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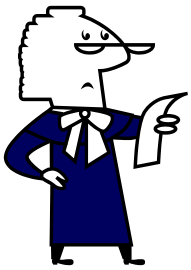
E-MAGAZINE-5



OSTEOPENIA AND OSTEOPOROSIS

Co-funded by the Erasmus+ Programme of the European Union

OSTEOPOROSIS:

A World Health Organisation (WHO) working group and consensus conference have defined osteoporosis as "A disease characterised by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk"

Bone mass density is maintained constant due to the equilibrium between bone formation and bone resorption *(Figure 1).*

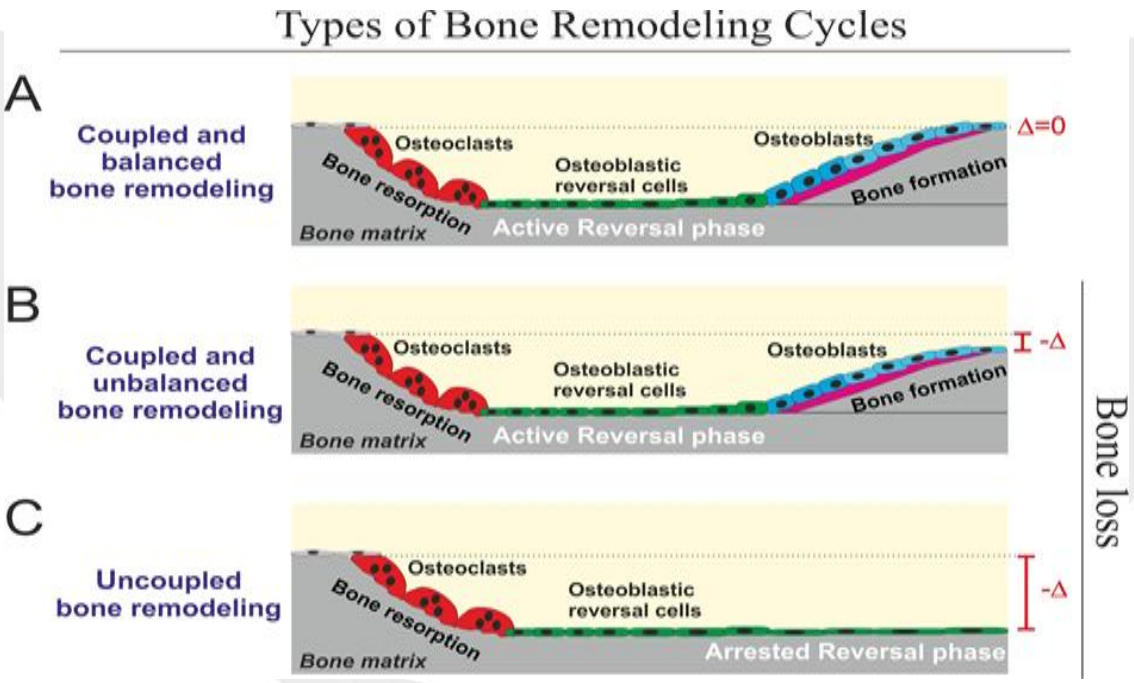


Figure 1. Types of Bone Remodeling Cycles

Remodelling is under the control of multiple systemic and local factors:

- Sex hormones,
- Parathyroid hormone (PTH),
- Growth hormone (GH)/Insulin-like growth factor-1 (IGF-1) ***(Figure 2),***
- Vitamin D,
- Proinflammatory cytokines,
- Genetic factors.

