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Iron overload in Talassemia is multifactorial and attributed primarily to

increased gastrointestinal iron absorption

It can also result from

chronic hemolysis and occasional blood transfusions.

Serum ferritin levels & LIC (liver iron concentration)

determined by magnetic resonance imaging (MRI)

positively correlate in Thallamic patients where

800 and 300 ng/mL of serum ferritin
correspond to
5 mg and 3 mg Fe/g dry weight (DW)

If untreated, iron overload will lead to organ dysfunction involving mostly the:

- Liver
- Heart
- endocrine organs
- and a wide spectrum of complications and clinical outcomes

Endocrine complications are mostly attributed to iron overload and suboptimal chelation

THALASSEMIA

Excess iron is first deposited in the form of hemosiderin in patients with thalassemia who are regularly transfused

↓

deposited in endocrine organs

↓

elevated oxidative stress through Fenton reaction

↓

destruction of cell membranes in endocrine glands

↓

sign and symptoms related to every gland will present

In a major thalassemia

Endocrinologists encounter these problems :

Growth (33%)

Health of bone (60%)

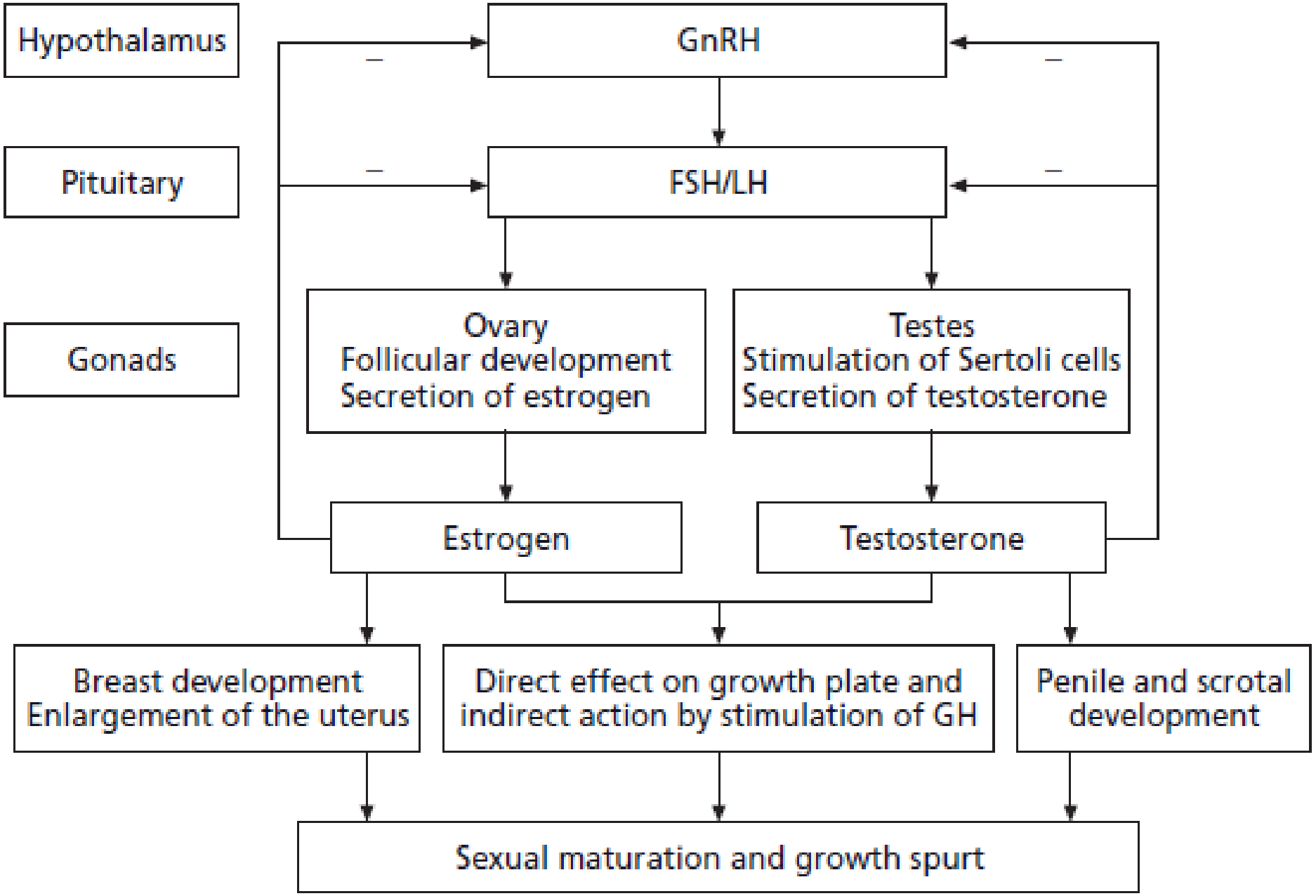
Fertility and sexual potency (40-55%)

Diabetes mellitus (6-13%)

Adrenal insufficiency (5-7%)

Thyroid insufficiency (10%)

Fertility and sexual potency



Overall feedforward and feedback loops in the HPGaxis

Brain

(Hypothalamus &Pituitary)

hemosideros is

Hypogonadotropic hypogonadism (hypo H) (the most frequent) (affecting females more than males)

Gonads (Testeses or Ovaries)

hemosiderosis

Hypergonadotropic hypogonadism (hyper H)

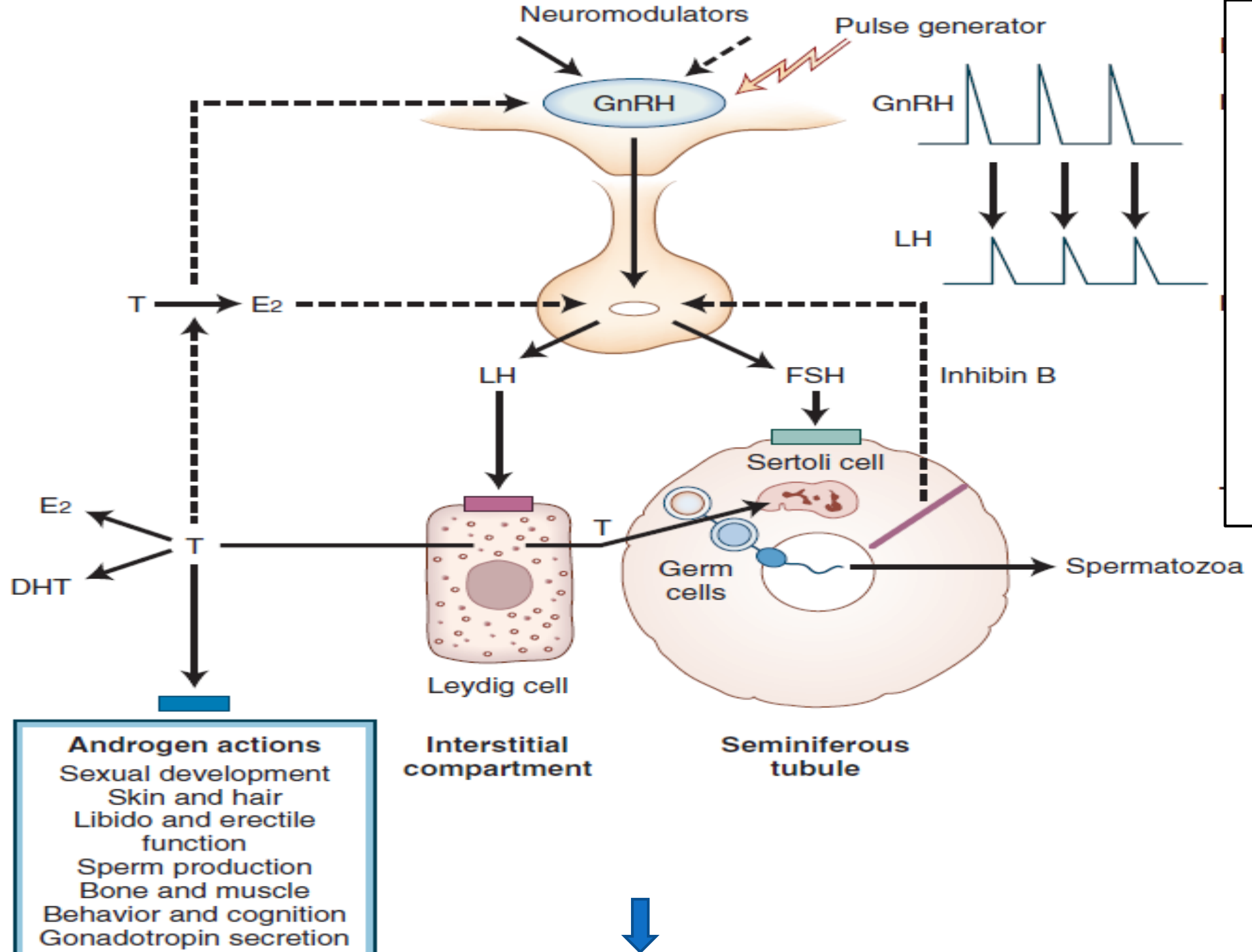
Final and main sequle is decrement of sexual hormons (ANDROGENS & ESTROGENS)

