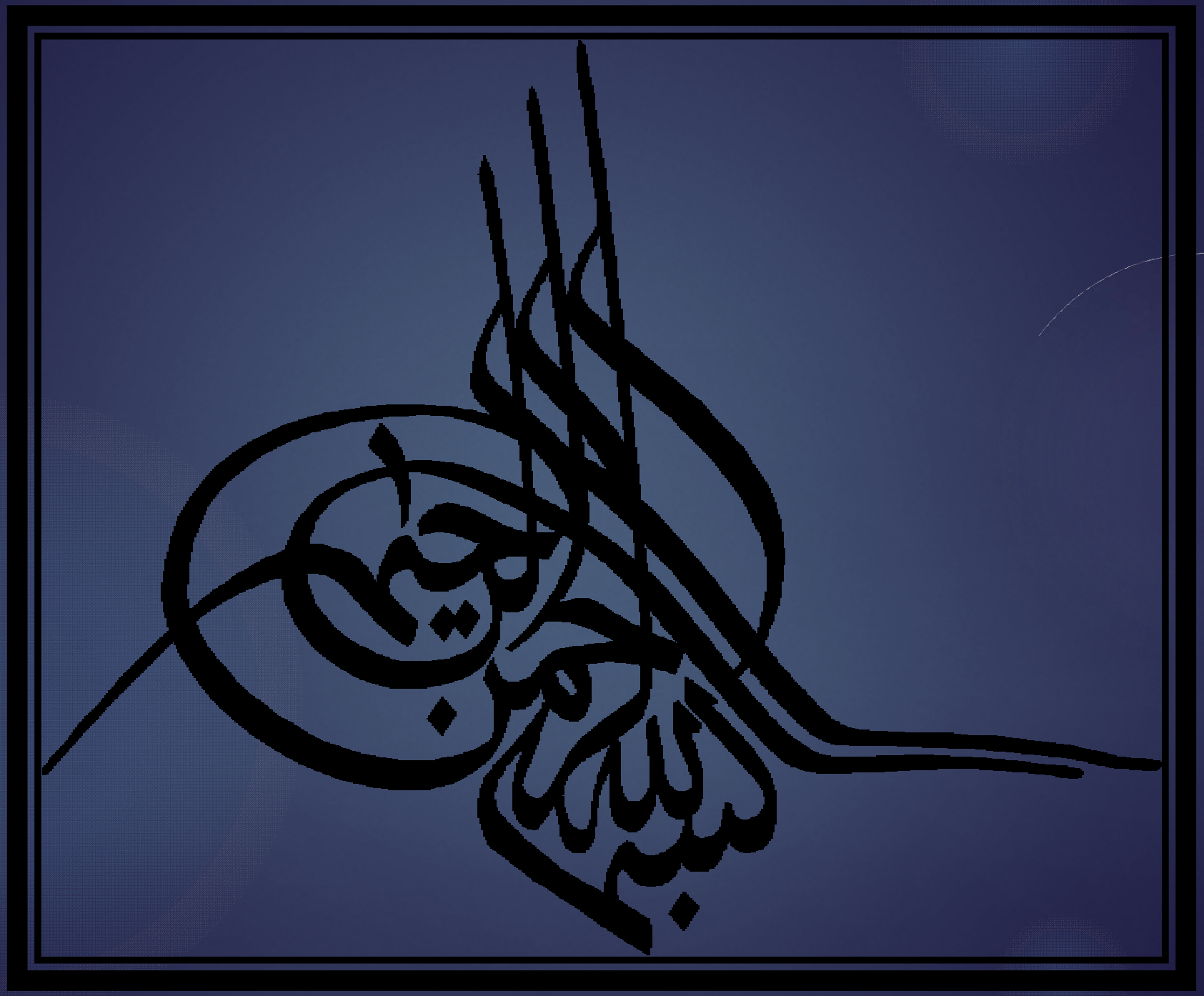
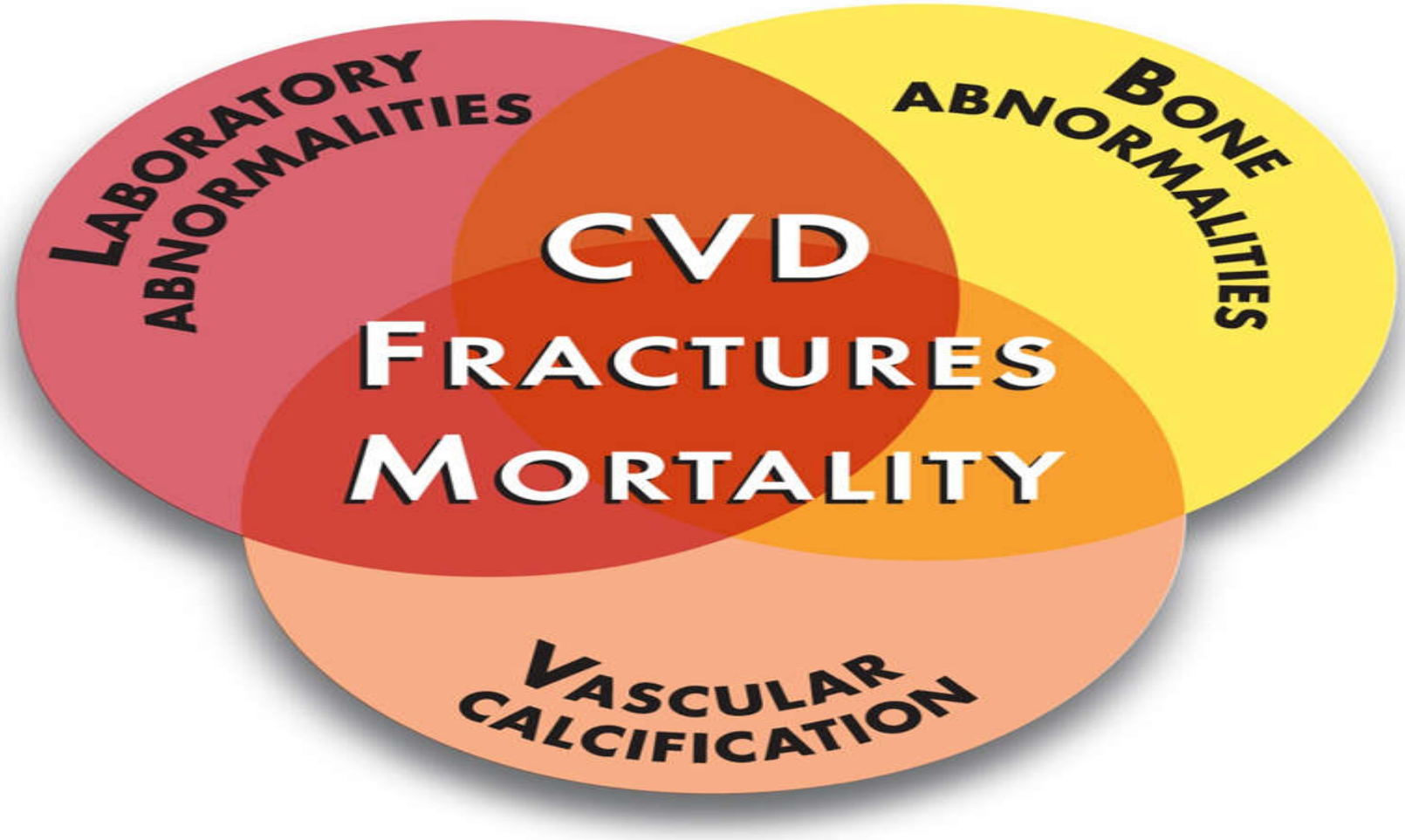


