12° Congresso Nazionale AME
6th Joint Meeting with AACE

Update in Endocrinologia Clinica

OSTEOMALACIA
DIAGNOSI
ROBERTO CESAREO

OSTEOMALACIA
DIAGNOSI DIFFERENZIALE

Table 2 Differential diagnosis of osteomalacia.

Type of disorder	Etiology
Disorders of vitamin D metabolism	Decreased bioavailability (due to nutritional deficiency, malabsorption, insufficient sunlight)
	Abnormal metabolism (due to TIO, XLH, renal and liver disease, 1α-hydroxylase deficiency, anticonvulsant medications)
	Abnormal target tissue response (due to vitamin D receptor defects)
Disorders of phosphate homeostasis	Decreased intestinal absorption (caused by malabsorption, malnutrition, aluminum hydroxide)
	Renal wasting (due to TIO, XLH, Fanconi's syndrome)
Bone matrix abnormalities	Hypophosphatasia and others
Inhibition of bone mineralization	Pharmacologic (drugs and chemicals, e.g. etidronate, fluoride, aluminum)
Calcium deficiency	Insufficient dietary intake

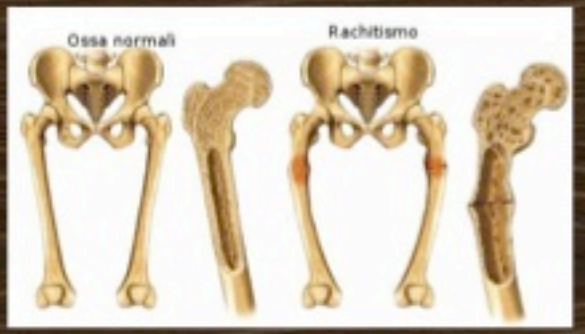
Abbreviations: TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia.

nature CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM

DIAGNOSI CLINICA

Il dolore osseo

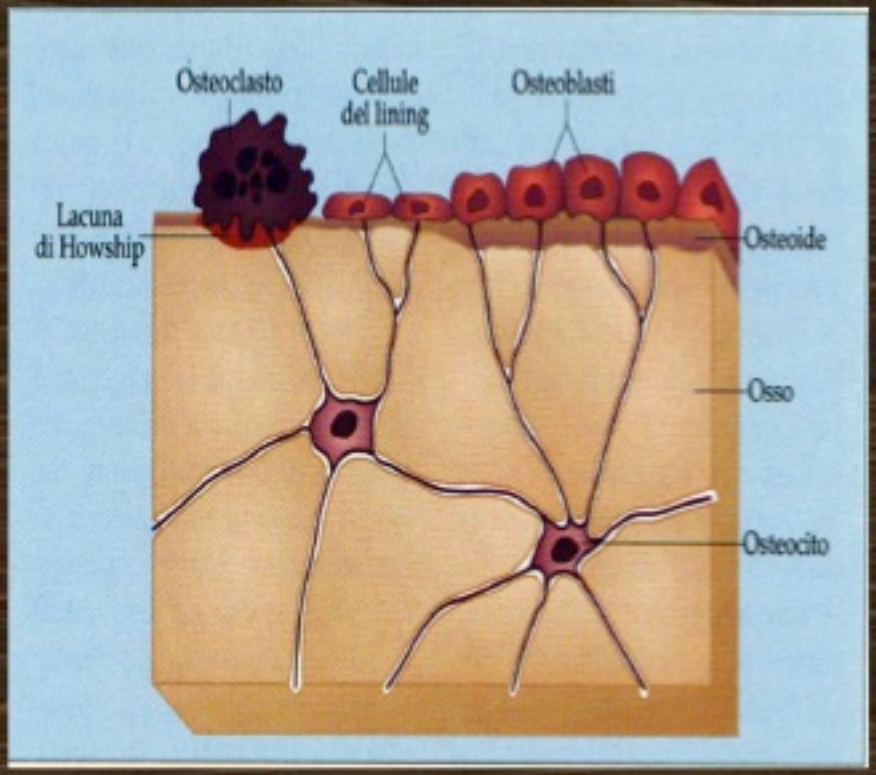
La parte Inferiore della colonna vertebrale
Bacino - Fianchi
Gambe –Costole

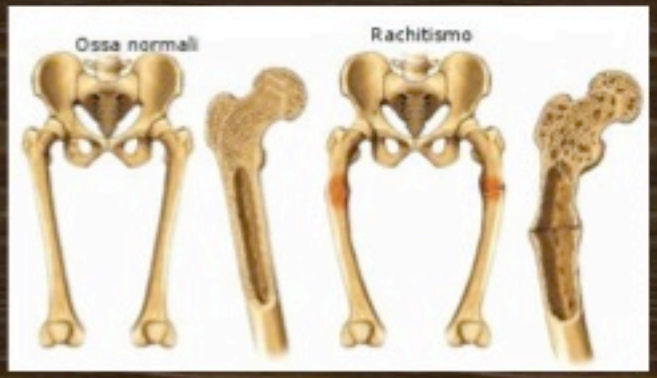


La debolezza muscolare

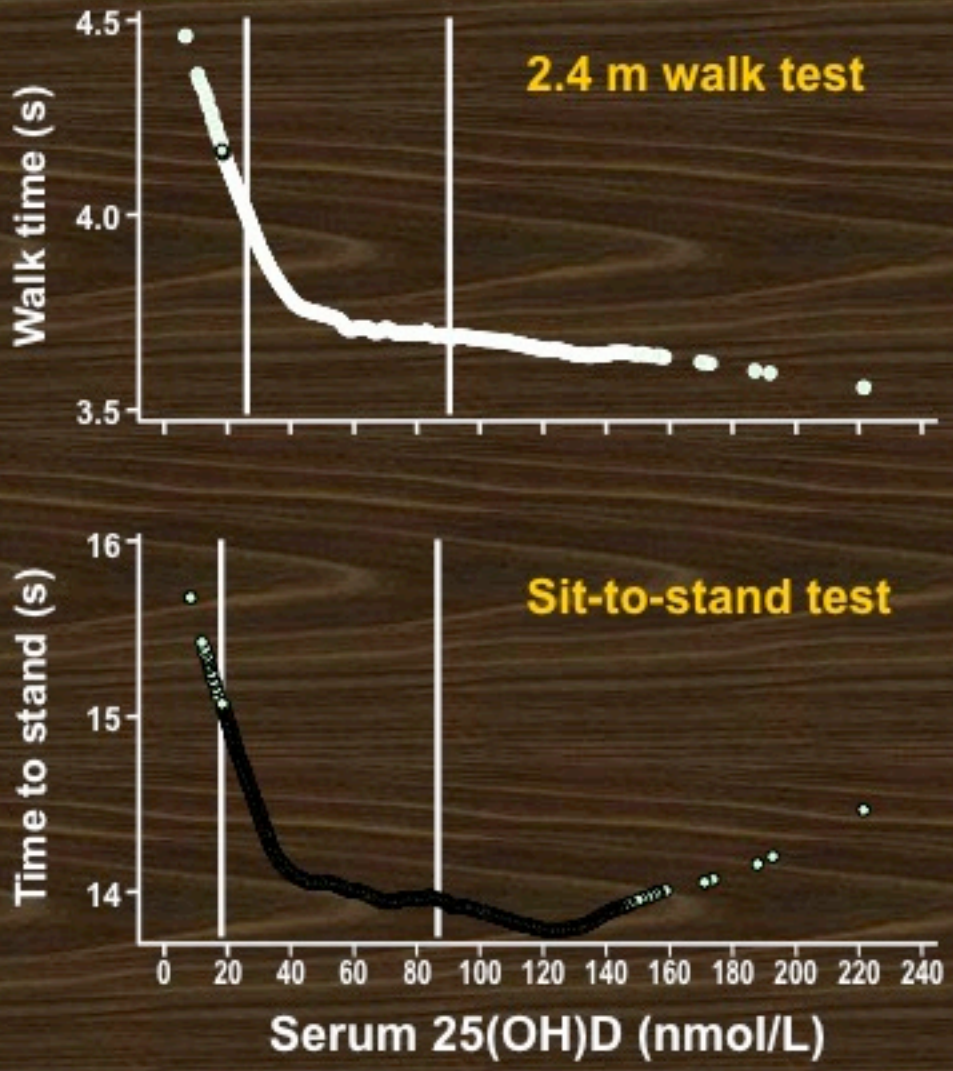
Diminuzione del tono muscolare
Debolezza cingoli scapolare e pelvico
Ridotta capacità di deambulare
Andatura ondeggiante

