

# Characterization of Salivary Gland Pain: A Review of the Literature

Caracterización del Dolor de Glándulas Salivales: Revisión de la Literatura

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MANCILLA, M.; ITURRIAGA, V.; MUÑOZ, J.; LANDAETA, H.; VELASQUEZ, N.; BORNHARDT, T. Characterization of salivary gland pain: A review of the literature. *Int. J. Morphol.*, 41(5):1364-1371, 2023.

**SUMMARY:** The salivary glands in pathological conditions produce countless different clinical presentations, and due to their complex neuroanatomy, their pain symptoms vary widely. However, in the literature to date, few studies characterize salivary gland pain. The aim of this study was to conduct a literature review concerning the clinical characteristics of pain in various salivary gland pathologies. A literature review was done through a systematic search of scientific articles in the Web of Science (WoS), MEDLINE, Scopus, and Elton B. Stephens Company (EBSCO) databases. The free terms “salivary gland”, “parotid gland”, “submaxillary gland”, “sublingual gland”, and “pain” were used along with the Boolean operators OR and AND. The search yielded a total of 1896 articles, of which 60 fulfilled the inclusion criteria and were ultimately included in this review. It is described that pain is a nonspecific symptom of a glandular pathology and is characterized mainly by the location of the pain, which is correlated with the anatomical location of the affected salivary gland. Among the painful salivary gland pathologies, we found inflammatory disorders, including infections, obstructions, disorders secondary to hyposalivation; systemic autoimmune diseases; neoplasms, and neuropathic pain disorders. The diagnosis and management of salivary gland pain require knowledge of the causes and mechanisms of the pain, and it is to recognize the signs and symptoms of salivary gland disorders to be able to diagnose and treat them.

**KEY WORDS:** Salivary glands; Salivary gland diseases; Salivary gland pain; Facial pain; Orofacial pain.

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## INTRODUCTION

The salivary glands (SG) are a group of specialized organs that secrete saliva. Saliva is a watery substance essential for various physiological functions such as the protection of the teeth and surrounding soft tissues, the lubrication of the oral cavity, speech, and the perception of taste in foods (Hernández & Taylor, 2020). The SG are complex networks of hollow tubules and secretory units in specific locations of the orofacial region. There are three major pairs of SG: parotid glands, submandibular and sublingual glands. In addition, numerous smaller SG are scattered diffusely throughout the upper aerodigestive tract (Scully, 2003). Although architectonically similar, these glands exhibit individual specificities according to their location. This is an important factor to consider when a differential diagnosis is required to locate pain in adjacent structures.

Under the International Classification of Orofacial Pain (ICOP, section 1.2.2), salivary gland pain (SGP) is described as pain caused by any lesion or disorder involving the SG (International Classification of Orofacial Pain, 2020). From the point of view of diagnosis and treatment of orofacial pain of glandular origin, a complex process is considered, which in many cases is made difficult due to the anatomical density of the structures of the region.

The etiology of the SGP may be due to various pathological processes, ranging from obstructions and infections to benign and malignant tumors of the SG. Consequently, the symptoms of SGP will depend on its origin, be it a primary disease, secondary to a pathology of local or systemic origin, and/or to the treatment of these. A careful

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medical history is the first step in diagnosing SGP. Almost all the diseases that affect the SG present as a painful or painless gland inflammation, which can include mouth dryness and local and/or systemic symptoms (International Classification of Orofacial Pain, 2020). Thus, their complex neuroanatomy, various etiologies, and varied clinical presentations contribute to the severity, characteristics, and impact of SGP. Hence, the aim of this article was to perform a literature review of the characteristics of pain in various SG pathologies.

