On characteristics of Burning Mouth Syndrome patients

A study based on clinical and salivary parameters

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Gothenburg 2018

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ISBN 978-91-629-0486-9 (Print)
ISBN 978-91-629-0487-6 (PDF)
Printed in Gothenburg, Sweden 2018
Printed by BrandFactory

To my family and to the patients suffering from Burning Mouth Syndrome

Content

Abstract

Burning Mouth Syndrome (BMS) is a condition with unknown aetiology that is characterised by a chronic unremitting burning sensation in the oral mucosa. This condition, which affects mainly middle-aged and older women, presents major challenges to the patients, physicians, and researchers. The lack of both, objective diagnostic criteria and effective treatment strategies renders difficulties in the management of patients suffering from BMS. The aims of this thesis were to: characterise the clinical symptoms and associated factors described by the patients; compare the whole saliva and saliva on the oral mucosa; and compare the salivary components in the patients with BMS and in age- and sex-matched controls. In **Paper I** it was found that 37% of the patients with BMS reported to have a combination of burning and scalding sensation as the most common BMS symptom and 45% of the patients reported to sense taste disturbances. The mean severity of the BMS symptoms experienced by the patients, measured on a visual analogue scale (VAS, 0-100) was 66. The patients with BMS expressed lower levels of satisfaction with their general and oral health, life-situation and reported more medications, diseases/disorders, xerostomia, allergy, skin diseases, bruxofacets, and less amalgam fillings than did the controls. Multiple logistic regression analysis, however, revealed that xerostomia and skin diseases had strongest association to BMS. In **Paper II** we compared whole saliva and oral mucosal saliva along with the effects of medication on the salivary flow-rate and xerostomia in patients with BMS and in controls. It was found that BMS associated diseases/disorders and drug usage coincided with less saliva on the tongue and less whole saliva. Systemic diseases and medication usage, however, did not have a significant impact on xerostomia in patients with BMS. The effect of glycosylation of the salivary mucin MUC7 and the presence of inflammatory markers in patients with BMS and controls were examined in **Paper III**. Overall, the types of oligosaccharides found on MUC7 in BMS patients and controls were similar. However, quantitative analysis of the individual oligosaccharides showed lower levels of sialylated and fucosylated structures, especially Sialyl-Lewis^x, in the patients with BMS. Analysis of inflammatory markers showed that patients with BMS represented a more heterogeneous group than the controls. This lead us to draw the conclusion that for some patients with BMS like symptoms, low-grade inflammation may be a contributing factor. This expands our knowledge of the clinical and salivary parameters associated with BMS. These studies are part of a larger project to design a disease model for BMS that would facilitate the diagnosis and treatment of patients with BMS in the future.

Keywords: Burning Mouth Syndrome, Parafunction, Skin diseases, Saliva, Drugs, Xerostomia, Mucins, MUC7, Sialyl-Lewis^x.

