

## Mineral-Bone Disorders in Chronic Hemodialysis Patients in Sub-Saharan Africa: Dakar Experience (Senegal West Africa)

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### ABSTRACT

**Introduction:** Mineral bone disorders (BMD) are almost constant complications in chronic hemodialysis patients. The objective of our study was to determine the prevalence and profiles of BMD in chronic hemodialysis patients.

**Patients and methods:** This is a six-year descriptive and analytical retrospective study from January 1st, 2010 to December 31st, 2015, at the hemodialysis department of the University Hospital Center (CHU) Aristide Le Dantec. Were also included patients on chronic hemodialysis for at least 3 months, with at least one prescribed amount of para-thyroid (PTH). For each included patient, the epidemiological, dialytic, diagnostic and therapeutic parameters were collected and analyzed.

**Results:** Over 86 patients, 71 (82.5%) had BMD. The average age was  $48.92 \pm 15.5$  years old, with a sex ratio of 0, 65. Nephroangiosclerosis was the most frequent initial nephropathy (56.3%). The dialysis seniority was  $5.2 \pm 2.9$  years old and 93% of patients profited from 3 sessions of 4 hours per week. Eleven patients (15.5%) had previous aluminum intoxication. Fifty-eight patients (81.6%) had secondary hyperparathyroidism, 12.6% had adynamic osteopathy (OA), and 1.4% had osteomalacia. In patients with secondary hyperparathyroidism, the average age was  $48.6 \pm 15$  years old. 37.9% of these patients had articular pains, 22.4% had bone pains and 13.8% had spontaneous fractures. Eleven patients had hypocalcemia and only one patient had mild hypercalcemia. 46.5% of patients had normal phosphatemia; 29.3% had hypophosphatemia and 24.13% had hyperphosphatemia. Average PTH was  $913.85 \pm 331.65$  ng/ml. 73% of patients had 25-OH-Vit D insufficiency; 72.7% of patients had high total PAL. Therapeutically, 91.4% of patients had been treated with

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calcium carbonate; 25.9% with a treatment based on non-calcium phosphorus chelators; 69% of patients received vitamin D and 15.5%, calcimimetic treatment. 22% of patients under medical treatment normalized their PTH. Parathyroidectomy was performed in 6.9% of patients. The average age in patients which presented an adynamic osteopathy was  $50 \pm 20$  years old. The average PTH was 56.86 ng / ml, the average calcemia was  $100 \pm 4.3$  mg/l, the average phosphatemia level was  $59.5 \pm 31.1$  mg/l and the average vitamin D was 17, 42 ng / l. Twenty-three patients (32.4% of cases) had vascular calcifications. They were valvular in 25.4% of cases.

**Conclusion:** the BMD remain frequent in our hemodialysis center and dominated by the secondary hyperparathyroidism. A strict and early prevention strategy is necessary to control and delay the appearance of troubles= for a better quality of life for this population.

**Keywords:** Mineral bone disorders; Hyperparathyroidism; adynamic osteopathy; osteomalacia; hemodialysis; Sub-saharan Africa; Dakar.

### Introduction:

In chronic hemodialysis, troubles of mineral and bone metabolism (BMT) are associated with high morbi-mortality [1]. The pick-up charge of BMT appears necessary but is complicated. Since the first recommendations for the clinical practice developed by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2003 [2], a swing has been given to the clinical research and to the reflection on the topic of mineral and bony metabolism in patients with chronic kidney insufficiency. New clinical and epidemiological data upgraded knowledges and justified the publication of new good clinical practice recommendations of the diagnosis, evaluation, prevention and the treatment of TMO-MRC by KDIGO in 2009 [3].

It is now clearly established that disturbances of mineral metabolism, the bone attack and extra-skeletal calcification, particularly cardiovascular calcification, are closely related to patients with chronic kidney insufficiency and are a major cause of morbi-mortality [4, 5]. These complications are not superposable from one hemodialysis center to another because they

depend in part on the therapeutic habits and used equipment. In the same center, they are not similar either from one patient to another [6]. The study of Vassalotti et al. shown that 60% of patients have a high PTH rate as soon as the GFR falls below 60 ml / min by 1.73 m<sup>2</sup> [7], similar results were found in Morocco [8]. In Senegal, the BMT prevalence in the dialyzed patients was 66.9%, with a secondary hyperparathyroidism's predominance [11]. The objective of our study was to determine the prevalence and profiles of TMO in our chronic dialyzed patients.

