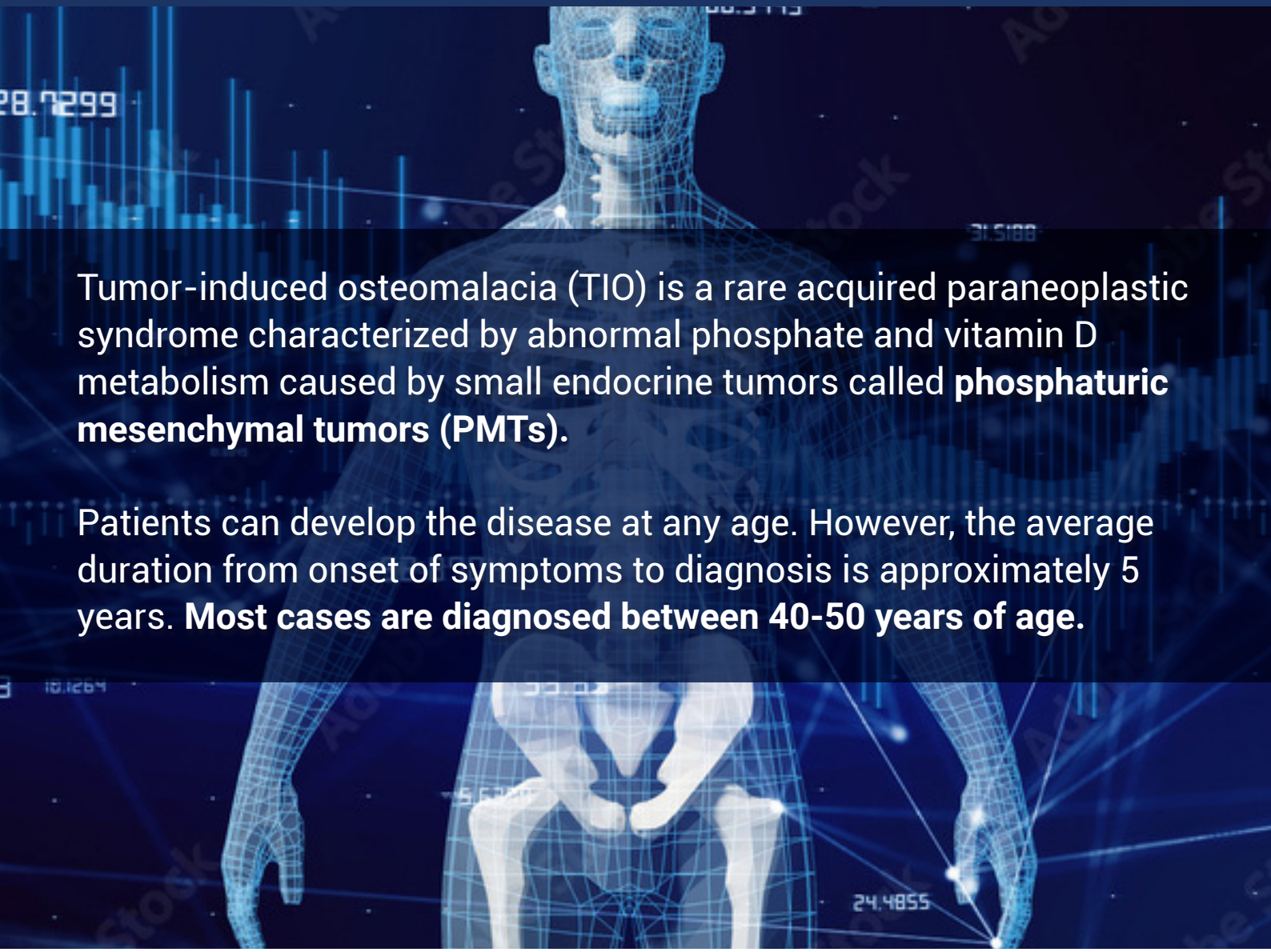
IOF SKELETAL RARE DISEASES
ACADEMY

Tumor-Induced Osteomalacia (TIO) in adults

Key information and diagnostic algorithm



Tumor-induced osteomalacia (TIO) is a rare acquired paraneoplastic syndrome characterized by abnormal phosphate and vitamin D metabolism caused by small endocrine tumors called **phosphaturic mesenchymal tumors (PMTs).**

