Meta-Analysis of Prevalence of Xerostomia in Diabetes Mellitus

ORIGINAL

Luiza Silveira Lessa^{1,2,3}, Patrícia Duarte Simões Pires²,
Renan Antônio Ceretta², Indianara Reynaud Toret Becker¹,
Luciane Bisognin Ceretta^{1,2,3}, Lisiane Tuon^{1,3},
Priscyla Waleska Simões^{1,2,3}, Fernanda Guglielmi Faustini Sônego^{1,2}

- 1 Multidisciplinary Residency Program in Primary Care/Family Health. Universidade do Extremo Sul Catarinense (UNESC), Criciúma, SC, Brazil.
- 2 Dentistry Course. Universidade do Extremo Sul Catarinense (UNESC) Criciúma, SC, Brazil.
- 3 Graduate Program in Public Health (PPGSCol). Universidade do Extremo Sul Catarinense (UNESC) Criciúma, SC, Brazil.

Abstract

Background: As with other complications of diabetes mellitus, the occurrence of dry mouth can lead to a poor quality of life. Therefore, this study aimed to identify the prevalence of xerostomia in patients with diabetes mellitus through a systematic review and meta-analysis.

Method: Systematic review and meta-analysis.

Results: After the screening process, 23 studies were included in the meta-analysis. Overall, the incidence of dry mouth was investigated in 1979 people with diabetes (cases) and 1225 controls. The global prevalence of diabetes in xerostomia was 42.22% (95% CI: 33.97%-50.92%). In the analysis by specific subtype, the overall prevalence was 37.42% (95% CI: 22.33%-55.44%) among individuals with Type 1 diabetes and 46.09% (95% CI: 23.99%-69.85%) among those with type 2 diabetes. The prevalence of xerostomia found in Asia (49.01%; 95% CI: 32.08%-66.16%) was higher than that found in Europe (40.04%; 95% CI: 29.58%-51.50%) and America (38.39%; 95% CI: 23.63%-55.65%). Analysis of the case-control studies showed a statistically significant association between xerostomia and diabetes mellitus (OR=3.15; 95% CI: 2.11-4.70; $p<0.001$).

Conclusion: Through the data collected, we can infer that the prevalence of xerostomia in individuals affected by diabetes mellitus types 1 and 2 was high and independent of geographic location.

Contact information:

Fernanda Guglielmi Faustini Sônego.
Multidisciplinary Residency Program in Primary Care/Family Health.

Priscyla Waleska Simões.
Multidisciplinary Residency Program in Primary Care/Family Health. Graduate Program in Public Health (PPGSCol).

Address: Universidade do Extremo Sul Catarinense (UNESC), Av. Universitária, 1105 -Bairro Universitário, CEP: 88806-000 -Criciúma-SC.
Tel: 55 48 3431-2500.

✉ fgfsonego@unesc.net
✉ pri@unesc.net

Keywords

Diabetes Mellitus; Xerostomia; Systematic Review; Meta-Analysis.

Introduction

Recent studies show that non-communicable chronic diseases (NCCD) are a major threat to the health of the population, accounting for 60.3% of all deaths in the world in 2008 [1]. In this context, diabetes mellitus is one of the four NCCD groups that cause the most deaths, along with cardiovascular diseases, cancer and respiratory chronic diseases [1].

Worldwide, it is estimated that the overall number of people between 20 and 79 years old with diabetes was 382 million in 2013 and will reach 592 million by 2035. In Brazil, which is fourth among the 10 countries with the highest prevalence of diabetes, the number of people with diabetes is projected to increase from 11.9 to 19.2 million in the same period [2]. These projections corroborate the data found in a national survey conducted in 2008, which noted that diabetes mellitus has been the chronic disease with the highest growth (37%) since 2003 [3].

According to the World Health Organization (WHO), diabetes mellitus consists of a disturbance in the production and/or action of insulin [4]. This hormone deficiency leads to hyperglycemia, often associated with dysfunction, damage and failure of various organs [5, 6].

Xerostomia, defined as a dry mouth sensation with or without salivary gland hypofunction, is an oral condition with variable etiology. Its prevalence increases with age, affecting approximately 30% of the population over 65 years old [7]. Considered one of the main oral disorders related to saliva, its symptoms include halitosis, pain, burning mouth, taste alterations, and difficulties in swallowing and speaking [8]. Additionally, patients with xerostomia may be at increased risk for dental caries, as they often resort to candies and acidic drinks to relieve their symptoms [8].

As with other complications of diabetes mellitus, the occurrence of dry mouth can lead to a poor quality of life. Therefore, this study aimed to identify the prevalence of xerostomia in patients with

diabetes mellitus through a systematic review and meta-analysis.

