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BONE CHANGES IN ADULT PATIENTS WITH CHRONIC KIDNEY DISEASE

Abstract of the doctoral dissertation

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CONTENTS OF THE DISSERTATION

Keywords: chronic kidney disease (CKD), mineral and bone disorders in chronic kidney disease (CKD- MBD), bone, parathormone (PTH), fracture, bone pain, dialysis.

1. INTRODUCTION

Prevalence of chronic kidney disease (CKD, defined as a decrease of glomerular filtration rate below 60ml/min/1.73m^2 or the presence of albuminuria, other morphological changes or persistent urinary sediment abnormalities for more than 3 months) is 10% in the USA and 7-10% in Romania. About 1% of these patients are in advanced stages of CKD (eGFR <45ml/min/ 1.73 m^2), when its complications also occur. Of these complications, CKD –mineral and bone disorder is an important cause of discomfort for CKD patients - from "mere" pain to fractures, thus lowering the quality of life of these patients.

2. OBJECTIVES OF THE STUDY

1. Establishing correlations between bone pain, biological parameters (serum calcium, phosphate, magnesium, alkaline phosphatase), radiological signs and histological lesions in chronic kidney disease.
2. Analysis of the peculiarities of fractures occurring in CKD patients.
3. Indications and value of parathyroidectomy in the treatment of CKD - mineral and bone disorder.

3. MATERIALS AND METHODS

Study groups were:

A. 52 patients with CKD not on dialysis who experienced bone pain

B. 116 dialysis patients:

1. 40 patients who had radiological bone lesions;
2. 60 patients who had fractures;
3. 16 patients with aseptic necrosis of the femoral head and 5 patients with Garden III and IV femoral neck fractures who had surgery for arthroplasty; a histomorphometric study has been performed on the resulting bone fragments.

C. Another group of dialysis patients who had parathyroidectomy.

Patients were cared for in the Clinic of Orthopaedics and Traumatology of the Constanţa County Hospital (A, B) and the Department of Nephrological Intensive Care of the "Doctor Carol Davila" Clinical Hospital of Bucharest (C).

The study patients were evaluated for:

- the existence and location of pain (diffuse or localized - in the hand, spine, pelvis, thorax, upper limb, lower limb);
- biochemical parameters (to determine whether there is a correlation between their values and the existence of pain): serum calcium, phosphate, magnesium, alkaline phosphatase; serum PTH dosing was possible only in patients who underwent parathyroidectomy;
- The existence of radiological manifestations, their type (subperiosteal erosions, Looser-Milkman fissures, radiolucency; radioopacity.) and their location.
- Dialysis vintage and eventually the primary renal disease were recorded.

I attempted to establish correlations between these parameters.

Reference values of biochemical parameters (Constanta County Emergency Hospital):

- - Serum calcium: 8.5-10.5mg/dL;
- - Serum phosphorus: 2.5 - 5.0 mg/dL
- - Serum magnesium: 1.8 - 2,3mg/dL
- - Alkaline phosphatase: 1.5- 4.0 UB (Bodansky units, to convert to IU multiply by 5.4)

Statistical analysis was performed using EpiInfo 6.04d (Centers for Diseases Control and Prevention, Atlanta, GA, USA) and SPSS v20 (IBM Corporation, New York, NY, USA) statistical software packages.

Further details can be found in the analysis of each group of patients.

4. RESULTS

4.1. Study of a group of pre-dialysis patients who had bone pain

There were 52 patients with pre-dialysis CKD who had bone pain.

Bone pain

We paid special attention to patients with bone pain as pain is the main (and first) symptom suggesting bone damage in patients with CKD.

These take various aspects in patients with predialysis CKD. Most commonly pain is diffuse, without precise location; may be associated with localized pain in the spine, hands, pelvis, ribs or scapula. When localized pain corresponds to Looser zones on radiographs, the diagnostic value of pain increases, making us think about low turn-over bone disease. Osteitis fibrosa cystica suggests high turnover bone disease. But the type of bone involvement can only be established by bone biopsy and histomorphometric examination.

Data analysis shows:

- diffuse pain in 33 (67.3%) patients which are:
  - associated with pain localized to the hand in 13 patients;
  - associated with pain in the spine in 6 patients;
  - associated with pelvic pain in 5 patients;
  - associated with pain in the lower limb in 4 patients;
  - associated with pain in the upper limb in 4 patients.
- diffuse pain associated with pain localized to two regions in 17 patients (spine or hand and hand and chest);
- localized pain associated: spine and other sites in 13 patients, in 3 patients hand and other locations, and hand and spine in 2 patients;
- localized pain, isolated in 5 patients (9.6%).

Table I. Values of biochemical parameters in the study group

No of patients (%)	Biochemical parameters			
	Serum calcium	Serum phosphorus	Serum magnesium	Alkaline phosphatase
Decreased	9 (17.3%)	4 (7.7%)	0 (0.0%)	0 (0%)
Normal	33 (67.3%)	10 (19.2%)	25 (48.1%)	6 (11.5%)
Increased	10 (19.2%)	38 (73,1%)	27 (51.9%)	46 (88.5%)

There is a significant proportion of patients with abnormal serum calcium (32.7%), phosphorus (80.2%), magnesium (51.9%) and alkaline phosphatase (88.5%). Only 2 patients had simultaneously serum calcium, phosphorus and alkaline phosphatase within normal limits!

