Management of hyperparathyroidism and bone disease in CKD and DM

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Aims

- Why bone disease develops in CKD
- Adynamic bone disorder
- Hyperparathyroidism
- Osteoporosis in CKD
- Treatment of osteoporosis

CKD- Mineral Bone Disorder

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:

- Abnormalities of Ca,PO_4, PTH or vitamin D metabolism
- Abnormalities in bone turnover, mineralisation, volume, linear growth or strength
- Vascular or other soft tissue calcification

Levels decrease as GFR worsens

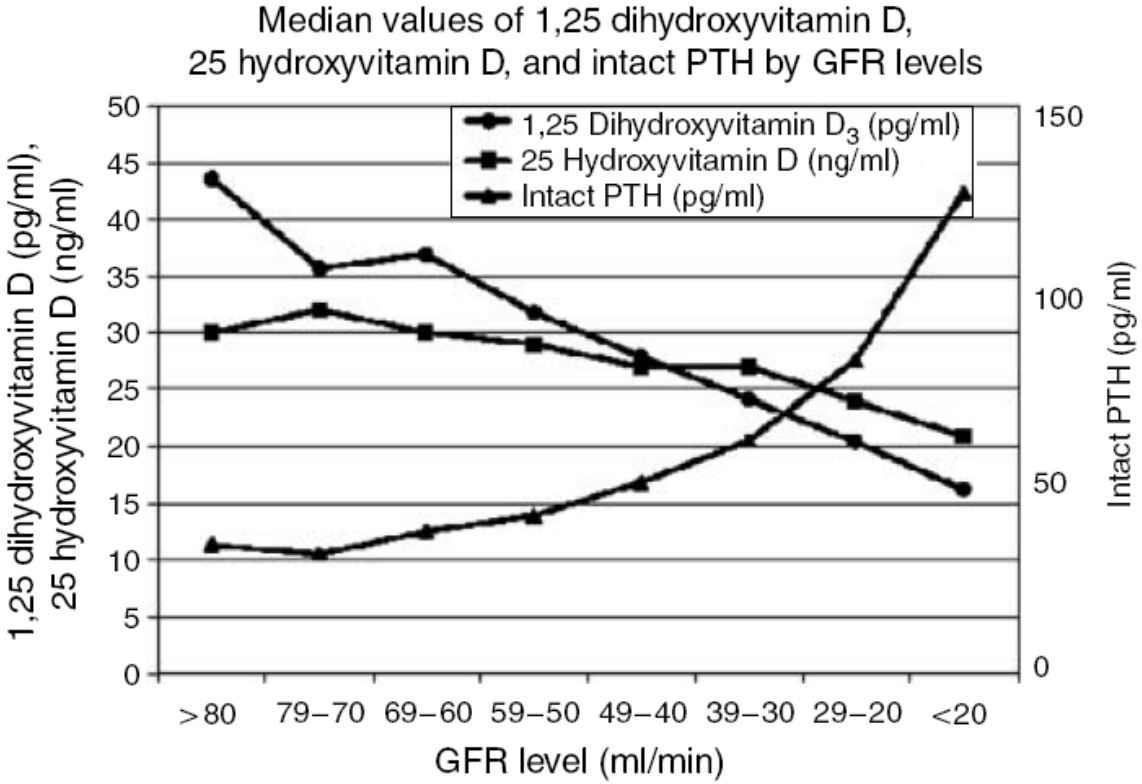


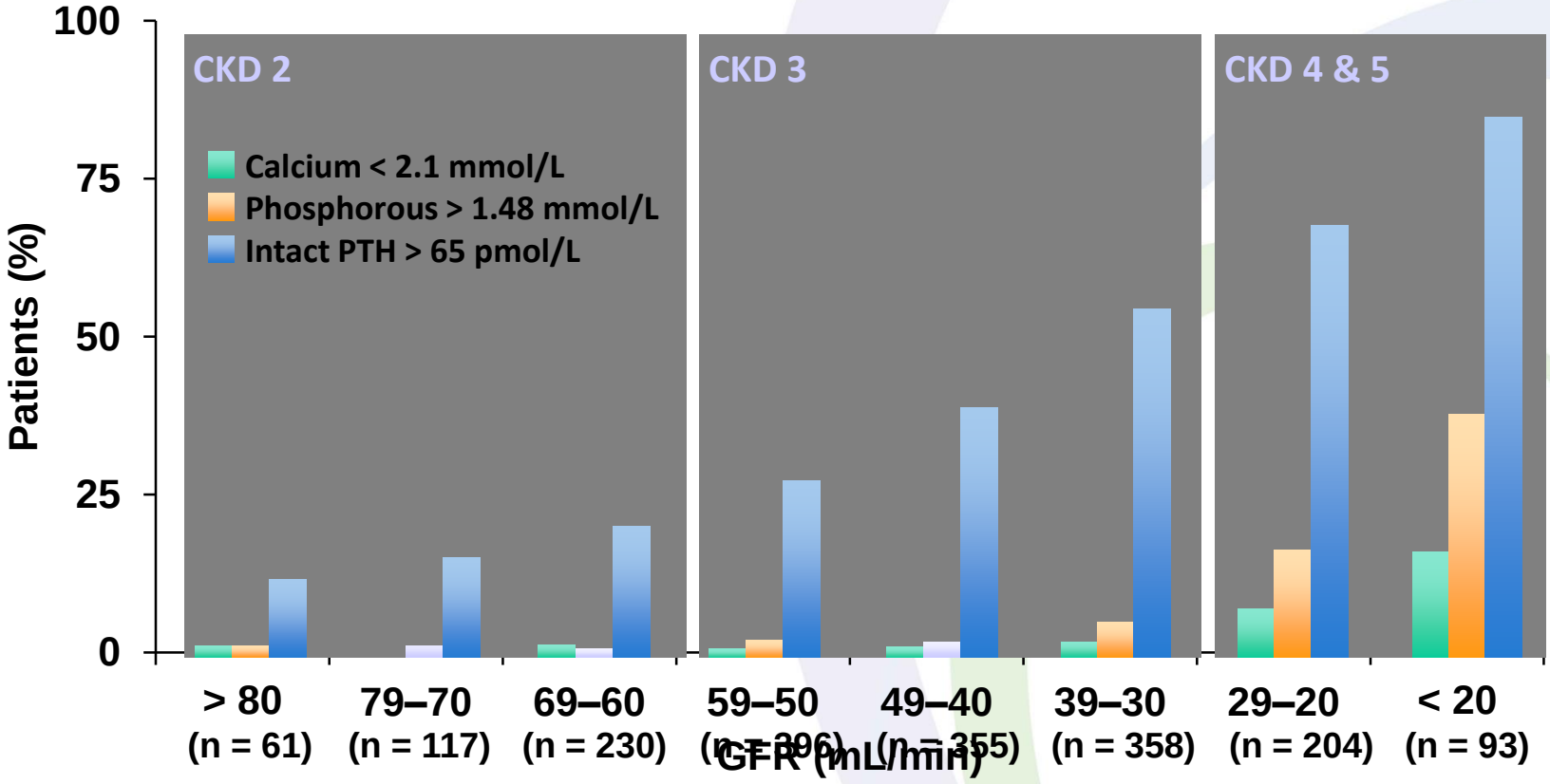
Figure 5 | Median values of 1,25 OH_2 D_3, 25(OH)D_3 and iPTH by GFR levels.

Delivering the best in care

University Hospitals Birmingham NHS Foundation Trust

Levin A et al KI 2007: 71; 31-38 (latitude 49^o)

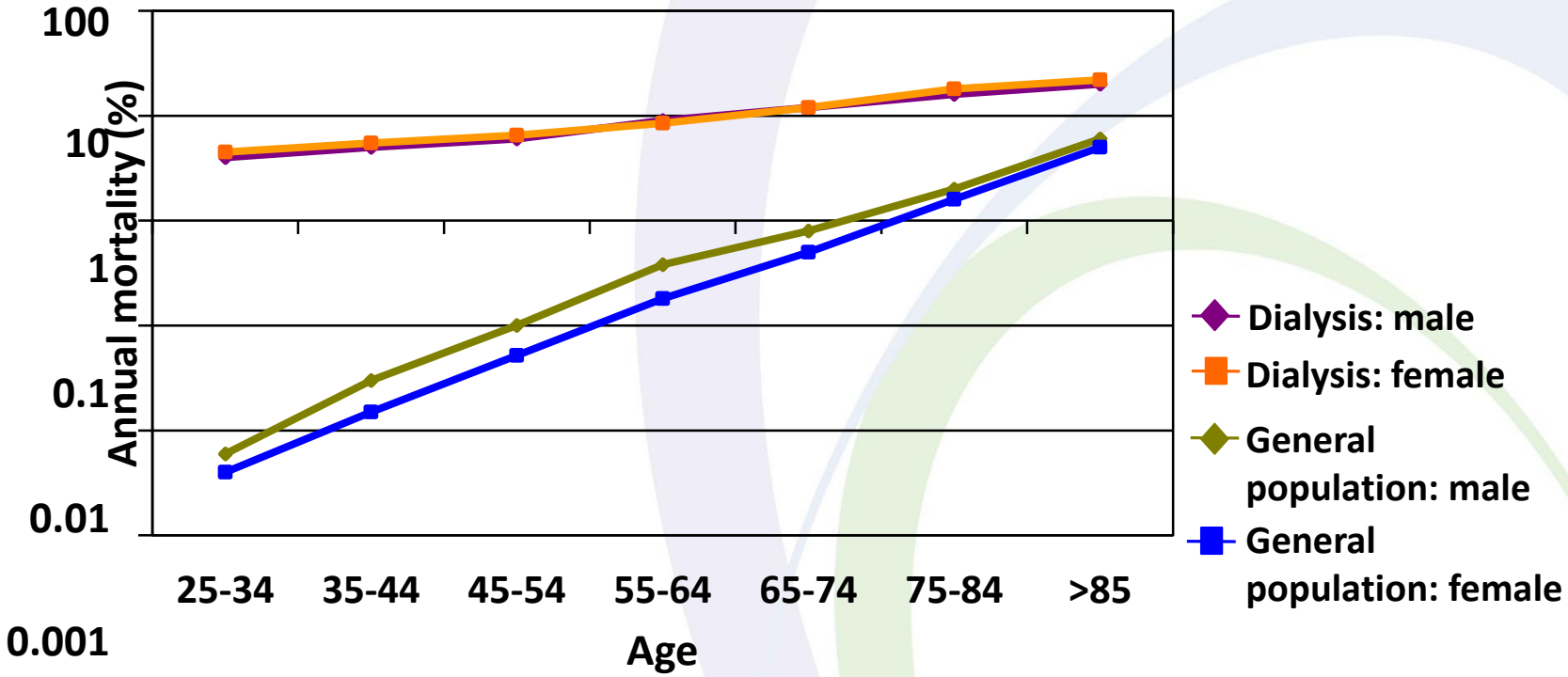
Prevalence of Abnormal PTH, Calcium and Phosphorous Levels With Decline in Kidney Function



