The clinical utility of bone turnover markers measurements and their use in UZL Hospital

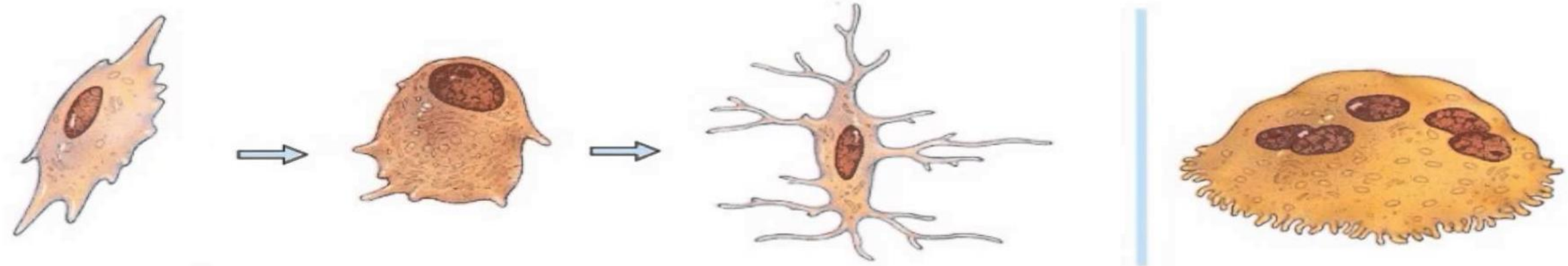
Nadia Makki

May 2017

Promotor
Dr. Jaak Billen

- Bone strength is proportional to bone mass, measured with DXA
- Bone quality depend on bone architecture, rate of bone turnover, quality of bone matrix.
- Bone turnover markers indicate the status of bone quality.
- Organic component of bone : 95% type I collagen.
- Inorganic component: minerals.

Bone Cells

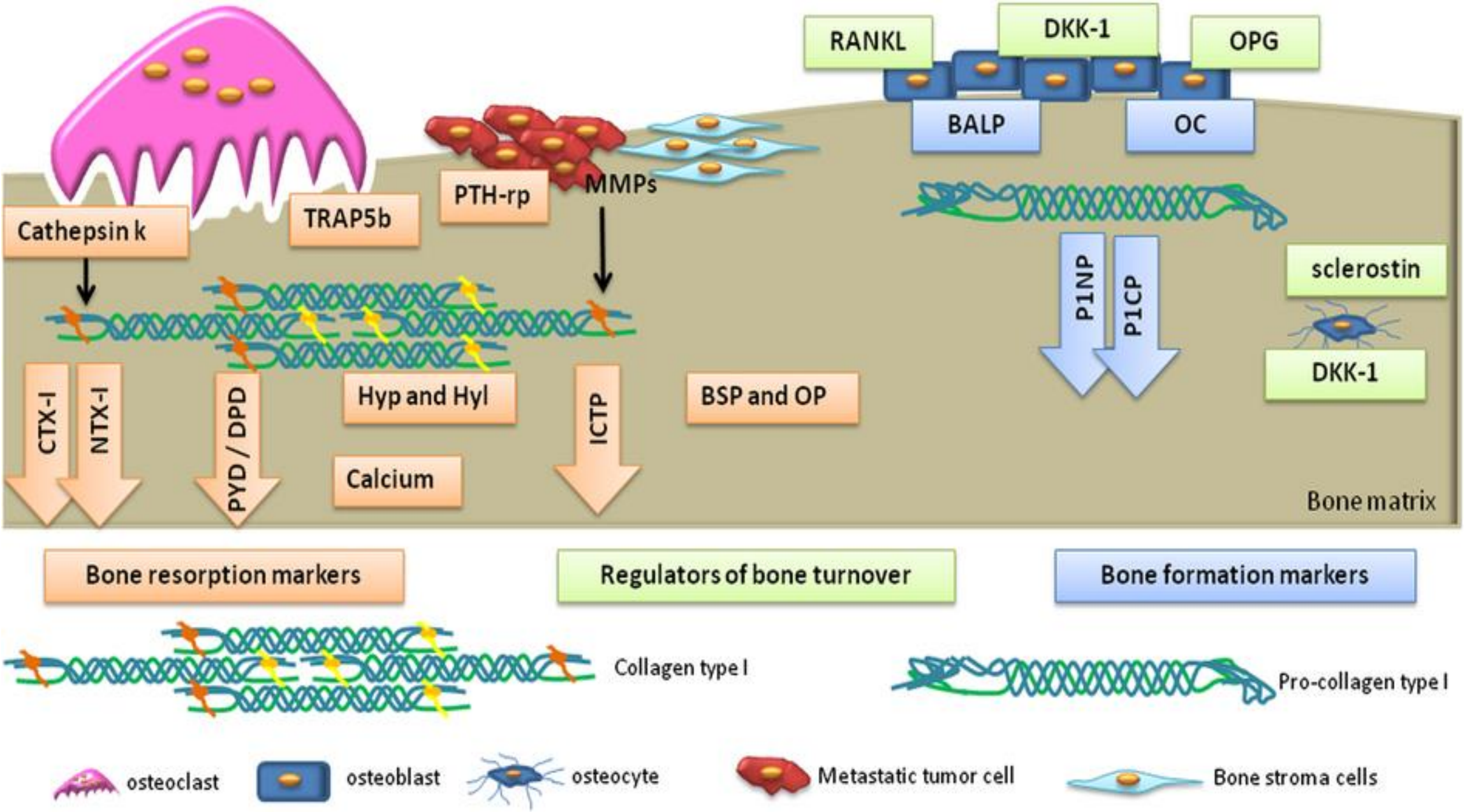


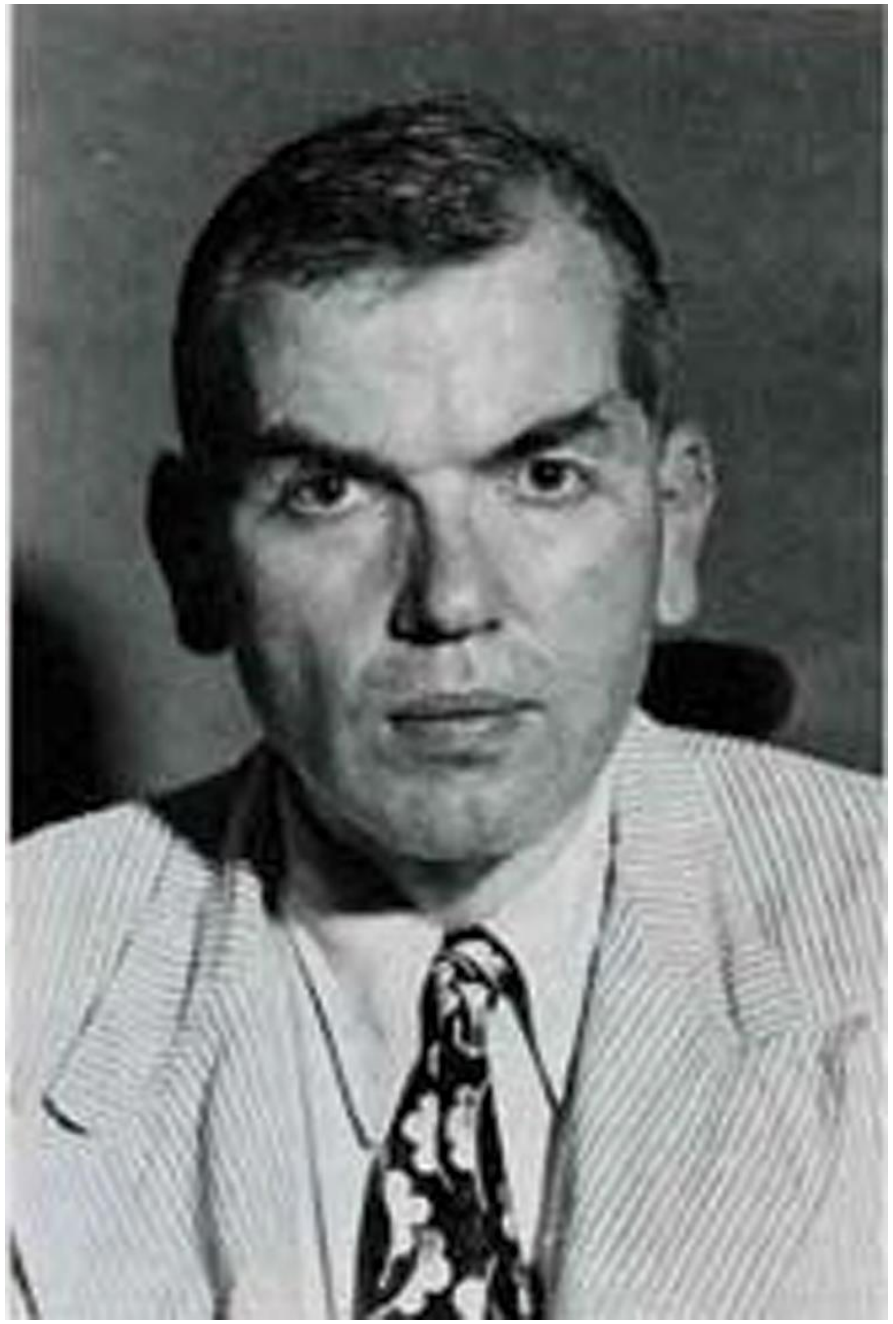
Osteogenic cell

Osteoblast

Osteocyte

Osteoclast


RANKL
DKK-1
OPG
BALP
OC
Cathepsin k
TRAP5b
PTH-rp
MMPs
P1NP
P1CP
sclerostin
DKK-1
CTX-I
NTX-I
PYD / DPD
Hyp and Hyl
ICTP
BSP and OP
Calcium
Bone matrix
Bone resorption markers
Regulators of bone turnover
Bone formation markers
Collagen type I
Pro-collagen type I
osteoclast
osteoblast
osteocyte
Metastatic tumor cell
Bone stroma cells



Fuller Albright

(January 12, 1900 – December 8, 1969)

Lack tissue specificity

High variability

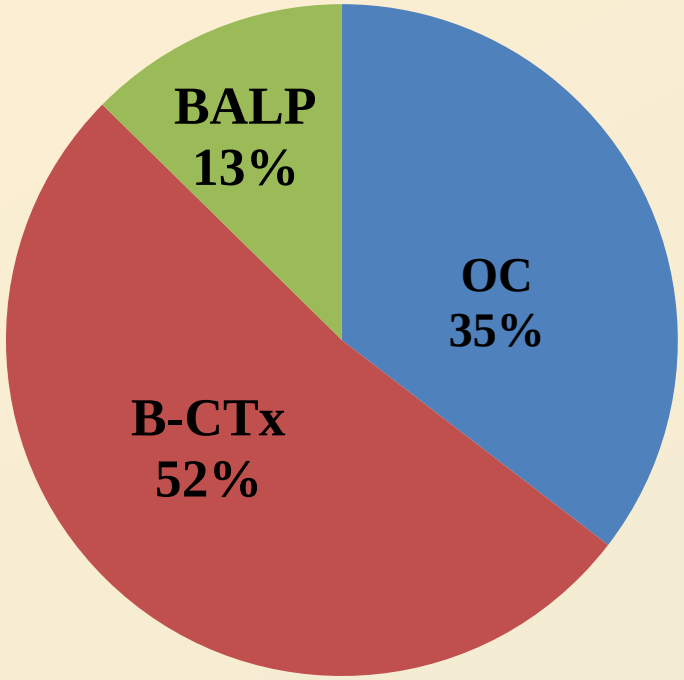
Establishment of reliable reference ranges

