Systemic Factors Affecting Pain Management in Dentistry

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KEYWORDS

• Systemic factors • Pain • Nutrition and orofacial pain • Hormones and orofacial pain • Infections and orofacial pain • Autoimmune and orofacial pain • Dental pain

KEY POINTS

- Systemic factors may have a significant impact on pain management in dentistry.
- Many systemic factors can predispose, cause, perpetuate, and worsen dental and orofacial pain.
- Hormonal, nutritional, systemic infections, neurodegenerative, and autoimmune are the most robust factors affecting dental and orofacial pain.
- Dental clinicians should consider screening patients for systemic factors that affect their pain experience.

INTRODUCTION

Pain as defined by the International Association for the Study of Pain (IASP) is an unpleasant sensory and emotional experience associated with or resembling that associated with actual or potential damage (IASP 2020).[1] Acute pain, if diagnosed and treated optimally, resolves with no long-lasting consequences. Acute pain serves as a warning signal and is typically protective. On the other hand, chronic pain does not have any protective functions and is considered to be a disease in itself.[2]

Orofacial pain as defined by the International Classification of Orofacial Pain (ICOP 2020)[3] is pain in the head that occurs below the orbitomeatal line, anterior to the pinnae, and above the neck, including the structures in the oral cavity. The ICOP

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classifies orofacial pain into 7 categories: orofacial pain attributed to disorders of dentoalveolar and anatomically related structures, myofascial orofacial pain, temporomandibular joint (TMJ) pain, orofacial pain attributed to lesion or disease of the cranial nerves, orofacial pains resembling presentations of primary headaches, idiopathic orofacial pain, and psychosocial assessment of patients with orofacial pain.[3]

Patients described as pro-nociceptive and/or having a possible genetic predisposition may be requiring additional or adjunct/alternative pain management modalities.[4,5] A specific example of a pain management issue in this regard may be congenital insensitivity to pain, where the pain presentation may be disproportionate to the degree of tissue damage or destruction.[6] Also, are patients who may be "nonresponders" to conventional pain management modalities. Clinicians also must consider the possibility of patients misusing/abusing medications or those who are already on long-term analgesic treatments.

There are several factors that affect a patient's experience of pain. These include both local and systemic factors. Dental pain is mostly of inflammatory origin. There can be a number of systemic factors that can affect and modify the process of inflammation, the pain pathways and, consequently, the pain experience. The systemic factors that affect patients' dental and orofacial pain experience include, but not limited to, hormonal, nutritional, systemic infections, neurodegenerative, and autoimmune, among others.[7]

HORMONAL

Thyroid Disorders

Disorders of the thyroid gland occur in the majority of cases due to insufficiency or excess of thyroid hormones (triiodothyronine; T3) and thyroxine (T4).[8] These can be secondary to multiple causes such as congenital, autoimmune, and iodine deficiency.[9] Thyroid hormones play an important role in development of tissues, basal metabolic energy processes, contraction, regeneration, and myogenesis in skeletal muscles. Muscle fatigue and weakness are frequently encountered in hypothyroidism and hyperthyroidism.[8,10] Peripheral neuropathy symptoms such as weakness of proximal muscles, delayed muscle relaxation/contraction, paresthesias, anesthesia, and hypoesthesia are encountered in hypothyroidism. Peripheral polyneuropathy is generally secondary to defects in neurons resulting in functional deficits.[8] Growing evidence also suggests that lack of thyroid hormones may be involved in the process of sarcopenia (reduction in quality/mass of skeletal muscle in the aging process). Alterations in thyroid hormone levels may worsen existing myopathies, for instance, muscular dystrophy.[10] Variety of rheumatologic manifestations may accompany autoimmune thyroiditis.[11]

The hypothalamic pituitary thyroid axis plays an important role in regulating serum levels of thyroid hormones.[12] Thyroid hormones may play a role in specialization and maturation of taste buds and have been implicated in dysgeusia, secondary burning mouth.[13,14] Both instances of hypothyroidism and Hashimoto's thyroiditis have been implicated in the genesis of secondary burning mouth symptoms.[15,16] Thyroid hormones play a role in tissue development, regulating the functions of the nervous system, and may play a role in peripheral, central neuropathies as well.[8,13]

