

## Review Article

# Maxillofacial Musculoskeletal Diseases

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## Abstract

Musculoskeletal diseases are a heterogeneous group of diseases/disorders/syndromes, deriving its origin from cartilage/bone, muscle, nerve and blood vessels and affecting all age groups. Its variegated composition leads to overlap of symptoms, multisystem involvement and a chronic course coexisting with metabolic and aging diseases. All these make musculoskeletal diseases a major health issue influencing the quality of life. Further, oral manifestations of these diseases are a significant component that adds on to its severity and disability levels. However, there have been fewer attempts to bring these disease groups under a common umbrella in terms of their clinical strategies and rehabilitation protocols. This paper mainly focuses on the oral/dental features of these diseases as a separate entity of maxillofacial musculoskeletal diseases. It also reviews its contemporary and future treatment options with the objective of rendering comprehensive care through a multidisciplinary approach.

**Keywords:** Musculoskeletal; Maxillofacial

## Introduction

Musculoskeletal diseases are a major cause of disability among elders [1]. Bone and joint decade initiative of World Health Organization identifies chronic musculoskeletal pain of 3 months or more as a common medical complaint with every 1 in 2 adults, older than 18 years [2]. Directly, they do not add on to the mortality rate of a community; however, its impact and influence on the quality of life and its driving nature towards terminal ill health conditions, makes it a serious socioeconomic issue [3]. Since the degree of limitations for performing routine life activities; locomotion, eating, own body care and sleeping, widely range among patients, understanding their treatment and rehabilitation needs are challenging for both the policy makers and care givers. Though the terminology of musculoskeletal denotes involvement of muscles and skeletal tissues, this group draws diseases, disorders and syndromes anatomically and functionally from four components: muscles, bone, nerves and vessels. Notwithstanding that, there is no single classification under which these diseases of diversified origin are placed. Further, musculoskeletal diseases often show a modified response in the maxillofacial bones; maxilla and mandible, unlike other long and flat bones. This is due to the 'additional variable' of masticatory stresses which are transferred to these bones through the teeth embedded in it. All these make maxillofacial musculoskeletal diseases an unattended or ill-understood group. These foster a strong cause for reviewing these diseases; considering the fact that little consensus exists even on its classification. This paper presents the major maxillofacial musculoskeletal diseases which have a direct bearing on the general and oral/dental health. It also evaluates its contemporary medical and surgical modalities along with future stem cell based treatment approaches.

## Maxillofacial musculoskeletal diseases

Musculoskeletal diseases directly or indirectly involve the oral tissues. However, their diagnosis often remains as an elusive issue in dental practice because many of the entities do not generally manifest as patient seek dental treatment. The disabling nature of these types of diseases also compromises the oral hygiene practices, further accentuating the damages. Some of the drugs used for musculoskeletal diseases alter the immune system and cause dental effects; delayed wound healing, increased bleeding tendencies and susceptibility to opportunistic infections [4]. (Table 1) enumerates the main diseases affecting maxillofacial bones [5]. (Figure 1 and 2) illustrate the different groups of musculoskeletal diseases originating from different tissues. The succeeding discussions focus only on the important diseases form this group from an oral/dental perspective.

## Osteogenesis imperfecta

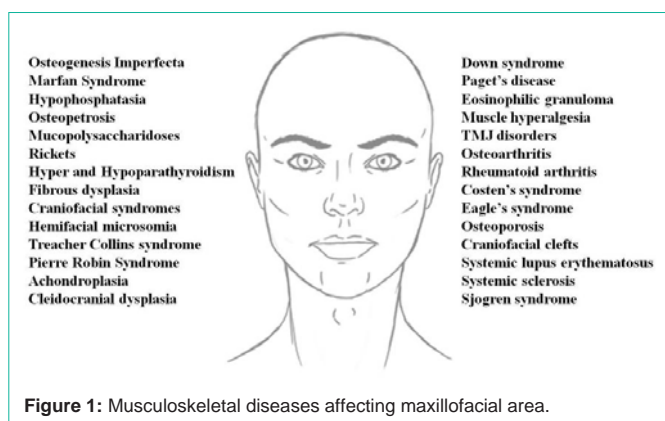
The disorder is inherited as an autosomal dominant/recessive or non hereditary pattern due to an abnormality in the type 1 collagen synthesis, which forms fragile and porous bone. Different types of Osteogenesis Imperfecta (OI) have been identified: OI type I and II, OI tarda, OI neonatal lethal, OI Vrolik, OI with blue sclera, OI progressively deforming with normal sclera/Type III, OI Type IV; all with a gene map locus at 17q21.31-q22.1. It features a triad of brittle bones, blue sclera and deafness (otosclerosis). Bone extremities are small/deformed and rib fractures are common. Calvarium is made of soft wormian bones that make them prone to intracranial hemorrhage and hydrocephalus. Muscular hypotony is due to the weak tendinous insertions into bones. Bone fractures are noticed form 2 to 4 years of age with several pseudoarthroses. Neural defects affecting cerebellum and pyramidal tracts arise from abnormal bone-nerve connections.

**Table 1:** Classification of maxillofacial musculoskeletal diseases\*.

Group	Inheritance**	Types
1. Defects in extracellular structural proteins	AD	Osteogenesis imperfecta
2. Defects in metabolic pathways, enzymes, ion channels and transporters	AR, AD AR	Hypophosphatasia Osteopetrosi
3. Defects in folding and degradation of macromolecules	AR	Mucopolysaccharidoses
4. Defects in hormone and signal transduction dependent rickets Mechanism	AR	Vitamin D resistant and
	AD	Hyperparathyroidism
	AD	Hypoparathyroidism
	AD	Fibrous dysplasia
	AD	Craniosynostosis
	AD	Achondroplasia
5. Defects in nuclear proteins and transcription factors	AD	Cleidocranial dysplasia
6. Defects in oncogenes and tumor suppressor genes	AD	Cherubism

\*Adapted and modified from Ref 5

\*\* AD- Autosomal dominant, AR- Autosomal recessive

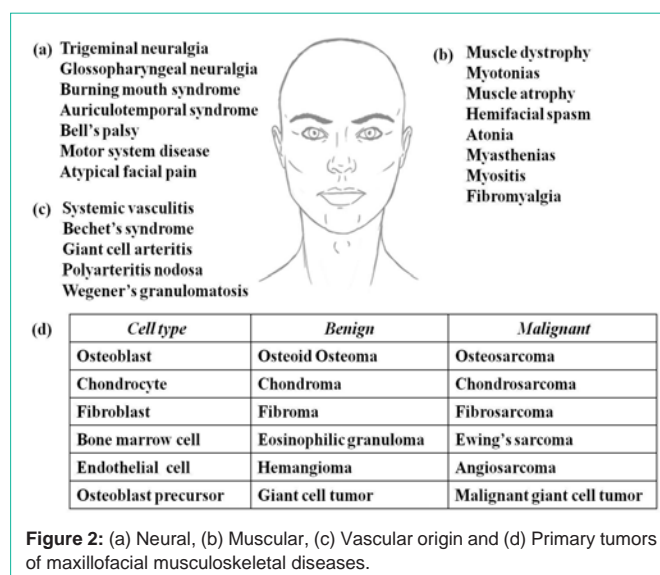


**Figure 1:** Musculoskeletal diseases affecting maxillofacial area.

Histologically, it has thin cortices and spongy bones, since osteoblasts are affected owing to defects in collagen synthesis. A variant of it; known as dentinogenesis imperfecta, shows defective dentition, maxillary hypoplasia, frontal bossing, cross bite and anterior open bite [6]. No definitive treatment exists for osteogenesis imperfecta, other than the interventions done for secondary infections. Type I cases survive, but Type IIs succumb to death in first year of life. For other groups, varying ranges of decreased life expectancy is seen.

