Review Article

Clinical anatomy of the inferior labial gland: a narrative review

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Objective: In this article we review the literature on the inferior labial gland from a clinical and anatomical perspective.

Background: Regardless of its importance in clinical practice, there are no medical literature that comprehensively reviewed the inferior labial gland.

Methods: A database search using PubMed and Google Scholar was conducted. The following keywords were used in the search: "lower labial salivary gland", "lower labial gland", "inferior labial salivary gland", AND "inferior labial gland".

Conclusions: The human labial glands are types of minor salivary gland that continuously secrete small amounts of mucous and serous substances to maintain oral health. The inferior labial glands are innervated by the inferior labial branch of the mental nerve, and the inferior labial branch of the facial artery is the main arterial supply to the lower lip. Although they only have an auxiliary role in saliva production compared to the major salivary glands, minor salivary glands provide a certain amount of lubrication in the oral cavity by the continuous outflow of saliva. The inferior labial gland not only promotes moisturization in the oral cavity but also secretes substances with antibacterial effects, which is important for the function of the oral cavity. A recent study showed that the rate of salivary secretion from the inferior labial glands does not change with age, and in some cases the inferior labial glands are used for diagnosing intractable diseases such as Sjogren's syndrome and cystic fibrosis. In addition, since the inferior labial glands themselves can be the site of cyst and/or neoplasia development, we should be careful to distinguish them from other diseases. Elucidation of the anatomy, physiology, and pathology of the inferior labial glands, is important for understanding human health and diseases.

Keywords: Inferior labial gland; minor salivary gland; salivary function; diagnostic material; clinical anatomy

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Introduction

The salivary glands in the oral cavity can be divided into two main categories: major and minor. The major salivary glands comprise the parotid, submandibular, and sublingual glands. Collectively, they are responsible for 95% to 97% of saliva production. The minor salivary glands produce the remainder. They are mainly concentrated in the buccal mucosa, labial mucosa, lingual mucosa, gingival mucosa (especially in the retromolar region), soft/hard palate, and floor of the mouth (1,2). Approximately 800–1,000 minor salivary glands are located deep to the oral mucosa, and saliva from their tissues drains directly into the oral cavity without passing through a duct. The minor salivary glands are poorly visualized on computed tomography (CT) and/or magnetic resonance imaging (MRI), but in some cases can be sources of diseases such as tumors, cysts, inflammation and infections. They are also used as material for diagnosing autoimmune diseases that cause xerostomia. The labial gland is one of the minor salivary glands. It lies in the adipose tissue developed in the labial mucosa. It contributes to providing appropriate moisture to the lips. Regardless of its importance in clinical practice, there are no medical literature that comprehensively reviewed the inferior labial gland. In this article, we present a literature review of the inferior labial gland from a clinical and anatomical perspective. We also present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/gs-21-143).

Methods

A database search using PubMed and Google Scholar was conducted on January 13, 2021 without any language limitations. The following keywords were used in the search: "lower labial salivary gland", "lower labial gland", "inferior labial salivary gland", AND "inferior labial gland".

Results

A total of 48 articles were found in the database. One abstract, two books, and two articles written in Chinese language were excluded. As a result, 43 articles were included and analyzed.

Discussion

Anatomy

The labial gland is one of the minor salivary glands, which are mainly found beneath the mucosal epithelium of the upper and lower lip and within the orbicularis oris muscle fibers (3) (*Figure 1*). The upper labial glands are on average distributed 11 mm outward from the corner of the mouth, while the inferior labial glands are on average widely distributed 16 mm outward from the corner of the mouth. The upper labial glands are densely located between and scattered outside the corners of the mouth; the inferior labial glands are scattered between and densely located outside the corners of the mouth (4). In other words, there are many well-developed labial glands in the upper lip, but only a few small labial glands are distributed in the lower lip (4) (*Figure 2*). A typical labial gland weighs around 50 mg and a density of 5–8 glands per square centimeter on the inner surface of the lips is usual. Stimulated flow from the labial salivary gland is around 5 mL/min/cm^2 (5). The inferior labial glands mainly consist of one duct that houses serous and mucous acini cells but produces mostly mucous secretions. Held in place by connective tissue, the inferior labial glands along with the other minor salivary glands are not encapsulated in such tissue but rather surrounded by it (1).