Bone Mineral Targets In CKD-ESRD

A. JENABI M.D.

Chronic Kidney Disease—Mineral and Bone Disorder

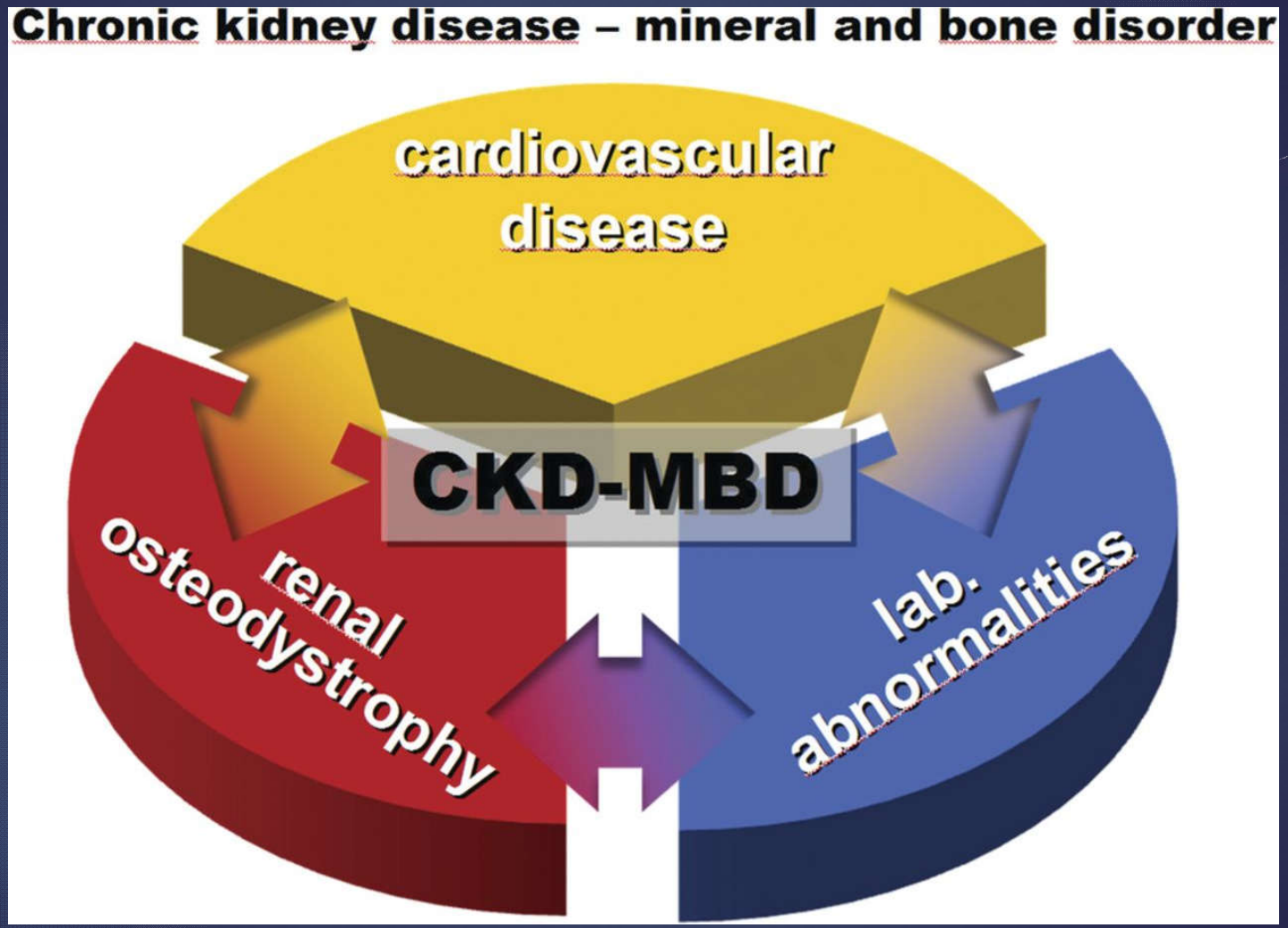


CKD-MBD

INTRODUCTION

- Since 2006, CKD-MBD has replaced the terms 'renal osteodystrophy' (ROD) which is now used to strictly define histological lesions.
- the various systemic complications of CKD-MBD including serum abnormalities (hyperphosphataemia low vitamin D levels etc.), bone histological lesions and the clinical features associated with CKD, namely extra-osseous and vascular calcifications, fractures and growth retardation
- Morbidity and mortality related to CKD-MBD is huge
- In this context, the assessment of the bone turnover is one of the most important (but not the only one) diagnostic tools. Indeed, the therapeutic strategies for the management of CKD-MBD (for example, use of phosphate binders or calcimimetics) depend, at least in part, on the bone turnover level of the patient.

CKD-MBD represents a synopsis of three closely related disease conditions:
laboratory abnormalities;
renal osteodystrophy;
cardiovascular disease



Mario Cozzolino et al. Nephrol. Dial. Transplant. 2014;ndt.gft514

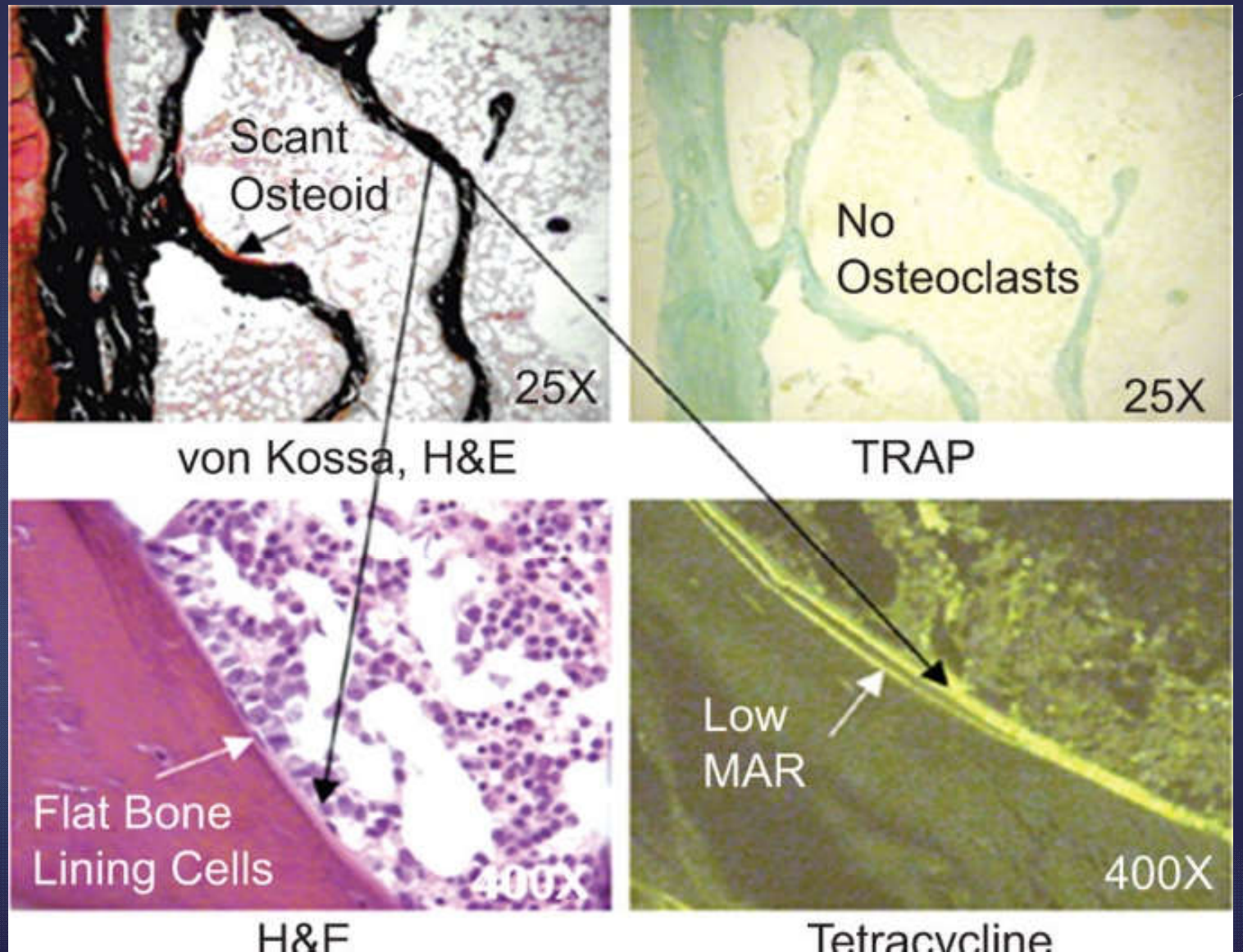
NDT
Nephrology Dialysis Transplantation

Bone Mineral Targets In CKD-ESRD

- Assessing bone turnover is **a key diagnostic tool** in the global management of chronic kidney disease-mineral and bone disorder (CKD-MBD).

- Since bone biopsy is invasive and cannot be repeated in clinical practice and because bone histomorphometry is less available due to the lack of specialized laboratories.

The gold standard to assess bone turnover is doubtless bone histology after tetracycline double labelling



Bone biopsy vs. bone biomarkers

- Bone biopsies are invasive and cannot be repeated. Moreover, bone histomorphometry is performed in a limited number of (hyper) specialized centres and may not be available for all clinicians.

- For these reasons, **bone biomarkers** are used for both the diagnosis and monitoring of bone turnover.

DEFINITION AND PATHOPHYSIOLOGY

- CKD affects not only **bone turnover** but also the two other components of bone, namely, **bone mineralization** and **bone mass**.
- Bone turnover consists in the succession of an osteoclastic resorption phase followed by a phase of formation,
- In CKD patients, the rate of turnover may be normal, high or low. Bone turnover and bone mass are physiologically linked, since the variations in bone mass are the result of changes in bone remodelling rate. However, bone mineral density measurement using dual energy X-ray absorptiometry (DEXA)is not a tool for assessing bone remodelling in CKD patients.

