# DIAGNOSTIC ALGORITM FOR IDENTIFYING THE TYPE OF BONE TURNOVER IN PATIENTS WITH RENAL OSTEOPATIA ON CHRONIC HEMODIALYSIS

**Dana Stoian[1], Dan V. Poenaru[2]**

## REZUMAT

**Introducere:** Prezența osteopatiei renale în evoluția cazurilor cu insuficiență renală cronică, este un lucru foarte bine ucnoscut. Abordul therapeutic al acesteia depinde în cea mai mare parte de tipul de turnover osos. Studiul de față își propune să evalueze impactul diagnostic, al diverselor metode de diagnostic. **Material și metode:**131 pacienți, din centrul de Dializă și Transplant renal, din Spitalul Clinic nr.1, selectași aleator. Fiecare pacient a consimșit participarea la întreaga perioadă de urmărire. Evaluarea a fost făcută prin: examne clinic, radiografii standard, DXA coloană lombară și șold nondominant, ultrasonometrie, determinări biochimice și hormonale specifice: iPTH, OS, FAL-O, 25HOvitaminD. Analiza statistică a datelor a utilizat curbele diagnostice ROC, pentru a calcula sensibilitatea, specificitatea, valoarea predictivă pozitivă, valoarea preditivă negativă, valoare pragg optim diagnostică. **Resultate:** Din otalul cazurilor, am identificat turnover osos accelerat la 61.8% din lot, 18 pacienți cu defecte de mineralizare osoasă associate, 16.79% subiecți au avut turnover osos dimineaut, restul de 21.37% având nevoie de urmărire periodică pentru încadrarea riguroasă. Folosind această clasificare ca standard, am evaluat calitatea diverșilor parametrii, în diagnosticul turnoverului osos crescut - iPTH >400 pg/mL, FAL-O >20 µg/l, 25HOD <30ng/mL, volum paratiroidian >0.5 cm3, OS > 13 ng/L, modificări radiologice- , respectiv turnover osos diminuat - iPTH < 80 pg/mL, FAL-O<13 µg/l, 25HOD< 20 ng/mL, OS< 3 ng/L-. Cea mai bună metodă de diagnostic a fost iPTH (AUC=0.855), FAL-O (AUC=0.8566), OS (AUC=0.302), 25 HOD (AUC =0.646). Asocierea treptată a acestor analize a crescut exponențial puterea diagnostică: turnover osos crescut- sensibilitate de la 50.080 (PTH izolat) la 98.78 (PTH + BAP), iar specificitatea până la 100 (PTH+FAL-O+25 HOD+ecografie). În cazul turnoverului diminuat, rezultatele au fost similare. De asemenea am identificat valorile discrimitative prag, optime, pentru cele mai importante metode diagnostice: turnover crescut: iPTH> 214 pg/ml, FAL-O > 76,3 µg/L, tunroner diminuat: iPTH < 122 pg/ml, FAL-O < 34 µg/L, OS < 3,1. **Concluzii** Combinarea ultrasonografiei regiunii cervicale anterioare, cu osteodensitometria cu raya X, dozărilor hormonale și cele ale markerilor de turnover osos, determină creșterea capacității diagnostice pozitive și discriminative.
**Cuvinte cheie:**

## ABSTRACT

**Introduction:** Uremic bone disease is a fact in the evolution of end stage renal disease patients. The type of bine disease remains a difficult task in face on the clinician. Bone biopsy is the golden standard of diagnostic, but is not recommended routinely and is not available to all hospital sites. **Material and methods:** 131 patients from the Hemodialysis and Renal Transplantation Center form the County Hospital nr.1, selected randomly, with their agreement of participating to the whole study. All patients performed: clinical evaluation, standard X-rays, DXA of lumbar spine and hip, QUS, biochemical assays and specific determinations: iPTH, OS, BAP, 25HOvitaminD. We analyze the data using ROC diagnostic curve to calculate sensitivity, specificity, PPV, NPV, best threshold values to compare different diagnostic methods. **Results:** From the 131 cases, we identified increased bone turnover in 61,8% cases, 18 patients with mineralization defects, 16.79% low turnover subjects, 21.37% needed a reevaluation after six months for diagnostic decision. Using this evaluation as standard, we analyzed all the different assays: iPTH >400 pg/mL, BAP >20 µg/l, 25HOD <30ng/mL, parathyroid volume >0.5 cm3, OS > 13 ng/L, positive X-ray changes in diagnostic of increased bone remodeling, respectively < 80 pg/mL, <13 µg/l, < 20 ng/mL, < 3 ng/L. The best diagnostic methods are iPTH (AUC=0.855), BAP (AUC=0.8566), OS (AUC=0.302), 25 HO-vitamin D (AUC =0.646). Combined stepwise approach increases the sensitivity of the diagnostic of high turnover: form 53.080 (for PTH alone) to 98.78 (PTH + BAP), and the specificity up to 100 (PTH+BAP+25 HO vitamin D + ultrasound). In the case of low turnover, the results were similar. We identified the best discriminative values for the most important diagnostic approaches: increased turnover: iPTH> 214 pg/ml, BAP > 76,3 µg/L, decreased turnover: iPTH < 122 pg/ml, BAP < 34 µg/L, OS < 3,1. **Conclusion:** Combining ultrasound, ostedensitometric, hormonal and bone turnover markers increases the diagnostic abilities of the clinician.
**Key Words:**

## INTRODUCTION

Bone impairment characterizes chronic renal failure, starting 3rd stage of disease, at it is almost universal present in end stage renal disease (ESRD), especially in patients treated with chronic hemodialysis. The first step on the evaluation, approach and treatment, in the diagnosis of renal bone disease, is to characterize the type of bone turnover: low, high, and medium.[1]

[1] 1st Department of Obstetrics-Gynecology [2] 2nd Department of Orthopedics and Traumatology, Victor Babes University of Medicine and Pharmacy, Timisoara

Correspondence to:
Ass. Prof. Dana Stoian, MD, PhD, Victor Babes University of Medicine and Pharmacy, 2 E. Murgu Sq., Timisoara, Tel. +40-256-204250.
Email: drd@nutritietimisoara.r

Received for publication: May. 18, 2011. Revised: Mar. 14, 2012.