## METHOD

A literature review was done through a systematic search of scientific articles in the Web of Science (WoS), MEDLINE, Scopus, and Elton B. Stephens Company (EBSCO) databases. The free terms “salivary gland”, “parotid gland”, “submaxillary gland”, “sublingual gland”, and “pain” were used along with the Boolean operators OR and AND. Articles in English conducted on humans in the last 20 years, from September 2000 to September 2020, were established as limits. The MEDLINE search strategy was: ((Salivary gland) OR (parotid gland) OR (Submaxillary gland) OR (sublingual gland)) AND Pain. The inclusion criteria were observational studies that described the clinical characteristics of SGP in humans. Letters to the editor, studies without specific results, abstracts, and presentations in poster form were excluded. The main variable was the identification of the clinical characteristics of pain in various SG

pathologies. Other variables of interest were: sociodemographic variables of the subjects, prevalence of SGP, differential diagnoses, and comorbidities. All the identified references were extracted through the Mendeley® Reference Manager to facilitate their handling, eliminating duplicate articles. The first stage of the review involved evaluating the titles and abstracts and identifying the selection criteria. The second phase involved evaluating the complete text, making the final selection, and extracting data. The Cochrane Collaboration Covidence® tool was used for this process.

## RESULTS AND DISCUSSION

The search yielded a total of 1896 articles; after eliminating duplicates, 862 articles were screened. Of these articles, 60 were finally included in this review, Figure 1 shows the flow diagram of the selection. Of the selected articles, 4 were present in the WoS database, 34 in MEDLINE, 21 in SCOPUS and 1 in EBSCO.

SGP is a nonspecific symptom of glandular pathology and is characterized mainly by the location of the pain, which is correlated with the anatomical location of the affected SG (International Classification of Orofacial Pain, 2020). To understand the behavior of SGP, it is important to consider the range of diseases that can affect the SG, similar to what is observed in other glands in the body.

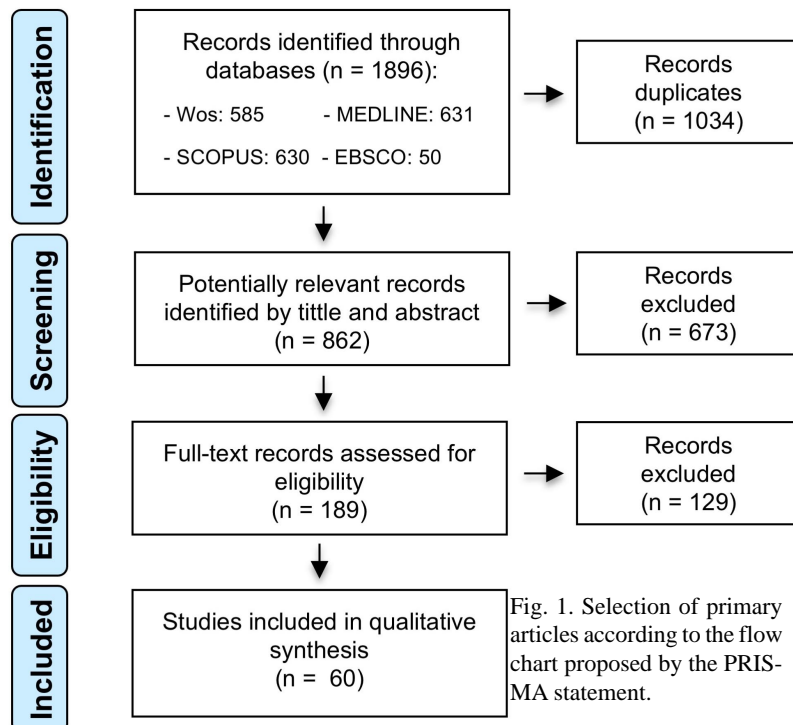


Fig. 1. Selection of primary articles according to the flow chart proposed by the PRIS-MA statement.

Among the pathologies that can affect SG, a great variety was found, which is summarized in Figure 2. Next, the relation between these conditions and SGP will be described in greater detail.

**Salivary glands inflammatory disorders.** Inflammation of a SG is called sialadenitis and are the most common conditions of SG (Scully, 2003).

