CME: New Guidance to Diagnose Tumor-induced Osteomalacia (TIO)

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Learning Objectives

Describe the latest recommendations for

- *Diagnosing patients with TIO*
- *Managing patients with TIO*

CME: New Guidance to Diagnose Tumor-induced Osteomalacia (TIO)

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New Guidance to Diagnose and Treat TIO

JIM Review

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Global guidance for the recognition, diagnosis, and management of tumor-induced osteomalacia

Suzanne M. Jan de Beur[1], Salvatore Minisola[2], Wei-bo Xia[3], Bo Abrahamsen[4,5,6], Jean-Jacques Body[7], Maria Luisa Brandi[8], Roderick Clifton-Bligh[9,10,11], Michael Collins[12], Pablo Florenzano[13], Pascal Houillier[14], Yasuo Imanishi[15], Erik A. Imel[16], Aliya A. Khan[17], M. Carola Zillikens[18] & Seiji Fukumoto[19]

Tumor Induced Osteomalacia

Rare paraneoplastic condition characterized by chronic hypophosphatemia and osteomalacia.	caused by excess FGF23 being produced by mesenchymal tumors.	tumor are usually benign but can be anywhere in the body, small, and difficult to locate.
TIO can also occur in advanced metastatic cancers (colon, prostate as a secondary paraneoplastic syndrome).	Muscle weakness, bone pain and fractures are typical presenting symptoms.	Delay in diagnosis is common, often for several years after onset of symptoms

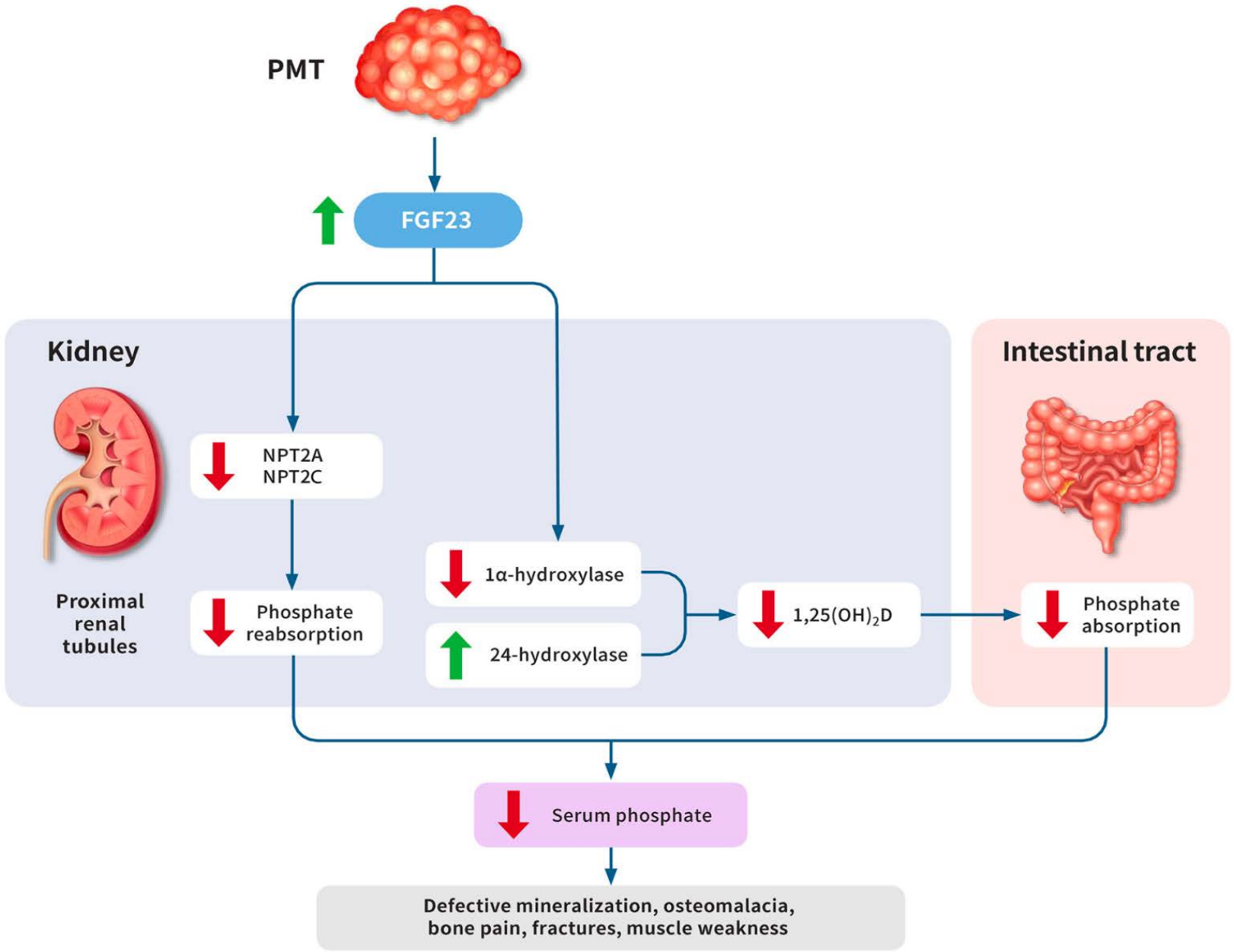
Jan de Beur SM et al. *J Int Med* 2023;293:309-328. Feng et al Endocr J. 2017:64:675-83.. Colazo JM et al. Bone Rep 2020. 14:100744. Chong WH, et al. *Endocr Relat Cancer.* 2011;18:R53-77. Leaf DE et al. *J Clin Endocrinol Metab*. 2013;98:887-91. Lyles KW et al. *Ann Intern Med.* 1980;93:275-8. Mak MP et al. *Support Care Cancer*. 2012;20:2195-7.