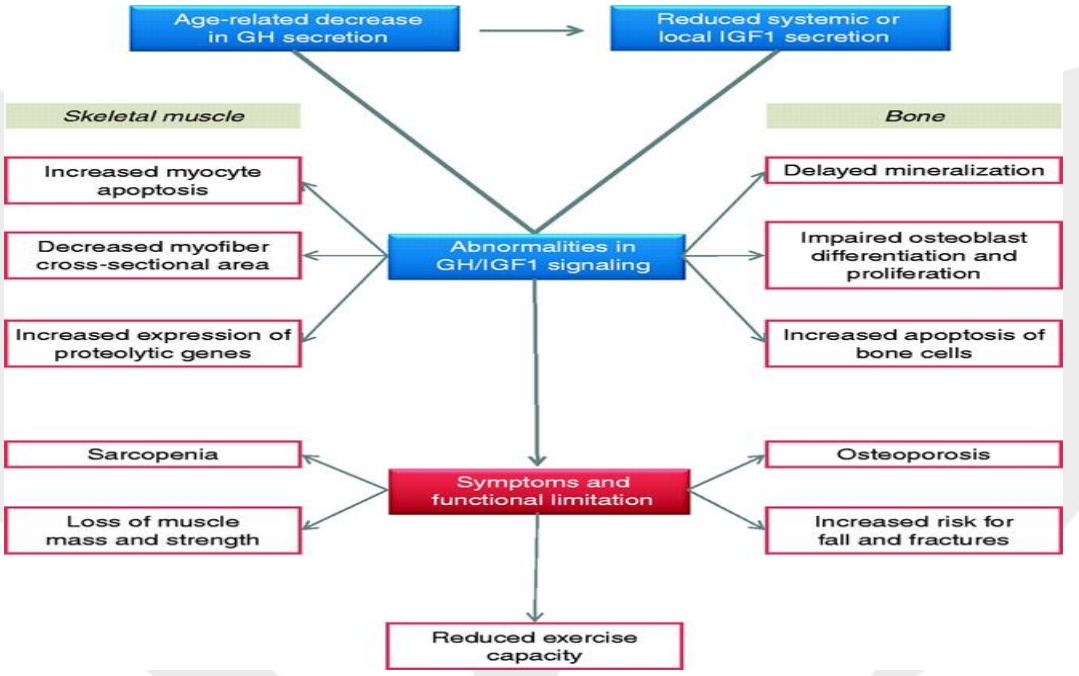


Figure 2. Abnormalities in GH/IGF1 signaling skeletal muscle and bones.

In the past, prior to transfusions, the pathogenesis of bone disease in TM was basically due to the ineffective erythropoiesis that resulted in bone marrow hyperactivity and hyperplasia.

Premature fusion of the epiphysis of the long bones leads to shortening of the proximal humerus *(Figure 3).*

The skull showed the characteristic "hair-on-end" appearance. The expansion of the osseous structures of the face may lead to prominence of the lateral margins of the malar eminences and anterior and medial displacement of developing teeth *(Figure 3).*