Sammanfattning på svenska

Burning Mouth Syndrome (BMS) är ett kroniskt smärtsyndrom som främst drabbar medelålders och äldre kvinnor efter klimakteriet. De som drabbas av BMS har munsveda och ofta smakförändringar utan synliga eller mätbara förändringar av den orala slemhinnan. Idag finns därför inga objektiva kriterier för BMS som diagnos och inga effektiva behandlingsmetoder. Detta gör det svårt; inte bara för den drabbade patienten, för vilken besvären innebär ett stort lidande, utan även för vårdgivare. Syftet med avhandlingen var att undersöka kliniska fynd, självrapporterade symtom och bakgrundsfaktorer samt saliv-relaterade förhållanden hos kvinnliga BMS-patienter. Dessa data kan leda till bättre diagnostik och behandling i framtiden. Studierna omfattade frågeformulär, kliniska undersökningar, salivsekretion och förekomst av mukosal saliv samt analys av salivkomponenter och då speciellt slemproteiner s.k. muciner. Vi fann att de flesta patienter med BMS upplevde brännande och stickande känsla och nästan hälften av patienterna upplevde smakförändringarna. BMS-symtomen var ofta besvärande, runt 70 på en skala från 0 (inte alls svåra) till 100 (outhärdliga). Vi fann också att patienterna var mindre nöjda med sin allmänna och orala hälsa och sin livssituation, jämfört med kontrollgruppen. Patienterna angav också att de oftare led av andra sjukdomar, att de använde fler mediciner, kände av muntorrhet (xerostomi) och hade fler allergier. Förutom ökad tandpressning (bruxism), hittade vi inga signifikanta skillnader för andra parafunktioner såsom tungpressning, kindlist, läpp-impressioner eller tandslitage. Genom multivariat analys visade sig endast xerostomi och hudsjukdomar vara associerade med BMS. Efterföljande analysen visade att BMS patienterna hade mindre saliv på tungan och helsaliv, vilket till skillnad från xerostomi var relaterade till förekomsten av systemiska sjukdomar och medicinering. En annan upptäckt var att salivens slemlager hos BMS-patienter var förändrat. Vi fann denna förändring på det skyddande kolhydratskikt som finns på ett av munhålans slemproteiner, mucinet MUC7. Förändringen bestod utav att en speciell typ av kolhydrater, som innehåller Sialyl-Lewis^x, hade minskat. Sialyl-Lewis^x är en kolhydrat som påverkar munhålans immunsystem. Minskad mängd Sialyl-Lewis^x verkade vara oberoende utav att BMS-patienter ibland uppvisade minskad oral bakgrunds-inflammation och ibland ökad oral bakgrunds-inflammation, i jämförelse med kontrollerna. Den högre åldern hos både kontroller och patienter i jämförelse med normalpopulationen antogs leda till en ökad spridning på nivån av bakgrundsinflammationen, ett fenomen som kallas för ”inflamm-aging”. Vi föreslår att graden av inflamm-aging kan utvärderas i framtiden som ett kriterium för att behandla BMS patienter. Studierna ingår i ett större projekt som förhoppningsvis kan bidra till att hitta en modell för BMS vilket i framtiden kan underlätta diagnostiken och behandlingen av patienter med BMS.

List of papers

This thesis is based on the following studies, which are referred to in the text by their Roman numerals:

I. **Acharya S**, Carlén A, Wenneberg B, Jontell M, Hägglin C. Clinical characterization of women with burning mouth syndrome in a case-control study. *Acta Odontologica Scandinavica.* 2018; 76: 279-286.

II. **Acharya S**, Hägglin C, Jontell M, Wenneberg B, Ekström J, Carlén A. Saliva on the oral mucosa and whole saliva in women diagnosed with burning mouth syndrome. *Oral Dis.* 2018;00:1-9.https://doi.org/10.1111/odi.12918.

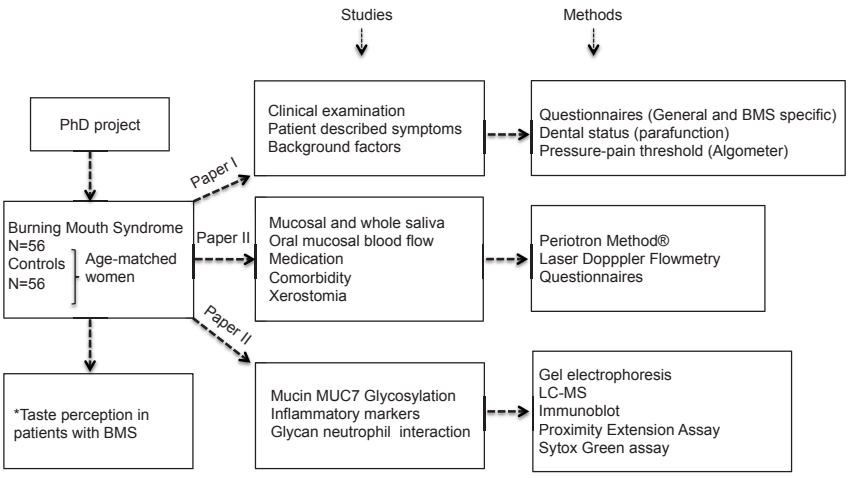
III. **Acharya S**, Chunsheng J, Jontell M, Carlén A, Bylund J, Karlsson NG. Reduced Sialyl-Lewis^x in patients with Burning Mouth Syndrome. *Manuscript.*

Reprints of **Paper I** and **Paper II** were made with the permission of the publisher.

