

Xerostomia Due to Systemic Disease: A Review of 20 Conditions and Mechanisms

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Abstract

Xerostomia is a common complaint of nearly half of the elderly population and about one-fifth of younger adults. It causes several signs and symptoms, and compromise oral functions and health-related quality-of-life. Multiple reasons are proposed to describe the etiology of xerostomia such as local factors, psychogenic factors, and systemic diseases. In order to manage xerostomia effectively, identification of the main causality is mandatory. The aim of this review was to present systemic diseases leading to xerostomia with their mechanisms of action. We used various general search engines and specialized databases such as Google, Google Scholar, Yahoo, PubMed, PubMed Central, MedLine Plus, Medknow, EBSCO, ScienceDirect, Scopus, WebMD, EMBASE, and authorized textbooks to find relevant topics by means of Medical Subject Headings keywords such as “xerostomia,” “hyposalivations,” “mouth dryness,” “disease,” and “systemic.” We appraised 97 English-language articles published over the last 40 years in both medical and dental journals including reviews, meta-analysis, original papers, and case reports. Upon compilation of relevant data, it was concluded that autoimmune diseases most frequently involve salivary glands and cause xerostomia followed by diabetes mellitus, renal failure, and graft-versus-host disease. Moreover, the underlying mechanisms of systemic disease-related xerostomia are: autoimmunity, infiltration of immunocompetent cells, granuloma formation, fibrosis and dehydration, deposition of proteinaceous substances, bacterial infection, and side-effects of medications.

Keywords: Disease, Hyposalivations, Mouth dryness, Systemic, Xerostomia

Introduction

Xerostomia is the subjective complaint of oral dryness, while salivary gland hypofunction is an objective matter characterized by reduced salivary flow.^[1] These two terms are often incorrectly used interchangeably.

Xerostomia is a frequent annoying condition. It is estimated that 12-47% of the elderly and 10-19.3% of people in their early 30's have been suffering from dry mouth.^[2-4] The symptoms of xerostomia are as follows: Cracked peeled atrophic lips, glossitis, progressive cervical, or cusp tip caries even with optimum oral hygiene, candidiasis, and

pale corrugated dry buccal mucosa. The size, texture and tenderness of salivary glands should be assessed. Xerostomia can lead to dysphagia, dysgeusia, oral pain, dental caries, oral infection, periodontal disease, and finally can affect the health-related quality-of-life.^[5-8] Malnutrition and psychosocial problems could be associated with dry mouth as well.^[8] The basis of xerostomia is the alteration in both quantitative and qualitative function of salivary glands.^[6] There are multiple causes with various mechanisms of xerostomia such as systemic diseases, anticholinergic effects of many drugs, psychological conditions, alcohol, head and neck radiation therapy, and physiological changes, but xerostomia-related systemic diseases have not been addressed as much as they worth it.^[9] In order to better understanding, diseases which cause xerostomia, the underlying mechanisms and the incidence or prevalence of dry mouth due to systemic conditions are summarized in Tables 1 and 2. Multiple methods have been described to manage xerostomia. Saliva substitutes, topical stimulants, and parasympathetic agonists such as pilocarpine and cevimeline are approved medications to treat xerostomia.^[10] Early detection of these diseases may

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Table 1: Mechanisms of xerostomia due to systemic diseases

Mechanism	Disease
Neuropathic	Diabetes ^[11] Parkinson's disease ^[24]
Immune and inflammatory-mediated	Viral infections HIV ^[26] EBV ^[48] CMV ^[50] HTLV-1 ^[55-58] GVHD ^[95] Rheumatoid arthritis ^[63] Primary biliary cirrhosis ^[69] SLE ^[64] Scleroderma ^[70-72] Autoimmune thyroid diseases ^[21-23]
Granulomatous reaction	Tuberculosis ^[77, 78] Sarcoidosis ^[74]
Storage of substances	Hemochromatosis ^[79,80] Amyloidosis ^[82-84]
Dehydration	ESRD ^[86,87] Diabetes ^[11]
Alteration in salivary gland structure	Scleroderma ^[71] Hemochromatosis ^[79,80] Amyloidosis ^[81] Actinomycosis ^[59-61] GVHD ^[95] CMV infection ^[49-51]
Genetic disorder	Ectodermal dysplasia ^[88-90]