**Inflammatory disorders secondary to infection.** The leading cause of sialadenitis is bacterial infection by Staphylococcus, which can be acute or chronic. The reduced salivary flow is the main predisposing factor, which permits the retrograde microbial colonization of the salivary duct, which may result in a suppurative infection (International Classification of Orofacial Pain, 2020).

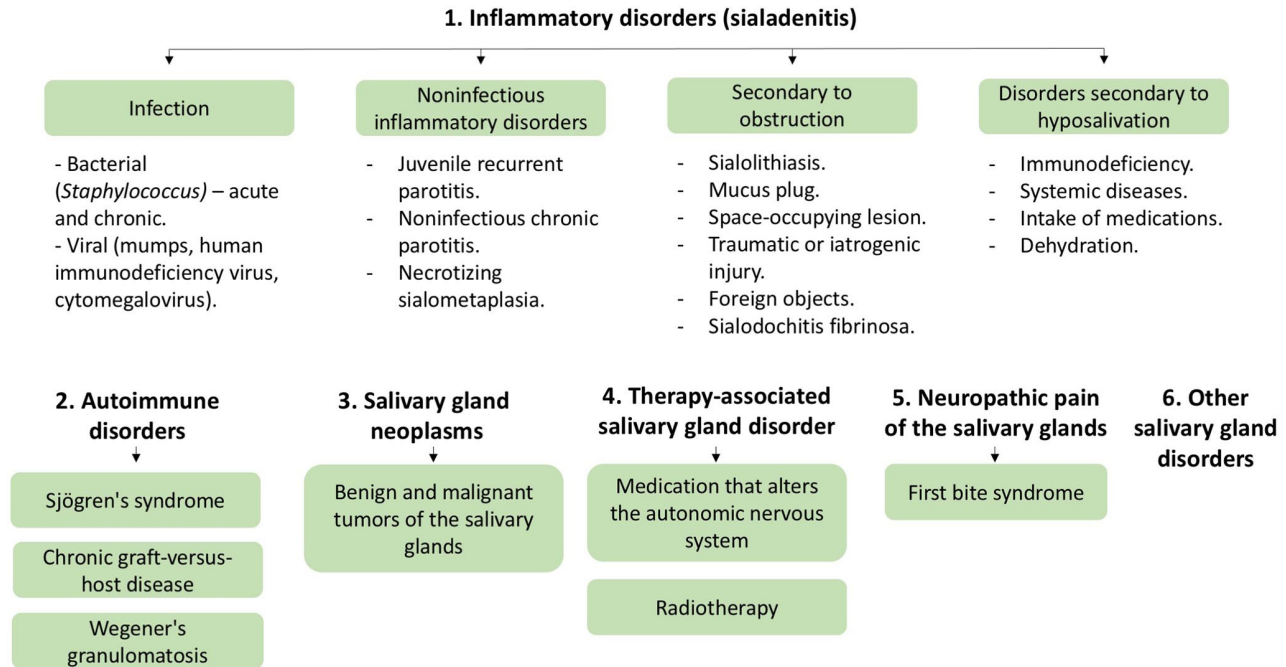


Fig. 2. Summary of conditions associated with salivary gland pain.

In acute sialadenitis, SGP generally occurs unilaterally, with the parotid gland being the most commonly affected (Hernández & Taylor, 2020). Associated with the pain, there may be a purulent secretion at the exit of the salivary duct, reddening of the overlying skin, or even formation of abscesses in the tissue of the inflamed gland, general malaise, fever, and cervical adenopathies (Wang *et al.*, 2006). Conversely, chronic sialadenitis can develop after acute sialadenitis if the predisposing factors are maintained.

On the other hand, viral infections of the SG include mumps, infection by the human immunodeficiency virus (HIV), and infection by the cytomegalovirus (CMV). Generally, these conditions include an increase in volume and nonspecific SGP. The mumps affect mainly children from 4 to 6 years, with the parotid gland being the preferred location; it presents with a sudden bilateral increase in volume and is painful to the touch (Wang *et al.*, 2006; International Classification of Orofacial Pain, 2020). Often, severe local pain is produced with mandibular movements, especially if there is a total obstruction of the duct. It is important to remember that up to 25 % of cases involve a unilateral condition to establish a differential diagnosis of SGP.

