Review Article

Osteodystrophies of jaws

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Abstract

Bone is a dense, semi rigid, porous, calcified connective tissue forming the major portion of the skeleton of most vertebrates. It consists of a dense organic matrix and an inorganic mineral component. Bone remodelling is a complex process by which old bone is continuously replaced by new tissue, which requires interaction between different cell phenotypes and is regulated by a variety of biochemical and mechanical factors. In a homeostatic equilibrium, the process of resorption and formation are balanced so that old bone is continuously replaced by new tissue and it adapts to mechanical load and strain. Several local and systematic factors which cause disturbances in bone resorption and deposition leads to abnormal or defective development of bone commonly termed as osteodystrophy - A defective ossification of bone usually is associated with disturbed calcium and phosphorus metabolism. The better understanding of molecular cellular biology and pathogenic mechanism aids to define the abnormalities in osteoblastic and osteoclastic lineages and to develop new therapeutic approaches.

Keywords: Bone remodeling, osteodystrophy, osteoporosis

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INTRODUCTION

Dystrophy is derived from the Greek word: dys - wrong, difficult, trophe-nourishment. In 1969, it was first defined as a hereditary, congenital or later appearing, slowly progressive defect, presenting slight intrafamilial variation and of unknown etiology.[1] It was suggested that conditions secondary to systemic factors should not be termed dystrophies, but others found it somewhat artificial to exclude entities with systemic manifestations from the definition.[1]

Dystrophies are progressive disorders appearing in tissues with initially displaying normal function. It is defined as process and consequence of hereditary progressive affections of specific cells in one or more tissues that initially had normal function.[1] The term "osteodystrophy" is used to describe the disorders of bone specifically or more generally of mineral metabolism in which there is major involvement of bone. It is the defective bone formation, maturation or mineralization. The common feature is the abnormalities in the development and maintenance of osseous system either of local nature or of a more generalized distribution. They are lesions other than neoplastic and inflammatory conditions due to disturbance in calcium and phosphorus metabolism or due to renal disease.

Osteodystrophies of jaws do not include recognized injuries restricted to jaws but constitute a group of generalized skeletal diseases which frequently manifest involvement of oral and maxillofacial region.[2] The maxilla and mandible

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suffer from both localized and generalized forms of skeletal disease.[2] Although the basic mechanisms are same, the peculiar anatomic arrangement of teeth embedded partially in bone, through which the bone may be subjected to an unusual variety of stresses, strains, often produces unusual response to primary injury.[2] Several articles reviewed the pathology of individual disorders but the common basic pathogenesis and classification for osteodystrophic lesions of jaws was not evidenced. The aim of this study was to present an acceptable etiopathogenesis and classification of osteodystrophic lesions from the existing literatures thereby bridging the necessary gap and initiating a world consensus in the categorization of osteodystrophies of jaws.

PATHOPHYSIOLOGY

Bone is a living organ that undergoes remodeling throughout life. Remodeling results from the action of osteoblasts and osteoclasts. Defects such as microfractures are routinely repaired by their coupling. In a homeostatic equilibrium, resorption and formation are balanced so that old bone is continuously replaced by new tissue so that it adapts to mechanical load and strain.[3]

The regulation of bone remodeling is both systemic and local.

The major systemic regulators include calcitonin (CT), parathyroid hormone (PTH), vitamin D3 [1,25(OH)2 vitamin D3] and sex hormones. They are the major hormonal regulators of osteoclastic bone resorption.[3,4] Factors such as insulin-like growth factors (IGFs), prostaglandins, tumor growth factor-beta, bone morphogenetic proteins, and cytokines are involved as well.[5]

Among the systemic regulators, 1,25(OH) 2D3 stimulates osteoblastogenesis through the differentiation of mesenchymal stem cells to osteoblasts. The PTH also induces the differentiation of committed osteoblast precursors by inducing the runt-related transcription factor 2 (RUNX 2) expression in the formation of preosteoblasts which gets converted in to osteoblasts. RUNX 2 is a key transcription factor associated with osteoblast differentiation. By inducing RUNX 2, PTH increases the osteoblast numbers and extends its survival. It also stimulates the proliferation and differentiation of osteoprogenitors to mature osteoblast through IGF-1.[3,4]

CT increases the osteoblast proliferation and suppresses the bone resorption by inhibiting the activity of osteoclasts. Estrogen inhibits the bone resorption by directly inducing the apoptosis of bone resorbing osteoclasts. Androgens also indirectly inhibits osteoclast and bone resorption through effect on osteoblast/osteocytes and the receptor activator of NF-kappa B/receptor activator of NF-kappa B ligand (RANK/RANKL), osteoprotegerin (OPG) system.[3,4]

