Manifestations of hyperparathyroidism in the jaws: Concepts, mechanisms, and clinical aspects

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Hyperparathyroidism is one of the most common endocrine disorders worldwide. In countries where routine biochemical screening is not common, symptomatic hyperparathyroidism predominates. Its manifestations include skeletal alterations, calcification of soft tissues, kidney stones, and functional alterations in other systems. Notably, jaw alterations can be the first clinical sign of hyperparathyroidism, including brown tumor, renal osteodystrophy, osteitis fibrosa, and leontiasis ossea, and knowing such conditions is of core importance for the multidisciplinary diagnosis and management of hyperparathyroidism. We aimed to perform a concise review, systematizing the concepts and mechanisms underlying hyperparathyroidism and associated gnathic alterations. In addition, a detailed description of the clinical aspects of the jaw manifestations is presented. (Oral Surg Oral Med Oral Pathol Oral Radiol 2022;133:547−555)

Hyperparathyroidism is characterized by increased activity of the parathyroid glands leading to elevated parathyroid hormone (PTH) levels. Primary hyperparathyroidism is the third most common endocrine disorder, and it is associated with parathyroid adenoma in >80% of cases.[1] Secondary hyperparathyroidism occurs owing to hypocalcemia, mainly related to chronic kidney disease (CKD), an increasing global health problem with an estimated 8%-16% prevalence worldwide.[2] Tertiary hyperparathyroidism is uncommon, and it is associated with autonomous secretion of PTH due to hyperplastic parathyroid glands as a result of long-standing secondary hyperparathyroidism.[3]

The tight control of calcium and phosphate levels is crucial for many vital physiologic functions.[4] Along with the active form of vitamin D, calcitonin, antiaging hormone klotho, fibroblast growth factor member 23 (FGF23), and estrogen, PTH plays an essential role in physiologic calcium and phosphate homeostasis, acting mainly in bone and kidney and indirectly in the intestine.[4] PTH excessive secretion and consequent metabolic derangements in hyperparathyroidism can alter several tissues and organs. In this scenario, craniofacial bones can be affected, including the jaws[5-8] in 4% of cases.[9] Considering cases with jaw manifestations, the mandible is more often affected, accounting for 41%-47% of cases, whereas 29% occur in the maxilla and 23%-30% affect both jaws.[7,8]

Different jaw manifestations can occur in individuals with hyperparathyroidism, including brown tumors, osteitis fibrosa/renal osteodystrophy, and leontiasis ossea, among others.[5-8] A better understanding of these conditions may lead to more appropriate clinical management. However, the literature on the definition of these concepts as well as on bone metabolism and bone metabolic diseases affecting the jaws is scarce. Therefore, the aim of the present study was to review the mechanisms underlying hyperparathyroidism and the jaw alterations it is more frequently associated with, including brown tumor, renal osteodystrophy, osteitis fibrosa, and leontiasis ossea. In addition, we described and discussed the clinical and microscopic aspects of these jaw manifestations.

In the search strategy, the terms "hyperparathyroidism," "primary hyperparathyroidism," "secondary hyperparathyroidism," "tertiary hyperparathyroidism," "chronic kidney disease," "chronic kidney disease-mineral and bone disorder," "osteitis fibrosa cystica," "renal osteodystrophy," "osteitis fibrosa," "osteomalacia," "adynamic bone disease," "brown tumour," "brown tumor," "jaws," "jaw," "mandible," "mandibular," "maxilla," "maxillary," and "gnathic" were used. They were connected with Boolean operators "AND" and "OR"

Statement of Clinical Relevance

Reviewing the concepts and clinical aspects of brown tumor, renal osteodystrophy, osteitis fibrosa, and leontiasis ossea, in addition to understanding the mechanisms underlying hyperparathyroidism and associated jaw alterations, can help clinicians to improve multidisciplinary diagnosis and disease management.

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when appropriate. Other important references derived from background knowledge or the list of references of studies have been included.