N = 1,814

Adapted from Levin A, et al. *Kidney Int.* 2007;71:31-38.

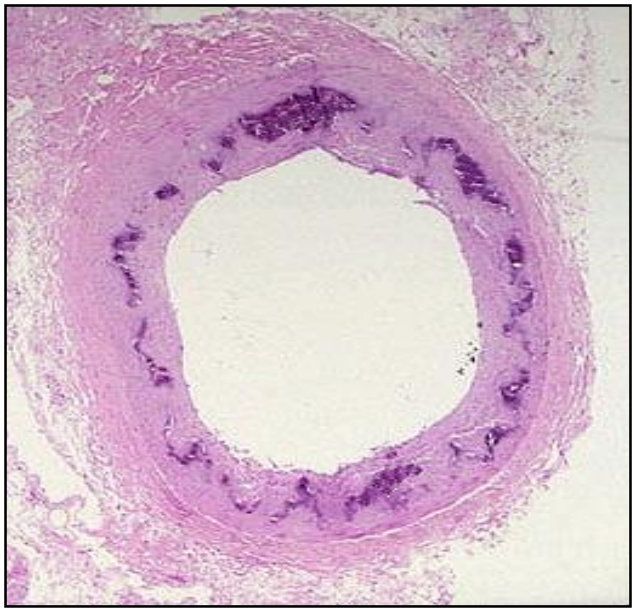
Cardiovascular Mortality Rates are Higher among Dialysis Patients