LE OSTEOMALACIE



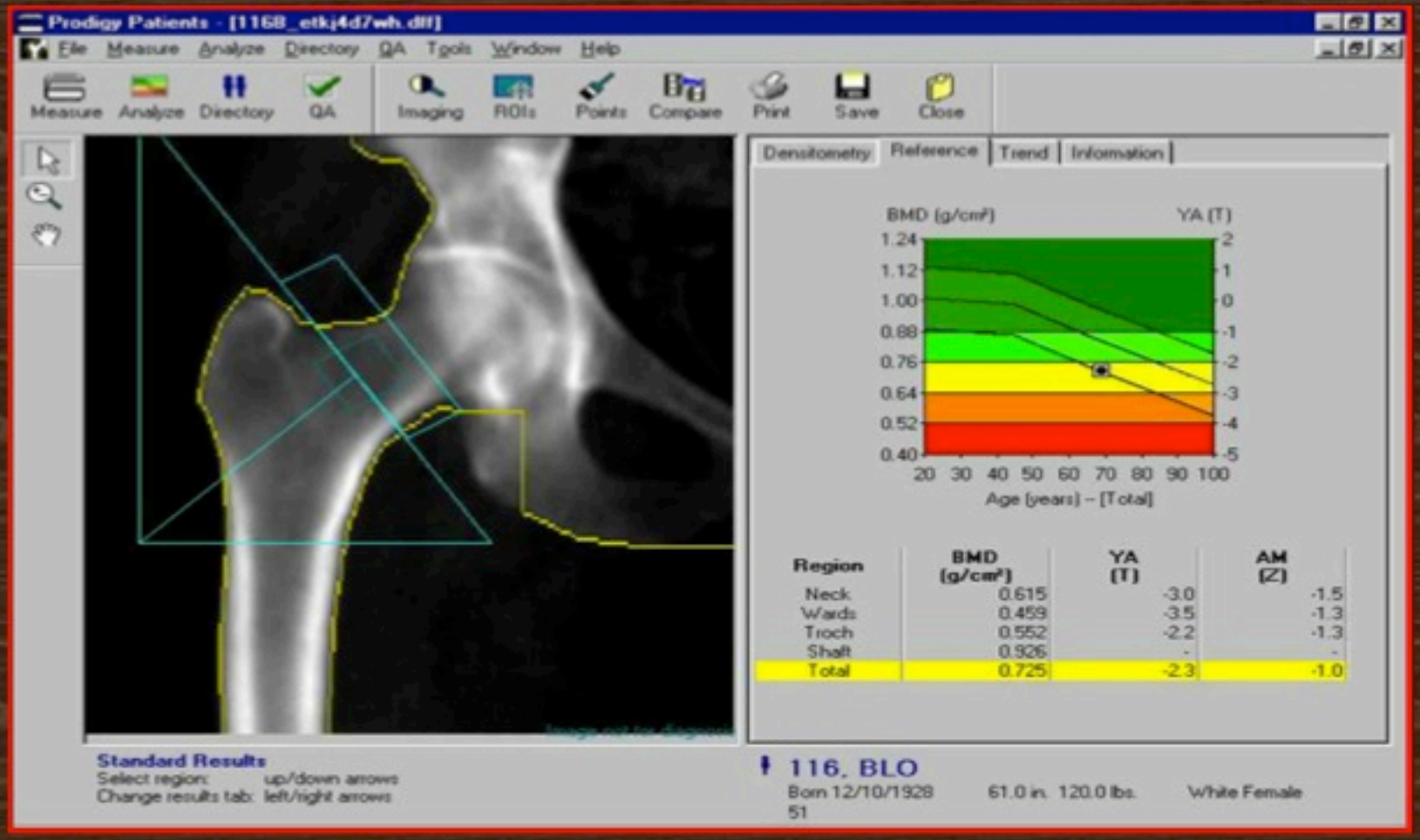

Ossa normali
Rachitismo

Miglioramento della miopatia con l'aumento dei livelli di Vit-D3

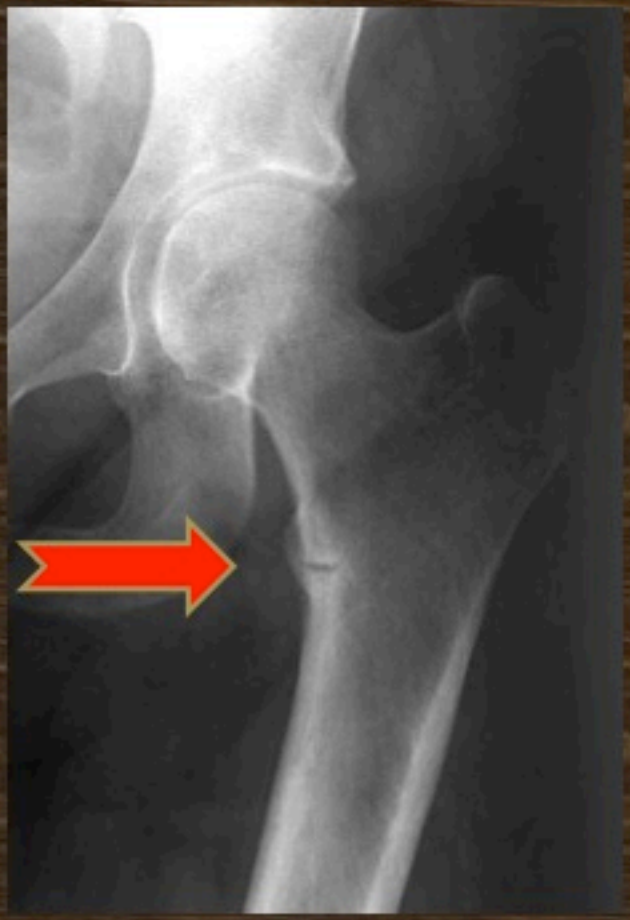


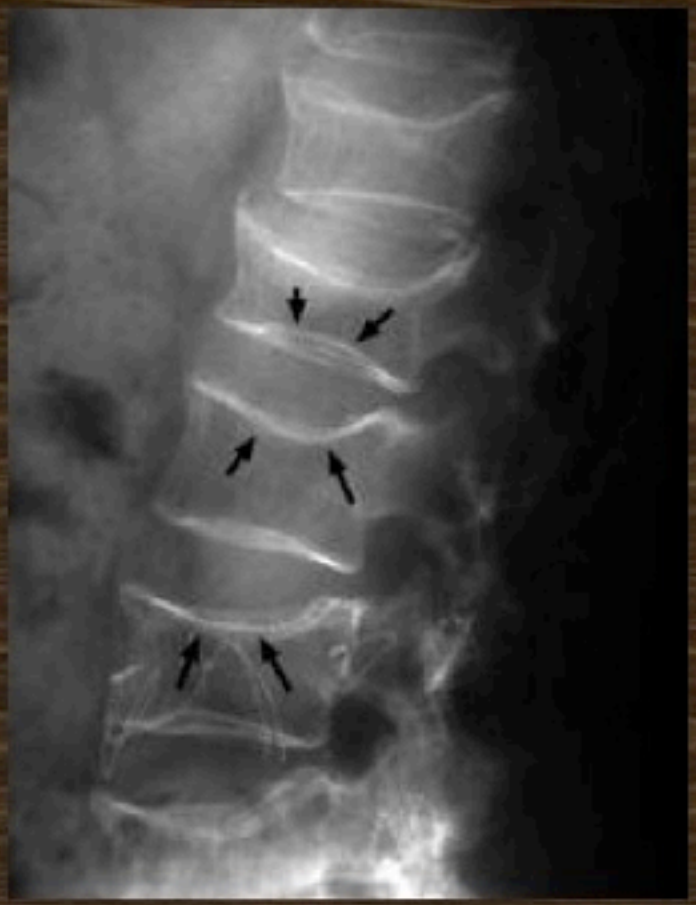
Bischoff-Ferrari H.A., Curr. Opin. Endocrinol. Diabetes, 2005