Diagnostic Delays are Common

95% of TIO cases are initially misdiagnosed

Rheumatic/musculoskeletal	lumbar disc herniation, spondyloarthritis, osteoporosis, rheumatic arthritis, bones metastases, connective tissue disease
Neurologic and muscular disorders	Motor neuron disease, multiple sclerosis, polymyalgia rheumatica, myositis, stroke, functional somatization

Jan de Beur SM et al. *J Int Med* 2023;293:309-328.



- *1,25(OH)2D, 1,25-dihydroxyvitamin D*
- *FGF23, fibroblast growth factor 23*
- *NPT2, type II sodium phosphate cotransporter*
- *PMT, phosphaturic mesenchymal tumor.*

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Hypophosphatemia

Inadequate intake or malabsorption

- malabsorption – small bowel (celiac, Crohn's)
- Vitamin D deficiency
- Gut phosphate binders
- TmP/GFR high or normal

Short term changes in Pi due to extracellular –> intracellular shifts

- Rx DKA - insulin drives phosphate intracellular
- Refeeding syndrome
- Hungry bone syndrome post PTX
- Acute respiratory alkalosis
- Leukemia or lymphoma

Renal phosphate wasting – TmP/GFR low

Fibroblast Growth Factor 23 (FGF23)

- FGF23-bone-derived hormone
- Regulates Pi homeostasis and vitamin D metabolism
- Impairs Pi reabsorption in the renal PCT and decreased Pi absorption in the intestines
- Increase in FGF23 plays a critical role in the development of metabolic/hypophosphatemic bone disease