**Noninfectious inflammatory disorders.** A less common inflammatory condition that may involve SGP is juvenile recurrent parotitis, characterized as presenting a two-phase distribution by age, with peaks at 2-5 and 10 years of age. It

presents with an intermittent increase in the volume of the parotid glands. It is generally associated with the cystic dilation of the salivary duct, nonobstructive sialectasis, and hypofunction of the SG. It is commonly associated with diffuse facial pain and fever. The symptoms are limited to approximately 3 days and can frequently reappear, with an average of eight episodes per year (Wang *et al.*, 2006).

Another condition with recurrent clinical behavior is chronic parotitis, a rare pathology that is important to recognize due to its cyclical and progressive nature (Harbison *et al.*, 2011). The symptoms generally begin as dysesthesia and itching, changing progressively to severe pain, where the crises can involve an increase in facial volume and otalgia. Patients usually experience acute and intermittent episodes of painful unilateral parotid inflammation, lasting from minutes to months. The symptoms can worsen worse or not with eating and certain alterations in taste, such as dysgeusia or phantogeusia (Mahalakshmi *et al.*, 2017). The physical examination demonstrates face fullness that covers the parotid gland, along with associated parotid sensitivity and overlying erythema, associated with fatigue, general malaise, and fever. In the same way, compression of the gland can produce a large volume of saliva with or without mucous secretion, associated generally with an unpleasant taste. In cases of untreated chronic disease, a hard, fibrous mass can be felt within the gland, which makes diagnosis by imaging essential (Mandel, 2008; Harbison *et al.*, 2011).

On the other hand, we found necrotizing sialometaplasia (NS). NS is a locally destructive nonneoplastic inflammatory condition of the SG that represents less than 0.03 %-1 % of the biopsied oral lesions, where 75 % of all cases occur in the posterior portion of the palate. Its etiology is unknown, but it is thought that it is the result of ischemia of the salivary tissue that leads to a local infarct. In bulimic patients, the direct traumatism of the fingers on the palate could cause NS, and/or possibly the chemical irritation of the stomach content. In addition, dental infiltrations and prosthodontics are well-documented predisposing factors (Ko *et al.*, 2016). It usually begins with an increase in volume, often erythematous, accompanied by an abrupt onset of diffuse SGP. Patients generally complain about sensory changes such as paresthesia or a sore palate prior to the onset of the pain. In 2 to 3 weeks, the necrotic tissue follows, leaving an ulcer in the form of a crater that generally resolves by itself in 3 to 12 weeks (Abdalla-Aslan *et al.*, 2020).

**Inflammatory disorders secondary to obstruction.** The obstruction of the SG duct system is quite a common cause of SGP. The most frequent causes of obstruction are secondary to sialolithiasis, a mucus plug, a space-occupying lesion, or a traumatic or iatrogenic injury. In addition, cases of obstruction produced by foreign objects within the salivary duct have been reported (Titiz *et al.*, 2007; Tabatabaee & Sanatkhani, 2019).

Obstruction due to sialoliths is the most common cause, being more prevalent in men than women and rare in children. Most sialoliths (80-92 %) occur in the submandibular gland, mainly in its ductal system, followed by the parotid gland (5-10 %), being rare in the sublingual gland and the other smaller SG (1-2 %) (Debnath & Adhyapok, 2015; Sigismund *et al.*, 2015; Lafont *et al.*, 2018; Datta *et al.*, 2020).

In these cases, symptoms mainly occur during meals due to the high stimulation of salivary secretion in a partially or totally obstructed gland; however, sometimes, the saliva is filtered by the duct, giving rise to an asymptomatic obstruction (Ahmed *et al.*, 2018; Sengupta & Bose, 2018). Patients with obstruction of the salivary duct frequently present intermittent acute pain associated with the increase in the volume of the affected SG, where the degree of SGP depends on the extent of the obstruction and the presence of a secondary infection (Arifa *et al.*, 2019; Pachisia *et al.*, 2019). On average, patients indicate pain of 4-5 on a visual analog scale (VAS), accompanied in many cases by pain or dysesthesia on stimulation with an acid taste (Lafont *et al.*, 2018).

