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Carlos Garcia Contreras
Master of Science Student, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Sergio Eduardo Nakagoshi Cepeda
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Jorge Arturo Gutierrez Longoria
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Jorge Yitzhak Garza Silva
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Juan Eduardo Arizpe Coronado
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Manuel Mantilla Ruiz
Professor, Universidad Veracruzana, Facultad de Odontología, Veracruz

Antonio de Jesus Sapien Uscanga
Professor, Universidad Veracruzana, Facultad de Odontología, Veracruz, Mexico

Zohar Carlos Perez Ayala
Dentistry Student, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Juan Manuel Solis Soto
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Corresponding Author:
Carlos Garcia Contreras
Master of Science student, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Oral and temporomandibular tuberculosis: A State-of-the-art literature review

Carlos Garcia Contreras, Sergio Eduardo Nakagoshi Cepeda, Jorge Arturo Gutierrez Longoria, Jorge Yitzhak Garza Silva, Juan Eduardo Arizpe Coronado, Manuel Mantilla Ruiz, Antonio de Jesus Sapien Uscanga, Zohar Carlos Perez Ayala and Juan Manuel Solis Soto

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Abstract
Introduction: Misdiagnosis of tuberculosis of the maxillofacial region can be fatal.
Objective: To review the literature on the epidemiology, diagnosis, treatment, and manifestations of systemic, oral, and temporomandibular tuberculosis.
Methodology: A literature review was carried out in PubMed and Google Scholar databases using the keywords: tuberculosis, oral, temporomandibular, epidemiology, diagnosis, treatment, manifestations, and the Boolean parameters and, or and not.
Results: In recent years, tuberculosis in Mexico has increased 27%. Molecular diagnostic tests are the diagnostic methods of first choice when tuberculosis is suspected. Antituberculosis chemotherapy effectively resolves most oral and temporomandibular manifestations. The main oral and temporomandibular manifestations are persistent ulcerative lesions and chronic joint wear and tear, respectively.
Conclusions: The oral health professional should be able to become the first line of control to break the chain of contagion of tuberculosis, thus reducing the morbimortality of those who suffer from it.

Keywords: Tuberculosis, oral, temporomandibular, epidemiology, diagnosis, treatment.

1. Introduction
Misdiagnosis of tuberculosis (TB) of the maxillofacial region can be fatal, correct diagnosis and timely treatment of oral and temporomandibular TB lesions is necessary [1, 2].
It is imperative to have a greater awareness of persistent or atypical lesions in the maxillofacial region due to TB [1], as it may go unnoticed [3-5], coupled with increased incidence[6] and emerging global resistance to anti-TB therapy [6, 7].
Colonization of mycobacteria to maxillofacial tissues can take place in several ways: a) By direct contact of connective tissue (where the integrity of the epithelium is compromised) with infected sputum or raw cow's milk infected with bovine bacillus (i.e., gingiva shed by bovine eruption). gingiva detached by dental eruption or active periodontal pocket, an empty alveolus by extraction or a dental pulp exposed by caries); b) Spread from an overlying soft tissue lesion; c) By hematogenous or lymphatic route (via a pulmonary, visceral or lymph node focus) and/or d) By congenital transmission (by aspiration/ingestion of infected amniotic fluid or by the transplacental route [8, 9].
The temporomandibular joint (TMJ) can become infected through hematogenous route when the bacilli invade the cancellous bone portion of the condyle, then the subchondral region, and continue to damage the cartilage, synovial membrane and joint space, however, they can also access through a perforation of the middle ear with some infected external agent thus communicating with the joint capsule in its posterior portion [9].
In this work, a literature review of the epidemiology, diagnosis, treatment and manifestations of oral and temporomandibular tuberculosis was performed.

2. Materials and Methods

Information was collected from articles published in English and Spanish on PubMed, SCOPUS and Google Scholar servers, with emphasis on the last 5 years. The quality of the articles was evaluated based on the standard guidelines, i.e., identification, review, choice and inclusion. The quality of the review was assessed using the measurement instrument for evaluating systemic reviews. Boolean logical operators AND, OR and NOT were used in the search. It was performed with the word "Tuberculosis ", together with the following terms: “oral”, “temporomandibular”, “epidemiology”, “diagnosis”, “treatment” and “oral manifestations”.