ESAMI STRUMENTALI

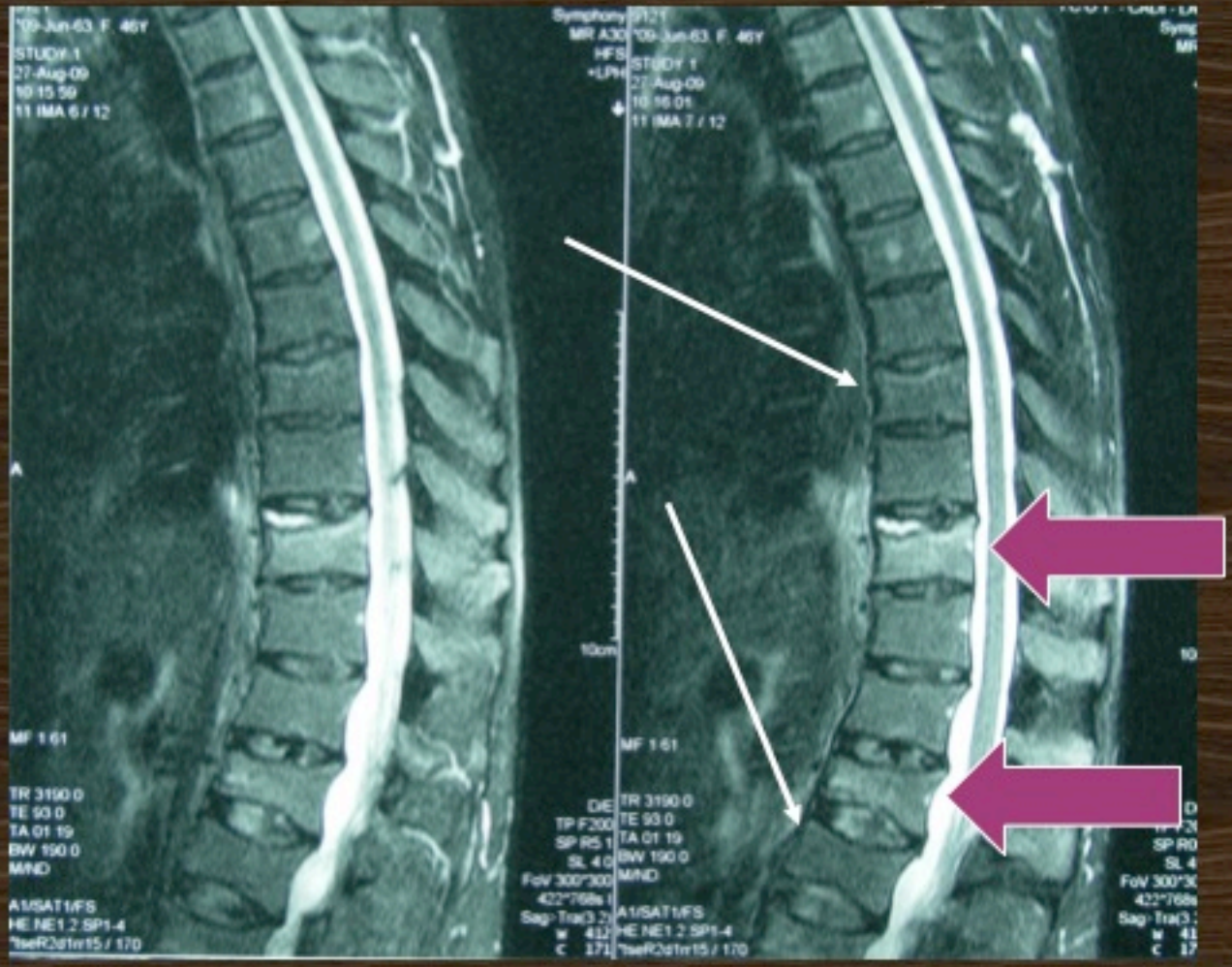


OSTEOMALACIA
DIAGNOSI RADIOLOGICA

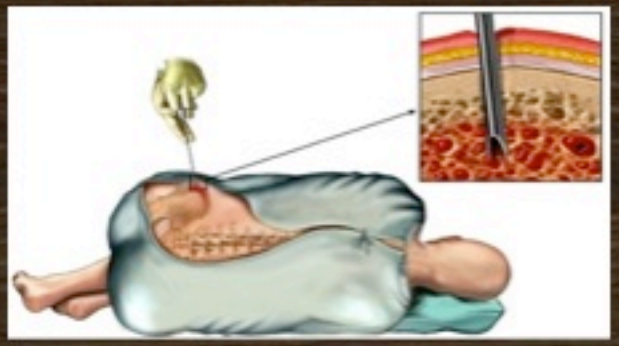


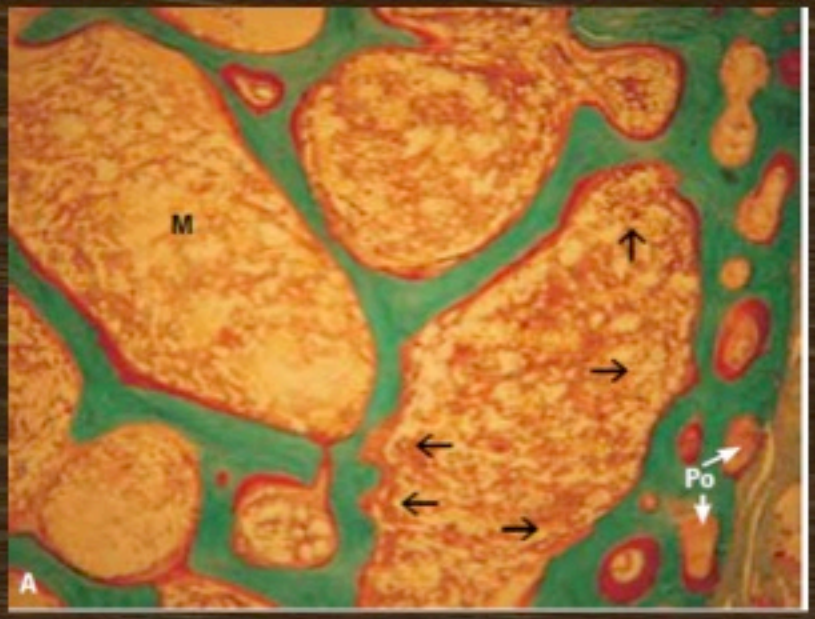


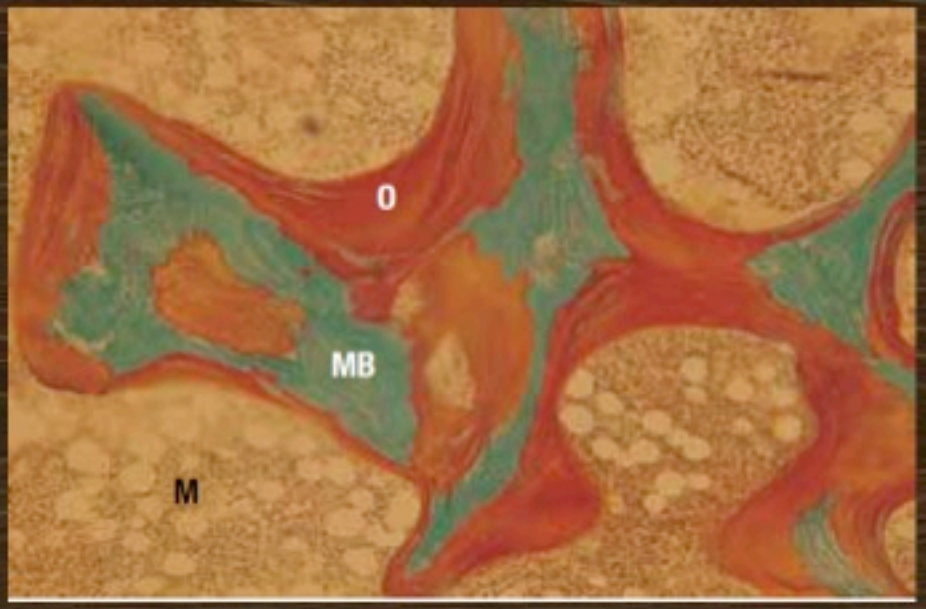
RMN RACHIDE DORSO LOMBARE



ISTOMORFOMETRIA







Quadro laboratoristico osteomalacia
Quadro classico

Ipofosforemia

Ipocalcemia

Fosfatasi alcalina aumentata

Ridotti livelli di 25-0H vit D

PTH aumentato

Calciuria ridotta

Rilievi biochimici tipici delle principali malattie metaboliche scheletriche

(in verde le alterazioni necessarie per porre la diagnosi)

	Ca	P	PTH	25(OH)D	Fosfatasi alcalina
Osteoporosi	=	=	=	= ↓	= ↑
Iperparatiroidismo primitivo	↑↑	= ↓↓	↑↑	= ↓	= ↑↑
Ipercalcemia neoplastica	↑↑	= ↓	↓	= ↓	= ↑↑
Osteomalacia	↓↓	↓↓	↑	↓	↑↑
M. di Paget	=	=	=	=	↑

= nella norma

↑ modesto aumento

↓ modesta riduzione

↑ notevole aumento

↓ notevole riduzione

Causes of Osteomalacia

	Ca	PO_4	25-D	1,25-D	PTH	Other
Vitamin D abnormalities						
D-deficiency	~↓	~↓	↓	±↑	↑	
Liver disease	↓	↓	↓	↓	N	
Renal disease	↓	↑	N	↓	↑↑	
1 α hydroxylase deficiency "vitamin D dependent rickets" type I	↓	↓	N	↓↓	↑	
Vitamin D Resistance "vitamin D dependent rickets type II"	↓	↓	N	↑↑	↑	
Hypophosphatemia						
x-linked hypophosphatemic rickets "Vitamin D Resistant Rickets" *PHEX mutation*	±↓	↓	N	Lower than expected for the PO_4	±↑	↑FGF 23
Autosomal dominant hypophosphatemic rickets *FGF23 mutation*						
Autosomal recessive hypophosphatemic rickets *DMP1 mutation*						
Excessive Klotho *Klotho mutation*						
Oncogenic osteomalacia *FGF23 secretion*						
HHRH "Hereditary hypophosphatemic rickets with hypercalciuria", *NaPi2c mutation*	N	↓	N	↑	N	↑urine calcium
Renal phosphate loss (including Fanconi's syndrome, Dent's disease, cadmium toxicity, heavy metal poisoning)	N	↓	N	N	N	
Excessive antacid intake	N	↓	N	±↑	N	
Toxicities						
Fluoride	N	N	N	N	N	
Etidronate	N	±↑	N	N	N	
Parenteral Aluminum	N	N	N	±↓	↓	
Imatinab	±↓	↓	±↓	N	↑	
Other						
Hypophosphatasia	N	N	N	N	N	↓↓Alk Phos
Acidosis	N	N	±↓	N	N	↓Bicarbonate

N = normal, ~ means mildly low, ± means abnormality seen sometimes, Alk Phos = alkaline phosphatase, which is usually increased in osteomalacia.