As far as local regulation of bone remodeling is concerned, a large number of cytokines and growth factors that affect bone cell functions have been recently identified. Furthermore, through the RANK/RANKL/OPG system, the processes of bone resorption and formation are tightly coupled. This takes place as a wave of bone formation to follow each cycle of bone resorption, thus maintaining skeletal integrity.[6] RANKL, expressed on the surface of preosteoblastic/stromal cells binds to RANK on the osteoclastic precursor cells. This binding is critical for the differentiation, activation and survival of osteoclastic cells. OPG inhibits the entire system by blocking the effects of RANKL.[6]

These local and systemic factors play a pivotal role in maintaining bone homeostasis. Any deviation or abnormality of bone remodeling occurs either due to disturbances in this osteogenic and osteoblastic balance or due to disturbances in deposition and resorption of hydroxyapatite crystals in the osteoid matrix thus causing variety of skeletal disorders.

The imbalance between osteoclast and osteoblast leads to various osteodystrophic lesions which can manifest as:

Osteoporosis

Osteoporosis is a skeletal disorder characterized by reduced bone mineral density (BMD) and bone mass, resulting in damaged bone structure. The reduction in bone strength, which manifests clinically as bones fractures[7] are commonly seen in conditions such as hyperparathyroidism and osteogenesis imperfecta (OI).[7]

Osteosclerosis

Osteosclerosis is characterized by abnormal hardening of bone and an elevation in bone density. Increased osteoblastic activity leads to increase in number and width of trabecular pattern and width of cortex[2] as seen in osteopetrosis, Paget's disease.[2]

Osteitis fibrosa

A resulting in the loss of bone mass like in osteoporosis but gross weakening of the bones occur as their calcified supporting structures are replaced with fibrous tissue. It is also known as peritrabecular fibrosis. The increase in osteolytic activity in this condition results in formation of cyst-like brown tumors as in von Recklinghausen's disease of bone.[8]

The disturbance in deposition/resorption of hydroxyapatite crystals in osteoid tissue needs better understanding of bone mineralization.

Hydroxyapatite, also called hydroxylapatite (HA) is a naturally occurring mineral form of calcium apatite with the formula $Ca_5(PO_4)_3(OH)$, but it is usually written $Ca_{10}(PO_4)_6(OH)$.

The stoichiometry of this bone mineral basically is that of hydroxyapatite precipitating from phosphate, calcium and water at a slightly alkaline pH

$$6\,HPO_4^{2-} + 2\,H_2O + 10\,Ca^{2+} \rightleftharpoons Ca_{10}(PO_4)_6(OH)_2 + 8\,H+.$$

Mineralization of hydroxyapatite begins with the process of endochondral ossification which starts when the hyaline cartilage acts as a template mold for the initial mineralization. In parallel, an ingrowth of blood vessels occurs, followed by the formation of the primary ossification centers in the diaphysis. Later, spongy bone is also formed in the epiphyses at the secondary ossification centers, with two regions of the hyaline cartilage remaining on the surface of the epiphysis (articular cartilage) and the epiphyseal plate (growth region). Appositional growth of the bone proceeds in the absence of a cartilage template. Mineral deposition involves two enzymes; first, carbonic anhydrase and second, alkaline phosphatase (ALP).[9] This process can be subdivided into four phases.

PHASES OF BONE MINERALISATION

Phase I: Bio-seed deposition catalyzed by carbonic anhydrase

Experimental evidence shows that Ca-phosphate/hydroxyapatite crystals formation starts in human cells, with the deposition of amorphous Ca-carbonate deposits. This reaction is enzymatically controlled primarily by the carbonic anhydrase-II. Carbonic anhydrase is the dominant enzyme that forms the Ca-carbonate bio-seeds. From those Ca-carbonate bio-seeds, the mineralization process progresses further to Ca-phosphate.[9,10]

Phase II: Hydrolytic cleavage of polyphosphate by alkaline phosphatase

Origin of the phosphate in bone mineral is from inorganic polyphosphates (polyP). Polyphosphate exists in a polymerized state, as inorganic polyP. The interesting feature of polyP is that besides (potentially) providing phosphate units for Ca-phosphate mineralization, this polymer delivers chemically useful energy during enzymatic hydrolysis using the enzyme ALP.[9,10] This is the enzyme which likewise present in the extracellular space and readily degrades polyP.