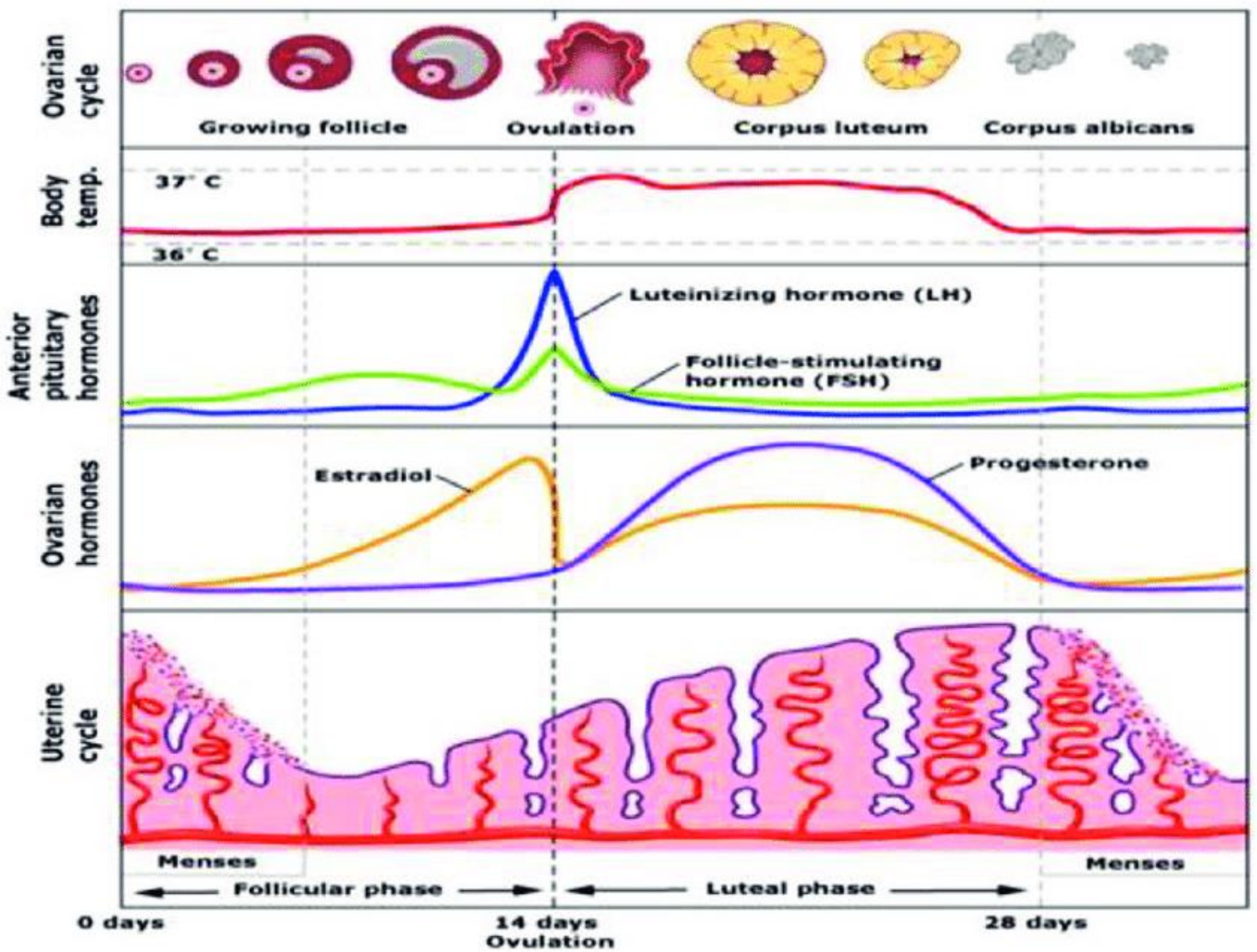
Delayed puberty and hypogonadism are the most common endocrine common complications in T and are attributed to iron-mediated damage leading to dysregulation of the hypothalamic-pituitary axis .

Delayed puberty is defined as no puberty in girls by 13 years and in boys by 14 years. Hypogonadism is defined as absence of testicular development in boys and breast development in girls by 16 years.

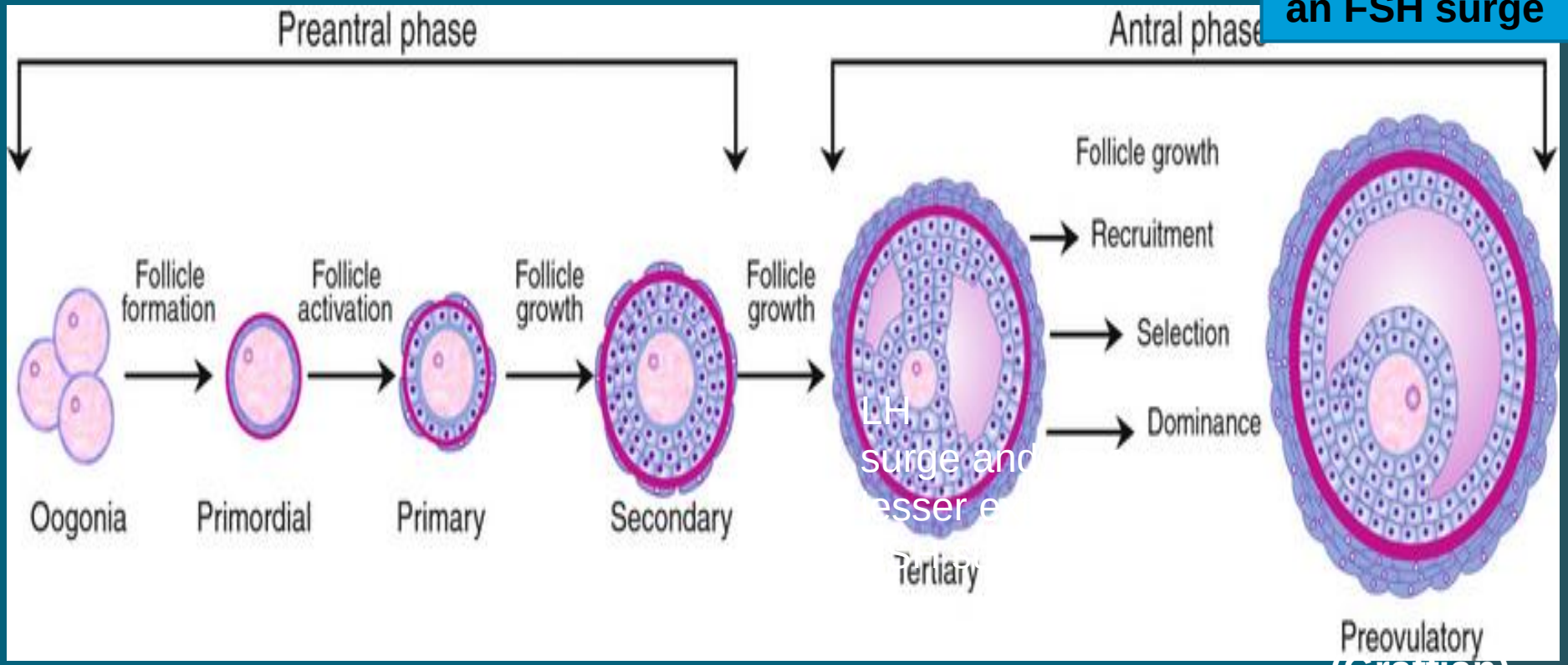
It has been shown to be correlated with early onset of transfusion therapy and serum ferritin levels of approximately 2000 ng/mL in TM patients and high LIC .