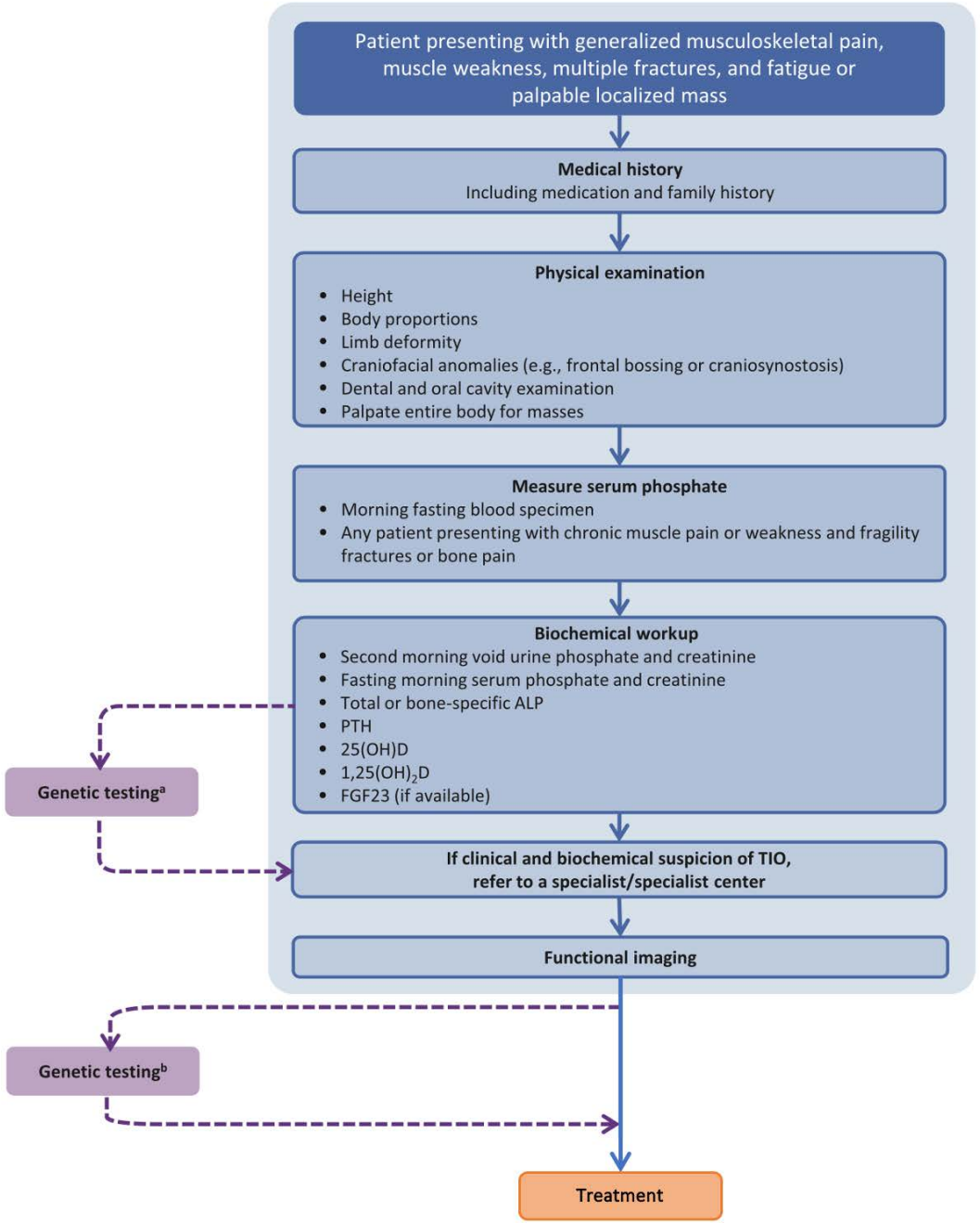
Athonvarangkul D, Insogna KL. *Calcif Tissue Int.* 2021;108:143-157.
Kinoshita Y, Fukumoto S. *Endocr Rev*. 2018;39:274-291.
González-Meneses López A. *Adv Ther.* 2020;37(Suppl 2):25-28.

Renal Pi Transport

- PCT – 60-70% of renal Pi reabsorption
- Major regulators – PTH, FGF23
- Minor regulators – PTHrP, calcitonin, atrial natriuretic peptide, acidosis, steroids inhibit Pi reabsorption
- Rate of Pi transport depends – abundance of NaPi cotransporters and magnitude of Na+ gradient across luminal membrane
- Pi entry into renal epithelium via type 2 NaPi cotransporters (SLC34 – solute carrier family)
- Type 2 NaPi – 2a and 2c are main transporters in PCT

Bergwitz C et al. Am J Hum Genet. 2006; 78:179-92.
Villa-Bellosta R et al. Am J Physiol Renal Physiol. 2009; 296:F691-9.

Diagnosing TIO



[a] Perform genetic testing before imaging in children, young adults, or those with suggestive family history.

[b] Perform genetic testing in adults without family history and negative functional imaging.

Differential Diagnosis of Hypophosphatemia

FGF23-mediated

Genetic

- Autosomal dominant hypophosphatemic rickets (*FGF23*)
- Autosomal recessive hypophosphatemic rickets (*DMP1*, *ENPP1*, *FAM20C*)
- Cutaneous skeletal hypophosphatemia syndrome/linear sebaceous nevus syndrome (*RAS*: *KRAS/HRAS*, *NRAS*)
- Fibrous dysplasia of bone (*GNAS*)
- Jansen's metaphyseal chondrodysplasia (*PTH1R*)

Acquired

- Chronic alcohol consumption
- Iron polymaltose, carboxymaltose or saccharated ferric oxide infusions- iron infusions increase FGF23
- **TIO**

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Differential Diagnosis of Hypophosphatemia

Non-FGF23-mediated

- HHRH (*SLC34A3*)- hereditary hypophosphatemic rickets with hypercalciuria
- Hyperparathyroidism
- IIH (*SLC34A1*)- idiopathic infantile hypercalcemia
- Renal Fanconi syndrome

Impaired actions of vitamin D metabolites

- Vitamin D deficiency
- Vitamin D metabolism defects

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Differential Diagnosis of Hypophosphatemia

Malabsorption, malnutrition

- Low dietary intake
- Impaired dietary absorption (e.g., celiac disease, gastric bypass, inflammatory bowel disease)
- Phosphate binders (sevelamer, antacids containing calcium, magnesium, aluminum)
- Alcoholism
- Premature infants