NA: Not assigned, SLE: Systemic lupus erythematosus, GVHD: Graft-versus-host disease, ESRD: End stage renal disease, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, EBV: Epstein-Barr virus, CMV: Cytomegalovirus, HTLV-1: Human T-lymphotropic virus type 1

aid to timely treatment of xerostomia. Some of these systemic conditions are so severe that distract the attention of health care workers away from the complications such as xerostomia, which might cause additional discomfort for the patient.

The aim of this study was to describe systemic diseases leading to xerostomia to provide physicians and dentists with an update and comprehensive source for their clinical practice.

Methods of Literature Search

We used various general search engines such as Google, Google Scholar, and Yahoo as well as bibliographic databases such as PubMed, PubMed Central, Medline Plus, Medknow, EBSCO, ScienceDirect, Scopus, WebMD, EMBASE, and three authorized textbooks to find relevant topics by means of medical subject headings keywords such as “xerostomia,” “hyposalivations,” “mouth dryness,” “disease,” and “systemic.” The search was accomplished in 2013 and limited to English-language articles published over the last 40 years in both medical and dental journals. Totally, 258 articles were identified. After provisional assessment of the titles and abstracts by two reviewers, 106 articles were

Table 2: Incidence or prevalence of xerostomia due to systemic diseases

Systemic disease	Prevalence or incidence of related xerostomia (%)
Diabetes type 1	38.5-53 ^[17,18]
Diabetes type 2	14-62 ^[15-17]
Viral infections	
HIV	1.2-40 ^[26,29,33]
HCV	5-55 ^[36,38,39,41,342]
EBV	NA
CMV	NA
HTLV-1	3.8-36.7 ^[55-58]
Autoimmune thyroid disease	NA
ESRD	28-59 ^[86,87]
Rheumatoid arthritis	NA
Primary biliary cirrhosis	47-73 ^[67,68]
Ectodermal dysplasia	33.3 ^[90]
GVHD	16-59 ^[91,93,94]
Hemochromatosis	NA
Parkinson's disease	NA
Sarcoidosis	6 ^[74]
Tuberculosis	NA
SLE	75 ^[64]
Amyloidosis	NA
Actinomycosis	NA

NA: Not assigned, SLE: Systemic lupus erythematosus, GVHD: Graft-versus-host disease, ESRD: End stage renal disease, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, EBV: Epstein-Barr virus, CMV: Cytomegalovirus, HTLV-1: Human T-lymphotropic virus type 1

found to be relevant to the topic, and out of them 97 were available for us including 20 reviews and meta-analysis, 59 original papers, and 18 case reports regarding systemic disease resulting to xerostomia. Our review included articles published between 1997-2013, in the years of 1974, 1980, 1983, 1987, 1989, and 1990.

Results

After compilation of information from relevant articles and updated textbooks, we categorized systemic diseases resulting in xerostomia to endocrine diseases, viral infections, bacterial infections, autoimmune diseases, granulomatous diseases, storage diseases, and some other unclassified diseases as follows. Meanwhile, the underlying mechanisms of xerostomia due to systemic diseases, and the incidence or prevalence of xerostomia in each disease were summarized in Tables 1 and 2.