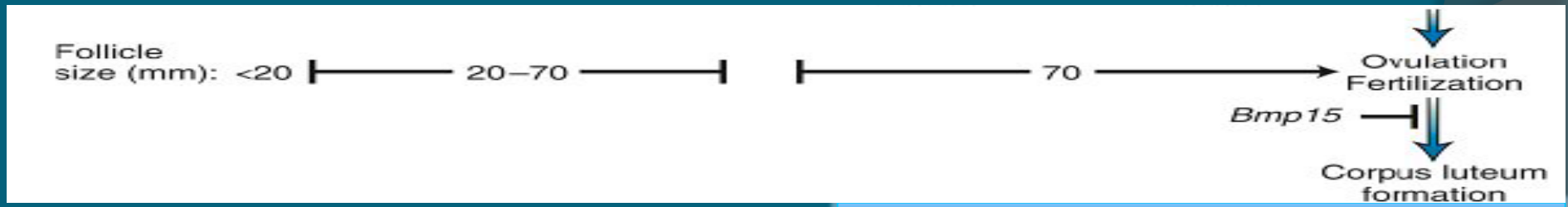
However, gonadal function of women with this complication is not affected and fertility can be salvaged


Neuromodulators
Pulse generator
GnRH
GnRH
LH
T
E2
LH
FSH
Inhibin B
Sertoli cell
E2
T
DHT
T
Germ cells
Spermatozoa
Leydig cell
Androgen actions
Sexual development
Skin and hair
Libido and erectile function
Sperm production
Bone and muscle
Behavior and cognition
Gonadotropin secretion
Interstitial compartment
Seminiferous tubule


Ovarian cycle
Growing follicle
Ovulation
Corpus luteum
Corpus albicans
Body temp.
37° C
36° C
Anterior pituitary hormones
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Ovarian hormones
Estradiol
Progesterone
Uterine cycle
Menses
Menses
Follicular phase
Luteal phase
0 days
14 days
Ovulation
28 days

LH surge
&
lesser extent, an FSH surge





dramatic rise in circulating estradiol level as midcycle approaches.

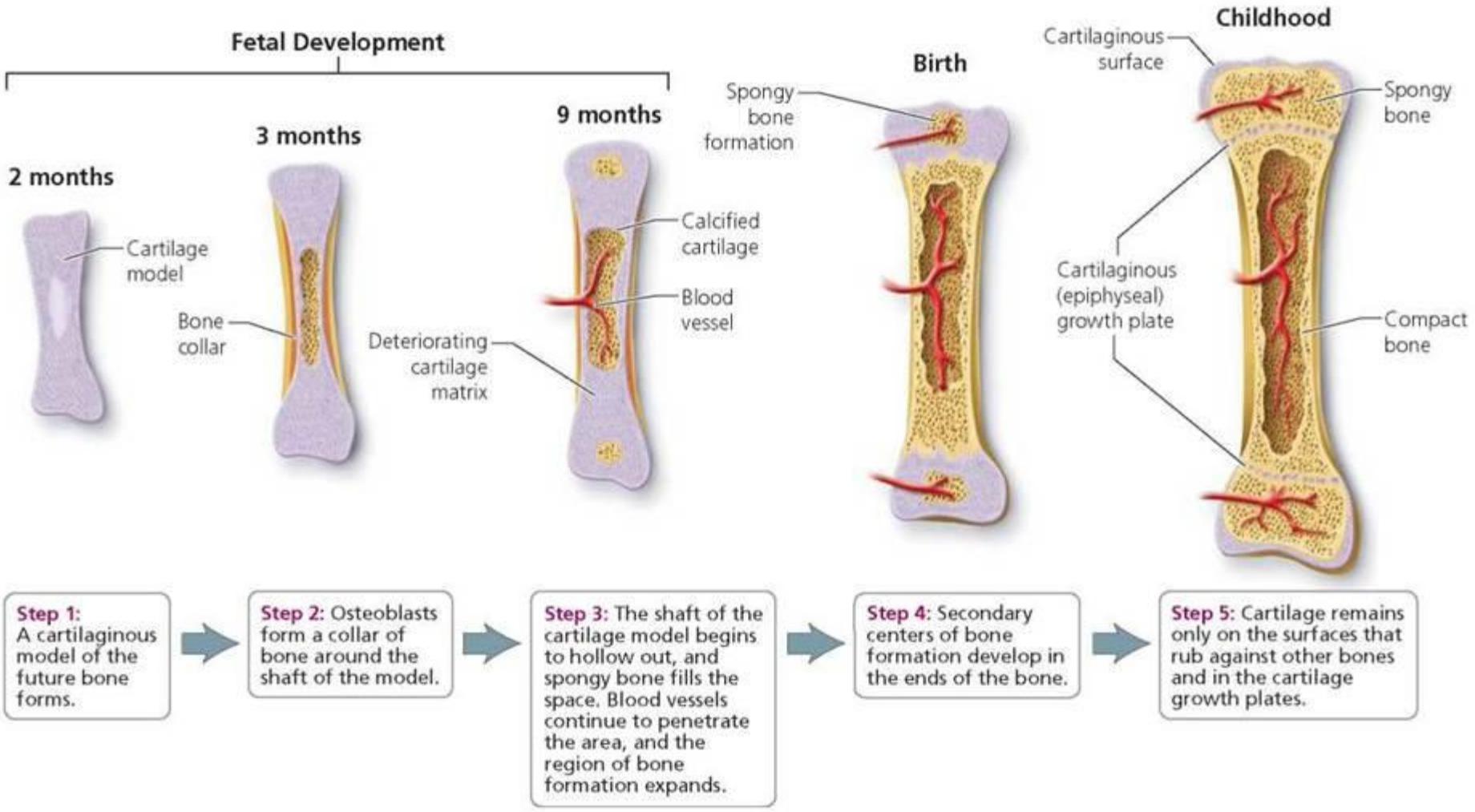
Literature still lacks accurate management guidelines for delayed puberty and hypogonadism in T.

Gonadal steroids (ethinyl estradiol, estrogen-progesterone hormone, and testosterone esters) and gonadotropin releasing hormone should be initiated for females >13 and males >16 years of age not showing pubertal change .

hCG, hMG, and intracytoplasmic sperm injection (ICSI) can be offered to males with spermatogenesis problems to assist in attaining pregnancy in the partner.

