biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
issue 08

Phosphocalcium metabolism in chronic kidney failure

CKD

Chronic kidney disease (CKD):

The rate of chronic kidney failure (CKF) increases as the population ages. In France, nearly 3 million French people currently suffer from it. Chronic kidney disease (CKD) is a nephron reduction, most frequently due to chronic vascular nephropathy or diabetes. The complications are anaemia, phosphocalcium metabolism disorders and increased cardiovascular mortality.

Chronic kidney failure-related mineral and bone metabolism disorders (CKF-MBD):

This new terminology covers:

- **Biological disturbances:** hypocalcaemia, hyperphosphoraemia, PTH elevation, vitamin D deficiency
- **Bone remodelling disorders:** mineralisation, volume, growth, fragility
- **Vascular and soft tissue calcifications:** major risk factor in cardiovascular mortality and morbidity.

CKF patients may have one, two, or all three of the above mentioned disorders. Kidney failure-related hypocalcaemia is multifactorial; hypocalcaemia / hyperphosphoraemia induces continuous parathyroid stimulation and increased PTH secretion; progressive appearance of secondary hyperparathyroidism. PTH elevation induces an increase in bone uptake responsible for the disorders observed in CKF.
The calcium receptor (CaSR) plays a central role in PTH secretion regulation, activated by extracellular Ca++. It enables rapid PTH secretion adaptation.

Role of nephrologists:

Renal osteodystrophy occurs in approximately 60% of patients during haemodialysis treatment. It is observed in different forms in CKF patients: normal bone remodelling, high bone remodelling, low bone remodelling. Although bone biopsy is the only certain diagnosis method, it is rarely indicated. Non-invasive techniques, such as pathology and imaging, are preferred instead (there is a good correlation between the plasma PTH concentration and bone biopsy).
In practice, nephrologists use PTH values as a basis: in over 90% of cases, PTH elevation (› 500 pg/ml) predicts high bone remodelling. A normal or diminished level should be interpreted with the other clinical, radiological and pathological parameters.

Role of pathologist:

Pathological CKF-MBD follow-up includes

- **Routine tests:** blood calcium, blood phosphorus, alkaline phosphatases
- **Plasma aluminium**
- **Vitamin D 250H assay** to assess the reserve status.
- **Intact PTH and bone ALP (+/- osteocalcin)** in order to document bone remodelling disorders.

PTH:

This substance makes it possible to maintain a stable extracellular calcium concentration. In kidney failure patients, accumulation of fragment 7-84, considered as a natural PTH antagonist, occurs.
PTH assay methods include:

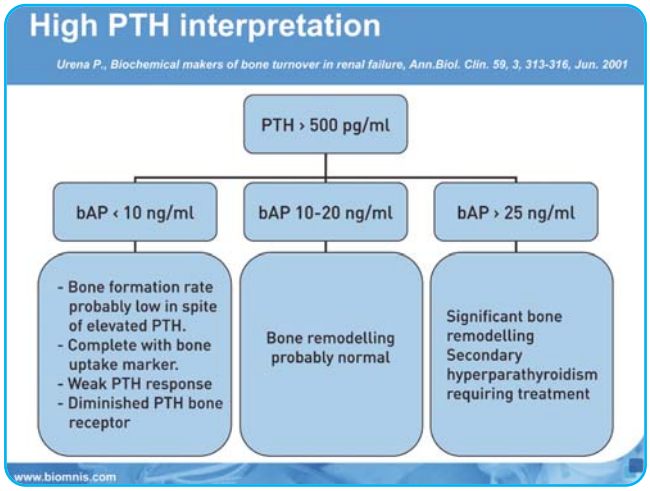
- **First generation kits:** no longer in use
- **Second generation kits** (intact PTH) by means of RIA technique or immunometry, use two different antibodies against the N-terminal portion and against the C-terminal portion. They assay PTH 1-84 and are correlated with the clinical profile.
- **Third generation kits** (biointact PTH): by means of immunometry, assay PTH 1-84 but not fragment 7-84.