Obstructions of accessory lobes of the parotid gland or parotid duct have been reported leading to SGP in the masseteric and genian regions associated with an increase in volume unrelated to meal times (Kim *et al.*, 2017). On the other hand, obstruction by mucus plug and some mucoceles can appear with the sensation of dysesthesia and/or mild pain (Jinbu *et al.*, 2003).

On the other hand, a link between recurrent SG obstruction and hypertrophy of the masseter muscle has been reported. The occurrence of SGP associated with a narrow parotid duct caused by an acute masseter curvature and dysfunctional relation with the buccinator muscle has been described. In these cases, patients usually experience painful unilateral inflammation, recurrent and sudden in the parotid region, mainly during meals and mastication, especially in the morning (Capaccio *et al.*, 2016).

Finally, Kussmaul disease or sialodochitis fibrinosa is rare. It is characterized by episodic obstructive inflammation of the SG, associated with pain at meal times (Shimada *et al.*, 2016). Its main characteristic is the discharge of fibrin clots in the oral cavity, described as gelatinous plugs expelled from the salivary duct spontaneously or on stimulation. It tends to present concomitantly with some allergic disorders (Hayashi *et al.*, 2016).

**Inflammatory disorders secondary to hyposalivation.** It is reported that a reduction in salivary flow can contribute to the development of inflammatory disorders of the SG, secondarily involved with SGP. This commonly occurs in immunodepressed patients, and mainly in older patients who suffer from hypofunction of the SG due to systemic diseases, intake of medications, or dehydration (International Classification of Orofacial Pain, 2020). A correlation is described between the reduction in salivary flow and obstruction of the salivary ducts due to the deposit of sialoliths and mucus plugs. Moreover, subjects with hyposalivation are more susceptible to retrograde infection of the ductal system; therefore, it is important to determine the salivary flow volume in the differential diagnosis of SGP.

### **Salivary gland disorders associated with systemic pathologies**

**Autoimmune disorders.** SGP not only occurs due to local pathologies; systemic pathologies can widely affect the SG. Systemic disorders that most commonly affect the SG are autoimmune disorders. Sjögren's syndrome (SS) is the most frequent autoimmune disorder affecting the SG. This multisystemic autoimmune exocrinopathy

mainly affects the salivary and lacrimal glands (Napeñas & Rouleau, 2014). Classically, SS is characterized by dry mouth, dry eyes, and arthralgia. The clinical manifestations of SS concerning the SG vary depending on the affected gland, presenting a nonspecific group of symptoms. It tends to coexist with recurrent or persistent inflammation of the SG, which may only present as an increase in the volume of the SG, which is frequently associated with SGP. Additional characteristics include dry mouth, difficulty forming the food bolus, a burning sensation in the oral mucosa, prolonged throat pain, and odynophagia (Al-Hashimi *et al.*, 2001; Capaccio *et al.*, 2018). From the imaging point of view, this can be accompanied by several microsialoliths in the glandular parenchyma (Kulkarni, 2005).

A less frequent condition associated with SGP is chronic graft-versus-host disease (cGVHD). This is an important delayed complication of allogeneic hematopoietic stem cell transplantation (allo HSCT) commonly used for high-risk and recurrent hematological neoplasms (Noce *et al.*, 2011; Bassim *et al.*, 2015). It frequently involves various oral manifestations, including SGP, manifesting as hyposalivation, xerostomia, and increased incidence of SG infection (Brand *et al.*, 2009). Its symptoms are quite nonspecific; however, the alteration of SG may be its first presentation.

