LITERATURE REVIEW OF INFLAMMATORY SALIVARY BIOMARKERS IN PATIENTS WITH BURNING MOUTH SYNDROME

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Introduction

Burning Mouth Syndrome (BMS) is a chronic oral pain condition with a likely neuropathic etiology. Clinically, the oral mucosa presents as normal despite patient symptoms of recurring oral mucosal burning sensation. Currently, curative treatments for BMS do not exist due to a lack of an universally accepted disease definition which limits research into BMS. Thus, researchers and clinicians are currently left to rely on patient memory recall for the characterization of pain symptoms and diagnosis. Although there appears to be no associated lab values linked with BMS to confirm diagnosis, the limited studies suggesting salivary biomarkers for BMS offer new, intriguing leads.

Purpose of Review: This objective was to compile the current published literature on the relationship between BMS and salivary biomarkers.

Materials and Methods

Methods: Studies assessing salivary biomarkers in BMS were identified through the PubMed Central database. BMS was identified using the following keywords "burning mouth syndrome" and "glossodynia," and "neuropathic oral pain." Keywords for salivary biomarkers included "salivary biomarkers," "inflammatory cytokines," "cytokines," and "inflammation." Only studies published between 2000 and 2023 were reviewed.

Table 1. Summary of biomarkers analyzed, patient population, and results of included studies

First author (Year), Journal	Subjects: 1. BMS number 2. Control number	Saliva Type	Biomarker(s) Studied	Significant Findings
Simcic (2006), Mediators Inflamm	1. 30 (unknown) 2. 30 (unknown)	UWS	IL-2 IL-6	Increased IL-2 and IL-6 in BMS
Boras (2006), Oral Dis	1. 28 (28 F) 2. 28 (28 F)	Unknown	IL-6 TNF-alpha	No significant findings in BMS
Amenabar (2008), Oral Surg Oral Med	1. 30 (6 M, 24 F) 2. 30 (6 M, 24 F)	UWS SWS	Cortisol	Increased cortisol in BMS
Trajkovic (2009), J Oral Pathol Med	1. 78 (27 M, 51 F) 2. 16 (unknown)	UWS	CGRP	No significant findings in BMS
Suh (2009), Arch Oral Bio	1. 40 (40 F) 2. 20 (20 F)	UWS SWS	IL-1beta IL-6 IL-8 TNF-alpha	No significant findings in BMS
Pekiner (2009), J Oral Pathol Med	1. 30 (11 M, 19 F) 2. 30 (9 M, 21 F)	UWS	IL-2 IL-6	No significant findings in BMS
Borelli (2010), Oral Dis	1. 20 (3 M, 17 F) 2. 20 (4 M, 16 F)	UWS	Nerve Growth Factor Substance P Tryptase	Increased nerve growth factor and tryptase but decreased substance P in BMS
Boras (2010), Med Oral Pathol Oral Cir Buccal	1. 26 (26 F) 2. 22 (22 F)	UWS	CGRP Neurokinin A Substance P	No significant findings in BMS
Kim (2012), Oral Dis	1. 28 (28 F) 2. 15 (15 F)	UWS SWS	alpha-amylase Cortisol DHEA Estradiol Progesterone	Increased cortisol (UWS), DHEA (SWS), estradiol (SWS) in BMS
Kim (2012), Oral Dis	1. 30 (30 F) 2. 20 (20 F)	UWS SWS	alpha-amylase Cortisol DHEA Estradiol Progesterone	Increased cortisol (UWS) in BMS
Souza (2015), Neuroimmunomodulation	1. 30 (1 M, 29 F) 2. 32 (1 M, 31 F)	Unknown	Cortisol IL-6 IL-10 TNF-alpha	Increased IL-6 and decreased TNF-alpha in BMS
Imura (2016), J Oral Pathol Med	1. 15 (15 F) 2. 30 (30 F)	UWS	alpha-amylase IgA	Increased alpha-amylase in BMS
Hye Ji (2017), Mol Pain	1. 19 (unknown) 2. 19 (unknown)	UWS	alpha-enolase IL-18 KLK13	Increased alpha-enolase, IL-18, KLK13 in BMS
Nosratzehi (2017), Spec Care Dent	1. 30 (4 M, 26 F) 2. 20 (4 M, 26 F)	UWS	alpha-amylase Cortisol	Increased alpha-amylase in BMS
Loncar-Brzak (2020), Dent J	1. 28 (28 F) 2. 12 (12 F)	UWS	DHEA Estradiol Progesterone	Decreased estradiol in BMS
Lopez-Jornet (2020), J Clin Med.	1. 51 (6 M, 45 F) 2. 31 (5 M, 26 F)	UWS	alpha-amylase IgA Uric Acid	Increased alpha-amylase, IgA, FRAP in BMS
Aitken-Saavedra (2021), J Clin Exp Dent.	1. 40 (40 F) 2. 40 (40 F)	UWS	Cortisol	Increased Cortisol in BMS

Results

A summary of papers examining salivary biomarkers in patients experiencing BMS is presented in **Table 1**. The only two biomarkers which were studied in at least four papers were alpha-amylase and cortisol. Three studies concluded that there is a significant increase in alpha amylase levels between BMS patients and the control group. In contrast, one study determined that there was no difference in alpha-amylase levels between the BMS and control group. Furthermore, four studies determined BMS patients will have higher cortisol levels compared to the control group. However, one study reported finding no differences between its study groups. Moreover, many studies also conflicted in their findings with regards to the specific biomarkers tested with one paper reporting a statistical significance while another declaring no difference. These contrasting findings can be seen with IL-2, IL-6, and estradiol.

Discussion

The papers reviewed in this study measuring salivary biomarkers in patients with BMS demonstrated inconsistent results. These results can be the result of small samples sizes or varying biomarkers being tested. Out of the seventeen studies collected, only two biomarkers were tested at least four times. As a result, a reliable conclusion of the biomarkers tested cannot be derived from the studies. Furthermore, a majority of the BMS patients studied were females which may skew the results. Lastly, many studies utilized different methods to analyze the saliva samples and used different units of measurements making detailed analysis difficult.

Conclusions

Literature regarding salivary biomarkers in BMS patients report varying results on the differences between study groups. In addition, there was a large range of biomarkers tested in patients. Large-scale studies are required as there will be a calibration of salivary biomarkers of inflammation analyzed. Doing so may clarify the contradicting literature found concerning salivary biomarkers and BMS. Current literature do no clearly determine which salivary biomarkers accurately diagnose patients with BMS and its prognosis.

Future Research

Center for Clinical and Translational Research of Penn Dental Medicine is conducting an observational study in BMS patients to track pain symptoms in real-time and collect saliva samples to analyze biomarkers. Patients 18 years and older with access to a smart phone will complete a questionnaire three times daily over a 12-week period. The study will potentially supply additional data on salivary biomarkers in context of pain symptoms to help characterize BMS.

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