The Hypothalamic–Pituitary–Adrenal Axis

Stress plays an important role in activating biophysiological, behavioral, and neuroendocrine responses thus activating an individual's adaptive responses to restore homeostasis. Neuroendocrine responses of hypothalamic–pituitary–adrenal (HPA) axis

involve hormones secreted by 3 organs namely adrenal cortex (cortisol and glucocorticoid hormones), pituitary (adrenocorticotropic hormone), and hypothalamus (corticotropin-releasing hormone) under circadian rhythm modulation. Patients undergoing dental treatment frequently report anxiety and stress that may in turn affect the prognosis of dental treatment by impacting patient compliance.[17] A systematic review concluded low-level evidence for the role of perceived stress and life stressors in the development of chronic musculoskeletal pain disorders such as arthritis and suggested future research.[18] Full description of the HPA axis is discussed elsewhere in this special edition.

Diabetes Mellitus

It is a chronic disorder that develops due to either an inability to produce or to effectively utilize insulin by the pancreas. The polyol pathway and formation of end products in advanced glycosylation may affect various organs and are primarily responsible for the numerous complications associated with diabetes.[19] Diabetic peripheral neuropathy mostly starts peripherally and moves centrally as contrast to central neuropathies starting axially and moving peripherally. Diabetes mellitus (DM) is associated with a higher prevalence of dental caries, periapical lesions,[20] and periodontal disease.[19,21] A recent systematic review reported that DM increases degeneration/inflammation in the dental pulp, and this may predispose patients to develop increased pain, particularly following dental treatment.[22] Patients with diabetes have a higher prevalence of taste disorders, xerostomia, burning mouth, candidiasis, fissured/geographic tongue, higher incidence of infections, and delayed wound healing.[19,23–25]

MUSCLE ISCHEMIA

Skeletal muscles are richly supplied by blood vessels to meet the demands of exercise or usage at relatively short notice.[26] Ischemia could be qualitative or quantitative. In quantitative ischemia, the muscle is actually devoid of sufficient/optimal blood supply by volume. Qualitative ischemia occurs when the volume of blood is relatively sufficient, but the "quality" is less than ideal. This can result in inadequate oxygenation and nutrition, conceivably causing tissue damage. Symptoms may include pain, muscle weakness, involuntary muscle contractions, and sensory disturbances.[27]

NUTRITIONAL DEFICIENCIES

Iron Deficiency Anemia

The condition could be primarily due to impairment in the dietary sources of iron, or of absorption or of iron processing in the body. There is inadequate iron in the body to form hemoglobin. Hemoglobin is needed to carry oxygen in the erythrocytes. In iron deficiency anemia, when there is less oxygenation to the muscles, this can lead to muscle fatigue and pain.[28] In addition, iron deficiency may play a role in the inflammatory pathways, which may lead to increased muscle pain. When there is reduced oxygenation, muscles resort to anaerobic metabolism, which results in lactic acid accumulation leading to pain and discomfort.

Management of iron deficiency may result in improvement in symptoms. Iron deficiency has been shown to have an independent association with chronic daily headaches.[29]

The condition is also associated with glossodynia.[30] The effect of iron deficiency anemia on the severity of associated fatigue has been clinically compared to that of severe abdominal pain.[31] The same literature also confirms the strong association

of this condition with chronic inflammatory systemic diseases. Anemia has also been shown to be associated with the pain of events involving vaso-occlusion.[32] Iron deficiency has also been reported in the literature as a perpetuating factor for myalgia.[33] The condition has also been shown to be associated with menstrually related migraine; additionally, the deficiency of ferritin was related to pain severity in migraine.[34] The clinician dealing with temporomandibular disorder (TMD)-associated myalgia, glossodynia, and myofascial pain should consider screening for iron deficiency in clinically appropriate cases. The astute clinician may be able to associate the coexistence of one or more systemic inflammatory conditions in their patients and constitute screening and prompt referral, thereby facilitating optimal pain management.