Endocrine diseases

Diabetes mellitus

Diabetes mellitus is an endocrine disease characterized by the deficit in production of insulin with consequent alteration of metabolism and balance of glucose concentration. According to its etiology, it is classified as Type 1 and 2.^[11] Type 1 diabetes mellitus is a metabolic dysfunction characterized by hyperglycemia resulting from definite shortage of insulin secretion caused by autoimmune illness and genetic factors.^[12] Type 2 diabetes mellitus (formerly known as

non-insulin-dependent diabetes mellitus) is the most common form of disease featured by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 diabetes results from interaction between genetic, environmental and behavioral risk factors.^[13] It is estimated that there will be 380 million persons with diabetes mellitus in 2025.^[14]

Patients with uncontrolled diabetes often report dry mouth, which is believed to be due to polyuria, dehydration, and autonomic dehydration.^[11] The prevalence of xerostomia was reported in 14-62% of diabetes mellitus 2 cases,^[15-17] and it was found in 38.5% and 53% of children and adolescents subjects with diabetes mellitus 1, respectively.^[17,18]

Thyroid disease

Autoimmune thyroid disease, including Graves' disease and Hashimoto's thyroiditis, is one of the most common immune-mediated conditions.^[19] Autoimmune thyroid disease is characterized by the presence of serum antibodies against thyroid-specific or thyroid-restricted antigens like the thyroid stimulating hormone receptor, thyroperoxidase, and thyroglobulin.^[20] The prevalence of autoimmune thyroid disease in the general population varies among countries. Prevalence has been estimated as 5-15% in women and 1-5% in men. In other words, autoimmune thyroid disease can be regarded as the most common autoimmune endocrine disease.^[21] A considerable number of patients with primary Sjögren's syndrome (pSS) along with thyroid disease diagnosed by laboratory data and clinical presentation were reported.^[22] The coexistence of Sjögren's syndrome and thyroiditis is frequent suggesting a common genetic or environmental predisposing factor with similar pathogenic mechanisms. pSS was reported to be 10 times more frequent in patients with autoimmune thyroid disease, while autoimmune thyroiditis was 9 times more frequent in pSS. Therefore, Sjögren's syndrome should be studied in patients with thyroid disease and vice versa.^[23]

Viral infections

Human immunodeficiency virus

Human immunodeficiency virus (HIV) infection is one of the most devastating infections in modern times. Oral manifestations of HIV infection occur in approximately 30-80% of patients.^[24] Oral lesions are among the early signs of HIV infection and can predict progression to acute immunodeficiency syndrome. The more common HIV-related lesions include oral candidiasis, herpes simplex infection, oral Kaposi's sarcoma, oral hairy leukoplakia, parotid gland enlargement, periodontal diseases (linear gingival erythema and necrotizing ulcerative periodontitis), human papilloma virus-associated warts, and ulcerative conditions including herpes simplex virus lesions, recurrent aphthous ulcers, neutropenic ulcers, and xerostomia.^[25,26] Xerostomia is due to the side effects of HIV medications (e.g., didanosine) or the proliferation of CD8⁺ cells in the major salivary glands.^[26] Parotid hypertrophy as a compensative reaction has been also found more commonly in HIV-positive children.^[27,28]

Xerostomia has been estimated as 1.2-40% in HIV-positive patients.^[26,29-33] Although the role of HIV on xerostomia is relatively clear, there is a controversy about xerostomia prevalence as demonstrated by Sontakke *et al.*, Pinheiro *et al.*, and Nittayananta *et al.*^[32-34] There is another conflict about xerostomia-related HIV medications in the literature, for example Lin claimed that xerostomia was not compounded by medications.^[35] In contrast, some researchers believe that taking anti-HIV drugs is effective on the prevalence of xerostomia.^[26,32]

Hepatitis C virus

The hepatitis C virus (HCV) is a linear, single-stranded RNA virus of the *Flaviviridae* family that was first identified in 1989.^[36] HCV infection is a major health problem among the general population, and its extrahepatic manifestations have also been reported like Sicca syndrome.^[37] Several autoimmune and immune complex-mediated disorders have been proposed to be related to HCV infection such as essential mixed cryoglobulinemia, which is frequently associated with Sjögren's syndrome. The association between HCV and Sjögren's syndrome may be related to the following reasons: (1) close association between HCV infection and mixed cryoglobulinemia, (2) the salivary gland tropism of HCV.^[38] However, some studies did not find any relationship between xerostomia and the presence of HCV infection.^[39,40] Xerostomia has been found among 5-55% of HCV-infected patients.^[36,38,39,41,42] Xerostomia is also an adverse event during ribavirin-interferon therapy.^[43,44]

