Società Medico Chirurgica di Ferrara dal 1846

Con il Patrocinio di:

Università degli Studi di Ferrara

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara
Azienda Unità Sanitaria Locale di Ferrara

Ordine dei Medici Chirurghi e degli Odontoiatri della provincia di FERRARA

AE

sie Società Italiana Endocrinologia

SIMG

SIOMMMS Società Italiana dell'Osteoporosi del Metabolismo Minerale e delle Malattie dello Scheletro

SIBioC Medicina di Laboratorio ETS

Membro di

EFLM

ifcc

UPDATE SULLA GESTIONE DEL RISCHIO DI FRATTURA

Marcatori ed ormoni dell'osso
Aspetti Analitici

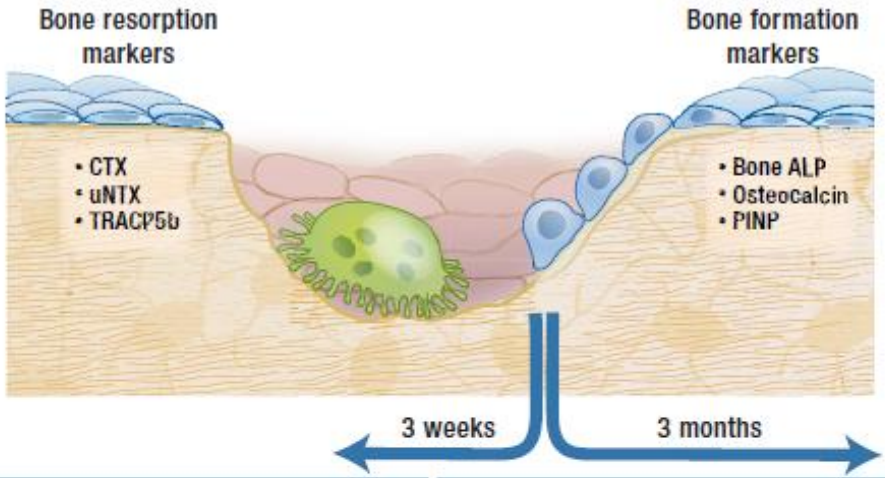
Martina Zaninotto

QI.LAB.MED.

UNIVERSITÀ DEGLI STUDI DI PADOVA

Spin-off dell'Università di Padova

Bone Turnover Markers
Basic Biology to Clinical Applications



Methodology		Clinical use	
Main assays	• ELISA • Automated immunoassays	Diagnosis and/or management	• Osteoporosis • Primary hyperparathyroidism • Osteomalacia • Paget's disease • Fibrous dysplasia • Hypophosphatasia • Metastatic bone disease • Chronic kidney disease-mineral bone disorder
Sources of variability	• Age • Gender • Ethnicity • Lactation/pregnancy • Menstrual cycle phase • Fasting/feeding • Seasonal/Circadian rhythm • Exercise/immobilization • Recent fracture/drugs	Monitoring drug use	• Anti-osteoporotic drugs

Schini M et al, 2023

Guidelines for the management of osteoporosis and fragility fractures

Ranuccio Nuti[1] · Maria Luisa Brandi[2] · Giovanni Checchia[3] · Ombretta Di Munno[4] · Ligia Dominguez[5] · Paolo Falaschi[6] · Carmelo Erio Fiore[1] · Giovanni Iolascon[3] · Stefania Maggi[6] · Raffaella Michieli[7] · Silvia Migliaccio[2] · Salvatore Minisola[1] · Maurizio Rossini[4] · Giuseppe Sessa[8] · Umberto Tarantino[8] · Antonella Toselli[7] · Giovanni Carlo Isaia[5]

Laboratory diagnosis

Bone turnover markers

Bone turnover markers are mainly used to obtain information about the extent of new-bone-formation and resorption processes. They are overall indicators of skeletal remodelling, and, therefore, vary considerably at analytical and biological level: therefore, there is no indication for their use in routine evaluations of individual patients. In

2019

Practical Considerations for the Clinical Application of Bone Turnover Markers in Osteoporosis 2023

Samuel D. Vasikaran[1] · Masakazu Miura[2] · Richard Pikner[3,4,5] · Harjit P. Bhattoa[6] · Etienne Cavalier[7] on behalf of the IOF-IFCC Joint Committee on Bone Metabolism (C-BM)

Role of BTMs

BTMs concentrations in blood or urine are thought to reflect bone remodelling rate and hence they have been used to research metabolic bone diseases including Paget's disease of bone, osteoporosis and osteomalacia as well as metabolic bone disease of chronic kidney disease (CKD-MBD) in the last several decades. BTMs are also used in clinical practice, in conjunction with other diagnostic modalities, especially imaging studies, for the diagnosis and or monitoring of metabolic bone diseases

BTMs are not useful for diagnosis of osteoporosis and are currently not included in fracture risk assessment, but are still useful in initial assessment of patients with osteoporosis to identify presence of secondary causes for osteoporosis, and are largely used for monitoring of therapy