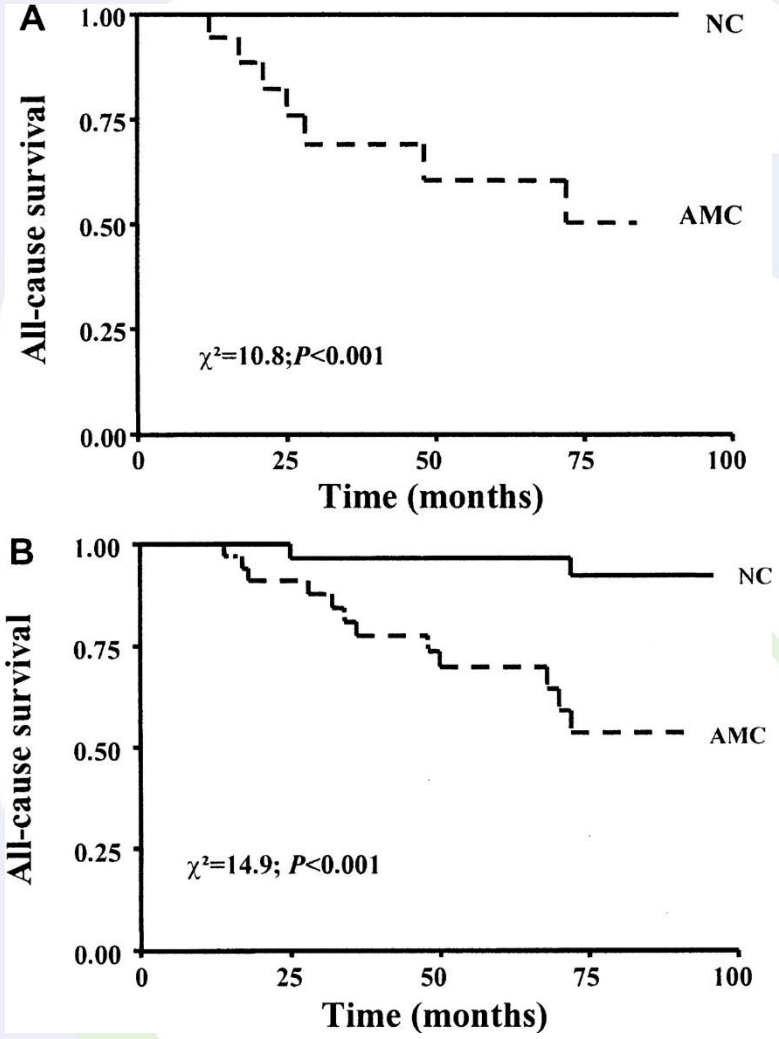


Adapted from Levey AS et al. *Am J Kidney Dis* 1998; 32: 853-906.

Medial vascular calcification

All cause mortality in patients with no calcification compared to those with medial calcification





London, G. M. et al. Nephrol. Dial. Transplant. 2003 18:1731-1740

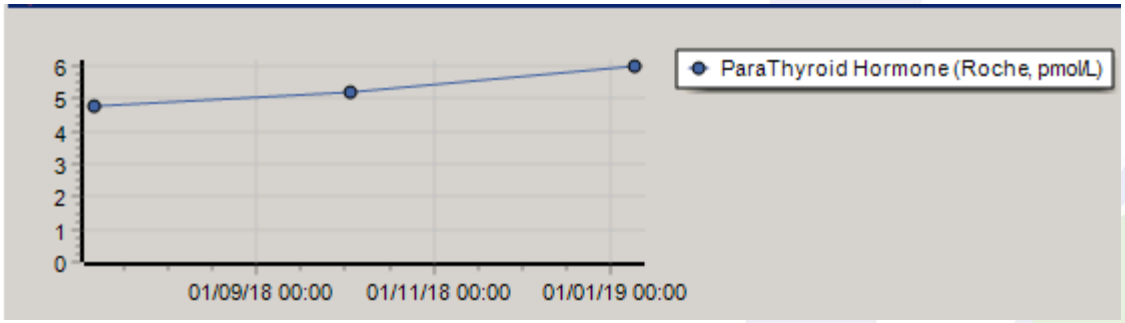
Case 1:

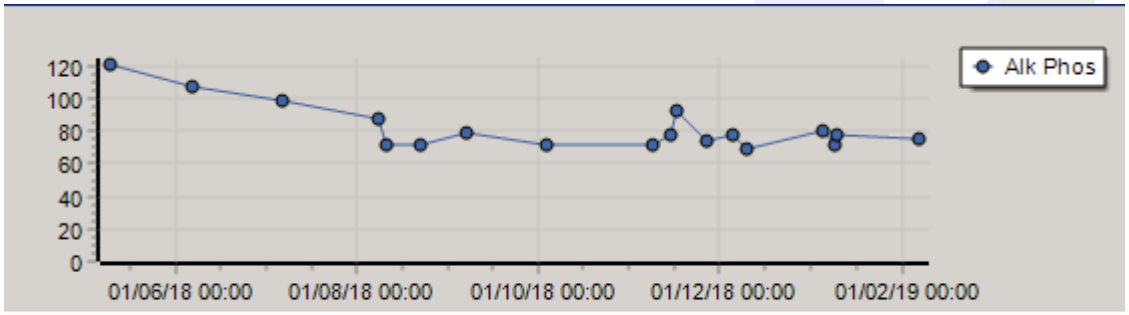
- 32 year old female
- Type 1 diabetes mellitus
- Haemodialysis patient
- Low impact rib fractures

Diabetes and bone disease

- Decreased bone formation (precedes CKD)
- More profound vitamin D deficiency
- Improving diabetes control should improve bone formation

Case 1: rib fractures





- KDIGO:
- PTH: 2-9 x upper limit of normal
- 13-62pmol/L

Adynamic bone disorder

- Low bone turnover / fragile bone
- Diabetes
- Aging
- Malnutrition
- Prevalence higher in peritoneal dialysis compared to haemodialysis
- Increased vascular calcification
- Not always related to low PTH

Case 2: 68yr old woman

- Haemodialysis patient
- Unknown cause of renal disease
- Spinal surgery in India after a fall
- DXA 2016: osteopenia
- PTH, Alk Phos, calcium and phosphate well controlled
- 2018 low impact fracture of pubic ramus