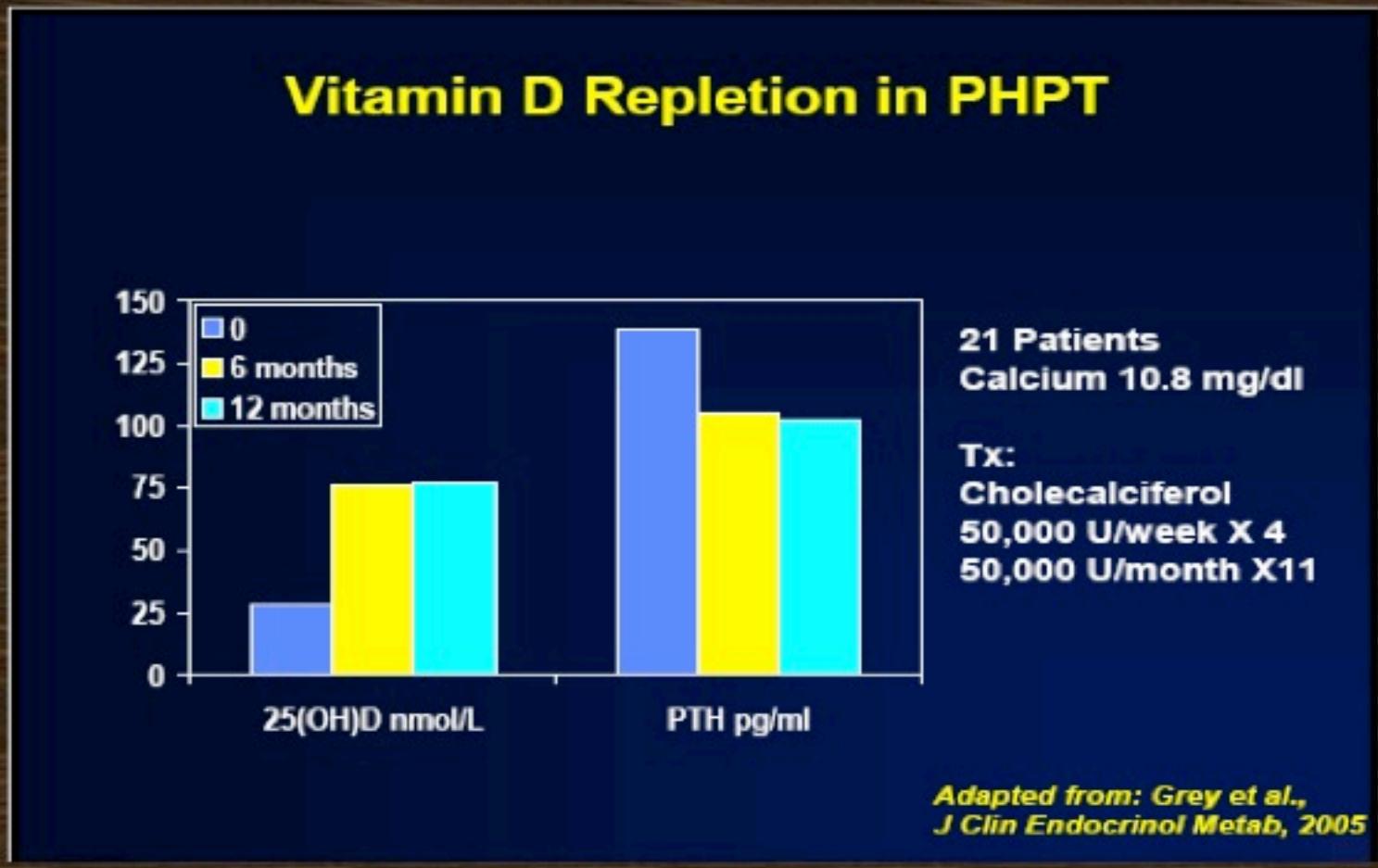
Classificazione clinica dei livelli di 25-OH-vitamina D	
Livello	**Interpretazione**
< 5 ng/mL (12.5 nmol/L)	Carenza di grado severo
< 10 ng/mL (< 25 nmol/L)	Deficit moderato: ridotta mineralizzazione ossea e aumentato rischio di frattura
10-30 ng/mL (25-75 nmol/L)	Ipovitaminosi D di grado lieve: aumento del PTH e del *turn-over* osseo
30-100 ng/mL (75-250 nmol/L)	Stato adeguato
> 100 ng/mL (> 250 nmol/L)	Tossicità

Pathologic service laboratory handbook Massachusetts General Hospital

25-OH D reference interval desired

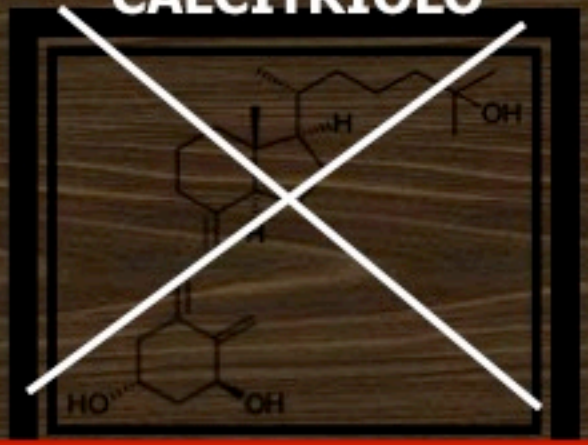
> 32 ng/ml

Vitamin D Repletion in Patients with Primary Hyperparathyroidism and Coexistent Vitamin D Insufficiency

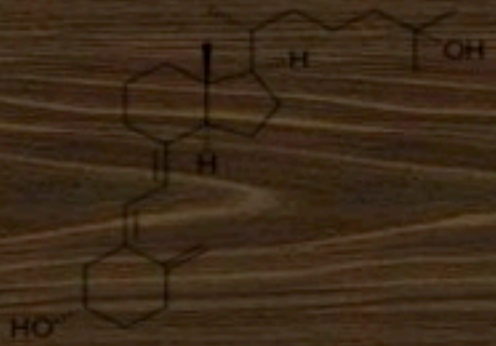


COSA DOSARE?

CALCITRIOLO



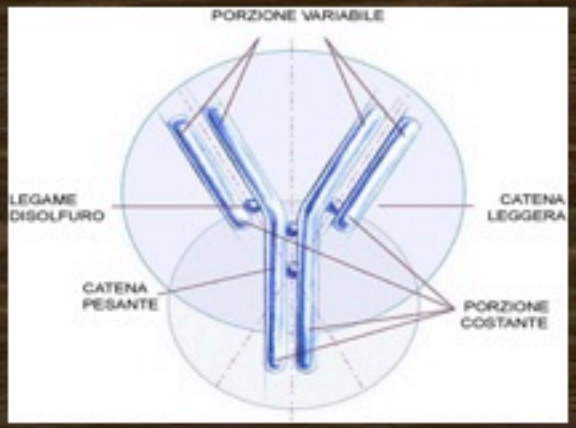
25 (OH) VIT. D



QUALE METODICA?