Although hystomorphometry remains the golden standard of diagnostic, there is no recommendation for routine bone biopsy. Pre-surgical evaluations, treatment with desferoxamine, evaluation of new diagnostic methods, are the absolute indication for bone biopsy.[1-3]

In the daily practice, the clinical, biochemical, hormonal and imaging techniques are used to realize a lesional profile for each patient. The classical assays (calcaemia and phosphatemia) do not bring any information regarding the level of bone turnover, with the exception of hypophosphatemia with defines a mineralization defect.[4,5] A non-suppressible hypercalcaemia suggests a severe/tertiary hyperparathyroidism. Intact PTH remains one of the most sensitive and specific assays for differentiating low from high bone turnover.[2,5-8] Markers of bone remodeling can add more information regarding bone turnover – bone specific alkaline phosphatase, respectively osteocalcin.[9,10] Evaluation of vitamin D status modulates the therapeutically approach and also can contribute to diagnosis of secondary hyper-parathyroidism. Significant vitamin D deficit (below 20 ng/ml) generates impairment of mineralization, regardless the iPTH level, length of disease, age, sex or type of renal lesion.[11] The information added by the imagistic methods are rather sparse: acro-osteolysis – 60%, extra-skeletal calcification – 20% in selected cases, or cortical fibrosis – 35%.[12] Visualization of the hyperplasic parathyroid is highly specific for secondary hyperparathyroidism.[9]

## AIM OF THE STUDY

We developed an algorithm for diagnosing the type of bone disease in patients with ESRD on chronic hemodialysis. Combining clinical, biochemical, hormonal and newer bone remodeling markers and bone density measurements can increase the diagnostic quality in our Hospital.

## MATERIAL AND METHODS

The study group comprised 131 cases, recruited for the patients of the Clinic of Hemodialysis and renal transplantation, at the Clinical Emergency County Hospital, Timisoara, that agreed to complete the follow up. The 63 females and 68 males, with mean age of 47.776 ± 12.32 years, under supplemental renal therapy for at least 10 months (mean 51.488 ± 4.686 months) were all evaluated by means of:

- Anamnesis, clinical exam, measurement of height, weight (after dialysis session);

- Seric biochemical assays: calcemia, phosphatemia, total alkaline phosphatase, iPTH (ELISA, normal values 8.0-68 pg/mL), 25-HO vitamin D (CHEIM Diasorin Liason, normal values over 30 ng/mL); we also determined the values for osteocalcine – OS (ELISA normal values: 3.1-13.7 ng/mL) and bone specific alkaline phosphatase – BAP (ELISA normal values lower than 90 U/L).

All cases performed standard X-ray evaluation of skull - profile, antero-posterior pelvis, bilateral hands and feet, antero-posterior image, lateral view of lumbar and/or toracal spine. DXA was performed on lumbar spine, non-dominant femoral neck.

**Diagnostic criteria:** iPTH over 400 pg/mL is characteristic for increased bone turnover.[6,13] The association of high turnover (BAP values > 90 U/L), or the presence of low turnover OS values, below 3.1 ng/mL, suggests the type of bone turnover.[14] Vitamin D deficiency implies bone mineralization defects. Visualization of the parathyroid glands on ultrasound examination confirmed secondary hyperparathyroidism.

The combined informations permitted to use the recommended iPTH values for ESRD patients: more than 3 times the maximum normative value for diagnosing secondary hyperparathyroidism, respectively values less than 100 pg/mL for low turnover bone disease.[2,6,13,15-19] 1000 pg/mL was the threshold value for iPTH in diagnosing severe, tertiary hyperparathyroidism.[1]

**Statistical analysis**

At the beginning we have stratified the cases as low, mixed or high turnover cases. We used the Receiver Operated Curve diagnostic test, to calculate the sensitivity, specificity, positive predictive value (PPV) and negative predicted value (NPV), likelyhood ratio for each test or test value. We also calculated the Area Under the Curve (AUC) to determine the best parametric test value in diagnosing each type of disease/condition.

The study was approved by our Ethics Committee, according to the WMA Declaration of Helsinki, revised in 2008.

## RESULTS

Using the mentioned diagnostic criteria, we identified 81 patients (61.8%) with increased bone turnover, 55 cases (41.98%) had all the criteria for secondary hyperparathyroidism, 18 patients had an associated mineralization defect, 22 patient (16.79%) were cleared cut diagnosed with low bone turnover, and (21.37%) subjects had nor enough elements

were neither of the types. Using this as standard for diagnostic, we evaluated all the diagnostic tests, their importance, quality and threshold values for identifying the type of bone turnover. The final spectrum of bone disease in our study group is presented in Figure 1.