### Materials and methods:

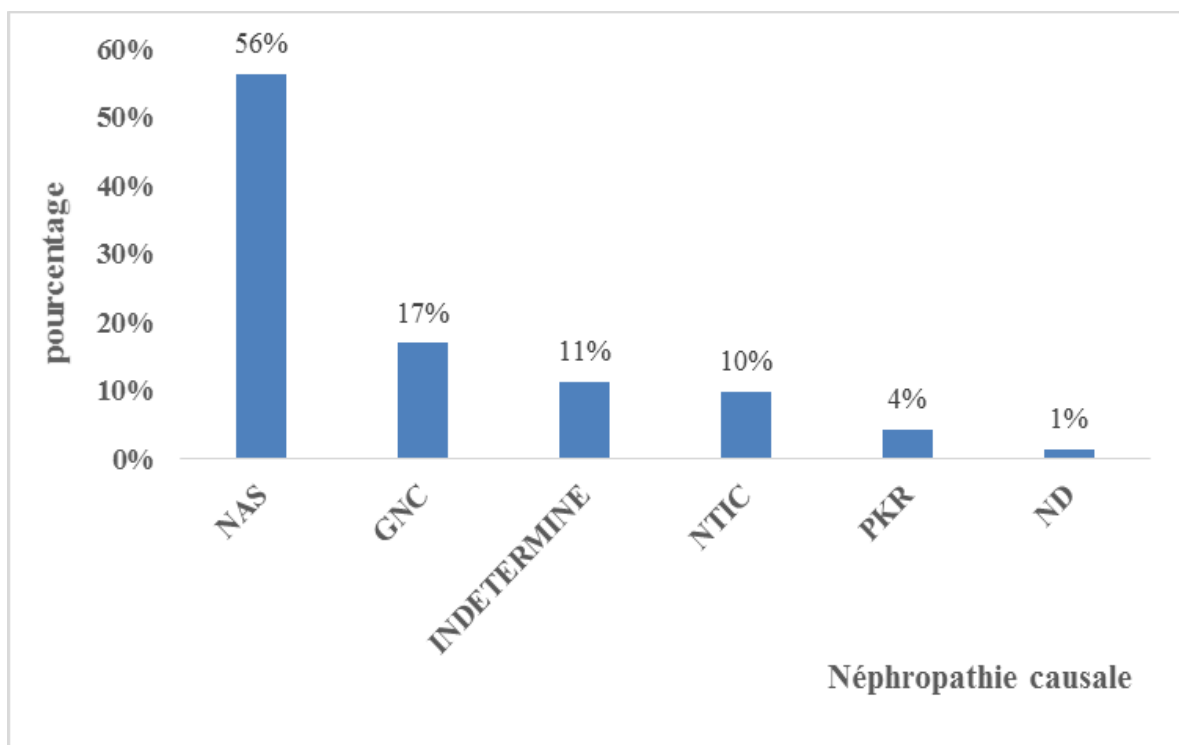
We realized a descriptive and analytical monocentric retrospective study in the nephrology-hemodialysis department of Aristide le Dantec hospital in Dakar over a period of 6 years, from January 1st, 2010 to November 31st, 2015. Were also included patients on chronic hemodialysis for at least 3 months, with at least one prescribed amount of parathyroid (PTH). The data were collected from the patient's medical records, using an exploitation sheet that

intend to specify the socio-demographic, clinical, and para clinical (biological and medical imaging) aspects of each patient included in the study. Biological abnormalities were defined as normal; the values recommended by KDIGO 2009 [73]. Data collection was done "Excel 2007 software". The data analysis was done using SPSS software (Statistical Package for Social Science) version 18. The averages and percentages were compared using the Student's test, the Chi-square test, and the exact Fischer test, according to their applicability conditions. Any

difference less than 0.05 was considered statistically significant

### Results:

Eighty-six chronic hemodialysis patients were studied, of whom 71 patients (82.5%) had mineral bone disorders. The average age of the patients was  $48.92 \pm 15.5$  years old. There were 43 women for 28 men, a sex ratio of 0.65. The first causative nephropathy was nephroangiosclerosis (NAS) found in 56.3% of cases. 11.3% of patients had indeterminate nephropathy (Figure 1).



