Oral and Maxillofacial Manifestations of Mineral and Bone Disorders Associated with Chronic Renal Failure

ANDRADA RALUCA DOSCAS[1]*, MIHAIL BALAN[1], MIHAI LIVIU CIOFU[1], DORIANA AGOP FORNA[1], MARIUS CRISTIAN MARTU[2], EUGENIA POPESCU[1]

[1]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Dental Medicine, Department of Oral and Maxillo-Facial Surgery, 16 Universitatii Str.700115, Iasi, Romania

[2]Grigore T. Popa University of Medicine and Pharmacy, Faculty of Medicine, Department of ENT, 16,Universitatii Str.,700115, Iasi, Romania

Chronic kidney disease (CKD) is a multifactorial syndrome and a global health concern. As renal function declines, there is a progressive deterioration of mineral homeostasis. Starting from stage 3 of CKD oral manifestations of mineral disorders can occasionally appear and become more frequent and evident in stage 5. We retrospectively analysed 43 patients diagnosed with end stage renal failure undergoing dialysis, hospitalized in our clinic for different oral and maxillofacial pathologies. The mean dialysis period was 5.43 years. Radiographic alterations afecting the jaws were found in all patients. The most common feature was partial or total loss of lamina dura, followed by alterations of the bony trabeculae. 9 patients presented brown tumors which are considered the final stage of secondary hyperparathyroidism associated with renal failure.

Keywords: chronic kidney disease, mineral and bone disorders, radiographic changes, brown tumor

Chronic kidney disease (CKD) is a multifactorial syndrome characterized by progressive and irreversible loss of renal function and it represents a major health concern. Patients with CKD usually develop end stage renal failure, necessitating dialysis or renal transplantation.

CKD is commonly associated with mineral and bone metabolism disorders (MBD) which is described as the presence of one or a combination of the following aspects: abnormalities of calcium, phosphorous, parathyroid hormone (PTH) or vitamin D metabolits; abnormalities of bone turnover, mineralization, growth, volume, or strenght; vascular or other soft tissue calcifications [1].

Phosphorous (P) is the key element in CKD-MBD. Once the renal function is declined, the capacity of the kidney to excrete P is diminished, leadind to hyperphosphatemia, and elevated level of fibroblast growth factor-23 (FGF-23), which both stimulate PTH secretion (fig.1). On the other hand, P inhibits 1-alpha-hydroxylase and interferes in the process of vitamin D convertion to calcitriol, leading to hypocalcemia, which also stimulates PTH production. The kidney fails to respond to elevated PTH which normaly promotes phosphaturia and calcium reabsortion, or to FGF-23 which also enhaces phosphate excretion [1]. Beside mechanical properties, the osseous tissue plays an essential role in phospho-calcium equilibrium of the organism, together with calcitonin, parathormone, calciferol and renal function [2]. The mineral and hormone imbalances specific to renal failure are critically important in the bone remodeling processes, leading to bone abnormalities in this patients.

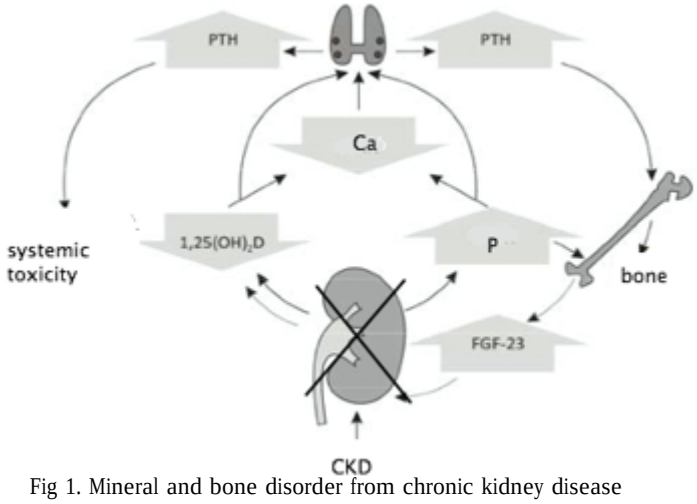

Fig 1. Mineral and bone disorder from chronic kidney disease

Oral manifestations of CKD-MBD can be an early sign of renal disease [3]. Radiological findings may vary, describing bone demineralization, decreased trabeculation and the thickness of the cortical bone, ground-glass appearance of the jaw, soft tissue calcifications, radiolucent giant cell lesions, lytic areas of bone, osteosclerosis, the absence of lamina dura, pulp chamber calcifications, widening of the periodontal space and abnormal healing after tooth extraction [4].