3. Results and Discussion

3.1 Epidemiology

In 2021, 10.6 million fell ill, being the second leading cause of death from infectious diseases (1.6 million people died in 2021), only behind SARS-COV-2 [10, 11]. The largest number of new cases came from Southeast Asia (46%), followed by Africa (23%) and the Western Pacific Region (18%), while the countries with the highest concentration of cases were Bangladesh, China, India, Indonesia, Nigeria, the Philippines, Pakistan and the Democratic Republic of the Congo. 25% of the world's population has suffered from this disease [12], of which 5-10% will develop TB disease (10.6 million people developed it during 2021) [10, 13], while others will eliminate the infection [14, 15]. 90% of those who develop the disease are adults [10]. It was first described by Dr Robert Koch on March 24, 1882 and is recognized as one of the oldest diseases of mankind as it has coexisted with humans for at least 15,000 years [16].

In the Americas, every day 850 people contract TB and 90 more die, and in 2021, 309,000 TB cases were estimated, of which 70% were reported [17]. 32,000 died, of which 11% corresponded to TB/HIV coinfection and a 90% reduction in deaths is expected by 2030 [10]. Mexico had a high incidence[18] of TB during 2022, more than 28,000 new cases of TB were reported [19], which meant an increase of 27.7% over the previous year [10] with a national incidence rate of 17.6 new cases per 100,000 inhabitants [18]. The most affected states in Mexico are Baja California, Sonora, Baja California Sur, Sinaloa and Tamaulipas with a higher incidence in men (63%) than in women (37%) [18, 20]. As far as is known, there is no official figure for the exact prevalence rate of TB in Mexico in 2022. If we consider that the population of Mexico during 2022 was 130.1 million [21], and that the incidence of cases was 28,000 [19], then we estimate that the prevalence rate was 0.02%.

In 2020, Pulmonary TB is the most frequent with 79.1% [20]; extrapulmonary TB was the remaining 20.9% of the total cases [20]. The mortality rate decreased from 2019 to 2020, being that of 2019 of 1.7 deaths per 100,000 population (the states with the most deaths were Baja California, Sonora, Nuevo Leon, Sinaloa and Chiapas, respectively [22]; while in 2020 the death rate was 1.59 per 100,000 population [20]. Most TB cases in 2019 in Mexico (62.7%) had at least one associated comorbidity, the most frequent being diabetes mellitus with 28.24%.

Maxillofacial manifestations correspond to only 10% of all extrapulmonary manifestations [9]. It can occur from neonatal age to old age [23]; however, it occurs mostly in those under 40 years of age [24]. The incidence of oral TB is quite low (between 0.05% - 5% of all TB cases) [6, 25]. Oral TB, also called tuberculous glossitis [26], is a primary infection in 42% of patients and secondary in 58% [25]. Carcinomas coexist with oral TB in the same lesion in 3% of patients [25]. In half of the occasions previously unknown systemic TB has been established due to a primary manifestation of oral TB, which resulted in timely and effective treatment [25]. From all the English literature, the most frequent localization of oral TB were India and Turkey leading the Asian zone with 44%, followed by UK leading the European zone with 27%, North America with 12%, Japan with 6% and lastly Africa and South America with 3% each [25]. Just under half of all cases of oral TB lesions were primary (42%) [25], although secondary TB lesions are reported to be prevalent [27]. M. tuberculosis and M. Bovis can be found in the mouths of immunocompetent patients; M. avium intracellulare can be found in immunocompromised patients [25, 28].

Mandibular TB involvement accounts for less than 0.2% of all extrapulmonary TB cases (Extra pulmonary TB accounts for 10-15% of systemic TB in immunocompetent patients; immunocompromised patients make up 50-60%), as the mandible contains less cancellous bone, and therefore, fewer blood and lymphatic vessels through which to colonize the bony medullary spaces [9, 29]. Tuberculous involvement of the mandibular condyle is even rarer [30]. Until 2010 only six reports of primary temporomandibular tuberculosis had been reported [29].

TB in Mexico increased by 27.7%, being pulmonary TB the most incident 79%, while oral TB affects from 0.05 to 5%, being temporomandibular TB even rarer, however, there is an increasing possibility of finding cases of oral or temporomandibular TB in the Mexican population, so it is necessary to be prepared to be able to identify it.

3.2 Diagnosis

3.2.1 Systemic Diagnosis

Currently, it is suggested to use molecular diagnostic tests such as automated nucleic acid amplification tests of moderate complexity performed on respiratory tract samples [31, 32], as they are highly accurate (sensitivity of 93.0% (90.9 to 94.7) and specificity of 97.7% (95.6 to 98.8) [32].

