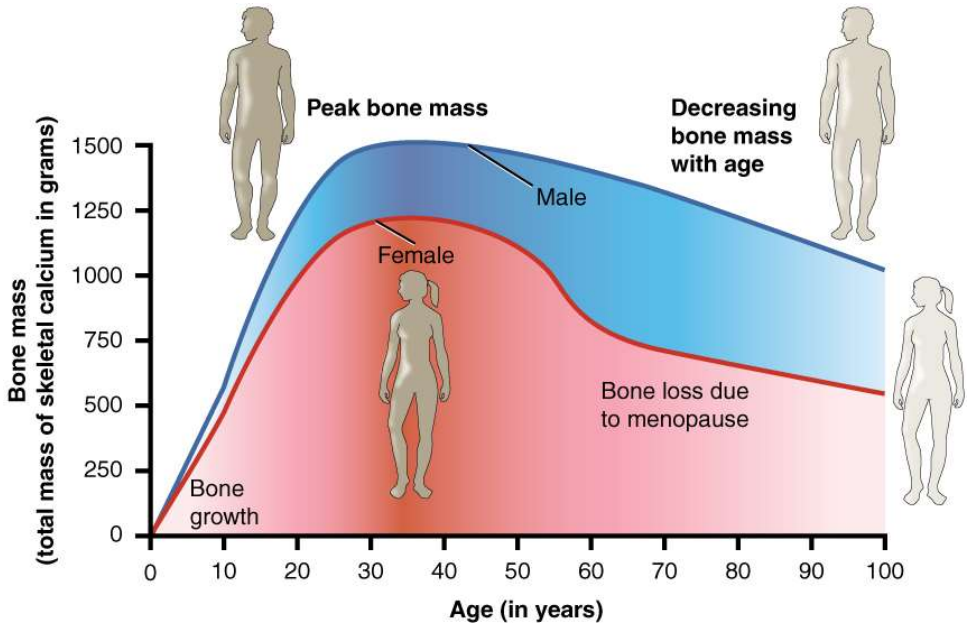
- Growth of bone
- Reaches peak bone mass

Early adolescence

- Plateau phase

Adulthood

- Decrease of bone mass



Question 1

- What causes low bone mineral density (BMD) and thus diminished strength of a bone?

A: Too many osteoclast causing excessive BMD breakdown

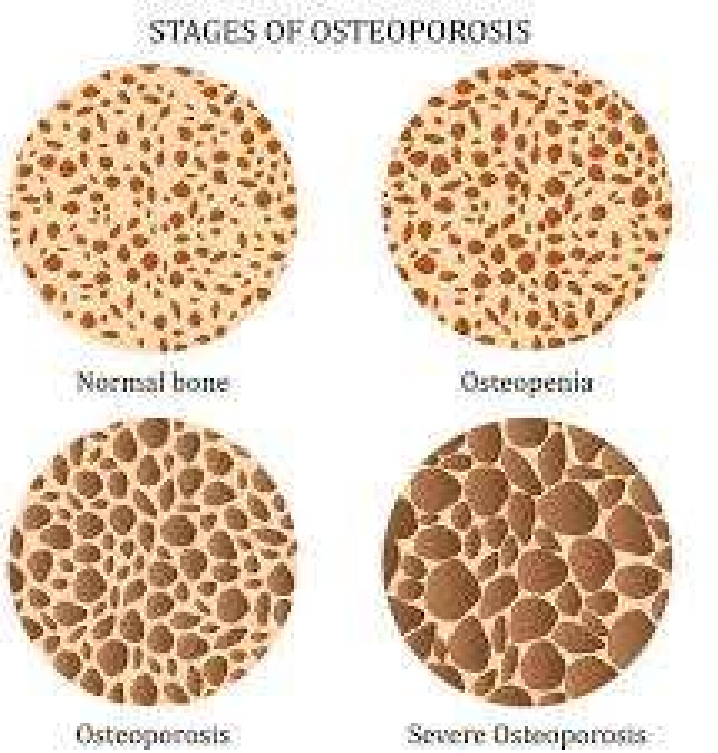
B: Too few osteoblasts causing low BMD

C: Imbalance between activity of osteoblasts and osteoclasts

Bone Mineral Density: what can go wrong?