Methods

Search strategy

A comprehensive search of MEDLINE (via PubMed), LILACS, SCOPUS, Central Register of Controlled Studies of Cochrane, IBECs, BIOSIS and Web of Science was performed for relevant studies published from July 1977 to December 2014 using MeSH descriptors and synonyms, including "xerostomia", "dry mouth", "mouth dryness", "oral dryness" and "buccal dryness" associated with "diabetes mellitus". The terms were combined using the Boolean operators "AND", "OR" and "NOT".

In addition, reference lists were checked in all of the recovered primary studies, and a search of grey literature was conducted. The overall search was limited to studies in humans, but there was no language restriction.

The primary analysis of recovered abstracts and titles was performed independently by four researchers (LSL, PP, PWS and FGFS). Publications considered potentially relevant that met the necessary criteria were selected for full reading, which was carried out by five researchers (LSL, PP, PWS, RC and IRTB). In both cases, disagreements regarding the inclusion or exclusion of each study were resolved by consensus involving other researchers (LT and LC).

The agreement between reviewers was measured through the Kappa statistical test (k) using a classification proposed by Higgins and Green [11], in which values ≥ 0.40 and < 0.59 were considered fair agreement, values ≥ 0.60 and < 0.74 were considered good agreement, and values ≥ 0.75 were considered excellent agreement.

Study selection

Cross-sectional and case-control studies assessing the prevalence of xerostomia in individuals affected

by diabetes mellitus were included. As to the diagnostic criteria, diabetes was diagnosed in only those individuals with fasting plasma glucose ≥ 126 mg/dL, random plasma glucose > 200 mg/dL associated with classic symptoms, plasma glucose > 200 mg/dL two hours after ingesting 75 g of oral glucose (Oral Glucose Tolerance Test - OGTT) or a glycated hemoglobin level (HbA1c) $\geq 6.5\%$ [9], and who were under medical care with a diagnosis of diabetes made prior to the study in which they were included.

Regarding xerostomia, because it is a subjective condition, the diagnosis was considered appropriate in cases where the presence of symptoms was reported by the subjects themselves, after being questioned by the researchers [8].

The prevalence analysis by specific subtype was performed in only individuals with types 1 and 2 diabetes mellitus as the other forms of the disease, gestational diabetes and other specific subtypes, stem from pre-existing conditions, capable of affecting the results. Additionally, these other forms are less common and therefore have been poorly explored in the literature.

To minimize possible risk factors for xerostomia and evaluate its prevalence solely in patients with diabetes mellitus, other illnesses associated with xerostomia, such as Sjögren's Syndrome, were excluded from the meta-analysis.

Data synthesis and statistical analysis

We collected data regarding year of publication, country, age and gender of the subjects, as well as the number of individuals with xerostomia and diabetes (with specific subtype), when specified by the authors.

For the meta-analysis, prevalence rates of xerostomia in people with diabetes were pooled using the random effects model [10]. Heterogeneity was calculated via Cochrane's Q and τ^2 tests, and inconsistency was presented by I^2 , which describes the percentage of variability that is due to heterogeneity rather than chance [10].

Additionally, case-control studies were summarized according to their odds ratios (OR) and pooled using the random effects model [11]. In studies in which only one cell of the 2×2 contingency table showed a value of 0 (zero), the value 0.5 was added to enable the OR calculation; however, those in which the value 0 (zero) occurred in two cells or more were removed from the analysis [11].

Given the heterogeneity, a subgroup analysis by continent (Europe, Asia and America) and specific subtype of diabetes (Type 1 and Type 2 Diabetes Mellitus) was carried out.

The possibility of publication bias (the tendency of studies with negative results to be less likely to be published) was assessed by Egger's test and graphical analysis of funnel plots. In funnel plots, each dot represents a study, its effect size or prevalence, and the standard error, for example [11, 12]. Among the cases, a logit transformation was performed on each study included for publication bias assessment.

The meta-analysis was conducted using R 3.1.1 software (Comprehensive R Archive Network, <http://cran.r-project.org/>), and the graphical representation was conducted using forest plots.

Results

Our initial search of the selected databases retrieved 187 potentially relevant publications for the analysis of titles and abstracts. Of this total, 53 articles were selected for full reading, whereas the remaining 134 were excluded due to study design, association with other diseases or lack of data related to the occurrence of xerostomia in people with diabetes. After reading 53 full papers, 30 were excluded due to insufficient data, data duplication, or associated diseases, qualifying 23 papers for the meta-analysis. This process is summarized in **Figure 1**. The agreement between the eligibility of studies was considered excellent ($k=0.91$) [11].