Various combinations of mineralization and turnover disorders lead to **four types** of bone lesions:

- **osteitis fibrosa (OF, high bone turnover),**
- **adynamic bone disease (ABD, low bone turnover)**
- **osteomalacia (mineralization defect)**
- **uraemic mixed osteopathy**

Pathophysiology of ROD

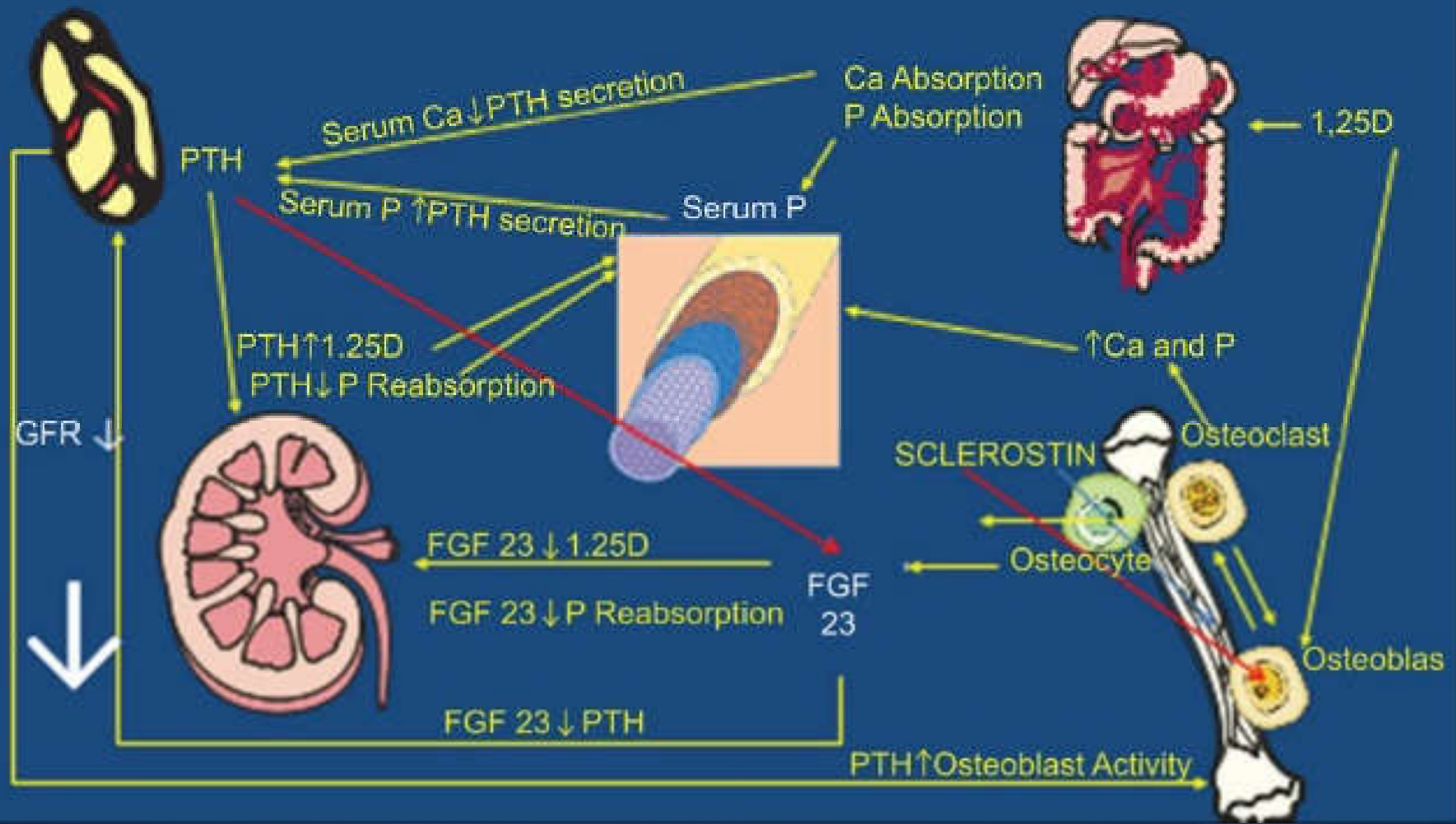
- The pathophysiology of ROD is complex and evolves constantly over the course of new discoveries.
- Phosphate retention, which seems to be one of the earliest events in CKD, is due to nephronic reduction
- **FGF23 production** by osteocytes occurs in bone (via unknown mechanisms) and leads to an increase in phosphate excretion by the remaining nephrons and a temporary maintenance of phosphate serum levels.

Pathophysiology of ROD, CONT,

- High bone turnover, serum PTH levels increase bone turnover
  - Bone remodelling is under the control of a number of local and systemic factors
- Low bone turnover
  - ***PTH has been excessively suppressed*** by calcium salts and/or 1-alpha-hydroxylated vitamin D derivatives
  - ***a bone resistance to PTH action***, (probably multiple) reasons,
    - a normal or even high serum level of PTH does not exclude low bone turnover.
    - Other risk factors peritoneal dialysis, age and diabetes.
    - Interestingly observed before dialysis who had not received any treatment
    - Recent works on CKD population reporting increase in serum levels of ***sclerostin, a potent negative regulator of bone formation***, are in line with this latter hypothesis.

The Interactions Between the Parathyroid Glands, Kidneys, Bone and Systemic Vasculature: The Bond Between Bone and Body

Miller PD, Sprague S, Shane E



- The KDIGO guidelines suggested that the measurements of serum parathormone (PTH) or bone-specific alkaline phosphatase (b-ALP) should be used to evaluate bone disease because markedly high or low values predict underlying bone turnover.

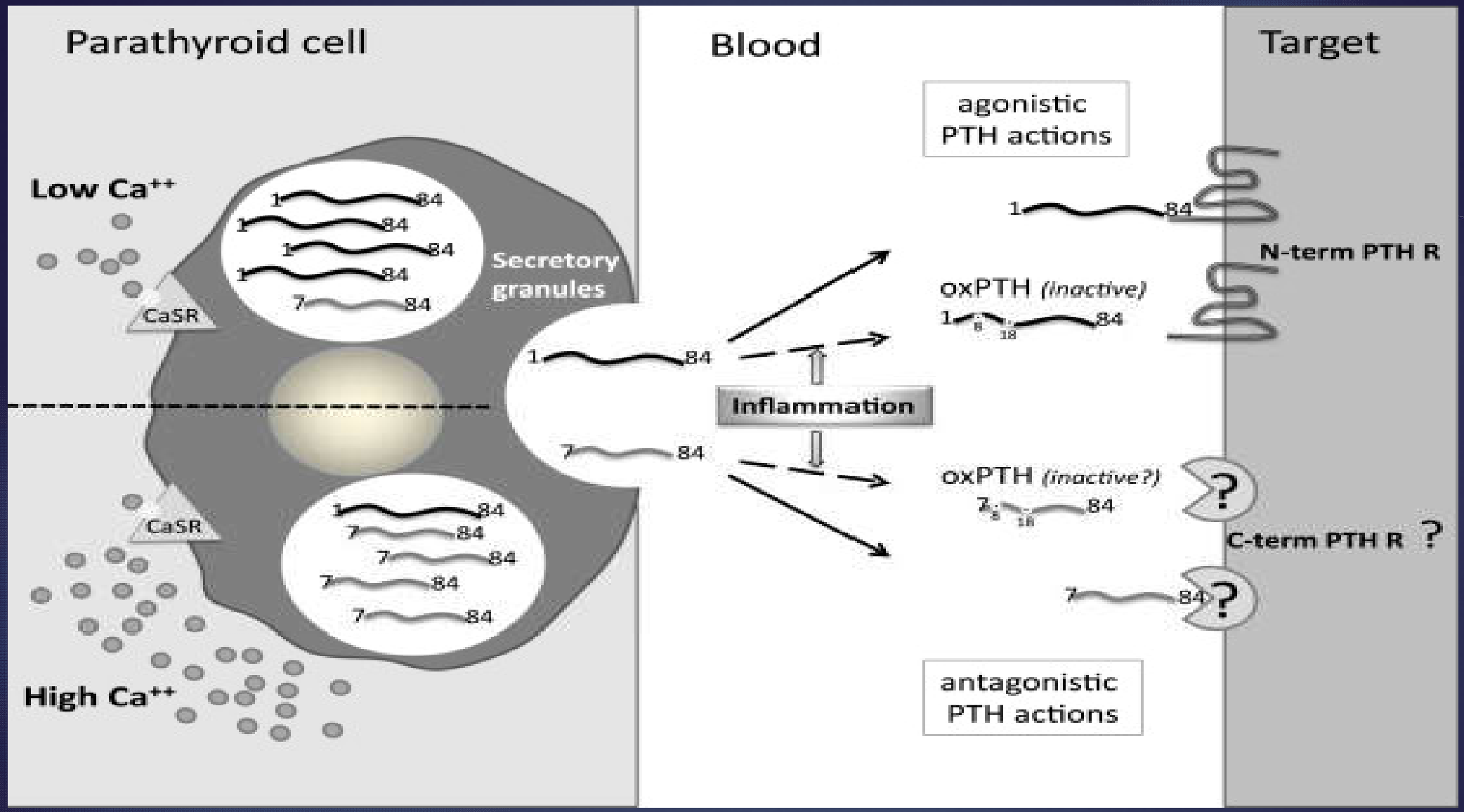
- KDIGO stressed that therapeutic strategies should not depend on a single PTH value but rather on the trend of several PTH values evolution. The guidelines actually make a recommendations about the frequency of PTH and b-ALP measurements according to the CKD stage.