Epstein-Barr virus

Epstein-Barr virus (EBV) is a human herpes virus that establishes long-term latent infection in B-lymphocytes named EBV infectious mononucleosis (EBV-IM).^[45] EBV-IM is a common infection that affects 25-30% of adolescents and adults up to 30 years of age.^[46] Association between EBV and autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, multiple sclerosis, autoimmune thyroiditis, inflammatory bowel diseases, insulin-dependent diabetes mellitus, systemic sclerosis, myasthenia gravis, autoimmune liver diseases, and Sjögren's syndrome have been suggested.^[47] It is proposed that the initiating event in pSS is an infection with EBV, and the autoimmune exocrinopathy that progresses to keratoconjunctivitis Sicca and xerostomia is sequelae to this process. It is noted that during EBV infection, there are multiple copies of the EBV-encoded small RNAs available to bind to the La ribonucleoprotein and when infection occurs in subjects who are genetically predisposed to autoimmunity and have an impaired T-cell-mediated response to EBV, there is a loss of immunological tolerance to La with production of anti-La (SS-B). Thus the inflammatory process in exocrine glands, which culminates in the Sicca syndrome is due to the combined effects of chronic EBV infection and autoimmunity. The mean titer of anti-EBV nuclear-antigen antibodies was significantly higher in Sjögren's syndrome patients than in normal people.^[48]

Cytomegalovirus

Cytomegalovirus (CMV) is a common infection with a seroprevalence among adolescents ranging from 47% to 89%.^[49] The persistence of CMV with alteration of cell surface expression in certain tissues may initiate the tissue destruction that leads to the clinical manifestations of Sjögren's syndrome. Ductal cells of salivary and lacrimal glands are immunologically attacked due to CMV antigenic expression. The destruction of these ducts leads to xerostomia.^[50] However, no relationship between xerostomia and anti-CMV antibodies was noted.^[51]

Human T-lymphotropic virus type 1

Human T-lymphotropic virus Type 1 (HTLV-1) is known to cause HTLV-associated myelopathy (HAM)/tropical spastic paraparesis and adult T-cell leukemia.^[52] It is estimated that 15-20 million persons are currently infected with HTLV-1 worldwide.^[53]

Retroviruses such as HTLV-1 and HIV infect immunocompetent cells, resulting in the destruction or overstimulation of T-cells, and act as potential triggers for autoimmune disease.^[54]

Previous studies reported a high prevalence rate of anti-HTLV-1 antibodies in the peripheral blood in 3.8-36.7% of patients with Sjögren's Syndrome.^[55-58]

Bacterial infections

Actinomycosis

Actinomycosis is an anaerobic bacterial infection affecting men more frequently between the ages of 30-60 years. Almost half of actinomycosis cases occur in the cervicofacial region, and salivary glands may be involved as well. The organism can colonize inside the ducts of both submandibular and parotid glands and leads to abscess formation in the submandibular and masseter spaces, respectively.^[59-61]

Autoimmune diseases

Rheumatoid arthritis

Rheumatoid arthritis is a systemic disease of connective tissue origin, which affects 1% of the world population. Women have a 3-fold higher incidence than do men. RA frequently presents with extra-articular features such as hematologic, neurologic, and cardiovascular involvement concomitant with dysfunction of lacrimal and salivary glands. Zalewska *et al.* showed impairment of salivary immunity system of the oral cavity in xerostomic patients with RA.^[62] Secondary Sjögren's syndrome is associated with xerostomia and occurs with autoimmune diseases most frequently with RA.^[63]