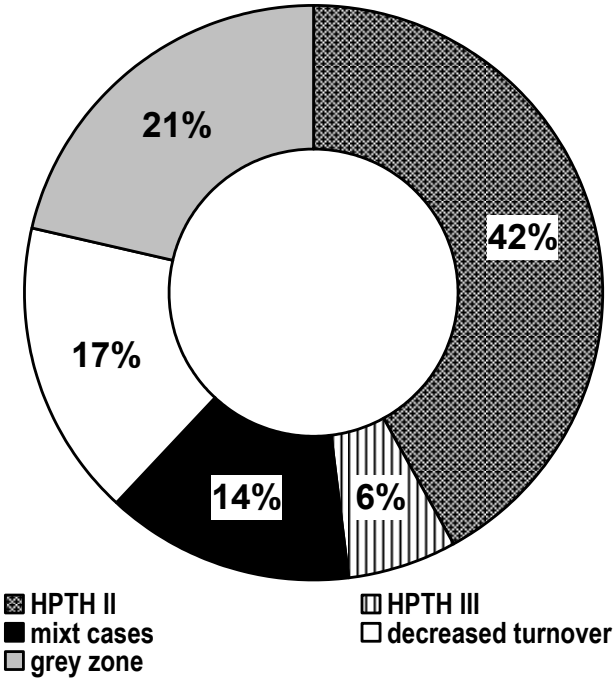


**Figure 1.** Type of bone turnover disease.

The phospho-calcic balance revealed normal Ca2+ and increased PO42- values in the majority of the cases (96.1%, respectively 68%). Transitory hypocalcemia was present in 2 patients, three cases had sustained, repeated hypercalcemia. There was no quality information revealed by these measurements in respect with type of bone disease. (Fig. 2)

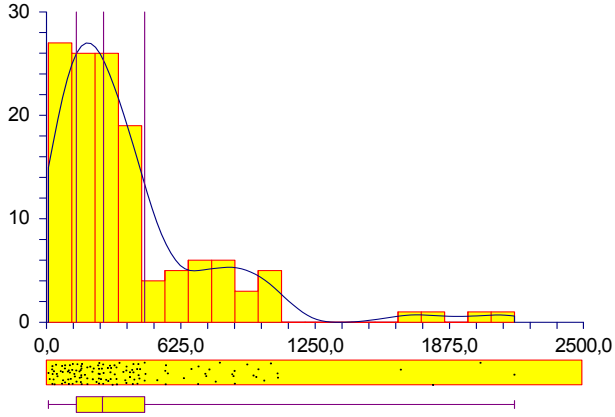


**Figure 2.** iPTH (pg/mL) values at M0.

As we can see, the majority of cases are between 200 and 1000 pg/mL. 15.25% of cases had „normal" PTH levels, 29% of cases were the grey, undefined levels. Excessive increased PTH levels were observed in 12.97% of cases.

After defining the exact cases with low and high turnover, we evaluated the quality of each PTH value in diagnostic of the speed of bone remodeling. In the case of PTH, the quality of different set points was analyzed. (Table 1)

**Table 1.** Different iPTH threshold for increased bone turnover.

| iPTH (pg/mL) | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| > 150 | 98.78 | 70 | 0.843 | 0.9722 |
| > 200 | 98.78 | 98 | 0.9878 | 0.98 |
| > 400 | 53.080 | 98.03 | 0.9772 | 0.568 |

In our case, the prevalence of secondary or tertiary hyperparathyroidism cases is 61.8%, but the identified one is different, depending the PTH cutoff value >73.2% (0.529-0.41568, 95% CI), of 61.2% (0.529-0.7017, 95% safety interval) respectively 32.8% (0.248-0.41568, 95% CI).

Using the ROC curve technique, the best iPTH value in identifying increased bone turnover is 214 pg/mL. (Table 2)

**Table 2.** iPTH values candidates for threshold for increased bone turnover.

| iPTH values | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| 204 pg/ml | 0.9878 | 0.97959 | 0.979 | 0.980 |
| **214pg/ml** | **0.9878** | **1.00** | **0.980** | **0.981** |
| 216pg/ml | 0.9756 | 1.00 | 0.960 | 0.962 |

For this value, the AUC (non-parametric De Long and Clarke Pearson technique) had a value of 0.855 (standard error 0.00331, 0.853-0.898, CI 95%). As a rule, any PTH value more than three times the upper normal value alerts the physician. (Fig. 3)

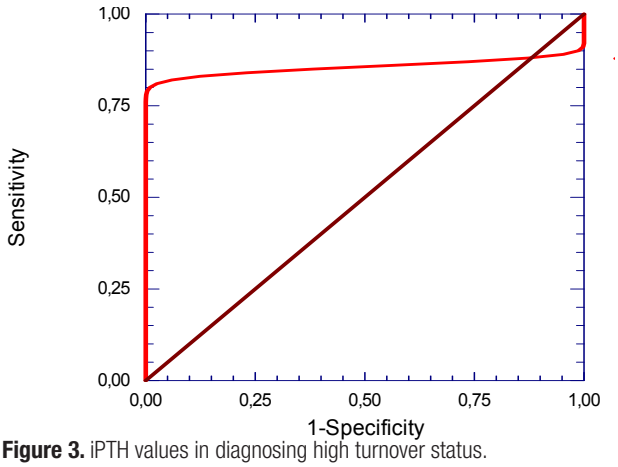


**Figure 3.** iPTH values in diagnosing high turnover status.

We also observed the diagnostic value of „normal iPTH values" in identifying low bone turnover.

Different recommended set points: 65 pg/mL, 120 pg/mL, or normal values were studied. 6,8,20 (Table 3)

**Table 3.** iPTH threshold in diagnosing adynmnic bone disease.

| Cutt-off point | Sensitivity | Specificity | Likew R | PPV | NPV |
|---|---|---|---|---|---|
| 65 pg/ml | 0.5714 | 1.00 | | 1.00 | 1.00 |
| 100 pg/ml | 0.8523 | 0.99091 | 10.4761 | 0.952 | 0.954 |
| 120 pg/ml | 0.875 | 0.934 | 13.375 | 0.97087 | 0.97334 |
| 150 pg/ml | 1.000 | 0.8723 | 7.857 | 0.600 | 0.6116 |
| 195 pg/ml | 1.000 | 0.7454 | 3.928 | 0.4285 | 0.4405 |

In our case, the optimal values for PTH are situated in the upper „normal value limit" of PTH, for ESRD cases. The candidate values are listed below. (Table 4) They were picked up for the whole PTH value list after drawing the ROC curve for each of the values. (Fig. 4) The best value was 122 pg/mL, with an AUC=0.99.