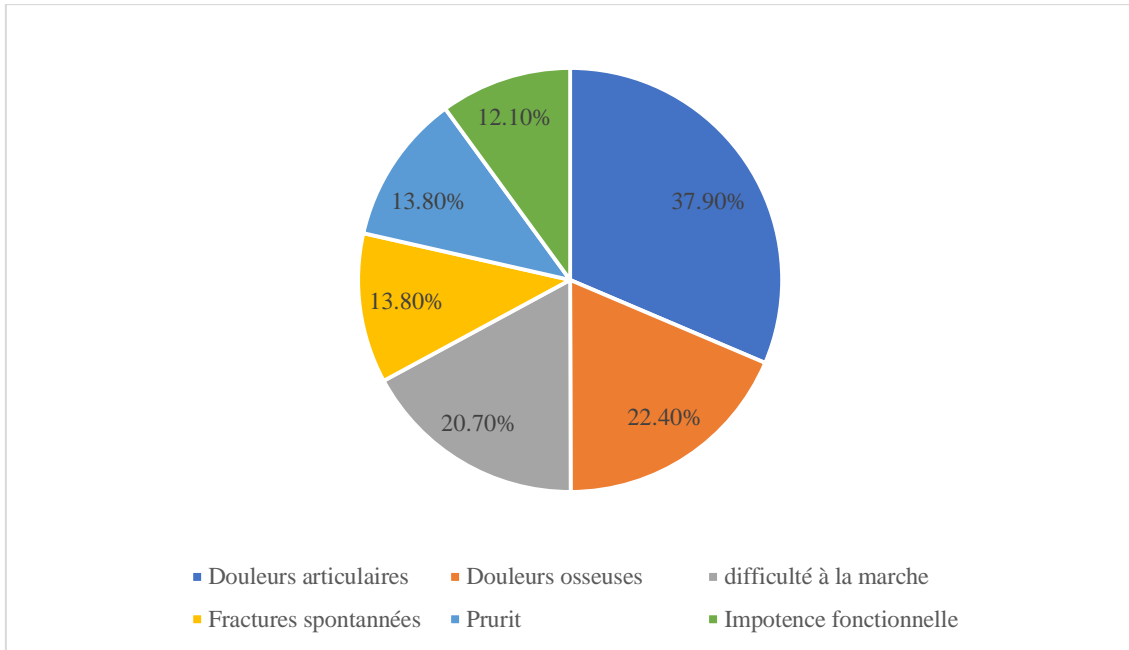
**Figure 1: Causal Nephropathies in our Chronic Hemodialysis Patients**

NAS: Nephroangiosclerosis; CNG: chronic glomerulonephritis; NTIC: Chronic tubulointerstitial nephropathy; PKR: Polycystic kidney disease; ND: Diabetic nephropathy.

The average length of hemodialysis was  $5.2 \pm 2.9$  years. Eleven patients (15.5%) had a precedent of aluminum intoxication. Fifty-eight patients (81.6%) had secondary hyperparathyroidism. Nine patients (12.6%) had adynamic osteopathy (OA). Only one patient (1.4%) of hemodialysis patients had osteomalacia.

### Secondary hyperparathyroidism

Fifty-eight patients had secondary hyperparathyroidism, including 39 women and 19 men, that to say a sex ratio of 0.48. The average age of the patients was  $48.6 \pm 15$  years old, with extremes of 20 and 78 years old. The diagnosis of secondary hyperparathyroidism was made within an average notice of  $3.68 \pm 2.3$  years after the start of dialysis. Clinically, 22 patients (37.9%) had articular pains, 13 patients (22.4%) had bone pains and 8 patients (13.8%) had pathological fractures (Figure 2).



- Articular pains
- Spontaneous
- Bone pains
- Pruritus
- Waking difficulty
- Functional significance

**Figure 2: Distribution of hemodialysis patients with secondary HPT based on clinical symptomatology.**



**Figure 3: Standard radio image of a bilateral pathological fracture of femoral collar in a 57-year-old chronic hemodialysis patient.**

Para clinically, the average PTH 1-84 was  $913.85 \pm 331.65 \mu\text{g} / \text{ml}$ . The average calcemia was  $90.75 \pm 7.67 \text{ mg/l}$  and the average phosphorus concentration was  $44.74 \pm 18.39 \text{ mg/l}$ . The average of 25 OH vitamin D was  $26.07 \pm 11.65 \text{ ng/ml}$ . The standard skeleton

radiographies objectified abnormalities in 13 patients: 5 cases of bone demineralization, 3 cases of osteocondensations, 2 cases of bone lysis, and 1 patient had multiple geodes on: the shoulder, the lower extremity of the radius, the trapezium, the scaphoid, the head of the proximal phalanx of the thumb and the spine and bones of the pelvis. Eight patients had fractures (three unilateral fractures of the femoral collar, two fractures of the inferior extremity of the radius, a bilateral fracture of the femoral collar (Figure 3), two patients had several fracture episodes:

- For the 1st: Right Clavicle then the 7th rib, femoral head and iliac wings, and then a fracture of the left clavicle (figure 3).
- 2nd: Right clavicle and then the femoral collar.