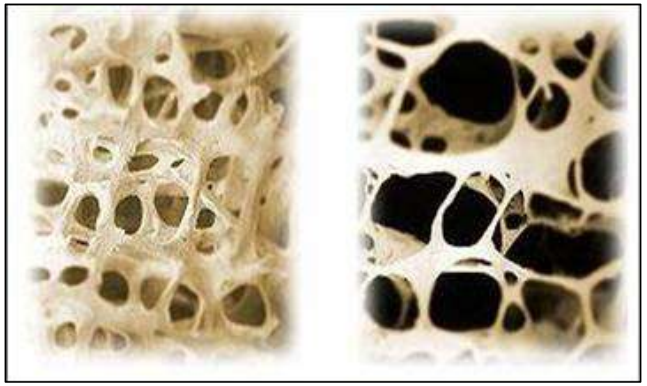
Osteoporosis

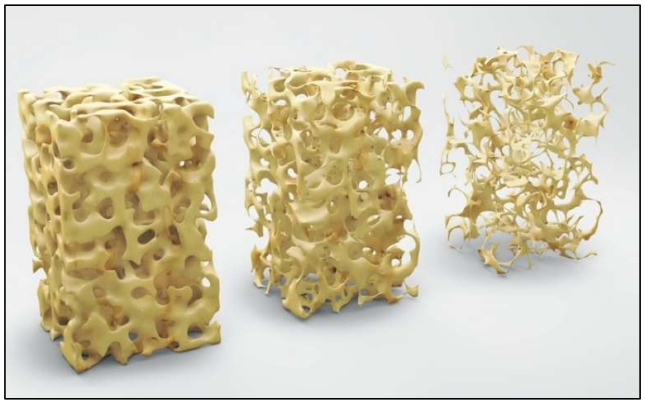
- Bone = living tissue: constantly being broken down and replaced.
- Osteoporosis occurs when the creation of new bone doesn't keep up with the loss of old bone. Bone mineral density (BMD) decreases