Vitamin B Deficiencies

Folate, also known as vitamin B9, is crucial for DNA synthesis, repair, methylation, and red blood cell production. It is vital for proper nervous system function. Folate deficiency can cause megaloblastic anemia; this can reduce the oxygen-carrying capacity of the muscles, which can lead to muscle weakness and pain. Folate is also proposed to be essential in myogenesis, proper muscle function, and its deficiency has been linked to sarcopenia.[35]

Vitamin B12 is essential for myelin production and red blood cell formation. A deficiency can lead to anemia, which reduces the oxygen supply to muscles, leading to muscle pain and weakness. A deficiency can also lead to neuropathy, which can present as muscle pain, tingling, or numbness, especially in the extremities. Peripheral neuropathies were associated with deficiencies of vitamin B12 and administration of B vitamins in general improved symptoms.[36] Supplementation of this vitamin was also found to be associated with early healing, lesser recurrence rate, and shorter treatment time for the management of oral ulcers.[37]

Vitamin C Deficiency

Vitamin C (ascorbic acid) has gained more momentum in the more recent literature as a key component in optimal wound healing, pain perception, and anti-inflammation, among others.[38] Vitamin C has been implicated in the synthesis of crucial neurotransmitters such as serotonin, glutamate, and dopamine. Further, recent literature points in the direction of vitamin C having a role in the synthesis of endorphins, essential for the pain modulatory system. Animal studies are showing that vitamin C supplementation leads to reduction of opioid drug tolerance and dependency. It may also have properties of improving the efficacy of analgesics. From the available literature, it appears that supplementation of vitamin C may enhance healing, reduce postoperative pain, and facilitate optimal pain management.[38]

Vitamin D Deficiency

The major health problem associated with vitamin D deficiency was rickets. However, vitamin D deficiency continues to be a problem in both the pediatric and adult populations.[39] A deficiency of vitamin D can affect calcium metabolism, leading to impaired muscle function, weakness, and fatigue culminating in pain upon physical activity.[40] Individuals with fibromyalgia syndrome show lower circulating levels of 25 hydroxy vitamin D (25-OH D) as this may lead to impairment of tissue structure and function. Supplementation with vitamin D can reduce musculoskeletal pain and improve the quality of life in patients with vitamin D deficiency.[40] Vitamin D receptors have been proposed to have interaction with the gene and opioid pathways.[41] Emerging literature points to the potential role in pain modulation by virtue of these pathways.

Vitamin D deficiency is proposed to be contributing to neurologic disorders and supplementation associated with mitigation of the effects/symptoms of neurologic disorders.[42] Studies have shown that vitamin D supplementation improved pain scores in chronic widespread pain.[43] It has also been shown to significantly reduce pain scores in patients with chronic pain.[44] The clinician managing pain may want to consider the vitamin D deficiency as contributing and/or perpetuating chronic pain. Therefore, mitigating these effects may involve appropriate supplementation.

Micronutrient Deficiencies

Zinc is an essential trace element that is required for the metabolic activity of many enzymes in the human body. Even a small deficiency can affect tissue growth, wound healing, taste acuity, connective tissue growth, and maintenance among others. Since zinc is essential for protein synthesis, cell division, and tissue repair, without adequate zinc levels, this can lead to muscle weakness and pain.[45]

Magnesium is a crucial mineral involved in various bodily functions, including muscle and nerve function. Magnesium acts as a natural calcium blocker, helping muscles relax after contraction.

Magnesium deficiency can cause muscle cramps, spasms, weakness, fatigue, and pain.[46]

Sodium is essential for maintaining proper muscle function, nerve impulse transmission, and fluid balance within the body. When sodium levels are deficient, it can lead to muscle-related symptoms such as muscle cramps or weakness. Hyponatremia can be dangerous where seizures, coma, or even death can occur, if left untreated. These conditions can vary from excessive water intake, using certain medications, medical conditions such as heart failure, kidney disease, or conditions such as syndrome of inappropriate antidiuretic hormone secretion, hormonal imbalances such as Addison's disease and hypothyroidism.[47]

Calcium plays a critical role in muscle function, and an imbalance can lead to muscle pain.

Calcium ions are essential for muscle contraction and for neurotransmitter release at the neuromuscular junction. Hypocalcemia can lead to muscle cramps and spasms as normal muscle contractions and nerve function is impaired. Calcium imbalance is also closely linked with hypoparathyroidism and vitamin D deficiency. Hyperparathyroidism results in insufficient production of parathyroid hormone leading to low calcium levels and associated muscle pain.[48–50]

Alpha lipoic acid (ALA) is an antioxidant that can reduce oxidative stress, which is linked to muscle pain and inflammation. ALA may reduce muscle soreness secondary to neuropathic pain and improve recovery, but more research is needed to explore this further.[51]