PARATHYROIDS, PTH, AND THEIR EFFECTS ON BONE CELLS

The parathyroid glands are located most often in the posterior edge of the thyroid gland, close to the superior and inferior aspects of thyroid lobes, and can also be ectopic.[10] The 4 parathyroid glands are responsible for producing PTH and are regulated mainly by circulating ionized calcium levels via the calcium-sensing receptor located on the surface of the chief cells. Figure 1 summarizes the mechanism of action of PTH in normal conditions. This hormone acts on bones, kidneys, and indirectly on the intestine, ensuring calcium and phosphorus homeostasis.[4,11] The indirect action on the intestine is based on the activation of the enzyme 1α-hydroxylase in the kidneys, which leads to conversion from inactive vitamin D [25(OH)D] to its active form [1.25$(OH)_2$D]. Thus, active vitamin D stimulates calcium absorption in the intestine.[4]

In the bones, PTH acts via the osteoprotegerin (OPG)–receptor activator of nuclear factor-κB ligand (RANKL)–receptor activator of nuclear factor-κB (RANK) system. RANKL binds to its receptor RANK on hematopoietic osteoclast precursors and osteoclast surface, leading to an increase in differentiation and activity of such cells. OPG inhibits bone resorption binding to RANKL and blocking its interaction with RANK.[11] Thus, the effect of PTH to enhance bone resorption is indirect through its actions on osteoblasts and osteocytes, stimulating RANKL, and suppressing OPG production.[11] Consequently, pathologic alterations in PTH levels unbalance this control mechanism and then can lead to skeletal manifestations.[11]

Several pathologic conditions can affect the parathyroid glands, ranging from hyperplastic processes to malignant neoplasms.[10] Such alterations cause an increase in PTH production and secretion. Other pathologic conditions, such as CKD and vitamin D deficiency, can also stimulate a compensatory increase in PTH production by the parathyroid glands.[12] All these conditions can result in hyperparathyroidism, which is classified as primary, secondary, or tertiary based on the cause of the increase in PTH levels[12] (Figure 2). In addition, ectopic increased production of PTH or PTH-related protein (PTHrP) in patients with malignant diseases can also occur.[13,14] PTHrP is closely related to PTH and is involved in hypercalcemia in individuals with cancer.[14]

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism is a common endocrine disorder that derives from a parathyroid adenoma in ~85% of cases, followed by hyperplasia in ~15% and parathyroid carcinoma in <1%.[1,15,16] The presence of these lesions causes an autonomous increased production of PTH.

Although asymptomatic hyperparathyroidism is common in developed countries owing to routine screening of calcium and PTH serum levels, in countries where such routine screening is not so common, symptomatic hyperparathyroidism with skeletal manifestations still predominates.[17] Moreover, in the scenario of symptomatic primary hyperparathyroidism, other possible manifestations are metastatic

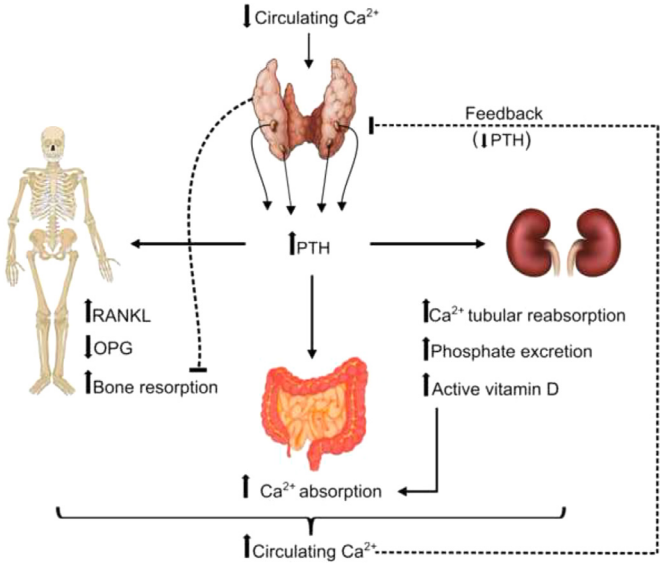


Fig. 1. Physiological parathyroid hormone (PTH) mechanisms. The decrease in circulating ionized calcium levels stimulates the production of PTH by the parathyroid glands. PTH acts on bones, kidneys, and indirectly on the intestine, activating mechanisms that raise serum calcium levels. This increased level stimulates the reduction of PTH production through a feedback mechanism (straight dashed line) and the production of calcitonin by the thyroid, which acts by reducing bone resorption (curved dashed line).