Only one patient had bone densitometry that revealed osteoporosis with a T score <- 2 in the lumbar spine and left femur. Twenty-three patients (39.7%) benefited from cervical ultrasound, it was normal in 17 patients (29.3%) and pathological in 6 patients (10.3%), of which 5 had objectified an adenoma and 1 a bilateral hyperplasia of the parathyroid glands. Therapeutically, 53 patients, or 91.4% of patients with hyperparathyroidism, had received treatment with calcium carbonate. Fifteen patients (25.9%) of the cases, had been treated with non-calcium phosphorus chelators (Fosrenol® or Renagel®). Forty patients (69% of cases) received vitamin D (native and / or alpha). Nine patients (15.5%) of the patients had a calcimimetic treatment. (Table I)

**Table I: Distribution of patients according to the treatment received.**

Treatment	Number of patients	Percentage
CaCO <sub>3</sub>	53	91.4%
Non-calcic chelatings of the phosphate	15	25.9%
Vitamin D Native and / or un-alfa ®	40	69%
Native	18	31%
Un-alfa ®	15	25.9%
Native + un-alfa ®	7	12.1%
Calcimimetics	9	15.5%

Under medical treatment only 36 patients (66%) had a regular biological check, among them:

- Twelve patients (22% of cases) had a normalization of PTH.
- Twenty-one patients (39% of cases) had persistence of hyperparathyroidism.
- Three patients (5.5% of cases) had developed hypoparathyroidism.

A parathyroidectomy (PTX) was performed in 4 patients or 6.9% of cases (two PTX subtotal, 1 left superior parathyroidectomy and right parathyroidectomy).

#### **Adynamic Osteopathy (AO)**

Nine patients had adynamic osteopathy. Three of them had a precedent of aluminum intoxication, and only one patient dialyzed with a 1.75 calcium dialysis bath. Three patients, 33%, were symptomatic: the bone pains represented

40% of symptoms, and were present in 2 patients, one of whom had low back pain, and the other a pain in the left leg (1/3 lower of the tibia). Pruritus, both walking difficulty, and coxalgia arthralgia were present in each patient. The average PTH was 56.86 ng / ml. The average calcemia was  $100 \pm 4.3$  mg / l, the average phosphate level was  $59.5 \pm 31.1$  mg / l and the mean vitamin D was 17.42 ng / ml. Three patients had a precedent of aluminum intoxication, the diagnosis of OA was made during the aluminum intoxication of one patient, and one year later in the other two. The serum aluminum level was measured in a single patient, it was 10 mg / l, and the Desferal test was not performed. None of our patients had a bone biopsy.

### Osteomalacia

Only one patient had osteomalacia, he was 55 years old, and he had been on hemodialysis for 2 years on vascular nephropathy. He had pains in the pelvic girdle. Biologically, the calcemia was normal at 93 mg / l, low phosphate at 28 mg / l, the PTH at the upper limit for chronic

hemodialysis (PTH = 515 ng / ml), and hypovitaminosis D at 16 ng / ml. Therapeutically, the patient benefited from a supplemented native Vit D but a control dosage was not achieved.

### Vascular calcifications

Twenty-three patients (32.4% of the cases) had vascular calcifications in all localities. Their average age was  $54.2 \pm 17.7$  years old, with extremes of 20 and 81 years old. Sixty-seven patients (94.4%) had a cardiac ultrasound which was normal in only 48 patients (67.6% of the cases). Eighteen patients (25.4%) of the population had valvular calcifications (mitral, aortic and / or tricuspid valves). Four patients (5.6%) had an abdominopelvic scanning. It has objectified in 50% patients vascular calcifications. Eleven patients benefited from Doppler vascular truncus, of which 9 or 82% had objectified vascular calcification. Eighteen patients (25.4%) had valvular calcifications and 6 patients (8.5%) had calcifications of the abdominal aorta (Table II).