INFECTIONS

Lyme and Lyme-like Diseases

A tick-borne spirochete, *Borrelia burgdorferi*, is considered one of the major causes for Lyme disease (LD). Early stages following the tick bite are often asymptomatic but later stages can result in arthritis, pain, and joint swelling.[52] In the orofacial region, LD can lead to facial nerve palsy, altered taste, myalgias, dry mouth, neck pain, sore throat, paresthesia, headaches, and TMJ disorders. Some of the common orofacial presentations include headaches, facial and/or neck rash, oculomotor, vestibular, and/or facial palsy, TMJ arthralgia, altered taste, stiff neck, and sore throat. Neuropathy presenting as dental pain has been reported in patients with LD. Other studies have reported the

presentation of LD as TMJ disorders, trigeminal neuralgia/neuropathy, toothache, dizziness, tinnitus, and hearing loss.[53–56] Lyme can affect multiple organs and can be difficult to detect especially in the early stages. LD should be a diagnostic consideration in patients presenting in endemic Lyme areas with orofacial pain inconsistent with dental findings.

Epstein–Barr Virus and Cytomegalovirus

Epstein–Barr virus (EBV) belongs to the gamma herpes virus family and is a double-stranded DNA virus. Studies have shown an increase in daily persistent headaches with the virus.[57,58] Studies have reported excessive sleeping, fatigue, and idiopathic hypersomnia in infected patients.[59] EBV has been suggested to be linked to the pathophysiology of rheumatoid arthritis (RA). Anti-EBV titers are elevated in patients with RA.[60] Studies have also shown a higher frequency of periodontal disease and EBV detection.[61] Cytomegalovirus (CMV) is a common double-stranded DNA virus belonging to the herpes viridae family. Oral ulceration in the soft and hard palate can be found in patients infected with human CMV and prevalent in immunocompromised individuals. In immunosuppressed adults, upon reactivation of the virus, it can lead to xerostomia, salivary dysfunction, and sialadenitis.[62]

Coronavirus Disease

Coronavirus is a single-stranded RNA virus and is part of the coronaviridae family. Some patients can present with loss of taste and smell, and it usually subsides in 3 to 4 weeks. However, as the pandemic is over, the long-term effects of the disease are being reported. Long-haul coronavirus disease (COVID) can impact multiple systems and present with a challenge in management. The prevalence of anosmia and dysgeusia has approximately been reported as 40%.[63] A study reported about 21% patient reporting of tooth pain, whereas 19% reporting in gingival pain accompanied with bleeding.[64] The exact mechanism is poorly understood but an interaction between the spike protein of the virus and cell surface protease transaminase protease serine 2 receptor has been postulated.[65] Studies have shown patients with COVID-19 developing a higher incidence of generalized body pain, facial pain, and headaches.[66] As a health care provider, it is important to distinguish various orofacial pain conditions and the long-term effects of the disease to prevent unnecessary treatment, financial burden, and time-loss.

Dengue

Dengue virus is an RNA virus and transmitted via mosquito bite and can lead to dengue fever. Many patients will be asymptomatic, but if the infection progresses, it can have severe health consequences. Dengue infection can result in a variety of symptoms including fever, loss of appetite, metallic taste, headaches, muscle and joint pain, rash generalized weakness and fatigue, muscle aches, bleeding gums, and vomiting. Headaches resembling migraines are reported in infected individuals.[67,68]

Chikungunya Virus

Chikungunya virus (CHIKV) is an arthropod-borne virus predominantly affecting populations in temperate climates.[69] The disease is usually self-limiting; however, in about 10% to 60% some symptoms may persist over years. Complications (in acute stage?) may involve hemorrhage as well as the involvement of the central nervous system, causing meningoencephalitis, Guillain–Barré syndrome, cranial nerve palsies, or neuropathies.[70] Musculoskeletal pain and neuropathy are often seen in the chronic phase (>90 days).[71–75] At this phase, clinical and radiographic features of CHIKV infection

can mimic those of rheumatic disease, such as RA.[76] In the orofacial region, TMJ arthralgia and pain with neuropathic features have been documented, but rarely in the chronic phase.[77] The risk factors for chronification of the disease include age above 35 years, preexisting arthralgia, and severity of the acute phase (greater number of joints involved, joint swelling, and high-grade fever).[78]

FIBROMYALGIA

Fibromyalgia is a chronic condition with widespread/global pain. It can be accompanied by fatigue, anxiety, joint and muscle stiffness, mood disorders, depression, sleep disturbances, and other cognitive and somatic symptoms.[79] It is generally agreed that the condition is an example of central sensitization, and the etiology may be multifactorial. Patients often display a lower pain threshold and show clinical presentation of allodynia and hyperalgesia.[80,81] Studies have shown xerostomia, dysgeusia, glossodynia, oral ulcerations, dysphagia, and orofacial pain to be prevalent in patients with fibromyalgia. The prevalence of TMDs has been reported in 75% of the patients. Patients often report jaw stiffness, myalgia, and headaches. Chronic migraines and tension-type headaches have also been reported to be highly prevalent in patients with fibromyalgia.[82–84] When patients present with TMD and concomitant fibromyalgia, an approach to address both the peripheral and central components of pain may be more desirable.

