Review Article

Xerostomia – A Comprehensive Review with a Focus on Mid-Life Health

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Abstract

Xerostomia is defined as the subjective complaint of a dry mouth. Xerostomia is common in menopausal women owing to the hormonal changes which take place during midlife. Studies show a higher incidence of oral cancer in the postmenopausal period which substantiates the theory of estrogen deficiency in carcinogenesis. Radiotherapy in the treatment of these cancers can lead to oral dryness. Other etiological factors of xerostomia include systemic diseases commonly occurring in middle-aged individuals and xerogenic drugs. Saliva plays a pivotal role in the maintenance of oropharyngeal health and xerostomia can severely impair the quality of life. The aim of this review was to provide vital information pertaining to the etiology, signs, diagnosis, and treatment of xerostomia with an emphasis on midlife health. The articles for this review were obtained from PubMed Central, Google Scholar, EBSCO, Science Direct, Medknow, Scopus, EMBASE, Web of Science, and authorized textbooks published between 1988 and 2021.

Keywords: *Menopause, midlife, oral dryness, radiotherapy, salivary pacemakers, sialogogues*

Introduction

Xerostomia is defined as the subjective complaint of a dry mouth.[1] The word xerostomia is derived from the Greek word for dry (xeros) and mouth (stoma).[2] Studies reveal that xerostomia is prevalent in 30% of the population aged over 65 years. This may be attributed to the usage of xerogenic drugs in this age group.[3] Xerostomia is also common in postmenopausal women.[2] The aim of this review is to provide vital information on the etiology, signs, diagnosis, and treatment of xerostomia.

Methodology

The articles for this review were obtained from PubMed Central, Google Scholar, EBSCO, Science Direct, Medknow, Scopus, EMBASE, Web of Science, and authorized textbooks published between the years 1988 and 2021 using keywords "xerostomia," "saliva," "menopause," "radiotherapy," "systemic diseases," "xerogenic drugs," "midlife," "treatment." Inclusion criteria included original research and review articles published in English in indexed journals.

Role of saliva

Saliva plays a pivotal role in the maintenance of oropharyngeal health and xerostomia can impair the quality of life.[2] Saliva acts as a mirror, reflecting the overall condition of the body and is an indicator of health. Saliva is a watery, clear fluid secreted by the three major salivary glands (parotid, submandibular, sublingual) and several minor glands.[1] Saliva is composed predominantly of water and organic and inorganic substances such as hormones, enzymes, antibodies, and growth factors.[2]

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Parasympathetic innervation (through muscarinic M3 receptors) controls the volume of saliva secreted and sympathetic innervation controls the composition.[1,4]

Saliva plays an important role in digestion, mastication, swallowing, speech, lubrication of the oral mucosa, taste enhancement, maintenance of the mucosal integrity, cleansing, as a buffering and antimicrobial agent, in denture retention and wearing and permits free movement of the tissues.[2,4,5]

Etiology

A. Based on Primary and Secondary Causes:
B. Etiological classification:
1. Iatrogenic
   - Drugs
   - Local radiation
   - Chemotherapy
   - Chronic graft versus host disease
2. Developmental causes
   - Salivary gland agenesis
3. Diseases of salivary glands
   - Sjogren's syndrome
   - Sialolithiasis
   - Sialadenitis
4. Infections
   - HIV
   - Hepatitis C virus
5. Metabolic disorders
   - Diabetes mellitus
6. Granulomatous Diseases
   - Sarcoidosis
   - Wegener's disease
7. Others
   - Menopause
   - Stress
   - Amyloidosis
   - Primary biliary cirrhosis
   - Cystic fibrosis[6-10]

Menopause

Menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. A common indicator that menopause is approaching is the onset of menstrual irregularity which usually occurs in the fourth decade of life.