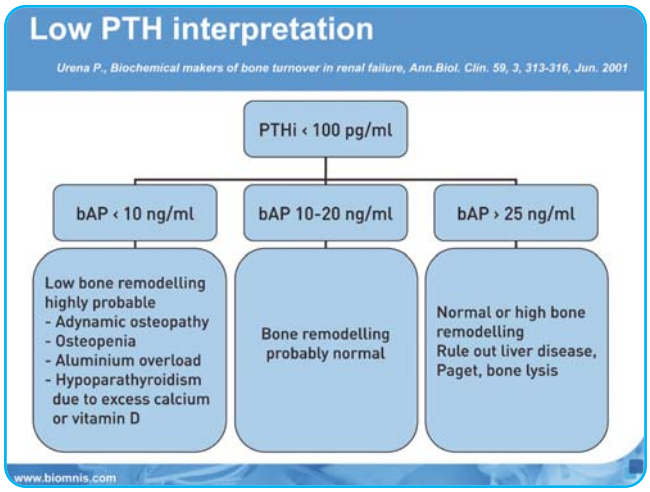
The variability in assay methods may complicate patient care. It is recommended to use second generation kits and perform follow-up by the same laboratory with the same techniques. The pre-analytical guidelines are as follows: sampling on serum with rapid centrifugation, the assay is stable if the serum is stored at ambient temperature (not more than 6 hours); otherwise, it should be frozen. EDTA plasma, which offers superior stability, can be used, but the values obtained may be 10 to 20% greater compared to serum assays. Finally,

it is necessary to determine specific reference values on samples free from vitamin D deficiency.

Bone alkaline phosphatases

The bone isoensyme (bAP) is not filtered by the kidneys or suitable for dialysis. It is produced by the osteoblasts, involved in bone formation and mineralisation. It is assayed using immunoenzyme methods with monoclonal antibodies. There is a high correlation between bAP and intact PTH in cases of CKF-MBD.





Osteocalcin or Gla-protein

This substance completes the evaluation as a specific bone formation protein; produced by osteoblasts under 1.25- OH2D3 control, degraded rapidly at ambient temperature. It must be frozen within one hour and assayed on a non-haemolysed sample. Analytical variability occurs depending on the kits. Finally, its sensitivity is inferior to bAP for bone remodelling disorders in cases of CKF.

Vitamin D

Exists in 2 compounds: vitamin D2 (ergo calciferol) and vitamin D3 (cholecalciferol) with desirable values between 30 and 80 ng/ml. In kidney failure patients, 25(OH)D and 1.25 (OH)2D3 are diminished. The reference assay methods for vitamin D are mass spectrometry after extraction and purification and HPLC. However, immune analysis on a Liaison system is easier and quicker: the assay principle is a chemoluminescence competition measuring a light signal inversely proportional to the quantity of vitamin D.

Therapeutics

Conventional treatments

Aim to treat the first stages of CKF without increasing the cardiovascular risk, prevent hypercalcaemia and limit phosphorus intake with a low dairy and animal protein diet; phosphorus chelators; vitamin D intake in its active form or in the form of synthetic derivatives.

Treatment of full-blown renal osteodystrophy

Introduction on the market of calcimimetic treatments acting directly on the calcium membrane receptors found on the surface of parathyroid cells. They increase the affinity of CaSR for calcium and induce a decrease in PTH secretion without increasing blood calcium or phosphorus levels.

Conclusion

- Major progress has been achieved in the last 10 years on the comprehension, prevention and treatment of biological disorders that cause secondary hyperparathyroidism in patients with CKF.
- Non-invasive pathological tests do not provide a completely reliable and reproducible evaluation of bone remodelling in patients suffering from CKF.
- It is important to remind clinicians and care provider teams of the importance of compliance with the pre-analytical conditions for the PTH and osteocalcin assay can occasionally be the source of analytical variability between repeated assays.