**Table 4.** Best PTH cut-off value for low bone turnover.

| Value | Sensibility | Specificity | Likew ratio | PPV | NPV |
|---|---|---|---|---|---|
| 120 pg/ml | 0.80264 | 0.99324 | 5.0327 | 0.9984 | 0.9983 |
| **122 pg/ml** | **0.80121** | **0.99452** | **5.0028** | **0.9986** | **0.9986** |
| 123 pg/ml | 0.8004 | 0.99507 | 4.9876 | 0.9988 | 0.9987 |

For the identified value, the AUC was excellent, AUC=0.99957, ES=0.00062, limits 0.993-0.999 (95% CI).

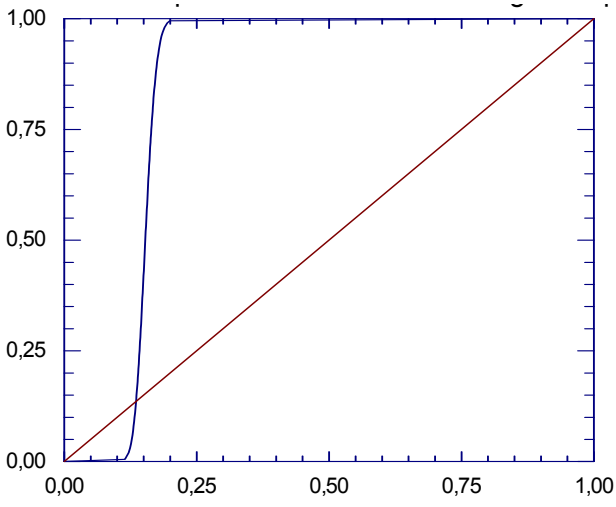


**Figure 4.** ROC curve for PTH=122 pg/mL in diagnosis of adynamic bone disease.

In the evaluation of one parameter, the cost benefit ratio is also very important. These values are presented in the next histogram, for different PTH values. (Fig. 5)

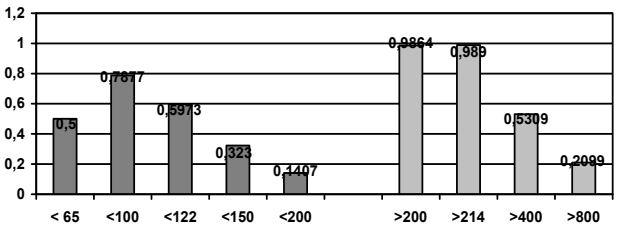


**Figure 5.** Cost benefit ratio for iPTH values in diagnosis the type of renal

The same approach was used for bone markers: bone specific alkaline phosphatase (BAP), and osteocalcin (OS).

From all increased BAP values, we identified the cut of point of 76.40 µg/L for diagnosing high turnover status (sensitivity of 74.49%, specificity of 0.89%), AUC= 0.85677, ES= 0.0325. (Fig. 6)

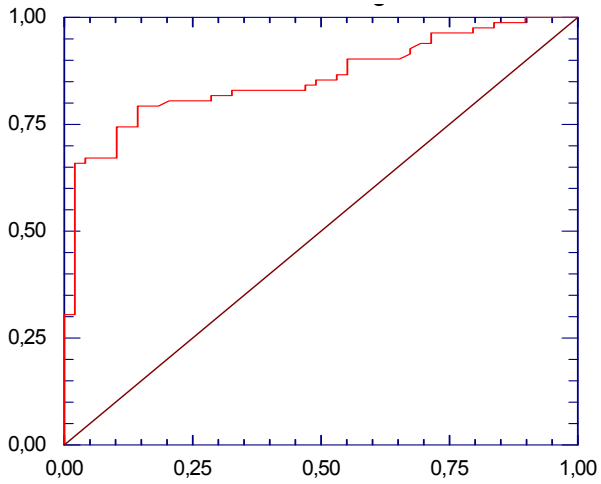


**Figure 6.** ROC curve for BAP in highturnover bone uremic disease.

There was also an excellent correlation between BAP and PTH values, in cases with high turnover status, correlation factor 0.7631, R2 = 0.432, p<0.002.[21-23]

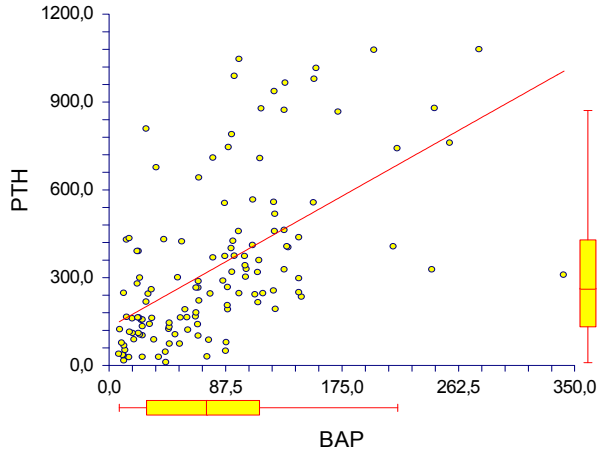


**Figure 7.** Linear regresion: BAP versus iPTH in cases with HPTH II.

For adynamic bone disease, the observed value was 20 µg/l, associated with very high specificity of 99.08%, but with a low sensitivity, of 33.36%. Despite

the decrease sensitivity, the diagnostic power is good, with an AUC=0.83139, SE=0.0039. (Fig. 8)