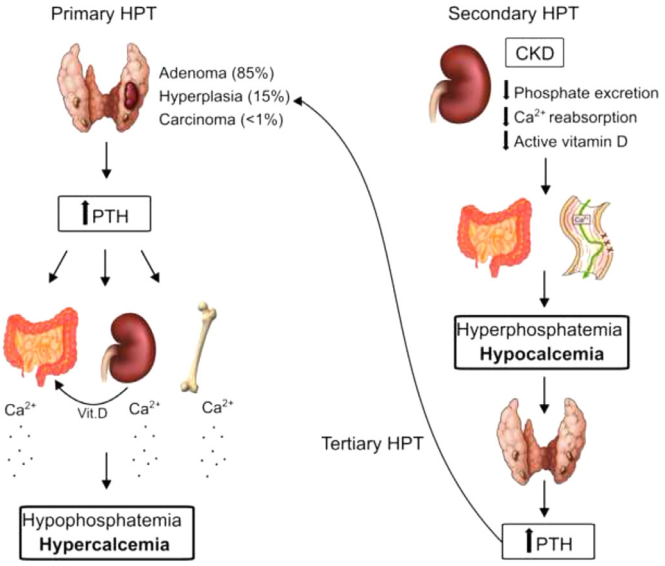


Fig. 2. Primary, secondary, and tertiary hyperparathyroidism. In primary hyperparathyroidism (HPT), elevated production of parathyroid hormone (PTH) due to parathyroid gland pathology leads to changes in bones, kidneys, and intestine, resulting in hypophosphatemia and hypercalcemia. In chronic kidney disease, poor kidney function leads to hyperphosphatemia and hypocalcemia, resulting in a compensatory increase in PTH production, characterizing secondary HPT. In tertiary HPT, the persistence of secondary HPT results in autonomous PTH production by parathyroid glands.

calcifications; kidney stones; and functional alterations in the central nervous, neuromuscular, digestive, and cardiac systems.[18]

SECONDARY AND TERTIARY HYPERPARATHYROIDISM

In secondary hyperparathyroidism, the increase in PTH levels is stimulated by an extrinsic abnormal change affecting calcium homeostasis.[12] The most important cause of hypocalcemia leading to secondary hyperparathyroidism is CKD.[12] Long-standing secondary hyperparathyroidism may lead to autonomous production of PTH by hyperplastic parathyroid glands, resulting in tertiary hyperparathyroidism.[3] Patients affected by CKD and secondary hyperparathyroidism often present with skeletal manifestations denominated renal osteodystrophy, which can involve the jaws.[6] A brief review of CKD and chronic kidney disease−mineral and bone disorder (CKD-MBD) is presented next.

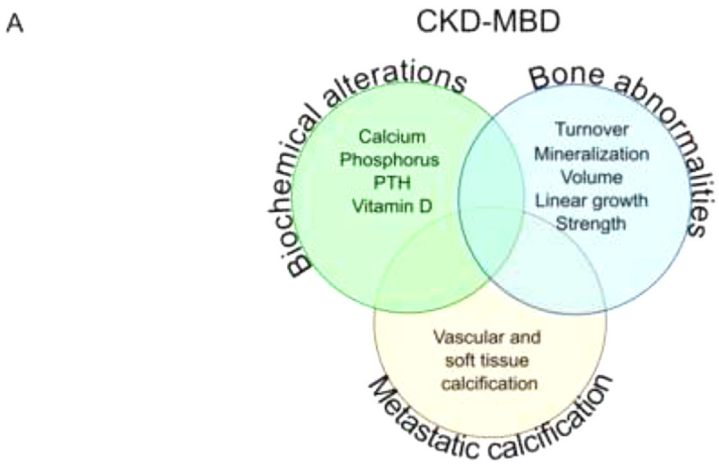
CKD and CKD-MBD

CKD is defined as abnormalities of kidney structure or function with health implications that persist for >3 months, with glomerular filtration rates <60 mL/min/1.73 m^2 or albuminuria.[19] The progressive failure in kidney function leads to alterations in mechanisms that control the serum levels of calcium, phosphorus, PTH, vitamin D, FGF23, and growth hormone.[19] These abnormalities mark a systemic condition of deranged mineral and bone metabolism denominated CKD-MBD, a complication of CKD.[19,20] In addition to alterations in biochemical parameters, abnormalities in bone turnover, mineralization, volume, linear growth, or strength and vascular or other metastatic soft tissue calcification are other possible manifestations of CKD-MBD[20,21] (Figure 3A).