Osteoporosis

Normal BMD Low BMD

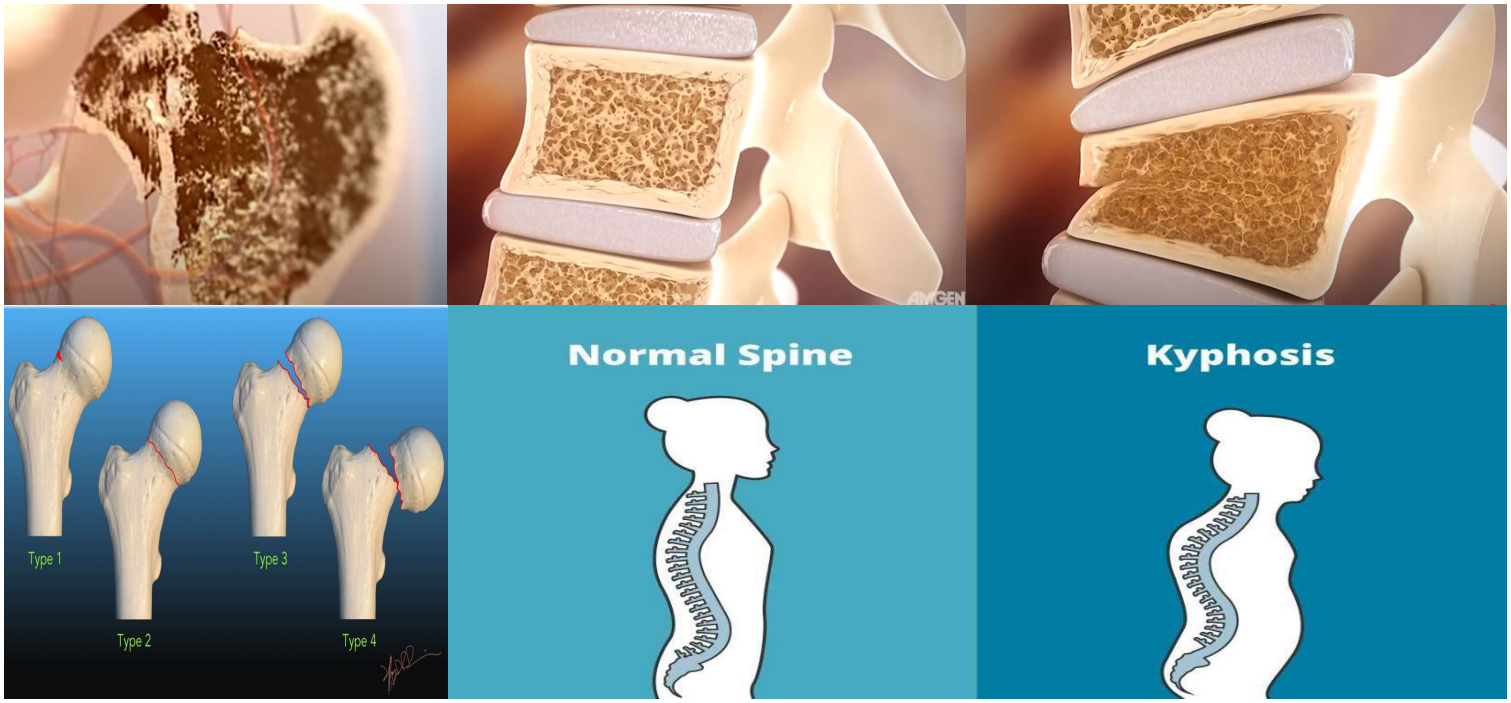




- Osteoporosis is bone with low BMD
- Bone is more fragile
- Result: fractures and or bone deformities

Osteoporosis

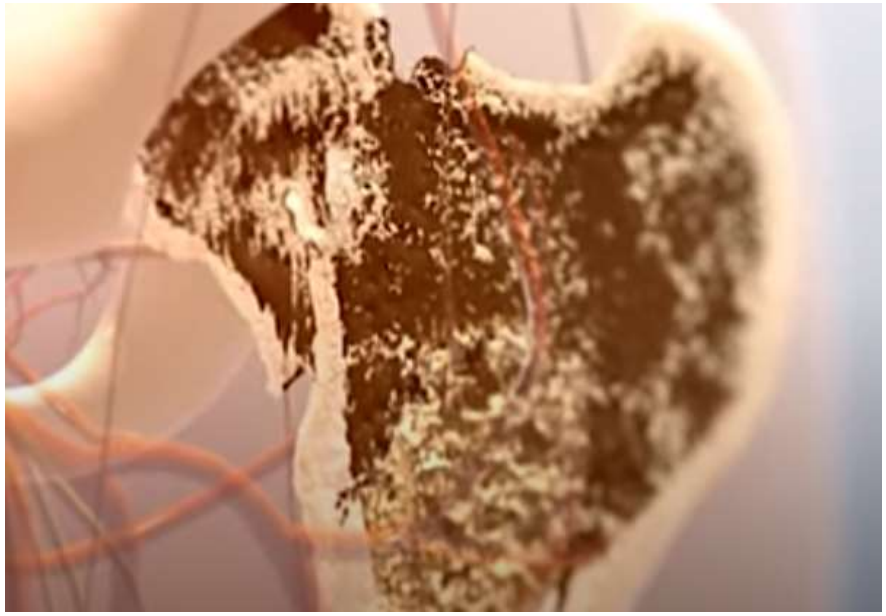
Complications



Osteoporosis

Many factors important

- Hormones
- Diet
- Sports/immobility
- Diseases
- Medication



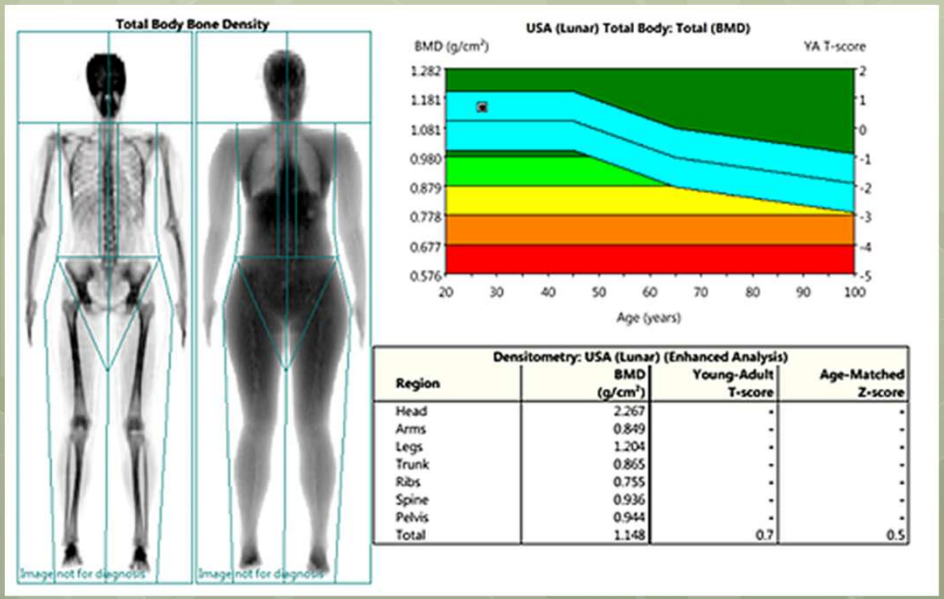
Question 2

- In classical galactosemia: what factors are important that can lead to diminished bone mineral density?