Patients can develop the disease at any age. However, the average duration from onset of symptoms to diagnosis is approximately 5 years. **Most cases are diagnosed between 40-50 years of age.**

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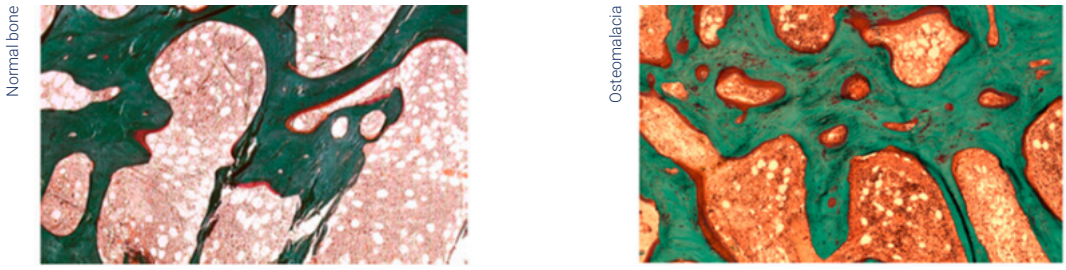
BACKGROUND – PATHOPHYSIOLOGY

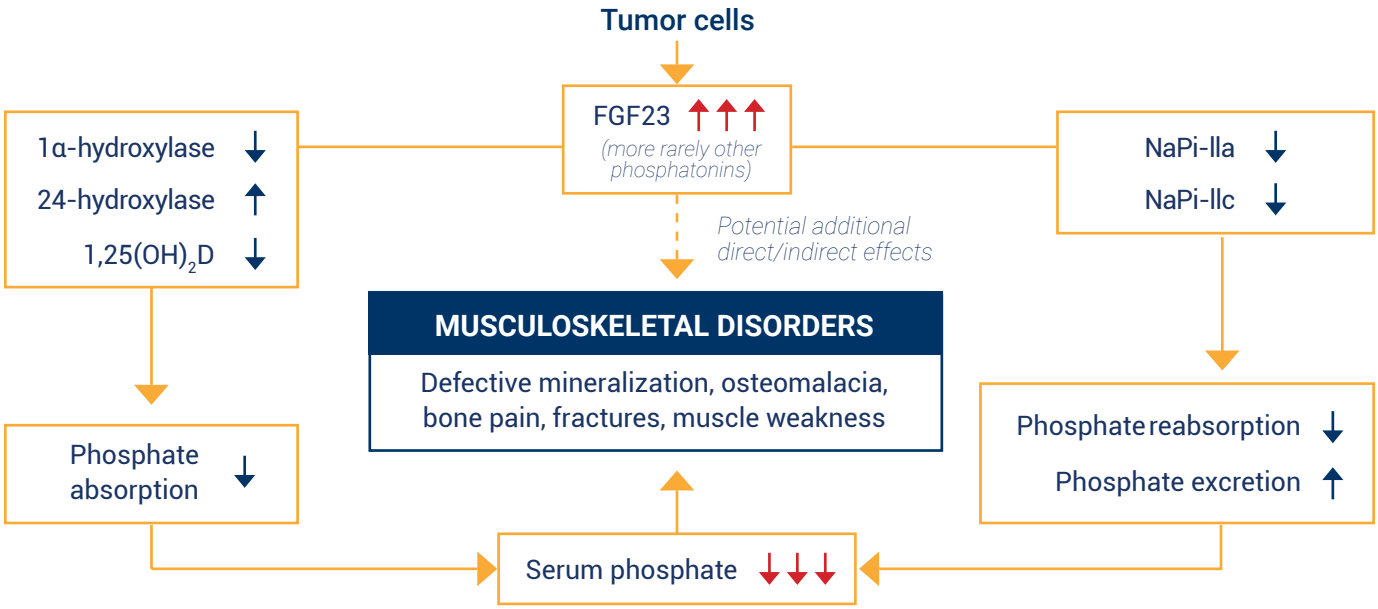
Tumor-induced osteomalacia (TIO) is a rare paranoplastic syndrome characterized clinically by tumoral production of fibroblast growth factor 23 (FGF23), muscle weakness, fatigue, musculoskeletal pain, and fractures.