In females with chronic anovulation, stimulation with gonadotropins can still increase estradiol and produce ova, but global assessment of the patient is necessary before induction of pregnancy

Health of bone


Fetal Development
2 months
Cartilage model
3 months
Bone collar
9 months
Deteriorating cartilage matrix
Calcified cartilage
Blood vessel
Birth
Spongy bone formation
Childhood
Cartilaginous surface
Spongy bone
Cartilaginous (epiphyseal) growth plate
Compact bone
Step 1: A cartilaginous model of the future bone forms.
Step 2: Osteoblasts form a collar of bone around the shaft of the model.
Step 3: The shaft of the cartilage model begins to hollow out, and spongy bone fills the space. Blood vessels continue to penetrate the area, and the region of bone formation expands.
Step 4: Secondary centers of bone formation develop in the ends of the bone.
Step 5: Cartilage remains only on the surfaces that rub against other bones and in the cartilage growth plates.

In thalassemia major

Bone disorders include
Rickets
Scoliosis
spinal deformities
nerve compression
fractures
severe osteoporosis

In early stages, patients may be asymptomatic but can present with

back pain
Dyspnea
neurological emergencies
sudden fractures.

The etiologies are often multifactorial

(disruption of dynamic balance between bone resorption & formation)

hormonal deficiency (PTH, GH, SEX HORMONS)

bone marrow expansion that has positive relation with severity of anemia

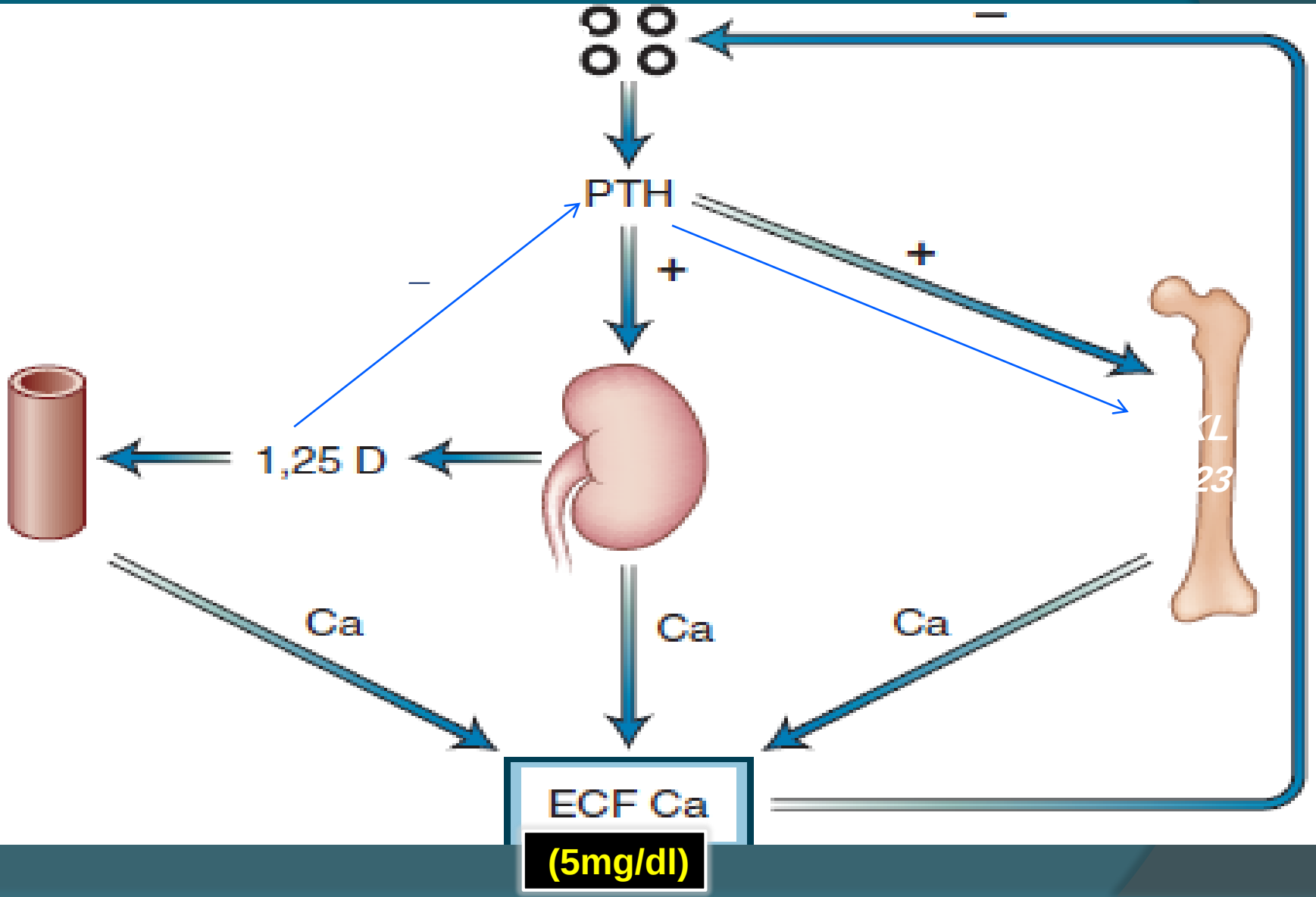
nutritional deficiency (Enlarged spleen &…)

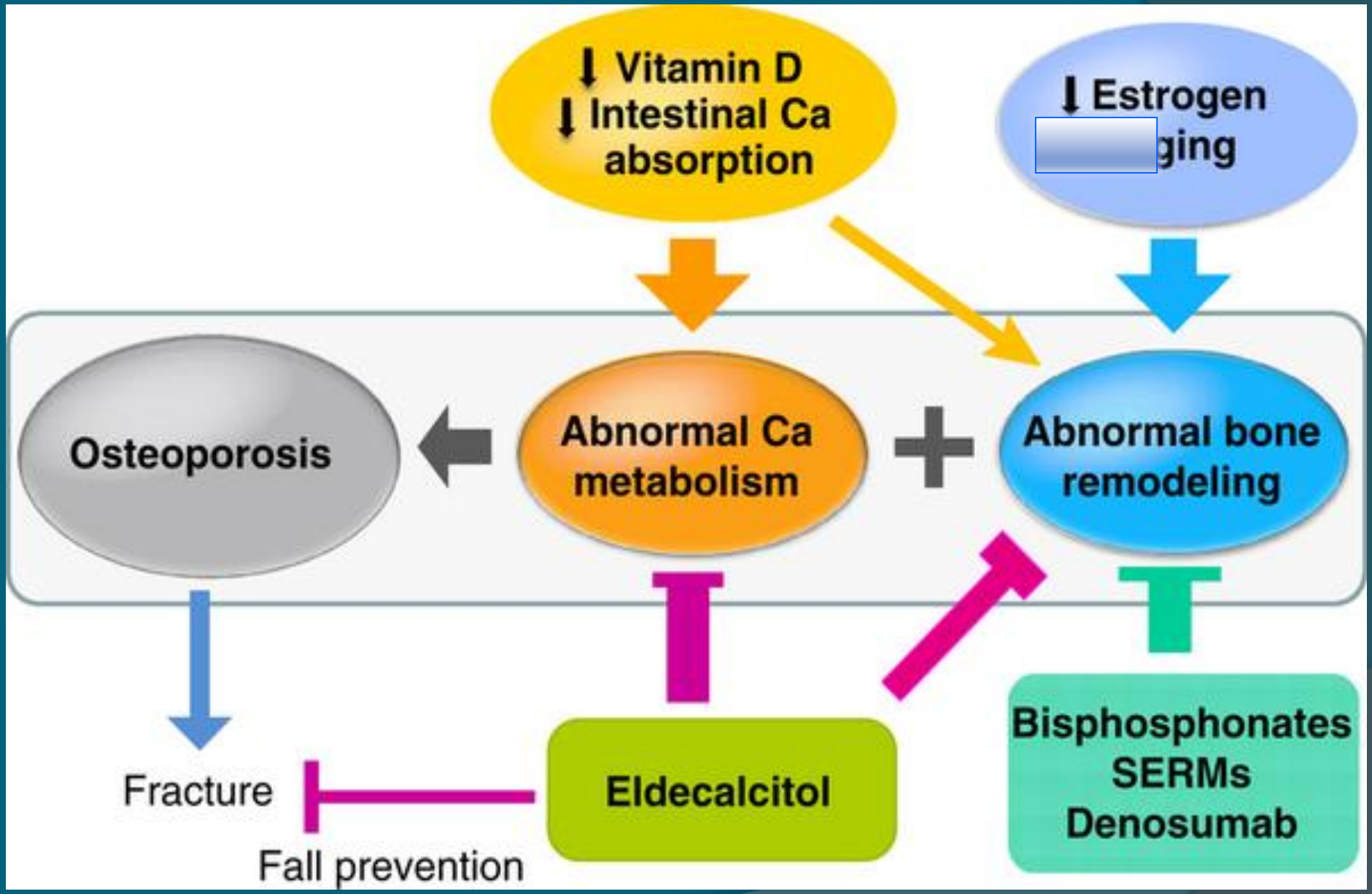
Iron overload can disrupt bone homostasis by significant inhibition of osteogenic differentiation and stimulation of osteoclastogenesis