Fracture risk

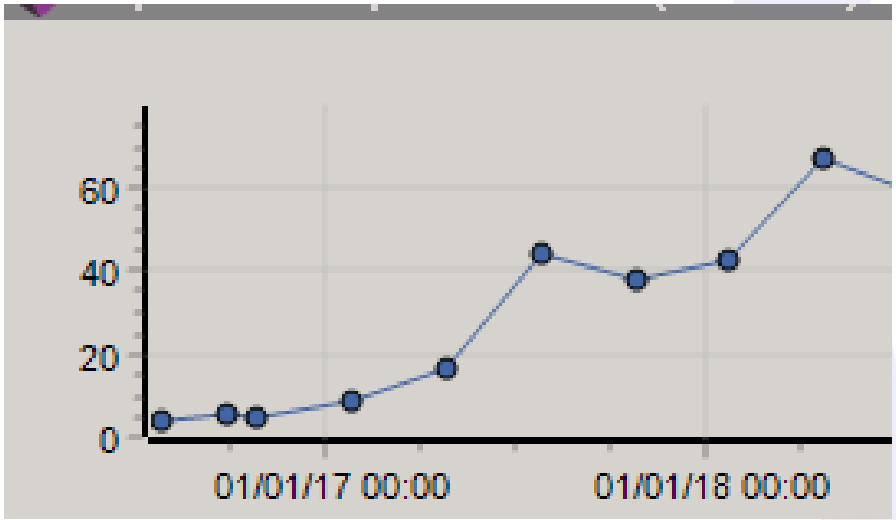
- Increased risk of fragility with CKD
- 4x higher rate of fracture compared to general population[1]
- Increasing fracture related mortality as CKD progresses
- Exact mechanism underdetermined but potential mechanisms (that could be independent or collectively impact are)….

1. KI 2006; &0:1358-1366

Potential mechanisms

- Phosphate retention
- SHPT
- Chronic acid loads
- High FGF23
- Sclerostin overproduction,
- Increased risk of falls,
- Steroid use
- Hypogonadism
- Hyperprolactinaemia
- Poor nutrition
- Vitamin D deficiency
- Inactivity
- Other medical conditions - IBD, malabsorption, liver dx)
- Diabetes

Case 2: 68 yr old woman



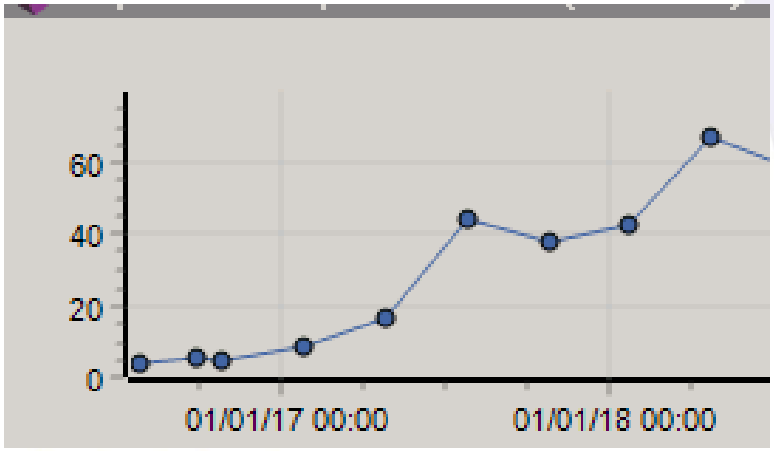
- PTH now increasing
- Alk Phos now high