A: Hormones mainly

B: Diet as patients refer to a galactose restricted diet

C: Both hormones and diet, but probably also other factors

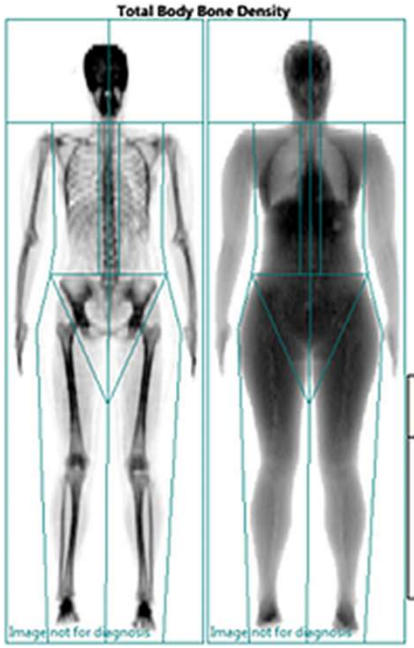


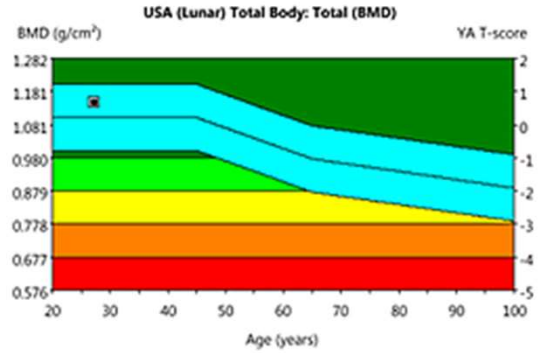
Densitometry: USA (Lunar) (Enhanced Analysis)

Region	BMD (g/cm²)	Young-Adult T-score	Age-Matched Z-score
Head	2.267	-	-
Arms	0.849	-	-
Legs	1.204	-	-
Trunk	0.865	-	-
Ribs	0.755	-	-
Spine	0.936	-	-
Pelvis	0.944	-	-
Total	1.148	0.7	0.5

How is bone mineral density measured?

How is BMD measured

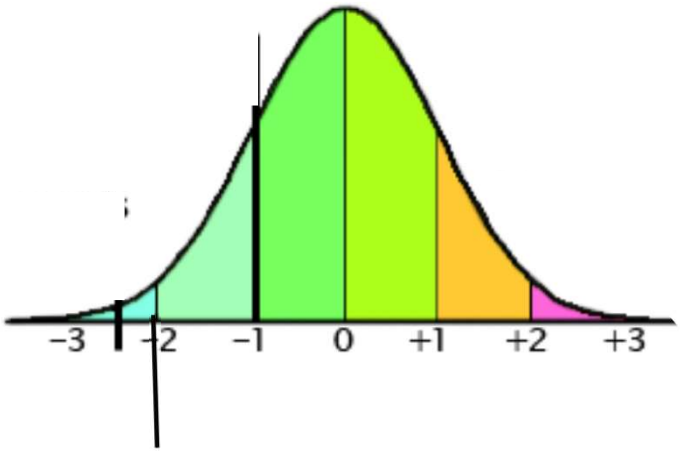




Densitometry: USA (Lunar) (Enhanced Analysis)

Region	BMD (g/cm²)	Young-Adult T-score	Age-Matched Z-score
Head	2.267	-	-
Arms	0.849	-	-
Legs	1.204	-	-
Trunk	0.865	-	-
Ribs	0.755	-	-
Spine	0.936	-	-
Pelvis	0.944	-	-
Total	1.148	0.7	0.5