Correlation between serum calcium and phosphorus values

Of the 33 patients with normal serum calcium, 20 had hyperphosphatemia.
Of the 10 patients with hypercalcemia, 8 had hiperfosforemie.
Of the 9 patients with hypocalcemia, 7 showed hyperphosphatemia.

Discussions

Biochemical parameters values are more difficult to interpret in the absence of PTH (and of a bone histomorphometric examination).

From the clinical experience:

- elevated alkaline phosphatase suggests high turnover bone disease – i.e. secondary hyperparathyroidism, rarely mixed lesions;
- normocalcemia and hyperphosphoremia suggest either low glomerular filtration rate or vitamin D therapy without phosphate binders association or insufficient dose;
- hyperphosphoremia and hypercalcemia suggest treatment with vitamin D without the addition of phosphate binders or an insufficient dose;
- appearance of hypocalcemia with hypermagnesemia suggests the absence of treatment with vitamin D or phosphate binders; or insufficient doses.

So the values of biological parameters are important for the management of the treatment.

Correlation of bone pain with radiological signs

Analyzing the correlation between the presence of bone pain and radiological signs we found that 31 (59.6%) of the 52 patients with bone pain had radiological signs such as:

- subperiosteal erosions of the phalanges - 11 patients;
- subchondral resorption on sacroiliac joints and the symphysis pubica - 0 patients;
- radiopacity with "rugger jersey"- like vertebrae - 4 patients (usually characteristic lesions of hyperparathyroidism)
- Looser zones (on pubic branches, pubis body, ribs, scapula) - in 6 patients (suggestive of osteomalacia);
- increased skeletal radiolucency - 21 patients.
- increased skeletal radiolucency is associated frequently with either subperiosteal erosions of the phalanges - 7 patients; or Looser zones - 5 patients and is isolated in 9 patients.

Correlation between biochemical parameters and existence of radiological manifestations.

It is statistically significant only for phosphorus (chi^2=19.54; p=0.0005) and non-significant for serum calcium (chi^2=0.57; p=0.75), magnesium or of alkalime phosphatase. (chi^2=1.39; p=0.23)

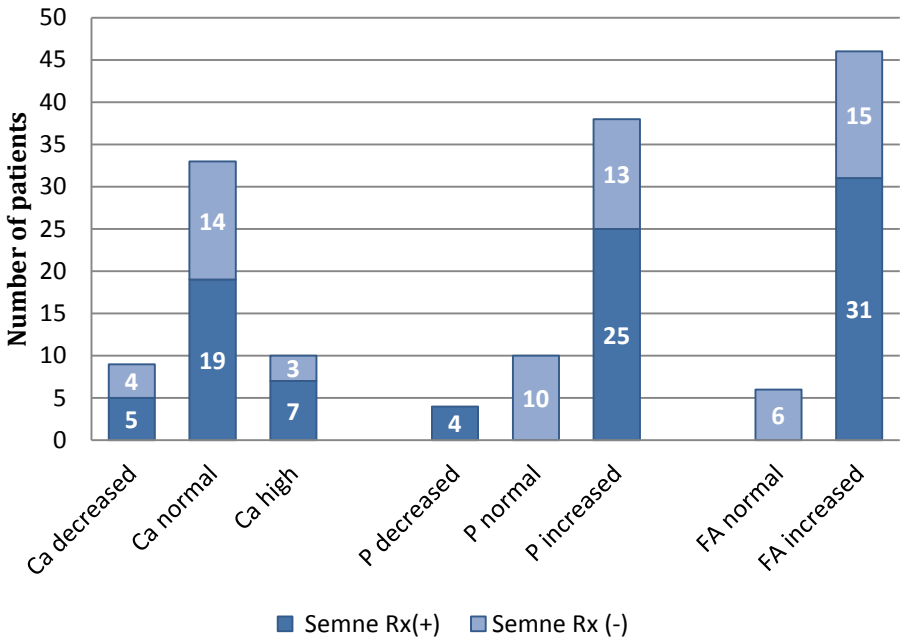

Figure 1. Correlation between the values of biochemical parameters and radiological lesions in adult patients with CKD in predialysis and bone pain.

General discussions

Data analysis summarized in one of the tables shows that diffuse pain is usually associated with localized pain, especially in hands and spine, followed by the association of diffuse pain with pain localized to two regions (hands and spine).

There are frequent cases of associations of spinal pain with other sites of pain.

Rarely are reported only diffuse, isolated bone pain (9.6%).

Only 31 patients of the 52 with bone pain had radiological signs.

Six of them had Looser zones. They could be labeled as having bone disease with low turn-over; however, they had an elevated alkaline phosphatase.

The other patients had radiological and biological aspect of high turnover bone disease (secondary hyperparathyroidism).

Patients with osteitis fibrosa had increased alkaline phosphatase, hiperphosphoremia and hypermagnesiemia, serum calcium was normal or slightly low. Those with radiological signs of low turnover (adynamic) bone disease had serum phosphorus and calcium within the normal range, magnesiemia slightly increased, and increased alkaline phosphatase (though it is classically accompanied by low levels of alkaline phosphatase).

We found a relative correlation between radiological signs and values of biological parameters. Location of pain corresponds to Looser zones on radiographs and their presence is accompanied by pain in that location.

Interpretation of biochemical parameters but must be done carefully, even in conditions that are known to the treatment of bone damage in chronic kidney disease and affect these parameters. Both biochemical parameters and radiological signs may suggest the type of bone histological lesions, but they do not correlate exactly.