One of the forms of renal osteodystrophy is the high turnover bone disease which is known as *osteitis fibrosa cystica* or brown tumors. This tumors are bony lesions caused by rapid osteoclastic activity and peritrabecular fibrosis, due to hyperparathiroidism. They can be located in any part of the skeleton but are most frequently encountered in the ribs, clavicles, hands, long bones and pelvic girdle [5]. In the maxillofacial region, there are reports of brown tumors located in maxillary bones, palatine bone, nasal bone and paranasal sinuses [6]. When involving the jaws, these tumors are more common in the mandible than in the maxilla and females over 50 years old are three times more affected than males [7.8]. The histopathological examination is characterized by the presence of a fibrous stroma associated with multinucleated giant cells and hemosiderin deposits which are responsable for the nomenclature of *brown tumor* [9,10]. These findings are not specific, making it necessary to perform differential diagnostic with other lesions such as: central or peripheric giant cell granuloma, infrabony cyst, cherubism and fibrous dysplasia [9]. Usually, the positive diagnostic is established

* *email: andrada.doscas@gmail.com; Phone: (+40)744808779*

in the presence of end stage renal failure and secondary hyperparathyroidism.

Experiemhtal part

A total of 43 patients diagnosed with stage 5 renal disease undergoing dialysis were admitted between 2007-2015 in the Oral and Maxillofacial Clinic, Sf. Spiridon Hospital, Iasi. Patients were evaluated in terms of age, gender, etiology of renal failure, duration of dialysis, reason for admission and local treatment. Also, general health status was evaluated through laboratory assessments, including hemostasis tests. Radiographs (ortho-pantomography and CBCT-cone beam computed tomography) were analyzed for changes in lamina dura, trabecular pattern, reduced bone density, pulpal calcifications, widening of periodontal space and radiolucent lesions specific to brown tmors.

Results and discussions

The study group consisted in 43 patients, 60% males and 40% females, with a mean age of 51.03 ±16.97 years and a median dialysis period of 5.43 years. The etiology of renal disease was mainly represented by chronic glomerulonephritis followed by ischemic nephropathy, renal polycystic disease and lupus nephritis (table 1).

Chronic glomerulonephritis	49%
Renal polycystic disease	9%
Ischemic nephropathy	19%
Lupus nephritis	7%
Other causes	16%

Table 1
THE ETIOLOGY OF RENAL DISEASE

Radiographic changes were found in all patients. The most common radiographic finding was partial/total loss of the lamina dura which was present in 60.64% of the patients (fig.2), followed by alterations in the bony trabeculae in 55.81% (fig.3), pulp calcification in 41.86% (fig.4), bone demineralization in 32.6%, widening of the periodontal space in 27.9%.

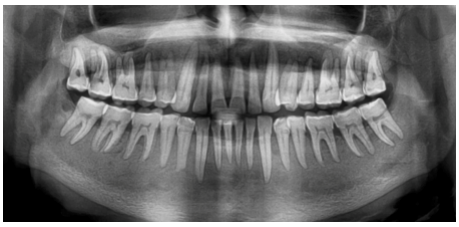

Fig.2. Radiograph showing general loss of lamina dura, altered trabecular pattern and widening of the periodontal space

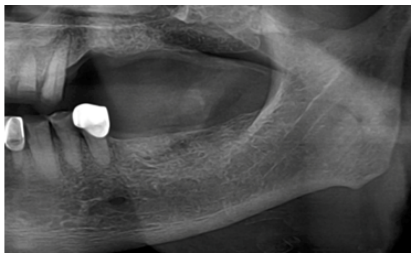

Fig.3. Radiograph showing altered trabecular pattern, bone demineralization

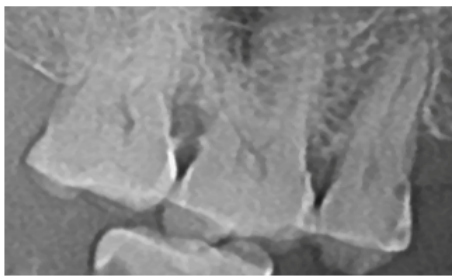

Fig. 4 Radiograph showing pulp calcifications in teeth 16, 17

Lamina dura could not be evaluated in 2 patients due to the severity of the periodontal disease. Also, pulp calcifications could not be appreciated in 3 patients because of the presence of tooth crowns and bridges.