PTH: INTEREST AND LIMITATIONS

- In dialysis patients, high PTH serum levels are not only associated with high bone turnover, but also with increased risk of all-cause mortality
- whereas low PTH levels are associated with low bone turnover and, at least in some studies, with early mortality.
- Low PTH as well as severe hyperparathyroidism has been associated with increased fracture risk.
- PTH is an 84 amino acid peptide hormone secreted by the parathyroid glands when ionized calcium serum level decrease
  - **intact' PTH assays**, also called second-generation PTH assays
  - **third-generation assays (bi PTH)** that measure 1–84 PTH but not 7–84 PTH became available**(1–84 PTH/7–84 PTH ratio**)
    - better correlated with the histomorphometric values
    - different levels of PTH in these ethnic groups (African-American vs. Caucasians)
    - predictive of all-cause mortality

Importantly parathyroid glands secrete 2 different molecules, acting on different and specific receptors with antagonistic biologic actions responsible for the controlled regulation of ionized calcium

- the 7-84 C-term peptide recently was shown to exert biologic effects, antagonistic to that of the N-term intact molecule, [7] and a specific C-term PTH receptor is invoked to explain these experimental biologic actions
- Secretory granules of the parathyroid chief cells directly produce significant amounts of the 7-84 C-term peptide from the cleavage of the intact molecule
- Moreover, the activity of the calcium-sensing receptor regulates the relative production of whole 1-84 PTH and of 7-84 C-term peptide in these secretory granules.
- when ionized calcium is high, more 7-84 PTH is produced and vice-versa.



- Schematic of PTH secretion regulation by ionized Ca, showing the direct synthesis of 7-84 C-term PTH by parathyroid chief cells. The possible confounding role of 7-84 C-term PTH and of oxidized PTH (oxPTH) on the final biologic action of 1-84 PTH is also shown.

Seminars in Nephrology, 2014-11-01, Volume 34, Issue 6,

KDIGO opinion

- According to these data, we share the opinion of the ***KDIGO*** experts that both generations of PTH assays seem similarly informative, and that there are currently not enough evidence to ask the medical laboratory to switch from a second-generation assay to a third-generation assay.

- Concerning the **1–84/7–84 ratio**, we acknowledge that further studies, especially bone biopsy studies, are mandatory to propose this ratio as a routine tool in dialysis patients all the more than that two PTH assays, one second- and one third-generation assay, are required to calculate this ratio, thus considerably increasing the cost of this evaluation.

lack of an international standard made of recombinant 1–84 PTH

- The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines proposed to maintain the serum PTH level within the 150–300 pg/mL range in dialysis patients
- the KDIGO work group proposed to use a target range for serum PTH based on multiples of the upper limit of the normal values rather than on absolute concentrations(two to nine times the upper normal limit)
  - Baretto et al., ABD was more likely to be found with PTH values <150 pg/mL and OF with PTH >300 pg/mL. However, they demonstrated that any type of bone lesion could be found for PTH values between 150 and 300 pg/mL and that only 3% of the patients had normal bone turnover
  - other studies reported PTH concentrations are associated with **mortality only for the highest concentrations (>400–600 pg/mL)**
  - This is a pragmatic approach which may reduce the inter-method discrepancies in the interpretation of PTH concentrations in dialysis patients.

Two very frequent causes of potentially elevated PTH levels,

- Vitamin D deficiency/insufficiency
- Decreased GFR

Table 1. Comparison, for 10 different PTH assays, of the reference range (in ng/L) and KDIGO target range for dialysis patients proposed by the kit manufacturers, and reference values and KDIGO target range established in our laboratories from the same population of 240 healthy subjects (120 men and 120 women) with a serum 25 hydroxy-vitamin D level >30 ng/mL and an eDFG (MDRD)> 60 mL/min/1.73 m^2.

Assay (name of the manufacturer)	Manufacturer's reference range	KDIGO target (x2–x9 upper normal) derived from manufacturer's range	Reference range obtained in our laboratories	KDIGO target (x2–x9 upper normal) derived from manufacturer's range
Second-generation assays				
Architect (Abbott)	15–68	136–612	16–65	130–585
Immulite (Siemens)	12–65	130–585	0.5–50	100–450
Vitros (Ortho-clinical)	7.5–53	106–477	11–48	96–432
Liaison N-tact (DiaSorin)	17.3–73	146–657	21–68	136–612
TiPTH (Scantibodies)	14–66	132–594	8–50	100–450
Elecsys (Roche Diagnostics)	15–65	130–585	14–50	100–450
DiaSorin IRMA (DiaSorin)	13–54	108–486	7–36	72–324
Access 2 (Beckman-Coulter)	12–88	176–792	10–47	94–423
Third-generation assays				
CA-PTH (Scantibodies)	5–39	78–351	7–31	62–279
Liaison (DiaSorin)	5.5–38	76–342	5–26	52–234

With some assays, the difference between the manufacturer's KDIGO range and the one derived from our own reference values established in vitamin D sufficient patients with an eDFG >60 mL/min/1.73 m² is huge.

FULL REVIEW

b-ALP: A NEW GOLD STANDARD?
confirmatory and complementary test to assess bone turnover

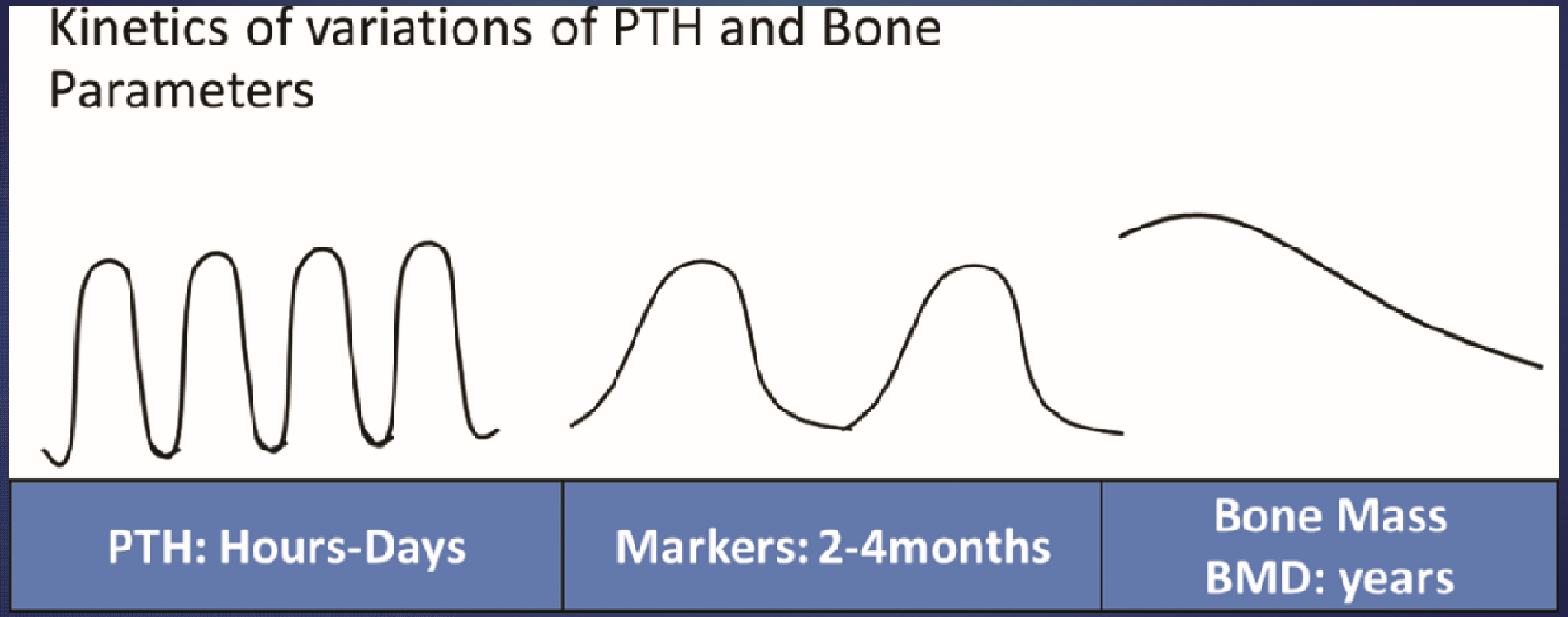
- ALPs are glycoproteins produced in different organs, like liver, placenta, kidney, leucocytes and intestine
- Assess bone turnover in CKD patients.
- Significant correlation between b-ALP and PTH in CKD patients
- similar or better sensitivity-specificity was shown for bALP to diagnose low versus high bone turnover in comparison with PTH
- Compared with association between PTH and risk of mortality

b-ALP: A NEW GOLD STANDARD? Cont,

- b-ALP is more stable than PTH and it is not influenced by fasting status and kidney functions.