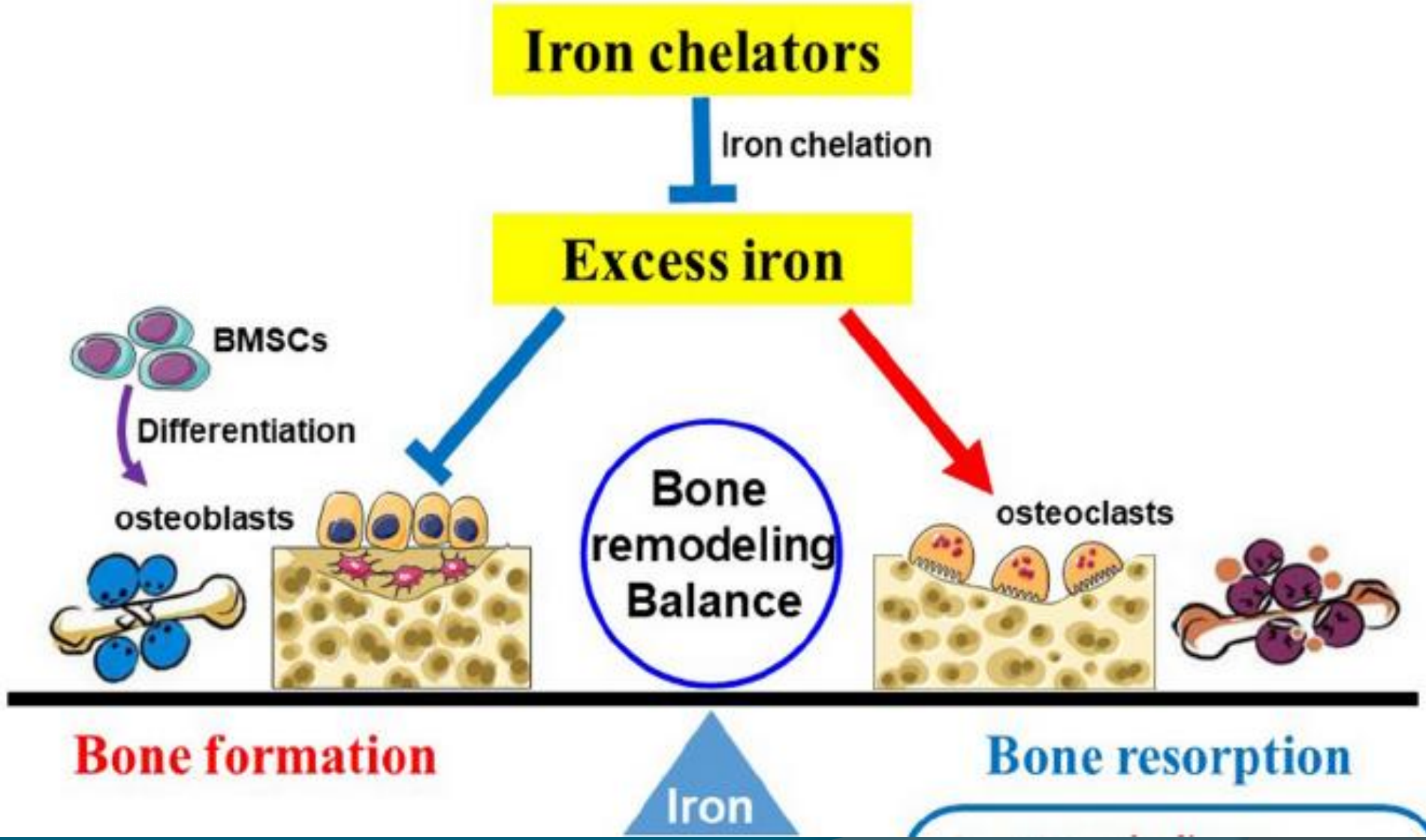
desferal toxicity??

THALASSEMIA MAJOR

PTH, CALCIUM, PHOSPHOR, VITAMIN D




↓ Vitamin D
↓ Intestinal Ca absorption
↓ Estrogen
ging
Osteoporosis
Abnormal Ca metabolism
Abnormal bone remodeling
Fracture
Fall prevention
Eldecalcitol
Bisphosphonates
SERMs
Denosumab

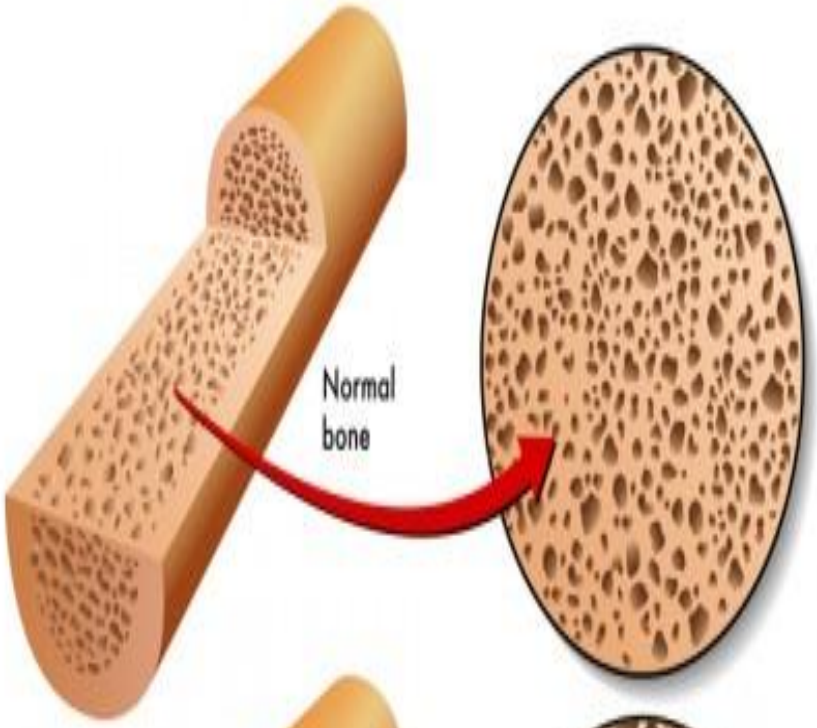

Iron chelators
Iron chelation
Excess iron
BMSCs
Differentiation
osteoblasts
Bone remodeling Balance
osteoclasts
Bone formation
Iron
Bone resorption