Osteoporos Int
DOI 10.1007/s00198-017-3906-6

POSITION PAPER

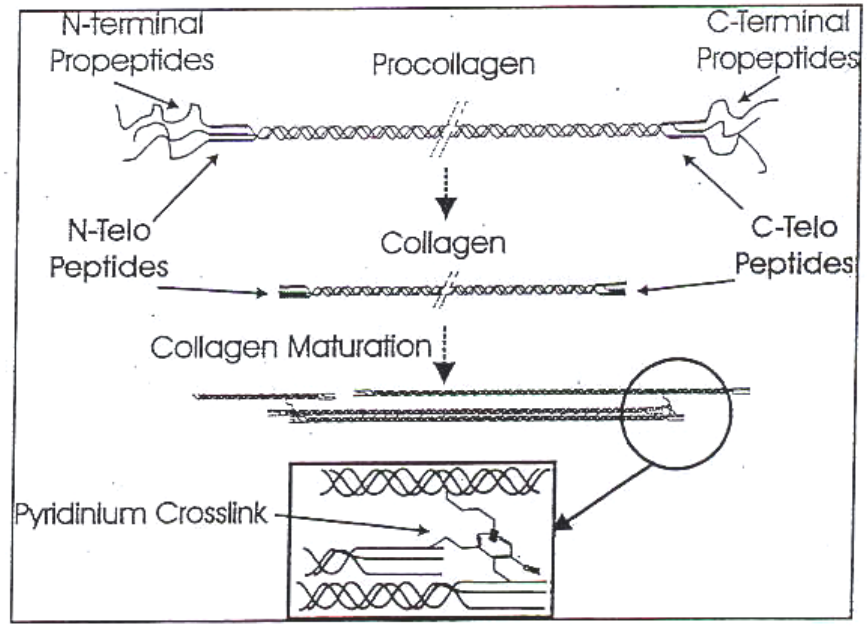
International Osteoporosis Foundation and European Calcified Tissue Society Working Group. Recommendations for the screening of adherence to oral bisphosphonates

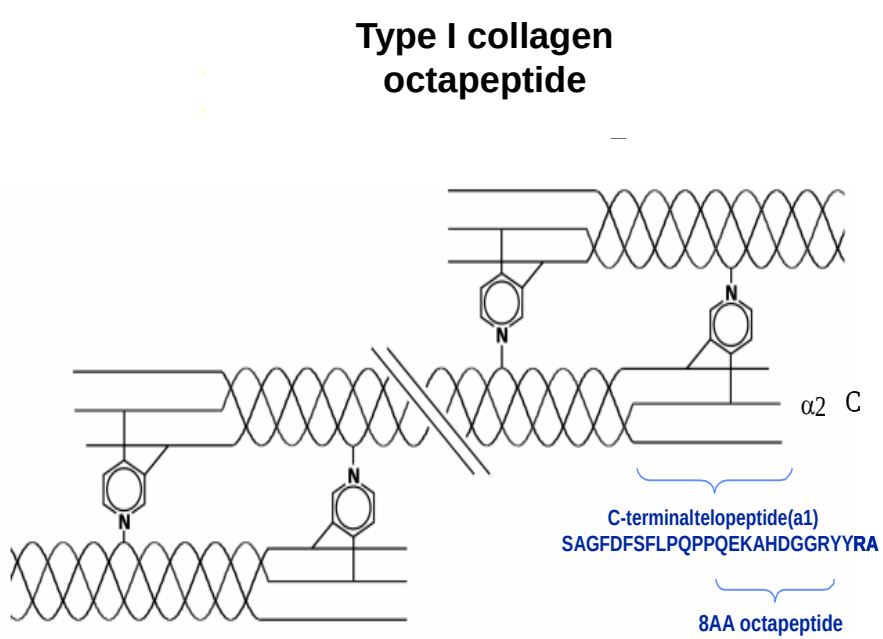
The Working Group (WG) proposed the following question: Can the bone turnover markers (BTMs) PINP and CTX be used to identify low adherence in patients with postmenopausal osteoporosis initiating oral bisphosphonates for osteoporosis?

Bone turnover markers

Measurement of bone turnover markers is considered as the most specific early method for measuring the biological effect of bisphosphonates. The WG focused on the two markers prioritized by the IOF, namely serum CTX and PINP.

Bone metabolism diagnostics
Current biomarkers





The IOF-IFCC Bone Markers Standard Working group

Recommendations for reference bone turnover markers

Serum CTx- ***choosed as reference standard for bone resorption***

Rationale

1. **The** ***standard in the assay is well characterised*****, is an 8-aa peptide and this allows the development of clearly defined reference standard**

2. ….it is likely that ***most CTx is derived from osteoclastic resorption*** **given that treatments that reduce bone turnover reduce such markers to very low levels**

3…

4. The ***biological and analytical variability*** **have been well documented**

5. The ***assay has been automated*** **and widely available**

6. The assay is ***available for serum or plasma***

The IOF-IFCC Bone Markers Standard Working group

Recommendations for reference bone turnover markers

Serum PINP- ***choosed as the reference standard for bone formation***

Rationale

1. **PINP *reflects the synthesis* of the most abundant protein of bone tissue**
2. **The *standard is less well characterised*; mw is much larger than 35,000 D.**
3. **….it is believed that *most PINP is produced during bone formation*; it has been evaluated already for fracture prediction and monitoring therapies**
4.
5. **The *biological and analytical variability* have been well documented**
6. **The *assay has been automated* and is widely avaialable**

Practical Considerations for the Clinical Application of Bone Turnover Markers in Osteoporosis 2023

Samuel D. Vasikaran[1] · Masakazu Miura[2] · Richard Pikner[3,4,5] · Harjit P. Bhattoa[6] · Etienne Cavalier[7] on behalf of the IOF-IFCC Joint Committee on Bone Metabolism (C-BM)

Table 4 Intra individual variation [within-subject (CV_I) biological variation (BV)] estimates for the reference BTMs for osteoporosis, PINP and β-CTX, with 95% confidence interval (CI), based on Cavalier et al.