Figure 1: Flowchart of study selection for meta-analysis.

Among the selected studies, published between 1989 and 2014, 8 were conducted in Europe [14, 15, 18, 19, 25, 28, 29, 32], 5 were conducted in Asia [13, 16, 23, 24, 30] and 100 were conducted in America [17, 20-22, 26, 27, 31, 33-35]. Overall, the occurrence of dry mouth was investigated in 1979

in people with diabetes (cases) and 1667 controls, whereas in 15 articles, the authors subdivided the outcome into types 1 and 2 diabetes mellitus (**Table 1**). The prevalence ranged from 3.33% (95% CI: 00.08%-17.22%) to 85.42% (95% CI: 72.24%-93.93%), reaching a global average of 42.22%

Table 1. Papers included in the meta-analysis.

Author	Country	Continent	Patients with xerostomia/ Cases	Prevalence (Cases) % (95% CI)	Patients with xerostomia/ Controls	OR (95% CI)
Al-Maweri 2013 [13]	Malaysia	Asia	119/391	30.43 (25.91-35.26)		
Arrieta-Blanco 2003 [14]	Spain	Europe	20/70	28.57 (18.40-40.62)	8/74	3.30 (1.34-8.10)
Belazi 2005 [15]	Greece	Europe	24/46	52.17 (36.95-67.11)	8/50	5.72 (2.21-14.83)
Ben-Aryeh 1993 [16]	Israel	Asia	9/39	23.08 (11.13-39.33)	3/20	1.70 (0.40-7.14)
Busato 2012 [17]	Brazil	America	27/51	52.94 (38.46-67.07)		

Author	Country	Continent	Patients with xerostomia/ Cases	Prevalence (Cases) % (95% CI)	Patients with xerostomia/ Controls	OR (95% CI)
Carda 2006 [18]	Spain	Europe	13/17	76.47 (50.10-93.19)	3/16	14.08 (2.61-75.77)
Collin 2000 [19]	Finland	Europe	25/45	55.56 (40.00-70.36)	28/77	2.18 (1.03-4.62)
Costa 2004 [20]	Brazil	America	10/26	38.46 (20.23-59.43)		
Gilbert 1993 [21]	USA	America	41/82	50.00 (38.75-61.25)	162/505	2.11 (1.32-3.39)
González-Guevara 2008 [22]	Mexico	America	119/162	73.46 (65.96-80.08)		
Javed 2009 [23]	Pakistan	Asia	41/48	85.42 (72.24-93.93)	0/40	448.20 (24.77-8107.12)
Khovidhunkit 2009 [24]	Thailand	Asia	95/154	61.69 (53.52-69.40)	18/50	2.86 (1.47-5.55)
Malicka 2014 [25]	Poland	Europe	23/93	24.73 (16.37-34.76)	10/63	1.74 (0.76-3.96)
Merchant 2012 [26]	USA	America	23/155	14.84 (09.64-21.43)		
Moreira 2009 [27]	Brazil	America	19/30	63.33 (43.86-80.07)	0/30	103.43 (5.76-1857.21)
Närhi 1996 [28]	Finland	Europe	5/12	41.67 (15.17-72.33)	9/32	1.82 (0.45-7.27)
Sandberg 2001 [29]	Sweden	Europe	13/36	36.11 (20.82-53.78)	29/102	1.42 (0.63-3.18)
Shrestha 2013 [30]	Nepal	Asia	88/200	44.00 (37.01-51.17)		
Sreebny 1992 [31]	USA	America	17/40	42.50 (27.04-59.11)		
Thorstensson 1989 [32]	Sweden	Europe	48/180	26.67 (20.36-33.76)	5/86	5.89 (2.25-15.41)
Vasconcelos 2008 [33]	Brazil	America	1/30	03.33 (00.08-17.22)		
Vasconcelos 2010 [34]	Brazil	America	5/40	12.50 (04.19-26.80)	2/40	2.71 (0.49-14.90)
Zielinski 2002 [35]	USA	America	16/32	50.00 (31.89-68.11)	12/40	2.33 (0.88-6.14)
Total			801/1979	42.22 (33.97-50.92)	297/1225	3.15 (2.11-4.70)

OR – Odds ratio / CI – Confidence Interval

(95% CI: 33.97%-50.92%). The heterogeneity found within the studies was high ($I^2 = 92.1\%$; $\tau^2 = 0.6153$; $p < 0.001$).