**Marfan syndrome**

It is a connective tissue disorder; with an autosomal dominant mode of inheritance, where FBN1 gene on chromosome 15, bands q15-q23, which codes fibrillin/connective tissue protein, is affected. The classic triad of Marfan's syndrome includes subluxated lenses, skeletal anomalies, and cardiovascular diseases. Aortic dilatation and aneurysms are common. It also involves the lungs, muscles, genitourinary system, and skin. Patients are tall with arm span being greater than the total height. Generally, hyper extensibility and habitual dislocations of joints, kyphosis and flat feet are seen. It shows long, narrow skull, high arch palate, malocclusion and temporomandibular joint disorders [7]. Though no specific treatment is available for the disease, cardiovascular complications are attended to reduce its morbidity and mortality.



**Figure 2:** (a) Neural, (b) Muscular, (c) Vascular origin and (d) Primary tumors of maxillofacial musculoskeletal diseases.

**Hypophosphatasia**

This disorder affects patients of all age groups, where bone mineralization is disturbed due to alkaline phosphatases deficiency [8]. The gene is ALPL, placed at band 1p36.1-34. The 'perinatal' type is lethal and 'infantile' type has 50% mortality. Premature loss of teeth, defective root cementum and hypocalcified teeth are dental findings. No definite therapy exists for the disease.

**Osteopetrosis**

Defects in osteoclast bone resorption causes increase in bone mass but results in poor quality thick sclerotic bone. Three distinct types are noticed; infantile (malignant), adult onset (benign) and intermediate. The first has an autosomal recessive inheritance, manifested in early life and is usually lethal. Skull and pelvis are sclerosed and obliterate brain foramens to give rise to neurologic symptoms. Involvement of sella turcica cause pituitary dysfunctions. Cranial nerve palsies of 3<sup>rd</sup>, 4<sup>th</sup>, and 7<sup>th</sup> nerves are also found. Serum calcium and urinary hydroxyproline remains normal, irrespective of the abnormal

bone resorption. Medullary bone spaces are reduced making the maxillofacial bones vulnerable to osteomyelitis after dental infections. Jaw fracture during tooth extraction is a potential complication. Teeth are defective with enamel/dentinal abnormalities and arrested root development [9]. Radiographically; when the jaws are involved, tooth roots are not visible due to osteosclerosis. Treatment involves calcitriol therapy, which stimulate inactive osteoclasts towards bone resorption. Corticosteroids and gamma interferons are also used for stimulating bone resorption.

### Mucopolysaccharidoses

They are a group of lysosomal storage diseases (Type I-VII) with autosomal recessive or X linked type II inheritance. Defect lies in the degradation of glycosaminoglycans. Skeletal findings include dwarfism, stiff joint articulations involving jaw bones [10]. Accumulation of keratan sulfate and chondroitin-6-sulfate in connective tissue causes abnormalities in dental tissues. No definitive treatment exists for mucopolysaccharidoses, other than symptomatic and supportive.

### Rickets

It includes a group of disorders in the vitamin D-calcium-phosphorus axis that forms hypomineralized bone matrix due to defective endochondral bone calcification [11]. The pitfalls in bone mineralization of growth plates show as growth retardation. Vitamin D deficient rickets occur in infants and children. Adults show osteomalacia with under-mineralized bones from abnormal metabolism of vitamin D and phosphate. Another variant; vitamin D resistant rickets is a form of hypophosphatemia with reduced body height. The dental tissues show characteristic features like hypocalcified globular dentin and elongated pulp horns making teeth prone to caries and infections. Other findings are gingival fistulas, defective cementum and poorly defined lamina dura around tooth root. Histologically, hypertrophic zones of growth plates show large number of disorganized cells termed as rachitic metaphysis, illustrating interferences in the calcification of osteoid matrix. Renal rickets occurs because of the inability of kidneys to synthesize 1- $\alpha$ -hydroxylase and convert 25-hydroxycholecalciferol to the active metabolite of vitamin D.

### Hyper and hypoparathyroidism

Primary type results from the adenoma/hypertrophy of the gland, which is common in Type I and II Multiple Endocrine Neoplasia (MEN) syndrome [12]. Secondary hyperparathyroidism is because of the hyperplastic parathyroid glands and low serum calcium. It can occur at any age, but more common in 5-6<sup>th</sup> decades with high predilection for females. Features are bone pain, tenderness, muscle fatigue, weakness, spontaneous fracture, myalgia and osteoporosis with concomitant involvement of jaw bones [13]. Hypoparathyroidism on the other hand causes hypocalcaemia and hyperphosphatemia, leading to neuromuscular excitability. Circumoral numbness, paresthesia of distal extremities, muscle cramping, and carpopedal spasm/tetany are also found. Management of hyperparathyroidism is centered on reducing hypercalcemia.

### Fibrous dysplasia

The disease begins in childhood with no distinct pattern of inheritance. It is a syndrome with precocious puberty, dermal

pigmentation, and generalized skeletal dysplasia. Defect occurs in the bone forming mesenchyme where osteoblast maturation and differentiation are affected. It is mainly due to the mutation in the GNAS1 gene; 20q13.2. It leads to hyper function of affected endocrines, premature puberty, hyperthyroidism, overproduction of growth hormones and cortisol [14]. It also causes high proliferation of melanocytes to form café-au-lait spots with irregular margins. The medullary bone is replaced in fibrous dysplasia; appears radiolucent on radiographs characteristically described as ground glass appearance [15]. The disease presents as monostotic, polyostotic, craniofacial and cherubism. Monostotic is the predominant one in which craniofacial bones is affected. The polyostotic forms manifest as a mild Jaffe's type and a severe Albright syndrome [16]. Cherubism, an autosomal dominant inheritance pattern is seen more in children. It presents with a broad and protruding/ bulging jaw with premature exfoliation of primary teeth, delayed eruption of permanent teeth and resulting malocclusion. Skull and facial bones are affected causing disfigurement and functional (eye) deficits like in maxillo-sphenoido-frontal bone disease. The eye signs are because of the compression of the optic nerve within the optic canal [17]. Treatment involves correction of underlying endocrine disorders and functional deformities. Vitamin D and bisphosphonates are also given for bony lesions.

### Craniofacial syndromes

Crouzon's syndrome belongs to the group of craniofacial deformities known as craniosynostosis; which shows premature fusion of cranial sutures making a brachiocephalic skull. Fibroblast growth factor receptor gene (FGFR)-2 mutations could be responsible for Crouzon syndrome. This in turn causes increased intracranial pressure - brain damage/blindness and head shape deformities [18]. It is inherited as an autosomal dominant condition with mutations in the fibroblast growth factor receptors. Generally, it shows maxillary hypoplasia, high arch palate and bifid uvula. Ocular abnormalities include shallow orbits, bilateral ocular proptosis, hypertelorism, divergent strabismus, optical atrophy, conjunctivitis and loss of visual accuracy. Nystagmus, coloboma of the iris, anisocoria, microcornea/megalocornea, cataract, blue sclera, and glaucoma and globe luxation is also seen. Other intracranial abnormalities include anomalous venous drainage and hydrocephalus. Calcification of the stylohyoid ligament, cervical spine C2-5/elbow/hand abnormalities and skin lesions also occur [19]. Decompression of cranium is done in increased intracranial hypertension. Plastic/cosmetic surgery of the face can resolve facial deformities to a large extent.