4.2. Study of dialysis patients with chronic kidney disease (CKD) with radiological signs

Forty dialysis patients with radiological signs were included in the study.

Bone changes observed at the patients studied:

- increased skeletal radiolucency: 28 patients
- subperiosteal resorption (hand): 21 patients
- Looser zones 13 patients
- radiopacity of spine: 7 patients

These signs may be isolated or associated:

- radiolucency associated with subperiosteal erosions, hand: 11 patients
- radiolucency associated with Looser zones: 7 patients
- radiopacity associated with subperiostal erosions, hand: 4 patients
- Looser zones associated with subperiosteal erosions, hand: 4 patients

Duration of dialysis:

- 4-5 years: 10 patients
- 6-7 years: 25 patients
- > 8 years: 5 patients

Associated lesions are more common in patients with dialysis vintage more than six years , the most frequent association being subperiosteal resorption with increased radiolucency radiolucent skeletal skeleton followed by increased association with Looser zones.

Patients whose dialysis vintage is 4-5 years show mostly signs of radiolucencies.

Radioopacity was observed mainly in patients with a duration of dialysis over 7 years.

Characteristics of bone pain in dialysis patients with radiological bone changes

35 (87.5%) of the 40 patients accused bone pain.

In the 35 patients who complained of bone pain anamnesis revealed:

- Unorganized, diffuse pain: 21 patients (52.5%)
- Spinal pain: 23 patients (57.5%)
- Hand pain: 18 patients (45.0%)
- Pelvic pain: 14 patients (35.0%)
- Chest pain: 4 patients (10.0%)
- Upper limb pain: 2 patients (5.0%)
- Pain in the lower limb: 5 patients (12.5%)

Diffuse pain is most often associated with localized pain:

- to a region: 18 patients (45.0%)
- two regions: 17 patients (42.5%)
- 3 regions: 5 patients (12.5%)

Regarding pain location and radiologic appearance one can note:

- Looser zones occur with localized pain corresponding to the fissure localization, the pain is frequently associated with diffuse pain or spinal pain;
- radiological signs at hand are accompanied by pain at this level; but they are frequently associated with diffuse pain or localized pain, especially in the spine.

The values of the biological parameters in dialysis patients with radiological signs

- calcemia:	- increased> 10.5 mg/dl	24 patients (60.0%)
	- low <8.5 mg/dl	1 patient (2.5%)
	- normal 8.5 to 10.5 mg/dl	15 patients (37.5%)
- phosphoremia:	- normal 2.5-4.5 mg/dl	2 patients (5.0%)
	- increased> 4.5 mg / dl	32pacienţi (80.0%)
	-low <2.5 mg/dl	6 patients (15.0%)
- Magnesiemia:	- normal 1.8 to 2.3 mg/dl	31 patients (77.5%)
	- increased> 2.3 mg/dl	9 patients (22.5%)
	- low <1.8 mg/dl	0 patients (0.0%)
- Alkaline phosphatase	- normal 1.5 to 4 UB	8 patients (20.0%)
	- increased> 4 UB	32 patients (80.0%)
	- low <1.5 UB	0 patients (0.0%)

Radiologic signs

Looser zones are described in 13 patients, but the biological values are appropriate (low) corresponding to low turnover bone disease in 6 patients, namely: low phosphoremia, normal or slightly increased alkaline phosphatase, normal serum calcium which suggest that they are patients with osteomalacia. Of the 13 patients with Looser zones, 7 patients had normal or high serum calcium, hiperphosphoremia and increased alkaline phosphatase, which advocates for secondary hyperparathyroidism; without OSAS biopsy can not differentiate between adynamic bone disease and osteomalacia (which adds delayed mineralization and decreased bone turnover).

Discussions

Data analysis suggest that:
- 6 patients meet the criteria for low turnover bone disease with: Looser-Milkman cracks, normal serum calcium, low phosphorus, normal or slightly elevated alkaline phosphatase, localized pain corresponding to cracks identified on radiographs.
- 7 patients with Looser zones radiologically, increased phosphoremia, normal or slightly elevated serum calcium, increased alkaline phosphatase, diffuse or localised pain at hand or spine which may suggest a mixed bone disorder; it stresses the need for bone biopsies;
- 27 patients had secondary hyperparathyroidism with normal calcium, increased phosphoremia and alkaline phosphatase, diffuse or localized bone pain in the hand or spine and radiological subperiosteal erosions in the phalanges of the hand, and increased skeletal radiolucencies less radiopacity ("rugger jersey" of spine).

For diagnostic classification one should take into account the following criteria:

- Safety features: histological lesions characteristic for osteitis fibrosa/ osteomalacia
- Major criteria: 1. Radiological [4]
  a. Looser zones advocates for low bone turnover
  b.” rugger jersey” vertebrar
  c. subperiosteal erosions advocates for secondary hyperparathyroidism
  2.Biological a. alkaline phosphatase
  b. phosphoremia
- Minor criteria
- location of pain
- increased skeletal radiolucency
- serum calcium

Subperiosteal resorption and radiolucency are the radiological signs most commonly seen in patients on dialysis. These signs are associated in most patients and are appearing 4-5 years after the start of dialysis; have a maximum of frequency at 6 to-7 years after the start of dialysis.

In terms of pain, the most common are unorganized, diffuse pain, followed by pain localized to hand and spine and then pelvic pain.