Twelve months of amenorrhea define the final menstrual period and any future cycle after this is unlikely.[11]

Menopause and the oral cavity

The period of menopause is associated with several physiological changes in the body including sweating, hot flushes, osteoporosis, cognitive diseases, cardiovascular diseases, skin changes, and urogenital infections. These changes are attributed to a reduction in the levels of estrogen and progesterone. Menopause does not spare the oral cavity and can lead to an array of symptoms such as burning sensation, dysgeusia, dry mouth and it can even alter the composition, buffering capacity, and pH of saliva.[12,13]

Xerostomia in menopause

Progesterone and estrogen are steroid hormones which are of paramount importance in the regulation of reproduction.[14] The oral mucosal cells and salivary glands have been found to contain receptors of sex hormones such as estrogen and progesterone, and consequently, these hormones can influence the quality and quantity of saliva.[15,16]

A study conducted by Leimola-Virtanen *et al*. demonstrated the presence of estrogen receptors in biopsies of normal tissues taken from the buccal mucosa, parotid gland, submandibular gland, and labial minor salivary glands. This suggests that estrogen plays a biological role in the homeostasis and normal functioning of the salivary glands and oral mucosa.[15] The estrogen receptor-beta has been found to be the most predominant subtype of estrogen receptor in the salivary glands and oral mucosa.[17]

Symptoms of oral dryness have been found to correlate negatively with the levels of estrogen and progesterone. A study by Mirzaii-Dizgah *et al*. on 70 menopausal women demonstrated that oral dryness is associated with decreased progesterone levels.[18] Negative correlations have been observed to exist between the levels of both salivary and serum levels of 17β-estradiol with symptoms of oral dryness in menopausal women.[19]

Postmenopausal women have been identified to have lower salivary flow rates compared to that of menstruating women.[16] Niklander *et al*. on a sample size of 566 patients reported an increased prevalence of xerostomia in menopausal women.[20] Minicucci *et al*. conducted a study on sixty premenopausal and menopausal women to evaluate the stimulated and unstimulated salivary flow. The study demonstrated that stimulated salivary flow rates were significantly lower in the menopausal group compared to the control. However, unstimulated flow rates did not exhibit such changes.[21]

Bone mineral density and oral dryness

A study was conducted by Farzaneh Agha-Hosseini *et al*. to compare the bone mineral density (BMD) of the lumbar spine in 60 postmenopausal women, with and without symptoms of oral dryness. A significantly negative correlation was noted between the BMD of the lumbar spine and the incidence of xerostomia. Reduction in BMD and the increased incidence of xerostomia may

both arise as a consequence of estrogen deficiency. It was concluded that oral dryness could serve as an indicator of decreasing BMD.[22]

Another study carried out by the same author in 60 menopausal women also demonstrated that low femoral BMD was associated with the perception of xerostomia.[23]

Effects of hormone replacement therapy on xerostomia

To provide relief from menopausal and postmenopausal symptoms, many women often undergo hormone replacement therapy (HRT). Oral discomfort is a common symptom in these women and studies show that both estrogen and progesterone replacement therapy can increase the flow rates of stimulated whole saliva.[24]

A study by Yalcin *et al*. on 348 patients revealed that oral dryness is higher in menopausal women not receiving HRT.[25] Another study by the same author suggested that salivary flow rates increase after HRT, alendronate, and calcium supplementation.[26]

A study by Eliasson *et al*. in 18 postmenopausal women indicated that supplementation with a low dose of estrogen (estriol) in postmenopausal women can increase the flow rates of minor salivary glands and thus reduce symptoms of oral dryness.[24] Other studies show similar results where patients report a relief of oral dryness after receiving HRT (estrogen).[13]

However, a study by Tarkkila *et al*. in 3173 women revealed contradictory results wherein the use of HRT was not associated with the prevention or reduction of oral symptoms.