### Hemifacial microsomia

It shows features like mid face flattening, deviation of nasal bone and chin, hypoplastic mandible, canting of occlusal plane, upper eyelid colobomas and sometimes cleft lip/palate [20]. When present with syndactyly, it is termed as Goldenhar's syndrome.

### Treacher collins syndrome (Mandibulofacial dysostosis)

This syndrome includes a group of disorders of the head and face with an autosomal dominant pattern of inheritance. It results from the disturbances in the differentiation of maxillary mesoderm. Gene responsible is 5q32-q33.1. Symmetrical deformity of the face is present with anti-mongoloid palpebral fissures, lower eyelid coloboma, external and middle ear hypoplasia, defective zygoma/mandible and

dental malocclusion with open bite. Macrostomia, high palate, facial clefts are features. Characteristically, patients present with 'bird faces' [21]. Though, there is no specific treatment, prognosis is good with most patients able to lead a normal life.

### **Pierre robin syndrome**

It presents in a triad of micrognathia, glossoptosis, and cleft palate [22]. For the newborns, breathing is compromised because of tongue pressure on the epiglottis. Cleft palate arises due to the trap of tongue between the palatine processes. Prognosis is good if early childhood survives respiratory problems. Micrognathia tend to become less noticed with growth. Aural and ocular anomalies, congenital heart disease, and malformation of the extremities are related findings. The complex facial features are addressed through a multidisciplinary approach; with main focus on maintaining the patency of airway.

### **Achondroplasia**

The disease is transmitted as an autosomal domain trait. It is caused by the mutation in the gene for fibroblast growth factor receptor: FGFR3; mapped to band 4p16.3. It presents with short stature, mid face hypoplasia, frontal bossing and malocclusion. Maxilla is retruded because of the growth restriction in the base of the skull [23]. Congenitally missing teeth are also noticed. Failure of endochondral ossification is evident in histology. However, if the patients survive initial years of life, they tend to lead a normal life.

### **Cleidocranial dysplasia**

It is a congenital disorder of bone showing clavicular hypoplasia with narrow thorax. There is late ossification of the skull, delayed closing of sutures with large open fontanelles [24]. It has an autosomal dominant pattern of inheritance, with rearrangement of long arm of chromosome 8(8q22) and another arm of chromosome 6. Mutations occurring in core binding factor alpha 1 gene, located on chromosome 6p21. Brachycephalic or wide skull is the feature. Calvarial thickenings of frontal, temporal and occipital bones, faulty development of brain foramina, dysplasia of paranasal sinuses are also seen. Maxilla, lacrimal and zygomatic bones are underdeveloped with high arch palate. Prolonged retention of deciduous teeth and delay in the eruption of successor teeth are noticed. The tooth root cementum also has defects. Crypt formation around impacted teeth and ectopic teeth are other findings [25]. Therefore, a multidisciplinary dental care is important for the normal development of dentition.

### **Down syndrome**

It is a frequent form of mental retardation with intelligence quotient of 25-30 with specific Mongoloid features and related somatic defects due to chromosomal aberrations. Trisomy 21, chromosomal translocation and mosaicism are the three cytogenetic types [26]. Brachycephalic head, short stature, broad and short hands are the skeletal anomalies. Abdominal protrusion, delayed and incomplete puberty, congenital defects of heart polydactyly/syndactyly are also seen. Oral manifestations include small mouth, macroglossia, maxillary hypoplasia, delayed tooth eruption, partial anodontia, enamel hypoplasia cleft lip/palate and juvenile periodontitis. Fissuring and thickenings of lips and angular cheilitis are also found [27]. 25% of the patients die during the first year of life out of respiratory infections and congenital heart disease. Oral care has an important role in the development of dentition and face.

### **Paget's disease**

It is inherited as autosomal dominant/recessive form. Age of onset of the disease is usually after 4-5<sup>th</sup> decades. There is increased resorption of bone by multinucleated osteoclasts and formation of irregular bones, which makes weak and deformed bones. Its symptoms are generally related to the compression of abnormal osseous tissues on adjacent structures. Pain and deformity of the lower extremities and fracture of femur and tibia are common. Head size increase and deafness secondary to osteosclerosis of the auditory system are also found. Hemorrhage from brittle abnormal bone can cause epidural/subdural hematoma [28]. Pelvis and spine are commonly affected. Pathological fractures, platybasia; soft cranial base sinking into cervical spine causing pain, numbness, defective gait, bladder and bowel incontinence are also frequent. A potential complication of abnormal bone is its malignant change into osteosarcomas, fibrosarcomas or rarely into giant cell tumors [29]. Radiographically, the findings can be a localized thinning and demineralization of bone known as osteoporosis circumscripta or a generalized and bizarre deformity involving several bones. It is described as a cotton wool appearance. A characteristic biochemical abnormality in Paget's disease is the highly elevated serum alkaline phosphatase level. The oral manifestations are enlarged maxilla with wide alveolar ridges, flat palate and expanding jaws. Defects in alveolar bone and cementum can cause pathologic migration of teeth, root resorption, malocclusion and sometimes tooth loss. The altered bone apposition and resorption affects the fit of the dentures [30]. Vitamin, hormone, calcitonin, bisphosphonates and radiation therapy are traditionally used for this condition marked by pathologic fractures and degenerative joint diseases.

### **Eosinophilic granuloma**

**(Multifocal Hand-Schuller-Christian Disease and unifocal skeletal and extra skeletal lesions):** This occurs in early life, marked by histiocyte proliferation in the skeletal/extra skeletal sites. Punched out bone destruction in skull is characteristic with exophthalmos and diabetes insipidus. Dysfunction of pituitary gland causing polyuria, dwarfism and infantilism are also noticed. Other features are facial swelling and asymmetry, sore mouth, ulceration, premature exfoliation of teeth and alveolar bone loss [31]. Dental conditions are corrected by the bony curettage of the lesions or by radiation therapy.

**Muscle hyperalgesia, referred pain and neck musculoskeletal disorders:** Transition of pain in musculoskeletal diseases from acute to chronic states is through peripheral and central sensitization, which manifests as tenderness and referred pain over a wider segment. Work place factors and their relationships to musculoskeletal disorders have been investigated, which have shown a correlation specifically with maxillofacial/neck shoulder diseases. Casual associations are there between repetitive work of these tissues which involve prolonged static loads/contraction and extreme working postures. A classical example is the back, neck and shoulder pain seen among dentists [32]. Seronegative spondyloarthritis are a group of related inflammatory joint diseases distinct from rheumatoid arthritis, which shows considerable overlap in their clinical features. Ankylosing spondylitis, a prominent condition of this group, secondary to chronic inflammatory arthritis, affects sacroiliac joint and spine, progressing to bony fusion of spine [33]. Osteomyelitis

of facial muscles consequent to staphylococci, pseudomonas and mycobacterium tuberculosis infections are another important group [34].

### Temporomandibular joint (TMJ) disorders

TMJ connects temporal bone of skull with the condyle of the mandible. It is termed either as a ginglymoid (rotation) or an arthroal (gliding) joint. The fibro cartilaginous joint surfaces are separated by an articular disc. The movements of the joint are highly dependent on the dental occlusion between maxilla and mandible [35]. Developmental defects of the TMJ can be aplasia and/or hypoplasia of the condyle. It is treated with the help of orthodontic appliances in minor disorders to osteoplasty in severe conditions. Traumatic disturbances cause luxation and subluxation (complete and incomplete dislocation). In such cases, reduction is accomplished through relaxation of muscles followed by guiding condylar head by downward and backward movement beneath articular eminence. Ankylosis is another severe form of the TMJ disease owing to forceps delivery, chin trauma forcing condyle to glenoid fossa, malunion of condylar fracture, congenital syphilis etc [36]. Surgery is the only option in these cases.