In this report, 34 patients undergoing dialysis were admitted in our clinic for dental extractions which required hospitalization due to the severity of their general health conditions.

The rest of them (9 patients) presented for bone deformation (fig.5) caused by the presence of brown tumor localised in the maxilla (5 cases) or in the mandible (4 cases) with consecutive functional disorders. The radiographic findings showed radiolucent lesions (fig. 6).

Table 2
BROWN TUMOR PATIENTS' DATA

Nb	Age/Sex	Dyalisis duration (years)	BT site	BT size (cm)	Evolution (months)	Sign/ Symptoms	Ca mg/ dl	P mg/ dl	iPTH pg/ml
1	19/F	5	Mandible	2/3	4	Facial asimetry, bone deformation	8.75	4.1	2205
2	21/M	10	Maxilla	3/4	24	Bone deformation, Haemorrhage	9.25	4.7	2127
3	13/F	7	Maxilla		3	Bone deformation	9.7	5	865
4	47/M	15	Maxilla	7/2	15	Haemorrhage Bone deformation	9.76	4.56	2500
5	46/F	17	Mandible	2/2	3	Facial asimetry, bone deformaton	9.04	5.05	1727
6	33/M	1/2	Maxilla	3/2	2	Bone deformation	8.6	3.0	1384
7	46/M	11	Maxilla	3/2	6	Facial asimetry, bone deformation	8.19	5.7	2145
8	58/F	7	Mandible	5/3	9	Hyperestesy in right mental nerve territory, bone deformation	8.2	5.5	1024
9	26/M	3	Mandible	6/4	18	Facial asimetry, bone deformation	9.68	3.81	1530

BT-brown tumor; Ca- calcium (normal range: adult 8.6-10mg/dl, child 12-18years 8.4-10.2mg/dl); p –phosphorous (normal range: adult: 2.5-4.5mg/dl, child 13-15 years: 2.8-4.8mg/dl), iPTH- intact parathormone (normal range:15-65pg/ml)

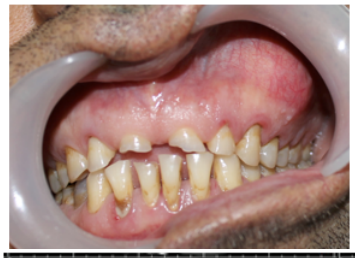

Fig 5. Intraoral aspect of a maxillary brown tumor

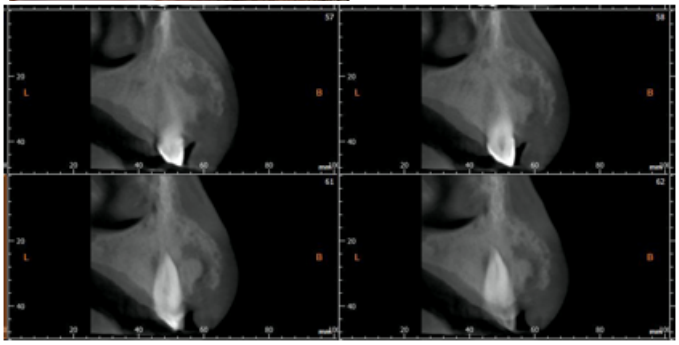

Fig.6 Cone beam computed tomography axial section showing expansile bone lession with osteolytic area surrounded by *ground glass appereance* bone

Their iPTH varied from 865pg/ml to 2500pg/mL (normal range recommended for end stage renal disease by Kidney Disease Outcome Quality Initiative- KDOQI is 150-300pg/mL), with a mean value of 1723 pg/ml (table 2).