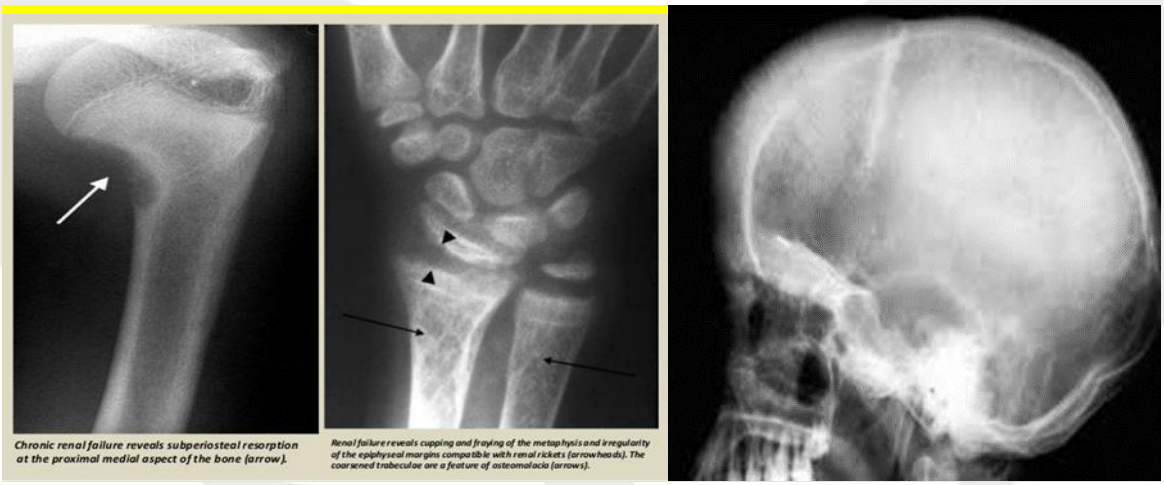


Figure 3. Bone changes in poor chelated and treated TM patients.

However, the use of hyper-transfusion protocols that suppress marrow hyperplasia and the proper use of iron chelators have markedly improved the bone abnormalities of TM patients.

PATHOPHYSIOLOGY:

Bone disease in this population results from a variety of inherited and acquired factors ***(Figure 4 and 5).***

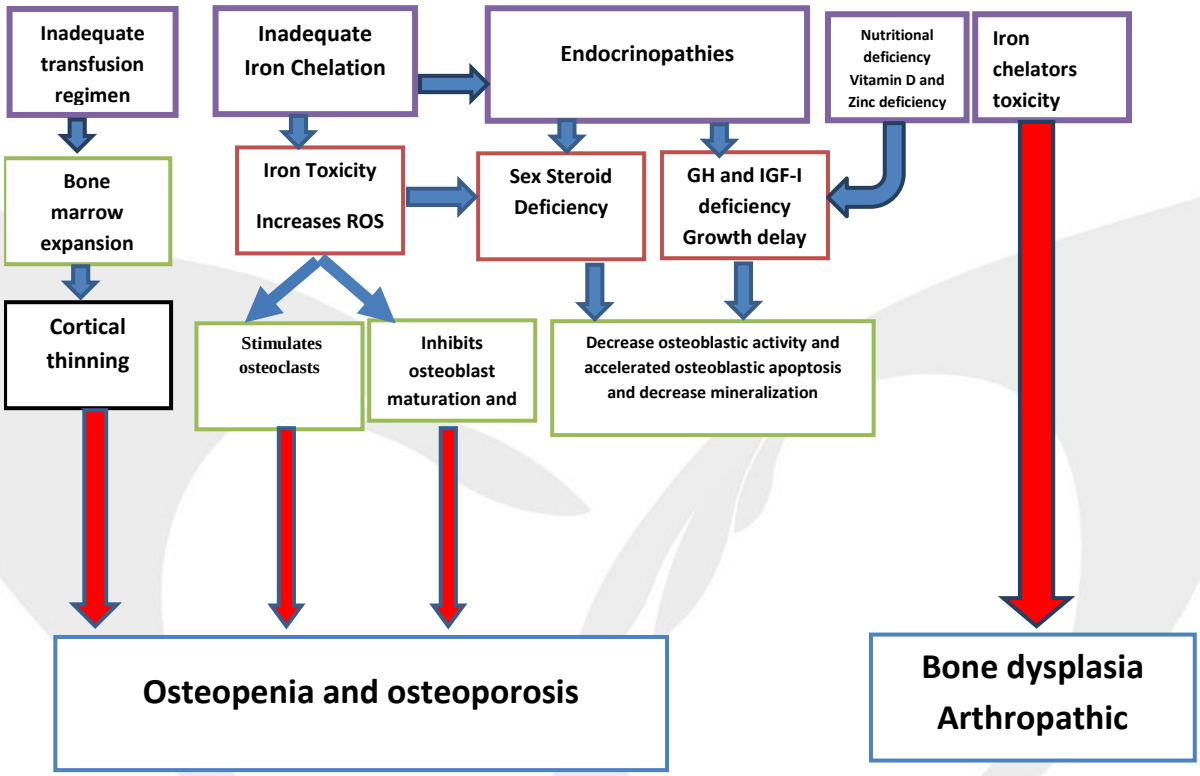


Figure 4. Pathophysiology of bone disease in thalassemia over time

(from: De Sanctis V et al. Bone disease in β thalassemia patients: past, present and future perspectives. Metabolism. 2018:80:66-79: modified).