Renal osteodystrophy

Renal osteodystrophy is part of CKD-MBD. As recommended by the Kidney Disease: Improving Global Outcomes organization, by definition, "renal osteodystrophy" refers specifically to the bone pathology derived from patients with CKD.[20] Hence, the term encompasses the bone morphologic alterations, which are quantifiable by histomorphometry of bone biopsy.[20]

The classification of renal osteodystrophy is mainly based on bone turnover (bone remodeling), mineralization, and volume. Osteitis fibrosa, osteomalacia, adynamic bone disease, and mixed uremic osteodystrophy are some subtypes.[20] Figure 3B summarizes the main features of high-turnover and low-turnover renal osteodystrophy types.[20,22,23] The high-turnovers osteitis fibrosa and mixed uremic osteodystrophy are the most common forms in end-stage renal disease, resulting mainly from secondary hyperparathyroidism and vitamin D deficiency leading to mineralization defect, respectively.[24] Osteomalacia is primarily caused by aluminum exposure with bone deposition and low levels of vitamin D.[23] Last, the adynamic bone disease is often seen in patients managed with excessive calcium and/or vitamin D therapy.[3,23]



B

Renal osteodystrophy

	High-turnover		Low-turnover	
	Osteitis fibrosa	Mixed uremic osteodystrophy	Osteomalacia	Adynamic bone disease
Mineralization	Normal	Abnormal	Abnormal	Normal
Bone volume	Variable	Normal	Low to medium	Low to normal
Peritrabecular fibrosis	Present	Present	Almost absent	Almost absent
Osteoid formation	Increased	Increased	Proeminent	Deficient
Osteoblasts and osteoclasts number and activity	Increased	Increased	Decreased	Decreased

Fig. 3. Manifestations of chronic kidney disease−mineral and bone disorder (CKD-MBD) and main features of renal osteodystrophy. **(A)** CKD-MBD manifests as 1 or more of the following 3 features: (1) biochemical alterations of calcium, phosphorus, parathyroid hormone, or vitamin D metabolism; (2) abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and (3) vascular or other soft tissue calcification (adapted from Moe et al.[21]). **(B)** High-turnover and low-turnover bone abnormalities (renal osteodystrophy) and their features regarding mineralization, bone volume, peritrabecular fibrosis, osteoid formations, and osteoblast and osteoclast number and activity.[20,22]

The changes in bone structure and function in patients with CKD vary according to endogenous (e.g., age, sex, genetic background, ethnicity) and exogenous factors (e.g., nutritional status, physical activity, drugs used for treatment, dialysis modality).[24] Such factors influence the occurrence of high-turnover or low-turnover types of renal osteodystrophy and the transition between them.[24]

Although bone biopsy is the gold standard for renal osteodystrophy diagnosis and classification by histomorphometry, in clinical practice, biochemical and imaging diagnoses are often used. The serum levels of PTH and alkaline phosphatase and imaging features may help in the differential diagnosis of some renal osteodystrophy subtypes.[24] For instance, Looser-Milkman zones (i.e., pseudofractures) on radiographic examination are suggestive of osteomalacia, whereas subperiosteal bone resorption, salt-and-pepper aspect of the skull, rugger jersey features of the spine, and

cyst-like lesions are observed in high-turnover conditions.[24] With regard to the jaws, in patients with CKD-MBD and hyperparathyroidism, some jaw radiologic findings, such as resorption of the cortices and lamina dura and effacement of the bony trabecula with a ground-glass appearance, reflect the microscopic replacement of resorbed bone by fibrous connective tissue, which is consistent with the high-turnover osteitis fibrosa subtype.[25]

HYPERPARATHYROIDISM AND THE JAWS

Brown tumor of hyperparathyroidism

Brown tumors are bone lesions that occur late in hyperparathyroidism[8] and result from abnormal bone metabolism in primary, secondary, and tertiary types of the disease. Owing to the early diagnosis of hyperparathyroidism, brown tumors have become rare in developed countries.[26]