Phase III: Transformation of Ca-carbonate to Ca-phosphate deposits: Nonenzymatic step

Both Ca-phosphate formation and Ca-carbonate deposition are exergonic processes. However, in contrast to amorphous calcium carbonate formation, which is enzymatically driven, the exchange of carbonate by phosphate in amorphous calcium carbonate occurs even under physiological conditions without the participation of an enzyme; the reaction is an exergonic one. If amorphous calcium carbonate is exposed to phosphate buffer, a transfer of phosphate to amorphous calcium carbonate proceeds resulting in the formation of amorphous calcium phosphate. In turn, the latter material sequentially undergoes a phase transition to HA.[11]

Phase IV: Maturation of the calcium phosphate to crystalline hydroxyapatite

Degradation of polyP by the ALP provides orthophosphate and calcium ions, which serves as a substrate for calcium phosphate/hydroxyapatite formation. The initially formed amorphous calcium phosphate is then converted into the crystalline form.[9,10]

DISSOLUTION OF HYDROXYAPATITE CRYSTALS

Bone resorption involves dissolution of crystalline hydroxyapatite followed by proteolytic cleavage of the organic component of bone matrix. The osteoclasts resorptive machinery consists of two important structural and functional features namely the bone-apposed ruffled border and an isolated resorption compartment.[12]

The resorption compartment is formed by attachment of osteoclasts to bone matrix through the unique structure termed the sealing zone. The ruffled border transports protons and proteolytic enzymes into the resorption compartment to dissolve minerals and degrade bone matrix proteins. Bone resorption involves dissolution of crystalline hydroxyapatite followed by proteolytic cleavage of the organic component of bone matrix.[13]

Enzyme H^+-adenosine triphosphatase (H^+-ATPase), which is abundantly present in the ruffled border membrane transports protons to acidify the resorption compartment.[12] The high concentrations of acid on a basic mineral liberate calcium:

$$[Ca_3(PO4)_2]_3Ca(OH)_2 + 8H^+ \leftrightarrow 10Ca_3 + 6HPO_4^{2-} + 2H_2O.$$

The source of the cytoplasmic protons is carbonic acid, which is generated by cytoplasmic carbonic anhydrase from carbon dioxide and water.

$$(CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-).$$

To maintain electroneutrality, Cl^- also transported into the resorption compartment via Cl^- channels which are charge-coupled to the H^+-ATPase and present in the ruffled border membrane.[12] The secretion of protons across the ruffled border membrane into the extracellular resorbing compartment leaves the conjugate base (HCO_3^-) inside the osteoclast, which must be removed from the cell. Furthermore, the osteoclast also must continuously supply Cl^- ions for secretion into the resorption compartment. These two tasks are accomplished by a passive chloride-bicarbonate exchanger in the basolateral membrane. The degradation of the organic component of bone matrix is accomplished by the lysosomal proteolytic enzyme cathepsin K. As mineral precipitates, acid accumulates, rapidly lowering the pH and stopping further precipitation.[12,13]

These abnormalities in bone formation and resorption leads to dystrophic bone diseases which can be categorized as:

- Inherited disorders
  - Osteopetrosis
  - OI.
- Metabolic disorders
  - Hypophosphatasia (HPP)
  - Renal osteodystrophyo
  - Rickets.
- Endocrinal disorders
  - Hyperparathyroidism.
- Fibro osseous lesions
  - Fibrous dysplasia
  - Paget's disease
  - Cherubism.

OSTEOPETROSIS

Osteopetrosis or "marble bone disease" is a congenital autosomal disorder with marked increase in density due to defective remodeling caused by failure of osteoclastic function. It was initially described by Albers-Schonberg.[14]

The etiology of osteopetrosis is purely due to defects in the osteoclasts which can be of two types - osteoclast-rich and osteoclast-poor forms. In the former, the osteoclasts are either normal or increased in number but are unable to form the ruffle border which is indispensable for resorbing bone. In the osteoclast poor form, there is a reduction in the number of osteoclasts which could be due to reduced number or absence of osteoclast progenitor/precursor cells. The defect is with osteoclastogenesis signaling, hence the progenitor cells do not progress into mature osteoclasts. The ability of mature osteoclasts to resorb bone is also reduced due to mutations in RANKL genes. Lack of bone resorption explains the pathogenesis of bone fragility. It occurs either due to the defect in osteoclast function which leads to inability to create acidic environment or due to reduction in number of osteoclast to resorb bone.[2,14]

Radiologically, long bones assume a "flask shape" or club shape, particularly in the proximal end of the humerus and distal end of femur. The vertebral spine shows thickening of the end plates causing a transverse band termed as "Rugger jersey" appearance. "Endobones" or bone in bone appearance is evident in the pelvis, spine and distal long bones.[15-17] These signs are usually considered pathognomic of osteopetrosis. Skull bones show progressive sclerosis with the base of the skull affected more. The maxillary sinus is generally sclerotic and may be completely obliterated in some cases. In the maxillofacial region, both maxilla and mandible show diffuse sclerosis with no corticomedullary differentiation. Multiple teeth may be unerupted or impacted. The teeth may be malformed and prone to caries. Ribs and long bones may show sign of old fractures. These patients are prone to fractures even with trivial injury.[17] Narrowing of the foramina may be demonstrable on CT scans causing cranial nerve entrapment neuropathies. The medullary spaces of jaws are reduced so that there is a marked predilection for the development of osteomyelitis.[14-16]