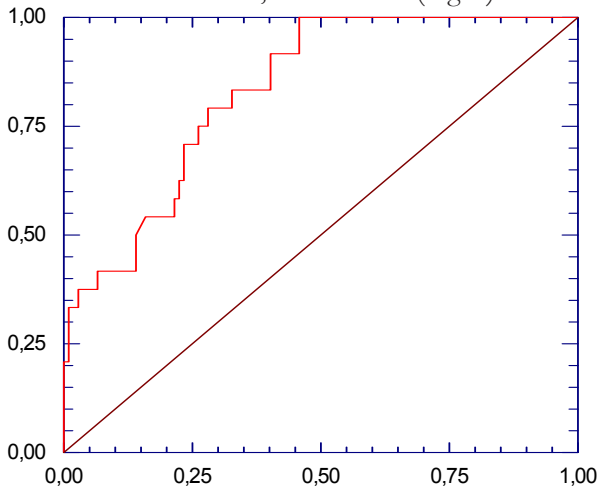


**Figure 8.** ROC curve BAP in diagnostic of low turnover status.

With this ROC technique we analyzed the best BAP value characterizing low turnover status.

**Table 5.** BAP cuttoff value for low turnover.

| Value | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| 29,70 µg/l | 0,54167 | 0,4583 | 0,18692 | 0,81308 |
| 30,80 µg/l | 0,54167 | 0,4583 | 0,19626 | 0,80374 |
| 32,10 µg/l | 0,54167 | 0,4583 | 0,20561 | 0,79439 |
| 32,50 µg/l | 0,54167 | 0,4583 | 0,21495 | 0,78505 |
| **34,00 µg/l** | **0,8083** | **0,94402** | **0,21495** | **0,78505** |

When we analyzed the information given by other clinical or biochemical parameter, we observed different diagnostic power for each of them, analyzed separately. (Table 6)

We did not define any threshold value for age, BMI, length of disease or of haemodialysis treatment.

**Table 6.** Diagnostic power of different parameters – high turnover status.

| Parameter | AUC | SD | Diagnostic values |
|---|---|---|---|
| **Age (years)** | 0.608 | 0.048 | Weak |
| **BMI (kg/msc)** | 0.505 | 0.045 | Weak |
| **HD lenght (month)** | 0.371 | 0.040 | Very weak |
| **Eficacy HD** | 0.602 | 0.058 | Weak |
| **25HO vit D** | 0.646 | 0.1166 | Fair |
| **OS** | 0.3206 | 0.085 | Very weak |

We did not find any significant impact of the clinical parameters on the diagnostic of the type of renal osteopathy. The only observed phenomenon, without any statistical significance, is that the old the patient, the longer the hemodialysis treatment, the more probable is the presence of high turnover status.

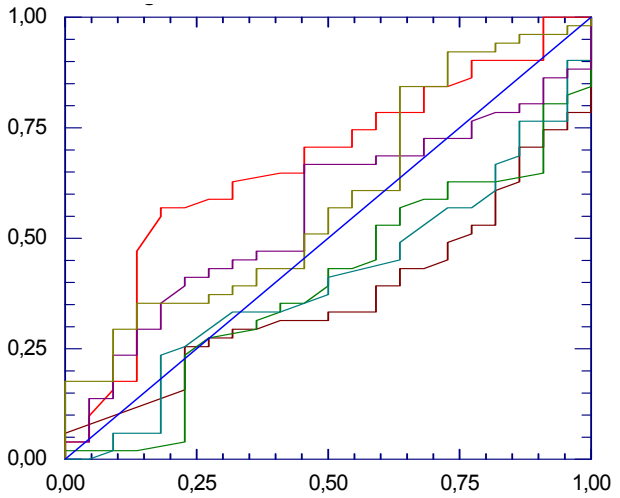


**Figure 9.** Diagnostic value of clinical and biochemial parameters in fibrocystic osteitis.

Despite the lower diagnostic value, we have identified the best threshold value for each of them in diagnostic of high turnover cases. (Table 7)

**Table 7.** OS, 25-HO-vitamin D and K values for identifiyng high turnover status.

| Cutoff val. | Sensib. | Specif. | PPV | NPV | Cost/benefit |
|---|---|---|---|---|---|
| **K > 1** | 0.5263 | 0.3704 | 0.6289 | 0.5650 | 0.1371 |
| **K = 1.08** | 0.5928 | 0.5501 | 0.6956 | 0.6146 | 0.312 |
| **OS > 13.7** | 0.643 | 0.6735 | 0.7682 | 0.762 | 0.445 |
| **OS = 11.8** | **0.682** | **0.6531** | **0.76712** | **0.76102** | **0.4685** |
| **25HOD < 15** | 0.3783 | 0.80 | 0.832 | 0.342 | 0.1728 |
| **25HOD < 20** | 0.6486 | 0.633 | 0.813 | 0.422 | 0.286 |
| **25HOD < 30** | 0.824 | 0.233 | 0.726 | 0.350 | 0.449 |
| **25HOD = 18.4** | **0.626** | **0.733** | **0.718** | **0.342** | **0.452** |

For low turnover status, the shorter the hemodialysis period, the greater the probability of adynamic bone disease. (Table 8) OS and vitamin D have a better discriminative value in these patients. (Fig.10)

The presence of a decreased osteocalcin value identifies 68.18% of the positive cases, only 13.85% of normal bone turnover situations being identified as low turnover (PPV=0.517, NPV=0.9313). Because of the high NPP of 0.9313, a normal vitamin D value makes the presence of adynamic bone disease very improbable.