Least significant change LSC

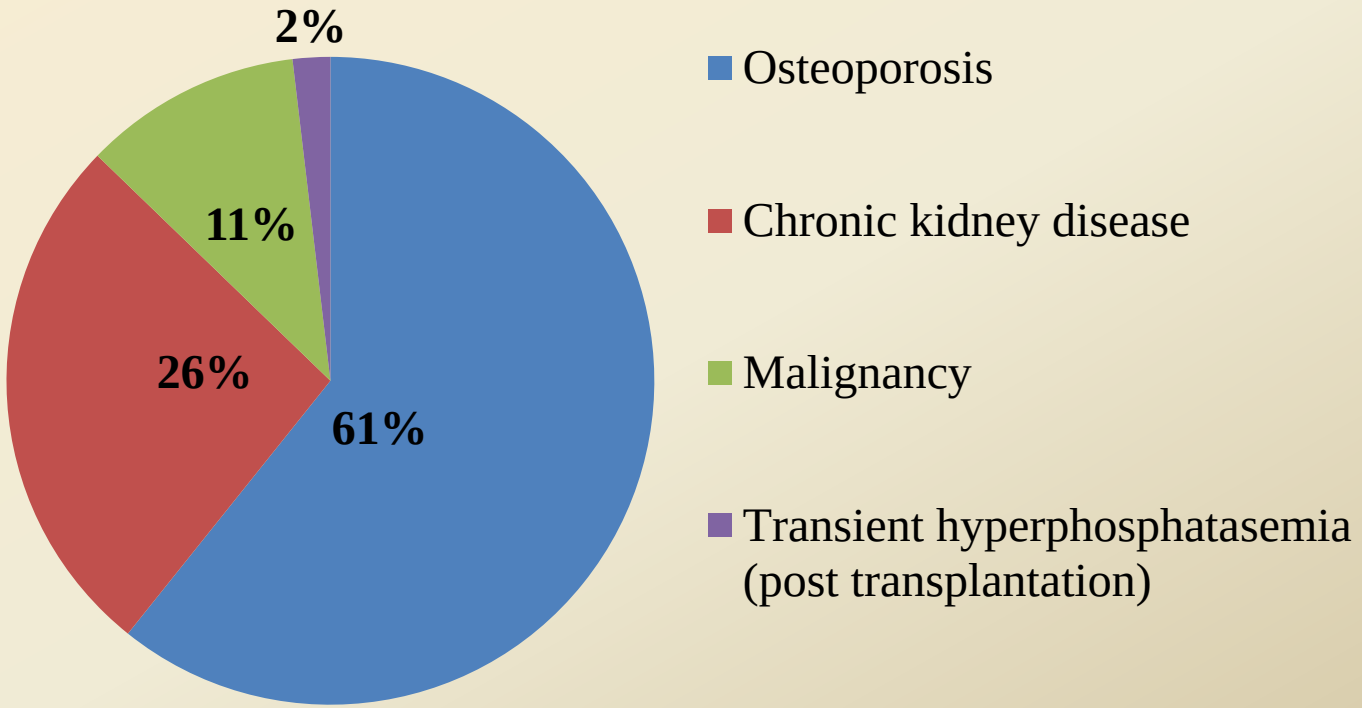
BTMs reflect changes in bone turnover more rapidly than changes in other clinical test

BTMs reflect the turnover rate of the skeleton as whole

Test requests



Indications



Conclusion from query

The most common indications for determining bone turnover markers in UZL hospital are

- Osteoporosis
- Chronic kidney disease
- Malignancy
- Post transplantation in pediatric patients

3 Questions

Which marker(s) is (are) the beste indicator(s) of bone turnover in follow up osteoporosis patient?

What is the value of bone specific alkaline phosphatase in monitoring the bone mineral status in patients with malignancy or post organ transplantation?

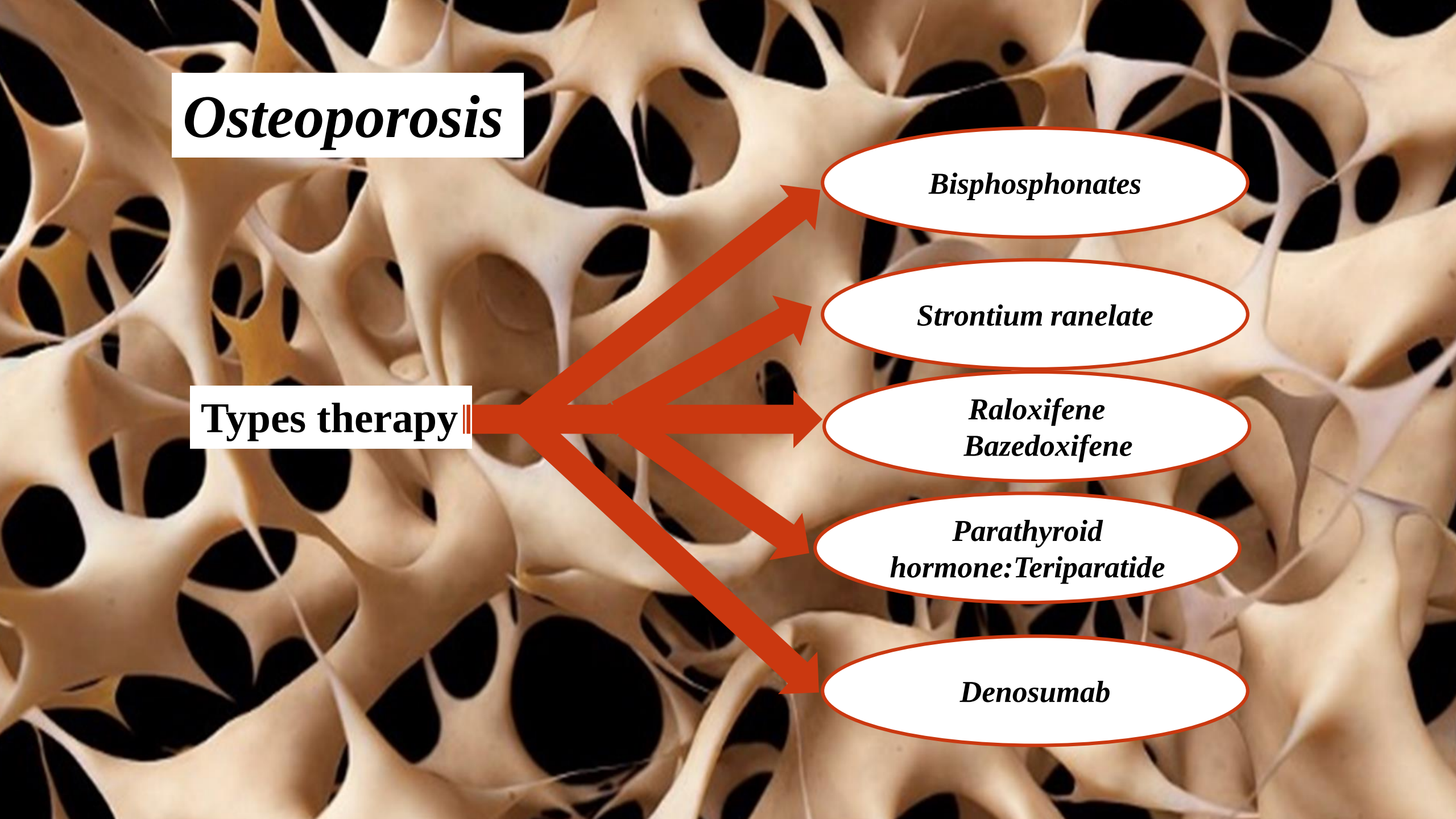
Which bone marker(s) is/are useful to assess bone metabolic states in CKD patients?

Osteoporosis

Diagnosis

Decision to start therapy

Monitoring and drug adherence


Osteoporosis
Types therapy
Bisphosphonates
Strontium ranelate
Raloxifene
Bazedoxifene
Parathyroid hormone:Teriparatide
Denosumab

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 25, 2003 VOL. 349 NO. 13

The Effects of Parathyroid Hormone and Alendronate Alone or in Combination in Postmenopausal Osteoporosis

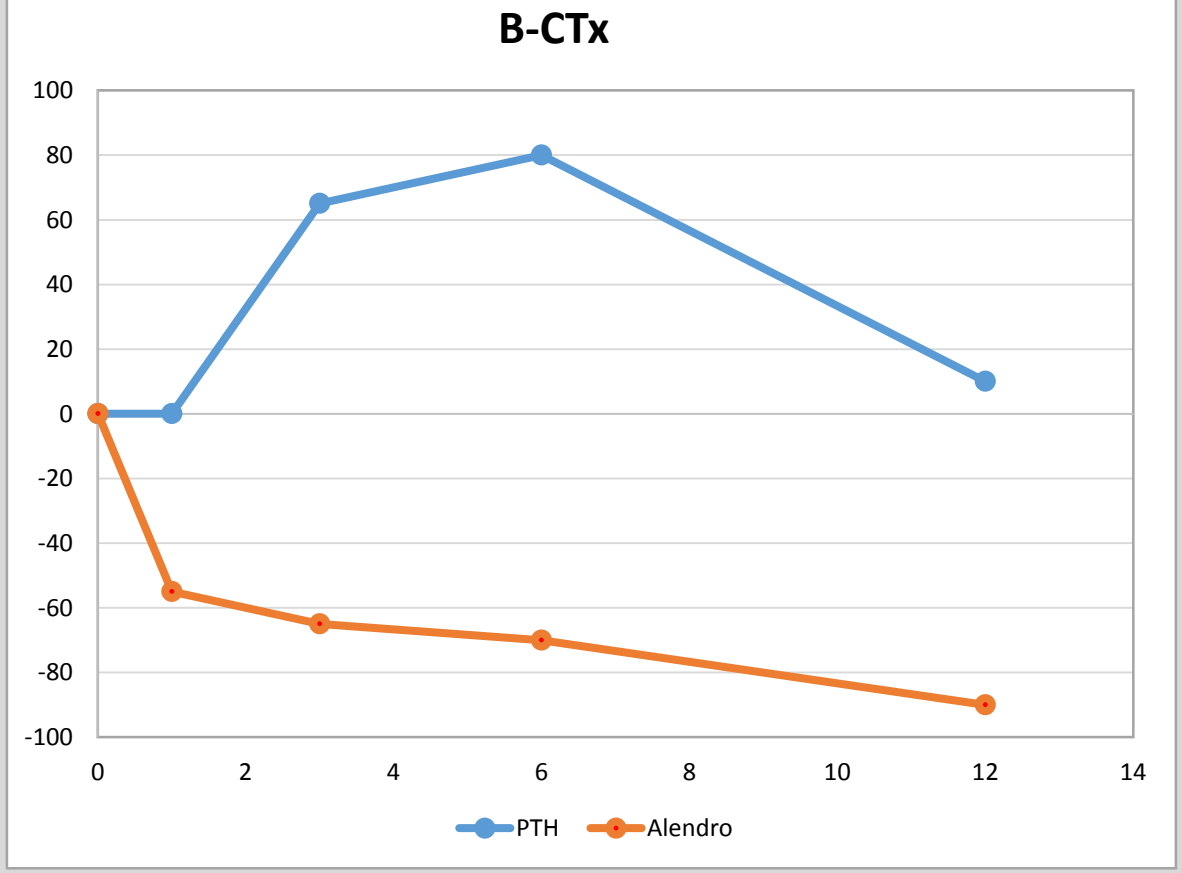
Dennis M. Black, Ph.D., Susan L. Greenspan, M.D., Kristine E. Ensrud, M.D., M.P.H., Lisa Palermo, M.A., Joan A. McGowan, Ph.D., Thomas F. Lang, Ph.D., Patrick Garnero, Ph.D., Mary L. Bouxsein, Ph.D., John P. Bilezikian, M.D., and Clifford J. Rosen, M.D., for the PaTH Study Investigators*