Transcellular shifts

- Diabetes ketoacidosis
- Hyperventilation
- Refeeding syndrome
- Respiratory alkalosis

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Differential Diagnosis of Hypophosphatemia

Medications

- Aminoglycosides
- Antiretrovirals (tenofovir, adefovir)
- Bisphosphonates
- Catecholamines
- Chemotherapies (cisplatin, ifosfamide, streptozocin)
- Diuretics (acetazolamide, thiazides, loop diuretics)
- Glucose or insulin infusion
- Imatinib
- Mannitol
- Salicylate

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Suspecting TIO

Symptoms are often nonspecific and develop slowly

Medical and family history- de novo mutations may be present and FHx may be negative

Often a diagnosis by exclusion

When to measure serum phospate? Any patient presenting with chronic muscle pain, weakness, fragility, fractures, or bone pain

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Tubular reabsorption of phosphate (TRP) and TmP/GFR

- ***(U_{PO4} x P_{cr}) / (U_{cr} x P_{PO4})***

  = (10 x 0.060) / (4.3 x 0.68) = 0.6 / 2.92 = 0.205

- ***TRP = 1 – PO_4 to creatinine clearance ratio***

  = 1 – 0.205 = 0.795

- ***Tubular maximum reabsorption of phosphate to GFR***

- ***=TmP / GFR = TRP x PO_4***

  = 0.795 x 0.68 = 0.54

  Consistent with renal PO_4 wasting

  (Normal Female 0.96 – 1.44)

  Normal Male 0.9-1.35

Payne RB. *Ann Clin Biochem* 1998; 35: 201-206.

Secondary (and Tertiary) Hyperparathyroidism

- 2nd to long term stimulation of parathyroid cells by:
  - **Low 1,25D**
  - **Phosphate supplements**
  - **High FGF23**
  - **High PTH – further increases urine Pi losses and increases FGF23**

Suspecting TIO

Medical History and Serum phosphate

- Measure serum phosphate in any patient presenting with chronic muscle pain, weakness, fragility fractures, or bone pain. **(A)**

Genetic Testing

- Perform genetic testing for hereditary hypophosphatemic disorders in a patient who has a family history of hypophosphatemia, personal or family history of short stature, lower limb deformity, or extensive dental anomalies. **(B)**
- Consider genetic testing to exclude hereditary hypophosphatemic disorders in a patient who has hypophosphatemia, renal phosphate wasting, elevated or inappropriately normal FGF23 with no evidence of personal or family history that may suggest a genetic cause, when no tumor can be identified with appropriate imaging, or when onset of disease is in childhood or young adulthood. **(B)**

Physical Examination

- Including height measurement, assessment of body proportions, limb deformity, craniofacial anomalies, including frontal bossing or craniosynostosis, and dental and oral cavity examination. Palpate the entire body for evidence of masses. **(A)**
- In patients with an unclear diagnosis, perform priority laboratory evaluations (indicators of TIO) (A) (next slide)

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Biochemical Features of TIO

Parameter	Adult reference range	Feature in TI0
Serum phosphate	0.81–1.45 mmol/L (2.51–4.49 mg/dL)	Decreased
Serum ALP	Male: 45–125 U/L. Female: 35–100 U/L	Increased
Serum calcium	2.15–2.55 mmol/L (8.6–10.2 mg/dL)	Slightly decreased / normal
Intact FGF23	0.45–1.86 pmol/dL (11.7–48.6 pg/mL)	Increased / inappropriately normal
C-terminal FGF23	21.6–91.0 RU/mL	Increased
Intact PTH	1.27–6.9 pmol/L (12.0–65.0 pg/mL)	Increased / normal
$1,25(OH)_2D$	47–130.3 pmol/L (19.6–54.3 pg/mL)	Decreased / inappropriately normal
25(OH)D	75–125 nmol/L (30–50 ng/mL)	Normal
TmP/GFR	0.80–1.35 mmol/L (2.48–4.18 mg/dL)	Decreased
%TRP	85-95	Decreased

%TRP, the fraction (or percentage) of filtered phosphorus that is reabsorbed by renal tubules; 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone; RU, reference units; TmP/GFR, ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate

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Clinical Pearls

What we know

- Very rare condition that is only beginning to be properly understand. New guidance is available to assist healthcare professionals in providing the best care possible for their patients with TIO.
- The key factor for improving identification and diagnosis of TIO is to raise awareness among physicians that serum phosphate should be measured in all patients with progressive weakness, unexplained bone and muscle pain, sudden onset of bone stress, or pseudofractures.

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Clinical Pearls

What we need to improve upon

- Increased understanding of TIO and standardization of the patient pathway, along with advances in diagnostic assays and treatment modalities. These should lead to improved patient outcomes in the future.

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