Secondary hyperparathyroidism

- KDIGO guidelines: CKD 5D
- PTH: 2-9 x upper limit of normal

  13-62pmol/L

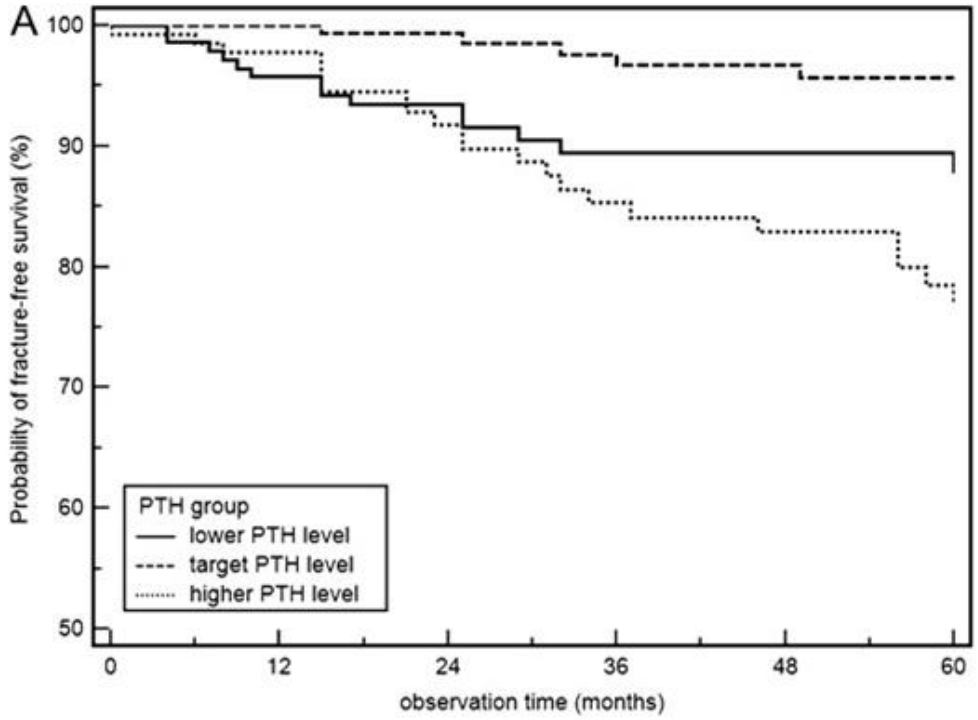
  monitor change



- Manage secondary hyperparathyroidism
- Alfacalcidol increased
- Ensure phosphate controlled
- Cinacalcet?

Fracture free survival in haemodialysis population in PTH ranges

Fig. 1.



PTH target 150-300pg/mL

(15-31pmol/L)

NDT 2012 27 (1):345-351

KDIGO guidelines CKDMBD 2017

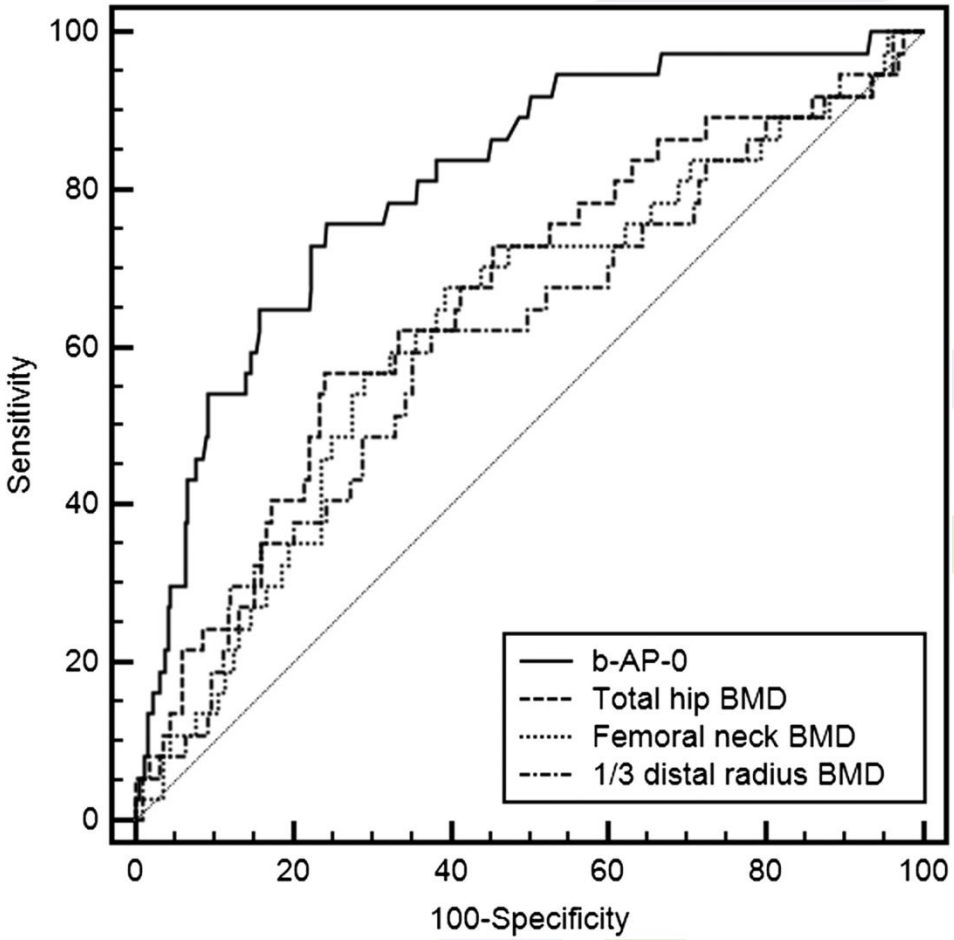
- **3.2.1: In patients with CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (*2B*).**