Children: Z-score



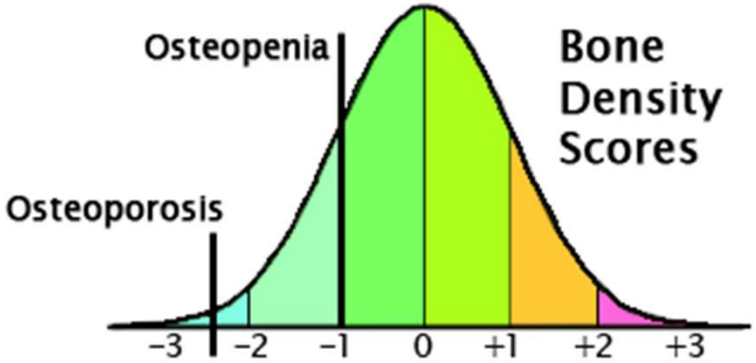
> -2 SD: normal BMD

-2 SD

Normal BMD > -2 SD

Diminished BMD ≤ -2 SD

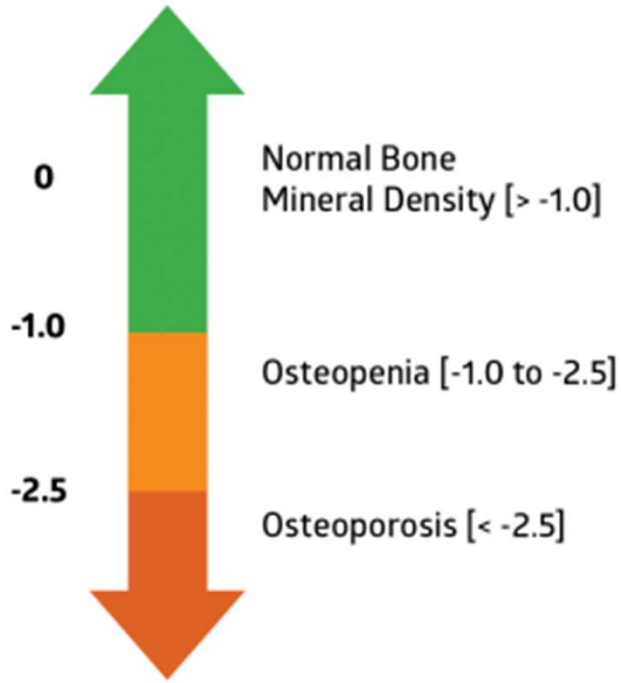
Adults: T-score



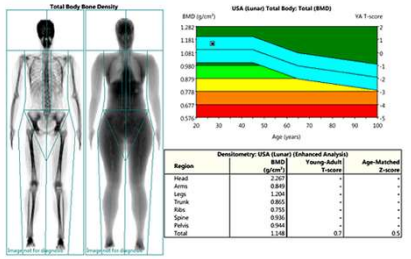
Osteoporosis ≤ −2.5 s.d. below 0

Osteopenia ≤ −1 s.d. below 0

s.d. = standard deviations



Question 3



- What is important to explain patients undergoing a DEXA scan ?

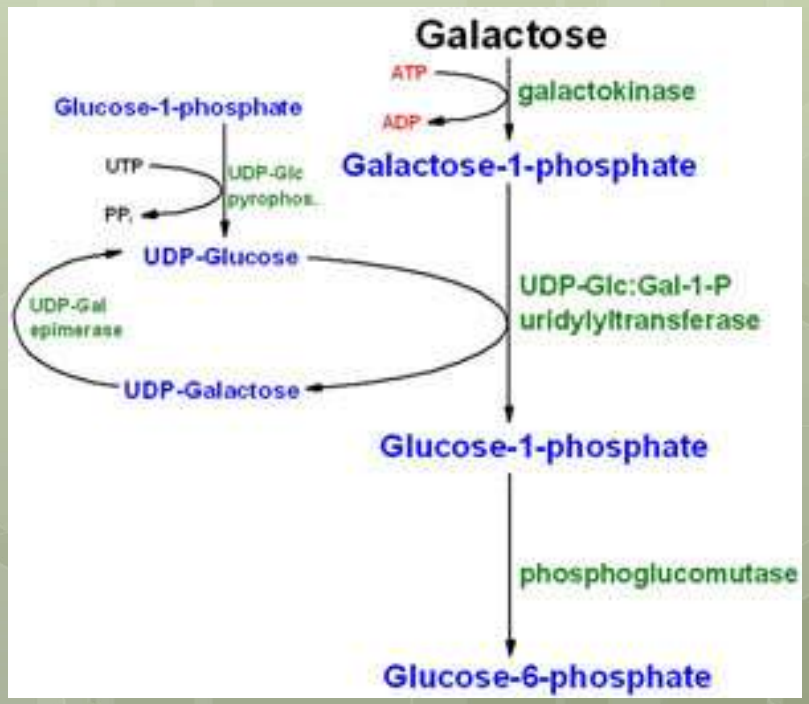
A: A DEXA scan is painless

B: You will not need to go into a tunnel or have an injection

C: You may be able to remain fully clothed.