Innervation

The major salivary glands are dominated by both parasympathetic and sympathetic nerves while the minor salivary glands are not innervated autonomically (6). Rather, the inferior labial glands are innervated by the inferior labial branch of the mental nerve (7,8) (*Figure 3*). The inferior labial branches go to the inferior labial region and branch off the autonomic fibers to the labial glands (8). The postganglionic fibers in the sympathetic division usually originate from the external carotid plexus via the maxillary and inferior alveolar arteries. As the mental nerve communicates with the marginal mandibular branch of the facial nerve, the external carotid plexus via the facial artery is also a candidate of the pathway of the postganglionic fibers.

The postganglionic fibers of the parasympathetic division via the mental nerve have not been much discussed.

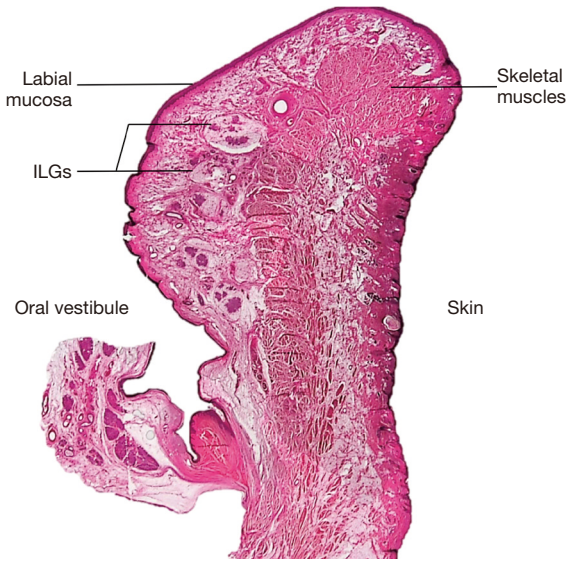

Figure 1 Parasagittal section of the lower lip. Note that the inferior labial glands (ILGs) are located between the labial mucosa and skeletal muscles.

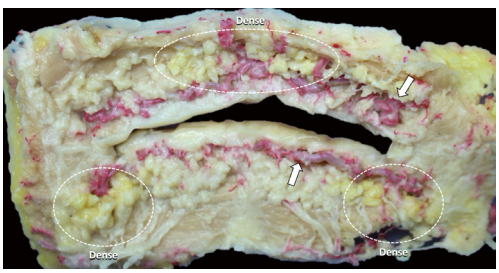

Figure 2 Posterior view of the lips after removal of the mucosa showing the superior and inferior labial glands. Note the superior and inferior labial branches (upper and lower arrow, respectively) of the facial artery supplying the upper and lower lip, respectively.

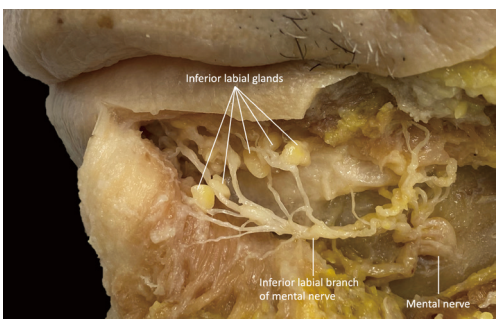

Figure 3 Inferior labial glands are innervated by the inferior labial branch of the mental nerve.

Segade *et al.* (1987) found that the otic ganglion in pigs innervates not only the parotid gland but also all other branches of the mandibular nerve such as the inferior alveolar and lingual nerves (9). Thus, the postganglionic fibers could originate from the otic ganglion via the mental nerve.

Blood supply

Branching from the facial artery, the inferior labial artery is the main blood supplier to the lower lip (see *Figure 1*). There are variations in which the inferior labial artery also acts as a supplementary or main supplier to the lower lip, but they are rare (10). The inferior labial artery runs along the level of the vermillion borders of the lower lip, mostly submucosally. This position is determined to be between the oral mucosa and the orbicularis oris muscle. From there, the inferior labial artery branches off, providing an accessory blood supply to the structures located in the mucosa including the inferior labial glands (11).

Function

The inferior labial gland, like all the minor salivary glands, has no specific neuronal regulation. These glands are mainly under muscarinic control and primarily use the Na^+-K^+-$2Cl^-$ cotransporter to drive transepithelial anion transport and also fluid secretion (12). Thereby, they continuously secrete small amounts of saliva to provide constant lubrication of the oral surface. In total, the minor salivary glands together produce around 10% of the entire salivary volume (13). In view of the large surface area they encompass in comparison to the major glands, each of which has a single large duct, their role in sustained and efficient saliva production for the oral cavity is even more important, especially when pathology affecting the innervation of the major salivary glands makes their role in creating a moist oral mucosa essential.