Brown tumors can affect one or more bones. The most commonly affected bones are the ribs, clavicles, and pelvis. Craniofacial involvement occurs in ~4% of cases, mainly affecting the mandibular posterior regions.[8,9] Microscopically, brown tumors are characterized by osteoclast-type multinucleated giant cells intermingled with ovoid and spindle-shaped mononuclear cells in a fibrovascular background with hemorrhage and hemosiderin deposits.[27] The histologic features are similar to those of other giant cell−rich lesions of the jaws,[28] and therefore the diagnosis of brown tumors requires the association of the clinicoradiologic, histopathologic, and biochemical findings. Table I summarizes the biochemical tests used and the most common primary, secondary, and tertiary hyperparathyroidism findings, based on previously proposed values.[29] Notably, brown tumors share the microscopic features with other giant-cell rich lesions of the jaws, and recently they also have been shown to harbor *KRAS* missense mutations at codons 12, 13, and 146, similar to sporadic central and peripheral giant cell granulomas of the jaws, as well as implant-associated peripheral giant cell granuloma.[27,30,31]

A recent study systematically reviewed 167 cases of brown tumors of the oral cavity, and they were related to primary, secondary, and tertiary hyperparathyroidism in 44.3% (74 of 167), 51.5% (86 of 167), and 4.2% (7 of 167) of cases, respectively.[8] Brown tumors can affect the maxilla and mandible as single[8,32,33] or multiple lesions.[8,34-39] The mandible is frequently affected, accounting for 70% of brown tumors occurring in the jaws.[8] Although often central, brown tumors can also be peripheral.[8,40] Brown tumors of the jaws are frequently well-defined unilocular or multilocular radiolucent/hypodense areas, but ill-defined lesions[32,35,39] and cortical bone erosion[8,18,39] might also occur. Although there may be no or mild manifestations during the oral clinical examination, some patients may present with bone expansion, facial deformity, and exophytic red-brown, occasionally ulcerated, lesions.[8,35,39,41-43]

Besides the brown tumors, loss of lamina dura, tooth displacement, tooth mobility, root resorption, malocclusion, limited mouth opening, pain, and periodontal enlargement are other bone and dental manifestations that may also be present.[18,34,37,44] Furthermore, the involvement of other bones by osteolytic lesions and areas with a salt-and-pepper appearance in the skull, reported in some cases, characterize the systemic impact of the endocrine condition.[35,36,39]

Although often sporadic, primary hyperparathyroidism rarely occurs in inherited syndromes, such as multiple endocrine neoplasia syndromes and hyperparathyroidism−jaw tumor syndrome. In hyperparathyroidism−jaw tumor syndrome, the jaw tumors are ossifying fibromas, which are distinguishable from brown tumors, and are not a direct effect of hyperparathyroidism.[45]

Other gnathic manifestations of secondary and tertiary hyperparathyroidism

Besides brown tumors, another possible manifestation in secondary hyperparathyroidism consists of ill- or well-defined mixed areas with poor corticomedullary distinction described as the "ground-glass appearance."[43,46,47] Pontes et al.[43] described these lesions affecting either the maxilla or mandible, individually or affecting both simultaneously, often diffusely.[43] In this context, the diagnosis is usually described as osteitis fibrosa/renal osteodystrophy. Its radiologic and microscopic features are similar to fibrous dysplasia.[48,49] However, although both

Table I. Biochemical tests and most common findings in hyperparathyroidism

Test	*Reference range**	*Primary HPT*	*Secondary HPT*	*Tertiary HPT*
PTH	10-65 pg/mL	Elevated	Elevated	Elevated
Calcium	8.4-10.2 mg/dL	Elevated	Decreased	Variable
Phosphorous	2.7-4.5 mg/dL	Decreased	Elevated	Variable
Alkaline phosphatase	39-177 IU/L	Elevated	Elevated	Elevated

HPT, hyperparathyroidism; *PTH*, parathyroid hormone.
*There is variation. The reference ranges in the table are from Misiorowski et al.[29]