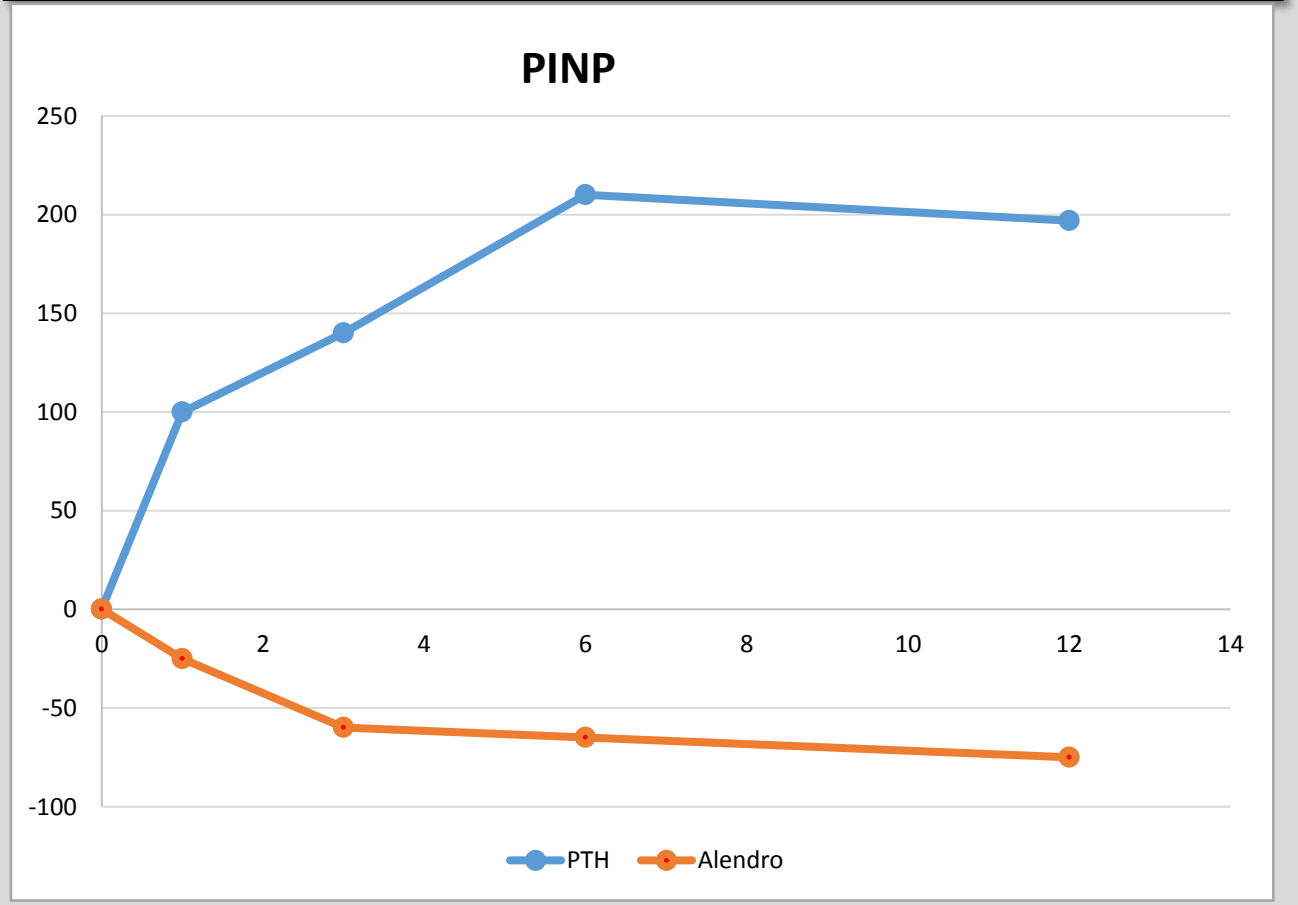
Arch Intern Med.
2005;165:1762-1768

ORIGINAL INVESTIGATION

Opposite Bone Remodeling Effects of Teriparatide and Alendronate in Increasing Bone Mass

Michael R. McClung, MD; Javier San Martin, MD; Paul D. Miller, MD; Roberto Civitelli, MD; Francisco Bandeira, MD; Molly Omizo, MD; David W. Donley, PhD; Gail P. Dalsky, PhD; Erik F. Eriksen, MD





Osteoporosis

Literature review (22 studies)

- **Population**
- **Study design**
- **Assay (method)**
- **Relation with BMD**
- **Relation with fracture risk**
- **Type treatment**
- **Follow up months**

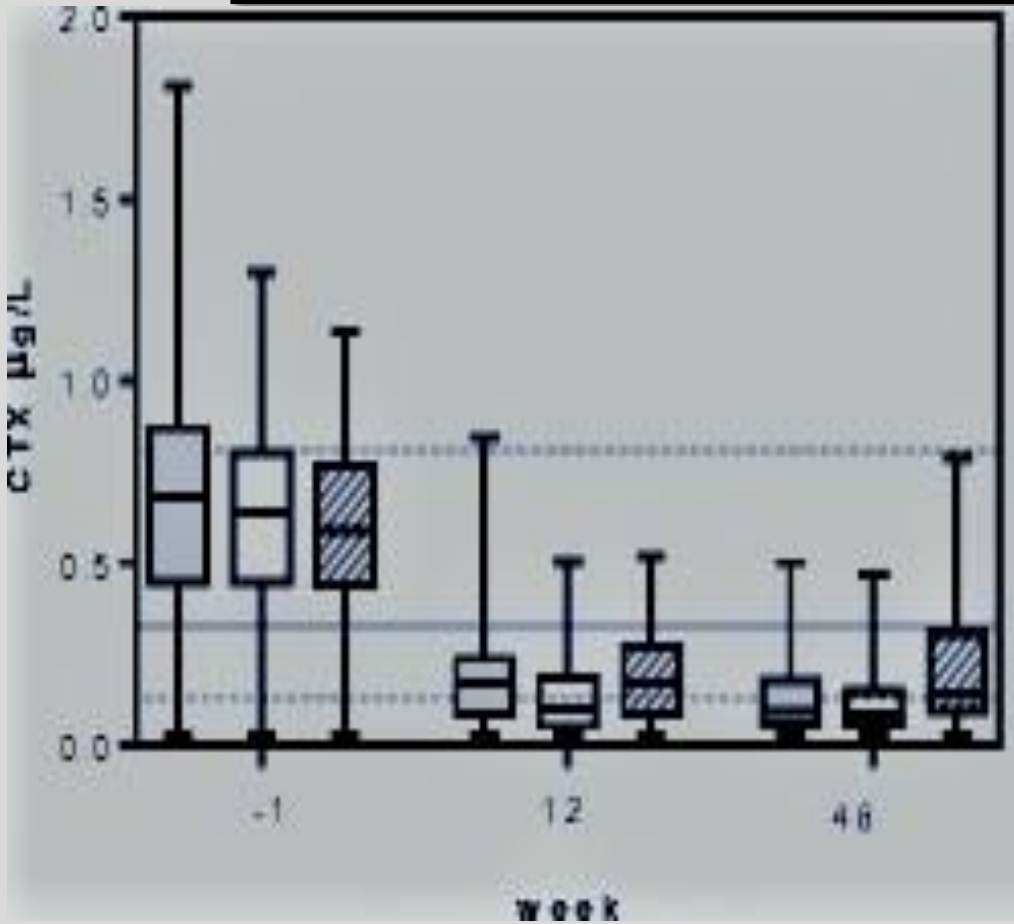
Potential reasons of discrepancies in results

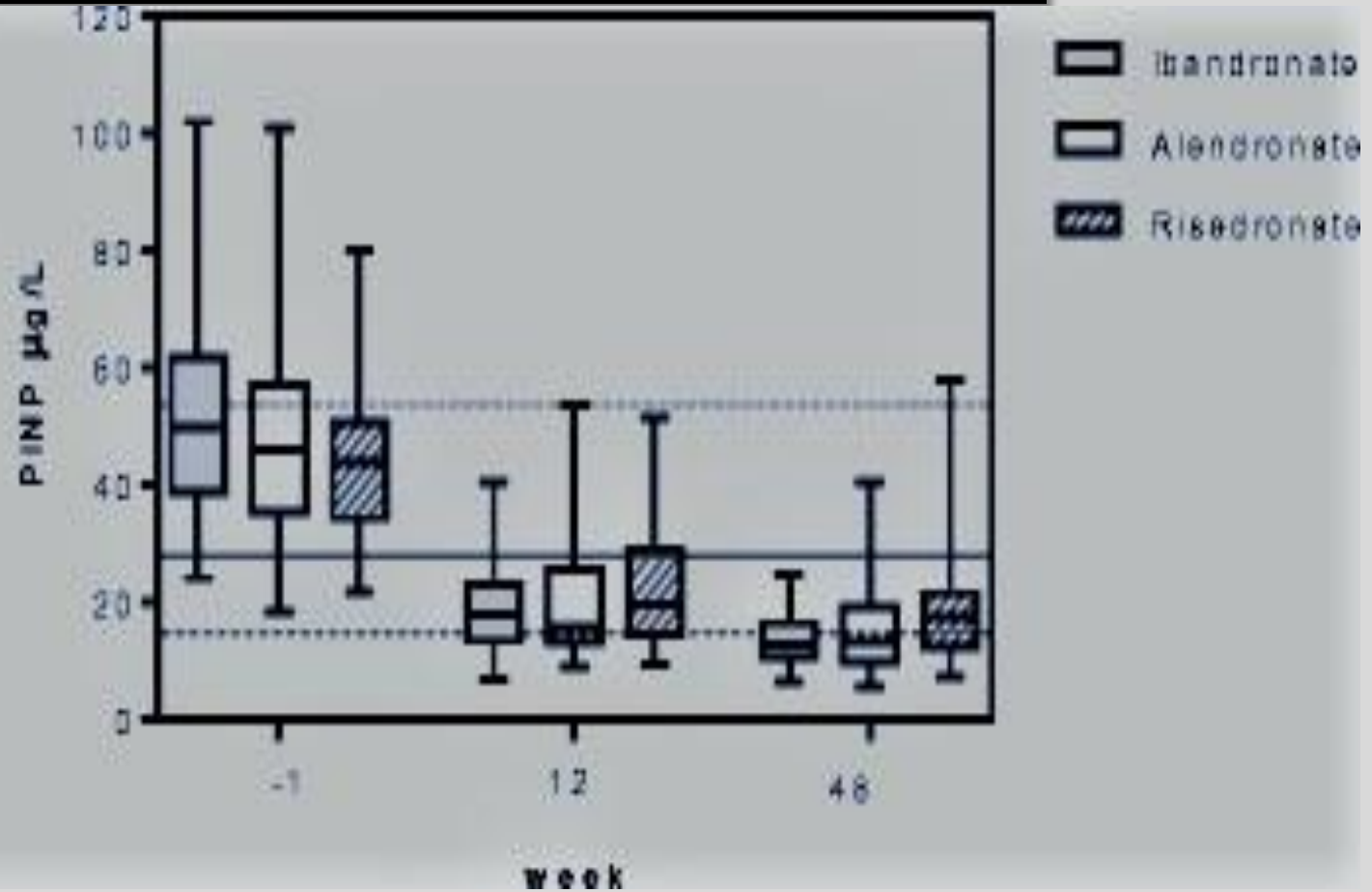
Osteoporos Int (2016) 27:21–31
DOI 10.1007/s00198-015-3145-7

ORIGINAL ARTICLE

Response of bone turnover markers to three oral bisphosphonate therapies in postmenopausal osteoporosis: the TRIO study

K. E. Naylor[1] - R. M. Jacques[2] - M. Paggiosi[1] - F. Gossiel[1] - N. F. A. Peel[3] - E. V. McCloskey[1] - J. S. Walsh[1] - R. Eastell[1]





How to define a responder ?