Treatment includes either bone marrow transplant or hematopoietic stem cell transplant. Treatment with calcitriol to stimulate dormant osteoclast has been tried with mixed success. Other therapies including interferon and corticosteroids have been reported.[17]

OSTEOGENESIS IMPERFECTA

OI comprises a heterogeneous group of heritable disorders characterized by impairment of collagen maturation. Except on rare occasions, the disorder arises from mutations in one of two genes that guide the formation of type I collagen: the COL1A1 gene on band 17q21 and the COL1A2 gene on band 7q22.1.

Collagen forms a major portion of bone, dentin, sclerae, ligaments and skin.[15,16] Mutations in the amino acid sequence of type I collagen can result in the formation of branched fibers responsible for brittle bone and abnormal mineralization. When the formation of crosslinks is inhibited, bone strength decreases despite normal mineralization. Improper collagen maturation altogether leads to characteristic clinical features such as extreme bone fragility, improper dentin formation and blue sclera.[15,16,18]

Sillence *et al*.[19] proposed a classification of OI into 4 types based on clinical and genetic findings in OI patients. This classification distinguished type I (mild OI, blue sclerae, autosomal dominant inheritance), type II (lethal perinatal OI, autosomal recessive inheritance, later subdivided in II-A, -B and -C based on radiographic features, type III (progressively deforming, autosomal recessive inheritance) and type IV (dominantly inherited OI with normal sclerae.[19,20]

About 50% of children and adults with OI have dental involvement of varying degree and severity. Although both dentitions may be affected, the deformity is generally more severe in the primary teeth. Teeth with DI have certain features, including amber bulbous crowns or gray-brown discoloration, constricted cementoenamel junctions, narrow roots, partial or total obliteration of the pulp chambers, and root canals with the evidence of periapical radiolucencies. The enamel is normal, but may shear rapidly due to deficient dentinoenamel junction, resulting in dentin attrition and loss of the vertical dimension.[19]

The main radiographic features are osteopenia, bone fractures and bone deformities. Radiographs reveal cortical bone thinning and excessive trabecular bone transparency. It also includes multiple wormian bones (defined as the presence of 10 or more wormian bones) that lend a "mosaic" or "paving" appearance to the cranial vault. In the long bones, bending and thinning of the diaphyses may be seen, sometimes complicated by progressive fractures in the concave aspect of the deformity that can recur after healing Bone densitometry by dual-energy X-ray absorptiometry is currently the optimal method to detect decreased BMD, but in children, accurate interpretation of the results requires a good knowledge of the potential pitfalls related to age, sex, pubertal stage and skeletal maturation.[18,20,21]

Oral and intravenous bisphosphonates are commonly prescribed for all OI types. In case of decreased bone mineralization, high fracture frequency and/or bone deformities, intramedullary rods will be placed in the majority of patients with OI types III and IV and sometimes in OI type I. In patients with dentinogenesis imperfecta, fractures and excessive wear of fragile teeth often occurs. This can be treated by capping teeth with hard polymers in order to prevent infections and facial deformities due to the loss of (parts of) teeth and/or malocclusion.[18,20]

METABOLIC DISORDERS

Hypophasphatasia

HPP is characterized by poor bone mineralization resulting from loss-of functional mutations in ALPL, encoding tissue-nonspecific alkaline phosphatase (TNAP). TNAP is an ectoenzyme that hydrolyzes (thus reducing) inorganic pyrophosphate which is a potent mineralization inhibitor. In addition to expression by chondrocytes and osteoblasts, TNAP is found in the dentoalveolar complex with wide expression in the periodontium, dentin pulp complex and enamel organ.[22,23]

Skeletal deformities (e.g., dolichocephalic skull and enlarged joints), a delay in walking, short stature and waddling gait accompany the childhood form. A history of fractures and bone pain is usually noted. Adults are often diagnosed during middle age. Premature loss of primary teeth is allied with infantile and adult subtypes.[22]

Radiographic finding includes enlarged pulp chambers and root canals with reduced alveolar bone. Histological analysis of extracted/exfoliated teeth reveals aplastic and hypoplastic cementum.[22]

The management includes symptomatic treatment to improve the clinical symptoms and the metabolic phenomenon. Vitamin D and calcium supplements can be given in these patients. Prosthetic replacement of prematurely lost teeth may be helpful in linguistic development and social integration of patients in preschool or school.[22]