Salivary antibody production is another major function of the inferior labial gland. Antibodies of each immunoglobin isotype to the antigens of several oral streptococcal bacteria have been detected in saliva collected from the labial salivary glands. This immune defense significantly hampers the growth of mutans streptococci after dental prophylaxis (14). Therefore, the ability of these glands to secrete mainly IgA (15,16) along

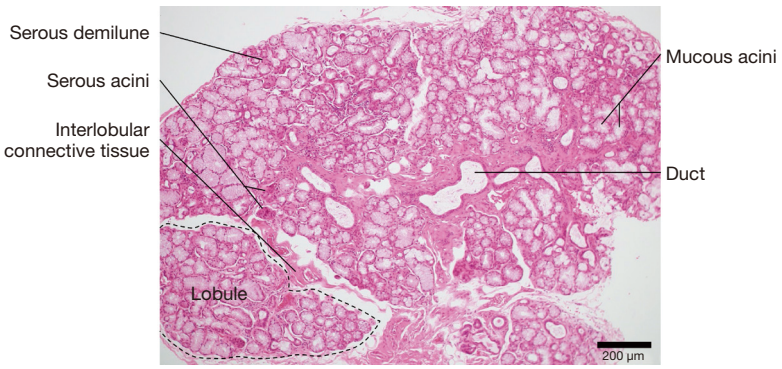

Figure 4 Non-pathological findings of the inferior labial gland with hematoxylin and eosin staining.

with IgG (16) and IgM (17) is vital in the immune defense against pathogens mounted by the oral cavity.

The mucinous acini cells found in the inferior labial glands produce other salivary proteins besides immunoglobins that influence the oral microbiome and the overall health of the oral cavity (*Figure 4*). Mucins are highly glycosylated proteins mainly produced by mucous acinar cells such as those in the inferior labial glands (18). Owing to their hydrophilic nature, mucins can serve as a protective barrier for the structures in the mouth against bacterial colonization or bacterial proteases. MUC5B is a particular type of mucin secreted by the labial salivary gland that allows S. sanguinis to coexist with *S. mutans*, thus hampering the formation of a single *S. mutans* colony and its subsequent biofilm (19,20). MUC1 is another mucin often produced by the labial salivary glands that is involved in signal transduction and scaffolding to hold the salivary proteins in place by forming a mucus layer. It therefore provides a framework for MUC5B to be held in place, enabling its influence on the oral microbiome to take effect (21,22).

Lysozymes are also produced by the labial salivary glands. They hydrolyze the B-1,4-glycosidic bonds between N-acetylmuramic acid and N-acetyl-D-glucosamine in the polysaccharide layer of the Gram-positive bacterial cell wall, so they are bactericidal. Aside from their ability to lyse harmful bacteria, lysozymes serve to aggregate oral bacteria, which facilitates their clearance from the oral cavity (23).

Aging

Studies have shown that the inferior labial salivary glands undergo age-related changes in form and function. In terms of structure, they show increased ductal and connective tissue volumes and fatty infiltration. There is also a rise in the number of inflammatory cell foci (24-27). Although the inferior labial salivary gland shows degenerative changes with age, recent studies by Eliasson *et al.* conclude that there is no change in the rate of salivary secretion. As for IgA secretion, the inferior labial glands of older subjects secreted saliva with a higher IgA concentration (28).

Diagnostic value

With the surgical failure and risk of obtaining biopsies from the major salivary glands, excision and biopsy of the inferior labial minor salivary glands have been used as a plausible alternative. Located on the inner surfaces of the lips, the inferior labial glands are easily accessible and readily available for biopsy. Since major exocrine disorders such as Sjogren's syndrome (SS) and cystic fibrosis are reflected in the labial glands, the inferior labial glands are important diagnostic materials for them (29). The following text includes an in-depth review of current research surrounding the use of inferior labial glands for elucidating and potentially diagnosing major systemic diseases.

Primary Sjogren's syndrome & non-Hodgkin's lymphoma

Primary Sjogren's syndrome is a chronic autoimmune disease affecting the exocrine glands and other organs. It is characterized by lymphocytic infiltration of the salivary and lacrimal glands leading to progressive loss of the glandular parenchyma with a decrease of function, leading in turn to chronic salivary hypofunction and keratoconjunctivitis sicca (30). Labial salivary gland biopsy has long been considered the gold standard for diagnosing