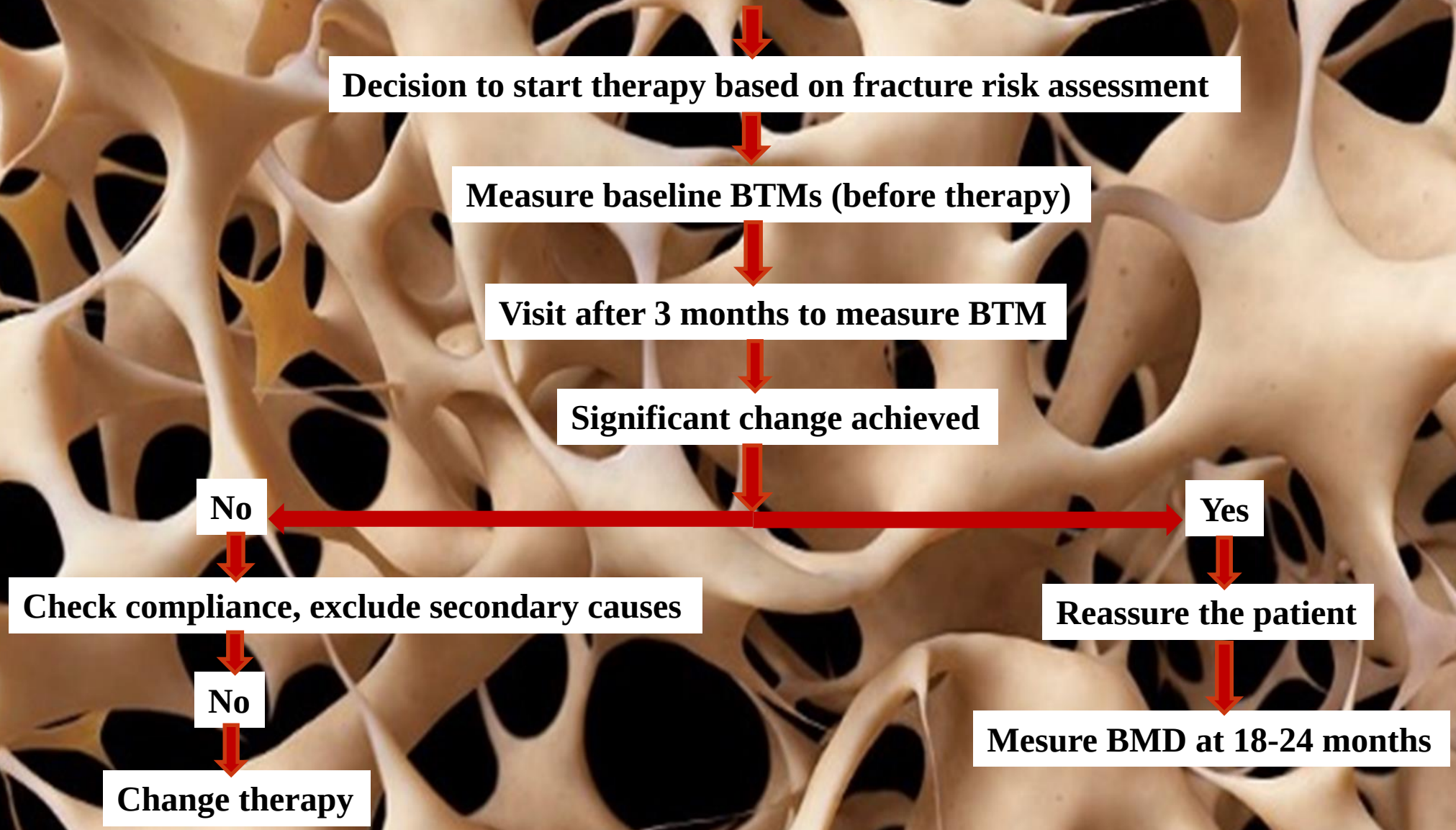
Least significant change (LSC)

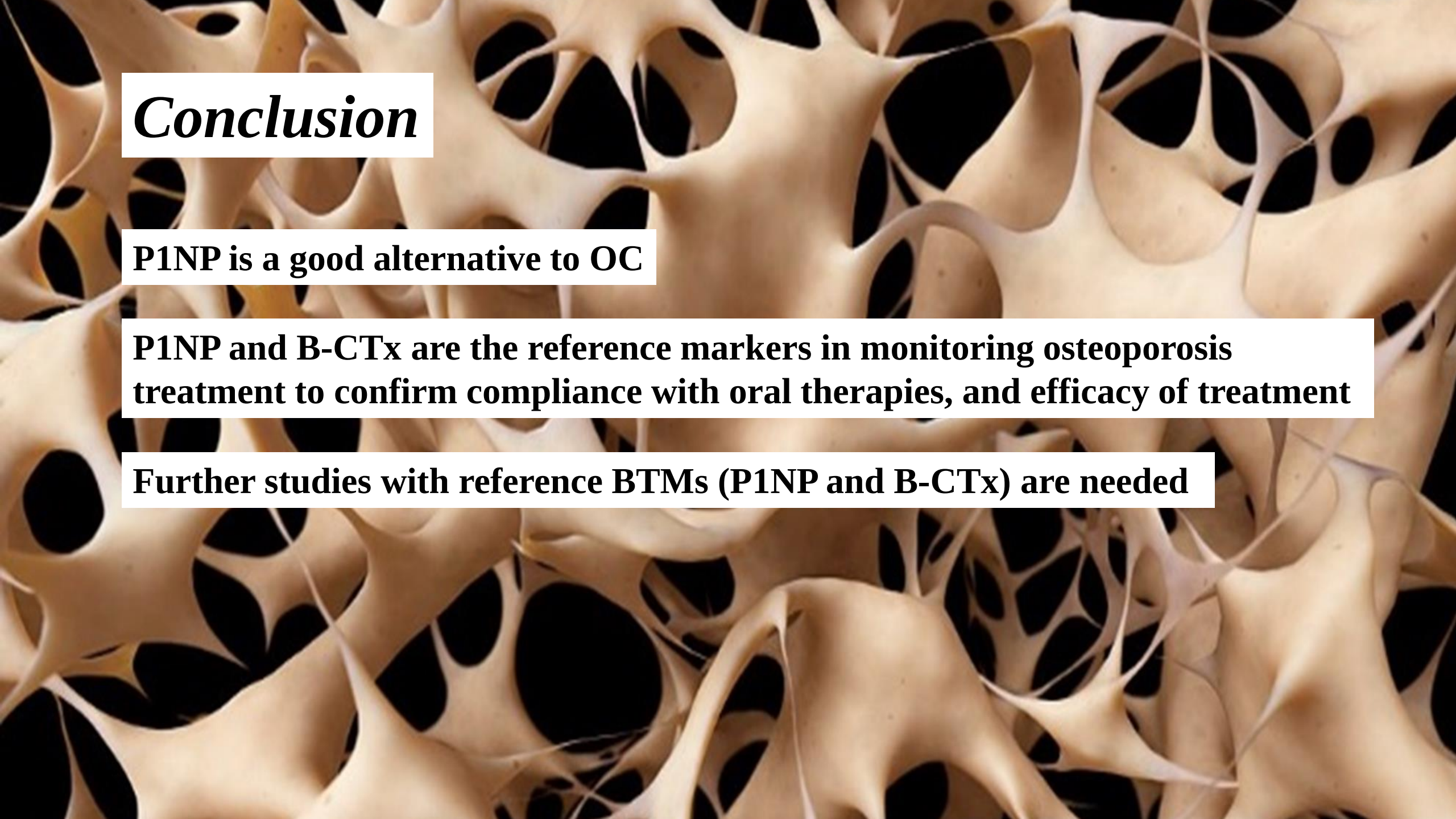
Reference interval (RI)

BTM	Visit	*n*	LSC (%)	LSC responders	Geometric mean (RI)	RI responders
CTX	Baseline	21	−45	–	0.32 μg/L (0.13 to 0.81)	3 (14 %)
	12 weeks	21		8 (38 %)		8 (38 %)
	48 weeks	20		12 (60 %)		8 (40 %)
PINP	Baseline	21	−27	–	28 μg/L (15 to 54)	2 (10 %)
	12 weeks	21		11 (52 %)		8 (38 %)
	48 weeks	20		13 (65 %)		9 (45 %)

Naylor, K. E. et al.2016

Algorithm for use of BTMs in therapy





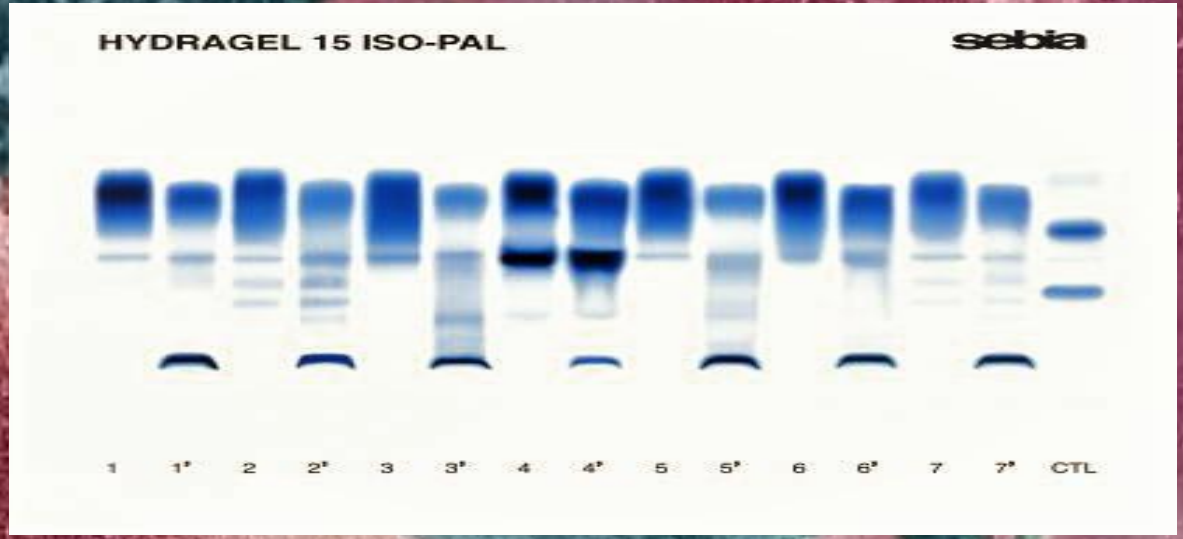
Conclusion

P1NP is a good alternative to OC

P1NP and B-CTx are the reference markers in monitoring osteoporosis treatment to confirm compliance with oral therapies, and efficacy of treatment

Further studies with reference BTMs (P1NP and B-CTx) are needed

BALP in clinical setting



Transient hyperphosphatasemia after organ transplantation in children

Osteosarcoma

Bone metastases

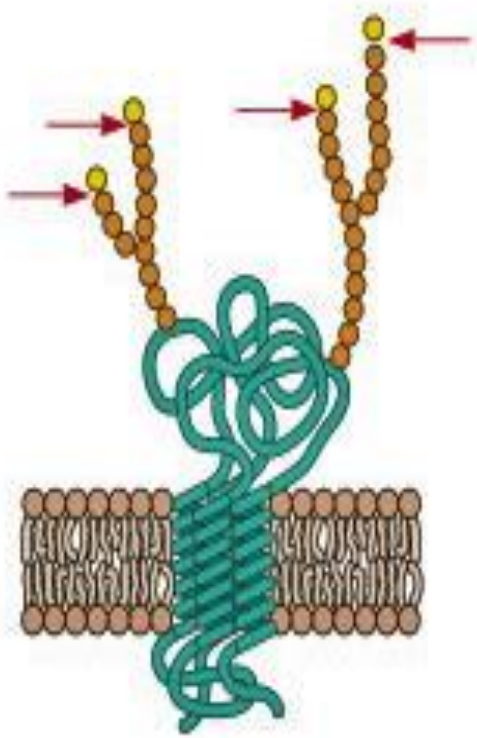
Transient hyperphosphatasemia after organ transplantation in children