Note that localized pain in the spine does not always correspond to typical radiological signs, "the sandwich vertebra," which makes us believe that they may be caused by other diseases (spondylosis). Also, we can interpret that we need more severe skeletal involvement in order to have proper radiological signs, which emphasizes the value of pain as a sign of bone damage even without radiological expression.

When pain is localized and corresponds with radiological signs of histologic lesions:

- localized pain and Looser zones may suggest adynamic bone disease;
- localized pain in the hand associated with subperiosteal erosion signs would indicate osteitis fibrosa lesions;
- spinal pain with radiologic appearance of "the sandwich vertebrae" advocates fibrous osteitis;
- increased alkaline phosphatase and hiperphosphoremia would advocate for secondary hyperparathyroidism.

The intuition of the existence of bone histological lesions with increased / decreased turnover cannot be based on a single criterion, the combination of at least three major and one minor criteria allows formulating an opinion.

The final diagnosis is given by the histological examination performed on biopsy specimen from the iliac crest or bone pieces collected at arthroplasty surgery (but late).

Pathophysiology of bone manifestations in adult patients with CKD is complex. Bone lesions develop slowly and are often quiet, especially before dialysis. Bone pain and altered biological parameters can offer an indication of installation / existence of bone lesions in these patients. Based on this information we conducted our research in order to determine the value of each parameter in an effort to make as early a diagnosis of bone lesions and consequently to apply appropriate therapeutic measures and find the means by which we can prevent the installation thereof.

The results obtained allow us to rank the importance of clinical signs, laboratory and radiological diagnosis.

They may be categorized such as:

- Certainty diagnostic criteria: histological lesions found on biopsy;
- Major diagnostic criteria;
- Minor diagnostic criteria.

We propose an algorhytm which is both useful and easy to use in practice on how to establish positive and differential diagnosis of skeletal related events in adult patients with CKD, taking into account other clinical situations that may affect bone quality and strength as primitive hyperparathyroidism (as it sometimes causes CKD), acidosis, vitamin D deficiency (primitive or complications of CKD) or osteoporosis.

Table II. Elements for positive and differential diagnosis of bone disease in CKD

Values	**Primitive HPTH**	**Secondary HPTH**	**Low turnover disease**	**Osteoporosis**	**Vitamin D defficiency**	**Phosphate Reabsorbtion defficiency**	**Acidosis**
Ca	↑	N ↑	N	N Scazut ↑	N	N	N ↓t
P	↓	↑	↓	N ↑ ↓	↓	↓	↓t
Alkaline phosphatase	↑	↑	N ↑	N	N ↑	N ↑	↑ N
Looser zones	-	-	+*	-	+ rareori **	-	-
Ssubperiostal lesions	+ -	+ -	-	-	+ -	+ -	+ -
Radiotransparency	+ + -	+ + -	+ + -	+ +	- +	+ -	+ -
Radioopacity	+ -	+ -	-	-	-	-	-
Pain * **	+	+	+ ****	+	+ -	+ -	+ -
Bicarbonate	↓	↓	N ?	N?	N ↓	N ↓	↓
Urinary Ca	↑	↓ N	↓	N?	↓	N ↓	N ↑
PTH	↑	↑	?	?	N	N	N

* - Looser zones are present and pathognomonic

** - Looser zones rarely present, disappear soon after treatment

*** - Diffuse pain or various sites draw attention and require further examination

**** - Diffuse pain associated with localized pain.

4.3 Fractures in dialysis patients.

From 2005 to 2010 were hospitalized and treated 2,100 patients with fractures with different locations, of which 60 dialysis patients (2.85% of all fractures).

The 60 dialysis patients with fractures were analyzed as follows:

- by gender: 36 female patients (60.0%)
  24 male patients (40.0%)
- by age: 20-30 years 4 patients (6.7%)
  30-40 years 14 patients (23.3%)
  40-50 years 16 patients (26.7%)
  > 50 years 26 patients (43.3%)
- after dialysis duration: 1-5 years: 2 patients (3.3%)
  5-10 years: 19 patients (31.7%)
  > 10 years: 39 patients (65.0%)

- after the site of the fracture:	fracture of humerus:	2 patients (3.3%)
	olecranon fractures:	3 patients (5.0%)
	Pouteau-Colles fractures:	22 patients (36.7%)
	femoral neck fractures:	7 patients (11.7%)
	tibial plateau fractures:	4 patients (6.7%)
	tibial shaft fractures:	2 patients (3.3%)
	bimaleolar fractures:	10 patients (16.7%)
	fractures of the calcaneus:	4 patients (6.7%)
	metatarsal V fractures:	6 patients (10.0%)

- after the fracture appearance:			
a) the number of pieces:	2 pieces:	38 patients (63.3%)
	> 2 fragments:	22 patients (36.7%)
b) after fragments displacement:	small displacement:	32 patients (53.3%)
	average displacement:	28 patients (46.7%)
c) after the skin lesions:	closed fracture:	56 patients (93.3%)
	open, type 1:	3 patients (5.0%)
	open, type 2:	1 patient (1.7%)
d) the presence of associated lesions:	no associated injuries:	58 patients (96.7%)
	tendon rupture:	2 patients (3.3%)
- by mode of production:	the fall of the same level:	41 patients (68.3%)
	fall from a different level:	9 patients (15.0%)
	accident:	10 patients (16.7%)
- by time:	the day of dialysis:	12 patients (20.0%)
	Interdialytic period:	48 patients (80.0%)

The choice of treatment was done according to a protocol developed in a complex team: nephrologist, anesthesiologist and orthopedic surgeon. The protocol included:

- cardio-respiratory balance
- biological balance
- balancing measures
- Choice of anesthesia
- Choice of therapeutic method: orthopedic or surgical
- The timing of surgery.