**Table 8.** Diagnostic power of different parameters – low turnover status.

| Parameter | AUC | SD | Diagnostic value |
|---|---|---|---|
| **Age (year)** | 0.5246 | 0.08701 | Very weak |
| **BIM (kg/msc)** | 0.4087 | 0.0964 | Very weak |
| **Lenght of treatment (month)** | 0.6944 | 0.0890 | Good |
| **K** | 0.3582 | 0.0988 | Very weak |
| **25HO vit D** | 0.41169 | 0.0175 | Weak |
| **OS** | 0.75355 | 0.047 | Very good |

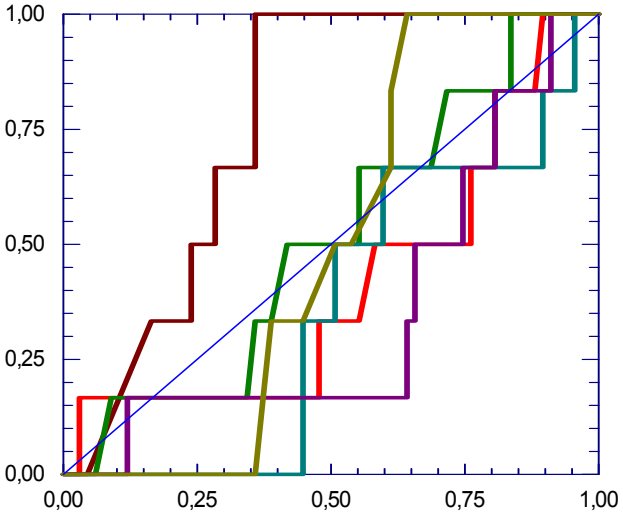


**Figure 10.** Diagnostic value of clinical and biochemial parameters in low turnover osteopathia

The information obtained by the measurement of Vitamin D was different, according to the used set point.

| | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|
| Moderate (<30 pg/ml) | 81.81% | 19.35% | 0.107 | 0.172 |
| Severe (< 20 pg/ml) | 36.36% | 40.86% | 0.067 | 0.758 |

Imagistic methods have variable impact in diagnosing the type of bone turnover. (Table 9) Radiological changes appear late in the evolution of renal osteopathia.[24,25] Bone demineralization is not characteristic on normal X-rays, but osteodensitometric measurements reveal bone loss more rapid. The presence of parathyroid adenoma suggests the diagnostic.[26]

Positive ultrasound was observed in 74 (91.3%) of the 81 cases with secondary hyperparathyroidism, 38 of them (51.31% of positive ultrasound cases, 46.9% of HPTH II cases) having a volume more than 0.5 cm3.[27] We used this recommended value for diagnosing secondary hyperparathyroidism.[27]

After evaluating the diagnostic utility of each parameter by itself, we start to look for the effect of combined information. First, we selected the best threshold values, for diagnostic of high or low turnover. (Table 10) Then we selected only the parameters that had a minimum level of good on ROC diagnostic curve evaluation.

**Table 9.** Imagistic test in the diagnostic of secondary hyperparathyroidism.

| Method | Incidence (%) | Sensit. | Specif. | PPV | NPV |
|---|---|---|---|---|---|
| **Osteitis** | 48 | 41.2 | 92.98 | 0.437 | 0.791 |
| **Calcifications p.m** | 22.9 | 8.47 | 65.27 | 0.166 | 0.465 |
| **Calcifictions v.** | 13.7 | 20.77 | 55.31 | 0.275 | 0.460 |
| **DXA spine** | 71.7 | 78.31 | 39.58 | 0.69 | 0.513 |
| **DXA hip** | 67.9 | 77.77 | 48.1 | 0.707 | 0.574 |
| **DXA femural neck** | 69.4 | 79.7 | 44.11 | 0.692 | -0.55 |

**Table 10.** Cuttoff values for each parameter.

| Parameter | Recommended threshold value | Optimum threshold value |
|---|---|---|
| **Turnover ↑↑↑ iPTH (pg/ml)** | > 200 | 214 |
| **BAP (µg/l)** | > 20 | 76,4 |
| **25(OH)D (ng/ml)** | < 30 | 18,4 |
| **Turnover ↓↓ iPTH (pg/ml)** | < 80 | < 122 |
| **BAP (µg/l)** | < 13 | < 34 |
| **OS (ng/l)** | < 3.0 | < 3.1 |

In our study, the combination allows a positive diagnostic in 97.14 of 100 cases, and 97.8 cases without disease are classified as healthy. The use of vitamin D measurement increases the sensitivity up to 98%, with a slight decrease of the specificity (because diagnosing of mixed cases). Introducing the 4th parameter, respectively ultrasound, the specificity will increase to 100%. (Fig. 11)

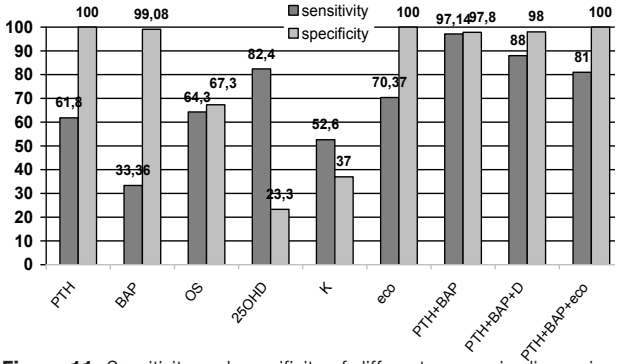


**Figure 11.** Sensitivity and specificity of different assays in diagnosing high turnover status (secondary hyperparathyroidism).