The condition can be completely asymptomatic and is suspected after a low ALP level is found during routine laboratory studies, although careful interrogation often reveals signs and symptoms during childhood or infancy.[22,23]

Renal osteodystrophy

Renal osteodystrophy is the term used to describe the many different patterns of the skeletal abnormalities that occur in patients with chronic kidney disease.[24,25]

Chronic renal failure leads to decrease in glomerular filtration rate and thereby decreases the elimination of phosphate. The excess phosphate binds with calcium in body and reduces the availability of free ionized calcium for metabolism which leads to hypocalcemic condition. The conversion of inactive form of Vit D into active form (1,25-(OH)2D3) by enzyme 1-alpha hydroxylase is also affected in renal failure cases which results in hypocalcemia. Osteitis fibrosa is a manifestation of the effects of high levels of PTH on bone and is associated with a high bone turnover. Both these conditions stimulates the increase in PTH secretion which results in bone demineralization and osteolysis.[24,25]

It can generate a wide range of oral facial and dental manifestations, such as gingival hyperplasia, periodontal disease, xerostomia, lichen planus, uremic stomatitis, candidiasis, herpes simplex, delayed dental eruption, enamel hypoplasia and dental mobility. The consequence of secondary hyperparathyroidism leading to changes in bone that are similar to those of fibrous osteitis cystica and to physeal changes resembling those of rickets.[24]

Increased levels of serum PTH and total ALP remain the most widely used biochemical tests for renal osteodystrophy. Multiple teeth in the erupting and exfoliating stage (mixed dentition) with wide open apex and narrow pulp chambers, delayed eruption of the permanent teeth compared to that age group was also observed. Diffuse lytic areas of bone were present with loss of inferior cortical thickness. In addition, there was reduction of trabecular pattern which assumed a ground glass appearance in radiographs.[24-26]

Hemodialysis is used approximately in 80% of affected patients. Dental treatment strategy should emphasize oral hygiene and patients should be reinforced frequently in hygiene performance. Symptomatic treatment should include oral antibiotics to prevent the future bacterial endocarditis and oral antifungals should be prescribed to prevent secondary candidal infection.[26]

RICKETS

Rickets is a common condition in children that occurs due to a defect in bone mineralization which leads to abnormalities of growth plate cartilage that are predominantly observed in long bones. It may occur due to deficiency of calcium, phosphorous or Vitamin D. The condition equivalent in adults known as osteomalacia which is a generalized softening of skeleton due to defective mineralization. Rickets in children is often accompanied by osteomalacia. The major problems of rickets in childhood are growth retardation and bone deformity. In contrast, adult patients with osteomalacia present with muscle weakness and bone pain.[15,16,27]

These anomalies lead to discordance between the production and the rate of mineralization of bone matrix, hence the accumulation of unmineralized matrix and poorly mineralized bone, causing as main clinical features severe body deformities, especially bowing of the legs, impaired growth and short stature. Radiologic findings usually include fractures, generalized osteopenia and growth failure in some cases craniosynostosis may be present and arched or curve legs.

Dental findings that are often characteristic include dentin defects, unusually large pulp chambers and enlarged pulp horns, in some cases the enamel is hypoplastic. These dental problems are more commonly associated with the primary than the permanent dentition. The most common intraoral radiologic findings include large pulp chambers, short roots, poorly defined lamina dura and hypoplastic alveolar ridge.[27,28]

On histologic analysis, the dentin exhibits large tubular clefts or lacunae and the enlarged pulp horns may extend beyond the dentinoenamel junction. The poorly formed dentin and close proximity of the pulp to the tooth surface may lead to a rapid necrosis of the pulp with periapical complications, because the bacterial ingress to the pulp is being facilitated, occurring spontaneous dental abscess without history of trauma or caries.

The main management strategy for the dental manifestations is the prevention of dental abscesses by prophylactic treatment. In the patients, this may be achieved through prophylactic pulp therapy, pulpotomy and pulpectomy, coverage of the molar teeth with stainless steel and restoration of the teeth with composite resins and resin glass ionomer cement. Professional dental care consisting of periodical examinations, topical fluoride application and the maintenance of good oral hygiene should be performed.[28]

ENDOCRINAL DISORDERS

Hyperparathyroidism

PTH regulates the calcium homeostasis. When the calcium level is low, it stimulates bone break down thereby releasing calcium in blood. It induces the osteoclast activation through its receptors in osteoblast. Elevated PTH causes increase in release of RANKL in osteoblast which binds to RANK in osteoclast precursor thereby leading to maturation of osteoclasts.[15,24]

Increased osteoclastic activity leads to dystrophic lesions in bone. The skeletal and neuromuscular changes manifest as bone pain/tenderness, muscle fatigue, weakness and spontaneous fractures, osteoporosis, osteopenia and cystic bone lesions.[15,24]