HPLC

IMMUNOMETRIA



Stato Vitaminico D

- I livelli sierici di 25(OH)D riflettono lo stato vitaminico D
- I livelli sierici di $1,25(OH)_2D$ non possono essere utilizzati per determinare lo stato vitaminico D, in quanto:
  - L'emivita della $1,25(OH)_2D_3$ è 10-20 h
  - Le sue concentrazioni sono ~ 1000 volte inferiori a quelle della 25(OH)D

Measure 25(OH) vitamin D, not 1,25(OH)2 vitamin D

There are only **a few situations where you would actually want to know the 1,25-D:**

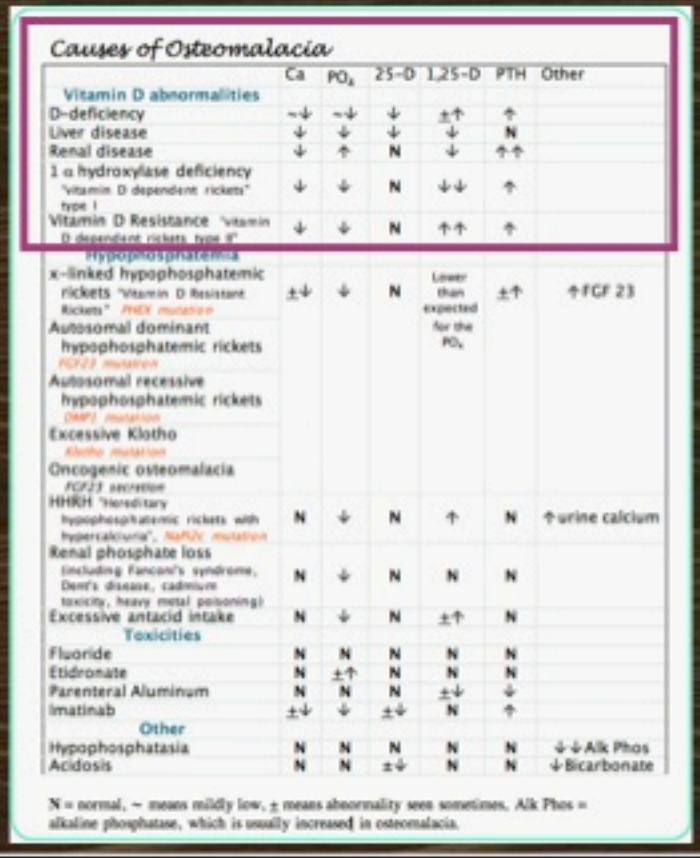
- Unexplained hypercalcemia
(looking for granulomatous disease or lymphoma)

- Some cases of nephrolithiasis or hypercalciuria

- Suspected tumor-induced osteomalacia

- Suspected genetic rickets (vit D dep. Rickets type-2

Susan Ott 2010



Causes of Osteomalacia

	Ca	PO_4	25-D	1,25-D	PTH	Other
Vitamin D abnormalities						
D-deficiency	~↓	~↓	↓	±↑	↑	
Liver disease	↓	↓	↓	↓	N	
Renal disease	↓	↑	N	↓	↑↑	
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Renal phosphate loss (including Fanconi's syndrome, Dent's disease, cadmium toxicity, heavy metal poisoning)	N	↓	N	N	N	
Excessive antacid intake	N	↓	N	±↑	N	
Toxicities						
Fluoride	N	N	N	N	N	
Etidronate	N	±↑	N	N	N	
Parenteral Aluminum	N	N	N	±↓	↓	
Imatinab	±↓	↓	±↓	N	↑	
Other						
Hypophosphatasia	N	N	N	N	N	↓↓Alk Phos
Acidosis	N	N	±↓	N	N	↓Bicarbonate

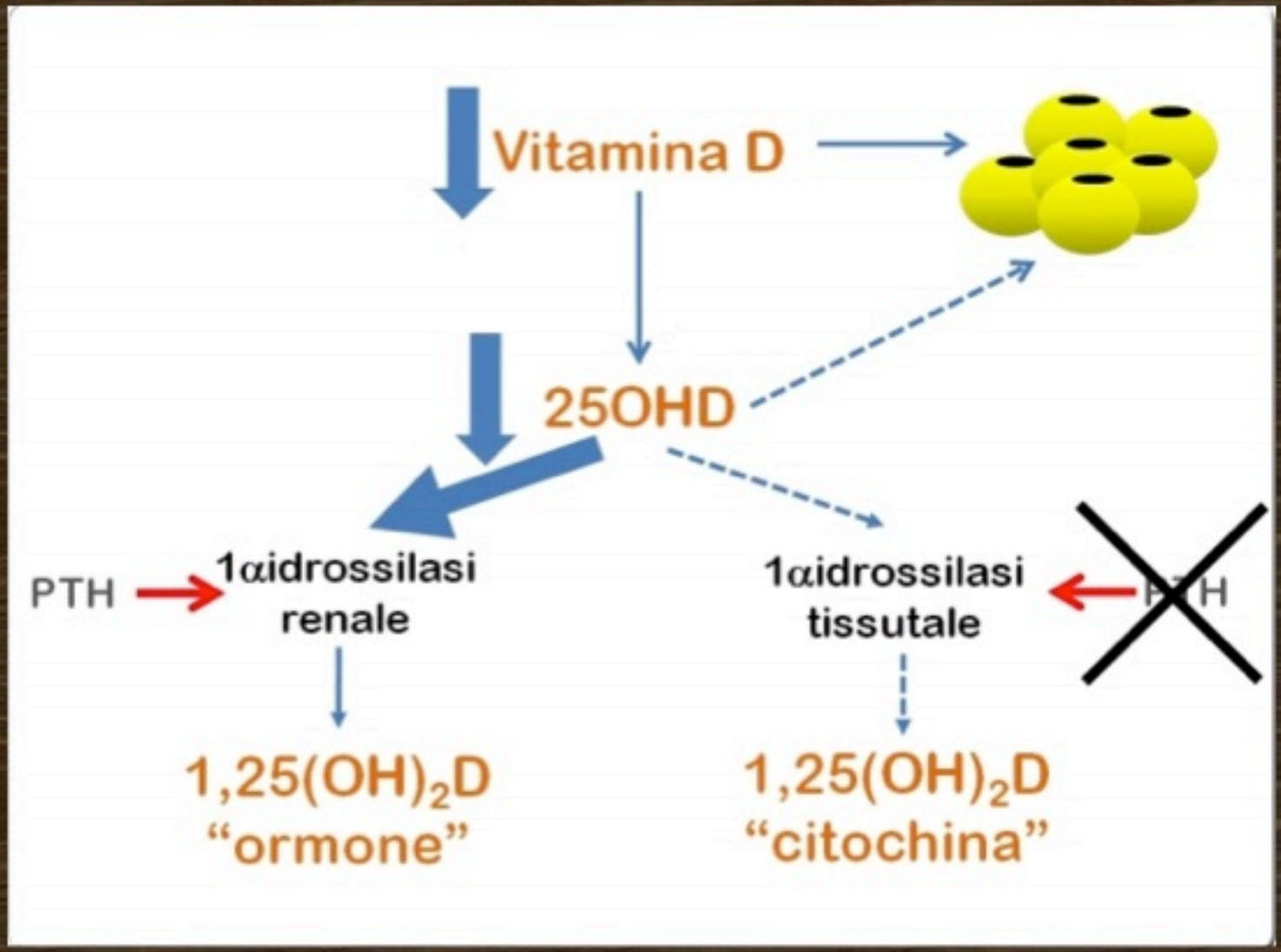
N = normal, ~ means mildly low, ± means abnormality seen sometimes, Alk Phos = alkaline phosphatase, which is usually increased in osteomalacia.

Tabella 13b.1

Diagnosi differenziale delle forme di rachitismo genetico

	Calcemia	25-OH-D	calcitriolo	PTH	Difetto presunto
VDDR 1	↓	↓ o N	↓↓	↑	1α-idrossilasi renale
VDRR2	↓	↓ o N	↑ o N	↑	Recettore (VDR)

1αidrossilasi tissutale e Vitamina D



OSTEOMALACIA
DIAGNOSI DIFFERENZIALE

Table 2 Differential diagnosis of osteomalacia.