Osteoarthritis of TMJ is associated with aging; where weight bearing joints are affected first [37]. Since TMJ is not a weight bearing joint, changes are induced in late stages only. Osteoarthritis involves a gradual deterioration of the joint cartilage with proliferation and remodeling of underlying bone. Pain, stiffness and loss of function are the main features. Degeneration of TMJ cartilage causes pain, clicking and altered dental occlusion leading to limited jaw opening. Tenderness is present over muscles of mastication/sternocleidomastoid/trapezius. Concomitant dentofacial deformities like short mandible, cross bite/open-bite/asymmetry are also present. The disease shows degeneration of articular cartilage/disc/synovium/subchondral bone through the mediation of neuropeptides, cytokines, serotonin and free radicals [38]. Supportive, symptomatic treatment is done for pain and discomfort, while condylectomy is considered for severe conditions. Rheumatoid arthritis of TMJ is another group, where females are affected more. It involves the synovial tissue between bones and joints. Though it is less prevalent than osteoarthritis, it manifests through severe symptoms. It destroys the joint cartilage and cause erosion of adjoining bone. Other systemic involvement is in the renal, vascular, ophthalmic and dental tissues. It is considered to have an autoimmune etiology. Inflammation originating from adjacent structures like otitis media, mastoiditis, osteomyelitis of temporal or condyle and radiotherapy also contribute to it. Rheumatoid arthritis affects oral health in multiple ways. Due to the restricted joint movement of hands, oral hygiene maintenance becomes difficult, which in turn invites dental caries, gingivitis and periodontitis. It also deteriorates the functioning of temporomandibular joint [39]. In children, rheumatoid arthritis cause malocclusion of protuberant maxilla, open bite, deformation of mandible with short body and reduction in the height of ramus. Periarticular fibrosis is another feature. Histologically, disease is associated with invasion of granular tissue over articular surface and destruction of articular cartilage. Cartilage cells exhibit degeneration and destruction with bony exostoses. Remarkable improvement is noticed with administration of cortisone. If joint movements are limited, condylectomy can regain mobility.

TMJ syndrome is a common cause of facial pain second to tooth ache [40]. They form a set of disorders involving the TMJ and masticatory muscles characterized by pain, tenderness, clicking and limited mouth opening. It has a higher prevalence among adult females. Joint overload is the key factor for the initiation of TMJ syndrome. Etiology is multifactorial and includes malocclusion, jaw clenching, bruxism, psychologic disorders, stress and trauma. Osteoarthritis, rheumatoid arthritis and ankylosis also lead to it [41]. Therefore, a combination therapy involving self care practices for relieving muscle spasms and restoring joint coordination is required. Non steroidal anti-inflammatory drugs can be of good help for symptomatic relief. Costen's syndrome is a type of TMJ disorder where the joint pain is either due to the posterior displacement of condyle causing pressure on the auriculotemporal nerve or due to the eccentric position of the condyle in the temporal fossa [42]. Temporomandibular disorders also present with ear complaints. This is due to the common features of TMJ and ear in terms of embryology, anatomy and function. Mostly, it is due to the same trigeminal innervation and by the auditory tube dysfunction. Associated findings are vertigo and tinnitus [43]. Musculoskeletal diseases of the cervical spine also affect the temporomandibular jaw functions [44]. A long styloid process often causes cervicofacial pain near ear and temporomandibular region with difficulty in swallowing known as Eagle's syndrome [45]. Osteoporosis is a generalized condition marked by reduced bone density with propensity towards fracture. Decline of estrogen in post menopausal women, accumulation of fat in bone marrow, genetic/ environmental factors, endocrine, and drugs are the chief causes. It also affects the maxillofacial skeletal tissues including TMJ [46]. Screening radiographs like transcranial views/ panoramic films, arthrography and tomograms/3D reconstructions/ stereolithography would show abnormalities of condylar head and temporal bone ankylosis/dysplasia/growth aberrations/trauma/ tumors. Arthroscopy would help in synovial fluid analysis and getting biopsy specimens [47]. MRI can complement the clinical diagnosis by rightly identifying the osteoarthritic changes of temporomandibular joint [48]. Symptomatic treatment is basic to temporomandibular disorders. Pharmacotherapy is useful for acute pain. Occlusal splints are helpful in harmonizing neuromuscular dysfunctions arising out of dental occlusion. Behavioral therapy is also used for managing chronic pain. A variety of pharmacologic agents are used. Tranquilizers, muscle relaxants, sedatives, and narcotics are given in serious and refractory cases. Dental appliances like occlusal splints/ night guards are used to aid in bruxism. Physical therapy involves exercises, external massages and other psychological means to address stress. Surgical options include arthroscopy, arthrocentesis, condylotomy, arthrotomy, coronoidotomy, coronoidectomy, styloidectomy and joint replacements with alloplastic implants [49-51]. From the foregoing, it follows that musculoskeletal dysfunctions cause a major amount of disability among different age groups of population: newborns, infants, pre-adolescent/adolescents, adults and elderly. Some of them are fatal, while most of them significantly affect the quality of life. They are also marked by specific oral findings, which are often hallmark of the disease. Surprisingly, no definitive treatment exists for individual entities of these groups; which has its pathogenesis related to wide ranging causes as shown in (Table 1). A common thread unifying these disease groups would be their multidisciplinary treatment protocol; found effective in ameliorating

the oral symptoms and in reducing the morbidity associated with these disorders.

### **Craniofacial clefts**

They occur due to the partial/complete failure of facial processes during intrauterine development. Cleft lip deformity is caused by the non fusion of the maxillary and median nasal processes, whereas cleft palate occurs due to the defects in the fusion of palatine process with maxillary process [20].

### **Systemic lupus erythematosus**

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by chronic inflammation mediated by auto antibodies and immune complexes towards organ damage affecting skin, kidney, blood cells and neural tissues. It manifests as a cutaneous (erythematous patches over face) systemic disorder with frequent ups and downs. Oral mucous membrane shows lesions similar to skin [52]. Genetic, environment and hormones can precipitate the immune dysregulation seen in lupus. Patients with SLE have autoantibodies against DNA, nuclear materials, ribosomes, platelets, erythrocytes, leukocytes etc. Since being a lifelong illness with possibility of end organ damage to vital organs, patients require long term monitoring to maintain quality of life.

### **Systemic sclerosis**

Systemic sclerosis is a multisystem autoimmune disease. It causes peripheral and visceral vasculopathy and progressive fibrosis of the skin and internal organs like heart, lungs and kidney. It shows induration of epidermis to underlying subcutaneous tissues. Tongue, soft palate and larynx are involved. Dysphagia, limitation in mouth opening and lymphocytic infiltration of minor salivary glands are also seen [53]. No adequate treatment is available for progressive systemic sclerosis, but partial remissions are seen with cortisone therapy.