**Table II: Distribution of vascular calcifications (VC) according to their location.**

CV Locations	Numbers	% patients	% of CVs
Valvular	18	25.4%	37.5%
Abdominal aorta	6	8.5%	12.5%
Carotids	6	8.5%	12.5%
Iliac arteries	6	8.5%	2.5%
Femoral arteries	4	5.6%	8.3%
Coronary arteries	1	1.4%	2%
Superior mesenteric artery	1	1.4%	2%

CV: Vascular calcifications

In our series, we noted a clear predominance of women with secondary hyperparathyroidism ( $p = 0.002$ ). The risk of hyperparathyroidism increased with duration of hemodialysis ( $p = 0.003$ ) and the involvement was more frequent in patients having dialysis between 5 and 10

years and  $\geq 10$  years. Moreover, we did not find a relationship between age and the occurrence of hyperparathyroidism ( $p = 0.55$ ). In our work, age was a factor associated with AO development ( $p = 0.039$ ), subjects under 39 years old were the most affected. Seniority in

hemodialysis was not associated with the risk of occurrence of AO. Vascular calcifications development was not influenced by the presence or absence of hyperparathyroidism ( $p = 0.19$ ), AO ( $p = 0.74$ ) or calcium bicarbonate intake ( $p = 0.12$ ). However, they were less common in patients under than 30 years of age ( $p = 0.006$ ). Chronic hemodialysis patients who had hyperparathyroidism were more likely to have spontaneous fractures ( $p = 0.039$ ). In addition, we didn't note any relationship between age, gender and seniority in dialysis and the occurrence of fractures in the study population.

### Discussion:

#### - Secondary hyperparathyroidism:

In our study, secondary hyperparathyroidism (HPT) was the most common TMB, it was present in 58 patients or 81.6% of cases. The prevalence of secondary HPT was significantly higher than that found in the series of NDIAYE, where HPT was present in 45.5% of cases, as well as the different series of the literature, where the rate varied between 30% and 60% on average. Studies by LLACH et al [9], SHERRAD et al. [10], and SECK et al. [11] respectively found a prevalence of 47.88%, 32.47% and 48%. This divergence could easily be explained by the low socio-economic level of our patients, who lack social coverage in the vast majority of cases; making difficult therapeutic treatment based on non-calcium phosphorus chelators and / or calcimimetics and even inconceivable according to their high cost.

Our patients had developed an HPT after an average delay of  $3.68 \pm 2.3$  years from the beginning of hemodialysis. This delay was therefore shorter than that found by MONTASSER et al. ( $4 \pm 2$  years) [12]. This could be explained by the fact that disturbances of phosphocalcic metabolism appear at an early stage of the MRC and require early management and regular monitoring. Most patients in our context consult at a very advanced stage of the MRC.

The clinical manifestations in our patients were greater than those found by TRAORE et al. [13] where 81.7% of patients were asymptomatic, 7.5% had bone pain and 5.3% had muscle pain.

However, from a recent series of HADDAM et al. in Algeria (2015) [14], all patients had a clinical bone syndrome. Fibrous osteitis remains asymptomatic for a long time, bone pain come usually late. In our patients, we observed a high frequency of articular and bone pain, probably because of the severity of the attacks as well as the delay in pick-up in charge of these patients.

In our series, the average calcemia was  $90.75 \pm 7.67$  mg / l. This concurs with the results of JEBRANE et al. found an average calcemia of  $99.5 \pm 13.3$  mg / l [8]. Eleven patients (18.96%) had hypocalcemia and only one patient had mild hypercalcemia, the frequency of hypocalcemia was significantly lower than that found in the HADDAM series [14] where hypocalcemia was present in 69% of cases. Hypocalcemia was also lower than that found in the TRAORÉ et al. where it was present in 77.4% of cases [13]. The hypocalcemia, which was inferior in our series compared to other series, could be explained by the therapies used in our context, notably the use, for financial reasons, of calcium carbonate in the pick-up in charge of hyperphosphatemia. Fourteen patients (24.13%) had hyperphosphatemia. The frequency of hyperphosphatemia in our series was higher than that found by GUILLAUME et al. [15] where it was 15%. However, in the series of TRAORE et al. [13], 91.4% of the studied population had hyperphosphatemia. This clear divergence of results could be explained by the fact that phosphatemia depends on dietary intake of phosphates, directly related to protein intake, not evaluated in our patients in the absence of dieticians in the service.