- Regarding the monitoring of bone turnover, the superiority of b-ALP could also be an argument.
- **The KDIGO guidelines presented b-ALP and PTH measurements as ‘**
- **complementary.**
- **Clinical the longitudinal follow-up of ptsobserve that these two biomarkers frequently change in opposite directions (PTH increasing and b-ALP decreasing or vice versa).**
- **PTH serum concentrations rapidly follow any acute modifications of calcium serum concentrations, whereas b-ALP bone turnover-related changes take longer because its serum levels will depend on bone remodelling, which is a process slower than PTH**
- **the half-life of b-ALP in serum is from 1 to 2 days, whereas the half-life of PTH is only few minutes.**

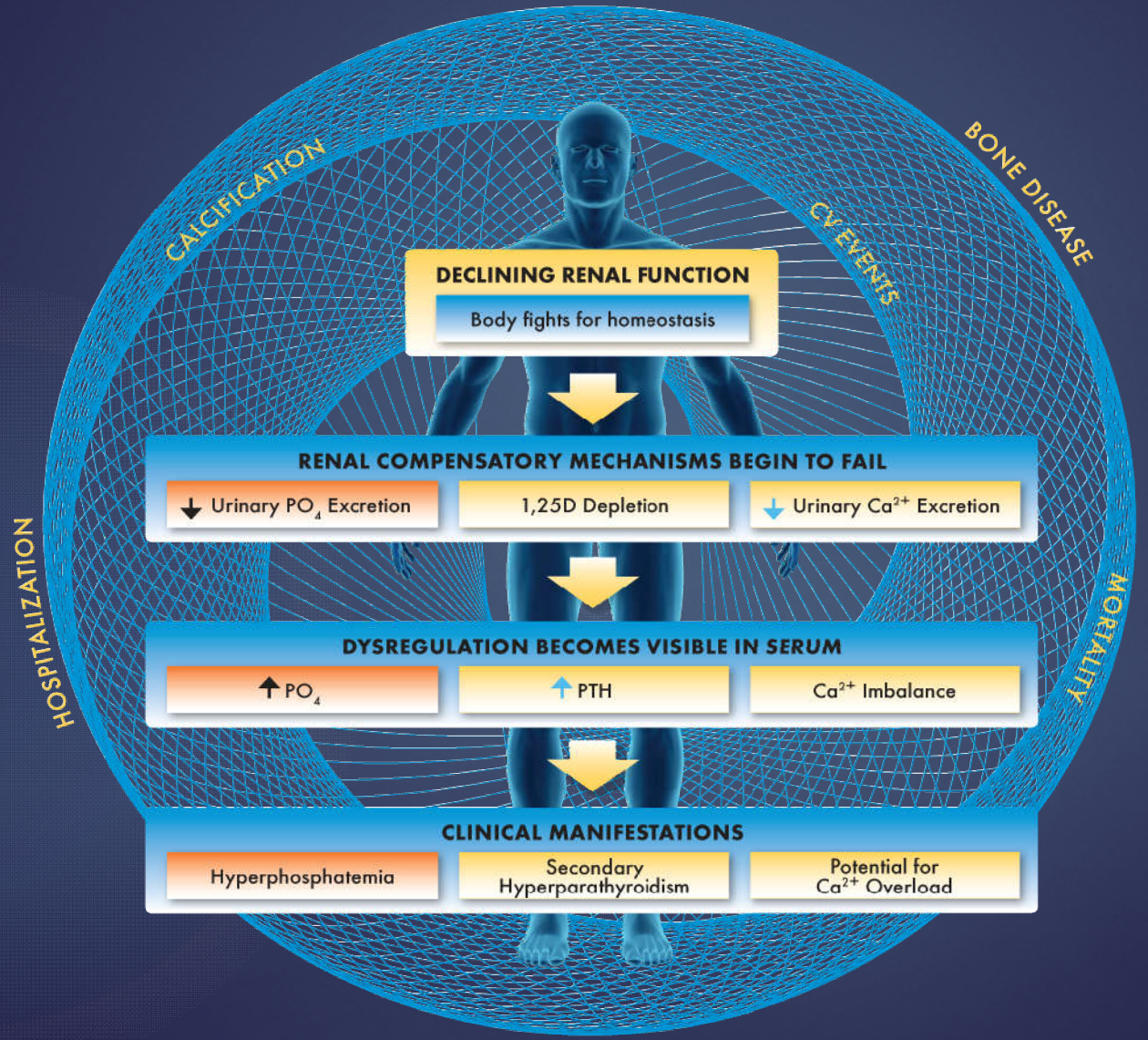
an **isolated measurement of serum PTH** is unlikely to provide a valid representation of bone turnover, except in cases with extremely low or high values. This is not to say that PTH measurement is useless but other bone biomarkers must probably be used in complement.



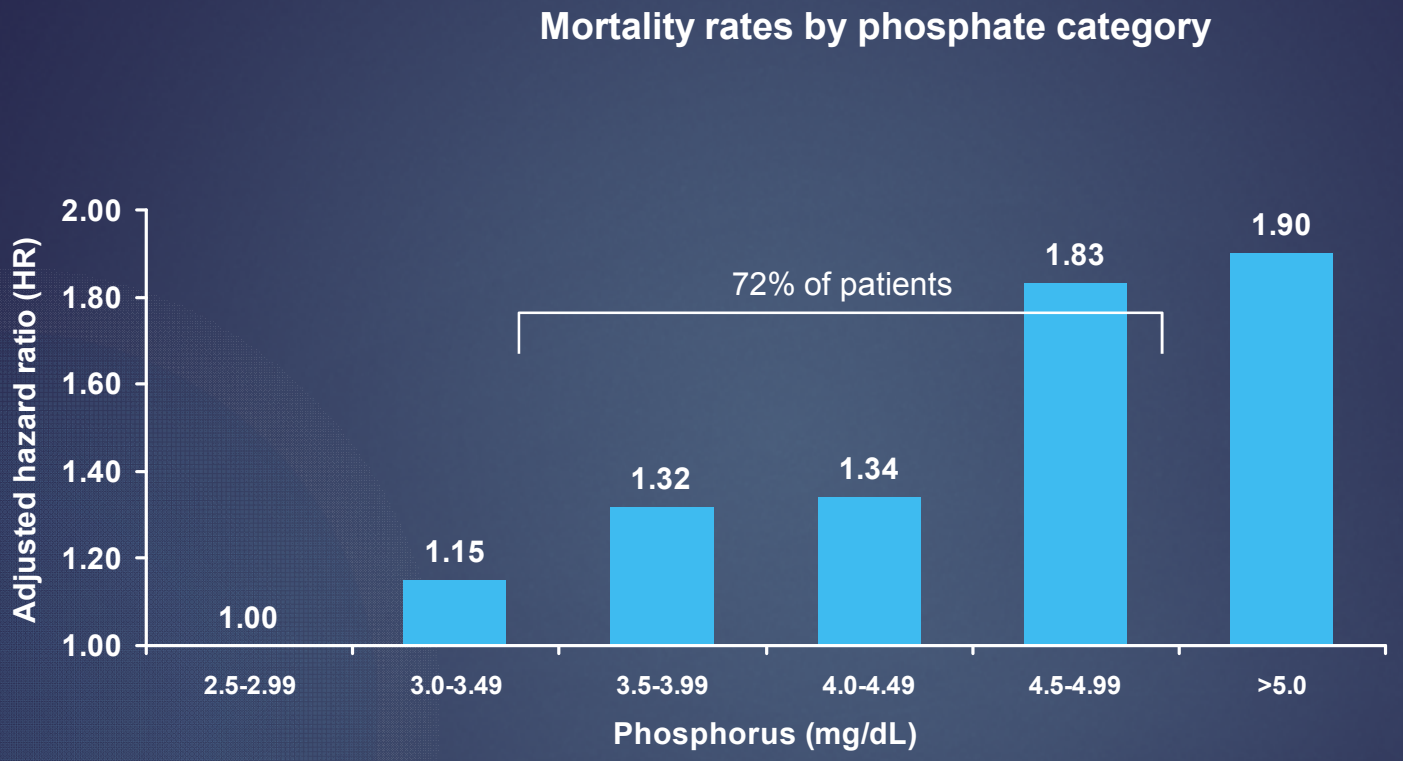
MAIN weak point of b-ALK

- Its serum concentration is obviously influenced by other local or systemic bone processes such as metastases, recent fractures and growth.
- recent data demonstrated that the specificity of b-ALP measurement is not perfect in patients with liver diseases

CKD-MBD: Dysregulation and Clinical Manifestations of an Increasingly Compromised System