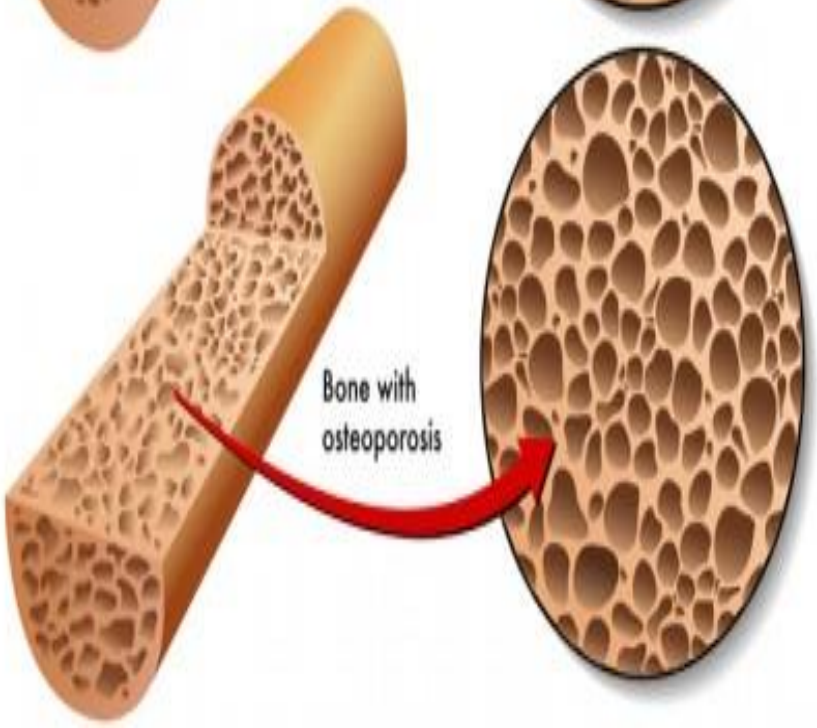
Iron chelators have been used to prevent iron overload in thalassaemia major patients, but these chelators have the possibility of removing minerals from the body?????

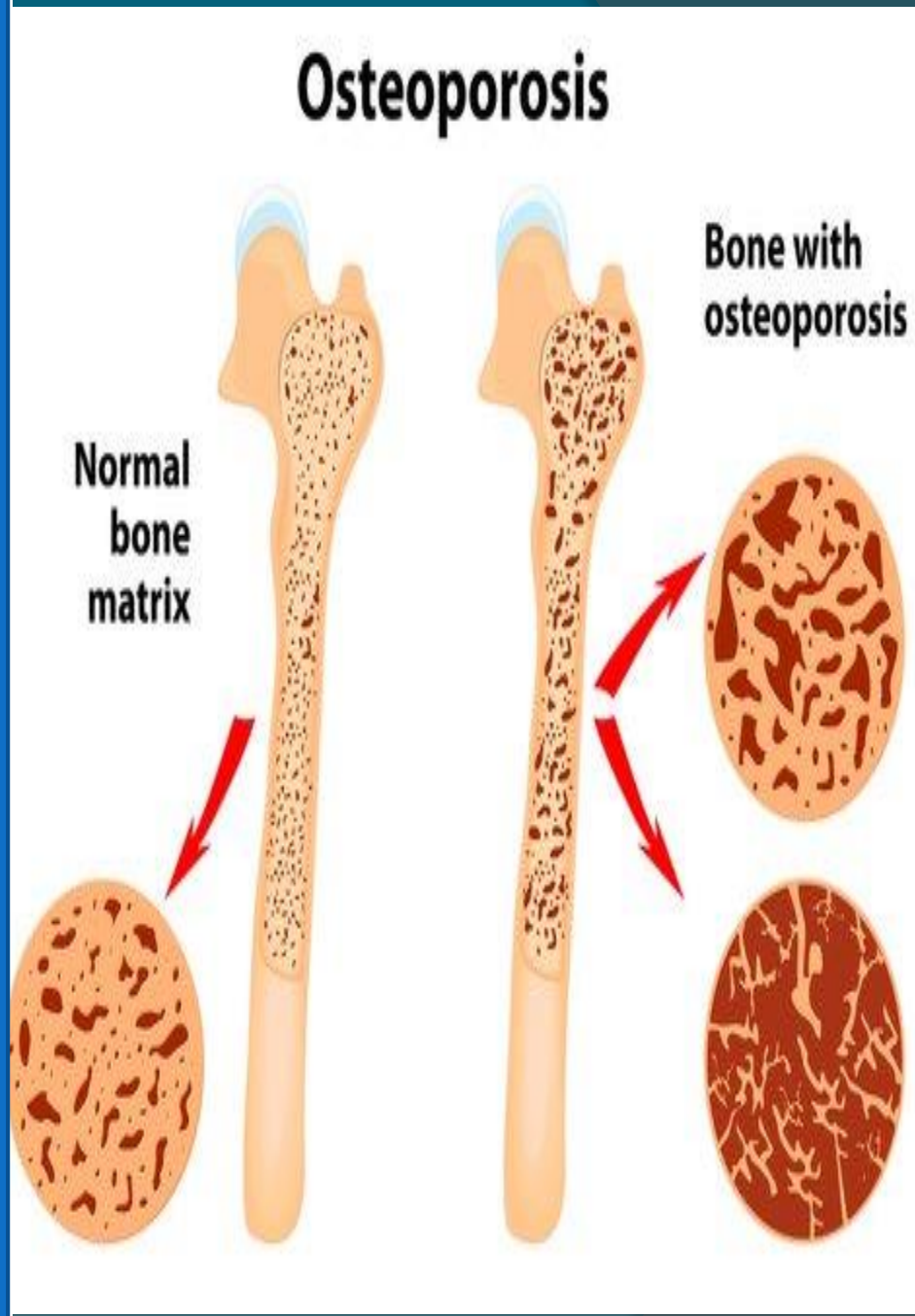
But in some recent studies iron chelators present as:

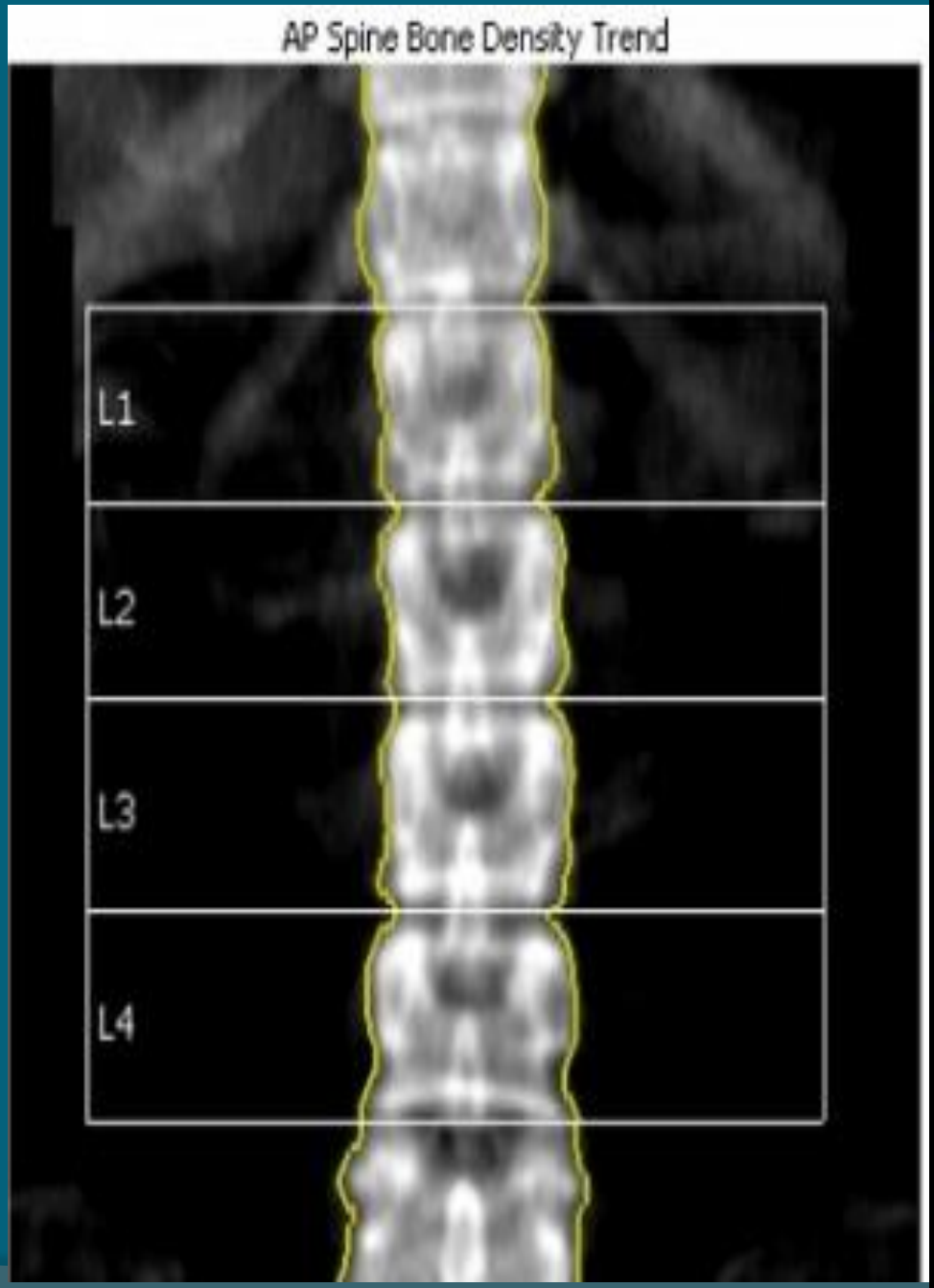
Iron chelators serve as antioxidants
Therapeutic effects of iron chelators on osteoporosis