Two of them were admitted for intensive bleeding after tooth extraction from the maxillary tumoral mass for which artery ligation was performed, bilateral external carotid in one case and left external carotid in the other case. 6 of this patients underwent tumor biopsy which confirmed the brown tumor diagnostic considerring the clinical context of end stage renal disease. Adult patients were referred for parathyroidectomy in other surgical clinic of Sf. Spiridon Hospital. Local excision and curettage of the lesions followed by wound packing for healing by secondary intention was performed in 2 cases, with good follow-up results (table 3).

Table 3

TREATMENT CONSIDERATION AND RECOMMENDATIONS

Pacient Nb	Treatment
1	Biopsy, PTx
2	Bilateral external carotid ligation, Biopsie, PTx
3	Biopsy, Referral to endocrinologist
4	Left external carotid ligation, Biopsy, PTx
5	Biopsy, PTx
6	Biopsy, PTx
7	Tumor resection, PTx
8	PTx
9	Tumor resection, PTx

PTx-parathyroidectomy

It is well known that 92% of patients with end stage renal disease develop secondary hyperparathyroidism [10]. This rate is expected to become higher in the near future, since life expectancy of end stage renal failure patients has risen. This hormone changes modify the balance between intr- and extra- cellular calcium levels, increasing bone resorbtion and reducing its density [11]. A change in the normal trabecular pattern may occur, resulting in a "ground glass appearance" of numerous small randomly orientated trabeculae [12]. Kansu et al. and Davidovich et al. stated that pulp calcifications are related to altered serum calcium-phosphorus ratio due to parathyroid disturbances [13,14]. Partial or total loss of lamina dura, altered trabeculae pattern and pulp calcifications were the most frequent radiographic findings in our study. 60.64% of our patients revealed lamina dura changes. However, in Rani's and Shakikabaei's studies this changes were seen in 70% and respectively 51.4% of dialysis patients [15,16]. Similar to our results, Handa et et. also found a high percentage of pulp calcifications [17]. Alterations in trabecular pattern were found in 51.81% of our patients and this result is comparable with the cases published by De Lacerda and Benmoussa [18,19].

9 patients from our study presented brown tumors. In Shakikabaei's research on 74 dialysis patients no such lession was found and Medeiros- Queiroz et al. reported only one brown tumor out of 154 cases [16,20].

Brown tumors represent the final stage of hyperparathiroidism [21]. Radiographically, this lesions appear as well-demarcated monolocular or multilocular osteolythic areas which can cause sometimes root resorbtion or changes in the trabecular pattern of the bone [8,21, 22]. Brown tumors can occur as solitary or multiple lessions in any bone and usually do not require specific treatment. In most cases, these tumors are painless, minimally tender, usually soft, but sometimes can appear elastic on palpation [23]. However, when facial bones are affected, according to size and localization, patients can develop functional and estethic disturbances such as deformity, dysphagia, respiratory distress, alteration of mastication, facial asimetry or lower lip paresthesia [24].

Treatment options for brown tumors may vary from conservative therapy to surgical approach. Patients with severe hyperparathyroidism require total or subtotal parathyroidectomy (PTx). Some authors suggest that the size reduction or even healing of such lesions is often achieved relatively fast [25]. Others sustain that total regression is rare, so PTx combined with enucleation and curettage of the brown tumor is the treatment of choice when the disease is resistant to medical therapy [9, 10, 26-28]. In some cases, new lesions appear or progress following subtotal parathyroidectomy [29]. Even though PTx is considered to be currative by a number of authors local surgical removal of the bone tumoral mass may be required because of the functional problems they can create for the patient [6, 30, 31]. This procedure is also recommended in anatomical sites that can compromise the local area by continuous expansion, such as the maxillary brown tumor, which can spread easily to the maxillary sinus [27]. Leal et al. concluded that brown tumors can be rapidly evolving lessions whose regression may be very low or not occur even after total Ptx, especially lythic lession in the maxilla, for which local surgery is recommended [7].

There are few cases described in the literature that report completely resolution of brown tumors of the jaw after medical treatment with high doses of vitamin D [32, 33] or calcitriol [34]. Pinto et al reported that in aggressive lesions, intralesional corticosteroid injections induces recalcification of the osteolytic cells and the regression of the tumor [35].