Osteoporosis is the most common finding secondary to hypocalcemia in HYPERPARATHYROIDISM. Most commonly affected bones are ribs, clavicles, pelvic girdle and mandible. A pathologic fracture may be the first symptom of the disease. Renal calculi are a common finding in this condition. Almost all patients with HPT have skeletal lesions in the advanced stages.[29,30]

Intraoral manifestations are obliteration of pulp chamber by pulp stone, alterations in dental eruption, loosening and

drifting of teeth, malocclusions, spacing of teeth, partial loss of lamina dura, periodontal ligament widening, teeth become sensitive to percussion and mastication, floating teeth, delay or cessation of dental development, brown tumor, generalized bone ratification of jaw, soft-tissue calcifications, caries, hypercalcemia may result in sialolithiasis mandibular tori.[29,30] The radiograph is typically described as loss of medullary trabecular pattern, jaw appears finely radiopaque described as clear "ground glass" appearance.[29]

The treatment of HPT is the first step in the management of the brown tumor, as spontaneous regression of the lesion often occurs. However, several cases of brown tumor that did not disappear or even grew after normalization of PTH level have been reported. In these cases, brown tumor resection should be the preferred treatment. Jaw enlargement is treated by recontouring of the maxilla and mandible. A three-dimensional reconstruction of the computed tomography scan was helpful in evaluating the facial deformities and in treatment planning.[30,31]

Fibrous dysplasia

Fibrous dysplasia is a skeletal and developmental anomaly of bone forming mesenchyme characterized by replacement of normal bone by cellular connective tissue intermixed with irregular bony trabeculae.[32]

The molecular etiology of the disease which leads to the arrest in differentiation that occurs in bone marrow stromal cells, is activating mutations in the GNAS gene.

GNAS codes for the alpha subunit of the signaling G protein, Gsa. Gsa is an important gene in the cell signaling pathway that leads to the generation of the intracellular second messenger, cAMP and activating mutations lead to ligand-independent cAMP/protein kinase A signaling. cAMP is involved in the signal transduction from multiple cell surface receptors, including PTH, follicle stimulating hormone and luteinizing hormone, thyroid stimulating hormone and melanocyte stimulating hormone.[32,33]

Hyperfunction of affected endocrine organs giving rise to precocious puberty, hyperthyroidism, growth hormone and cortisol overproduction. The increased proliferation of melanocytes resulting in large café-au-lait spots with irregular margins. Elevated cAMP also impairs the osteoclast differentiation leads to fibrous dysplasia. In fibrous dysplasia, the medullary bone is replaced by fibrous tissue, which arise radiolucent on radiographs showing ground glass appearance.[15,16]

Many lesions are discovered incidentally on radiographs and are asymptomatic. Such lesions ordinarily pose no risk for pathologic fracture or deformity, and only clinical observation is warranted. Bisphosphonates, primarily pamidronate, have been used most extensively for patients with polyostotic diseases supplemented with calcium (500–1500 mg/day) and Vitamin D (800–1200 IU/day). Surgical procedures may be required for correction of a deformity, prevention of pathologic fracture and/or eradication of symptomatic lesions.[33]

CHERUBISM

Cherubism is a rare disease of autosomal dominant condition characterized by painless symmetrical enlargement of jaw as a result of replacement of bone with fibrous connective tissue[15,16,34] and present as painless enlargement of jaws.

This condition occurs due to mutation in SH3BP2 gene on chromosome 4p16.3 which leads to the production of overactive proteins which is expected to disrupt critical signaling pathways in cells associated with maintenance of bone tissue and some immunological effector cells. The over reactive protein likely causes inflammation of jaw bones and triggers the pathologic activation of osteoclast and disruption of jaw development.[15,16,34]

The hallmark of cherubism is the development of symmetrical multilocular radiolucent expansile lesions in the mandible and/or the maxilla, which typically first appear at the age of 2–7 years. Submandibular and cervical lymph nodes are enlarged during the early stages of cherubism. Lesions in patients with the progressive form of cherubism result in extensive bone resorption and leave only a fenestrated shell of cortical bone. Fibrous tissue masses can expand the cortical bone and lead to facial swelling. When expansile fibrous tissue masses invade the floor and walls of the orbits they can cause upward tilting or displacement of the globes.[34,35]

The arrangement of primary teeth can be disturbed. The disruption of the secondary dentition can include absent teeth (mostly molars), rudimentary development of molars, abnormally shaped teeth, partially resorbed roots or delayed and ectopically erupting teeth. Tooth extraction may be needed, especially if teeth are "free-floating" in cherubism lesions or if they become ectopically impacted.[34-36]