On the other hand, Wegener's granulomatosis (WG) is an inflammatory idiopathic systemic disease characterized by necrotizing granulomatous inflammation and small-vessel vasculitis, mainly of the respiratory tract and kidneys. The oral manifestation of GW occurs in 6 % to 13 % of patients, and the mouth can be the initial site of clinical presentation in a small fraction of cases (5 - 6 %) (Chegar & Kelley, 2004). The condition of the major SG is rare, and it generally occurs in association with other characteristics of upper and lower respiratory tract disease. The symptoms of the SG in WG may manifest as a unilateral or bilateral increase in the volume of one or more of the major SG, night sweats, or arthralgia. Paralysis of the facial nerve can arise if the parotid gland is involved (Almouhawis *et al.*, 2013; Chouhan *et al.*, 2019).

**Salivary gland neoplasms.** It is recognized in the literature that neoplasms are rare causes of SGP. This classification includes benign and malignant tumors of the SG. Generally, they are not directly associated with pain; rather, the pain is related to the obstruction of the gland or the salivary duct (Mahammed *et al.*, 2008; Son *et al.*, 2018; Barros *et al.*, 2020).

In patients with pain due to SG cancer, the symptoms are nonspecific. In some patients, pain can be one of the main symptoms, including throat pain, functional pain (swallowing, chewing), and pain in the region of the tongue, teeth, and ears. Symptoms vary from slight discomfort to intense pain (Guevara-Canales *et al.*, 2016; Armstrong *et al.*, 2020). There is a correlation in terms of the location of the neoplasm and its symptoms. In the case of the minor SG, those in the upper aerodigestive tract can also be involved, producing dysphagia and otalgia (Adil *et al.*, 2013; Armstrong *et al.*, 2020). It may be related to first-bite syndrome (described later), with these symptoms being the first presentation of the neoplasm (Deganello *et al.*, 2011; Diercks *et al.*, 2011; Guss *et al.*, 2013; Masood *et al.*, 2018).

Although not always an indication of nerve invasion, SGP in SG neoplasms can serve as a marker of possible nerve invasion in patients who do not manifest clinically identifiable weakness of the facial muscles, particularly when they present characteristics of neuropathic pain (Mohammed *et al.*, 2008; Swendseid *et al.*, 2017; Aframian *et al.*, 2019).

**Therapy-associated salivary gland disorder.** It is important to recognize that the SG are controlled by the autonomic nervous system (ANS), namely the parasympathetic division; therefore, any medication that alters the ANS can secondarily produce an alteration in the function of the SG. Oral manifestations secondary to drug use are from the reduction of the salivary flow, which can then induce pain in orofacial structures resulting from the increase in the susceptibility to certain pathologies such as tooth decay, fungal infections, bacterial infections, aphthous lesions, and dysphagia, and can also produce pain and inflammation of the SG (Abdollahi & Radfar, 2003).

Another type of therapy that affects the SG is the radiation administered to the head and neck region for primary or secondary malignant neoplasms. In general terms, it can produce mucositis and atrophy of the SG, where the serous acinar glands are more affected than the mucous acinar glands. This produces a hyposalivation disorder with clinical characteristics similar to SS (Bansal *et al.*, 2004; Adeyemo *et al.*, 2011; Wu *et al.*, 2015). In this same sense, the function of the SG is affected after ablation therapy with high-activity radioactive iodine in patients with differentiated thyroid cancer. The radioactive iodine actively accumulates in the SG tissue, and sialadenitis is a frequent aftereffect, along with decreased salivary secretion and xerostomia, which produce infection and SGP (Mandel & Mandel, 2003; Kaya *et al.*, 2016).