In chronic renal failure, a hole range of changes occur in the oral cavity that are associated with CKD itself or with CKD therapy and almost 90% of end stage renal disease patients develop oral signs and symptoms [36-39]. Apart from the ones related to mineral and bone disorders as exposed in this paper, other oral manifestation connected

to different complications of CKD may appear, like periodontitis, uraemic odor, xerostomia, mucosal petechia/ ecchimosis or uremic stomatitis [39-41].

Conclusions

Mineral and bone metabolism disturbances associated with chronic renal failure can cause various manifestations in the maxillofacial area. The most frequent radiologic findings are loss of lamina dura and changes in the trabecular pattern.

Brown tumors of the jaw are a rare and severe expression of secondary hyperparathiroidism assocciated with renal failure.

The maxillofacial expression of mineral and bone disorders from CKD can serve as indicators of the severity of renal disease.

Multi-disciplinary follow-up of this patients as well as appropriate management of oral manifestations can improve their quality of life.

References

1. KIDNEY DISEASE: improving global outcomes (KDIGO) Transplant work Group. Am. J. Transpl., **9** (Suppl.3), 2009, p. s1-157
2. COTOI, O.S., SUCIU, M., PACURAR, M., ORMENISAN, A., Rev. Chim.(Bucharest), **66,** no.2, 2015,p. 219
3. MAHNAZ, F.,Quintessence Int., **42**, 2011, p. 78-88.
4. ALAMO MARTI, S., GAVALDA ESTEVE, C., J.Clin.Exp.Dent., **3**, no.2, 2011, p.112-119.
5.TRANDAFIR, V., TRANDAFIR, D., BOISTEANU, O., GOGALNICEANU,D., POPESCU, E., Jurnalul de Chirurgie, **6**, no.4, 2010, p. 420-425.
6. NABI, Z., ALGAILANI, M., ABDELSALAM, M., et al., Hemodial. Int., no. 14, 2010, p. 247-249.
7. LEAL, C.T.S., LACATIVA, P.G.S., GOMES, E.M.S., NUNES, R.C., et al., Arc. Bras. Endocrinol. Metab., **50,** no.5, 2006, p. 963-967
8. VERMA, P., VERMA, K.G., VERMA, D., PATWARDTHAN, N., J. Oral. Maxillofac. Path., **18**, no. 2, 2014, p. 267-270.
9. QAISI, M., LOEB, M., MONTAGUE, L., CARLOSS, R., Case.Rep.Med.,**1**, 2015, p.1-10.
10. PINAR SUMMER, A., ARIK, N., SUMMER, M., KARAGOZ, F., Saudi Med. J., **25**, no.12, 2004, p. 2010-2020.
11.PINTO, M.C., SASS, S.M.G., SAMPAIO, C.P.P., CAMPOS, D.S., Braz. J. Otorhinolaryngol., **76**, no.3, 2010, p. 384-387.
12. HATA, T., IREI, I., TANAK, K., NAGATSUKA,H., HOSODA, M., Int. J. Oral Maxillofac. Surg., **35**, no.4, 2006, p. 378-382.
13. DAVIDOVICH, E., SCHWARTZ, Z., DAVIDOVITCH, M., EIDELMAN, E., BIMSTEIN, E., J. Clin. Periodontol., **32,** no. 10, 2005, p.1076-1082.
14. KANSU, O., OZBEK, M., AVCU, N., ASLAN, U., et al., Dentomaxillofac. Radiol., **38**, no.8, 2009, p.542—545.
15. RANI, S.H., J. Pharm.Biomed. Sci., no. 26, 2013, p. 397-405.
16. SHAKIBAEI, Z., TOHIDI, E., GHOLYAF, M.,GARMRUDI, B., GARMRUDI, E., J. Dent. Mat. Tech., **3**, no.4, 2015, p. 180-187.