It can also be detected histologically by acid-fast staining (Ziehl-Neelse), by quantitative fluorescence PCR [33], and direct sputum smears [5].

Diagnostic tests have been developed with oral swabs that could facilitate TB diagnosis clinically when sputum collection is limited or challenging [34]. However, storage conditions may decrease sensitivity [35].

It is important to perform a complete anamnesis to make the correct diagnosis of systemic involvement and thereby obtain control to avoid spread associated with medical care, while therapeutic options are still considered adequate [25].

3.2.2 Oral Diagnosis

It is recommended to continue using molecular diagnostic tests since the sensitivity of diagnosis with culture and susceptibility tests decreases when samples are obtained from the oral cavity [24].

Incisional, deep tissue (punch) or aspiration biopsy can also be performed and can be complemented with lymph node biopsy when there is lymphedema (100% sensitive) [25] to verify them with Ziehl-Neelsen staining (53% sensitive) [25], where you can observe acid-fast bacilli[36] or PCR test (60% sensitive) [25] direct tissue (formalin-fixed or paraffin-embedded biopsy sections) targeting the 6,110 insertion sequence of TB [37, 38] or the 65 kDa heat shock protein (Hsp65) [39].

Sometimes, superficial biopsies present false negatives due to epithelial hyperplasia [40], so multiple biopsies may be

necessary [41].

In 26.8% sputum test was used, in 24.7% culture was used and in 24.7% purified protein derivative (PPD) or Mantoux test was used [23].

A biopsy of an ulcer present on the tongue may show intense granulomatous inflammatory features with small red rods of mycobacterial organisms, as well as epithelioid cells and giant cells of Langerhans [42]. An adherent gingival lesion biopsy may show fibrotic stroma containing inflammatory infiltrates, multinucleated giant cells and proliferating capillaries suggesting a nonspecific reactive lesion that helps to rule out a gingival malignancy [4]. A soft palate lesion biopsy may show granulomatous inflammation with Langhans-like giant cell content [33].

However, it has been shown that 47% of the time no bacilli were found after Ziehl-Neelsen staining, and 40% of the time PCR was negative, so obtaining a negative result on either test does not reject the possibility of oral tuberculosis [5, 25]. Mycobacterial culture tests can also yield false negatives 37.5% of the time [25]. When in doubt, a direct sputum smear test is appropriate, as it has been observed to have the lowest number of false negatives (16.4%) [25]. Staining and culture tests appear to have more false negatives when collected from the palate and lips [25]. Similarly, exfoliative cytology may be useful as another complementary tool to help establish a diagnosis [36]. Diagnostic testing for TB osteomyelitis can be supplemented with technetium 99m MDTP (methylene diphosphonate) scintigraphy [25]. Performing toluidine blue application on the ulcerative lesion is negative [5]. The fact that there is no lymphedema is not a pathognomonic sign [5]. Having obtained the TB vaccine (bacillus Calmette-Guerin), does not guarantee that oral TB lesions will not develop [25]. Some differential diagnoses to consider are persistent and neoformative oral ulcers such as primary gingival carcinomas, metastatic lymphoproliferative malignancies, Wegener's granulomatosis, sarcoidosis, microscopic polyangiitis, pemphigus, erosive lichen planus, mucous membrane pemphigoid, Crohn's disease, Wegner's granulomatosis, aphthous ulcer, traumatic ulcer, syphilitic ulcer, actinomycosis, deep fungal infection, drug-induced hypertrophy, leukemic infiltrate and Kaposi's sarcoma as they may present with similar morphology [4, 5, 40, 43].

3.2.3 Temporomandibular Diagnosis

It is usually diagnosed late when damage to the joint is notorious [9].

Some more specific features such as the amount of bone resorption, synovitis, effusion and presence of an abscess could help to differentiate the diagnosis through CT scan and MRI [9]. When there are no signs of lung damage, it becomes challenging to establish an obvious and correct diagnosis [36, 6, 4]. Confirmation of the diagnosis of TB infection requires radiological imaging, biopsy and mycobacterial culture, however, more tests with higher sensitivity are required because conventional tests only confirm the diagnosis when there is a high mycobacterial load in the TMJ [8].

The best diagnostic method to detect TB is currently molecular diagnostic tests, so the oral health professional should be the first line of control to break the chain of contagion by being able to diagnose in a timely manner, without considering the inclusion of TB in the differential diagnosis of ulcerative lesions.