Type of disorder	Etiology
Disorders of vitamin D metabolism	Decreased bioavailability (due to nutritional deficiency, malabsorption, insufficient sunlight)
	Abnormal metabolism (due to TIO, XLH, renal and liver disease, 1α-hydroxylase deficiency, anticonvulsant medications)
	Abnormal target tissue response (due to vitamin D receptor defects)
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Bone matrix abnormalities	Hypophosphatasia and others
Inhibition of bone mineralization	Pharmacologic (drugs and chemicals, e.g. etidronate, fluoride, aluminum)
Calcium deficiency	Insufficient dietary intake

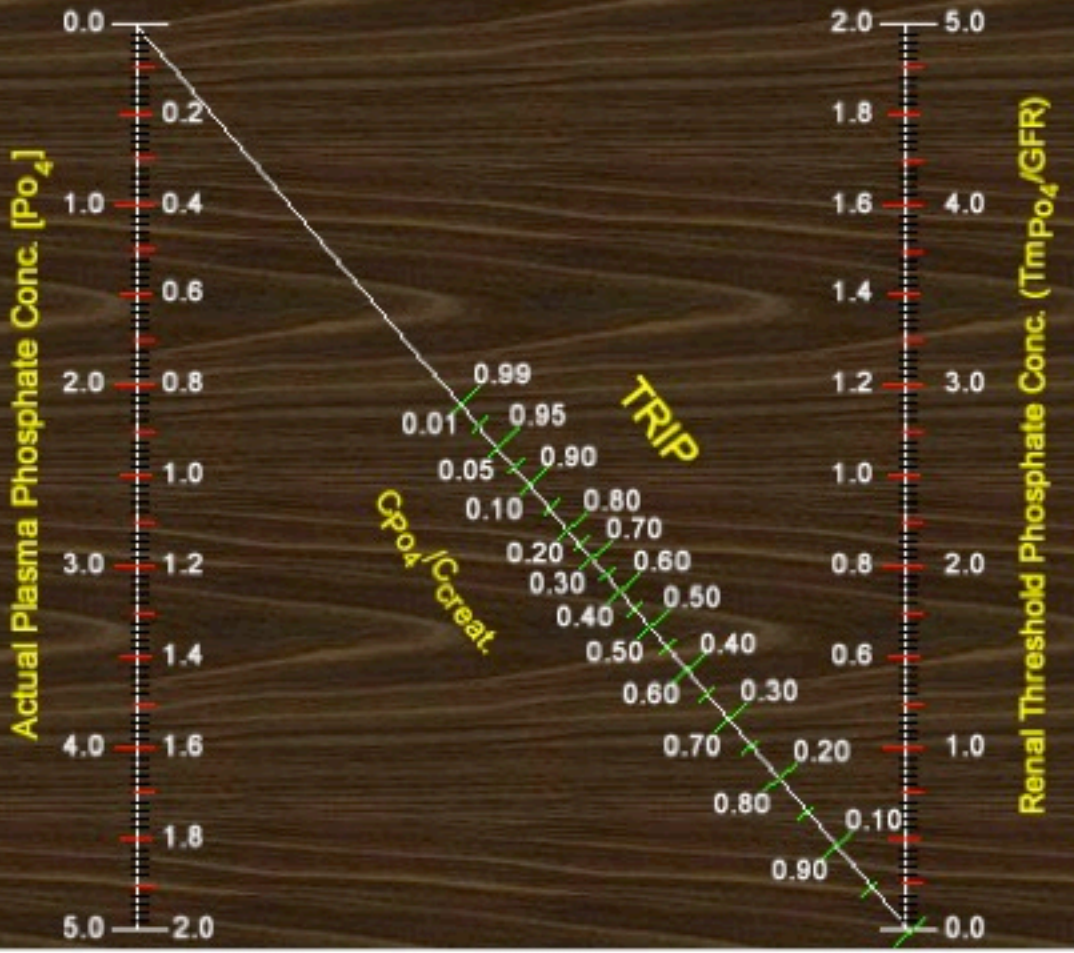
Abbreviations: TIO, tumor-induced osteomalacia; XLH, X-linked hypophosphatemia.

nature CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM

IPOFOSFOREMIA

- IPOFOSFOREMIA LIEVE = valori compresi tra 1,0 e 2,5 mg/dL (generalmente asintomatica)
- IPOFOSFOREMIA SEVERA = valori inferiori ad 1,0 mg/dL

NORMOGRAMMA PER IL CALCOLO DEL RIASSORBIMENTO TUBULARE DI FOSFATI (% TRP)



100×(1−((urine phosphate/urine creatinine)×(serum creatinine/serum phosphate))).

When phosphate is normal, the normal range is between 85 and 95%.

Causes of Osteomalacia

	Ca	PO_4	25-D	1,25-D	PTH	Other
Vitamin D abnormalities						
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Liver disease	↓	↓	↓	↓	N	
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Excessive antacid intake	N	↓	N	±↑	N	
Toxicities						
Fluoride	N	N	N	N	N	
Etidronate	N	±↑	N	N	N	
Parenteral Aluminum	N	N	N	±↓	↓	
Imatinab	±↓	↓	±↓	N	↑	
Other						
Hypophosphatasia	N	N	N	N	N	↓↓Alk Phos
Acidosis	N	N	±↓	N	N	↓Bicarbonate

N = normal, ~ means mildly low, ± means abnormality seen sometimes, Alk Phos = alkaline phosphatase, which is usually increased in osteomalacia.

Physiological Regulation and Disorders of Phosphate Metabolism

- Sindrome di Fanconi
- Tossicità da metalli pesanti (cadmio)
- Rachitismo ipofosforemico con ipercalciuria (Mutazione di NaPi2c)
- Osteomalacia da Idrossido di Alluminio

Causes of Osteomalacia

	Ca	PO_4	25-D	1,25-D	PTH	Other
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Excessive antacid intake	N	↓	N	±↑	N	
Toxicities						
Fluoride	N	N	N	N	N	
Etidronate	N	±↑	N	N	N	
Parenteral Aluminum	N	N	N	±↓	↓	
Imatinab	±↓	↓	±↓	N	↑	
Other						
Hypophosphatasia	N	N	N	N	N	↓↓Alk Phos
Acidosis	N	N	±↓	N	N	↓Bicarbonate