17. HANDA, S., BHAYANA, G., ATREJA, G., Int. J.Clin. Cases Investig., **6**, 2015, p. 6-12.
18. DE LACERDA, J.C., GOMES, C.C., OLIVEIRA, C.S., GOMEZ, R.S., Oral Surg., **1**, 2015, p. 149-152.
19. BENMOUSSA, L., RENOUX, M., RADOI,L., J.Oral Maxillofac Surg., **73**, no.11., 2015, p. 2142-2148.
20. MEDEIROS- QUEIROZ, .S, GOMES AMORIM, A., DIAS , A.L.,et al., Braz .J. Oral. Sci., **12**, 2013, p. 125-31.
21. NEVILLE, B.W., DAM, D.D., ALLEN, C.M., BOUGOUT, J.E. Oral and Maxillofacial Pathology, 2nd ed. Philadelphia:WB Saunders, 2002.
22. NOLETO, J.W., MARCHIORI, E., SAMPAIO, R.K., IRION, K.L., COLLARES, F.B., Radiol. Bras., **40**, 2007, p. 167-171.
23. AL-GATANY, M., CUSIMANO, M., SINGER, W., et al., J. Neurosurg., **98**, 2003, p. 417-420.
24. DI DANIELE, N., CONDO, F., FERRANNINI, M., BERTOLI, M., ROVELA, V., Int. J. Endocrinol., **1**, 2009, p.1-3.
25. MARRONE, L.F., ETTORE, G.C., PASSAVATI, G., J. Nephol., 14, 2001, p.415-419.
26. KEBEBEW, E., Duh, Q.Y, Clark, O.H., Arch. Surg, **139**, 2004, p. 974-977.
27. TRIANTAFILLIDOU, K., ZOULOUMIS, L., KARAKINARIS, G., et al., Am. J. Otolaryngol., **27**, 2006, p. 281-286
28. PROIMOS, E., CHIMONA, T.S., TAMIOLAKIS, D., TZANAKAKIS, M.G., PAPADAKIS, C.E., J. Med. Case. Rep.,**3**, 2009, p.7485.
29. MENARD, P., PAUZLE, F., PHILLIPE, B., et al., Ver. Stomatol. Chir. Maxillofac., **94**, 1993, p. 276-280.
30. PECHALOVA, P.F., PORIAZOVA, E.G., Acta Medica, **56**, no.2, 2013, p. 83-86.
31. OILIVIERA, F.M., MAKIMOTO, T.E., SCALISSI, N.M., MARONE, M.M., et al., Arch. Endocrinol. Metab., **59**, 2015, p. 455-459.
32. FRANCISCO, A.L., Clin. Ther., 26, 2004, p. 1976-1993.
33. BUCHWALD, P.C., WESTIN, G., AKERSTROM, G., Int. J. Mol. Med., **15**, 2005, p. 701-706.
34. GARCIA, G.M., LEANZA, H., NAJUN, Z.C., BARRENECHE, M., Medicina B. Aires, **56**, no.1, 1996, p.59-62.
35. PINTO, L.P., CHERUBINIM, K., SALUM ,F.G., YURGEL, L.S., Pediatr. Dent., **28**, no.6, 2006, p. 543-546.
36. SOLOMON, S., URSARESCU,I., PASARIN, L., VEISA, G., MARTU, S., Balk. J. Dent. Med., **19**, 2015, p. 153-157.
37. MARTU S., URSARESCU, I.G., LUCHIAN, I., MARTU, A., PASARIN, L., AVESALON-SINCAR, C., SOLOMON, S., Int. J. Sci. Res., **3**, no. 4, 2014, p.359-361.
38. SINCAR, C.D., IOANID, N., RUDNIC, I., MARTU, I., SOLOMON, S.M., PAVEL, L.L., REZUS, C., MARTU, S., PLESEA CONDRATOVICI, C. Rev. Chim.(Bucharest), **68**, no.3, 2017, p. 605
39. PROCTOR, R., KUMAR, N., STEIN, A., MOLES, D., PORTER, S., J. Dent. Res., **84**, no.3, 2005, p. 199-208.
40 VEISA, G., DONCIU, M., SEGAL, L., HURJUI, L., NISTOR, I., URSARESCU, I., MARTU, S., BURLEA, L., SOLOMON, S. Rev. Chim.(Bucharest), **67**, no.1, 2016, p.103
41. SOLOMON, S.M., SINCAR, C., RUDNIC, I., PASARIN, L., URSARESCU, I.G., MARTU, M.A., IOANID, N., MARTU, S. Rom. J. Oral Rehab., **7**, no.3, 2015, p.97-102

Manuscript received: 6.01.2017