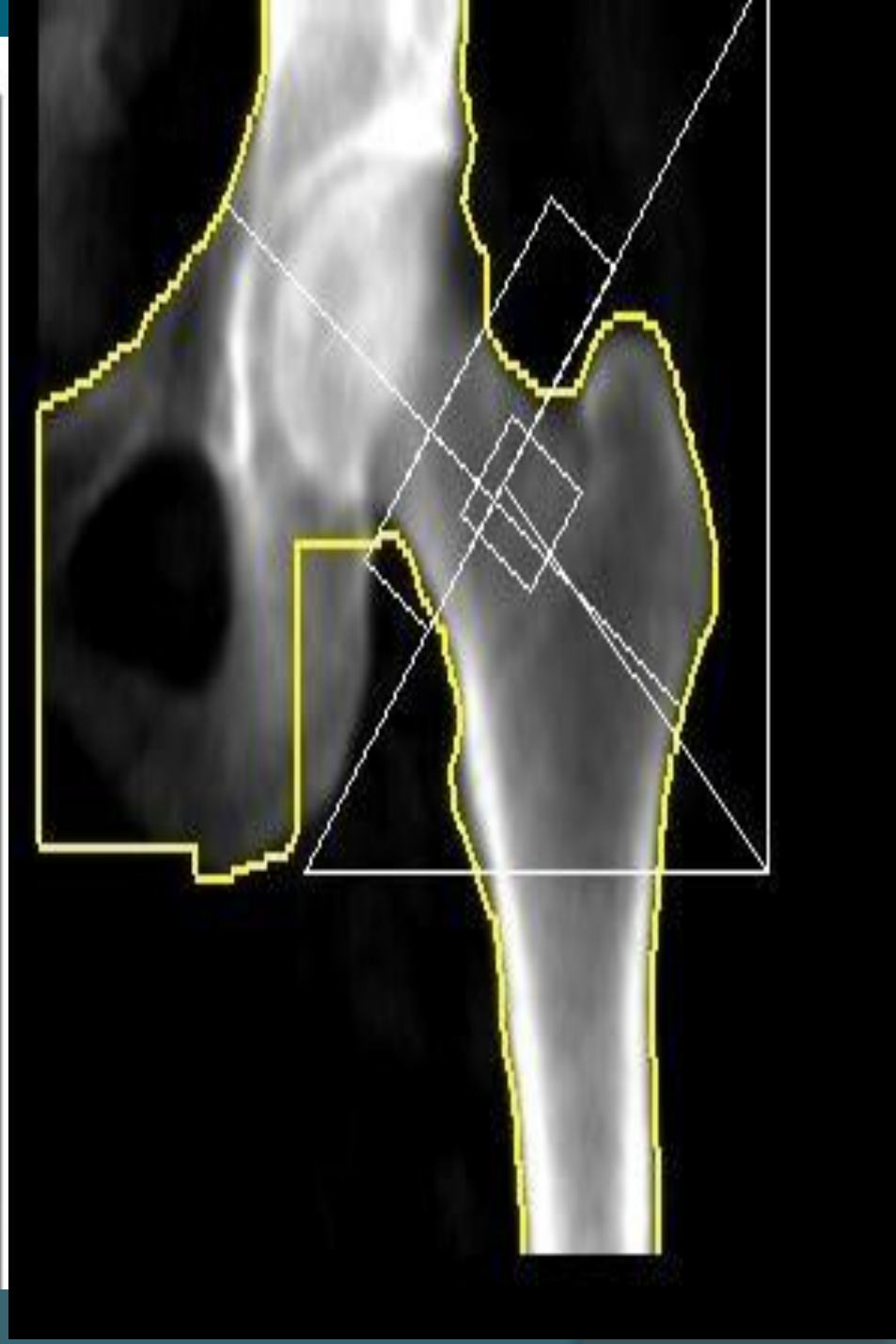
Iron chelators can be used as osteo protective drugs for treating the osteoporosis ????