Serum Phosphorus Levels and Mortality in CKD Non-Dialysis Patients

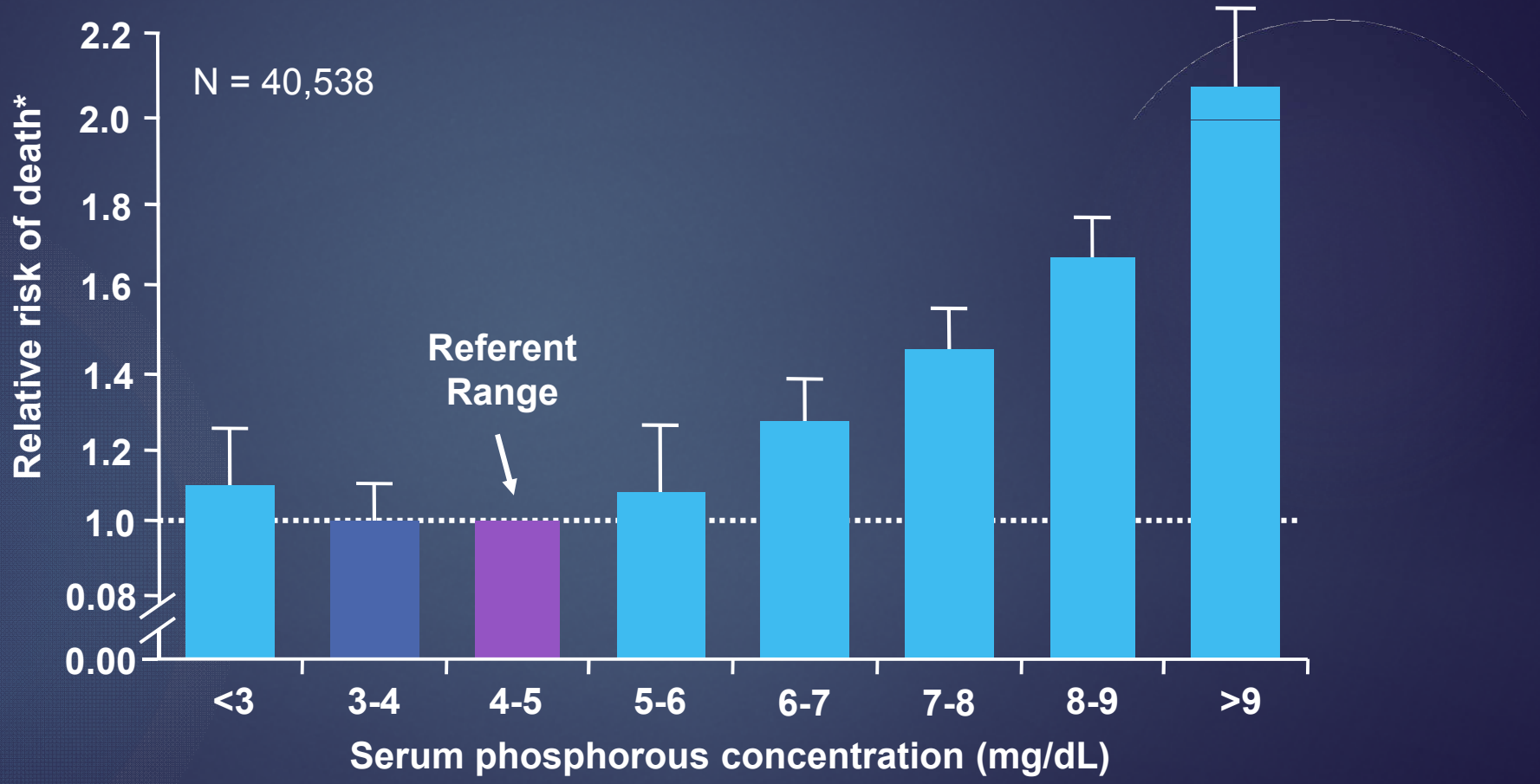


(n=3,289)

- Mortality risk increases as phosphorus levels rise, even within normal range
- Each 0.5 mg/dL increase in serum phosphorus was associated with increased mortality
- Statistically significant increases in mortality were noted when phosphorus levels reached 3.5 mg/dL or above

Adapted from Kestenbaum B, Sampson JN, Rudser KD, et al. *J Am Soc Nephrol*. 2005;16:520-528.

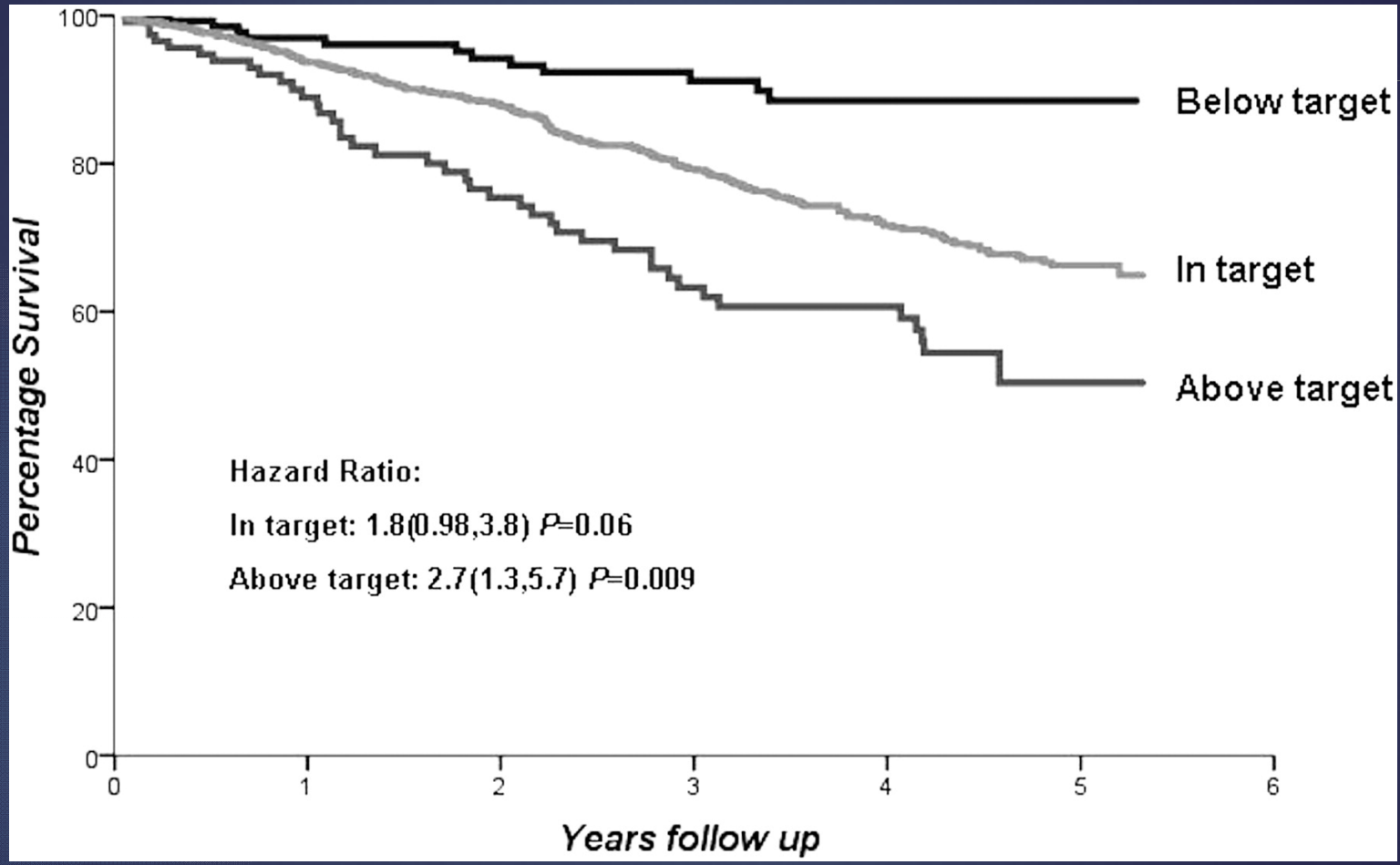
Elevated Serum Phosphorus and Mortality Risk in Dialysis Patients



*Multivariable adjusted

With permission from Block GA, Klassen PS, Lazarus JM, et al. *J Am Soc Nephrol*. 2004;15:2208-2218.

Survival according to phosphate levels relative to KDOQI guidelines.