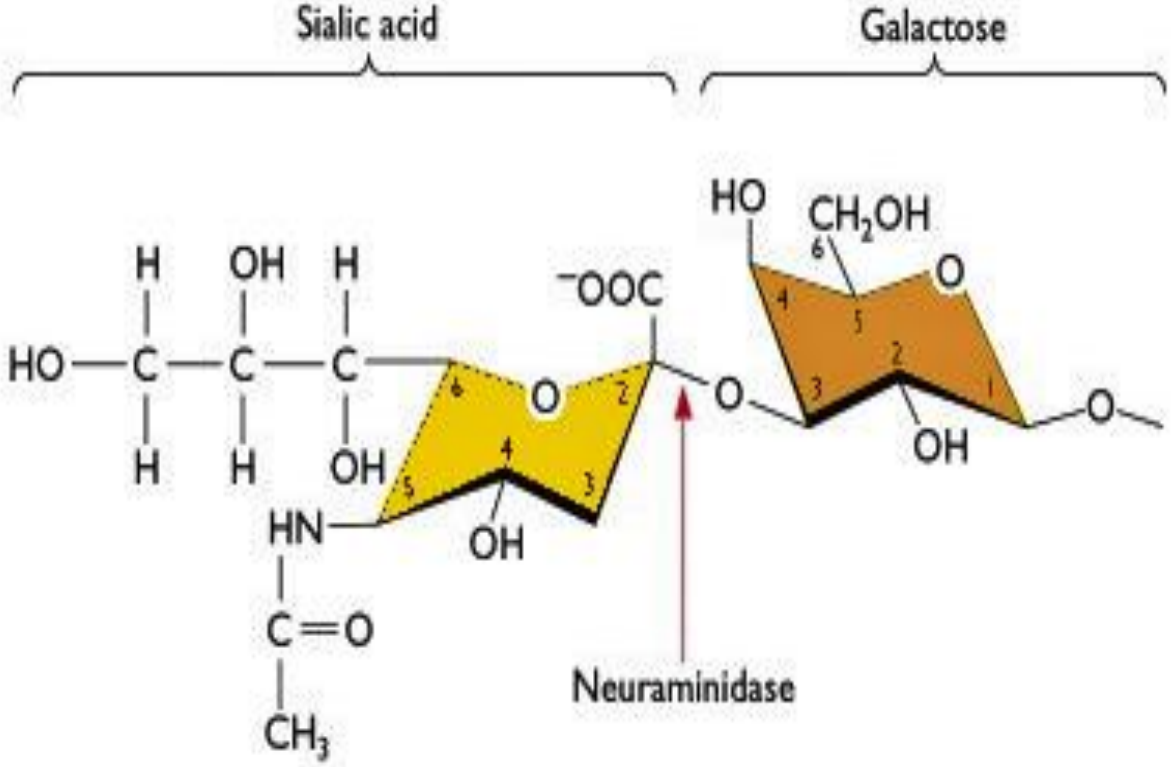
Introduction

Pathogenesis

Literature

Guidelines (ELTR 2014)





Virology blog 2009

Pediatr Int. 2016 Aug;58(8):726-31. doi: 10.1111/ped.12914. Epub 2016 Apr 21.

Transient hyperphosphatasemia after pediatric liver transplantation.

Yoshimaru K[1], Matsuura T[1], Hayashida M[1], Kinoshita Y[1], Takahashi Y[1], Yanagi Y[1], Esumi G[1], Taguchi T[1].

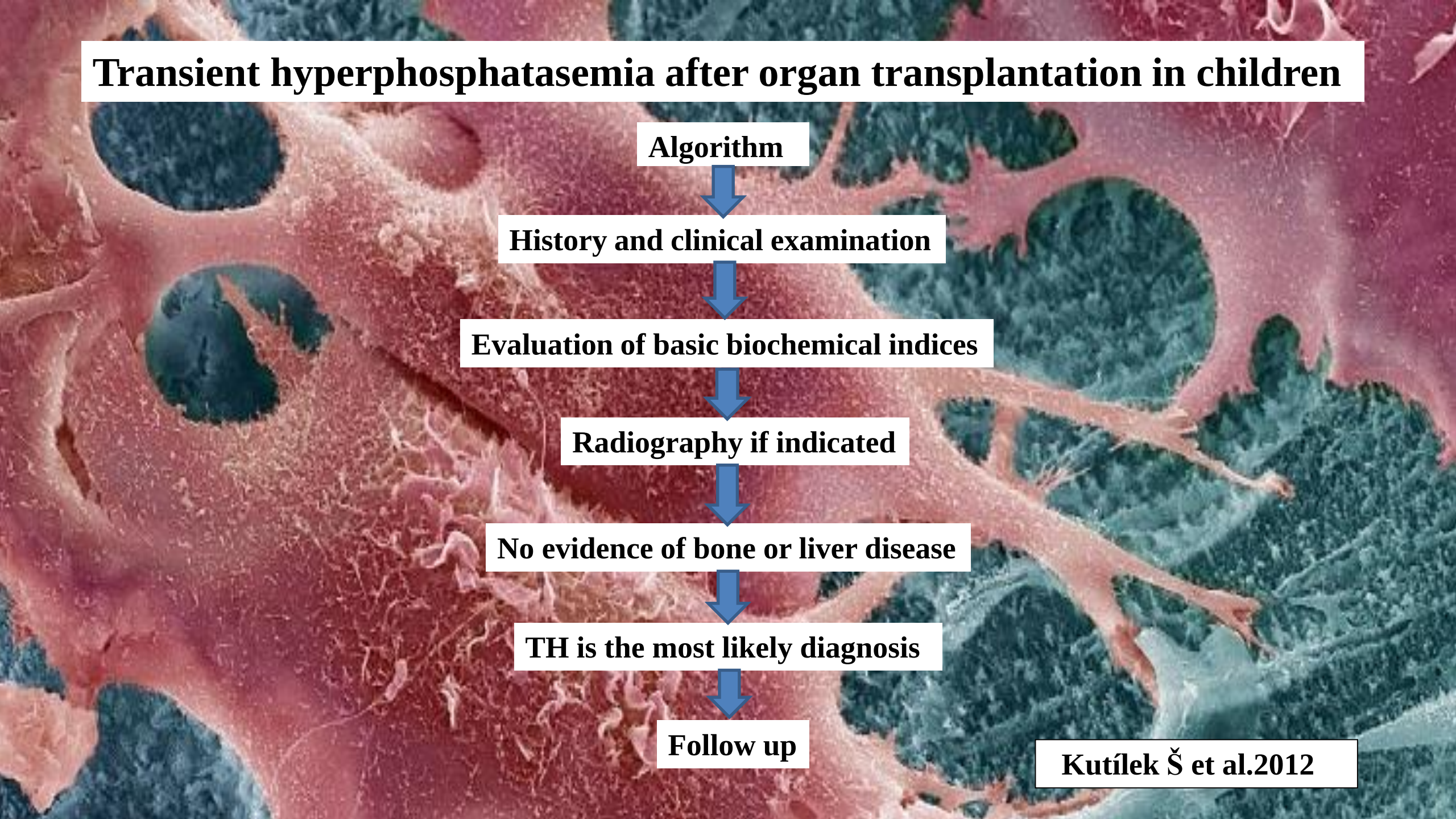
Author information

1 Department of Pediatric Surgery, Reproductive and Developmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

	Study, Year	No. patients	Incidence of TH (%)	Age range	Peak ALP (IU/L)	Duration of TH	Agarose gel electrophoresis	Liver biopsy	Estimated etiology of TH	IS	Steroid	Albumin	ST
1	Koneru *et al.* 1989[8]	6	2.2	2–6 years	NA	2 weeks–16 months	No	No	–	CsA	NA	NA	NA
2	Egawa *et al.* 1995[9]	4	2.9	15–32 months	7220	1–3 months	No	No	Growth acceleration after withdrawal of PSL	Tac	yes	NA	NA
3	Lachaux *et al.* 1996[10]	1	NA	9 months	4600	3 months	No	NA	-	CsA	yes	NA	NA
4	Ranchin *et al.* 2002[11]	3	5.2	1–9 years	5574	42–204 days	No	No	-	CsA, Tac	Yes	NA	NA
5	O'Riordan *et al.* 2002[12]	6	4.3	11–198 months	13 740	6–77weeks	Yes	Yes	Chronic cholangiopathy, CMV hepatitis	CsA, Tac	Yes	no	yes
6	Arikan *et al.* 2006[13]	2	2.8	2.6–4 years	21 110	18 days–8 months	No	Yes	Rotavirus	CsA, Tac	Yes	NA	yes
7	Hranjec *et al.* 2008[14]	1	NA	3 years	10 099	5 months	No	No	EBV	Tac, MMF	Yes	NA	NA
8	Present study	5	6.0	1–8 years	31 018	60–173 days	Yes	No	–	Tac, MMF	Yes	Yes	Yes

CMV, cytomegalovirus; CsA, cyclosporin A; EBV, Epstein–Barr virus; IS, immunosuppressive agent; LT, liver transplantation; MMF, mycophenolate mofetil; NA, not available; ST, sulfamethoxazole/trimethoprim; Tac, tacrolimus; TH, transient hyperphosphatasemia.

Transient hyperphosphatasemia after organ transplantation in children



Kutílek Š et al.2012

BALP in Osteosarcoma

Introduction

Literature

Guidelines

Cancer. 1979 Jun;43(6):2178-81.

Prognostic significance of alkaline phosphatase measurements in patients with osteogenic sarcoma receiving chemotherapy.

Thorpe WP, Reilly JJ, Rosenberg SA.

J Chemother. 1994 Jun;6(3):204-10.

Prognostic significance of serum lactate dehydrogenase in patients with osteosarcoma of the extremities.

Bacci G[1], Ferrari S, Sangiorgi L, Picci P, Casadei R, Orlandi M, Iantorno D, Battistini A, Zanone A.

Author information

1 Chemotherapy Department, Istituto Ortopedico Rizzoli, Bologna, Italy.

Tumori. 2004 Sep-Oct;90(5):478-84.

Prognostic significance of serum lactate dehydrogenase in osteosarcoma of the extremity: experience at Rizzoli on 1421 patients treated over the last 30 years.

Bacci G[1], Longhi A, Ferrari S, Briccoli A, Donati D, De Paolis M, Versari M.

Author information

1 Chemotherapy, Department of Musculoskeletal Oncology, Istituto Ortopedico Rizzoli, Bologna, Italy. gaetano.bacci@ior.it

Eur J Surg Oncol. 2009 Oct;35(10):1030-6. doi: 10.1016/j.ejso.2009.01.011. Epub 2009 Feb 20.

Prognostic factors in localized extremity osteosarcoma: a systematic review.

Bramer JA[1], van Linge JH, Grimer RJ, Scholten RJ.

Author information

1 Department of Orthopedic Surgery (G4 221), Academic Medical Center, Meibergdreef 9, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands. jbramer@wxs.nl

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii113–iii123, 2014
doi:10.1093/annonc/mdu256

Bone sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

The ESMO/European Sarcoma Network Working Group*

No specific laboratory tests for the diagnosis of bone sarcoma are available. However, some are useful in the follow-up in ES and osteosarcoma and may also be of prognostic value, such as alkaline phosphatase (AP) and lactate dehydrogenase (LDH)

BALP in bone metastasis

Introduction

Literature

Guidelines

Advantages of use of BTMs in oncology setting

- Easily collected (not invasive)
- A variety of assays are available
- May decrease the frequency of imaging
- Predominantly osteolytic lesions in renal cell carcinoma; osteoblastic lesions in prostate cancer

Disadvantages of use of BTMs in oncology settings

- Lack of tissue specificity
- Fluctuation of urinary creatinine
- Effect hormonal therapies on resorption markers
- Both osteolytic and osteoblastic lesions in other types of cancers

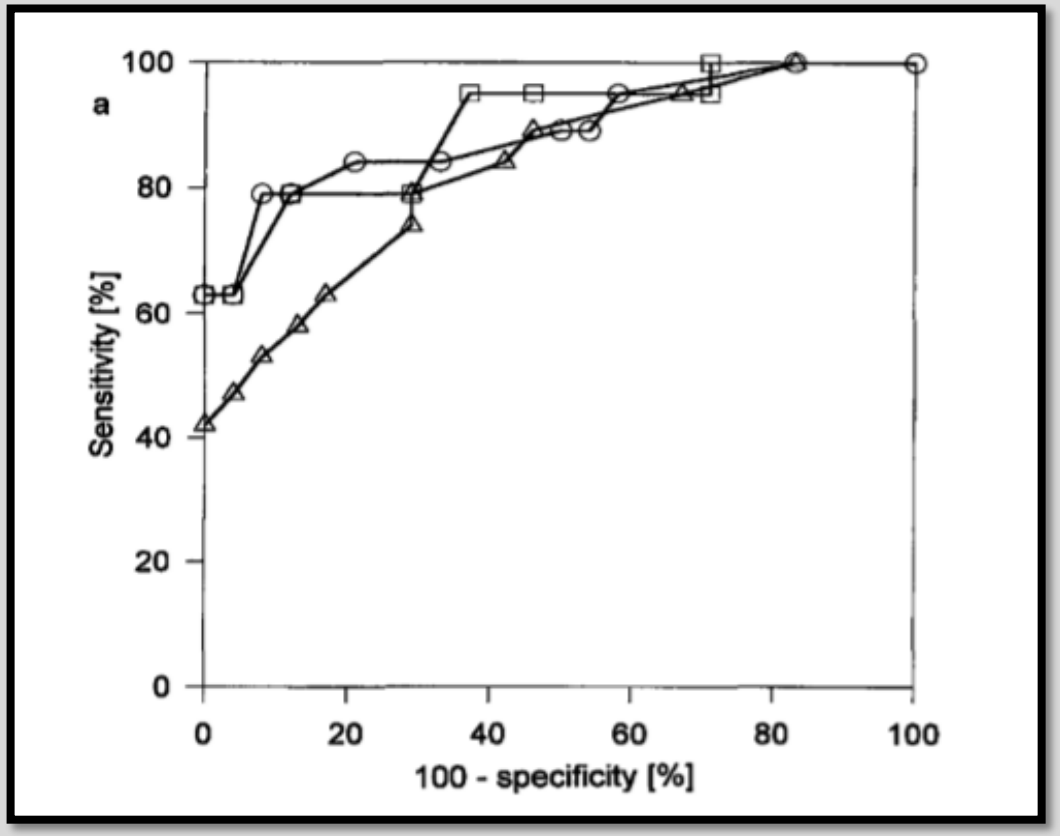
Eur J Clin Chem Clin Biochem. 1997 Feb;35(2):89-94.