### **Sjogren's syndrome**

It is an autoimmune disease with wide ranging systemic manifestations [54]. Decreased lacrimal/salivary gland function, xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement are the main findings. Primary Sjogren's presents alone, whereas secondary Sjogren's occurs along with autoimmune rheumatic diseases. Joint disease in primary Sjogren's is of an intermittent polyarticular arthropathy type with arthralgias and myalgias. Extreme fatigue is highly troublesome for the patients. Other systemic involvement is with lungs, liver, kidneys, vasculature, and blood. Dry skin is a major feature. The main pathophysiology of Sjogren's is chronic immune stimulation. B cell hyper reactivity is expressed through hypergammaglobulinemia and circulating autoantibodies. Organ specific autoantibodies are against salivary ducts, thyroid gland, gastric mucosa, erythrocytes, pancreas, prostate and nerve cells and they contribute to tissue dysfunction before inflammation is apparent. Histologically, there is focal lymphocytic infiltrate; T, B and plasma cells, with a predominance of activated CD4+ helper T cells, around the glandular ducts. They produce interleukins and tumor necrosis factor. Cough is often the main respiratory symptom after xerotrachea. Other pulmonary complications are lymphocytic alveolitis, interstitial pneumonitis, fibrosis, and pseudo lymphoma. In the renal involvement, it affects kidney tubules causing renal tubular acidosis. Interstitial inflammation is predominantly lymphocytic with fibrosis and tubular atrophy.

### **Neural origin of maxillofacial musculoskeletal diseases**

Trigeminal neuralgia is a short duration severe pain in the maxillofacial area over the anatomical distribution of 5<sup>th</sup> cranial nerve [55]. It is usually initiated by trigger zones, where older adults are affected more with a greater female predilection. A similar and severe type is glossopharyngeal neuralgia [56]. Burning mouth syndrome is a diffuse burning sensation of mucosa, lips and tongue in the absence of specific mucosal lesions [57]. It has a psychosomatic association with etiology being dry mouth, mucosal disorders, gastro esophageal refluxes, vitamin deficiency, diabetes, menopause and psychologic disorders/stress. Auriculotemporal syndrome is due to the damage of auriculotemporal nerve and subsequent re-innervation of sweat glands by parasympathetic salivary fibers, which causes gustatory sweating; of the face and temporal area during eating [58]. Bell's palsy or 7<sup>th</sup> cranial nerve syndrome is due to an abrupt/isolated/unilateral peripheral facial nerve paralysis without specific cause. The affected corner of the mouth droops with drooling saliva and watering of the eye. Inability to close or wink the eye leads to infections. When patient smiles; paralysis becomes more obvious because corners of mouth do not rise nor close. Patient has a masked appearance [59]. Motor system diseases are a group of disorders with unknown etiology. They manifest with progressive muscular atrophy, amyotrophic lateral sclerosis and progressive bulbar palsy. They all undergo corticospinal, anterior horn cell degeneration with tongue and pharyngeal involvement. Muscular weakness, reflex loss, sensory disturbances, difficulty in speaking/swallowing, hoarseness of voice and impairment of palatal movements are also present [60]. There is no specific treatment for the motor system disease; many times it is fatal, though temporary remissions are also noticed. Atypical facial pain is a group of conditions in which there is a vague deep and poorly localized pain in the region supplied by 5<sup>th</sup> and 9<sup>th</sup> cranial nerve and 2<sup>nd</sup> and 3<sup>rd</sup> cervical nerves. Unlike neuralgias, it do not show trigger zones and the pain persists for weeks [61]. Tricyclic antidepressants give reasonable relief.

### **Muscular origin of maxillofacial musculoskeletal diseases**

Muscle dystrophy involves the progressive degeneration of skeletal muscle fibers albeit normal neuromuscular junctions. Important types are: severe generalized familial muscular dystrophy- which begins in early child hood with inability to walk or run. It is rapidly progressing with facial muscular enlargement and weakness of extremities. The mild restricted muscle dystrophy on the other hand is a slowly progressing one with inability to close eyes even during sleep because of weakness of facial muscles. Lips develop looseness and protrusion with myopathic facies where patients cannot smile and whistle [62]. No definitive treatment exists for these groups of diseases. Myotonias imply failure of muscles to relax after cessation of voluntary contraction. 3 forms are there: dystrophic, congenital and acquired. Dystrophic myotonia show facial muscle weakness, ptosis of eyelids and atrophy of masseter/sternocleidomastoid muscles [63]. Masseteric atrophy is generally seen in the lower half of the face with pharyngeal/laryngeal involvement. Histology has enlarged and scattered muscle fibers, centrally placed nuclei in long rows, hypertrophy of fibers and degenerative changes like muscle proliferation/intense basophilic cytoplasm/phagocytosis [64]. Hemifacial spasm involves repeated, rapid painless irregular, non rhythmic contraction of facial muscles in adults due to a peripheral facial nerve lesion. It starts as brief

**Table 2:** Current treatment protocols in maxillofacial musculoskeletal (MSK) diseases.

Non steroidal anti inflammatory (NSAIDs) drugs	Disease modifying anti rheumatic drugs	Biologic disease modifying anti rheumatic drugs	Surgical procedures for MSK diseases
Celecoxib 100-200mg	Hydroxychloroquine 200-400mg	Anti TNF	Soft tissue release
Etoricoxib 60-120mg	Sulfasalazine 2-4g	Rituximab	Tendon repairs
Ibuprofen 600-1600mg	D-penicillamine 250-750mg	Abatacept	Synovectomy
Meloxicam 7.5-15mg	Methotrexate 5-30mg	Anakinra	Osteotomy
Naproxen 500-1000mg	Gold 50mg/month i.m	Tocilizumab	Excision arthroplasty
Indomethacin 50-200mg	Azathioprine 50-150mg		Joint replacement arthroplasty
Ketoprofen 100-200mg	Cyclophosphamide 0.5-1g i.v		Arthrodesis
Piroxicam 20-30mg	Ciclosporin 150-300mg		
	Corticosteroids		

transitory twitching of periorbital muscles triggered by fatigue/tension/facial activity followed by sustained spasm that later spreads to entire half of the face. Opposite to these is reduction or complete absence of tone in facial muscles manifested as congenital variants in atonic diplegia, lipid/glycogen storage diseases, Mongolism, cretinism and achondroplasia. Infantile muscle atrophy and dystrophy show loss of muscle tone [63]. Myasthenias generally denote abnormal weakness and fatigue in muscles following activity. Myasthenia gravis is an acquired autoimmune disorder characterized by weakness of skeletal muscle and fatigability on exertion, mostly in the middle aged women. Antibodies are directed towards acetylcholine receptor at neuromuscular junctions. It can also be of an idiopathic origin. Muscles of mastication and facial expression are involved and cause drooping of jaw, difficulty in deglutition, slurring speech, altered taste sensation, diplopia and ptosis [65]. Myositis is the inflammation of muscle tissue with infections as well as certain physical and chemical injuries. It can also be of an unknown origin as in dermatomyositis which shows characteristic calcinosis cutis, erythematous skin eruptions, edema, progressive muscle weakness with abnormal electromyograms (EMG). Diffuse stomatitis/pharyngitis with telangiectatic lesions of vermilion border of the lip/jaw muscles/tongue/pharynx are usual [66]. Heterotopic ossification is bone formation at abnormal anatomical sites. Traumatic myositis ossificans is an important type of it, which is normally preceded by an injury or trauma of the muscle. Myositis ossificans of masseter and temporal muscles occur as calcified lesions causing difficulties in mastication [67]. Fibromyalgia is another important group in the musculoskeletal diseases [68]. It is associated with sleep inability, as seen with decreased delta sleep. This is due to abnormal peripheral and central pain amplifications done through spinal cord via altered cerebrospinal fluid substance-P, 5-HT hydroxytryptamine/serotonin. It can also be due to a decrease in blood flow at the caudate and thalamus.

### Vascular origin of maxillofacial musculoskeletal diseases

Systemic vasculitis involves the inflammation of nerves and blood vessels with damage to skin, kidney lung, heart, brain, and gastro intestinal tract. Bechet's syndrome is prominent of them with oral ulcers and erythematous skin lesions [69]. When large vessels are affected, it is called giant cell arteritis [70], medium vessel involvement is as in classical polyarteritis nodosa and those in smaller vessels form microscopic polyangiitis, Wegener's granulomatosis and

Henoch Schonlein purpura [71]. Specific treatment is seldom found for these cases.