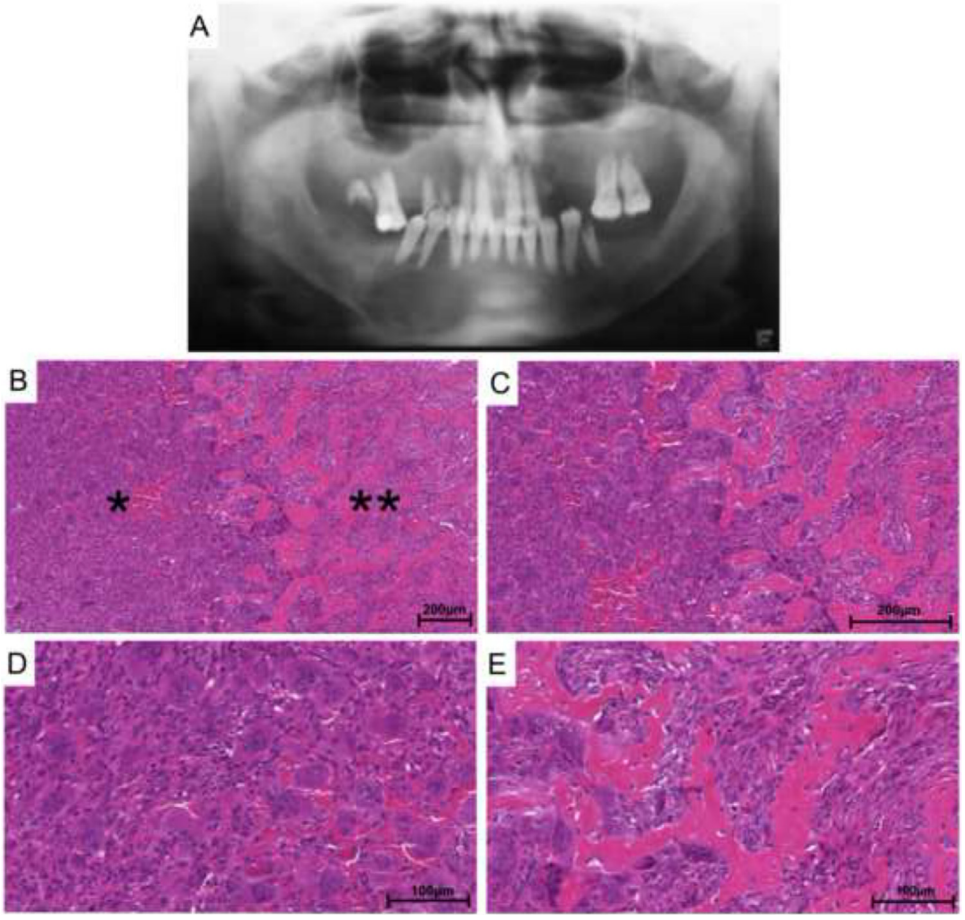


Fig. 4. Radiographic and microscopic features of a case showing the simultaneous presence of a brown tumor and osteitis fibrosa in a patient with secondary hyperparathyroidism. **(A)** Panoramic radiograph of a 43-year-old female patient presenting mixed radiolucent/radiopaque ill-defined lesions diffusely affecting mandible and maxilla, with areas of ground-glass appearance. In addition, loss of lamina dura around teeth and basal cortical thinning are observed. **(B)** Area of brown tumor (asterisk) adjacent to osteitis fibrosa (double asterisk) (hematoxylin and eosin [H&E] stain, original magnification 50×; scale bar 200 μm). **(C)** Brown tumor and osteitis fibrosa intersection at greater magnification (H&E, original magnification 100×; scale bar 200 μm). **(D)** Brown tumor area characterized by osteoclast-like multinucleated giant cells intermingled by ovoid or spindle-shaped mononuclear cells in a fibrovascular background with hemorrhage foci (H&E, original magnification 200×; scale bar 100 μm). **(E)** Area depicting trabeculae of osteoid surrounded by osteoblasts and osteoclasts, and peritrabecular fibrosis, consistent with osteitis fibrosa (H&E, original magnification 200×; scale bar 100 μm). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06357.

conditions show a ground-glass appearance, unlike osteitis fibrosa/renal osteodystrophy, fibrous dysplasia exhibits clear corticomedullary distinction on radiographs.[49,50] In addition, these conditions can be microscopically distinguished by a relative absence of osteoclasts in fibrous dysplasia, whereas trabeculae of osteoid are surrounded by osteoblasts and osteoclasts in osteitis fibrosa/renal osteodystrophy.[25] Interestingly, de Lacerda et al.[51] described a case of simultaneous presence of osteitis fibrosa and brown tumor in an individual with secondary hyperparathyroidism. Radiographic and microscopic features of a case of brown tumor and osteitis fibrosa simultaneously occurring in a patient are shown in Figure 4.