Diagnostic value of some biochemical bone markers for the detection of bone metastases in prostate cancer.

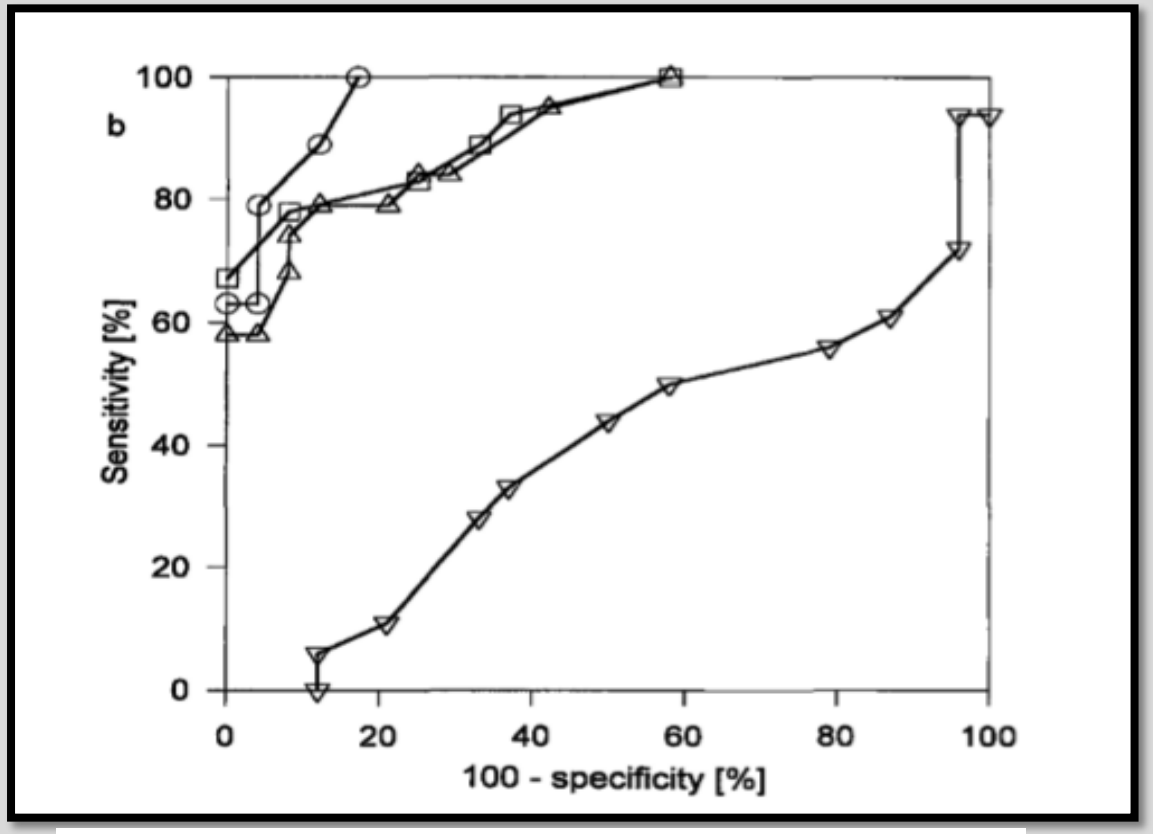
Westerhuis LW[1], Delaere KP.

Author information

1 Department of Clinical Chemistry, Ziekenhuis De Wever & Gregorius, Heerlen, The Netherlands.



ALP□, BALP○, P1CP△



B-CTx○, DPYD□, NTX△, Ca. in urine▽

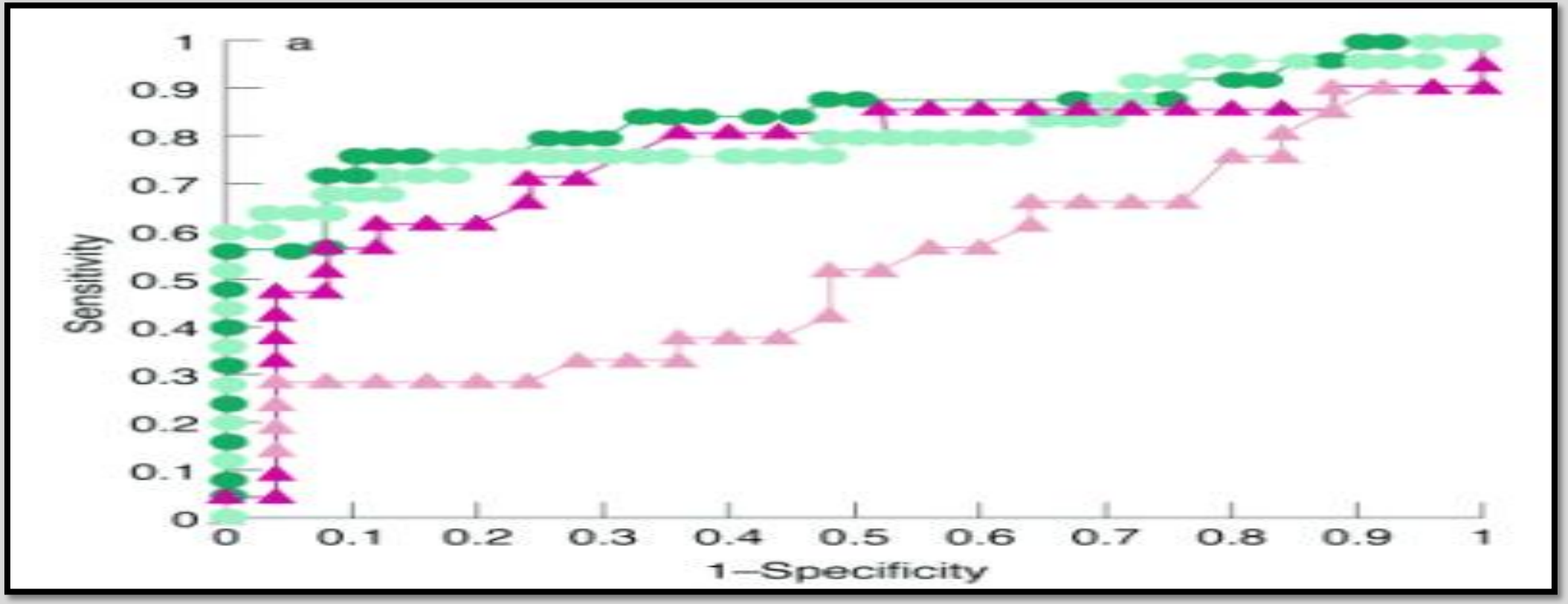
BJU Int. 2001 Mar;87(4):348-51.

The serum level of the amino-terminal propeptide of type I procollagen is a sensitive marker for prostate cancer metastasis to bone.

Koizumi M[1], Yonese J, Fukui I, Ogata E.

Author information

1 Department of Nuclear Medicine, Cancer Institute Hospital, Tokyo, Japan. mitsuru@jfcr.or.jp



Roc curve for P1NP (green), P1CP (purple), BALP (light green) and BGP (light purple)

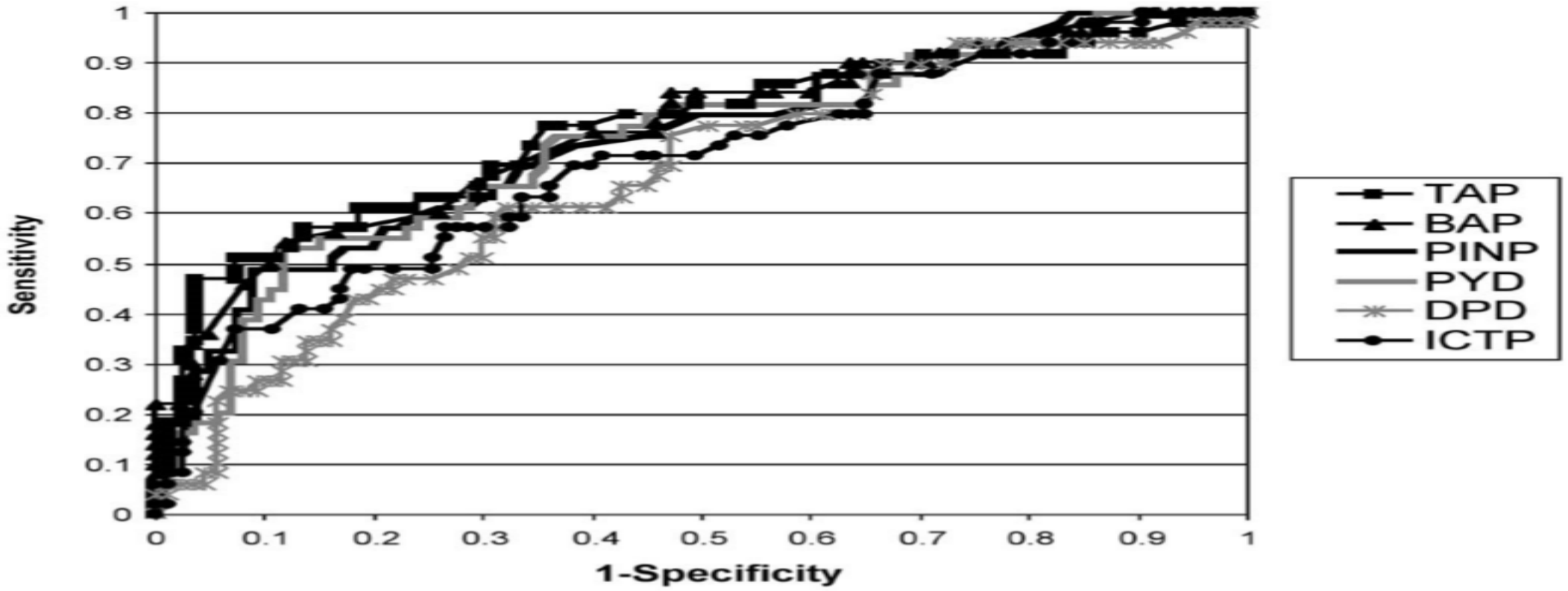
Anticancer Res. 2004 Sep-Oct;24(5B):3193-201.

Comparison of bone scintigraphy with bone markers in the diagnosis of bone metastasis in lung carcinoma patients.

Ebert W[1], Muley T, Herb KP, Schmidt-Gayk H.

Author information

1 Thoraxklinik Heidelberg gGmbH, University of Heidelberg, Heidelberg, Germany. prof.ebert@t-online.de



The area under the ROC curves for TAP (0,765), for BALP (0,764), for P1NP (0,742)….