Mild forms of cherubism without facial dysmorphology, dental and ocular involvement may not require treatment as cherubism is expected to regress spontaneously after puberty. Management in these cases consists of longitudinal observation. Surgical intervention is indicated when aesthetic or functional concerns arise including nasal obstruction, proptosis or facial deformity. Options for

surgical management include partial resection, contour resection, curettage or a combination of these. Surgical procedures should be performed after puberty when the lesions are quiescent.[35]

PAGETS DISEASE

Paget's disease which is characterized by excessive and abnormal remodeling of bone is a common disorder in middle-aged and elderly patients. The excessive remodeling gives rise to bone that are extensively vascularized, weak, enlarged and deformed with subsequent complications.[15,16]

Paget's disease of bone is characterized by enhanced resorption of bone by giant osteoclast with the formation of disorganized woven bone by osteoblast.[15,16] This hyperactive osteoclast causes massive destruction of lamellar bone. As a result, there was an increased osteoblastic response as a compensatory mechanism. The rapid deposition of vascular connective tissue and remodeled lamellar bone leads to poorly mineralized overgrowth of bones resulting in severe musculoskeletal impairments with neurologic and cardiovascular complications.

Clinical symptoms include pain, deformity, and may lead to fracture of the affected bone, even though the initial course of the disease may be asymptomatic. The enlarged and deformed bones may compress surrounding nerves and vessels causing neurological symptoms such as hearing loss; inexplicably, it is quite unusual in the facial bones. Facial disfigurement may be consequence of enlargement of the maxilla and/or mandible. Radiograph shows characteristic cotton wool appearance and other radiographic finding include well-circumscribed radiolucency, loss of lamina dura, pulpal radio-opacity, root resorption and hypercementosis.[37]

Therapeutic agents commonly used include CT, bisphosphonate and mithramycin. Pain management and surgery are also used when indicated.[37]

CONCLUSION

The mysteries of bone biology are being unraveled at an unprecedented pace, and our understanding of bone-remodeling diseases and targeted therapies is rapidly evolving. The newer methods in molecular and cellular biology should enable us to define the abnormalities in cells of the osteoblastic and osteoclastic lineages that lead to bone disease and to develop new approaches based on a fuller understanding of the pathogenic mechanisms in these disorders. Elucidation of the signals that regulate bone remodeling could further improve the understanding of mineralization and bone-formation disorders and may allow us to develop new anabolic therapies to build bone. In future, we can expect the development of even more new therapies to evolve from a better understanding of the complex molecular aspects of bone turnover.

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REFERENCES

1. Warburg M, Møller HU. Dystrophy: A revised definition. J Med Genet 1989;26:769-71.
2. Shafer WG, Hine MK, Levy BM. Shafers – Text Book of Oral Pathology. 5th ed. New Delhi: Elsevier Inc.: 2006. p. 674-701.
3. Raisz LG. Physiology and pathophysiology of bone remodeling. Clin Chem 1999;45 (8 Pt 2):1353-8.
4. Siddiqui JA, Partridge NC. Physiological bone remodeling: Systemic regulation and growth factor involvement. Physiology (Bethesda) 2016;31:233-45.
5. Feng X, Teitelbaum SL. Osteoclasts: New insights. Bone Res 2013;1:11-26.
6. Hadjidakis DJ, Androulakis II. Bone remodeling. Ann N Y Acad Sci 2006;1092:385-96.
7. Yedavally-Yellayi S, Ho AM, Patalinghug EM. Update on osteoporosis. Prim Care 2019;46:175-90.
8. Satpathy AS, Dasgupta A, Dutta C, Mohan NV, Satpathy S. Osteitis fibrosa cystica of mandible in hyperparathyroidism-jaw tumor syndrome: A rare presentation and review of literature. Natl J Maxillofac Surg 2017;8:162-6.
9. Wang X, Schröder HC, Müller WE. Amorphous polyphosphate, a smart bioinspired nano-/bio-material for bone and cartilage regeneration: Towards a new paradigm in tissue engineering. J Mater Chem B 2018;6:385-412.
10. Müller WE, Schröder HC, Wang X. The understanding of the metazoan skeletal system, based on the initial discoveries with siliceous and calcareous sponges. Mar Drugs 2017;15:172.
11. Müller WE, Neufurth M, Huang J, Wang K, Feng Q, Schröder HC, *et al*. Nonenzymatic transformation of amorphous CaCO3 into calcium phosphate mineral after exposure to sodium phosphate *in vitro*: Implications for *in vivo* hydroxyapatite bone formation. Chembiochem 2015;16:1323-32.
12. Blair HC, Teitelbaum SL, Ghiselli R, Gluck S. Osteoclastic bone resorption by a polarized vacuolar proton pump. Science 1989;245:855-7.
13. Kattimani VS, Kondaka S, Prasad K. Hydroxyapatite – Past, present, and future in bone regeneration. Bone and Tissue Regeneration Insights 2016;7:9-19.
14. Sharma SS, Saravanan C, Sathyabama V, Satish C. Osteopetrosis of the mandible masquerading as tubercular osteomyelitis. BMJ Case Rep 2013.
15. Shafer WG, Hine MK, Levy Shafers BM. Shafers – Text Book of Oral Pathology. 6th ed. New Delhi: Elsevier Inc.; 2006. p. 731-6, 699-701.
16. Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology. 2nd ed. Philadelphia: W. B. Saunders Company; 2001. p. 542-4, 534-5.
17. Bénichou OD, Laredo JD, de Vernejoul MC. Type II autosomal dominant osteopetrosis (Albers-Schönberg disease): Clinical and radiological manifestations in 42 patients. Bone 2000;26:87-93.
18. van Dijk FS, Cobben JM, Kariminejad A, Maugeri A, Nikkels PG,