In the analysis by specific subtype, the prevalence was 37.42% (95% CI: 22.33%-55.44%) among individuals with Type 1 diabetes and 46.09% (95% CI: 23.99%-69.85%) among those with type 2 diabetes, as shown in **Figure 2**.

Regarding the analysis by continent, the prevalence of xerostomia found in Asia (49.01%; 95% CI: 32.08% -66.16%) was higher than that in Euro-

pe (40.04%, 95 %: 29.58%-51.50%) and America (38.39%; 95% CI: 23.63%-55.65%) (**Figure 3**).

The assessment of the research subjects' profiles revealed a majority of women ($n = 1337$ vs. $n = 975$ for men) both in the groups with diabetes and the controls. The mean age of the participants in the 19 studies ranged from 10.3 (± 4.2) to 79.8 (± 4.3) in the in people with diabetes and from 11.23 (± 2.7) to 78.5 (± 3.6) in the controls.

In the analysis of case-control studies [14-16, 18, 19, 21, 23-25, 27-29, 32, 34, 35], the characte-

Figure 2: Prevalence of xerostomia in patients with diabetes mellitus types 1 (a) and 2 (b).

Figure 3: Prevalence of xerostomia in patients with diabetes mellitus by continent.

Figure 4: Analysis of case-control studies.

ristics were summarized according to odds ratios (**Table 1** and **Figure 4**). The pooled data showed a statistically significant association between the occurrence of xerostomia and diabetes mellitus (OR = 3.15; 95% CI: 2.11 to 4.70; $p < 0.001$), and the heterogeneity was moderate ($I^2 = 57\%$; $\tau^2 = 0.3053$; $p = 0.0033$).

The assessment of the publication bias of the 23 studies included in the meta-analysis and the 15 case-control studies is illustrated in the funnel plots shown in **Figure 5**. In the first chart, which shows the prevalence among the cases, the logit transformed prevalence of the analyzed studies is presented on the x-axis and the inverse of the standard error of each study is shown on the y-axis.

In the second chart, relating to the case-control studies, the inverse of the standard error is also shown on the y-axis and the OR of each study is placed on the x-axis. In both cases, the near symmetric distribution of the data suggests that there is no

publication bias, which was confirmed by Egger's test in the cases ($p = 0.4569$) and the controls ($p = 0.7714$).

Discussion

Xerostomia is a very frequent oral condition, capable of affecting oral functions and compromising the patient's general well-being [36]. Due to its complexity, its treatment requires an interdisciplinary approach that must be centered on improving quality of life, decreasing possible complications and promoting palliative care [37]. Its etiology has been associated with, among other factors, the presence of systemic diseases, including diabetes mellitus [36].

The findings of this systematic review and meta-analysis showed an overall prevalence of xerostomia of 42.22% (95% CI: 33.97%-50.92%) in people with diabetes and a statistically significant associa-

Figure 5: Funnel plots estimating publication bias in cases (a) and case-controls (b).

tion between xerostomia and diabetes mellitus (OR = 3.15; 95% CI: 2.11-4.70; $p < 0.001$). According to several authors, this association may be due to some characteristics of diabetes mellitus, such as dehydration by hyperglycemia, diabetic neuropathy, structural changes in the salivary glands and polyuria, which results in a subsequent reduction in the secretion of saliva [31, 38, 39, 40, 41]. The increased diuresis in people with diabetes leads to a significant decrease in extracellular fluids that directly affects salivary production [18]. According to Moore [42], in periods of metabolic disorder, dehydration raises the osmotic gradient from the blood vessels in relation to the salivary glands, limiting saliva secretion and therefore exacerbating xerostomia symptoms [42]. Regarding structural aspects, a prospective observational study conducted by Rivera and Mendoza [43] found scientific evidence of cellular changes caused by diabetes mellitus and reduced salivary flow. According to the authors [43], this association had not been previously reported in the literature.

Apart from systemic diseases, recent studies noted the use of medication, especially polypharmacy, as one of the main risk factors for developing xerostomia [8, 44]. Among the drugs associated with decreased salivary flow, which can cause dry mouth, there are psycholeptics, psychoanaleptics, oral antidiabetics, respiratory agents, quinine, antihypertensive agents, urinary antispasmodics, glucosamine, non-steroidal anti-inflammatory drugs, opioids, ophthalmologic drugs and magnesium hydroxide [45]. Thus, it is possible that the prevalence of xerostomia found in people with diabetes may be related, additionally, to the medications used to treat diabetes mellitus, its comorbidities and complications.

However, it is known that the feeling of dry mouth is not always associated with salivary gland hypofunction [7]. Corroborating this statement, a case-control study carried out in Greece showed normal levels of salivary production by more than a third of people with diabetes affected by xerosto-

mia [15], suggesting that psychological factors may also influence the triggering of the disease [46].