Case 2: 68 yr old woman

- DXA scan

	Lumbar spine	Total Hip
T score	-2.1	-3.5
Z score	-0.5	-2.2

- FRAX Major osteoporotic fracture 33%



From: Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study

Nephrol Dial Transplant. 2011;27(1):345-351. doi:10.1093/ndt/gfr317

Differences between CKD-MBD and postmenopausal osteoporosis

	CKD-MBD	**Post-menopausal Osteoporosis**
PTH levels	Increased	Usually normal
Alkaline Phosphatase	Increased	Usually normal
Bone Mineral Density	Weakly related to fracture risk	Predicts risk of fracture
Bone loss	Mostly in cortical bone	Trabecular and cortical bone
Bone formation rate	Either very low (ABD) or very high	Generally normal or slightly increased
Vascular calcification	Strongly associated	Weakly associated
Laboratory findings	Abnormal	Normal or mildy abnormal

- CKD-MBD and osteoporosis co-exist frequently
- Very difficult to diagnose osteoporosis in setting of CKD
- The WHO classification may not apply to CKD
- Need to exclude adynamic bone disorder (ABD)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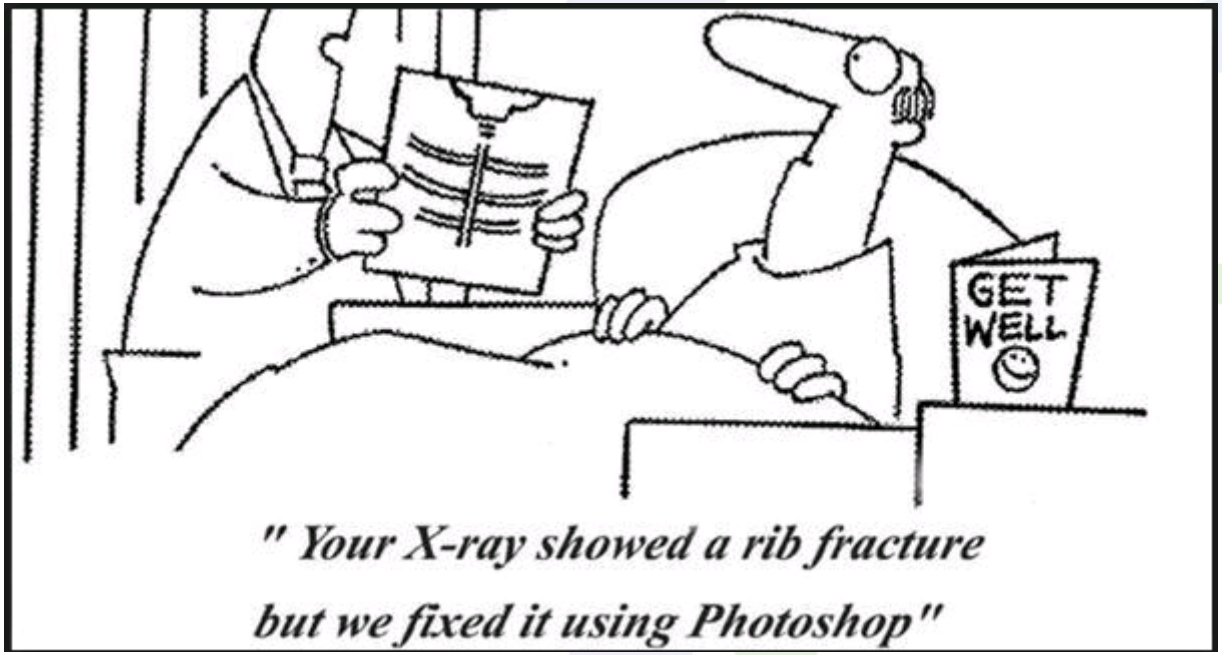
"Lose some weight, quit smoking, move around more, and eat the carrot."

Management

- Lifestyle measures
- (Adequate calcium and Vit D, exercise, cessation of smoking, alcohol intake, fall prevention)
- GFR <30 – effects of Ca and Vit D supplements on fracture risk not studied
- Repleting vitamin D in severe CKD may be beneficial (J clin endocrinol metab 2011)
- Hypogonadism – specialist advice



" Your X-ray showed a rib fracture

but we fixed it using Photoshop"

Osteoporosis management in CKD?