For the choice of therapeutic method (orthopedic or surgical treatment) was taken into account primarily the overall balance and then each fracture appearance.

For patients who required surgical treatment, surgical intervention was performed 30-36 hours following a hemodialysis session.

They chose the less aggressive anesthesia:

- for the upper limb: truncal or locoregional anesthesia
- for the lower limb: locoregional anesthesia, epidural or spinal.

Osteosynthesis technique was chosen based on the type of fracture and the following rules were taken into account:

- to be the least invasive: percutaneous techniques whenever possible
- enable swift postoperative mobilization.

Orthopedic treatment was used whenever possible.

Fractures of the upper limb

1. For **fractures of the humerus** was used:
a) 2-3 nailes introduced percutaneously above the olecranon for diaphyseal fracture
b) open osteosynthesis for comminuted fractures and fixation with screws.
2. for **olecranon fractures** it has been chosen axial screw fixation; wire loop fiation was avoided due to the fear of damage induced by the wire loop passed through a poor quality bone.
3. Pouteau-Colles type fractures using percutaneous nailes in 18 patients.

Fractures of the lower limb

1. **Fractures of the femoral neck** - seven fractures occurred in patients with CKD on dialysis for at least seven years who have fallen from the same level (6 patients); one patient suffered a fatigue fracture. All patients with femoral neck fractures were older than 50 years.

After the type of fracture there were: - Garden type I fractures - 2 patients
- Garden type II fractures - 1 patient
- Garden type III fractures - 3 cases
- Garden type IV fractures - 2 patients

A). For patients with Garden I and II fractures was chosen fixation with 2 or 3 screws applied percutaneously under supplemented locoregional anesthesia, under radiographic control
B) For patients with Garden III and IV fractures treatment consisted of cemented total endoprosthesis implantation. Regardless of patients' age cemented prosthesis was preferred, considering the current status and perspective of worsening of the bone lesions. Total hip endoprosthesis implantation surgery is a risk both intra- and postoperatively requiring special measures concerning monitoring of imbalances that may occur, avoid infection and clotting disorders.Early mobilization is essential, and this is an extra reason for choosing prosthesis cementation.

2. **Tibial plateau fractures** (4 patients) occurred in patients on dialysisfor 4-8 years who accused previous mild or moderate knee bone pain. They accused acute pain and functional impotence of the leg and knee joint swelling. Radiographic examination revealed fractures of the tibial plateau with low or moderate displacement by clogging.

3. **Tibial shaft fractures** (2 patients). Less massive osteosynthesis material was used.

4. **Bimalleolar fractures (10 patients).** The clinical presentation and type of fracture have no particularly compared with fractures that occur on healthy skeleton, but radiologic appearance highlights a changed, fragile skeleton structure. Avoid using solid osteosynthesis material, preferring percutaneous osteosynthesis and when required opening, choose less massive profiles The most frequent complication of these fractures is complex regional pain syndrome of ankle and foot, which is distressing for a long time and is rebellious to treatment.

5. **Calcaneus fractures** (4 patients)
a) patchy fracture of tuberosity - 1 patient
b) fracture with vertical clogging - 2 patients

In all 4 cases percutaneously inserted nailes were used for reduction. These fractures are extensively encumbered by the complex regional pain syndrome.

6. **Fracture of the Vth metatarsal base (6 patients)** - Simple fracture in 5 patients with small displacement and in 1 patient with important dislocation. In this type of fracture we opt for reduction and nail placement allowing an early mobilization and avoids disimpaction of the fracture site.

Discussions

Fractures have an increased incidence in patients on dialysis (13.4%, 60 patients with fractures of the 477 dialysis patients in Constanţa County, according to Romanian Renal Registry Report 2011), compared to the general population (0.38% of 2100 patients with fractures -a total population of 540,448 people over 20 years in Constanta county). Factors that may explain this decrease in bone strength are in the context of bone damage in chronic kidney disease and increased fragility of these patients with reduced mobility.

Fractures in patients with CKD on dialysis may occur in mild or moderate trauma and usually occur after five years of dialysis treatment.

Over 50% of patients have a history of osteoarticular painful bouts of mild to moderate intensity. One chooses the least invasive surgical technique, allowing early mobilization as soon as possible.

Treatment consists in postoperative mobilization, adjuvant treatment.

Consolidation time is 20-30 days longer than in patients not on dialysis. A common complication is complex regional pain syndrome, especially after Pouteau-Colles fractures and fractures of the ankle and foot, followed by fractures of the tibial plateau.

Recovery is more difficult and spans a longer time than “regular” bone fractures.