D: The amount of X-rays is very low

E: all of the above answers



BMD and Classical Galactosemia – literature

BMD in classical galactosemia

- Has been found decreased
- First reported by Kaufman et al in 1993
- Reviewed in 2016 by van Erven et al
- 2019: largest dataset of patients from the GalNet Registry described by Rubio-Gozalbo et al.

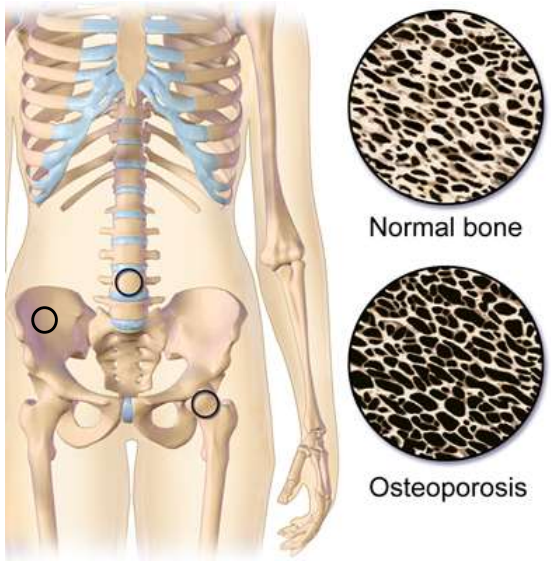
Kaufman et al. *J Ped 1993*: 15 prepubertal children (11 boys, 4 girls). BMD significantly decreased p=0.008
Van Erven et al. *JIMD 2016;* Bone health in classic Galactosemia: systematic review and meta-analysis
Rubio-Gozalbo et al. *Orphanet J Rare Dis. 2019.* The natural history of classcial galactosemia: lessons from the GalNet registry

BMD in classical galactosemia

International Galactosemia Network Registry:

Data derived from

- 15 countries
- 32 centers
- Including 509 patients



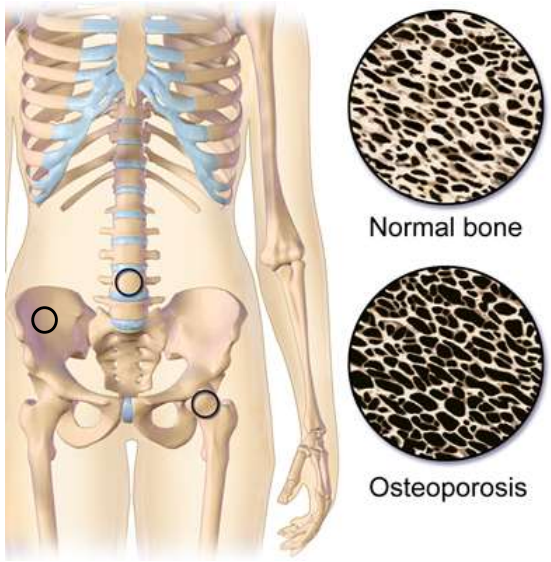
Rubio-Gozalbo et al. *Orphanet J Rare Dis. 2019* The natural history of classcial galactosemia: lessons from the GalNet registry

BMD in classical galactosemia

International GalNet Registry:

Median BMD Z-score of lumbar spine:
-0,8 SD (Range -5,1 to 4.0 SD)

Median BMD T-score of lumbar spine:
-1.1 SD (Range -4.0 to 4.3 SD)

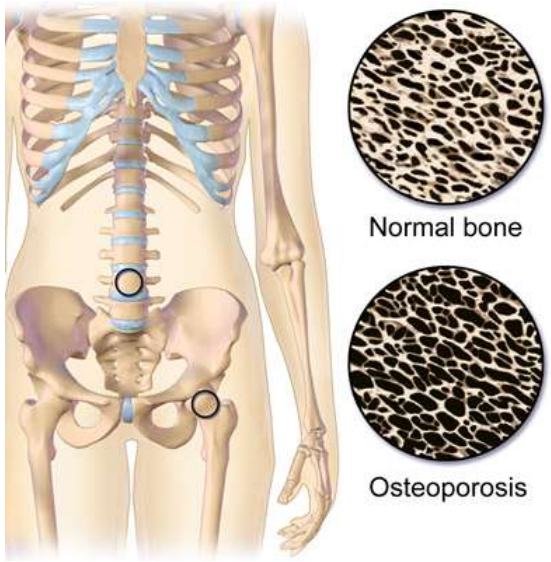


Rubio-Gozalbo et al. *Orphanet J Rare Dis. 2019* The natural history of classcial galactosemia: lessons from the GalNet registry