Conclusion

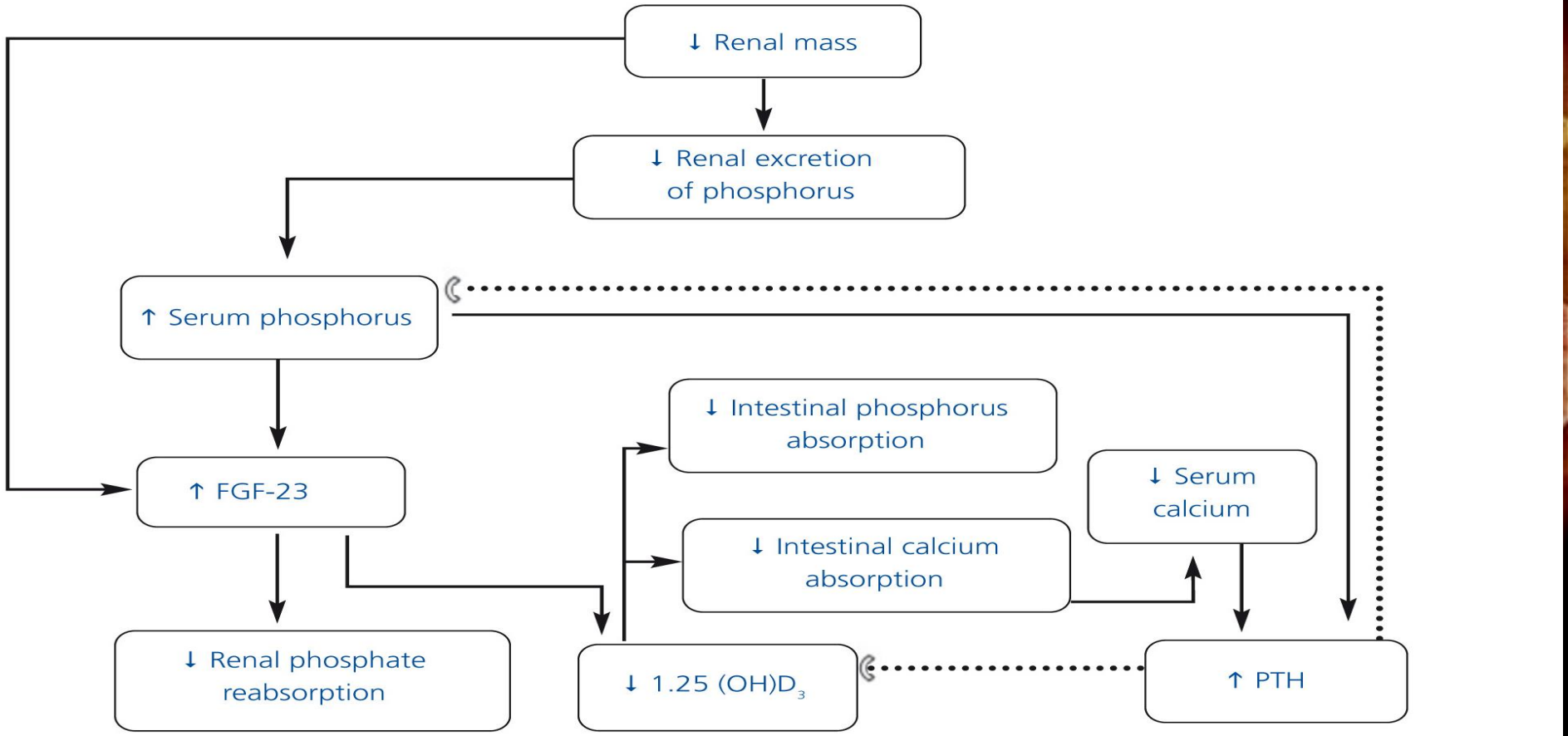
No added value of BALP

Several markers have shown promise

BTMs in general are not ready to be used in bone metastasis setting

Chronic kidney disease-mineral bone disease (CKD-MBD)

Pathophysiology

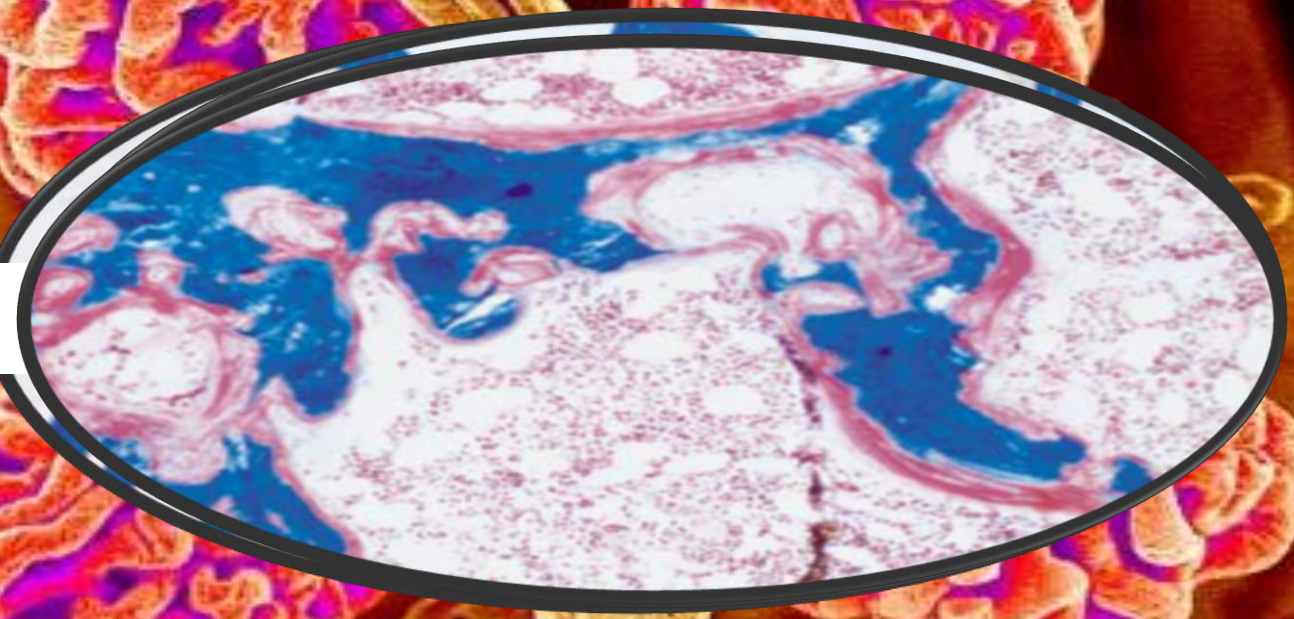


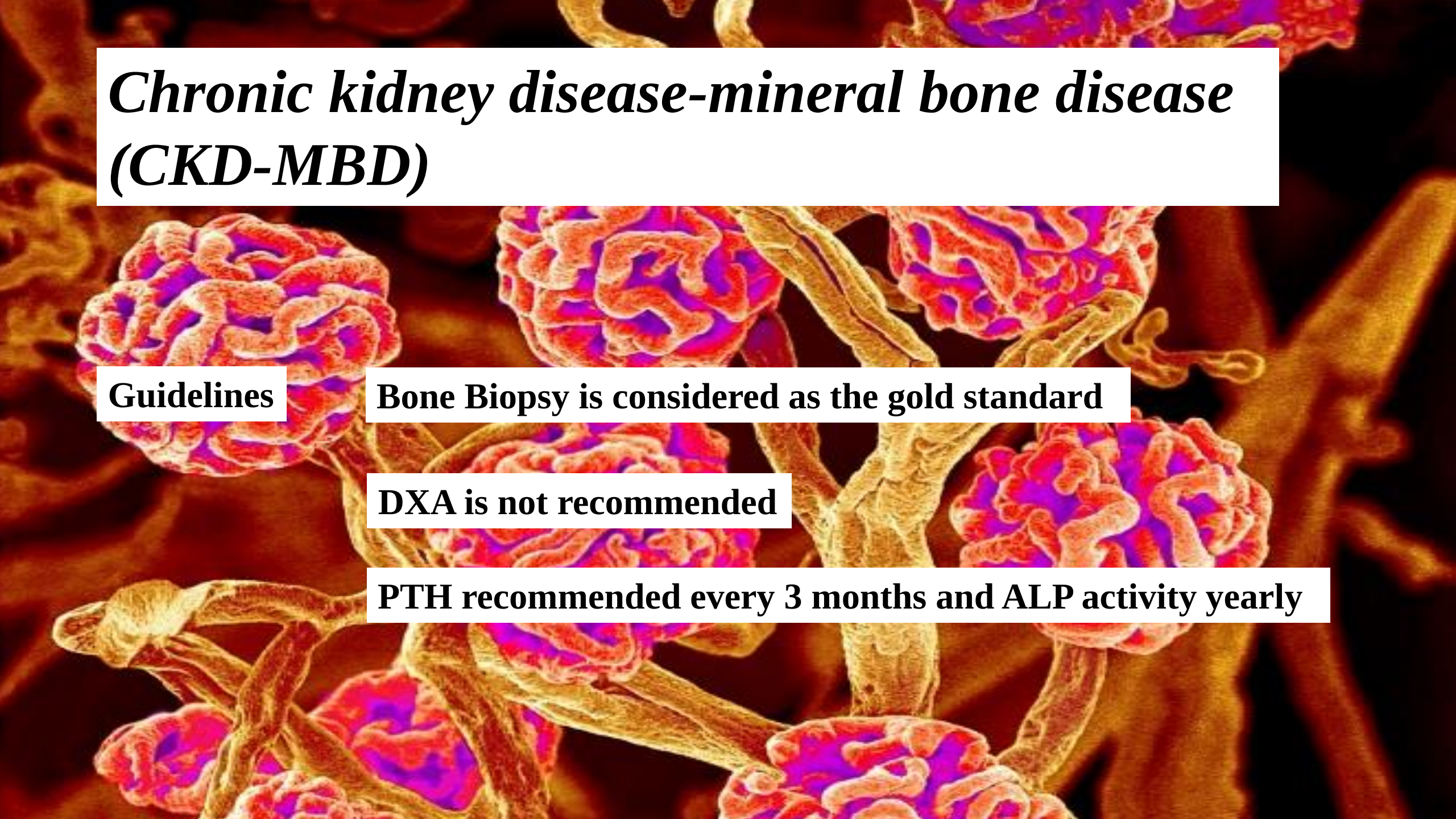
Chronic kidney disease-mineral bone disease (CKD-MBD)

Types

Osteomalacia

e disease





Chronic kidney disease-mineral bone disease (CKD-MBD)

Guidelines

Bone Biopsy is considered as the gold standard

DXA is not recommended

PTH recommended every 3 months and ALP activity yearly

Chronic kidney disease-mineral bone disease (CKD-MBD)

A look back in the history!

K/DOQI (suggested I-PTH target levels in dialysis patients)

Kidney Int. 2008 Mar;73(6):771-7. doi: 10.1038/sj.ki.5002769. Epub 2008 Jan 9.

K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients.

Barreto FC[1], Barreto DV, Moysés RM, Neves KR, Canziani ME, Draibe SA, Jorgetti V, Carvalho AB.

Author information

1 Division of Nephrology, Department of Internal Medicine, Federal University of São Paulo, São Paulo, Brazil. fellype.barreto@terra.com.br

KDIGO (PTH expanded range for dialysis patients)

Chronic kidney disease-mineral bone disease (CKD-MBD)

Utility of NKF-KDOQI and KDIGO iPTH thresholds for diagnostic decision-making

	NKF-KDOQI[a]				KDIGO[b]			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Differentiating low from nonlow turnover bone disease, or "When do I stop therapy?"	68.5%	61.2%	71.6%	57.7%	65.7%	65.3%	73%	57%
Differentiating high from nonhigh turnover bone disease, or "When do I start therapy?"	58.0%	77.7%	34.8%	90%	37.0%	85.8%	34.9%	86.9%

Abbreviations: iPTH, intact parathyroid hormone; KDIGO, Kidney Disease: Improving Global Outcomes; NKF-KDOQI, National Kidney Foundation–Kidney Disease Outcomes Quality Initiative; NPV, negative predictive value; PPV, positive predictive value.

[a]Using serum iPTH < 150 pg/mL for lower and >300 pg/mL for upper threshold.