A majority of the studies in the literature suggest that the oral changes associated with menopause are clearly due to the deficiency of sex hormones and the subsequent replacement of these hormones seems to improve symptoms of oral discomfort. However, xerostomia alone in postmenopausal women should never be the sole reason for commencement of HRT. Further longitudinal studies are required to compliment these findings. A close communication and rapport between the dentist and gynecologist are highly advisable to help manage oral symptoms in menopausal patients.[16]

Other causes of xerostomia

Mechanism of xerogenic drugs

Although radiotherapy was considered to be the most common etiologic factor, recent studies show that certain drugs are the leading cause of xerostomia, especially among the middle aged and elderly.[2,8] These drugs interfere in the transmission of signals at the parasympathetic neuroeffector junctions. At therapeutic doses, this damage is reversible.[7]

Sialolithiasis

Sialoliths are the primary etiological factor in the obstruction of salivary flow and may cause xerostomia.[8]

Diabetes mellitus

Patients with uncontrolled diabetes frequently suffer from xerostomia resulting from polyuria and autonomic dehydration.[8,9]

Amyloidosis

Amyloidosis is a disease characterized by the deposition of an extracellular protein-like material called amyloid. Amyloid can deposit in the salivary glands causing glandular destruction and xerostomia.[9]

Sarcoidosis

Sarcoidosis is characterized by the deposition of noncaseating granulomas in the organs. Although the lungs are the most commonly involved organ, extrathoracic involvement like the salivary glands also occurs resulting in xerostomia.[10]

Diseases co-existing with Sjogren's syndrome

Sjogren's syndrome is an autoimmune disease of unknown etiology characterized by chronic inflammation and lymphocytic infiltration of the epithelia and exocrine glands mainly lacrimal and salivary glands. Other autoimmune conditions co-existing with Sjogren's syndrome such systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis, primary biliary cirrhosis, and mixed connective tissue disease are often associated with xerostomia.[2,9]

Systemic sclerosis

Xerostomia may be caused by fibrosis of the acinar cells of the salivary glands, excretory ducts, capillaries, and lymphocytic infiltration.[2,9]

Rheumatic diseases

Progressive infiltration of the lymphocytes in rheumatic diseases can trigger dysfunction of the salivary glands leading to inflammation, acinar cell atrophy, and connective tissue proliferation causing xerostomia.[2]

Signs and symptoms

Xerostomia can lead to difficulty in speech, chewing, swallowing, dysgeusia, burning sensation of the oral mucosa, and halitosis.[2,5,8]

The clinical signs may include cracking of lips, corrugated and pale oral mucosa, depapillated tongue, candidiasis, angular cheilitis, parotid gland enlargement, increased incidence of periodontal disease and caries and frothy saliva with reduction in pooling of saliva.[2,4-6,8]

Diagnosis

Diagnosis of xerostomia is made with the help of a thorough medical history, based on the symptoms, questionnaires, visual analog scales, and clinical examination.[2,8] Sialometry is an invaluable tool in the diagnosis of xerostomia for measuring salivary flow rate. Other diagnostic tools include sialography to understand the ductal morphology or to detect sialoliths and other masses, salivary scintigraphy to evaluate salivary gland function, ultrasonography to assess the ductal and acinar morphology and biopsy to rule out sarcoidosis, Sjogren's syndrome, amyloidosis, HIV-associated diseases, and malignancy.[6,8]

Magnetic resonance imaging of salivary gland is preferred over computed tomography due to superior soft tissue visualization in the former.[8]

Measurement of salivary flow rates

The daily average flow of whole saliva varies between 1 and 1.5 liters in a healthy individual. Percentage contributions of unstimulated saliva flow are 20% from parotid, 65% from submandibular, 7% to 8% from sublingual, and <10% from minor salivary glands.[27-29]

Normally, unstimulated whole saliva flow rate is 0.3–0.4 ml/min (milliliters per minute); below 0.1 ml/min rate is considered abnormal. For stimulated saliva, a rate <0.5 ml/gland in five min or <1 ml/gland in ten min is significantly low.[27]

Sialometry is the most commonly employed modality in the diagnosis of xerostomia.

Salivary flow collection can be broadly classified into two types: whole saliva collection (combined secretions of all salivary glands) and collection from a specific salivary gland.