### Maxillofacial musculoskeletal diseases: Treatment options

These deformities are treated by a team of maxillofacial surgeons, neurosurgeons, plastic surgeons, psychologists, ophthalmologists, speech and language therapists, orthodontists, audiologists, geneticists and nursing assistants. Maxillary osteotomies include Le Fort I, II and III surgeries to correct deformities in the Anteroposterior/vertical/transverse planes. Mandibular osteotomies are done most often at ramus for advancement and set back sagittal split surgeries. Interpositional bone grafts are at times combined with any of these osteotomies. Adjunctive procedures like genioplasty enable correction of chin deformities [72]. (Table 2) shows the medical and surgical treatment options for maxillofacial musculoskeletal diseases; which features a common approach, either medical or surgical.

### Stem cell based approach in musculoskeletal diseases

Skeletal muscle is one of the abundant tissues in the body, which aids in movement, temperature maintenance and mediating several metabolic activities. The primary units of skeletal muscles are myofibers with a multinucleated syncytial structure that expresses specific proteins- actin and myosin for eliciting muscle contraction and relaxation. They originate from its progenitors known as myoblasts. A part of the myoblasts with myogenic potential is retained as muscle stem cells. These include the myogenic precursor cells, satellite cells, pericytes, mesoangioblasts, muscle interstitial cell, fibro-adipogenic progenitor cells and hematopoietic cells. They play an important role in repair and at the same time offer tremendous options in skeletal muscle regeneration [73]. Mesenchymal stem cells (MSCs) are now widely attempted for bone regeneration. MSCs modulate the immune responses through anti-inflammatory cytokines and by inhibiting the activities of T, B, natural killer (NK) and Antigen Presenting Cells (APC) [74]. MSCs in the joints were first isolated from the synovium; in superficial layer of the articular cartilage. Also, it is seen in joint ligaments, menisci, adjacent adipose tissue and synovial fluid [75]. Synovial membrane lines the non articular surface of the joint cavity filled with synovial fluid. It contains two types of cells: macrophage like type A synoviocytes and type B Fibroblast Like Synoviocytes (FLS). At present, Platelet Rich Plasma (PRP) also forms a major strategy to concentrate endogenous cytokines and growth factors for the treatment of musculoskeletal diseases [76]. Alternatives to total

joint replacement for osteoarthritis with stem cells are being tried for [77]. This is because of the limited life span of artificial prosthesis. New scaffold designs might prove effective in developing tissue engineered cartilages. This may be through direct injection of stem cells 'Autologous Chondrocyte Implantation (ACI) strategy' into the joint or by rejuvenating endogenous stem cells to optimum levels. Role of induced pluripotent stem cells in cartilaginous diseases are also increasingly been explored, considering their better chondrocyte differentiation capabilities [78,79]. With reports of 'Tendon Progenitor Stem Cell (TPSC) populations', challenge of tendon repair is expected to be easy [80]. Cell based therapies using autologous hematopoietic/mesenchymal stem cell transplants are emerging for systemic lupus erythematosus [81] and systemic sclerosis [82] treatment also. Considering the ethical and stringent legal issues on the usage of embryonic stem cells for therapeutic purposes, other promising options would be to use stem cells from human exfoliated deciduous teeth (SHED), third molar teeth or induced pluripotent stem cells (iPSCs) for musculoskeletal regeneration. New treatment and preventive strategies for maxillofacial musculoskeletal diseases would see increased collaboration between clinicians and scientists from the disciplines of stem cells and tissue engineering for musculoskeletal regeneration. Major impetus on this would be for regenerating articular cartilages/bone/muscles and in osteocyte/chondrocyte replacement.

### Aging and related events of musculoskeletal diseases

Diseases of aging like metabolic syndrome, diabetes, atherosclerosis, neurodegenerative diseases, osteoporosis, and cancer are closely related to musculoskeletal diseases. The corresponding molecular changes are telomere and mitochondrial dysfunctions and the conglomeration of events of inflammation, oxidative stress and cell senescence [83]. Gene expression profiling of adult stem cells have been done to assess the effects of age in the setting of osteoarthritis or its reverse. The critical pathways in these are Wnt pathway, which determine stem cell fate in terms cell self-renewal, differentiation, aging and senescence [84]. Its cross talk with fibroblast/transforming/transcription growth factors, prostaglandins and bone morphogenetic proteins to a downstream target of  $\beta$ -catenin through SMAD, FoxO and mTOR signaling pathways and its further interaction with T cell members/lymphoid enhancing factors are crucial towards stem cell guided therapies [85-87].

### Conclusion

Maxillofacial musculoskeletal diseases form a large and diversified group of chronic disorders causing pain and distress affecting the quality of life. Its varied presentation among different populations and age groups, genetic inheritance and interaction with systemic functions are clinical challenges. In view of their well defined oral manifestations and similar treatment protocols, rationale of assembling maxillofacial musculoskeletal disorders in a common platform is helpful for clinicians, researchers and patients. Dental specialists with their better knowledge of oral tissues can render effective solutions for these diseases in a multidisciplinary team. Needless to mention, an improved understanding of this less focused group is highly essential for its emerging future stem cell based treatment protocols.

### References

1. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ.* 2003; 81: 646-656.
2. US. Bone & Joint Decade. The burden of musculoskeletal diseases in the United States 2008. Accessed on 2014.
3. Dominick KL, Ahern FM, Gold CH, Heller DA. Health related quality of life among older adults with arthritis. *Health Qual Life Outcomes.* 2004; 2: 5.
4. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res.* 2007; 22: 1479-1491.
5. Superti-Furga A, Bonafé L, Rimo DL. Molecular-pathogenetic classification of genetic disorders of the skeleton. *Am J Med Genet.* 2001; 106: 282-293.
6. Elnagdy G, Refaiey M, Aglan M, Ibrahim R, Badry T. Oro-dental manifestations in different types of osteogenesis imperfecta. *Austr J Basic Appl Sci.* 2012; 6: 464-473.
7. De Coster PJ, Martens LC, De Paepe A. Oral manifestations of patients with Marfan syndrome: a case-control study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2002; 93: 564-572.
8. Barcia JP, Strife CF, Langman CB. Infantile hypophosphatasia: treatment options to control hypercalcemia, hypercalciuria, and chronic bone demineralization. *J Pediatr.* 1997; 130: 825-828.
9. Bakeman RJ, Abdelsayed RA, Sutley SH, Newhouse RF. Osteopetrosis: a review of the literature and report of a case complicated by osteomyelitis of the mandible. *J Oral Maxillofac Surg.* 1998; 56: 1209-1213.
10. De Almeida-Barros RQ, Oka SC, Pordeus AC, de Medeiros PF, Bento PM, Godoy GP. Oral and systemic manifestations of mucopolysaccharidosis type VI: a report of seven cases. *Quintessence Int.* 2012; 43: e32-38.
11. Zambrano M, Nikitakis NG, Sanchez-Quevedo MC, Sauk JJ, Sedano H, Rivera H. Oral and dental manifestations of vitamin D-dependent rickets type I: report of a pediatric case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003; 95: 705-709.
12. Potts TJ. Diseases of the parathyroid gland and other hyper and hypocalcemic disorder. In: Harrison's principles of internal medicine. New York. McGraw Hill, 1998; 2: 2241-2243.
13. Triantafyllidou K, Zouloumis L, Karakinaris G, Kalimeras E, Iordanidis F. Brown tumors of the jaws associated with primary or secondary hyperparathyroidism. A clinical study and review of the literature. *Am J Otolaryngol.* 2006; 27: 281-286.
14. Park BY, Cheon YW, Kim YO, Pae NS, Lee WJ. Prognosis for craniofacial fibrous dysplasia after incomplete resection: age and serum alkaline phosphatase. *Int J Oral Maxillofac Surg.* 2010; 39: 221-226.
15. Xavier SP, Ribeiro MC, Sicchieri LG, Brentegani LG, Lacerda SA. Clinical, microscopic and imaging findings associated to McCune-Albright syndrome: report of two cases. *Braz Dent J.* 2008; 19: 165-170.
16. Worawongvasu R, Songkamol K. Fibro-osseous lesions of the jaws: an analysis of 122 cases in Thailand. *J Oral Pathol Med.* 2010; 39: 703-708.
17. Carvalho Silva E, Carvalho Silva GC, Vieira TC. Cherubism: clinicoradiographic features, treatment, and long-term follow-up of 8 cases. *J Oral Maxillofac Surg.* 2007; 65: 517-522.
18. Carinci F, Pezzetti F, Locci P, Becchetti E, Carls F, Avantaggiato A, et al. Apert and Crouzon syndromes: clinical findings, genes and extracellular matrix. *J Craniofac Surg.* 2005; 16: 361-368.
19. Silva DLD, Neto P, Xavier F, Carneiro SG, Palheta ACP, Monteiro M, et al. Crouzon's syndrome: Literature review. *Intl Arch Otorhinolaryngol.* 2008; 12: 436-441.
20. Lowe LH, Booth TN, Joglar JM, Rollins NK. Midface anomalies in children. *Radiographics.* 2000; 20: 907-922.
21. Neville BW, Damm DD, Allen CM, Bonqoute JE. Text book of Oral and Maxillofacial Pathology. 3rd ed. Philadelphia: WB Saunders Elsevier. 2009; 45-46.