Measurand	Mean value (95% CI)	CV_A % (95% CI)[a]	CV_I % (95% CI)
PINP, µg/L	63.7 (62.3–65.0)	3.7 (3.6–3.9)	8.8 (8.4–9.3)
β-CTX, ng/L	514.3 (499.5–529.1)	5.0 (4.8–5.3)	15.1 (14.4–16.0)

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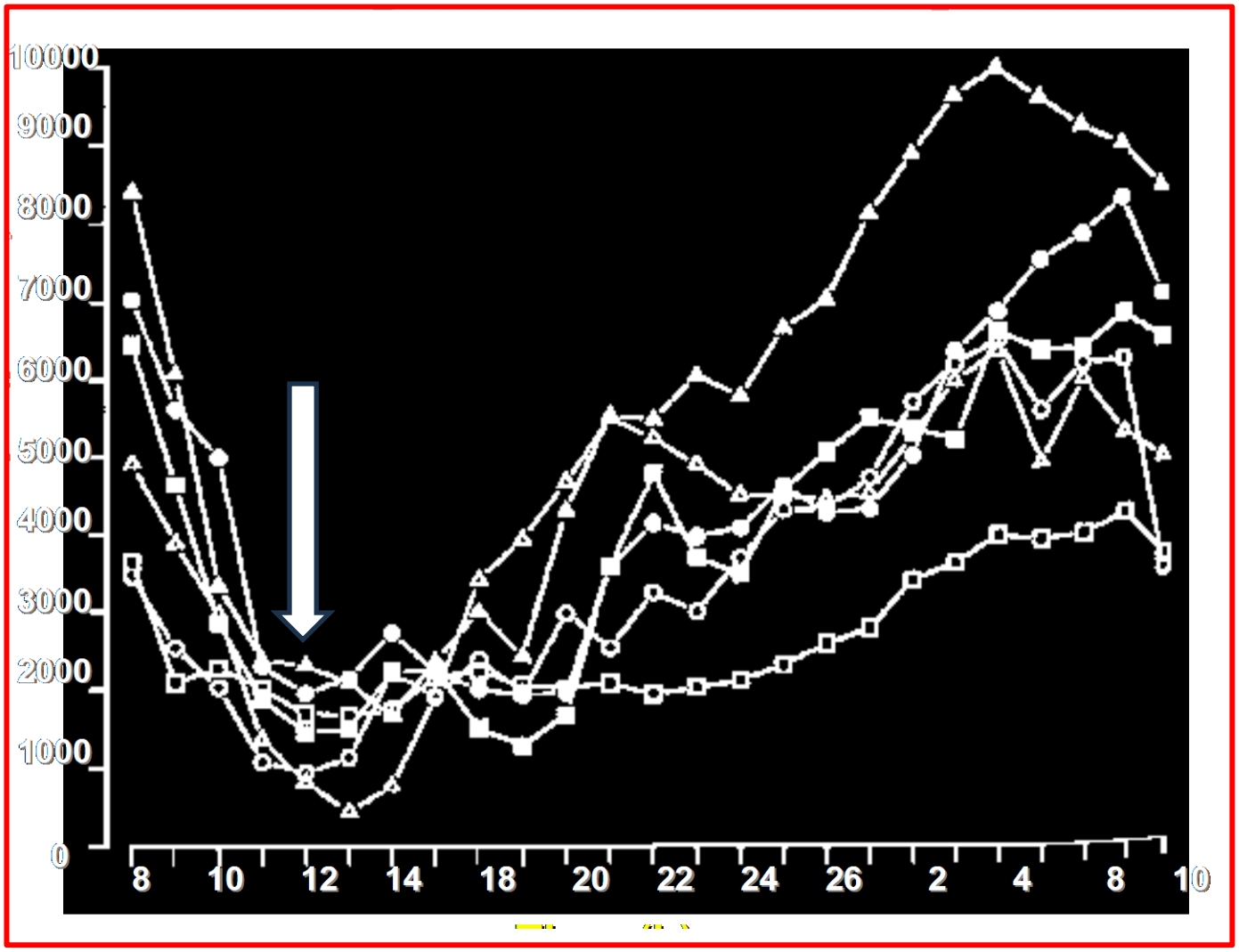
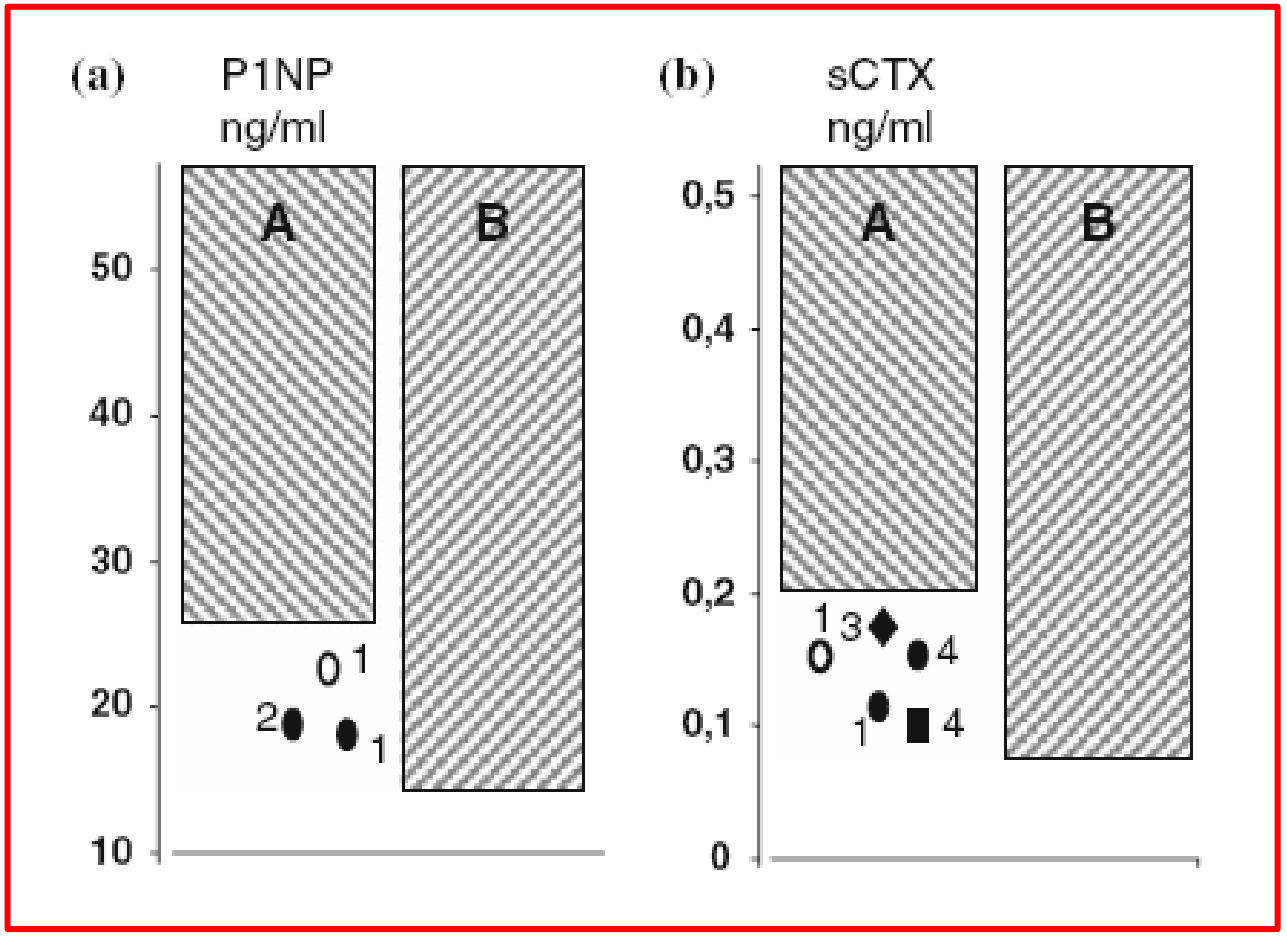
Serum or urine	Measurand	CV_I
Serum	Procollagen type I *N*-propeptide (PINP)	7.4
	C-terminal telopeptide type I collagen (β-CTX)	10.9
	Osteocalcin	6.4
	Alkaline phosphatase, bone (B-ALP)	6.2
	Acid phosphatase tartrate-resistant (TRACP)	8.0
Urine	Deoxypyridinoline/creatinine, first morning	13.8
	Hydroxyproline/minute—excretion rate, first morning	36.1
	N-telopeptide type I collagen concentration	15.5
Serum	Parathyroid hormone (PTH)	25.9