van Rijn RR, *et al*. Osteogenesis imperfecta: A review with clinical examples. Mol Syndromol 2011;2:1-20.
19. Bollerslev J, Andersen PE Jr. Radiological, biochemical and hereditary evidence of two types of autosomal dominant osteopetrosis. Bone 1988;9:7-13.
20. Abukabbos H, Al-Sineedi F. Clinical manifestations and dental management of dentinogenesis imperfecta associated with osteogenesis imperfecta: Case report. Saudi Dent J 2013;25:159-65.
21. Renaud A, Aucourt J, Weill J, Bigot J, Dieux A, Devisme L, *et al*. Radiographic features of osteogenesis imperfecta. Insights Imaging 2013;4:417-29.
22. Jingala VK, Tangade P, Puniya H, Gupta V, Singh V, Kaira M, *et al*. Hypophosphatasia rare but there. J Contemp Dent 2016;6:184-8.
23. Foster BL, Ramnitz MS, Gafni RI, Burke AB, Boyce AM, Lee JS, *et al*. Rare bone diseases and their dental, oral, and craniofacial manifestations. J Dent Res 2014;93:7S-19.
24. Slatopolsky E, Gonzalez E, Martin K. Pathogenesis and treatment of renal osteodystrophy. Blood Purif 2003;21:318-26.
25. Cushner HM, Adams ND. Review: Renal osteodystrophy—pathogenesis and treatment. Am J Med Sci 1986;291:264-75.
26. Parthiban J, Nisha VA, Asokan GS, Prakash CA, Varadharaja MM. Oral manifestations in a renal osteodystrophy patient-a case report with review of literature. J Clin Diagn Res 2014;8:ZD28-30.
27. Jagtap VS, Sarathi V, Lila AR, Bandgar T, Menon P, Shah NS. Hypophosphatemic rickets. Indian J Endocrinol Metab 2012;16:177-82.
28. Souza AP, Kobayashi TY, Lourenço Neto N, Silva SM, Machado MA, Oliveira TM. Dental manifestations of patient with vitamin D-resistant rickets. J Appl Oral Sci 2013;21:601-6.
29. Mittal S, Gupta D, Sekhri S, Goyal S. Oral manifestations of parathyroid disorders and its dental management. J Dent Allied Sci 2014;3:34-8.
30. Khalekar Y, Zope A, Brahmankar U, Chaudhari L. Hyperparathyroidism in dentistry: Issues and challenges!! Indian J Endocrinol Metab 2016;20:581-2.
31. Rolighed L, Rejnmark L, Christiansen P. Bone involvement in primary hyperparathyroidism and changes after parathyroidectomy. Eur Endocrinol 2014;10:84-7.
32. Leet AI, Collins MT. Current approach to fibrous dysplasia of bone and McCune-Albright syndrome. J Child Orthop 2007;1:3-17.
33. DiCaprio MR, Enneking WF. Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J Bone Joint Surg Am 2005;87:1848-64.
34. Gde ML, Almeida JD, Cabral LA. Cherubism: Clinicoradiographic features and treatment. J Oral Maxillofac Res 2010;1:e2.
35. Kozakiewicz M, Perczynska-Partyka W, Kobos J. Cherubism – Clinical picture and treatment. Oral Dis 2001;7:123-30.
36. Papadaki ME, Lietman SA, Levine MA, Olsen BR, Kaban LB, Reichenberger EJ. Cherubism: Best clinical practice. Orphanet J Rare Dis 2012;7 Suppl 1:S6.
37. Karunakaran K, Murugesan P, Rajeshwar G, Babu S. Paget's disease of the mandible. J Oral Maxillofac Pathol 2012;16:107-9.