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an inflammatory connective tissue disease with characteristic autoantibodies. SLE is much more common in women than men. It may occur at any age, but appears most often in people between the ages

of 10 and 50. More than 75% of patients with SLE are affected with xerostomia. Coexistence of Sjögren's syndrome and SLE has been found in 1/3 of SLE patients. SLE has been shown to be associated with a decreased unstimulated salivary flow rate.^[64]

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a cholestatic autoimmune disease predominantly of middle-aged women with progressive destruction of interlobular bile ducts.^[65] The most autoimmune disease in PBC patients is Sjögren's syndrome^[66] whose symptoms have been observed in 47-73% of patients^[67,68] Xerostomia as well as dysphagia seems to be associated with PBC.^[69]

Scleroderma

Progressive systemic sclerosis or scleroderma is a chronic sclerotic disease with deposition of extracellular matrix throughout connective tissue and vascular abnormalities, which leads to tissue hypoxia.^[70] Fibrosis of capillaries, excretory ducts and acini of salivary and lacrimal glands are associated with xerostomia as oral manifestations of scleroderma.^[71] Lymphocytic infiltration has been observed among 15% of patients with systemic sclerosis, which is a sign of secondary Sjögren's syndrome.^[72]

Granulomatous diseases

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease with unknown etiology characterized by the presence of noncaseating granulomas that can affect any organ (mostly lungs and lymph nodes).^[73] Coexistence of parotid and submandibular gland swelling and xerostomia has been reported in sarcoidosis patients.^[74-76] Mansour *et al.*, identified five patients representing both clinical and histological features of Sjögren's syndrome and sarcoidosis, suggesting inclusion of sarcoidosis as diagnostic criteria for Sjögren's syndrome.^[74]

The salivary glands could be affected by sarcoidosis as well, which was reported in 6% of the cases. Parotid salivary gland enlargement was also detected in 6% of the patients.^[74] Parotid gland enlargement in patients presenting with Sicca symptoms is believed to be of clinical significance. Such finding might be more likely associated with sarcoidosis, especially in patients presenting with negative serologic profiles.^[74]

Tuberculosis

Tuberculosis (TB) is a chronic bacterial infection, caused by Mycobacterium TB leading to formation of granulomas in infected tissues. The lungs are most commonly affected, but other tissues, including the salivary glands, may be involved. Patients with TB may experience xerostomia and/or salivary gland swelling, with granuloma or cyst formation within the affected glands. Salivary gland enlargement usually presents as part of a characteristic symptom complex, however salivary

gland changes have been reported in the absence of systemic symptoms.^[77]

Granulomatous diseases such as sarcoidosis and TB may cause salivary gland hypofunction and lead to xerostomia.^[78]

Storage diseases

Hemochromatosis

Hemochromatosis is defined as a pathological condition with iron overload in vital organs with a hereditary/primary cause.^[79] Organs commonly affected by hemochromatosis are liver, heart, and endocrine glands. Iron deposition in salivary glands causes hyposalivation. Patients with normal ferritin level had normal salivary flow rate, whereas those with high levels of ferritin showed decreased stimulatory salivary flow rate.^[79,80]

Amyloidosis

Amyloidosis is characterized by deposition of an extracellular protein-like material called amyloid. Amyloidosis causes various effects on different organs with a variety of extensions. In addition, amyloidosis may be associated with multiple myeloma or chronic infections. Amyloidosis may be accompanied with oral involvement in the form of macroglossia (10-40%), oral amyloid nodules, and dry mouth due to amyloid infiltration and destruction of salivary glands.^[81] A case of pSS manifested as localized cutaneous nodular amyloidosis has been reported.^[82] Meanwhile, a relationship between amyloidosis and xerostomia has been documented.^[82-84]