We used the same approach for the diagnostic of low turnover status. (Fig. 12)

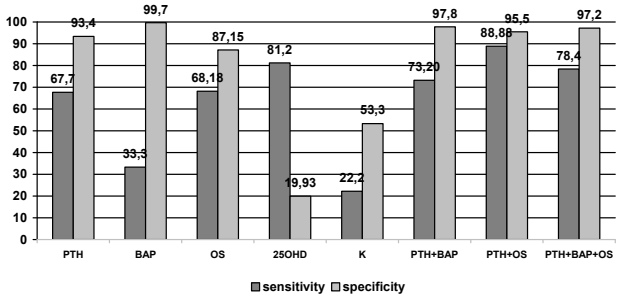


**Figure 12.** Sensitivity and specificity of different assays in diagnosing low turnover status (adynamic bone disease).

## DISCUSIONS

At the beginning of the survey, total alkaline phosphatase was the mostly used marker in evaluation of the renal osteopathy. TAP values in the upper quartile should alert the physician in respect to the presence of bone disease.[10] In our study, we found a relatively low diagnostic importance in identifying increased bone turnover (AUC=0.559 ± 0.059), with a low sensitivity of 58.53% but a better specificity (75.67%) for TAP values higher than 220 U/L.

The sensitivity of 98.78% and the high specificity (of 100%) is similar with the data from the literature.[6] The specificity was so high because there were no cases with increased PTH values and decreased BAP, or OS, or radiographic aspects of osteomalacia. In the daily practice, the presence of high PTH with decreased bone turnover markers dictates attention and active surveillance of the cases before defining the type of bone turnover.

The PTH threshold value in diagnosing high turnover is a matter of controversy: some authors consider a positive diagnostic in the presence of iPTH over 400 pg/mL, but active treatment is indicated in cases with PTH over 300 pg/mL.[1,5,8,17,18] Too high set points are associated with a 100% specificity, but a lot of cases are undiagnosed because a lower sensitivity.[6] Values over 200 pg/mL are associated with a good balance between sensitivity (80%) and specificity (92%).[19]

The same approach was used for bone markers: bone specific alkaline phosphatase (BAP), and osteocalcin (OS). BAP is considered the most sensitive test for direct measurement of bone remodeling, in cases with ESRD.[17] Increased values, with or without increased PTH, suggest high turnover, associated with normal or decreased PTH values, when adynamic bone disease is present.[9,17,19]

We observed an excellent correlation between BAP and PTH values, in cases with high turnover status, correlation factor 0.7631, $R^2 = 0.432$, $p < 0.002$.[21-23]

The quality of decreased BAP values in identifying low bone turnover is certified, at the same cutoff point.[2,19] For positive diagnostic of low turnover, a value less than 13 μg/l is more sensitive. In our study, such values are associated with a sensitivity of 33.0% and a specificity of 99.05%.

The information obtained from the vitamin D status evaluation is very different when we consider different levels of deficiency: mild: 50-30 ng/mL, moderate: 20-30 ng/mL, or severe <20 ng/mL.[28,29] The more severe the nutritional deficit of vitamin D, the more the stimulation of parathyroid, respectively increasing bone turnover.[30,31]

Associated evaluation of iPTH and BAP is the best way to identify high turnover cases.[22] This combination increase the sensitivity and the specificity, and permits to define cases with secondary hyperparathyroidism for iPTH values more than 200 pg/mL as compared with 400 pg/mL, when iPTH is used alone.[5,21,23]

The literature defines the best combination: decreased iPTH levels, decreased BAP and or OS levels.[20,26] In our study, the sensitivity of decrease BAP is relatively low : <10 μg/l - 12.5%, 13 μg/l - 33.3%. The association of „apparent normal PTH values" increases the sensibility up to 73.2%, while the association of low OS values determines an increase of the specificity by the sensitivity (99.7% versus 97.8%). Although OS is not currently recommended in the evaluation of ESRD, combined use of OS and PTH information identified 88.8% from the low turnover cases.[5]

## CONCLUSIONS

- The evaluation of turnover type in the majority of ESRD patients, can be done by means of noninvasive assays; the usual clinical, biochemical and radiological data do not bring many information in respect to the turnover type;
- Upper quartile or increased TAP values can suggest an increased bone turnover; normal or decreased TAP values do not exclude fibrocystic osteitis;
- Using only iPTH values for positive diagnostic of secondary hyperparathyroidism, the cutoff value is 400 pg/mL, respectively 80 pg/mL, for low turnover;
- Associating stepwise different diagnostic methods increases the sensitivity (up to 97.8%) and the specificity (up to 97.8%);
- The same algorithm permits the use of better cutoff values: 200 pg/mL or 100 pg/mL for iPTH with an increase in diagnostic specificity;
- The measurement of 25-(OH)-vitamin D is essential in therapeutical approach;

- Demographic data do not help much in the discriminative diagnostic;

- In general, a treatment length less than 18 months associates more frequent adynamic bone disease;

- The best associations are:

- For high turnover: iPTH + BAP or iPTH + BAP + 25HO-D + ultrasound;

- For low turnover: iPTH + OS + BAP;

- We identified the threshold values valid for the ESRD population from our region, Banat:

- Increased turnover: iPTH> 214 pg/ml, BAP >76.3 μg/L;

- Decreased turnover: iPTH <122 pg/ml, BAP <34 μg/L, OS <3.1.