Moreover, diffuse jaw enlargement in renal osteodystrophy has been classified as uremic leontiasis ossea or just leontiasis ossea.[46,49] However, because "leontiasis ossea" is a nonspecific clinical term and is also applied to other causes of facial bone enlargement, such as fibrous dysplasia and Paget disease of bone, some authors recommend the term "expansive renal osteitis fibrosa" as a more appropriate term regarding the CKD-MBD context.[49] Leontiasis ossea affecting the jaws has also been reported in tertiary hyperparathyroidism.[52]

In patients with CKD-MBD, the combination of cortical bone thinning, coarsened medullary trabeculations, osteolytic lesions, and a salt-and-pepper

appearance of the skull are interpreted as cysts and called "osteitis fibrosa cystica" by some authors. However, this term must be used with caution because the radiolucent images are consequences of PTH-induced bone loss instead of true cystic structures.[49]

Another aggressive condition in the context of CKD-MBD and hyperparathyroidism that has jaw manifestation is the Sagliker syndrome.[43,53] The prevalence of this syndrome is estimated to be <1 in 1,000,000.[54] In addition to the radiographic features of the jaws described above for osteitis fibrosa/renal osteodystrophy, other clinical characteristics are uglifying facial appearance, maxillary and mandibular swellings, short stature, skull and bone alterations, malocclusion, fingertip changes, severe psychological problems, and depression.[53] The etiopathogenesis of Sagliker syndrome is still unclear,[55] and *GNAS1* and *FGF23* mutations have been reported in blood DNA.[55,56]

TREATMENT OF HYPERPARATHYROIDISM AND ITS RELATED JAW ALTERATIONS

The classification of hyperparathyroidism is crucial to guide the multidisciplinary approach of jaw alterations because the normalization of PTH levels is the first step. In classic primary hyperparathyroidism, the surgical removal of a single parathyroid adenoma or multiple hyperplastic glands is indicated for the regularization of hormone levels.[3] The treatment of secondary hyperparathyroidism includes hemodialysis or kidney transplant to reestablish renal function. In addition, a low-phosphate diet, phosphate-binding drugs, vitamin D analogs, and calcium mimetics are also prescribed when necessary.[3] In cases of progressive secondary hyperparathyroidism, subtotal parathyroidectomy (i.e., removal of 3-3.5 glands) or total parathyroidectomy either with or without autotransplantation are indicated, as it is for tertiary hyperparathyroidism, with additional pre- or postoperative care depending on individual conditions.[3] Hyperparathyroidism treatment details are beyond the scope of this article, and there are excellent published papers focusing on this subject.[3]

Management of the jaws' alterations after the mentioned medical treatments will depend on the systemic conditions of the patient and the location, size, and clinical behavior of the lesions.[8] In regard to brown tumors, they usually regress after PTH levels are controlled, and the "wait and see" approach after the endocrine regularization is prudently suggested. Occasionally, the regression can take a long time, or the lesions can even increase in size, and sometimes functional or esthetic problems are present. In these cases, systemic or intralesional corticosteroids and calcitonin have been used to reduce the lesion size, and surgical approaches such as excision, resection, curettage, and osteoplasty have also been described.[57] Osteitis fibrosa/renal osteodystrophy in the jaws frequently leads to expansion and facial asymmetry with unusual total regression. Therefore, osteoplasty with bone recontouring is a common practice, mainly when there are functional or esthetic demands.[46]

CONCLUSIONS

Hyperparathyroidism management requires a multidisciplinary approach for both diagnosis and treatment, with dentists and oral and maxillofacial surgeons playing an important role. Because jaw lesions are often the first clinical sign of hyperparathyroidism, clinicians must be able to suspect a more complex systemic condition and investigate it. The dosage of PTH, calcium, phosphorus, and alkaline phosphatase are essential for the diagnosis of hyperparathyroidism-related jaw lesions. There is a lack of clarity in the definition of concepts of bone diseases occurring in the hyperparathyroidism context. Such lack of uniformity in definitions may be partially attributed to the fact that there are 3 types of hyperparathyroidism with distinct pathogenesis, and they are often studied from different perspectives. In addition, the scenario in renal patients may be more complex than that in patients with nonrenal causes of hyperparathyroidism. Therefore, the discussed and integrated concepts in the present review can help investigators and clinicians to improve their diagnostic approach, their communication with the multidisciplinary team, and their management of the lesions.

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