Bone remodelling in thalassemia :

Decreased bone formation and/or increased resorption seem to occur in TM patients. Recent studies have proven that the receptor activator of the nuclear factor-kappa B ligand (RANKL), a cytokine that enhances osteoclastic function, was elevated in thalassemic patients.

An increased serum levels of Dickkopf-1 (Dkk1) and sclerostin have been found in these patients

Higher circulating levels of Dkk1 and sclerostin correlated with reduced bone mineral density of lumbar spine and distal radius as well as with increased bone resorption and reduced bone formation markers.

- Genetic Factors

Genetic factors have significant effect in the pathogenesis of osteopenia and osteoporosis in TM patients.
Polymorphisms of several genes influencing bone mineral density (BMD) have been studied.

These include:

- collagen type I A1 (COLIA1),
- vitamin D receptor (VDR)
- transforming growth factor-beta (TGF- β).

Other factors involved in the etiology of osteopenia/osteoporosis in TM patients *(Figure 5)*

- Family history, age, physical activity, smoking
- Acquired factors, such as:

a) bone marrow expansion, secondary to ineffective erythropoiesis

b) direct toxic effects of iron overload on the osteoblasts (number and activity)

c) deleterious effects of desferrioxamine on the bone metabolism, negative impact of chelation therapy on fibroblast proliferation and collagen synthesis

d) associated endocrine complications calcium and zinc deficiencies and low vitamin D levels