Cyrcadian rythm of CTx



Determinants of BTM in healthy women



A) Normal ranges in premenopausal women aged 20-25 y
B) Normal ranges in women aged -45 y

Expected values in healthy subjects

Total P1NP

	Post-menopausal			Pre-menopausal
	All	HRT[b] yes	HRT no	All
N	444	154	290	129
5th percentile	16.27	14.28	20.25	15.13
Median	37.09	28.48	42.94	27.80
Mean	40.43	31.74	45.05	30.10
95th percentile	73.87	58.92	76.31	58.59

Beta- CTx

Age range (years)	Men			Women		
	N	GM[b] (pg/mL)	95 % RI (pg/mL)	N	GM (pg/mL)	95 % RI (pg/mL)
< 29.9	39	492	238-1019	58	378	148-967
30-39.9	80	459	225-936	111	308	150-635
40-49.9	234	382	182-801	257	296	131-670
50-59.9	248	345	161-737	281	440	183-1060
60-69.9	303	316	132-752	234	408	171-970
>70	135	302	118-776	88	362	152-858
Pre-menopause	-	-	-	449	306	136-689
Post-menopause	-	-	-	578	424	177-1015

European Biological Variation Study (EuBIVAS): within- and between-subject biological variation estimates of β-isomerized C-terminal telopeptide of type I collagen (β-CTX), N-terminal propeptide of type I collagen (PINP), osteocalcin, intact fibroblast growth factor 23 and uncarboxylated-unphosphorylated matrix-Gla protein—a cooperation between the EFLM Working Group on Biological Variation and the International Osteoporosis Foundation-International Federation of Clinical Chemistry Committee on Bone Metabolism

Table 10 Reference change values (RCV) for a decrease in BTM following antiresorptive therapy based on the biological variation (BV) estimates

Measurand	RCV (%)
PINP	− 19.9
β-CTX	− 30.8

$$CD = K \sqrt{CV_A^2 + CV_I^2}$$

$$K = 2.77$$

-RCV, CD, LSC-

the least amount of change between two consecutive BMD measurements can be considered clinically significant

Cavalier E et al, 2020

Editorials

Controversies in Family Medicine

Should Bone Turnover Markers Be Used Routinely to Monitor Oral Bisphosphonate Osteoporosis Therapy?

TABLE 3

A 63-year-old postmenopausal woman treated with oral alendronate for osteoporosis

Background:

- History of breast cancer treated with lumpectomy, radiation therapy, and 5 years of tamoxifen
- Outside DXA scans showed a progressive decline in her lumbar spine T-score from –3.1 to –3.3
- Femoral neck bone density was stable
- Past medical history was otherwise unremarkable
- No history of lactose intolerance, celiac disease, or chronic glucocorticoid use
- She did not take calcium supplements, but took over-the-counter vitamin D
- No history of antifracture therapy.

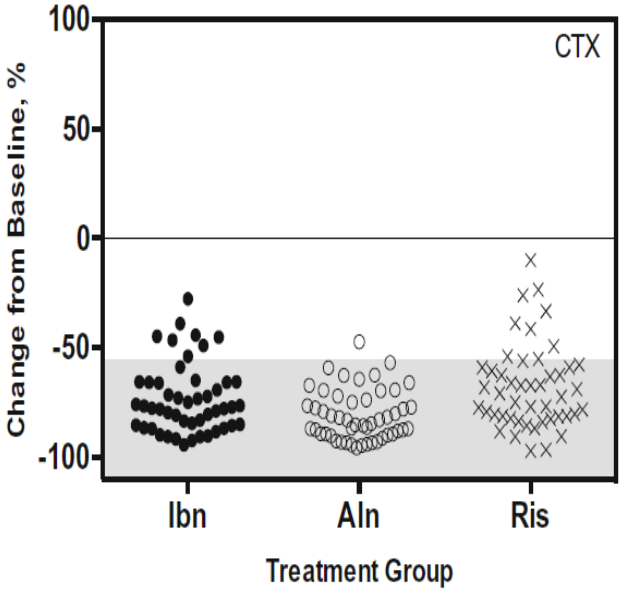
The patient was prescribed oral alendronate 70 mg once weekly.