JOINT HYPERMOBILITY SYNDROMES

Patients with joint hypermobility are highly prone to TMDs and often present pain, clicking, jaw locking, and crepitations. The oral mucosa is thin and can lead to bleeding and ulceration. It is important to manage these patients with an interdisciplinary approach to avoid complications and have a successful outcome.[85–87] Global pain, psychological, and other systemic comorbidities are common in joint hypermobility syndromes. The clinician should recognize the possible vulnerability of these patients to joint hyperextensions and possible injury, as that may occur during dental procedures necessitating prolonged mouth opening. These patients also present with fibromyalgia and other central sensitization syndromes.

MEDICATIONS AFFECTING PAIN MANAGEMENT

The concept of preemptive analgesia (using analgesics, anesthetics, or other classes of medications) has gained momentum in the pain management field.[88] Most of the dental procedure and pathology-related pain are of inflammatory origin. Conceivable, drugs with predominantly anti-inflammatory properties are appropriate for optimal dental-related pain management. The prime classes of medications that exhibit these anti-inflammatory qualities are nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids. Among the factors that may preclude NSAIDs are conditions such as gastritis, hyperacidity, gastric/duodenal ulcers, gastroesophageal reflux disease, hypertension, cardiovascular morbidities, among others.[89] Conditions such as diabetes, immunosuppression, glaucoma, osteoporosis among others may form a relative contraindication for steroids.[90,91]

Long-term antithyroid medication use may be associated with minor complications such as arthralgia and myalgia.[91] Statins may induce myalgias and use of certain statins may be associated with statin-induced necrotizing autoimmune myopathy as a rare side effect.[92] Long-term use of statins may be associated with proximal myopathies.[93] When patients on any drugs, including statins, present with myalgia, a proper

history regarding the initiation of the medication, dosage adjustment history, possible drug and food interactions, and the temporal relationship to the pain should be explored.[7]

AUTOIMMUNE DISORDERS

Several autoimmune disorders may affect the pain in the orofacial region and thereby modify pain management in dentistry. The prototype of these disorders is RA and systemic lupus erythematosus (SLE). RA affects the hard and soft tissue structures of joints, including those associated with the TMJ.[7,94] The prevalence of RA in the general population is approximately 1.5%.[7] These patients may present to the clinician with complaints of muscle and/or joint pain. It may also manifest as patient's complaints of jaw tiredness and ache upon opening the mouth for dental procedures. The savvy clinician should be able to screen the patient for these entities when a higher suspicion is raised on the probability of these diseases. The orofacial and TMJ involvement in SLE have been well documented in the literature. These include global myalgia, joint pains, pain on chewing, and "stuck" feeling in the jaw.[7] Identification and prompt referral to the appropriate medical specialist are crucial for optimal care of these patients.

NEURODEGENERATIVE DISORDERS

The neurodegenerative disorders of interest to the dental clinician in terms of pain management in dentistry include Parkinsonism syndromes (including Parkinson's disease, [PD]), Alzheimer's disease, and multiple sclerosis, among others. Pain is one of the chief non-motor symptoms of PD.[95] Oral burning sensations and painful TMDs contribute to the reduced quality of life in PD.

SUMMARY

Several local and systemic factors may play an important role in pain management during dental procedures. The savvy clinician should be able to screen the patient for these entities when a higher suspicion is raised on the probability of these diseases and refer them to appropriate specialists for successful interdisciplinary management.

CLINICS CARE POINTS

- Comprehensive medical history is essential to delineate any possible systemic factors affecting pain experience.
- A thorough review of systems should form the foundation of pain management, since multiple factors can affect the prognosis of pain management in dentistry and orofacial pain.
- This would facilitate early recognition and trigger prompt referrals to the appropriate medical professionals.
- These succinct steps help to reduce the health care burden and form the scaffolding for interdisciplinary pain management.

DISCLOSURE

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