4.4. Histological study of bone lesions in dialysis patients

We have studied 20 dialysis patients in Constanta County that had implanted cemented total endoprosthesis for aseptic necrosis of the femoral head (15 patients) or femoral neck fractures (5 patients with fractures of Garden type III and IV) . The excised bone segments (head and femoral neck) were prepared for histology. Serum calcium, phosphate, serum alkaline phosphatase magnesium were obtained; PTH dosage was not available at the time of the study. Radiological examination was also performed. Histological examination focused assessment following parameters:

Table no. III. Histomorphometric parameters

Name	Symbol	Normal values
Total trabecular bone volume	VT	21±5
Relative osteoid volume	VO	2,5±1
Osteoid surface	SO	15,6±6
Osteoid thickness (µm)	GO	9,5±0,5
Osteoblastic surfaces / total area	SOb/ST	5,1±3
Osteoblastic area / osteoid area	Sob/SO	30,0±10
Mineralization front	FM	80±10
Mineralization speed	VM	0,64±0,3
Osteoclastic resorbtion area	SROc	0,5±0,05
Number of osteoclasts / mm^2	Osc	0,20±0,09

Osteoid tissue is non-mineralized bone collagen. It is secreted by osteoblasts and after a latency period of two weeks it begins mineralization within the surface. During this process any newly formed bone is boarded by osteoid edges. Osteoid edge thickness (GO) is normally 9.5 ± 0.5 µm, and any value that exceeds this is regarded as abnormal.

Osteoid thickness increases when osteoid mineralization is delayed or slowed. This can be found in renal osteodystrophy, vitamin D deficiency, low calcium / phosphorus ratio, malabsorption. Skeletal manifestations of chronic kidney disease patients not yet on dialysis or on dialysis are expressed by histological lesions:

I. The high turn-over bone disease (fibrous osteitis)
II. Low turn-over bone disease (adynamic bone disease, osteomalacia, bone aluminum deposition)

I. Lesions of fibrous osteitis is manifested by:
1. Hiperresorbţie osteoclastic
a. The increase of% areas covered by osteoclast resorption
b. the increase in the number of osteoclasts per mm2 of section of bone
2. Hiperosteoformarea is manifested by:
a. increasing the volume of osteoid
b. increased osteoid surface
c. increased osteoid thickness
d. increase osteoblastic index

Osteoblastic index represents the percentage of osteoid surface covered by active osteoblasts.
The fibrous osteitis osteoid edges have normal thickness and mineralization fronts are followed by normal percentage and rate of mineralization not significantly different from normal.
Fibrous osteitis occurs within secondary hipeparatiroidismului caused by chronic kidney disease; is present when glomerular filtrate is still 80ml / minute and becomes even more clear when glomerular filtration falls below 50ml / minute.
Patients starting dialysis already have these injuries and stresses they gradually so that histological lesions of hyperparathyroidism is observed in approximately 80-90% of patients who did not preventive treatment; with intensive treatment, however, as an adynamic bone disease. [4]

II. Lesions of osteomalacia are expressed by [3]:
1. hiperosteoid:
a. increased osteoid volume
b. volume increased osteoid surface
2. mineralization defects:
a. increased osteoid thickness edges
b. decrease bone mineralization rate
c. high osteoid surface
d. Low mineralization front

Both Adynamic bone disease and osteomalacia are characterized by decreased bone turnover; the main difference is that in osteomalacia there osteoid mineralization delay its accumulation.
Another type of bone disease Adynamic is represented by the Intoxication aluminum (in the phosphate sequestrants water or dialysis) [8]; diagnosis in this case is put through a special staining bone biopsy.
Osteomalacia can be shown by bone scan showing areas hiperfixaţie appropriate areas microfracture invisible on the radiograph.

Tabel nr. IV. Changes in bone histomorphometry parameters in patients with increased/ reduced turn-over renal bone disease

Name	High turn-over bone disease	Low turn-over bone disease
Total bone volume		
Relative osteoid volume	↑	↑
Osteoi aread	↑	↑
Osteoid thickness (µm)	↑	↑
Osteoid surface/ total surface		
Osteoblast surface/ osteoid surface	N	↑
Mineralization front	N	↓
Mineralization speed	N-↓	↓
Osteoclastic resorbtion surface	↑	↓
Numer of osteoclasts / mm	↑	↓

Analysis table highlights:
- 15 patients with aseptic necrosis of femoral head
- 5 patients with femoral neck fracture and Garden 3, 4
- 9 female patients (45%)
- 11 male patients (55%)

In terms of dialysis vintage:
- 5-6 years in 3 patients (15%)
- 7 years in 5 patients (25%)
- 8 years in 9 patients (45%)
- > 8 years in 4 patients (20%)

For patients with femoral neck fracture dialysis vintage was:
- 8 years in 3 patients (15%)
- > 8 years in 2 patients (10%)

For patients with aseptic necrosis of the femoral head dialysis vintage was:
- 5-7 years in 8 patients (40%)
- 8 years in 7 patients (35%)

Reviews:
It appears that fractures occur mostly in females who have a duration of dialysis for at least eight years. Aseptic necrosis of femoral head is more common in males: 11 males and 4 females, and dialysis duration is 5-7 years in 8 patients, eight years in 7 patients.

Histological study was performed on slides obtained from bone pieces collected during total hip prosthesis implantation, using fragments of the femoral head and neck. Parameters investigated were enrolled in the previous table.