e) chronic liver disease

f) nutritional deficiencies

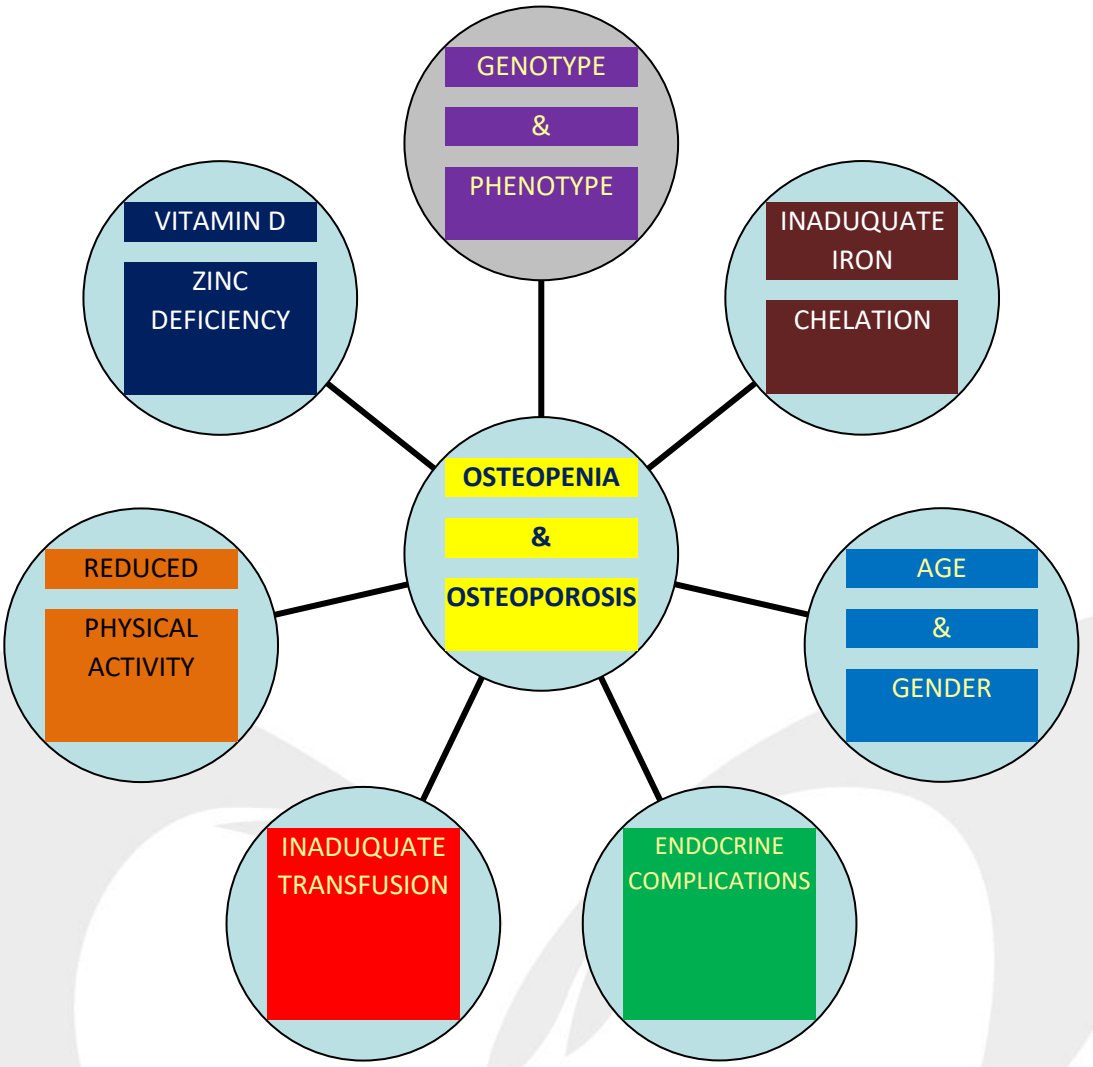


Figure 5. Inherited and acquired factors in TM patients with osteopenia and osteoporosis.

DIAGNOSIS

- **Markers of bone metabolism:**

Are subdivided into bone formation and bone resorptive markers.

- **Bone formation markers:**
  - osteocalcin (OC),
  - bone-specific alkaline phosphatase (BAP),
  - alkaline phosphatase (AP),
  - osteoprotegerin (OPG),
  - procollagen type 1 amino terminal propeptide (P1NP)
  - procollagen type 1 carboxyl terminal propeptide (P1CP).
- **Resorptive markers:**
  - N-terminal cross-linked telopeptide of type-I collagen (NTX),
  - C-terminal cross-linked telopeptide of type-1 collagen (CTX),
  - tartrate-resistant acid phosphatase (TRAP), RANKL (Receptor Activator of Nuclear factor Kappa beta Ligand),
  - pyridinoline (PYR),

- deoxypyridinoline (DPD),
- hydroxyproline (HP),
- sclerostin.

BONE MINERAL DENSITY (BMD)

- The most reliable and widely used method for measuring bone mineral density (BMD) is dual energy x-ray absorptiometry (DXA) which assesses bone mass at the lumbar spine and proximal femur ***(Figure 6).***