3.3 Treatment

3.3.1 Treatment for systemic manifestations

Long-term antituberculosis chemotherapy with a multidrug regimen (six to nine months of a two-month intensive phase of isoniazid (INH), rifampicin (RIF), pyrazinamide and ethambutol (EMB) for, followed by a continuation phase with four months of treatment with INH and RIF) is suggested [44].

If there is HIV co-infection, it is suggested to include antiretroviral therapy [44]. If there is multidrug resistance and rifampicin without resistance to fluoroquinolones, oral regimen with the inclusion of bedaquiline instead of an injectable agent for nine to 11 months is recommended [7]. If multidrug, rifampicin and fluoroquinolone resistance is present, bedaquiline, pretomanid and linezolid (use under operational research conditions) are suggested for six to nine months with the possibility of extension to 11 months [7].

3.3.2 Treatment for oral manifestations

Oral manifestations, and any other type of extrapulmonary TB, respond well to conventional oral systemic antituberculous treatment for 6 to 15 months resolving completely without complications [4-5, 33]. If resistance to first-line drugs is suspected, antimicrobial susceptibility testing is suggested [45]. Oral lesions tend to resolve in 8 months on average [25], with low recurrence rate (a secondary case of upper lip infiltration) [46]. If the lesion does not improve, surgical excision and continuation of antituberculous chemotherapy are suggested [47-48].

An ulcerative lesion present on tongue may take up to one year to completely resolve [42]. The lesion on attached gingiva, such as palatal, may improve considerably after 20 days of oral systemic tuberculous treatment, taking three months for complete resolution[4]. In gingiva such as soft palate gingival lesion, it takes one month after a combined application of drugs.

The application of steroid ointment (betamethasone) on ulcerative lesions may have an apparent improvement after two weeks, however, upon cessation of use the lesions recur [5]. However, its use is not recommended on TB lesions as it has been shown that the lesion may expand diffusely after application of the ointment.

3.3.3 Temporomandibular Treatment

Temporomandibular TB should be treated early, because if it is not treated within the first five years, it could prove fatal [9]. Among the treatments for early cases is systemic anti-TB therapy for six to nine months, for moderate lesions it is recommended to add aggressive debridement with primary closure of the joint keeping under close observation of the patient to determine the need for surgical retreatment to drain an abscess or debride infected tissue and in severe cases a condylectomy and curettage of the glenoid cavity may be required to prevent devastating spread to the intracranial region [9, 49-50].

In patients with growth potential, costochondral grafting, distraction osteogenesis and orthognathic surgery have also been proposed [8]. In these patients, TB severely alters mandibular bony morphology as it affects the growth potential of the TMJ, resulting in facial asymmetry, however, aesthetics and symmetry can be improved by performing angular osteotomy followed by 10 mm distraction osteogenesis using a uniplanar distractor to improve the horizontal and vertical components of the mandible [8].

Early and accurate detection can be the difference between near complete joint recovery (90-95% of normal function) and osteoarthritic changes that evolve into severe joint destruction [9]. Antituberculous chemotherapy effectively resolves most oral and temporomandibular manifestations, thus reducing the morbidity and mortality.

3.4 Manifestations

3.4.1 Systemic Manifestations

The most common manifestation of TB is persistent lymphadenopathy [24]. Some symptoms are accelerated weight loss, anorexia, intermittent fever, cough (sometimes productive), sputum, malaise, asthenia, chest pain, cachexia, night sweats, chills, lethargy, severe hemoptysis or vomiting, dyspnea, rapid deterioration, scaly rash on the head and trunk [37], erythema nodosum [51], lesions on the neck, wrist and body [37], erythema nodosum [51], lesions on the neck, wrist and body [10, 25]. Enlargement of regional lymph nodes and neck is not a pathognomonic sign [25].

3.4.2 Oral Manifestations

The oral manifestations of TB are predominantly in the form of a single persistent superficial non-healing ulcer, indurated margins, ill-defined with stellate shape, undermined edges and a hard necrotic base (58%) or covered with greyish or yellowish slough (42%) [25]. They may also show as a painless, warm, expansive swelling fixed to the buccal tissue; granulomatous enlargement, nodular masses measuring from 1 mm to a few cm, confluent erosions, indurated lesions, diffuse soft tissue papules or even lesions within the mandible or maxilla that may be in the form of simple bony radiolucency, osseous sequestration, periosteal reaction, cortical erosion or tuberculous osteomyelitis presenting a swelling with signs of atypical osteitis, periodontal disease with vertical bone loss or destructive osteolysis[25]; may also present outflow of blood, exudate or pus through the paranasal sinuses or post-extraction alveoli and even discharge of bone spicules through the gums may occur [4, 25, 33] Lips may present macrocheilia [25].