Others

End-stage renal disease

End-stage renal disease (ESRD) represents a clinical state or condition with irreversible loss of the endogenous renal function to a degree, which is sufficient to render the patient permanently dependent upon renal replacement therapy in the form of dialysis or kidney transplantation. ESRD leads to accumulation of certain toxic elements, which affects normal functions of the body, and may have significant complications including cardiovascular disease, immune deficiency, anemia, renal function impairment, and bone disease.^[85] Xerostomia was found in 28-59% of ESRD patients due to inability of kidneys to reabsorb sodium and the resultant polyuria.^[86,87]

Ectodermal dysplasia

Ectodermal dysplasia is a hereditary disease causing anomalies in tissues of ectodermal origin. The significance of this disease lies in severe hypodontia, and an accompanying hypoplasia of the alveolar process. The clinical condition is aggravated by a significant xerostomia as a result of salivary gland aplasia or hypoplasia.^[88,89] However, in some patients with ectodermal dysplasia with the presence of salivary glands, hyposalivation have been reported. In a study of 39 patients with ectodermal dysplasia, salivary flow rate was decreased in 13 (33.3%) patients.^[90]

Hematopoietic stem cell transplantation and chronic graft-versus-host disease

Chronic graft-versus-host disease (cGVHD) is a multi-organ involvement that occurs post hematopoietic stem cell transplantation (HSCT), with the mouth being one of the most frequently affected sites.^[91] The pathogenesis of GVHD is based on donor graft T-lymphocytes that recognize antigenic disparities between donor and recipient and the dysregulation of a broad panel of cytokines. GVHD occurs in 40-70% of patients treated by bone marrow and peripheral blood stem cell transplantation.^[92] Oral manifestations are common in patients diagnosed with chronic graft-versus-host-disease.^[91] Hull *et al.* mentioned xerostomia as the most common oral symptom in patients with history of HSCT with the majority of patients (53%) having clinical markers of oral cGVHD.^[93] Noce *et al.* reported that 59.1% of patients diagnosed with cGVHD had salivary gland dysfunction.^[91] Boer *et al.* showed a decrease in salivary flow rate (16% of patients) and a relation between hyposalivation intensity and elapsed time after HSCT.^[94] There is similarity in oral clinical manifestations of GVHD and Sjögren's Syndrome because of the same autoimmune nature, but differences have also been found.^[95] The suggested pathophysiological mechanisms of xerostomia and hyposalivation observed in GVHD are lymphocytic infiltration, parenchymal destruction, and fibrosis within salivary gland tissue.^[95]

Parkinson's disease

Parkinson's disease (PD) is a relatively common, progressive, debilitating, and neurological disorder. Cardinal symptoms are resting tremor, bradykinesia, akinesia, restricted mobility, and postural instability. Levodopa (L-DOPA) has been used as a primary drug for over 30 years. L-DOPA is converted into dopamine in the dopaminergic neurons by DOPA decarboxylase enzyme. Proulx *et al.* have reported that patients with PD produce less saliva than normal. Factors influencing the production of saliva include the use of levodopa and female gender.^[96] Hyposialorrhea is an early autonomic manifestation of PD.^[97]

Conclusion

Salivary glands are involved due to many systemic diseases with the resultant complication of xerostomia. Autoimmune diseases, diabetes mellitus, ESRD, and GVHD are frequently associated with salivary hypofunction. The underlying mechanism of xerostomia differs in terms of disease. Autoimmunity accounts for xerostomia related to SLE, RA, PBC, thyroid disease, and some viral infections. Some conditions affect salivary glands through infiltration of immunocompetent cells or granuloma formation such as HIV infection, GVHD, sarcoidosis, and TB. Polyuria and dehydration is responsible for dry mouth associated with diabetes and end-stage renal failure, while GVHD and scleroderma cause xerostomia because of fibrosis. Deposition of proteinaceous substances and bacterial infection are also mentioned as alternative mechanisms for xerostomia.

Identification of the main reason of xerostomia helps attain timely diagnosis and more appropriate treatment plan.

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