22. Maranhao SC, Sobrinho ALPDC, Freitas CE, Veiga PDC, Medrado ARAP, Almeida Reis SRD. Pierre Robin Syndrome: From the initial diagnosis to complete rehabilitation. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2014; 117: e-131.
23. Barone CM, Eisig S, Jimenez DF, Argamaso RV, Shprintzen RJ. Achondroplasia: pre- and postsurgical considerations for midface advancement. *Cleft Palate Craniofac J*. 1994; 31: 74-77.
24. Cooper SC, Flaitz CM, Johnston DA, Lee B, Hecht JT. A natural history of cleidocranial dysplasia. *Am J Med Genet*. 2001; 104: 1-6.
25. Currell V, Clancy R, Diamond D. Cleidocranial dysplasia. *Curr Orthop*. 2007; 21:159-162.
26. Korenberg, JR, Pulst, SM, Gerwehr, S. Advances in the understanding of chromosome 21 and Down syndrome. *Down syndrome: advances in medical care*. Wiley-Liss, New York. 1992: 3-12.
27. Scully C. Down's syndrome and dentistry. *Dent Update*. 1976; 3: 193-196.
28. Siris ES, Ottman R, Flaster E, Kelsey JL. Familial aggregation of Paget's disease of bone. *J Bone Miner Res*. 1991; 6: 495-500.
29. Woo TS, Schwartz HC. Unusual presentation of Paget's disease of the maxilla. *Br J Oral Maxillofac Surg*. 1995; 33: 98-100.
30. Kaplan FS, Horowitz SM, Quinn PD. Dental complications of Paget's disease: the need for hard facts about hard tissues. *Calcif Tissue Int*. 1993; 53: 223-224.
31. Key SJ, O'Brien CJ, Silvester KC, Crean SJ. Eosinophilic granuloma: resolution of maxillofacial bony lesions following minimal intervention. Report of three cases and a review of the literature. *J Craniomaxillofac Surg*. 2004; 32:170-175.
32. Chowanadisai S, Kukiattrakoon B, Yapong B, Kedjarune U, Leggat P. Occupational health problems of dentists in Southern Thailand. *Int Dent J*. 2000; 50, 36-40.
33. Koidis PT, Basli I, Topouzelis N. Ankylosing spondylitis associated with craniomandibular disorder-a combined orthodontic and prosthodontic therapeutic approach. *World J Orthod*. 2009; 10:371-377.
34. van Merkesteyn JP, Groot RH, van den Akker HP, Bakker DJ, Borgmeijer-Hoelen AM. Treatment of chronic suppurative osteomyelitis of the mandible. *Int J Oral Maxillofac Surg*. 1997; 26: 450-454.
35. Schellhas KP, Pollei SR, Wilkes CH. Pediatric internal derangements of the temporomandibular joint: effect on facial development. *Am J Orthod Dentofacial Orthop*. 1993; 104: 51-59.
36. Paesani D, Westesson PL, Hatala M, Tallents RH, Kurita K. Prevalence of temporomandibular joint internal derangement in patients with craniomandibular disorders. *Am J Orthod Dentofacial Orthop*. 1992; 101: 41-47.
37. Ishimaru J, Goss AN. A model for osteoarthritis of the temporomandibular joint. *J Oral Maxillofac Surg*. 1992; 50: 1191-1195.
38. Okeson JP, de Leeuw R. Differential diagnosis of temporomandibular disorders and other orofacial pain disorders. *Dent Clin North Am*. 2011; 55: 105-120.
39. Appelgren A, Appelgren B, Eriksson S, Kopp S, Lundeberg T, Nylander M, et al. Neuropeptides in temporomandibular joints with rheumatoid arthritis: a clinical study. *Scand J Dent Res*. 1991; 99: 519-521.
40. Clark G, Seligman D, Solberg W et al. Guidelines for the examination and diagnosis of temporomandibular disorders. *J. Am Dent Assoc*. 1983; 3:7-14.
41. Korszun A, Papadopoulos E, Demitrack M, Engleberg C, Crofford L. The relationship between temporomandibular disorders and stress-associated syndromes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998; 86: 416-420.
42. Costen JB. A syndrome of ear and sinus symptoms dependent upon disturbed function of the temporomandibular joint. 1934. *Ann Otol Rhinol Laryngol*. 1997; 106: 805-819.
43. Parker WS, Chole RA. Tinnitus, vertigo, and temporomandibular disorders. *Am J Orthod Dentofacial Orthop*. 1995; 107: 153-158.
44. Jaber JJ, Leonetti JP, Lawrason AE, Feustel PJ. Cervical spine causes for referred otalgia. *Otolaryngol Head Neck Surg*. 2008; 138: 479-485.
45. Murthy PS, Hazarika P, Mathai M, Kumar A, Kamath MP. Elongated styloid process: an overview. *Int J Oral Maxillofac Surg*. 1990; 19: 230-231.
46. Dervis E. Oral implications of osteoporosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005; 100: 349-356.
47. Schellhas KP. Internal derangement of the temporomandibular joint: radiologic staging with clinical, surgical, and pathologic correlation. *Magn Reson Imaging*. 1989; 7: 495-515.
48. Lewis EL, Dolwick MF, Abramowicz S, Reeder SL. Contemporary imaging of the temporomandibular joint. *Dent Clin North Am*. 2008; 52: 875-890, viii.
49. Sheikholeslam A, Holmgren K, Ruse C. A clinical electromyographic study of long term effects of an occlusal splint on the temporal and masseter muscles in patients with functional disorders and nocturnal bruxism. *J Oral Rehabil*. 1986; 13:137-145.
50. Freund B, Schwartz M, Symington JM. The use of botulinum toxin for the treatment of temporomandibular disorders: preliminary findings. *J Oral Maxillofac Surg*. 1999; 57: 916-920.
51. McKenna SJ, Cornella F, Gibbs SJ. Long-term follow-up of modified condylotomy for internal derangement of the temporomandibular joint. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1996; 81: 509-515.
52. Lo MS1, Tsokos GC. Treatment of systemic lupus erythematosus: new advances in targeted therapy. *Ann N Y Acad Sci*. 2012; 1247: 138-152.
53. Wood RE1, Lee P. Analysis of the oral manifestations of systemic sclerosis (scleroderma). *Oral Surg Oral Med Oral Pathol*. 1988; 65: 172-178.
54. Mathews SA, Kurien BT, Scofield RH. Oral manifestations of Sjögren's syndrome. *J Dent Res*. 2008; 87: 308-318.
55. Vecchiet L, Giamberardino MA, Saggini R. Myofascial pain syndromes: clinical and pathophysiological aspects. *Clin J Pain*. 1991; 7 Suppl 1: S16-22.
56. Olds MJ, Woods CI, Winfield JA. Microvascular decompression in glossopharyngeal neuralgia. *Am J Otol*. 1995; 16: 326-330.
57. Buchanan J, Zakrzewska J. Burning mouth syndrome. *Clin Evid*. 2002; : 1239-1243.
58. Kaddu S, Smolle J, Komericki P, Kerl H. Auriculotemporal (Frey) syndrome in late childhood: an unusual variant presenting as gustatory flushing mimicking food allergy. *Pediatr Dermatol*. 2000; 17: 126-128.
59. Shuaib A, Lee MA. Recurrent peripheral facial nerve palsy after dental procedures. *Oral Surg Oral Med Oral Pathol*. 1990; 70: 738-740.
60. Nager GT, Proctor B. Anatomic variations and anomalies involving the facial canal. *Otolaryngol Clin North Am*. 1991; 24: 531-553.
61. Gouda JJ, Brown JA. Atypical facial pain and other pain syndromes. Differential diagnosis and treatment. *Neurosurg Clin N Am*. 1997; 8: 87-100.
62. Griggs RC, Mendell JR, Miller RG. The muscular dystrophies. In: *Evaluation and treatment of myopathies*. FA Davis, Philadelphia. 1995; 1: 122-128.
63. Drennan J. Neuromuscular disorders. In: *Lovell and Winter's Pediatric Orthopedics*. JB Lippincott, Philadelphia 1990; 381.
64. Kubota M, Nakano H, Sanjo I, Satoh K, Sanjo T, Kamegai T, et al. Maxillofacial morphology and masseter muscle thickness in adults. *Eur J Orthod*. 1998; 20: 535-542.
65. Sasakura Y, Kumasaka S, Takahashi T, Shindo J. Myasthenia gravis associated with reduced masticatory function. *Int J Oral Maxillofac Surg*. 2000; 29: 381-383.
66. Heffner RR, Armbrustmacher VW, Earle KM. Focal myositis. *Cancer*. 1977; 40: 301-306.
67. Steiner M, Gould AR, Kushner GM, Lutchka B, Flint R. Myositis ossificans traumatica of the masseter muscle: review of the literature and report of two