The average PTH was  $913.85$  pg / ml, these figures are significantly higher than those found in by TRAORÉ et al. [13], BENABDELLAH et al. [16] and HADDAM et al. [14], with average PTH of  $436.11 \pm 200$  µg / mL, of  $508 + -380$  µg / ml and  $680$  µg / ml respectively. The clear

superiority of PTH in our series could be explained by the fact that there are currently different kits on the market for the determination of PTH, with a great variability in the values obtained, as well as a difference of the definition of hyperparathyroidism in terms of the series. The dialysis reference values are 2 to 9 times the upper limit of the kit used (approximately 130-585 pg / ml for a 2nd generation assay). A new dosage measure the "bio-intact" PTH that only take into account the PTH 1-84 is now available [17]. The optimal concentrations of intact organic PTH associated with normal dialysis bone remodeling are still unknown, so that this dosage is still not widely used in Europe and not recommended by the recent KDIGO consensus conference [3].

In our series, 91.4% of the patients had a treatment based on calcium bicarbonate, 15 patients (25.9%) had been treated with non-calcium phosphorus chelators (Fosrenol® or Renagel®), 40 patients (69%) received vitamin D (native and / or one-alfa) and only 9 patients (15.5%) received calcimimetic therapy. This concurs with the results found in the series of TRAORE et al. where calcium carbonate and vitamin D were combined in 68.8% of cases, calcium carbonate was used in 17.2% of cases and vitamin D in 12.9% of cases [13]. In France, in the series of GUILLAUME et al., 51% of patients were treated with cinacalcet, of which 10% had been weaned after 12 months [18].

Cinacalcet can lower serum PTH levels without increasing calcemia or phosphatemia, a major drawback of calcium and calcitriol treatments [19]. The modest use of calcimimetics in our training, because of their cost and the absence of medical insurance in the majority of our patients, explains the fact that 12 patients (22%) had a control of hyperparathyroidism with maintenance of the PTH in the recommended targets for one hemodialysis patient. In our series, surgical parathyroidectomy was performed in 4 patients (6.9% of cases). Our results were close to those of MNIF et al. in Tunisia [20], as well as those of GUILLAUME et

al. in France [18] where 10% of patients had had a parathyroidectomy (PTX).

#### Adynamic osteopathy (AO)

In our series, 9 patients (12.67%) had adynamic osteopathy, this is close to the results found by SECK et al. [11] and JEBRANE et al. [8] with respectively 17.79% and 17.94% of cases. However, the prevalence of AO was higher in the series of SHERRARD et al. (30.76%) [10], those of CHANGSIRIKULCHAI et al. where it was 41.1% of cases [21], as well as those of NDIAYE with 51.6% of renal osteodystrophy [22].

#### Osteomalacia:

In our series, only one patient (1.4%) had osteomalacia. This joins the results found by Changsirikulchai S [21] and Seck et al. [11] where osteomalacia represented 3.6% and 1.26% of TMOs, respectively.

#### Vascular calcifications (CV)

At 5D stage, more than 50% of patients have vascular calcification. However, in our study 23 patients (32.3%) had vascular calcifications, whose 18 had valvular calcifications. In the study conducted within our department by Ka et al. 39 patients (76.47%) among the 51 had at least one cardiovascular calcification with valve localization in 68% of cases [23]. This could be explained by the fact that the prevalence varies according to the type of studies and techniques used. KDIGO recommends the use of cardiac echocardiography for the detection of valvular calcification in patients with 3-5D CKD, and lateral abdominal X-ray for the presence or absence of vascular calcification [3]. These techniques, because of their high irradiation sensibility and their efficiency, are reasonable alternatives to the scanner. In our series, the CV were less frequent in younger patients ( $p = 0.006$ ), which is concurs with literature data.

In our study, the rate of PTH did hadn't influenced the occurrence of CV ( $p = 0.19$  for hyperparathyroidism,  $p = 0.74$  for OA). This concurred with numerous studies (Bellasi [24], Sayarliogu [25] and Strozecki [26]) who did not find an association between biological



parameters including calcemia, phosphorus and PTH and Valvular calcifications. But STROZECKI et al [26] had found a significant correlation between the phosphocalcic product and CV.

### Conclusion:

Mineral-bone disorders are common in our chronic hemodialysis patients. The pick-up in charge remains a complex area and is in a constant evolution. The last recommendations make it possible to apply an individualized therapeutic strategy in order to optimize the pick-up in charge of these disorders. However, in our sub-Saharan African countries, where socioeconomic conditions are precarious, the rate of patients meeting all criteria remains very low.

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