patients with primary Sjogren's syndrome (*Figures 5*,*6*). It is often used when other diagnostic measures and laboratory values are inconclusive (31). Focal lymphocytic sialadenitis found in the inferior labial glands is characteristic of Sjogren's syndrome. In the biopsy procedure, around six to seven glands with notable swelling are harvested and the inflammatory infiltrates are scored and graded according to the method of Greenspan and Daniels (32). Development of non-Hodgkin's lymphoma (NHL) is the major adverse outcome of Sjogren's syndrome (33), and recent studies have established the predictability and diagnostic capacity of inferior labial gland biopsies and their value in early diagnosis of NHLs developed from SS (33-37). *Table 1* (33-37) summarizes the use of labial gland biopsies and the diagnostic markers used in confirmed SS patients for potential diagnosis of NHLs over the past 20 years. Increasing numbers of case reports and cohort studies exploring the use of inferior labial salivary glands to diagnose NHLs in patients with SS strongly suggest that further establishment and exploration of a standardized testing mechanism should be incorporated into the SS biopsy process to capture the possibility of NHL development comprehensively.

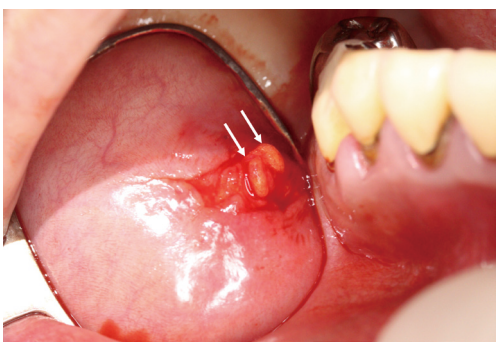

Figure 5 The inferior labial glands (arrows) during the biopsy and pathology of the gland for diagnosis of Sjogren's syndrome.

Cystic fibrosis (CF)

Currently, CF is diagnosed through clear clinical presentations and symptoms, the sweat chloride test, and genetic testing for the two known disease-causing CFTR mutations. However, for patients with limited phenotypes, the diagnostic process can be more complex. Other methods such as nasal potential difference measurements or current intestinal measurements can be used (38). Labial salivary gland biopsy is another potential diagnostic material that can be explored and used for patients who fall into this pathology. Although the inferior labial glands of patients with and without CF have the same ultrastructure, those from CF patients contain more mucin (39). Aside from mucin accumulation, it has also been shown by Sweney *et al.* that most pediatric patients display acinar plugs of eosinophilic material in the inferior labial glands upon biopsy, which normally appear as one ages (40). Also, when the biopsy is processed for fixation, the epithelium of the mucous membrane separates from the glandular tissue; in normal biopsies the connective tissue layers remain intact (39). Most recently, using the non-invasive technique of optical coherence tomography, a lower density of labial salivary glands has been demonstrated in CF patients than in a group without the disease (41).

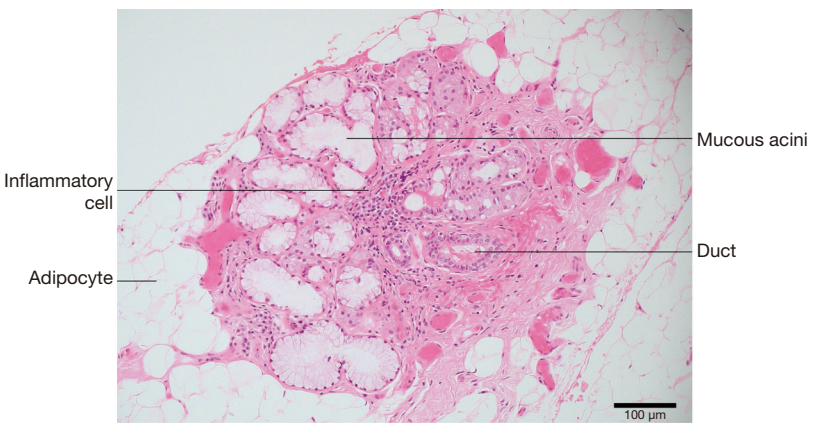

Figure 6 Dilation of salivary gland ducts and atrophy of acinar cells are seen with hematoxylin and eosin staining. Increased numbers of capillaries are seen in the interstitium. Lymphocyte infiltration around the duct is inconspicuous.

Table 1 Use of labial gland biopsies and the diagnostic markers in confirmed SS patients for potential diagnosis of NHLs

Author	Year	Study type	NHL subtype	Diagnostic marker(s)
Van Mello *et al.* (34)	2005	Case Report	MALT	Monoclonal kappa and lambda light chain; CD 43, CD 20, CD3
Theander *et al.* (33)	2011	Cohort Study	DLBCL	Evaluation of H&E stained paraffin-embedded labial gland for germinal centers
Keszler *et al.* (35)	2013	Case Report	MALT	Evidence of kappa light chain restriction and positive staining for Bcl-2; CD 23, CD20, CD5, CD3
Ramos *et al.* (36)	2017	Case Report	MALT	Lambda and kappa light chains; CD138, CD23, CD20, CD10, CD5, bcl-2, cyclin-D1
Kapsogeorgou *et al.* (37)	2018	Cohort Study	MALT, NMZL, LP, DLBCL, SLL, BALT	Micro-RNA 200b-5p

BALT, B cell bronchial associated lymphoid tissue; DLBCL, diffuse large B cell lymphoma; LP, lymphoplasmacytic; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin's lymphoma; NMZL, nodal marginal zone lymphoma; SLL, small lymphocytic; SS, Sjögren's syndrome.