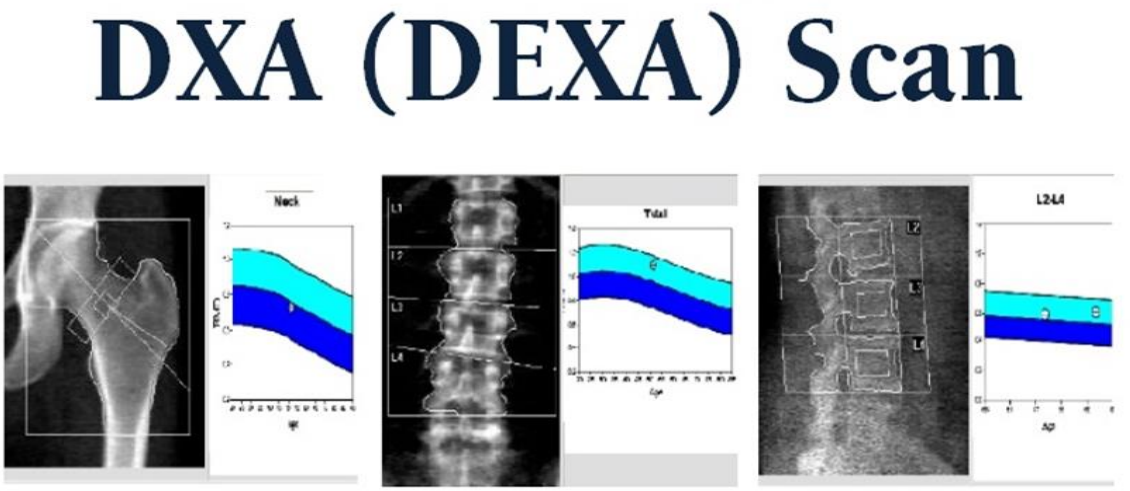


Figure 6. DEXA scan at lumbar and femoral neck sites

Osteoporosis is defined as a bone density 2.5 SD below the young adult mean (T-score) (Table 1).

Osteopenia is defined as a bone density between 1.0 and 2.5 SD below the young adult mean (T-score) (Table 1).

Table 1. World Health Organization (WHO) definition of osteoporosis

Diagnostic Category	T-score	Bone Mineral Density
Normal	>–1	Within 1 SD of a young normal adult
Osteopenia	–1 to –2.5	Between 1 and 2.5 SD below that of a young normal adult
Osteoporosis	<–2.5	>2.5 SD below that of a young normal adult
Severe osteoporosis	<–2.5 and ≥1 fragility fracture	>2.5 SD below that of a young normal adult

Adapted from WHO Technical Report Series

Osteopenia has been observed in 76% of TM patients and osteoporosis in 49% of patients.

TREATMENT

The primary approach in successfully treating osteopenia/osteoporosis in TM patients should be the careful management of TM itself.

Preventive treatment

In the case of patients suffering from chronic disease it is important that all the risk factors present in each case are identified and treated or attenuated in the best manner possible.

Treatment of established osteoporosis

For hypogonadal TM patients with established osteoporosis, hormone replacement therapy (estrogen for females, testosterone for males), calcium and vitamin D (VD) supplementation, and an exercise program should be considered.

Bisphosphonates

The increased bone turnover rate observed in thalassemic patients justifies the use of powerful anti-resorption drugs, such as Bisphosphonates (BPs).

BPs are a group of molecules analogous to inorganic pyrophosphate. They concentrate within bones, binding specifically to its inorganic components.

These potent osteoclast inhibitors could achieve a safe and efficacious improvement in BMD and reduction in bone complications and pain in TM patients.

To date, alendronate, pamidronate, and zoledronate seem to be effective in increasing BMD and normalizing bone turnover.

Other treatments include calcitonin, which is a potent inhibitor of osteoclasts and is used in combination with the daily administration of calcium.

Zinc supplementation

Hypozincemia is common in thalassemic patients and has been associated with low bone mass.

CONCLUSIONS

Treatment with transfusion and chelation therapies has significantly extended the lifespan of TM patients.

Despite the recent advancements, osteopenia and osteoporosis still remain significant causes of morbidity in young adults in both sexes.

The development of osteopenia/osteoporosis in TM patients is multifactorial with both epigenetic and inherited factors.

The early identification of osteopenia and osteoporosis is of paramount importance, since delayed diagnosis and inadequate treatment may lead to significant osteoporosis, skeletal abnormalities, fractures, spinal deformities and nerve compression.

Recommendations for the prevention and treatment of osteopenia/osteoporosis in thalassemia:

- A pre-transfusional haemoglobin level of 9-9.5 g/dL
- Regular iron chelation therapy

- Calcium and vitamin D supplementation
- Zinc supplementation, if needed
- Regular physical activity
- Hormone replacement therapy with sex steroids in hypogonadal patients
- Use of bisphosphonates