Bone mineral density and bone turnover markers:

	Before treatment	3 months	1 year
T-scores:			
Lumbar spine	NA		–2.6
Left femoral neck	NA		–1.5
Right femoral neck	NA		–1.5
Bone turnover marker: C-terminal telopeptide of type I collagen	653 pg/mL	361 pg/mL (45% reduction from baseline)	188 pg/mL (72% reduction from baseline)

Doshi BK et al, 2023

Biomarkers of bone turnover
Change from baseline after 3 months of treatment



Shadow zone
Change>LSC

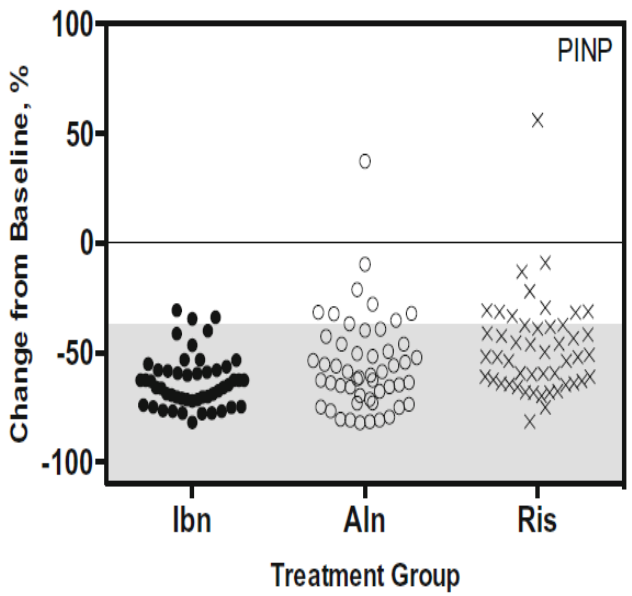
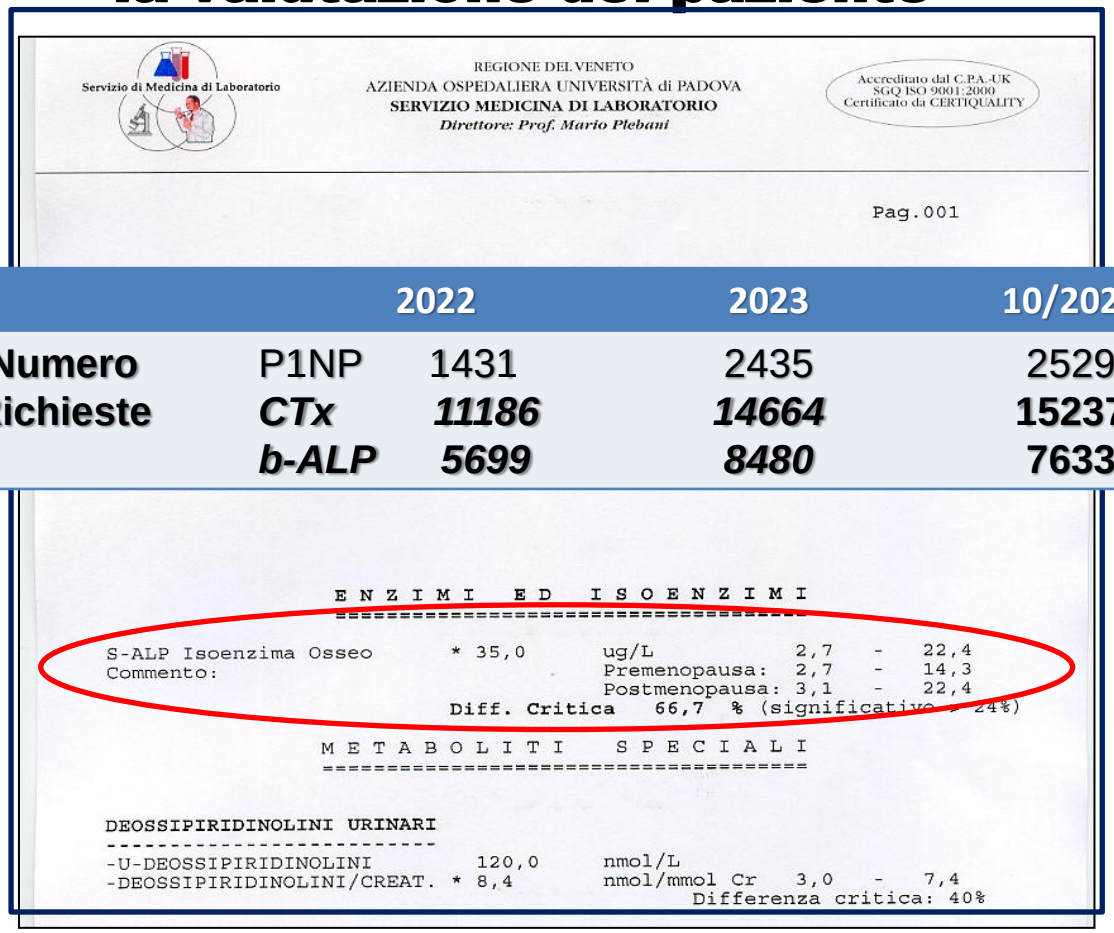


Table 3 Detection rate as percent of cases in the overall cohort with the prespecified decrease > LSC in CTX, PINP, or both after the initiation of treatment

BTM	*N*	*N* with decrease > LSC	*N* with decrease < LSC	Detection rate (%)
CTX	146	127	19	86.9
PINP	149	125	24	83.9
CTX + PINP	146	138	8	94.5

Laboratorio clinico e metabolismo osseo: la valutazione del paziente

		2022	2023	10/2024
Numero Richieste	P1NP	1431	2435	2529
	CTx	***11186***	***14664***	**15237**
	b-ALP	***5699***	***8480***	**7633**