The analysis highlights thevaluaes obtained:
- Total bone volume (VTO) is more than 21-12 patients under 21 in 8 patients
- Relative osteoid volume (VO) is increased in all patients, the values were between 2.5 to 4 regardless of age, diagnosis and duration of dialysis
- Osteoid surface (OS) is increased in all patients being between 16 and 28
- Thickness osteid (GO) is increased in all patients was between 10.1 and 16
- Osteoblast surface / total area (SOB / ST) is increased to 14 patients being between 16 and 17.1 and is normal or slightly decreased in 6 patients being between 5.4 and 3.1
- Surfaces osteoblast / osteoid surfaces (SOB / SO) is normal or slightly increased in 15 patients and is low in 5 patients
- Mineralization front (FM) is normal in 11 patients, decreased in 4 patients and increased in 5 patients
- The rate of mineralization (VM) is normal in 15 patients being between the values 0.59 to 0.65 and very low in 5 patients with the value of 0.12
- Osteoclastic resorption surface (SOR) is normal in 5 patients and increased in 15 patients with value between 0.7 and 1.2
- The number of osteoclasts per mm2 is increased in 15 patients and decreased in 5 patients

Considering qualification criteria for the type of histological lesions - bone marrow fibrosis or osteomalacia analyzed parameter values allow the classification of patients in these types of histological lesions:
- 5 patients with histological evidence of osteomalacia
- 12 with histological lesions of bone marrow fibrosis
- 3 patients with intermediate lesions dominated osteoclastic resorption surfaces covered by osteoclasts in greater numbers than normal

The analysis highlights the value of biochemical parameters:

Serum alkaline phosphatase (AF) is increased in all patients regardless of diagnosis, age and duration of dialysis, which shows that there is bone remodeling regardless of histological type of lesion. [9]
In patients with osteomalacia amount of alkaline phosphatase was between 10 and 19 Bodansky units (BU).
In patients with fibrous osteitis alkaline phosphatase value was between 5 and 11 Bodansky units (BU).
Phosphorus levels are elevated in all patients regardless of histological type of lesions: fibrous osteitis or osteomalacia.
Serum alkaline phosphatase is an indicator of bone reshaping and the question is whether there is a correlation between increased serum alkaline phosphatase and histological type of lesion. It can be argued that increased serum alkaline phosphatase is a bone reshaping - increased bone resorption, but not type specific histologic lesion: fibrous osteitis or osteomalacia.
Increased serum alkaline phosphatase along with hyperphosphataemia turning to the diagnosis of secondary hyperparathyroidism. Alkaline phosphatase increased by hipofosforemie guided by osteomalacia diagnosis. Alkaline phosphatase increased PTH dosing requires better diagnostic orientation.
Increased serum alkaline phosphatase and increased levels of PTH are indicators of secondary hyperparathyroidism.
Also, increased serum alkaline phosphatase in a patient dialysate may be an element that could justify scintigraphy to detect radiological areas are not covered Looser these areas signifying low bone strength of the region, which predisposes to fracture or fatigue after minor trauma .
Also, increased serum alkaline phosphatase is a criterion for exclusion diagnosis of osteoporosis.
Increased serum alkaline phosphatase along with biological samples, scintigraphy, guided therapeutic program of a dialysis patient.
Magnesium levels are normal or slightly elevated in all patients, and normal calcium levels in 15 patients and easy scşăzute (<8.5 mg / dl) in 5 patients, which Appears that there is no correlation between these values and the type of histological lesions.

In four patients there were Looser zones which are pathognomonic for osteomalacia (patients numbers 4,7,8 and10) associated with increased radiotransparency in these patients; they had was femoral neck fracture. In 12 patients there is subperiosteal resorption in hands associated with increased radiolucency of the skeleton increased in 10 patients and associated with radioopacity ("rugger jersey" vertebra) in 4 patients. In these patients the clinical diagnosis was avascular necrosis of the femoral head.

As a working method has been used separate preparation of each table and then overlapping the tables with subsequent findings:
- histological lesions in patients with osteomalacia (numbers 4, 7, 8, 10, 15) overlap those with femoral neck fractures.
- 5 patients with Looser zones overlap those with cervical fractures
- histological lesions of osteomalacia patients overlap with fractures of the femoral neck; the values of lab tests, especially elevated alkaline phosphatase and low phosphorus advocates osteomalacia. It is also noticed that the other 16 patients show overlap between clinical diagnosis and histological lesions of bone marrow fibrosis in 15 patients, 1 patient with femoral neck fracture with corresponding histological lesions of bone marrow fibrosis. Radiological signs advocating for secondary hyperparathyroidism and biological parameter values are non-specific; alkaline phosphatase is elevated, serum phosphorus is normal or slightly increased in 15 patients and in 5 patients is low.

Considering these coincidences we believe that the presence of Looser zones, hiperphosphoremia and increased alkaline phosphatase allow „framing" these patients as suffering from osteomalacia even if we do not have the histological proof of the lesions; while in patients with radiological signs of subperiosteal erosions in hands and "rugger jersey/sandwich" vertebra who have elevated alkaline phosphatase, normal or increased phosphorus may be suspected of secondary hyperparathyroidism. This requires furher investigation (dosing PTH and possibly bone biopsy).

It can be concluded that not in all cases the bone biopsy is needed to clarify the classification of patients as suffering from osteomalacia or secondary hyperparathyroidism.

4.5 Analysis of a cohort of patients with secondary hyper-parathyroidism who required parathyroidectomy

MATERIAL AND METHODS

A cohort study was performed on 238 chronic kidney disease (CKD) stage 5D (dialysis) patients who underwent subtotal parathyroidectomy (PTX) with auto transplantation in a single center, by a single skilled surgeon (Assoc. Prof. Bogdan Stănescu, MD, PhD, „CI Parhon" Institute of Endocrinology), over 11 years (1999-2010). Surgery was subtotal parathyroidectomy with autotransplantation of a ragment with a vascularized pedicle in the sternocleidomastoid muscle (the "sternal fork") to maintain a degree of parathyroid function and to ease reintervention if it became necessary. Baseline demographic data (age, sex), cause of chronic kidney disease, dialysis vintage, symptoms, radiological appearance of bone, laboratory data (calcium, total and ionic, phosphorus, alkaline phosphatase and parathormone), the outcome of surgery and survival of patients were recorded.