Eddington H et al. CJASN 2010;5:2251-2257

Clinical Journal of the American Society of Nephrology CJASN

KDOQI and KDIGO

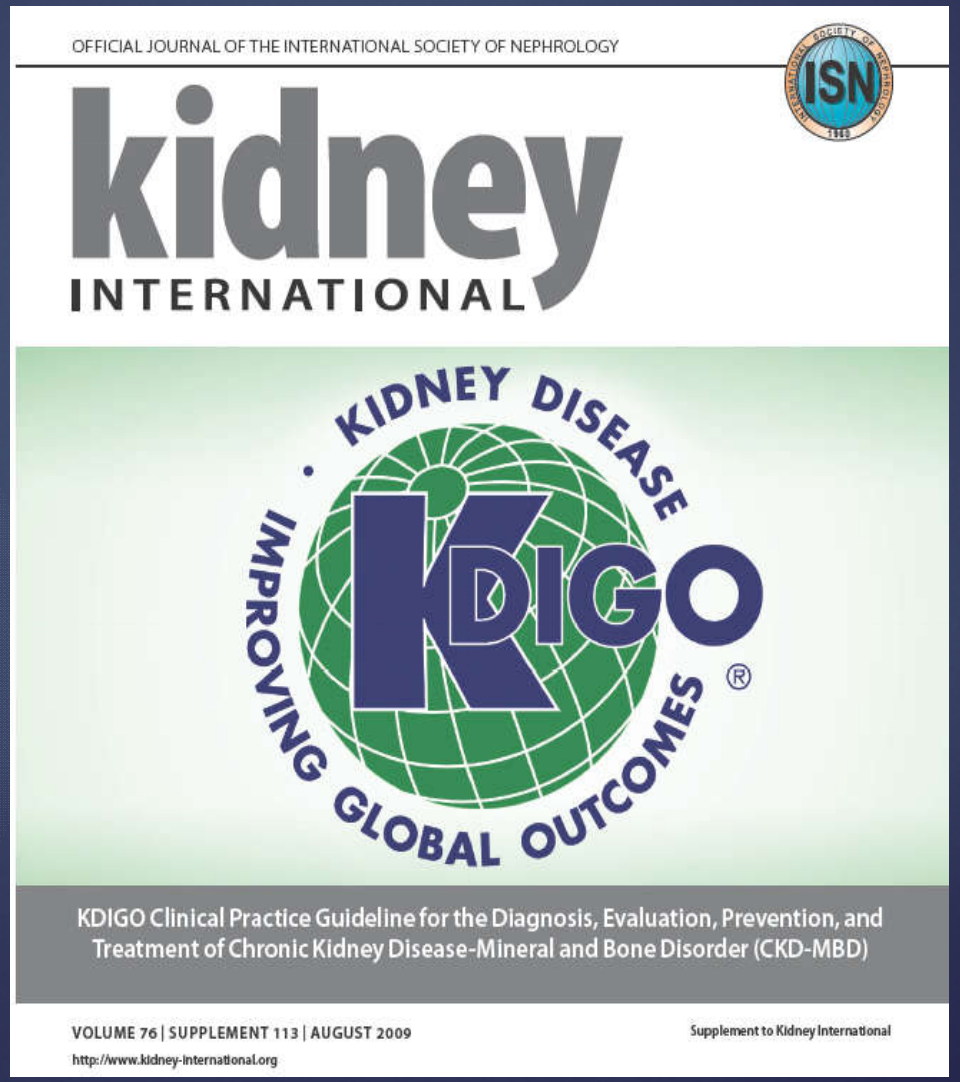
NKF- Kidney Disease Outcome Quality Initiative

2003 Targets for treatment

Kidney Disease Improving Global Outcomes

2009 Range of risks

KDIGO: Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD



KDIGO: Diagnosis of CKD-MBD Biochemical Abnormalities

Diagnosis of CKD-MBD: Biochemical Abnormalities

- In the initial CKD stage[a], the recommendation is to monitor serum levels of:
  - Phosphorus, Calcium, PTH, Alkaline phosphatase
- In CKD stages 3-5D[b], frequency of monitoring serum calcium, phosphorus, and PTH should be based:
  - On the presence and magnitude of abnormalities
  - The rate of progression of CKD
- In children[c], the suggestion is to begin monitoring in CKD stage 2

a. 3.1.1 (1C); b. 3.1.2 (not graded);
c. 3.1.1 (2D)

KDIGO. Kidney Int. 2009; 76 (Suppl 113):S1-S130

Diagnosis of CKD-MBD: Biochemical Abnormalities

- In patients with CKD stages 3-5D, the suggestions[a] are to:
  - Measure 25(OH)D (calcidiol) levels
  - Repeat testing on the basis of:
    - Baseline values
    - Therapeutic interventions
  - Correct vitamin D deficiency and insufficiency in accordance to treatment strategies recommended for the general population

a. 3.1.3 (2C)

KDIGO. Kidney Int. 2009; 76 (Suppl 113):S1-S130

Diagnosis of CKD-MBD: Biochemical Abnormalities

- In patients with CKD stages 3-5D,
  - The recommendation[a] is that therapeutic decisions should be based on:
    - Trends versus a single laboratory value
    - All available CKD–MBD assessments
  - The suggestion[b] is that medical practice should be guided by:
    - The evaluation of individual values of serum calcium and phosphorus together
    - Rather than the Ca x P product

a. 3.1.4 (1C); b. 3.1.5 (2D)

KDIGO. Kidney Int. 2009; 76 (Suppl 113):S1-S130

KDIGO: Grading of Recommendations

Strength of Recommendation	Implications
Level 1	"We recommend …" "Most patients should receive the recommended course of action."
Level 2	"We suggest …" "Different choices will be appropriate for different patients."
Not Graded	

Grade for Quality of Evidence	Quality of Evidence
A	**High**
B	**Moderate**
C	**Low**
D	**Very Low**

"The strength of a recommendation is determined not just by the quality of evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs."

KDIGO. *Kid Int.* 2009; 76 (Suppl 113):S1-S130

KDIGO Focus: Normal Treatment Target Ranges for Phosphorous and Calcium

Stage	Target PO_4[1,2]	Target Ca[1,2]
3	KDIGO: Maintain Normal KDOQI: 2.7-4.6 mg/dL	KDIGO: Maintain Normal KDOQI: Normal for Lab
4-5	KDIGO: Maintain Normal KDOQI: 2.7-4.6 mg/dL	KDIGO: Maintain Normal KDOQI: Normal for Lab
5D	KDIGO: Towards Normal KDOQI: 3.5-5.5 mg/dL	KDIGO: Maintain Normal KDOQI: 8.4-9.5 mg/dL

Emphasis on individual levels of serum calcium and phosphorus rather than Ca x P product

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) *Kidney Int*. 2009;76(suppl 113):S1-S130.
2. National Kidney Foundation (NKF). KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 suppl 3):S1-S201.

KDOQI / KDIGO - treatment recommendations in 5D:

Laboratory values	KDOQI Recommend.	Grading	KDIGO Recommend.	Grading
iPTH (pg/mL)	150 to 300	Evidence	Suggested range 2 to 9 x ULN	2C
Corrected Ca (mg/dL)	8.4 to 9.5	Opinion	Suggested to maintain in the normal range	2D
P (mg/dL)	3.5 to 5.5	Evidence	Suggested to lower toward the normal range	2C
CaxP (mg^2/dL^2)	<55	Evidence	Not suggested to direct clinical practice	N/A

KDIGO Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76 (Suppl 113)

KDIGO Focus: Consider Normal Limit for PTH

Stage	Treatment Target Range
3	KDIGO: Upper Limit of Normal* *(2C)* KDOQI: 35-70 pg/mL
4	KDIGO: Upper Limit of Normal* *(2C)* KDOQI: 70-110 pg/mL
5	KDIGO: Upper Limit of Normal* *(2C)* KDOQI: 150-300 pg/mL
5D	KDIGO: 2 to 9 times Upper Limit of Normal *(2C)* KDOQI: 150-300 pg/mL

*In patients with CKD stages 3-5 *not on dialysis,* in whom serum PTH is progressively rising and remains persistently above the upper limit of normal for the assay despite correction of modifiable factors, treatment with calcitriol or vitamin D analogs is suggested. *(2C)*

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD) *Kidney Int*. 2009;76(suppl 113):S1-S130.
2. Adapted from National Kidney Foundation (NKF). KDOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 suppl 3):S1-S201.

KDOQI / KDIGO - PTH TARGETS

CKD Stage	Target iPTH (pg/ml) KDOQI	Grading	Target iPTH (pg/ml) KDIGO	Grading
3	35 - 70	Opinion	Not known	2C
4	70 - 110	Opinion	Not known	2C
5 ND	150 - 300	Evidence	Not known	2C
5D	150 - 300	Evidence	2 to 9 x ULN	2C

KDIGO Clinical Practice Guideline for CKD-MBD. *Kidney Int* 2009;76 (Suppl 113)

1. TABLE 1 Target Levels for Calcium, Phosphorus, and Parathyroid Hormone

	KDOQI	KDIGO	JSDT
Calcium			
CKD stage 3-5	Normal range	Normal range	N/A
CKD stage 5D	Normal range	Normal range: 8.4-10 mg/dL	Preferably 8.4-9.5 mg/dL
Phosphorus			
CKD stage 3-4	2.7-4.6 mg/dL	Normal range	N/A
CKD stage 5	3.5-5.5 mg/dL	Normal range	N/A
CKD stage 5D	3.5-5.5 mg/dL	Toward normal range	3.5-6 mg/dL
Intact PTH			
CKD stage 3	35-70 pg/mL	Optimal level is unknown	N/A
CKD stage 4	70-110 pg/mL	Optimal level is unknown	N/A
CKD stage 5	200-300 pg/mL	Optimal level is unknown	N/A
CKD stage 5D	200-300 pg/mL	2-9 times above upper limit of normal	60-180 pg/mL