Servizio di Medicina di Laboratorio

REGIONE DEL VENETO
AZIENDA OSPEDALIERA UNIVERSITÀ di PADOVA
SERVIZIO MEDICINA DI LABORATORIO
Direttore: Prof. Mario Plebani

Accreditato dal C.P.A.-UK
SGQ ISO 9001:2000
Certificato da CERTIQUALITY

Pag.001

E N Z I M I E D I S O E N Z I M I

S-ALP Isoenzima Osseo	* 35,0	ug/L	2,7	-	22,4
Commento:		Premenopausa:	2,7	-	14,3
		Postmenopausa:	3,1	-	22,4
		Diff. Critica	**66,7**	**%**	(significativo > 24%)

M E T A B O L I T I S P E C I A L I

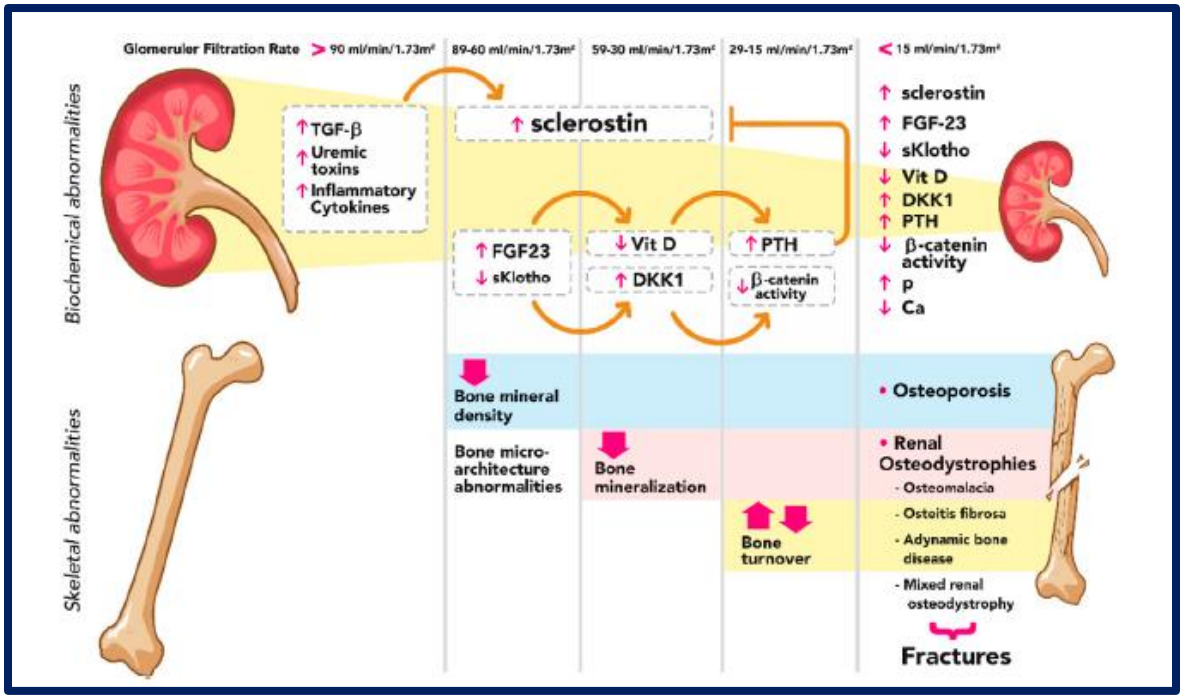
DEOSSIPIRIDINOLINI URINARI

-U-DEOSSIPIRIDINOLINI	120,0	nmol/L			
-DEOSSIPIRIDINOLINI/CREAT.	* 8,4	nmol/mmol Cr	3,0	-	7,4
		Differenza critica: 40%			

Fonte

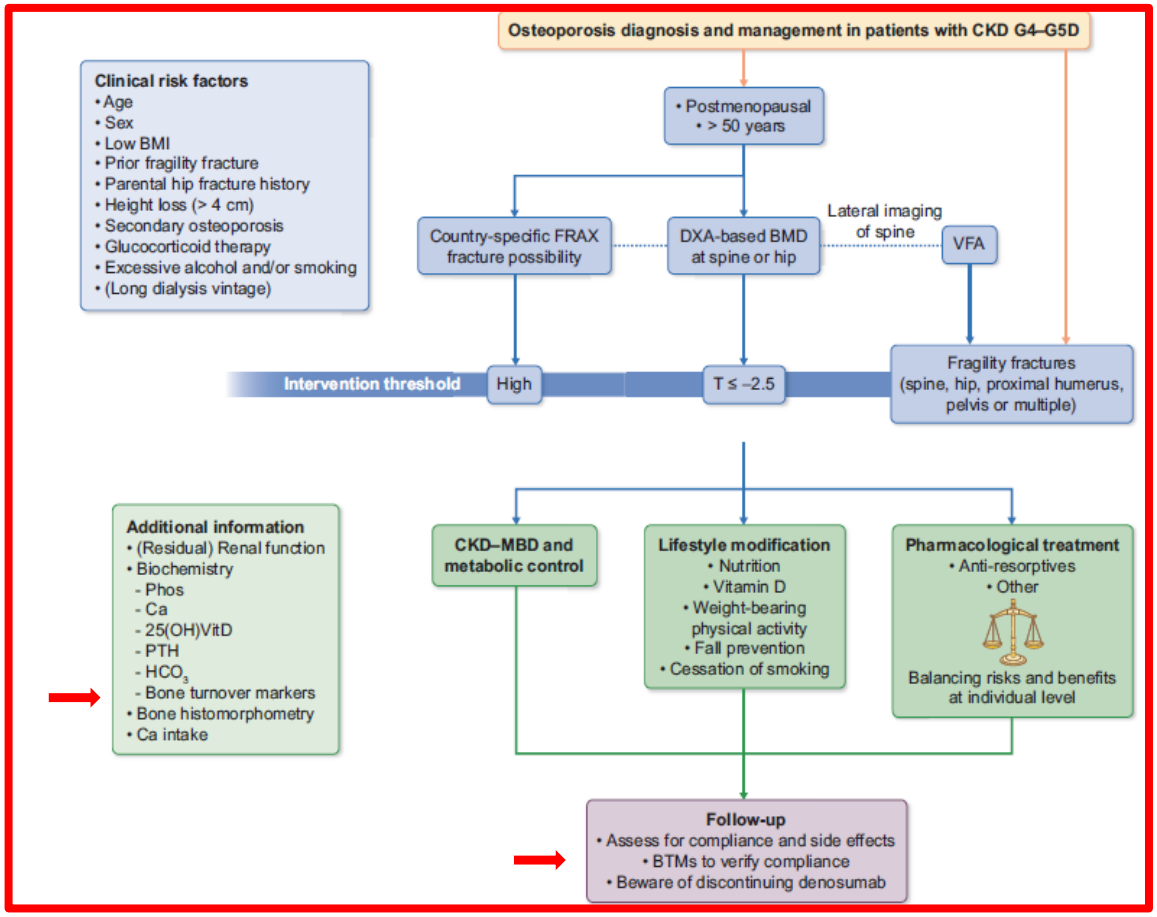
UOC Medicina di Laboratorio Azienda Ospedale-Università Padova