Of all these oral lesions, the ulcerative form is the most frequent (55%) [52, 25], becoming painless[5] followed by tumefaction (24%), suppuration with or without fistula (10%), nodules (8%), alveolar involvement by previous extraction (8%), granulomatous plaques/growths/indurations (5%), diffuse inflammation (4%) and finally collision tumors as the least frequent (2%) [25].

The most frequent location of TB is the tongue (26.6% - 32%) [23, 25], followed by the mandibular bone (21.4%), gingiva (15.8%), lips (8.9%), buccal mucosa (8.2%), soft palate (8.2%) and finally the hard palate as the least frequent (4.8%) [25]. It can also come to affect the uvula, salivary glands, lymph nodes [9].

It may present on the tip of the tongue [42] or on its latero-ventral surface [5] as an ulcer on the palatal gingiva as an extensive, erythematous, persistent lesion with a nodular, pebbly enlargement [4].

Oral manifestations are usually secondary to pulmonary changes [42], however, cough, hemoptysis, fever or any other particular symptom of pulmonary tuberculosis is not necessarily present [4]. The buccal mucosa frequently shows manifestations without presenting pulmonary signs at the same time (primary oral infection) [25, 27]. In contrast, the lips are often associated with pulmonary tuberculosis (secondary oral infection) [25]. Women showed more manifestations in gum and mandibular bone than men [25]. Oral TB lesion can coexist with cancerous lesions (one in collision tumor in buccal mucosa, another in adenoid cystic carcinoma that did not resolve with anti-TB treatment after 6 months [53] and a couple more of tuberculous osteomyelitis coexisted with a central mucoepidermoid carcinoma [54-55]. It can also present in the maxilla resembling maxillary sinus carcinoma [1].

Palpation of enlarged lymph nodes is not pathognomonic since 45.8% of patients presented only submandibular lymphedema, while its swelling of several areas (submandibular and submental) is only present in 22.8% of cases [25].

Among the symptoms we can find that it usually presents pain, together with odynophagia without caseification of the dependent lymph nodes, aphonia, burning sensation [25, 4], reflux, excessive salivation, halitosis and intraoral bleeding [25]. Tongue function can also be compromised [56].

However, painless lesions may also occur and may even be serendipitously discovered [25, 57]. Both oral and temporomandibular lesions show various non-pathognomonic aspects [6, 10, 58, 59]. Early identification and association of oral manifestations may provide timely diagnosis and early treatment of systemic tuberculosis [42].

3.4.3 Temporomandibular Manifestations

The most common temporomandibular TB lesion is chronic joint wasting of the condyle that resembles arthritis, osteomyelitis, or any other type of chronic joint disease [9], and may present without pulmonary manifestations [9]. It presents with non-pathognomonic signs such as a mobile preauricular swelling, of firm consistency with pain on palpation that gradually increases in volume in just a few months and presents with continuous, pulsating, intense, severe pain radiating to the temporal region, presenting with gradual trismus with deviation towards the affected side during opening [9]. A reduced space of the affected TMJ can be seen on orthopantomography, in addition to destruction of the mandibular condyle with proximal sclerosis and erosion of the mandibular fossa seen on computed tomography [9].

It frequently manifests unilaterally, affecting the cancellous portion of the epiphysis and metaphysis of the long bones [9, 60]. In patients with growth potential, unlike the ankylosis that any other infection might produce, TB produces condylar hypoplasia and thus hypoplasia of the condyle-branch length [8].

The main oral and temporomandibular manifestations are persistent ulcerative lesions and chronic joint wear, respectively. It is possible to presumptively recognize this entity with the signs and symptoms, which will provide the possibility of a timely diagnosis and early treatment of systemic tuberculosis, thus preventing it from evolving and having unfortunate consequences.

4. Conclusions

The epidemiology of TB during 2023 in Mexico increased by 27%. This prompts the oral health professional to know how to diagnose it by means of molecular tests in order to carry out a timely and effective treatment through anti-TB chemotherapy as the first choice to solve without delay the main oral and temporomandibular manifestations, such as persistent ulcerative lesions and chronic joint wear, thus becoming the first line of control to break the chain of contagion, reducing morbidity and mortality of those who suffer from TB.

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5. References

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