Even though whole saliva collection has interference with nonsalivary elements such as food debris, epithelial cells, nasal secretions, and gingival fluid, it is a commonly employed method owing to its simplicity.[30,31]

Whole saliva collection can be either stimulated or unstimulated. Stimulation of salivary glands will reveal the functional status. Stimuli can be gustatory or mechanical. Mechanical stimulation contributes to parotid gland response and gustatory stimulus contributes to response of all three major salivary glands. The methods of collection of whole saliva are described in [Table 1].[2,5,31,32]

Before collection of saliva, the patient is instructed to refrain from drinking, eating, smoking, and oral hygiene practices for a minimum of 90 min.[5]

Table 1: Methods of collection of whole saliva

Type of saliva collection	Methods	Technique
Unstimulated	Passive drainage	Collection in a graduated container
	Active drainage	Regular expectoration in a graduated container
	Suction	Pooled saliva in floor of mouth is vacuumed and collected in graduated container
	Absorption	Preweighted cotton or gauze inserted in mouth and then weighed again
	MST	A calibrated paper strip is placed on the floor of the mouth and readings are measured at 1, 2, and 3 min interval
Stimulated	Mechanical	Chewing paraffin or unflavored gum and spitting in graduated container
	Gustatory	Citric acid application in lateral borders of tongue and spitting method
	Absorption	Preweighted swab chewed for a certain time and weighed

MST: Modified Schirmer test

To prevent any variability in body hydration, patients must be asked to drink 300 ml of water 2 h before the investigation. Consecutive collection must be carried out at a standard time.[31]

The collection of gland specific saliva requires specialized apparatuses. Lashley or Carlson-Crittenden cup is used for the parotid gland and Wolf collector for the submandibular and sublingual glands.[5] The salivary flow rate of the minor salivary glands can be determined using micropipettes or absorbent filter paper.[4,5]

Among various sialometric tests, modified Schirmer test has emerged as a standardized, inexpensive, easy to perform chair side investigative modality for xerostomia and correlates well with the volumetric spitting method [Table 1].[31,32]

Management

The primary aim should be to identify and address the underlying cause of xerostomia.[6]

If an offending drug is identified, any modification in the drug regimen should be carried out only under the advice of a physician. It is best to avoid the intake of xerogenic medications at night when the normal salivary flow is at its lowest.[5]

Lifestyle modifications

Lifestyle modifications include maintenance of good oral hygiene and abstinence from cariogenic food, adequate hydration, usage of bedside humidifiers, avoiding spicy and dry food, avoiding caffeinated or carbonated drinks, alcohol and smoking, avoiding mouthwashes containing alcohol, and promoting

stress reduction.[1,2,7,31] The usage of fluoridated toothpastes/varnishes and antimicrobial rinses can further prevent dental caries.[6,7]

Mechanical and gustatory stimulation

Vitamin C tablets stimulate salivation by acting as a reducing agent, causing breakage of disulfide bonds between the residues of cysteine in proteins, resulting in reduced salivary viscosity.[1]

The usage of hard candies and sugar-free chewing gums is recommended for the relief of xerostomia in individuals with residual salivary gland function.[7]

Low-level laser therapy (904 nm) can stimulate salivary flow and regeneration.[2]

Sialogogues

Pilocarpine is a parasympathomimetic drug possessing muscarinic action. It is prescribed for at least 3 months at five mg (thrice daily [TID]). Cevimeline has a higher affinity for the M3 muscarinic receptors. It is also prescribed for a minimum of 3 months at 30 mg TID. The adverse effects of these drugs include hyperhidrosis, diarrhea, nausea, cutaneous vasodilation, bronchoconstriction, polyuria, and hypotension and are contraindicated in asthma, chronic pulmonary disease, gastric ulcers, uncontrolled hypertension, narrow angle glauca and in patients under beta adrenergic blockers.[5] Other drugs under clinical trials include bromhexine and anetholtrithione.[2,4]

Saliva substitutes

Salivary substitutes are indicated in patients with impaired salivary gland function with xerostomia.[7] Substitutes may be in the form of a liquid, spray, or gel.[2] Salivary substitutes should provide lubrication, be long lasting and offer protection to the oral tissue from bacterial colonization and activity.[7] Salivary substitutes are composed of salivary enzymes including lysozymes, peroxidase, glucose oxidase, mucins, glycoproteins, polymers like carboxymethyl cellulose, and ions such as phosphate, fluoride, and calcium.