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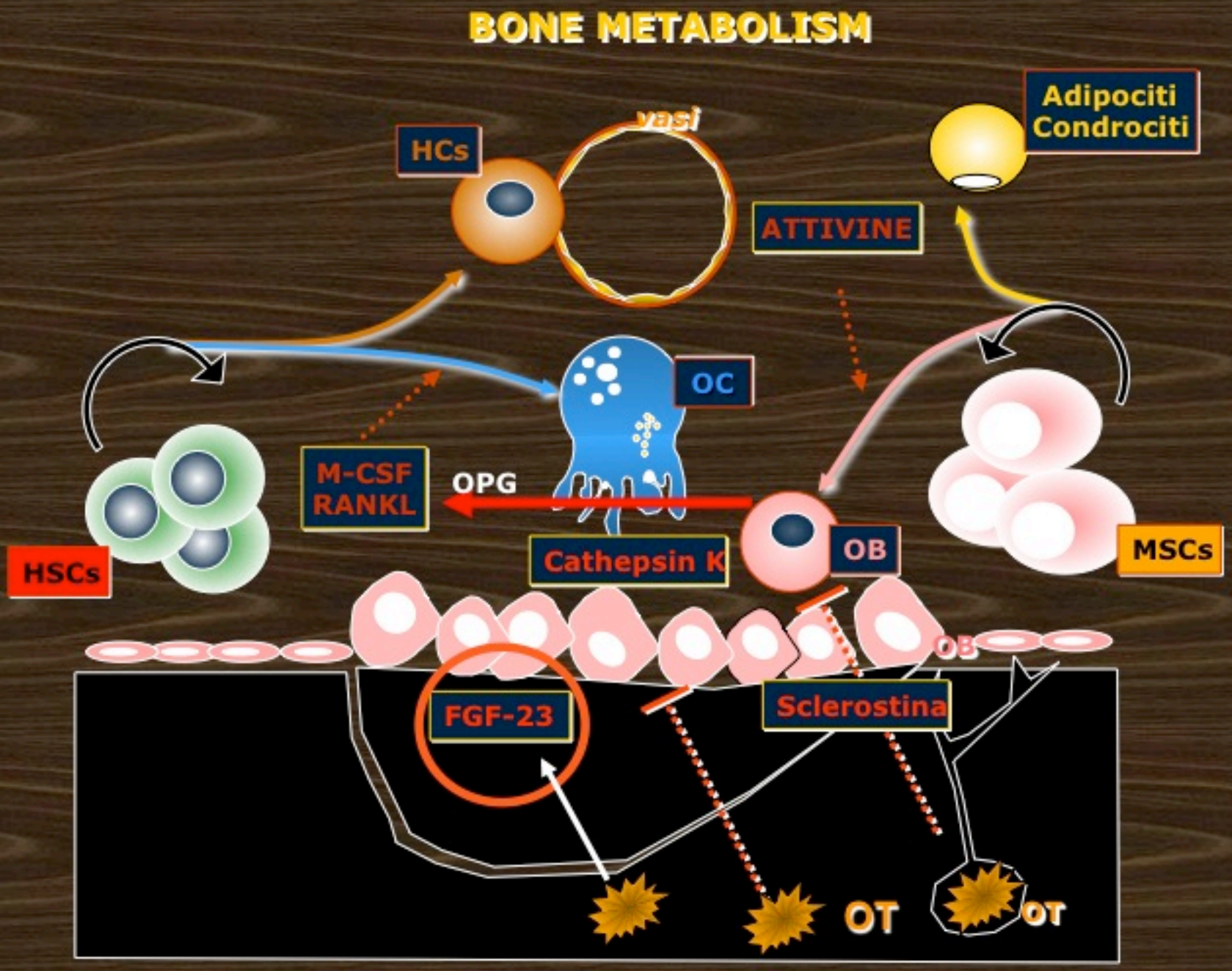
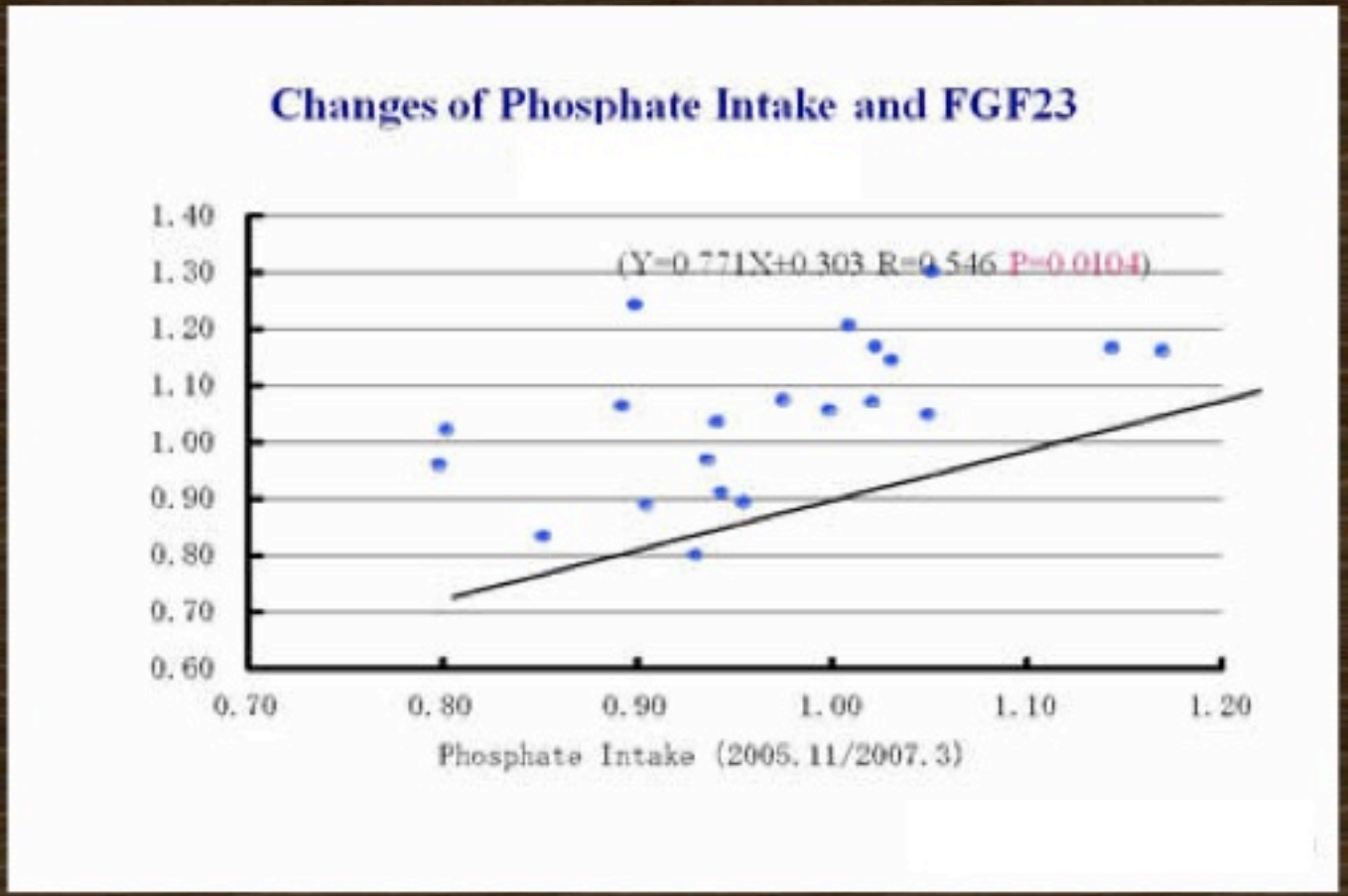
Physiological Regulation and Disorders of Phosphate Metabolism

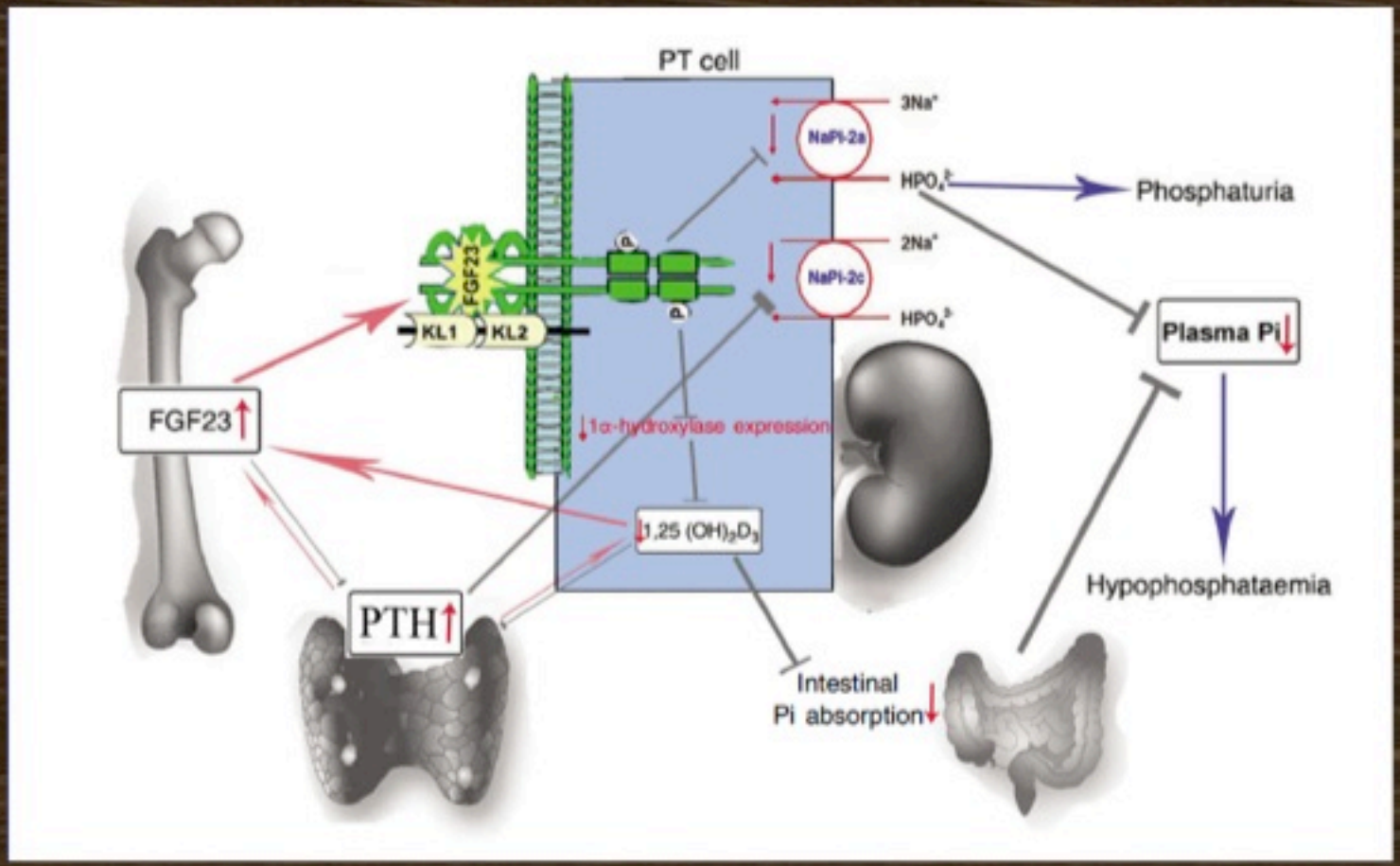
Disease	Gene mutation	Clinical manifestation
Autosomal dominant hypophosphatemic rickets (ADHR)	missense mutations of FGF-23	hypophosphatemic rickets/osteomalacia, resistance to vitamin D
Autosomal recessive hypophosphatemic rickets (ARHR)	dentin matrix protein 1 (DMP-1)	hypophosphatemic rickets/osteomalacia, resistance to vitamin D
X-linked hypophosphatemic rickets/osteomalacia	phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX)	hypophosphatemic rickets/osteomalacia, resistance to vitamin D
McCune-Albright syndrome	guanine nucleotide binding protein, alpha stimulating 1 (GNAS 1), somatic mosaicism	hypophosphatemic rickets/osteomalacia; fibrous dysplasia
Phosphaturic mesenchymal tumors, mixed connective tissue variant (PMTMCT)	acquired disease – enhanced expression of FGF-23	hypophosphatemic rickets/osteomalacia