Mineralization of bone matrix: normal bone (left) and osteomalacia (right)
Fusaro M, et al., Nutrients 2022

FGF23 is produced by a number of tissues including osteoblasts and osteocytes. FGF23 is a hormone which regulates phosphate metabolism. In binding to renal FGF receptor 1 and co-receptor α-Klotho complex, FGF23 inhibits sodium phosphate co-transporters (NaPi-IIa, NaPi-IIc), resulting in reduced renal phosphate reabsorption. In addition, FGF23 blocks the conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), leading to decreased phosphate absorption from the intestine.

In TIO, the uncontrolled increased FGF23 production is typically caused by small, slow growing, benign phosphaturic mesenchymal tumors (PMTs) that may be localized to almost any part of the body that has either bone or connective tissue. Thus, TIO is characterized by defective bone mineralization (osteomalacia in adults, or rickets in children) due to high phosphatonins' levels.



Effects of pathological increase in FGF23 secreted from tumor cells on phosphate homeostasis
Modified from Brandi ML, et al., Bone. 2021

PMT TUMORIGENESIS: *FN1-FGFR1* AND *FN1-FGF1* TRANSLOCATIONS ELEVATED α-KLOTHO EXPRESSION

A key pathogenic mechanism of TIO is the uncontrolled tumoral production of FGF23. Recently, certain fusion genes have been identified in a subset of PMTs. The most common fusion gene is the *FN1-FGFR1* (*FN1* encoding fibronectin, *FGFR1* encoding fibroblast growth factor receptor 1). A rarer fusion gene, *FN1-FGF1* has also been identified. In both known fusions, it is likely that fibronectin stimulates overexpression of the fusion gene product. In the fusion negative PMTs, α-Klotho, an obligatory co-receptor for FGFR1, is often over expressed. In both situations, increased FGFR1 signaling is the end result with PMT tumorigenesis and /or FGF23 hypersecretion.

DIAGNOSIS

TIO is challenging to diagnose as the manifestations are non-specific, often leading to a delayed diagnosis. Moreover, patients are frequently misdiagnosed with several other common rheumatologic, neurological, psychiatric conditions including osteoporosis, somatic syndrome, intervertebral disc herniation, etc.
Patients presenting with FGF23-mediated hypophosphatemia require a through clinical and laboratory evaluation to distinguish TIO from other genetic and acquired causes of FGF23 excess.

Key elements that guide diagnosis:

- Unexplained low serum phosphate
- Age of onset of symptoms
- Absence of family history of rickets/osteomalacia
- Muscle weekness (usually more proximal than distal)

Clinical presentation

Symptoms of chronic hypophosphatemia

- Bone pain
- Difficulty in walking
- Muscle weakness
- Pathological multiple fractures (mainly long bones)
- Pseudofractures

Laboratory Analysis

Serum values	Urine values
Low phosphate* Elevated or inappropriately normal intact FGF23* Low or inappropriately normal $1,25(OH)_2D_3$ Elevated bone alkaline phosphatase Normal calcium (typically normal in TIO) Intact PTH may be high due to chronically low $1,25(OH)_2D_3$ Normal 25(OH) vitamin D	Elevated or inappropriately normal phosphate** Reduced TmP/GFR***

TmP/GFR: tubular maximal reabsorption of phosphate adjusted for glomerular filtration rate
*Fasting before sampling is required to give an accurate result
** Second morning void urine or urine collected over 24 hours
*** TmP/GFR is calculated from fasting paired plasma and second morning void urine samples obtained 2 hours after the first void urine for phosphate and creatinine

TUMOR LOCALIZATION

After establishing the diagnosis of TIO, the next step in management is identification of lesion (or lesions).

Functional imaging

Recommended modalities to localize metabolic active PMT cells

- Somatostatin receptor scintigraphy (SRS)
  - ^{68}Gallium DOTA-Phe^{1}-Tyr^{3}-Thr^{8} octreotide (^{68}Ga-DOTATATE) PET/CT
  - ^{111}Indium-labeled pentetriotide (OctreoScan™) SPECT/CT)
- Glucose transporter imaging
  - ^{18}F fluorodeoxyglucose (^{18}F-FDG) PET/CT

Anatomical imaging

Of the suspicious areas to confirm the specific location of the tumor and its surrounding tissues to assist surgical planning

- Contrast-enhanced CT
- Resonance imaging (MRI)

Densitometry in TIO

Although it is commonly used in the bone density assessment, dual-energy X-ray absorptiometry (DXA) does not exclude nonmineralized bone. Therefore, this is not a good measure of bone mass in patients with osteomalacia. On the other hand, it can be safely and reliably used to monitor mineralization of the osteoid during treatment and serves as an important measure of bone disease healing.