Neonatal hemochromatosis (NH)

NH is a fatal neonatal iron storage disease in which iron is deposited at hepatic and extrahepatic sites, leading to liver and multiorgan failure (42). Because the onset of the disease occurs in utero, affected infants are often either stillborn, premature, or small with signs of organ failure at birth (43). Therefore, early diagnosis is important for extreme medical intervention because the condition worsens over time (44). Recent case studies have revealed iron deposits in the inferior labial salivary glands of NH patients. However, the sample is small so false positives or negatives are likely (45). Nonetheless there are proponents for the use of inferior labial salivary gland biopsy along with clear clinical presentations for diagnosing NH, and more researches are indicated to incorporate inferior labial gland biopsy formally into the diagnostic protocol of NH (46,47).

Ocular sarcoidosis

Sarcoidosis is an immune-mediated inflammatory disorder that can present as uveitis. Some features suggesting sarcoidosis uveitis include the following five signs: granulomatous iritis with fat keratic precipitates, iris nodules, string of vitreous opacities, retinal perivasculitis, and spotty retinochoroidal exudates. Because these features are common and because ocular presentations of sarcoidosis potentially precede systemic signs, sarcoidosis must be considered as an underlying cause of undiagnosed uveitis (48-51). With a low diagnostic yield for sarcoidosis, inferior labial gland biopsy has been shown to be useful for diagnosing sarcoid uveitis in patients with confirmed sarcoidosis. It has been suggested that inferior labial gland biopsy is useful as a second-line investigation for patients with granulomatous uveitis and radiological patterns compatible with sarcoidosis for an earlier intervention to treat the uveitis (52).

Other pathologies

Mucocele

Oral mucoceles that typically involve the minor salivary glands found in the lower lip and the buccal mucosa originate from a traumatic incident leading to duct laceration and leakage (53). Focusing on the inferior labial glands, a lacerated duct will lead to a spread of mucin around the inferior labial submucosal connective tissue. After mucus extravasation, an immune response follows that leads to tissue granulation and inflammatory cell inundation in order to control the mucin spread. Over time the area is pseudoencapsulated with fibrous tissue (54,55). Like any mucocele that originates from mucus extravasation, inferior labial gland mucoceles can undergo sequences of appearance and disappearance (56). Conventional treatment modalities for inferior labial glands include simple surgical excision using the underlying orbicularis oris muscle as a cleavage plane (57). Other nonsurgical treatments include intralesional corticosteroid therapy, cryosurgery, micromarsupialization, and carbon dioxide laser (58).

Tumors

The minor salivary glands are the second most common locations for salivary gland tumors following the parotid

gland (59,60). The palate is the most common location for minor salivary gland tumors, and the lips are the second most common. Tumors arise more commonly in the superior than the inferior labial salivary glands. However, a tumor arising from the inferior labial salivary glands is more likely to be malignant. The most common malignancy arising from the inferior labial glands is mucoepidermoid carcinoma (61,62).

Conclusions

The human labial glands, a subset of the minor salivary glands, are important structures for oral health. Their continual secretion of saliva is important for immune defense by preventing dryness of the oral tissue around the lips and by producing antibacterial secretions.

Tumoral lesions that occur in the lower lip include cystic diseases such as mucocele and dermoid cysts, benign tumors such as fibroma and schwannoma, and malignant tumors such as mucoepidermoid carcinoma and adenocarcinoma. Among these, about half or more of the tumoral lesions that occur in the lower lip are reported to be malignant tumors derived from the inferior labial glands (59,63). We must be very careful in differentiating these diseases.

The inferior labial gland is expected to be used not only for its original salivary gland function and as diagnostic material for autoimmune diseases, but also as transplant material for improving severe dry eye symptoms (64,65). However, our knowledge of the minor salivary glands, including the labial glands, is still limited compared to the major salivary glands. We hope that further research focused on the function of the labial glands and the derivation of new diagnoses and techniques will help to improve our understanding of their role in health and disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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