- Bisphosphonate
- Denosumab
- Teriparatide

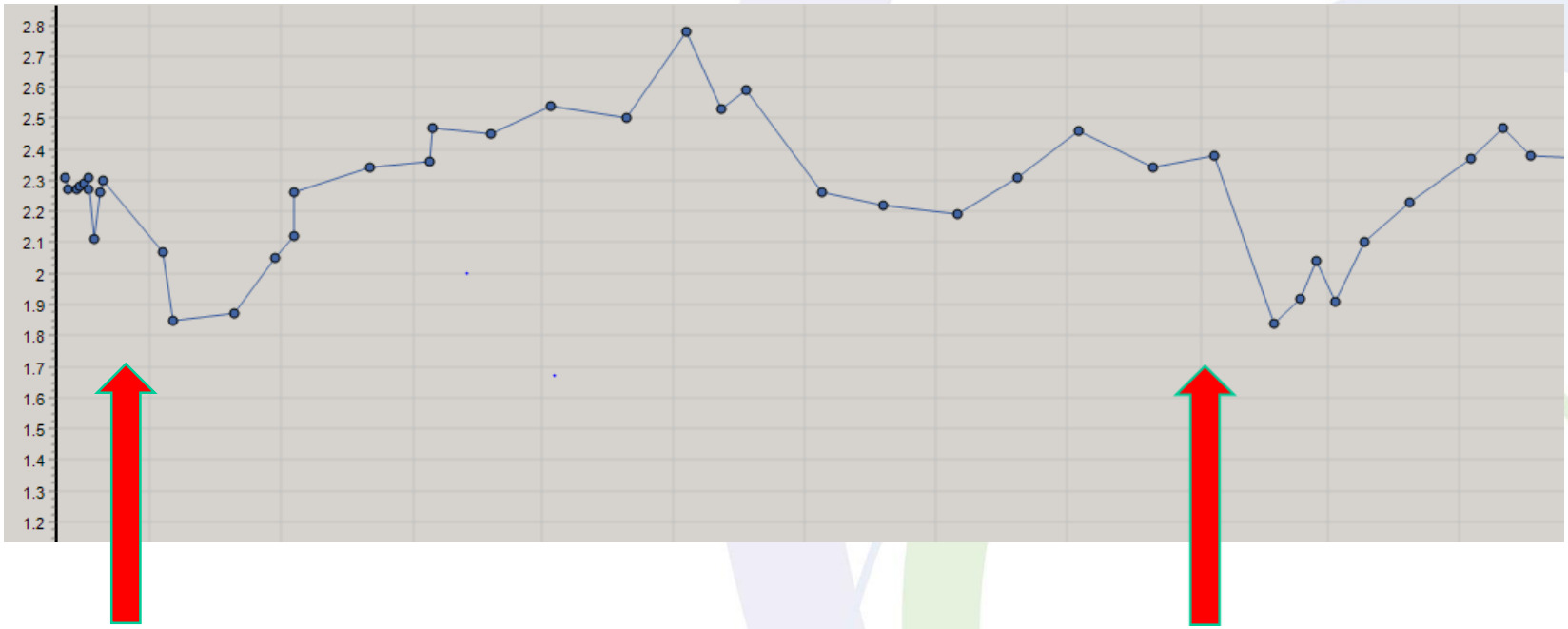
Bisphosphonate

- GFR >30 ml/min
- Suppress bone turnover
- Renal excretion
- Retained in bones / long half life
- Drug ‘holidays’

Denosumab

- Monoclonal antibody blocks RANKL to inhibit osteoclasts leading to less bone loss.
- 6 monthly injections
- Increased risk of hypocalcaemia in CKD
- Unknown length of treatment
- No drug holidays
- Rebound spinal fractures if stop treatment

Denosumab in CKD causes significant drop in calcium



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Treatment of osteoporosis

- Teriparatide
  - Stimulates bone formation
  - Little data in poor renal function
  - ? Beneficial in ABD

Do we really know what is happening in these patient's bones?

KDIGO guidelines CKD-MBD 2017

- **3.2.2: In patients with CKD G3a–G5D, it is reasonable to perform a bone biopsy if knowledge of the type of renal osteodystrophy will impact treatment decisions (*Not Graded*).**
- **4.3.3: In patients with CKD G3a–G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, we suggest that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy *(2D)*.**

Birmingham

- Specialist Renal and Endocrine meeting to discuss complex patients
- Try and do no harm
- No bone biopsy service (yet?)

How can we prevent fractures?

- Lack of accurate and non-invasive diagnostic tools.
- Metabolic abnormallities associated with CKD-MBD are poor markers for bone disease and cannot discriminate between turnover types and abnormal mineralisation.
- Bone turnover markers are not validated in CKD and ESRD and are used infrequently.
- Transiliac crest bone biopsy remains the gold standard tool; however, bone biopsy is invasive, expensive, painful, and is available at only a few centres worldwide.

Summary:

- CKD MBD complex process
- No easy, non-invasive test to diagnose bone disease in CKD
- Osteoporosis in CKD should only be treated with specialist advice
- We don’t have many answers