Pathophysiology of bone disease in chronic kidney disease: from basics to renal osteodystrophy and osteoporosis



Aguilar et al, 2023

Pragmatic approach to patients with CKD G4-G5D and osteoporosis



Evenpoel P et al, 2021

Calcified Tissue International (2021) 108:512–527
https://doi.org/10.1007/s00223-020-00781-5

REVIEW

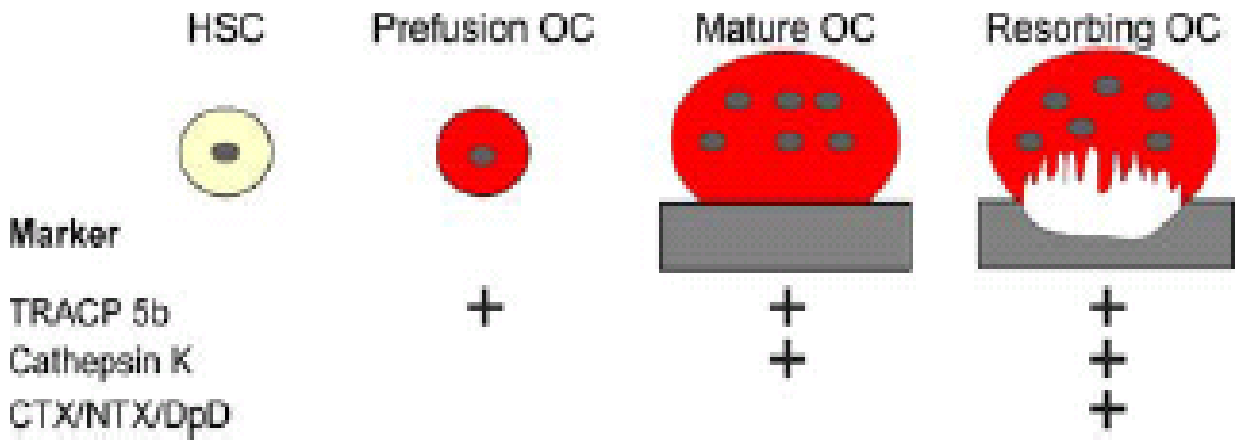
The Non-invasive Diagnosis of Bone Disorders in CKD

Table 2 Serum bone turnover biomarkers (

Biomarker	Common acronym	Renal clearance
Without renal clearance[#]		
Bone formation		
Total alkaline phosphatase	tAP, TAP, AP, ALP	No*
Bone-specific alkaline phosphatase	BSAP, bAP, BAP, BALP	No
Procollagen type 1 N-terminal propeptide[&]	Intact P1NP, PINP	No (intact PNP)
Bone resorption		
Tartrate-resistant acid phosphatase 5b	TRAP5b, TRACP-5b	No
With renal clearance[#]		
Bone formation		
Osteocalcin	OC, BGP, BGlaP,	Yes
Procollagen type 1 N-terminal propeptide	P1NP, PINP	Yes (total P1NP)
Procollagen type 1 C-terminal propeptide	P1CP, PICP	Yes
Bone Resorption		
Carboxy-terminal cross-linking telopeptide of type 1 collagen[&]	CTX, CTX-1, CTX-I	Yes
Amino-terminal cross-linking telopeptide of type 1 collagen	NTX	Yes
Cross-linked carboxyterminal telopeptide of type 1 collagen (generated by matrix metalloproteinases)	ICTP o CTX-MMP	Yes