Normal bone

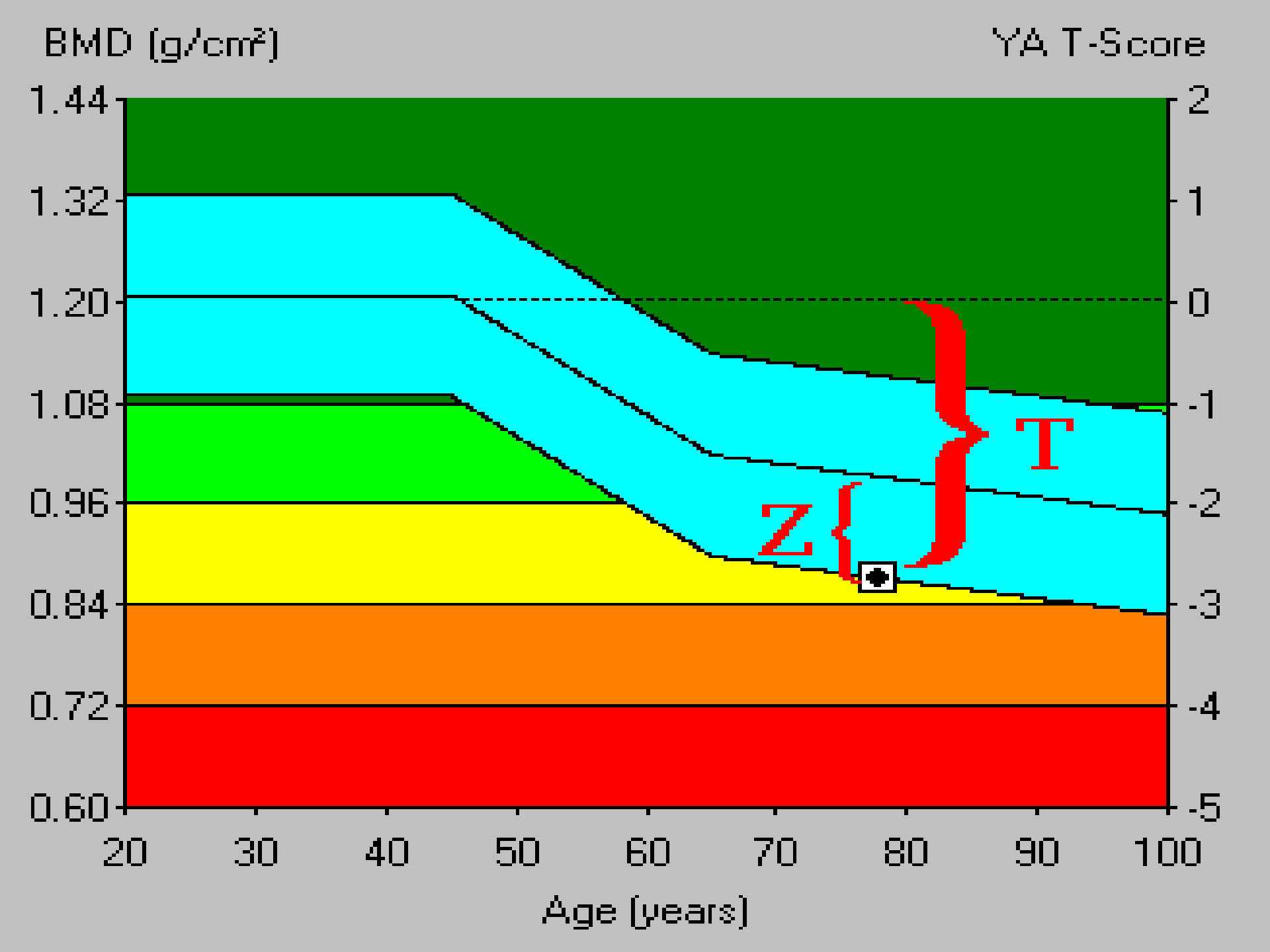

Bone with osteoporosis


Osteoporosis
Normal bone matrix
Bone with osteoporosis


AP Spine Bone Density Trend
L1
L2
L3
L4



	BMD(g/CM2)	T-score	Z-score
L1			
L2			
L3			
L4			
L1-L4			
femor			
wrist			


BMD (g/cm²)
YA T-Score
1.44
1.32
1.20
1.08
0.96
0.84
0.72
0.60
2
1
0
-1
-2
-3
-4
-5
20
30
40
50
60
70
80
90
100
Age (years)
Z
T

T-Score	% of Bone Loss
0.0	0
-1.0	10%
-2.0	20%
-2.5	25%
-3.0	30%
-4.0	40%

Threapetic solutions:

Nutritional corrections and supplements

Vitamin D supplements (active or other forms)

Bisphosphonates

Testostrone enanthate & estrogens

Growth

Growth and maturational delay are the complications of thalassaemia.

Growth failure in thalassaemia major (TM) has been recognised for many years, and has persisted despite major therapeutic advances

Main causes for short stature include:

Chronic anemia & tissue hypoxia

Malnutrition & malabsorption((Pancreas insufficiency (exocrine & endocrine))

Ca-Ph-Vit D Imbalances

GH deficiency & dysregulation of the GH-IGF-1 axis

Hypogonadism

Othe endocrinopathies (diabetes & hypothyroidism….)

Cardiomyopathy ,Liver insufficiency & Renal insufficiency

❖ Failure to weight gain is more prevalent than short stature

The patients tend to show body disproportion, with truncal shortening but normal leg length.

The child with TM has a particular growth pattern, which is

relatively normal until age 9-10 years

&

after this age a slowing down of growth velocity and reduced or absent pubertal growth spurt are observed

Three phases of growth disturbances according to age of presentation are well recognized, and have different etiologies:

first phase : growth disturbance is mainly due to hypoxia, anemia, ineffective erythropoiesis and nutritional factors

second phase late childhood , growth retardation is mainly due to iron overload affecting GH-IGF-1 axis.

After the age of 10-11 years (third phase), delayed or arrested puberty is an important contributing factor to growth failure in adolescent thalassemics , who do not exhibit a normal growth spurt.

Diabetes

Diabetes is a significant complication of β-thalassemia major (β-TM) and most patients receive fragmented diabetes care.

The overall prevalence of diabetes in patients with thalassemia major was estimated 9 percent. The difference in reporting the prevalence of diabetes in patients with thalassemia major in Iran was 1.8-34% and it seems the most prospective reason for this difference, different diagnostic criteria.

No relationship between serum ferritin and development of diabetes was noted.

In this patient insulin was started after definite diagnosis.

The development of diabetes in thalassemia is attributed to :

- impaired insulin excretory function secondary to chronic iron overload in the pancreas (transfusional&Poor chelator therapy..)
- selective immune system activation against pancreatic *β*-cells leading to cell damage (autoimmunity)
- pancreatic cell death due to fat transformation.
- impaired insulin sensitivity was associated with inflammation markers and somatic iron overload (secondary to liver dis, HCV INF..)
- Global epidemic T1DM & T2DM

A pancreatic MRI $T2^*$ coupled with a gradient echo sequence is recommended for detecting pancreatic fat and predicting the incidence of diabetes .

A serum ferritin level of around 3000 ng/mL has been shown to be associated with a higher risk of developing diabetes .

Iron-mediated diabetes can be partially reversed if treated earlier .

High doses of insulin are required to correct blood glucose levels in these diabetic patients .

Experts recommend early screening and detection of glucose impairments and insulin resistance in all thalassemia patients starting at age of 8 to 10 years as the disease can be halted before developing into overt-diabetes in adulthood .

According to TIF NTDT guidelines, patients with β-TI who are ≥10 years should undergo annual fasting blood sugar and if indicated oral glucose tolerance test

Hypothyroidism

Hypothyroidism is a late consequence of iron deposition in the thyroid gland that ultimately leads to parenchymal fibrosis .

Prevalence of hypothyroidism ranges from 4% to 24.4% in *β*-TM and 2 to 3% in *β*-TI .

Splenectomy is a specific risk factor for hypothyroidism in *β*-TI. The risk of hypothyroidism is significantly increased with every 1 mg Fe/kg DW elevation in LIC.

According to the TIF NTDT guidelines, free thyroxine (FT4) and thyroid-stimulating hormone need to be performed annually on all *β*-TI patients ≥10 years .

Thyroid dysfunction, if detected early, can also be reversed with combined desferrioxamine (DFO) and deferiprone (DFP) chelation??.

No correlation was found between thyroid functional status and ferritin plasma levels??.(another study)

In a study from North America, 90 percent of chelated patients showed no thyroid dysfunction .

In the Optimal Care Study, hydroxyurea (HU) treatment was found to be protective against hypothyroidism in *β*-TI when compared to transfusion therapy, which was found to be a risk factor .

However, low doses of HU (8–15 mg/kg/day) did not alter thyroid function in *β*-TI patients in one study . (More studies are required)

Hypoparathyroidism

Hypoparathyroidism

In TM, contributing factors include poor compliance with desferrioxamine and elevated serum ferritin levels reaching 3000 ng/mL, which is correlated with hypoparathyroidism as well .

Hypoparathyroidism, seen in up to 6.7% of TM patients, is not well studied in β-TI .

β-TI patients ≥10 years need to be screened for this complication by ca, ph, and vitamin D every year and by parathyroid hormone level if indicated .

Calcitriol is recommended for mild hypocalcemia and intravenous calcium administration followed by oral vitamin D for severe cases with tetany .

Early iron chelation to prevent hypothyroidism and hypoparathyroidism is recommended by the Thalassemia Clinical Research Network.

Liver damage may also play an important role in determining the altered lipoprotein pattern in beta-thalassemia .

In addition, vitamin E plays an important role in the reduction of LDL oxidation .

A study conducted on 30 individuals with TI has shown that the content of plasma and LDL *α*-tocopherol was significantly lower as compared to the control group .

While the studies showing the efficacy of vitamin E are limited to 15 patients with TI that were treated with 600 mg/day for a period of 9 months, the levels of vitamin E started to increase within 3 months as well as the levels of LDL .

Routine lipid profile investigation in young *β*-TI patients is not recommended .

Thank you

Happy days in
namak abrood congress