[b]Using serum iPTH < 130 pg/mL for lower and >585 pg/mL for upper threshold (2× and 9× upper limit of normal for assay).

sprague, S.M. el al.2016

Chronic kidney disease-mineral bone disease (CKD-MBD)

Clin Chim Acta. 2013 Feb 18;417:35-8. doi: 10.1016/j.cca.2012.12.009. Epub 2012 Dec 21.

Parathormone and bone-specific alkaline phosphatase for the follow-up of bone turnover in hemodialysis patients: is it so simple?

Delanaye P[1], Dubois BE, Jouret F, Krzesinski JM, Moranne O, Cavalier E.

Author information

1 Division of Nephrology-Dialysis-Hypertension, University of Liège, CHU Sart Tilman, Liège, Belgium. pierre_delanaye@yahoo.fr

Other promising bone markers?

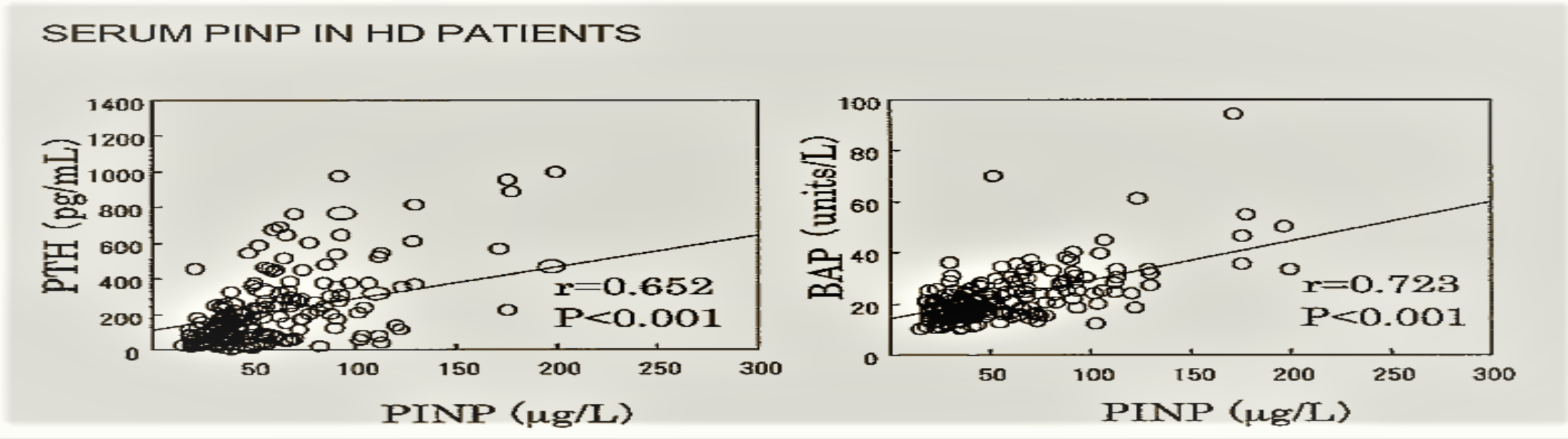
Am J Kidney Dis. 2002 Oct;40(4):802-9.

Clinical usefulness of the serum N-terminal propeptide of type I collagen as a marker of bone formation in hemodialysis patients.

Ueda M[1], Inaba M, Okuno S, Nagasue K, Kitatani K, Ishimura E, Shimizu M, Miki T, Kim M, Nishizawa Y.

Author information

1 Department of Metabolism, Endocrinology, and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.



Correlations between serum P1NP values and values of other biochemical markers of bone metabolism in 195 male HD patients. PINP values significantly positively correlated with those of serum PTH (r 0.652; P < 0.001) and two other serum markers of bone formation: BAP (r 0.723; P < 0.001)

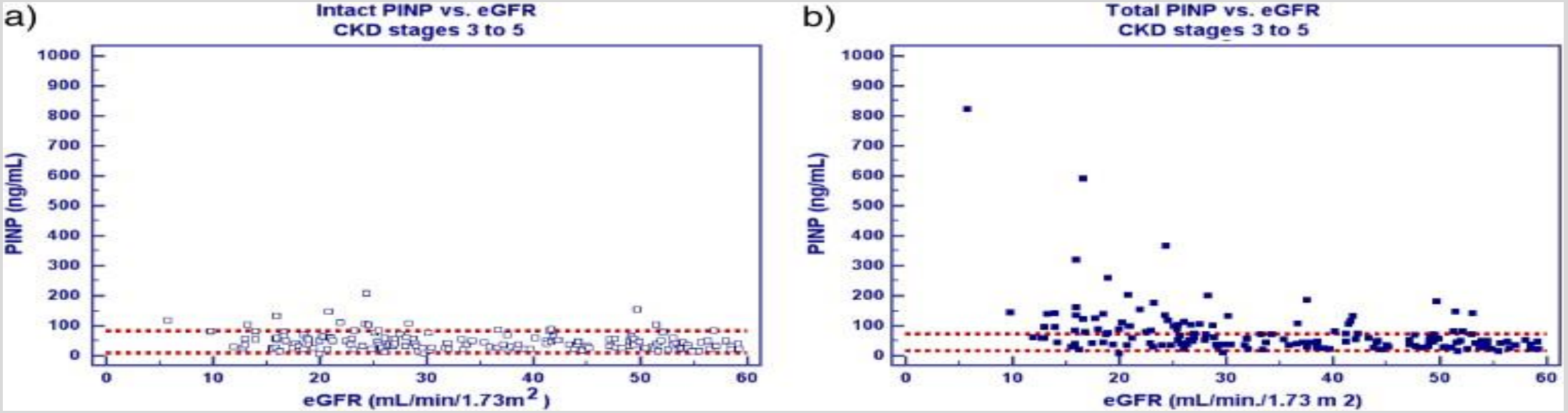
Clin Chim Acta. 2013 Oct 21;425:117-8. doi: 10.1016/j.cca.2013.07.016. Epub 2013 Jul 26.

Aminoterminal propeptide of type I procollagen (PINP) in chronic kidney disease patients: the assay matters.

Cavalier E[1], Lukas P, Carlisi A, Gadisseur R, Delanaye P.

Author information

1 Department of Clinical Chemistry, University of Liege, CHU Sart-Tilman, Liege, Belgium. Electronic address: Etienne.cavalier@chu.ulg.ac.be.



Distribution of IDS iSYS Intact (a) and Roche Elecsys Total (b) P1NP values obtained in 157 CKD stage 3–5 patients according to the eGFR value. The dashed lines represent the reference ranges proposed by the manufacturers.

Chronic kidney disease-mineral bone disease (CKD-MBD)

Conclusion

No biomarker so far clearly proved to be superior to iPTH

PTH is still the most used biomarker

The place of bone markers in in CKD-MBD still need to be further studied

Longitudinal studies that compare BTMs with the gold standard (bone biopsy) are required

In summery

P1NP and B-CTx are the reference markers in monitoring osteoporosis treatment

BTMs in general are not ready to be used in bone metastasis setting neither for screening nor in the diagnosis of bone metastasis in place of established diagnostic techniques

No added value of BALP in osteosarcoma or in transient hyperphosphatemia

PTH still the most used biomarker in CKD-MBD patients.

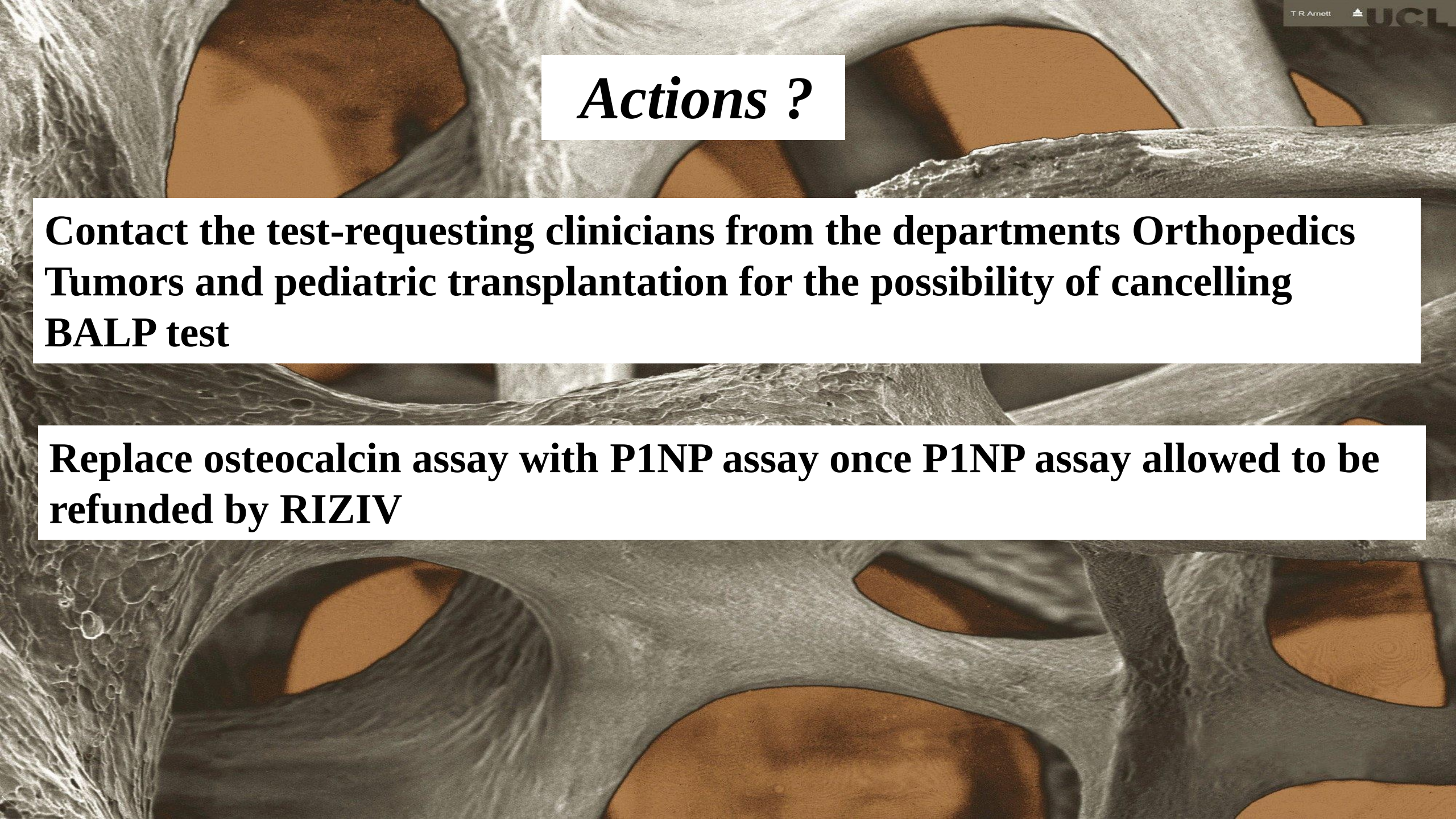
Some laboratories in Flanders where bone markers tests are performed

	UZL	VUB	UZG	UZA	SAINT-LUC	SINT-JAN	JESSA
OC	YES	YES	X	YES	YES	YES	YES
P1NP	YES*	X	YES	X	YES	YES	X
B-CTx	YES	YES	YES	YES	YES	X	YES
NTX	X	YES	X	X	X	X	YES
DPD	X	X	X	YES	X	X	X
ISO-ALP	YES	YES	X	YES	X	YES	YES

** referred to UCL Saint-Luc laboratory*

Cost

Name of the test	Number of tests/year	Total cost per test	Incom RIZIV 100%B	
OC	230	14.51 euro	9 euro	Manual in house assay (no reagent cost but personnel cost)
PINP	**2**	**24 euro**	**NO**	**Mainly reagent kit cost**
B-CTx	337	8.02 euro	12 euro	Mainly reagent kit cost
BALP	82	182.53 euro	12 euro	Reagent kit cost+ personnel cost



Actions ?

Contact the test-requesting clinicians from the departments Orthopedics Tumors and pediatric transplantation for the possibility of cancelling BALP test

Replace osteocalcin assay with P1NP assay once P1NP assay allowed to be refunded by RIZIV


Thank you