Milk can also be used as a salivary substitute and it serves as a buffer, moisturizes the oral cavity, reduces the solubility, and favors remineralization of enamel.[8]

Salivary pacemakers

Salivary pacemakers are devices which provide neuroelectrostimulation and increase the secretion of saliva. The first generation (Salitron-Biosonics, Fort Washington, United States of America) consists of a probe placed intraorally over the mucosa on a daily basis for a few minutes. The second generation (GenNarino Saliwell Ltd. Germany) consists of a custom made removable intraoral appliance resembling a mouthguard. The third-generation device (The Saliwell Crown Saliwell Ltd. Germany) resembles a dental implant and is remote controlled.[8,33]

Denture wearers

Adequate denture hygiene must be maintained. Dentures should be soaked in chlorhexidine 0.2% overnight.[8] Denture adhesives and soft denture liners may be used. Wetting the denture before placing into the mouth and applying artificial saliva over the denture will help reduce the discomfort. "Split denture technique" has been suggested by Dabas *et al*. This has a reservoir which contains salivary substitutes.[34]

Prevention of radiotherapy-induced xerostomia

Various studies report an increased incidence of oral cancer in postmenopausal women. These findings validate the theory of estrogen deficiency in the initiation of carcinogenesis. Xerostomia may be prevented or reduced in these patients by sparing the salivary glands from the cytotoxic effects of radiation by the following techniques.[35]

Parotid gland sparing radiotherapy

Techniques such as three-dimensional conformational radiotherapy and intensity-modulated radiotherapy can be utilized to minimize radiation dose to the salivary glands.[2]

Cytoprotectants

Cytoprotectants such as amifostine prevent radiation-induced damage of deoxyribonucleic acid in healthy tissues and organs.[2] It is converted to the active form "thiol" by the enzyme alkaline phosphatase which then accumulates in normal cells eradicating free radicals. The recommended dose for amifostine is 200 mg/m^2 once daily as a 3 min intravenous infusion 15 to 30 min before radiotherapy.[3]

Salivary gland transfer

In head-and-neck radiotherapy, if the submandibular gland lies in the path of radiation, the gland can be surgically transferred to the submental region or transiently to a distant site such as the forearm so that it can be spared from the effects of radiation, thus preventing xerostomia.[2,3,36]

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy promotes angiogenesis, regeneration, revascularization, stem cell recruitment, collagen synthesis and increases oxygen tension, especially in irradiated tissues restoring near normal to normal salivary flow.[37]

Acupuncture

Acupuncture increases the parasympathetic activity of

the body enhancing salivary flow. It can be employed as a preventive measure in patients who are to undergo radiotherapy in the head-and-neck region. The acupuncture points include the ears bilaterally and the radial aspect of the index fingers. This is done three to four times weekly and thereafter on a monthly basis.[7]

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation stimulates the auriculotemporal nerve carrying the secretomotor fibers to the parotid gland and has been found to increase salivary flow.[38]

Stem cell therapy

Murine studies have demonstrated that salivary glands damaged secondary to radiation can be rescued by stem cell therapy. Studies have elicited the differentiation of bone marrow stem cells into acinar like cells.[39]

Future modalities

Immunosuppressive drugs such as thalidomide, cyclosporine, human interferon-alpha, salivary substitutes with increased mucosal retention are under trial for treatment of xerostomia.[1,8,31,40]

Conclusion

Xerostomia is a commonly occurring problem in the middle aged and the elderly population. If left untreated, it can adversely affect the quality of life. Health-care workers should have a thorough understanding regarding the etiology, diagnosis, and management of xerostomia to provide preventive and therapeutic measures to improve the patient's over all well-being, comfort, and function.[6]

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Conflicts of interest

There are no conflicts of interest.

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