BMD in classical galactosemia

In accordance with the review of Van Erven in 2016 in which 4 studies were included

- lumbar spine (112 patients): Z-score of -0,6
- adults: lumbar spine BMD T score -0,9

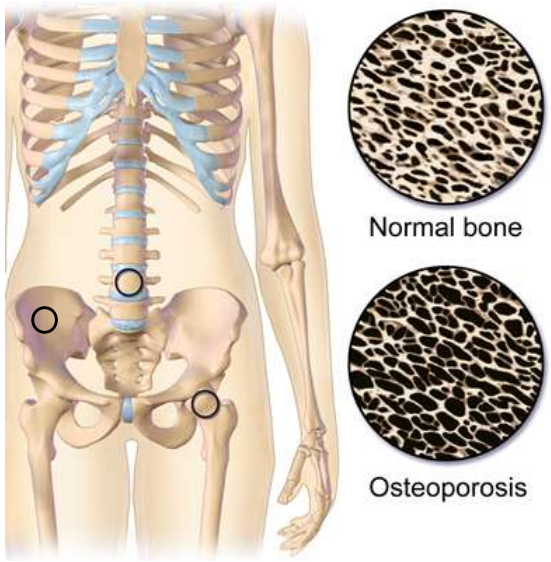


Van Erven et al. *JIMD 2016;* Bone health in classic Galactosemia: systematic review and meta-analysis

BMD in classical galactosemia

International GalNet Registry:

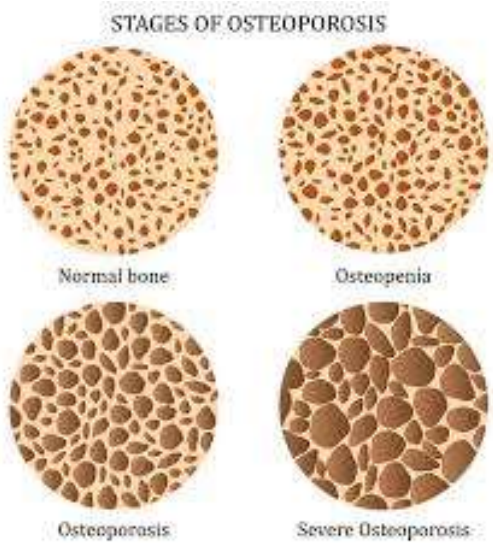
- A diminished BMD: 26,5% (66% female)
  (T score ≤ -1 or Z score ≤ -2 SD)
- Fracture prevalence: 9,9% (Medium age 24 years)



Rubio-Gozalbo et al. *Orphanet J Rare Dis. 2019* The natural history of classcial galactosemia: lessons from the GalNet registry

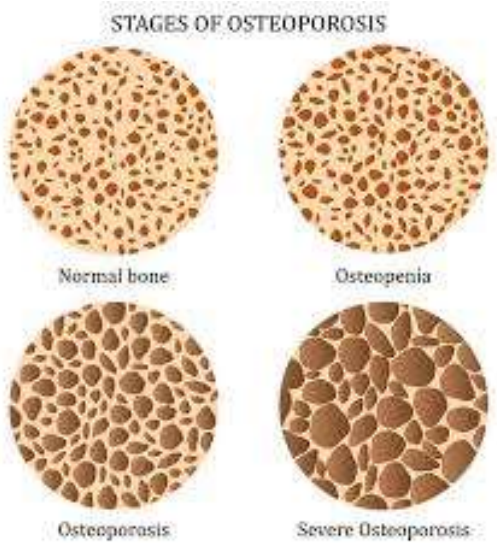
Risk factors for diminished BMD

- Diet restrictions: vitamin D and calcium
- Ovarian insufficiency in women
- Limited physical activity in some patients
- Unknown intrinsic disease related factors



In classical galactosemia

- International GalNet Registry:
  - Calcium and vitamin D supplementation: 68 versus 71%
  - Vitamin D deficiency (< 50 nmol/L): 26,5%
  - Physical activity according to the World Health Organization advice: 75%