**Neuropathic pain of the salivary glands.** There are few reported cases of SGP with neuropathic characteristics. It is described that first bite syndrome is a rare idiopathic disorder. It is thought to be the result of the loss of sympathetic innervation of the parotid gland from the superior cervical ganglion (Wemyss *et al.*, 2019) as a possible complication of the surgery of parapharyngeal spaces (tonsillectomy, resection of SG neoplasms, etc.) (Chiu *et al.*, 2002; Houle & Mandel, 2014; Scholey & Suida, 2015; Topf *et al.*, 2018). The symptoms are characterized by pain in the region of the parotid gland, which can radiate to the ear. Its main clinical characteristic is the appearance of severe pain that coincides with the first mouthful at each meal and which gradually disappears with successive chewing movements (Costa *et al.*, 2011; Redon *et al.*, 2018). The pain is characterized as severe, acute, and sharp or electric, with a maximum score on the first bite, then gradually decreasing. It may be produced in some cases by swallowing (Ali *et al.*, 2008; Albasri *et al.*, 2011; Avinçsal *et al.*, 2017).

**Other salivary gland disorders.** It is established within ICOP (International Classification of Orofacial Pain, 2020) that SGP may be due to a lesion or disorder known to cause pain in the SG, but that has not been identified in the previous sections. In this sense, it is important to establish that the pain develops in close temporal relation to the lesion or disorder, or that the pain led to its discovery.

## CONCLUSIONS

SG disorders are common in the general population, and SGP has a negative impact on a person's quality of life. Orofacial pain is a common manifestation in patients with SG disorders. SGP is often associated with a locoregional pathology, but it may be a sign of a systemic pathology, which complicates its differential diagnosis. The diagnosis and management of SGP require knowledge of the causes and mechanisms of the pain in patients with an SG pathology since, although in the great majority of cases it has an inflammatory component, it might also be neuropathic. Since pain is usually multifactorial, each dimension of the patient's pain must be addressed. Therefore, the clinician must know the signs and symptoms of salivary disorders and be able to diagnose and treat them.

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**MANCILLA, M.; ITURRIAGA, V.; MUÑOZ, J.; LANDAETA, H.; VELASQUEZ, N.; BORNHARDT, T.** Caracterización del dolor de glándulas salivales: Revisión de la literatura. *Int. J. Morphol.*, 41(5):1364-1371, 2023.

**RESUMEN:** Las glándulas salivales en condiciones patológicas producen un sinnúmero de presentaciones clínicas diferentes, y debido a su compleja neuroanatomía generan variaciones en su sintomatología dolorosa. Sin embargo, en la literatura hasta ahora son escasos los estudios que caracterizan el dolor de glándulas salivales. El objetivo de este estudio fue realizar una revisión de la literatura respecto a las características clínicas del dolor en diversas patologías de glándulas salivales. Se realizó una revisión de la literatura, a través de la búsqueda sistemática de artículos científicos en las bases de datos Web of Science (WoS), MEDLINE, Scopus y Elton B. Stephens Company (EBSCO). A través de los términos libres: "salivary gland", "parotid gland", "submaxillary gland", "sublingual gland", "pain", junto con los operadores booleanos OR y AND. La búsqueda arrojó un total de 1896 artículos, de los cuales 60 cumplieron los criterios de inclusión y fueron finalmente incluidos en esta revisión. Se describe que el dolor es un síntoma poco específico para la patología glandular y está caracterizado principalmente por la localización del dolor, el cual se correlaciona con la ubicación anatómica de la glándula salival afectada. Dentro de las patologías dolorosas de glándulas salivales encontramos los trastornos inflamatorios, incluidas infecciones, obstrucciones, trastornos secundarios a hiposalivación; enfermedades sistémicas autoinmunes; neoplasias y trastornos de dolor neuropático. El diagnóstico y manejo del dolor de glándulas salivales requiere del conocimiento de las causas y mecanismos del dolor, siendo necesario reconocer los signos y síntomas de los trastornos de glándulas salivales para ser capaces de diagnosticarlos y tratarlos.

**PALABRAS CLAVE:** Glándulas salivales; Patología de glándula salival; Dolor de glándula salival; Dolor facial; Dolor orofacial.

**SOURCES OF SUPPORT.** This research was supported by the Temporomandibular Disorders and Orofacial Pain Program, the Sleep & Pain Research Group and the Project DI20-0018 from the Universidad de La Frontera. The funders did not participate in the development, design and execution of the project that was carried out independently.

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