Bover J et al, 2021

Assessment of osteoclast number and function



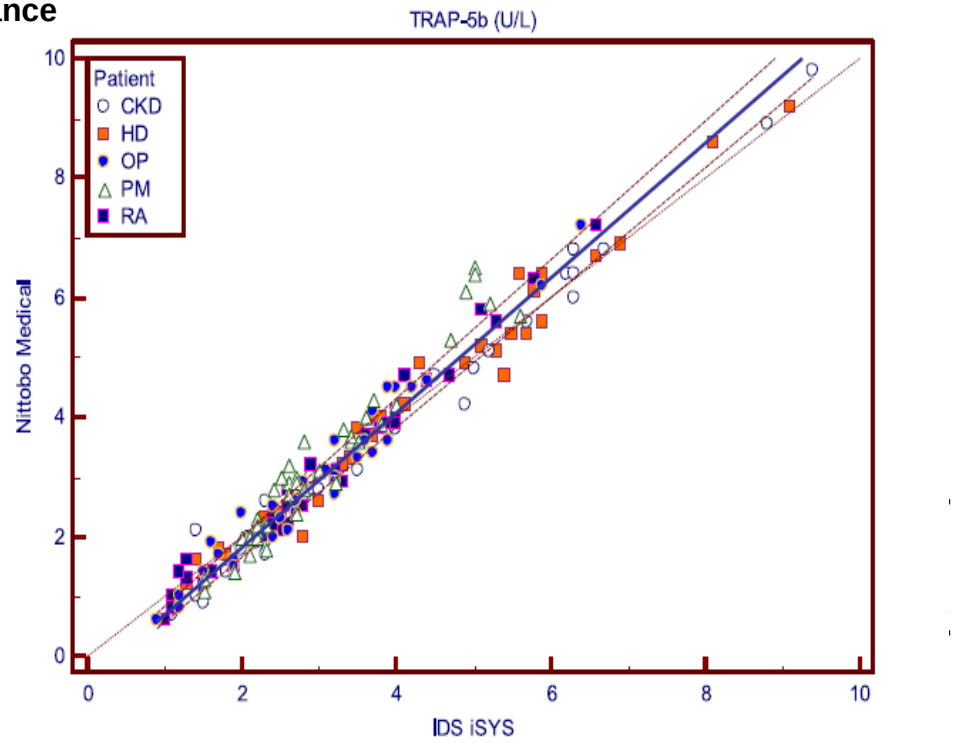
In contrast to collagen-based markers, TRACP may reflect different aspects of osteoclast function; osteoclast adhesion, osteoclast number and degradation of non-collagenous proteins

TRACP-5b: measurement methods

Analytical performance

Sample	Mean, U/L	Intr SD,
1	0.841	0.0
2	2.006	0.0
3	5.64	0.2
4	9.95	0.3
5	15.03	0.6

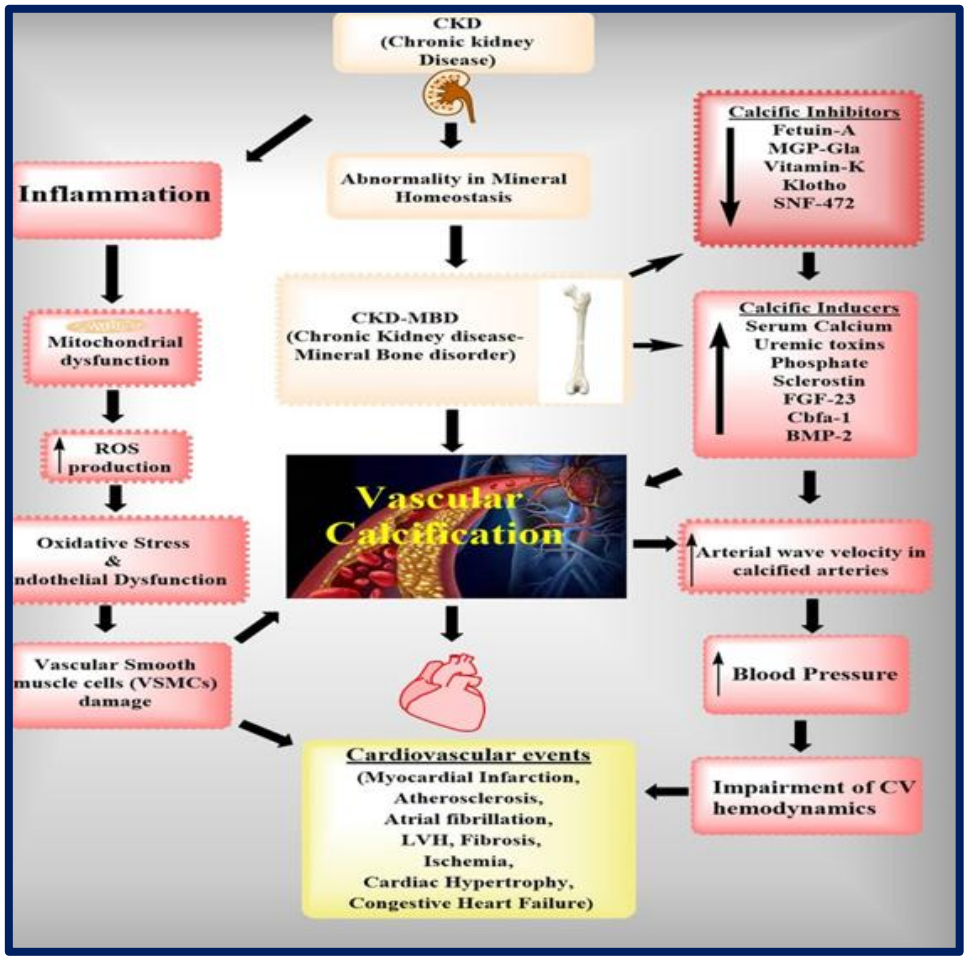
The results in bold are hig
of variation based on biol



Reference range

Population	Number of subjects	Ag				
Males	119	1				
Females <45 years old	50	1				
Females >60 years old	120	60.1–91.5	71.4 ± 7.0	0.7–8.6	1.1 (1.0; 1.2) – 8.1 (7.1; 9.2)	0.9–7.1

The kidney-vascular bone axis in CKD-MBD



Kaur R et al, 2022

LA MEDICINA DI LABORATORIO:

LA CULTURA DEL RINNOVAMENTO

Editorial

Mario Plebani*

Value-based laboratory medicine: the time is now

In the context of value-based laboratory medicine, a fundamental goal is to achieve not only efficiency but effectiveness, as the authors underline that "the effectiveness of clinical laboratory is achieved through understanding of the medical needs and delivering timely and high-quality tests. The role of clinical laboratories is closely linked to the increase in value; therefore, the main objective of the clinical laboratory professionals is to enhance the value of laboratory testing, optimizing their correct use both in the test selection request phase and in the reporting phase"

2024