Our data revealed high heterogeneity [10] in the analysis of prevalence of xerostomia in cases ($I^2 = 92.1\%$; $\tau^2 = 0.6153$, $p < 0.001$). To explore this heterogeneity, a subgroup analysis by continent and specific subtype of diabetes was performed.

In subjects affected by Type 1 diabetes mellitus, prevalence rates of xerostomia were between 16.26% (95% CI: 10.22%-23.99%) and 85.42% (95% CI: 72.24%-93.93%). In individuals affected by type 2 diabetes mellitus, the prevalence ranged from 3.33% (95% CI: 00.08%-17.22%) to 76.47% (95% CI: 50.10%-93.19%).

Seeking to explain the results above, in assessing the demographic profile of the studied sample, differences were observed regarding the age of individuals with Type 1 and Type 2 diabetes, who had been subdivided into children and/or adolescents and adults and/or elderly. Considering that xerostomia prevalence increases with age [7, 47], it is speculated that the age pattern found may have contributed to the increased prevalence among subjects with type 2 diabetes mellitus. However, this matter was not included in the meta-analysis due to insufficient data in these subgroups.

For studies included in the meta-analysis in which both diabetes subtypes were evaluated separately and compared, the difference between the prevalence of xerostomia in Type 1 and Type 2 diabetes was not statistically significant [25, 26].

As to the analysis by continent, the prevalence of xerostomia was similar in different parts of the world: 49.01% in Asia (95% CI: 32.08%-66.16%), 40.04% in Europe (95% CI: 29.58%-51.50%), and 38.39% in America (95% CI: 23.63%-55.65%). These results may represent a negative association between the presence of xerostomia and risk factors related to the specificities of each continent. This characteristic differs from diabetes mellitus, which features an uneven distribution around the world, with a higher prevalence in developing countries [2].

Because the subgroup analysis did not reveal much about heterogeneity, it is believed that the variation in the prevalence of xerostomia among the studies included in the meta-analysis may be due to the lack of standardization of diagnostic criteria [48].

Xerostomia is defined as dry mouth and, therefore, it is a subjective condition diagnosed by patient anamnesis [8]. In this regard, factors such as the level of discomfort for each individual and characteristics of the interview conducted by the researcher can influence the final outcome [8].

The sensitivity and specificity of using questionnaires as a diagnostic method for dry mouth was assessed by Sreenby and Valdini in 1988 through a study involving 529 individuals [49]. According to the authors, the positive response to the question "do you have the feeling of dry mouth frequently?" in an isolated manner demonstrated 93% sensitivity and 68% specificity, as well as a positive predictive value of 54% and a negative predictive value of 98%. When associating three other questions related to different symptoms of xerostomia, specificity and positive predictive value increased to 91% and 75%, respectively.

Although all 23 studies included in our meta-analysis diagnosed xerostomia using methods considered clinically appropriate, we observed differences regarding the number and content of the questions administered to the participants. For instance, some diagnoses were based solely on one question such as "Did you have the feeling of dry mouth every day for the last six months?" [17] or "Do you get the feeling of dry mouth frequently?" [34], whereas others used several questions: "Do you have the feeling of dry mouth frequently, " "Do you get the feeling of dry mouth during meals?" and "Do you have difficulty swallowing food without the help of a liquid substance?" [35].

According to Hopcraft and Tan [8], using only one question as a diagnostic method may be considered problematic because it often refers to specific situa-

tions or periods in which the patient can experience xerostomia, basing the classification on an arbitrary cutoff point.

The prevalence of xerostomia by gender was not included in the meta-analysis as only three studies among those qualified for this step assessed the presence of xerostomia in men and women separately. In all cases, the authors reported that the prevalence was significantly higher among women [22, 30, 31], data that corroborate other findings in the literature [50, 51].

In this regard, it is possible that the greater number of women in the study sample contributed to the increase in the overall prevalence of xerostomia between individuals affected by diabetes mellitus.

Conclusion

Through the data collected, we were able to infer that the prevalence of xerostomia in individuals affected by Type 1 and Type 2 diabetes mellitus was high and independent of geographic location. This association between two diseases that bring together different fields of healthcare reinforces the importance of interdisciplinary work in favor of the patient.

The heterogeneity found between all studies was high among cases and intermediate among case-controls, so we recommend that the data presented here be interpreted with caution. In this regard, we emphasize the need to standardize the diagnosis of xerostomia to ensure the methodological quality of future studies.

Conflict of Interest

The authors have declared no Conflict of interest.

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