RESULTS

Baseline characteristics of the study group are presented in **Table V**. The cohort includes young patients, with a low prevalence of diabetes, a low comorbidity score but a high dialysis vintage.

Table V. Baseline characteristics of the study group.

Parathyroidectomies	N=238
Follow-up (median)	3 [2 to 5] years (N=166)
Patients characteristics	
Sex (M)	N=109 (46%)
Age (median)	54 [44 to 61]
Primary renal disease	
Primary glomerulonephritis	70%
Diabetic nephropathy	0.5%*
Comorbidities (Davies score)	0.5±0.6
Renal replacement method	
Hemodialysis	97%
Peritoneal dialysis	3%
Renal transplantation	0%*
Renal replacement therapy duration (median)	8.5 [5 to 12] years

*The number of diabetic and transplant patients operated on afterwards increased.

Symptoms are presented in **Table VI**; they were the main reason patients accepted surgery.

Table VI. Symptomatology of patients with severe secondary hyperparathyroidism

Symptom	% of patients
Bone pain	89.0%
Muscle pain	50.0%
Pruritus	10.0%
Tumoral calcinosis	2.6%
Spontaneous femoral fractures	3.0%
Calcific uremic arteriolopathy	1.3%

As most of the patients had severe hyperparathyroidism, there were significant radiological skeletal modifications (**Table VII**).

Table VII. Radiological signs in patients with severe secondary hyperparathyroidism

Sign	% of patients
Thinning of cortical bone	98%
"Salt and pepper" skull	95%
Acroosteolysis	56%
Osteosclerosis of vertebral bodies	33%
Brown tumours	2%

Indications for PTX were the clinical symptoms and serum PTH >800pg/mL refractory to medical therapy. Median weight of the glands was 3.6g [2.8-5.5]. The early post surgery morbidity was low (2 cases of cervical hematoma).
The pain began to resolve immediately post surgery and tumoral calcinosis regressed in 2-3 months. Two out of three patients with calcific uremic arteriolopathy (CUA) survived.
PTH, ionic calcium (iCa) and phosphatemia (PO4) decreased (**Table VIII**) and 95% patients had iCa <4mg/dL (with "hungry bone syndrome"). Calcium decrease correlated inversely with pre surgery PTH ($r=-0.24$; $p<0.0001$).

Table VIII. **Biochemical parameters pre- and early post parathyroidectomy**

Parameter	PrePTX	PostPTX, early
PTH (pg/mL)	1600 [1180-2200]	24 [9-70]
Ionic Calcium (mg/dL)	5±0.4	3.3±0.5
Phosphorus (mg/dL)	8.2±1	4.6 ±1.2

After a median follow-up of 3 [2-5] years of 166 patients, reintervention was necessary in 3 patients (1.3%) due to anterior mediastinal ectopic glands. Even postparathyroidectomy there were difficulties in controlling the parameters of the phosphorus-calcium metabolism (**Table IX**). 80% of patients had a PTH<150pg/mL, 15% a PTH>800pg/mL, 59% a low total Ca and 46% a high PO4.

Table IX. Phosphorus-calcium metabolism, long term follow up (2-5 years)

Parameter	PostPTX, follow-up	Within K/DIGO range
PTH (pg/mL)	37 [14-110]	5%
Ionic Calcium (mg/dL)	4.1±0.6	27%
Phosphorus (mg/dL)	5.1±1.3	46%

Only 3 patients (who requested early discharge in spite of inadequate control of serum calcium) died at home in the first 30 days after surgery because of hypocalcemia. The cumulative chances of survival were 96 and 86% at 1 and 5 years.

CONCLUSION

In a cohort of young dialysis patients, with low prevalence of diabetes mellitus and a low comorbidity score but a high dialysis vintage, total PTX with autografting in experienced hands is a low risk procedure. The risk of "hungry bone syndrome" was proportional to the pre-surgery PTH levels and usually required admission of the patients. PTX had the greatest impact on clinical symptoms, and could be life saving in cases of distal CUA. However, the proportion of patients in target for mineral metabolism parameters 3 years after PTX is rather low and hypoparathyroidism was the prevailing outcome. The possibility of a time-dependent risk for recurrence is low.

5. CONCLUSIONS

1. Pain is the alarm for the appearance of bone lesions in chronic kidney disease (CKD). Pain is associated with radiological signs in 59.6% of patients with CKD; radiological signs are, however, belated.
2. Hiperphosphoremia was statistically correlated with the existence of bone lesions in CKD.
3. Bone biopsy reveals and identifies the histological type of lesion: osteitis fibrosa, osteomalacia or mixed lesions.
4. Fractures occur in 13.4% of patients with CKD compared to an incidence of 0.38% in patients from the general population. They generally occurred in patients who had a dialysis vintage of over 5 years. Consolidation of fractures in patients with CKD needed 20-30 days more than in patients without CKD and is encumbered by complications (complex regional pain syndrome, infections); recovery also takes longer.
5. Parathyroidectomy is indicated in secondary and tertiary hyperparathyroidism; it is a safe procedure and has a favorable impact on symptoms and quality of life of patients with CKD. Control of biochemical parameters is optimal in the early postoperative period and then decreases over time.

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