## REFERENCES


1. Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, American Journal of Kidney Diseases, October 2006.
2. Ferreira M: Diagnosis of renal osteodystrophy: When and how to use biochemical markers and non-invasive methods: When bone biopsy is needed. Nephrol Dial Transplant 15:S8-S14, 2000.
3. Malluche HH, Langub MC, Monier-Faugere MC: The role of bone biopsy in clinical practice and research. Kidney Int. 1999;73:20-25.
4. Lorenzo V, Torres A, Hernandez D, Rodriquez J, Gonzales – Posada JM, Losada M. Estudio con biopsia osea sin decalcifar de la incidencia y fomas de presentation de la ostedistrifia renal. Med Clin. 1991;96:561-65.
5. Faugere MC, Qi OL, Geng ZP, Malluche HH: What serum levels of parathyroid hormone discriminate between high vs normal or low bone turnover in dialyzed patients? J Am Soc Nephrol. 1994;5:878-86.
6. Llach F, Bover J: Renal osteodystrophies în Brenner BM: Brenner and Rector's The Kidney, W B Saunders Company, 2000.
7. Wang M, Hercz G, Sherrard DJ, et al. Relationship between intact 1-84 parahtyroidhormone and bone histomorphometric parameters in dialysis patients without aluminium toxicity. Am J Kidney Dis. 1995:26:836-44.
8. Torres A, Lorenzo V, Hernandez D, et al: Bone disease in predialysis, hemodialysis and CAPD patients: Evidence of a better bone response to PTH. Kidney Int. 1995;47:1434-42.
9. Fletcher S, Jones RG, Rayner HC, et al. Assesment of renal osteodystrophy in dialysis patients: use of bone alkaline phosphatase, bone mineral density and parathyroid ultrasound in comparision with bone histology. Nephron, 1997:75:412-9.
10. Schmidt-Gayk HE, Roth HJ, Bregulla A, et al. Classical serum biochemistry and new biochemical markers. In The Spectrum of renal ostedystrophy, Drueke TB and Salusky I, Oxford Press 2nd Ed. 2002.
11. Coen G, Mantella D, Manni M, et al. 25-HO vitamin D levels and bone histomorphometry in hemodialysis renal osteodystrophy, Kidney Int. 2005;68:1840-8.
12. Bardin T, Laredo JD: Les complication osteo-articulaires de l'hémodialyse. Rev Im Med. 1991;3:223-30.
13. Reichel H,Deibert B, Schmidt-Gayk H, et al. Calcium metabolism in early chronic renal failure: implications for the pathogenesis of hyperparathyroidism. Nephrol Dial Transplant. 1991;6:191-9.
14. Minisola S, Pacitti MT, Romagnoli E, et al. Clinical validation of a new immunoradiometric assay for human osteoclacin. Calcify Tissue Int.1999;64:365-9.
15. Goodman WG, Ramirez JA, Belin TR, et al. Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. Kidney Int. 1994;46:1160-6.
16. Reichel H, Esser A, Roth HJ, at al. Influence of PTH assay methodology on differential diagnosis of renal bine disease. Nephrol Dial Transplant 2003;18:759-68.
17. Wang M, Hercz G, Sherrard DJ, et al. Relationship between intact 1-84 parahtyroidhormone and bone histomorphometric parameters in dialysis patients without aluminium toxicity. Am J Kidney Dis. 1995;26:836-44.
18. Faugere MC, Qi OL, Geng ZP, et al: What serum levels of parathyroid hormone discriminate between high vs normal or low bone turnover in dialyzed patients? J Am Soc Nephrol.1994;5:878-86.
19. Urena P, Hruby M, Ferreira A, et al. Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. J Am Soc Nephrol.1996;7:506-12.
20. Coutteney M, D'Haese PC, Hoof VO, et al. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in hemodialysis patients. Nephrol Dial Transplant 1996;11:1065-72.
21. Wang M, Hercz G, Sherrard DJ, et al. Relationship between intact 1-84 parahtyroidhormone and bone histomorphometric parameters in dialysis patients without aluminium toxicity. Am J Kidney Dis 1995;26:836-44.
22. Qi Q, Monier-Faugere MC, Geng Z, et al. Predictive value of serum parathormone levels for bone turnover in patients on chronic maintenance dialysis. Am J Kidney Dis. 1995;26:622-31.
23. Garnero P, Delmas PD. Assesment of the serum levels of bone alkaline phosphatase with a new imunoradiometric assay in patients with metabolic bone disease. JCEM 1993; 77:1046-53.
24. Duda RI, O'Brien JF, Katzmann JA, et al. Cocurrent assays of circulating bone Gla protein and bone alkaline phosphatase: effect of sex, age and metabolic disease. JCEM 1988;66:1957-62.
25. Kosowicz J, Bolko P, Swiderki A. Results of bone scintigraphy, densitometry and radiography in secondary hyperparathyroidism in patient with renal failure. Pol Arch Med Wewn 2003;109:125-35.
26. Kauppila LI, Polak JF, Cupples LA et al. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis.1997;132:245–50.
27. Fukagawa M, Kitaoka M, Tominaga Y, et al. Imaging and intervention of parathyroid hyperplasia. In The spectrum of renal osteodystrophy, Druecke T and Salusky I, , Oxford University Press, 2nd Ed. 2002, p. 422-38.
28. Fugakawa M, Kitaoka M, Kurokawa K. Value of parathyroid sonography in secondary hyperparathyroidism. Nephrol Dial Transplant.1997;12:2461.
29. Hutchinson AJ, Whitehouse RW, Boulton HF. Correlation of bone histology with parathyroid hormone, vitamin D3 and radiology in end stage renal disease. Kidney Int.1993;44:1071-7.
30. Ghazali A, Fardellone P, Pruna A, et al. Is low plasma 25(HO)vitamin D a major risk factor for hyperparathyroidism independent of calcitriol? Kidney Int. 1999;55:2169-77.
31. Fournier A, Fardellone P, Archard JM, et a;. Importance of vitamin D in uremia, Nephrol Dial Transplant.1999;14:819-23.