- additional cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997; 84: 703-707.
68. Rhodus NL, Friction J, Carlson P, Messner R. Oral symptoms associated with fibromyalgia syndrome. *J Rheumatol.* 2003; 30: 1841-1845.
69. Burton-Kee JE, Mowbray JF, Lehner T. Different cross-reacting circulating immune complexes in Behçet's syndrome and recurrent oral ulcers. *J Lab Clin Med.* 1981; 97: 559-567.
70. Clark GT, Seligman DA, Solberg WK, Pullinger AG. Clinical manifestations of giant cell (temporal) arteritis. *Clin Rheum Dis* 1980; 6: 389-415.
71. Erickson VR, Hwang PH. Wegener's granulomatosis: current trends in diagnosis and management. *Curr Opin Otolaryngol Head Neck Surg.* 2007; 15: 170-176.
72. Sabherwal R, Irvine G, Sandy J. Orthodontic management of a Le Fort II and midline palatal fracture. *Br Dent J.* 2007; 202: 739-740.
73. Shanti RM, Li WJ, Nesti LJ, Wang X, Tuan RS. Adult mesenchymal stem cells: biological properties, characteristics, and applications in maxillofacial surgery. *J Oral Maxillofac Surg.* 2007; 65: 1640-1647.
74. Corcione A, Benvenuto F, Ferretti E, Giunti D, Cappiello V, Cazzanti F, et al. Human mesenchymal stem cells modulate B-cell functions. *Blood.* 2006; 107: 367-372.
75. Tuan RS. Stemming cartilage degeneration: adult mesenchymal stem cells as a cell source for articular cartilage tissue engineering. *Arthritis Rheum.* 2006; 54: 3075-3078.
76. Bottini N, Firestein GS. Duality of fibroblast-like synoviocytes in RA: passive responders and imprinted aggressors. *Nat Rev Rheumatol.* 2013; 9: 24-33.
77. Gerter R, Kruegel J, Miosge N. New insights into cartilage repair - the role of migratory progenitor cells in osteoarthritis. *Matrix Biol.* 2012; 31: 206-213.
78. Nie H, Lee CH, Tan J, Lu C, Mendelson A, Chen M, et al. Musculoskeletal tissue engineering by endogenous stem/progenitor cells. *Cell Tissue Res.* 2012; 347: 665-676.
79. Mobasheri A, Kalamegam G2, Musumeci G3, Batt ME4. Chondrocyte and mesenchymal stem cell-based therapies for cartilage repair in osteoarthritis and related orthopaedic conditions. *Maturitas.* 2014; 78: 188-198.
80. Smith RK1. Mesenchymal stem cell therapy for equine tendinopathy. *Disabil Rehabil.* 2008; 30: 1752-1758.
81. Sun L, Wang D, Liang J, Zhang H, Feng X, Wang H et al. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum.* 2010; 62: 2467-2475.
82. van Laar JM, Sullivan K. Stem cell transplantation in systemic sclerosis. *Curr Opin Rheumatol.* 2013; 25: 719-725.
83. Jiang SS1, Chen CH, Tseng KY, Tsai FY, Wang MJ, Chang IS, Lin JL. Gene expression profiling suggests a pathological role of human bone marrow-derived mesenchymal stem cells in aging-related skeletal diseases. *Aging (Albany NY).* 2011; 3: 672-684.
84. Baksh D, Boland GM, Tuan RS. Cross-talk between Wnt signaling pathways in human mesenchymal stem cells leads to functional antagonism during osteogenic differentiation. *J Cell Biochem.* 2007; 101: 1109-1124.
85. Almeida M, Han L, Martin-Millan M, O'Brien CA, Manolagas SC. Oxidative stress antagonizes Wnt signaling in osteoblast precursors by diverting beta-catenin from T cell factor-to forkhead box O-mediated transcription. *J. Biol. Chem.* 2007; 282:27298-27305.
86. Manolagas SC, Almeida M. Gone with the Wnts: beta-catenin, T-cell factor, forkhead box O, and oxidative stress in age-dependent diseases of bone, lipid, and glucose metabolism. *Mol Endocrinol.* 2007; 21: 2605-2614.
87. Rached MT, Kode A, Xu L, Yoshikawa Y, Paik JH, Depinho RA, et al. FoxO1 is a positive regulator of bone formation by favoring protein synthesis and resistance to oxidative stress in osteoblasts. *Cell Metab.* 2010; 11: 147-160.