Body biopsy in TIO

Bone biopsy is helpful for assessing the severity of bone disease in TIO. However, this is impractical and seldom necessary for a diagnosis of TIO.

TREATMENT

Complete tumor resection

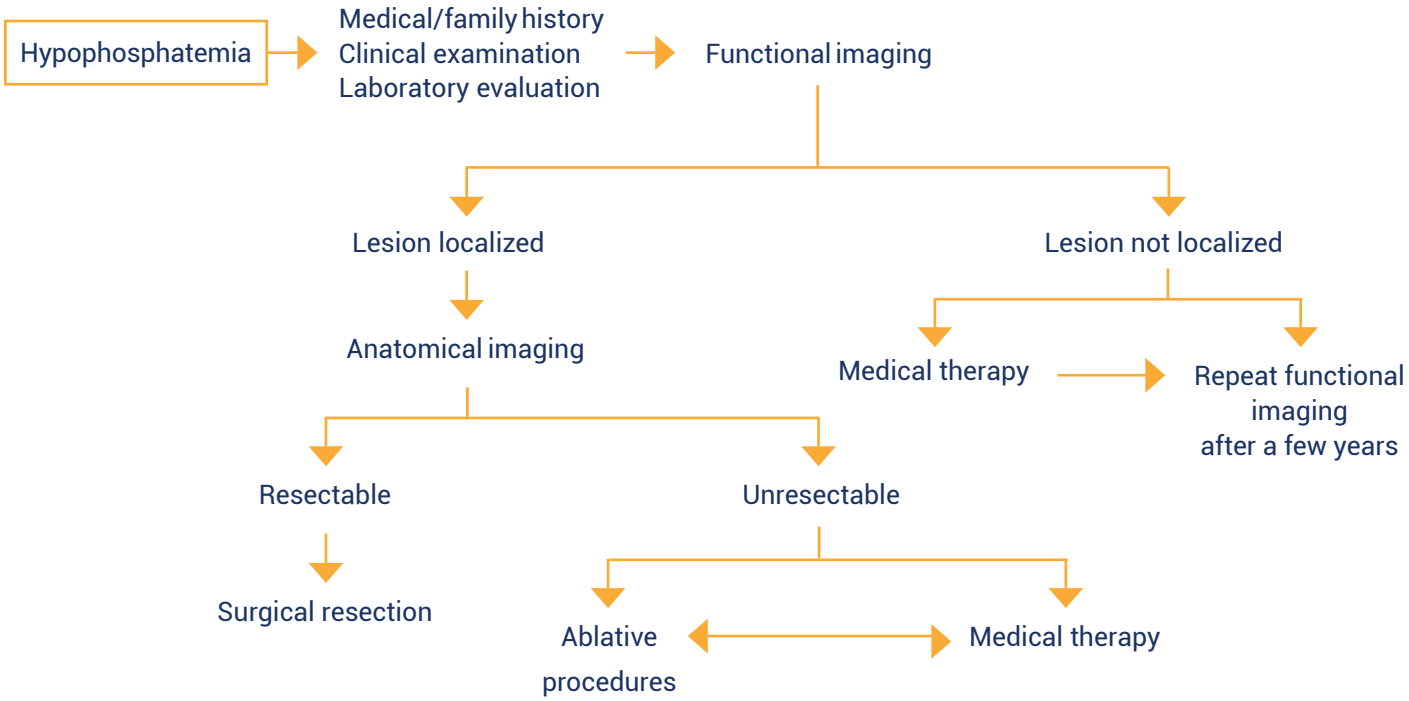
Ablative procedures

- External beam radiation, image-guided ablation with radiofrequency, cryoablation

Conventional medical treatment

- Oral phosphate supplementation in combination with active vitamin D analogs
- Human monoclonal antibody against FGF23 (burosumab)
  Burosumab (CRYSVITA®) is a recombinant human monoclonal antibody against FGF23. As of June 2022, burosumab is approved in the USA for the treatment of FGF23-related hypophosphatemia in TIO associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localized, in adult and pediatric patients aged 2 years and older.

ALGORITHM OF IDENTIFICATION AND TREATMENT FOR TUMOR-INDUCED OSTEOMALACIA



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