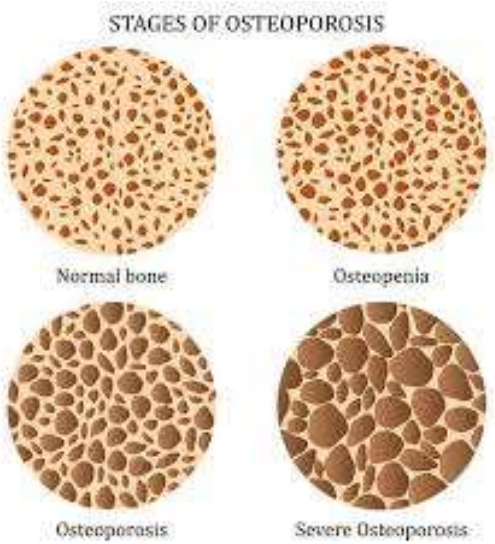


Rubio-Gozalbo et al. *Orphanet J Rare Dis.2019* The natural history of classcial galactosemia: lessins from the GalNet registry

BMD and Classical Galactosemia - recommendations

International clinical guideline

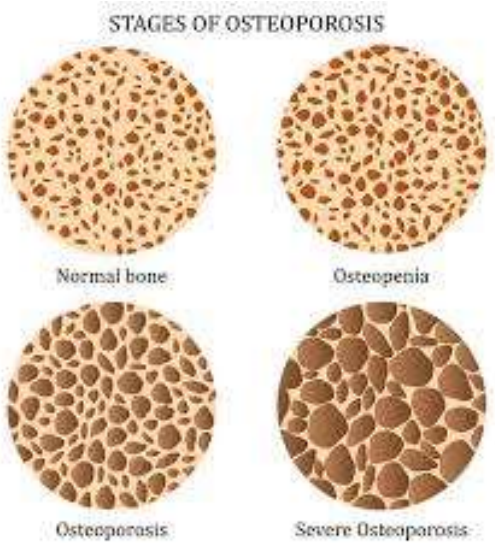
- Website: www.galactosaemia.eu
- The summary of the guidelines has been translated into different languages to make it accessible to families and patients.



Welling et al. *JIMD 2017.* International clinical guideline for the management of classic galactosemia: diagnosis, treatment, and follow up.

International clinical guideline

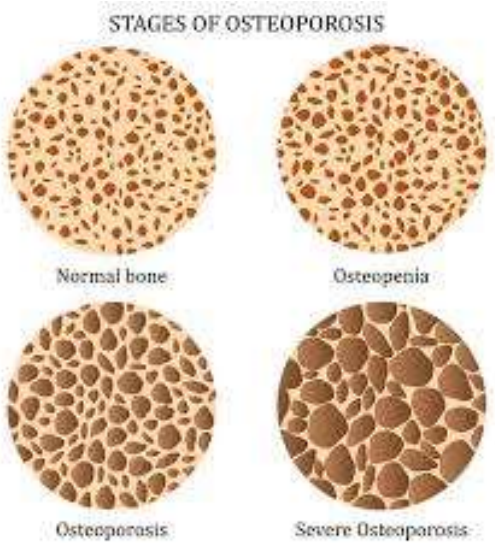
- Assess BMD by dual energy X-ray absorptiometry (DXA) scan at age 8-10 years and after puberty
- In case of normal BMD repeat every 5 years. In case of reduced BMD repeat according current bone health guidelines.
- Secondary amenorrhea: hormone replacement therapy



Welling et al. *JIMD 2017.* International clinical guideline for the management of classic galactosemia: diagnosis, treatment, and follow up.

International clinical guideline

- Annual dietary assessment of calcium and vitamin D with measurement of plasma 25(OH)vitamin D to optimize calcium and vitamin D intake from diet (and supplementation)
- Stimulate regular exercise



Welling et al. *JIMD 2017.* International clinical guidline for the management of classic galactosemia: diagnosis, treatment, and follow up.

In conclusion

- A (mild) diminished BMD is found in classical galactosemia
- Because the life expectancy is normal, optimizing BMD is important to diminish fracture risk at elderly age
- Optimizing calcium and vitamin D in diet, stimulating exercise and if necessary hormone replacement therapy are important factors regarding bone metabolism

Questions or input!

- You can ask your questions now via the Q&A button
- Move your mouse to get the Zoom menu bar at the bottom of your screen
- The panelists will try to answer your question or combine with other questions
- If time runs short, we may have to 'dismiss' your question
- If your question wasn't answered, you can send your question to chairman@galactosaemia.eu