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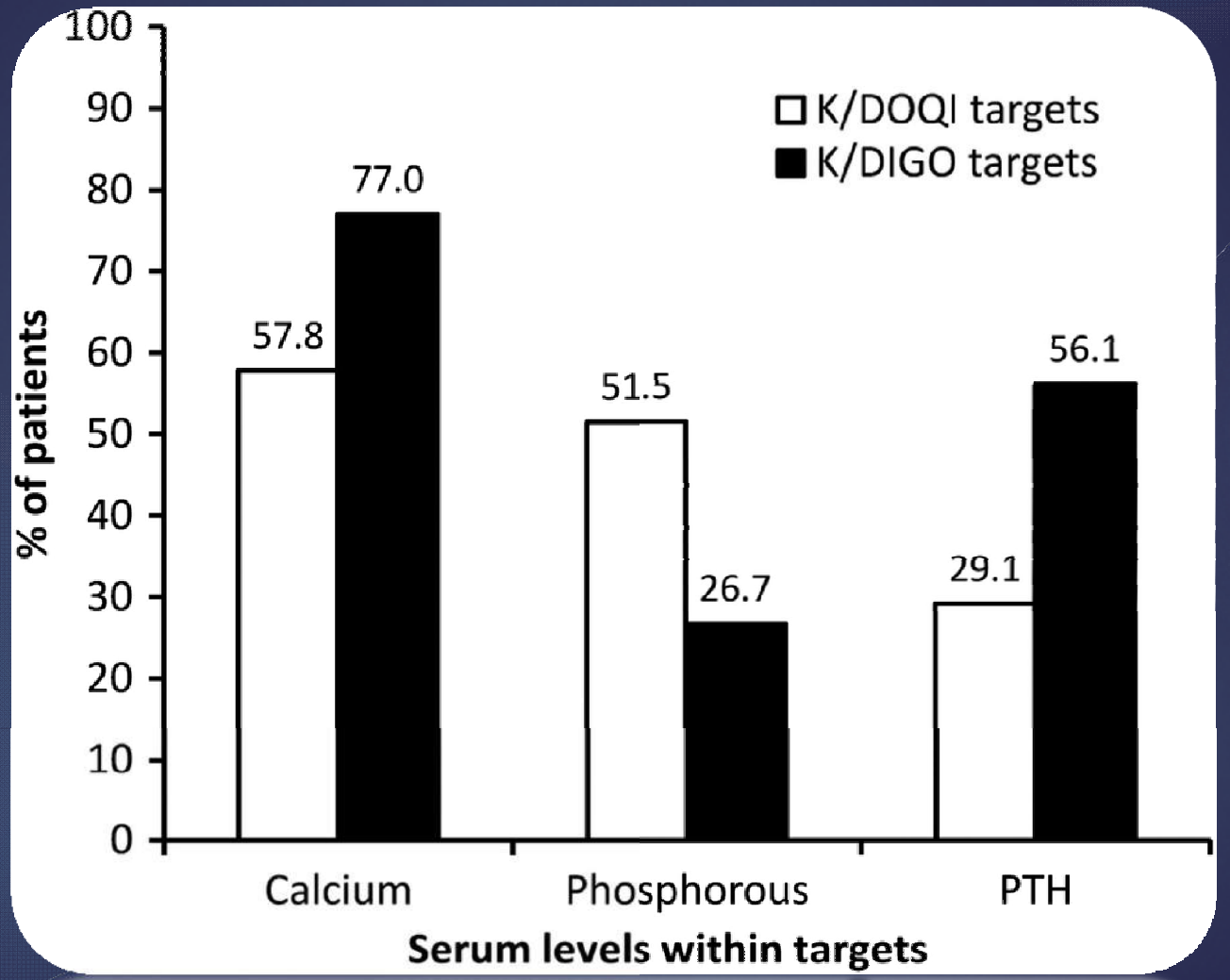
Percentage of patients within K/DOQI and K/DIGO targets for serum calcium, phosphorous and PTH.



José Luis Fernández-Martín et al. Nephrol. Dial. Transplant. 2012;ndt.gfs418

NDT Nephrology Dialysis Transplantation

Evaluation of CKD-MBD: Biochemical Abnormalities

Phosphate and Calcium

CKD Stage	KDIGO
3	Every 6–12 months
4	Every 3–6 months
5 or D	Every 1–3 months

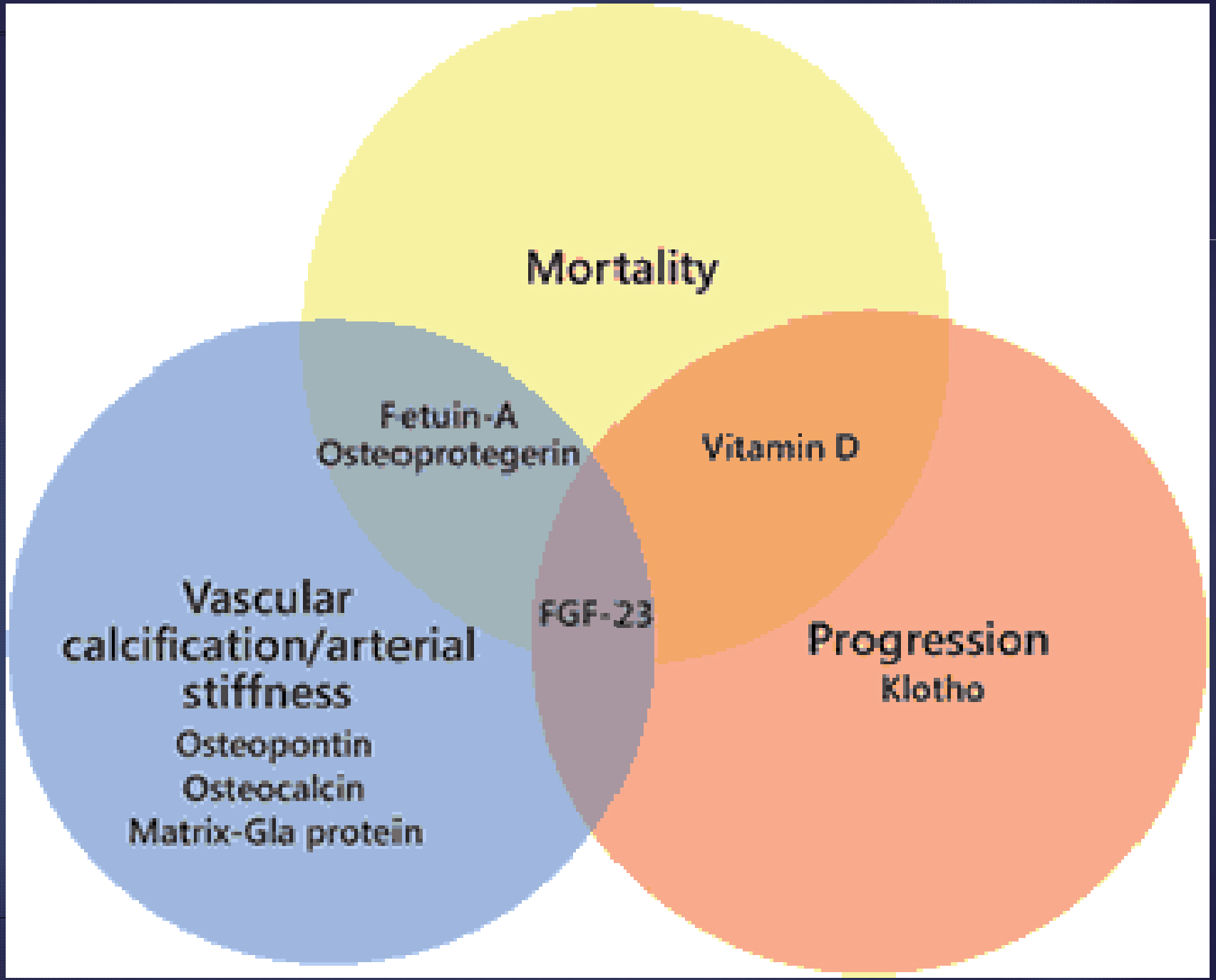
Evaluation of CKD-MBD: Biochemical Abnormalities

PTH

CKD Stage	KDIGO
3	Based on baseline level and CKD stage
4	Every 6–12 months
5 or D	Every 3–6 months

‘NEW’ BONE TURNOVER BIOMARKERS IN DIALYSIS PATIENTS?

- serum procollagen type 1 N-propeptide
- serum C-terminal telopeptide of type I collagen, s-CTX)
- the tartrate-resistant acid phosphatase 5B (TRAP-5B)
  - The KDIGO guidelines recommended that the bone derived markers of collagen synthesis and breakdown, including CTX, should not be routinely measured in patients with chronic kidney disease stages 3–5D. The primary rationale for this recommendation was that the levels of such markers did not appear to be more effective at predicting clinical outcomes or bone histology than serum PTH or b-ALP.


Mortality
Fetuin-A
Osteoprotegerin
Vitamin D
Vascular calcification/arterial stiffness
Osteopontin
Osteocalcin
Matrix-Gla protein
FGF-23
Progression
Klotho

CONCLUSION

- Nobody can question the interest of bone histology in the validation of biomarkers to assess bone turnover.
- Biomarkers are, and still remain, surrogate markers for bone turnover.
- Among these biomarkers, PTH is still the most used
- By far, PTH is not the best bone biomarker both from a physiological point of view and a biological point of view
- the KDIGO recommendation to measure alkaline phosphatase and especially b-ALP which can be considered as a true ‘bone biomarker’. The biological profile of bALP is also probably better than PTH.
- Again, as underlined by the KDIGO guidelines, important therapeutic decisions based on bone biomarkers assessment must take into account their longitudinal variations rather than one isolated biological result.