BONE METABOLISM
Adipociti
Condrociti
vasi
HCs
ATTIVINE
OC
M-CSF
RANKL
OPG
HSCs
Cathepsin K
OB
MSCs
OB
FGF-23
Sclerostina
OT
OT

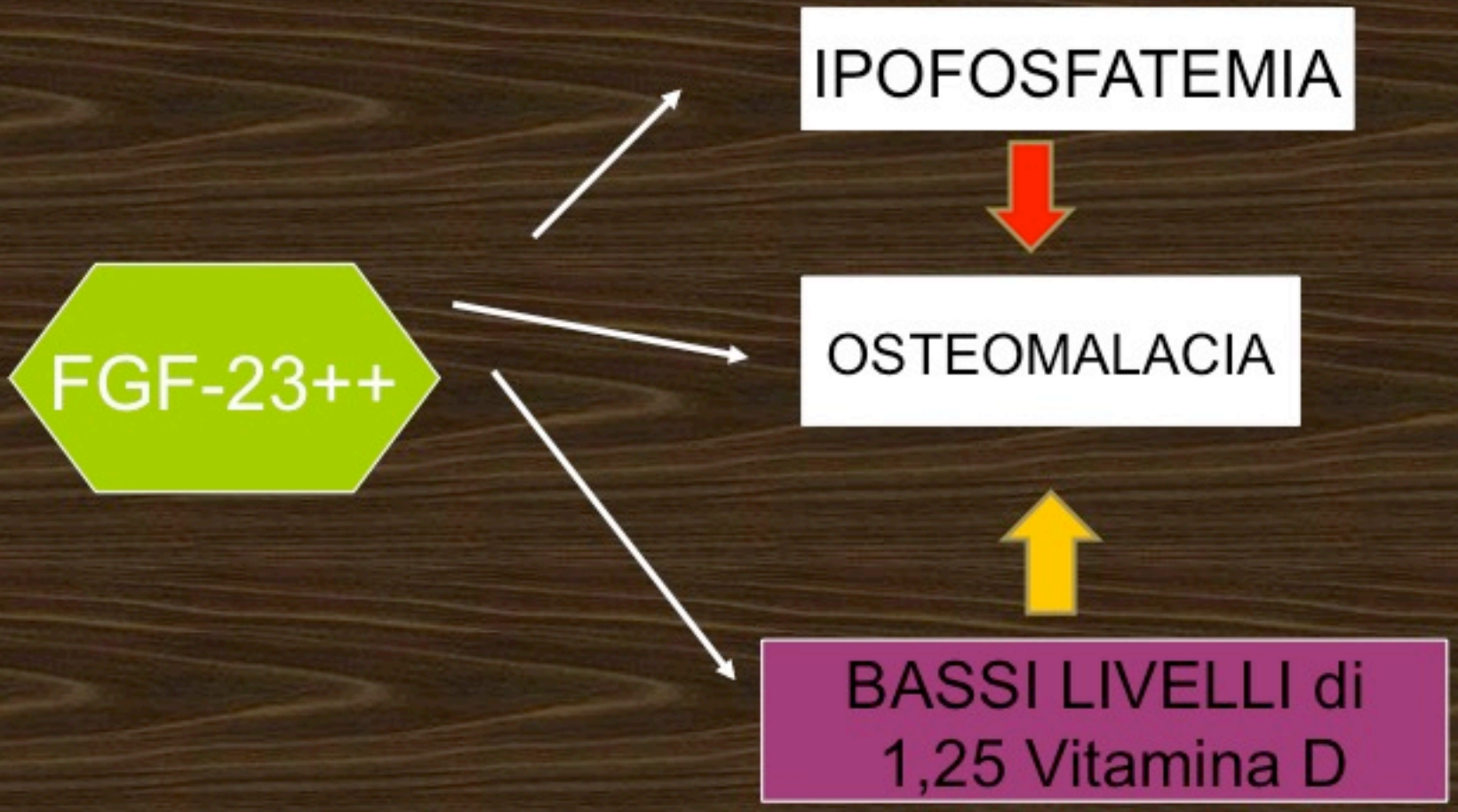
FGF-23 E FOSFOREMIA



IPOFOSFATEMIE



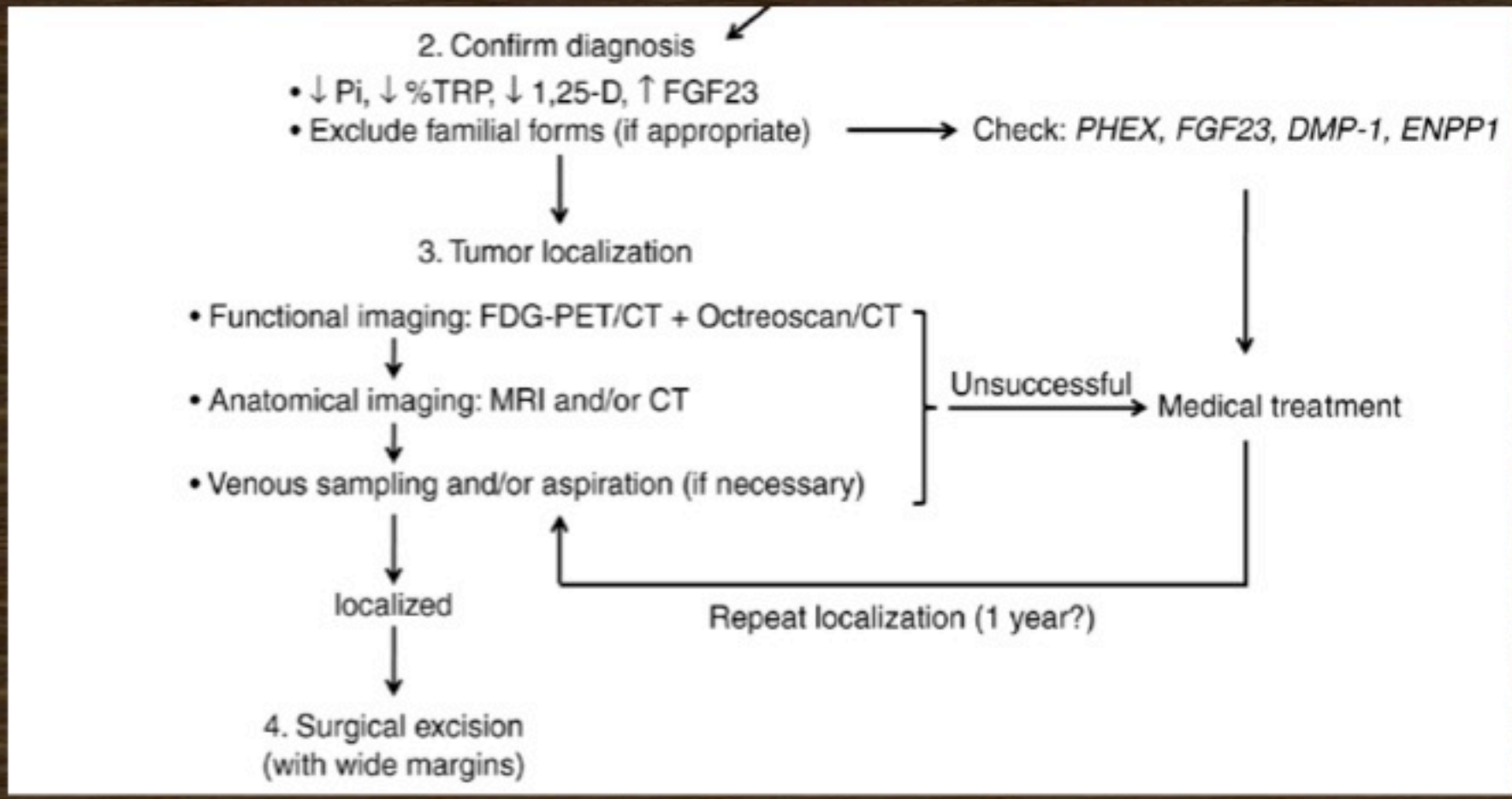
OSTEOMALACIE FGF-23 DIPENDENTI



Osteomalcia ipofosforemica
Osteomalacia oncogenica

- Ipofosfatemia
- Iperfosfaturia
- PTH normale o lievemente aumentato
- Normali valori di 25 (OH) Vit D_3
- **Basse concentrazioni sieriche di 1-25 (OH) Vit D_3**
- Elevati livelli di fosfatasi alcalina
- **Secrezione di FGF-23** da tumori di origine mesenchimale benigni o con bassa invasività

OSTEOMALACIA TUMORE INDOTTA FLOW-CHURT DIAGNOSTICA



TU RICONOSCI SOLO CIÒ CHE CONOSCI; NON SAI CIO' CHE NON CONOSCI
(WATSON)