Abbreviations

BMS	Burning mouth syndrome
CBC	Complete blood count
GalNAc	*N*-acetylgalactosamine
GlcNAc	*N*-acetylglucosamine
IASP	International Association for Study of Pain
ICHD	International Classification of Headache Disorders
NETs	Neutrophil extracellular traps
NeuAc	*N*-acetylneuraminic acid
OHIP	Oral health impact profile
OHRQL	Oral health related-quality of life
PPT	Pressure pain threshold
RAS	Recurrent aphthous stomatitis
Si-Le^x	Sialyl-Lewis^x
sIgA	Secretory Immunoglobulin A
SWS	Stimulated whole saliva
UWS	Unstimulated whole saliva
VAS	Visual analogue scale
VIP	Vasoactive intestinal peptide

Overview of PhD project



*Part of PhD project but not included in the current thesis

Schematic of projects comprising this thesis: **Paper I** investigated the clinical characterisation and patients described symptoms of BMS and associated factors. **Paper II** featured the comparison of saliva on the oral mucosa and whole saliva in the patients with BMS and in controls. It also assessed a deeper investigation into factors such as medication and comorbidity (for instance, systemic diseases), which could affect saliva. **Paper III** compared the glycosylation of one of the important salivary mucins, MUC7 in the patients and the controls. It further characterised the specific MUC7 oligosaccharides in the participants. Additionally, the presence of inflammatory markers and the interaction of specific oligosaccharides with innate immune cells, neutrophils were assessed.

1 Introduction

The oral cavity often acts as a mirror of general health and disease. Oral mucosal diseases affect the soft tissues of the mouth and result in morbidities that have physical, social and psychological consequences for the patients [1]. Burning, stinging or sore sensations in the oral mucosa can be either acute or chronic, and may share certain features. Recurrent aphthous stomatitis (RAS), oral lichen planus (OLP), and vesiculobullous diseases are common causes of mucosal soreness and pain for which visible changes in the oral mucosa can be observed. However, pain in the oral mucosa can also occur in the absence of clinical or laboratory findings e.g., in Burning Mouth Syndrome (BMS). BMS, which is a chronic pain syndrome, was first described by Portal in 1803 [2]. It mainly affects peri-/postmenopausal women and is characterised by an unremitting oral burning sensation often in combination with taste disturbances, and in absence of detectable changes to the oral mucosal or other clinical findings making it difficult for clinicians to arrive at the correct diagnosis [3]. These conditions represent a debilitating disorder with very poor prognosis and subjects with BMS are heavy consumers of healthcare resources [4]. The cause of BMS is unknown although a wide range of factors has been suggested [5]. As there are no objective criteria for the diagnosis of BMS, patient described symptoms and characteristics are of importance. Only scant consideration has been given to the potential role of saliva and none attention has been paid to the role of mucosal saliva in BMS. In this thesis, self-reported and clinically assessed characteristics, whole and mucosal saliva and salivary mucins are examined. Elucidation of these factors contributes to the development of a model for BMS, which should facilitate the development of effective treatment strategies. The current thesis is part of a larger project on BMS, which hypothesises that elderly women who have had a stressful life in parallel with parafunctional oral habits will later in life experience a burning sensation of the oral mucosa and taste disturbances as a sequel to biochemical and biophysical changes of the saliva. The clinical characteristics and salivary profile of patients with BMS are described in the following section, to put the work of the thesis in the context of the results from previously conducted studies.

2 The Burning Mouth Syndrome

2.1 Definition of BMS

A universally standardised and validated definition of BMS based on objective diagnostic criteria has not yet been established. The nomenclature related to BMS in the literature has been a source of considerable confusion, as this condition has been given various synonyms, such as stomatopyrosis, glossopyrosis, stomatodynia, glossodynia, sore mouth, sore tongue and oral dysesthesia, in attempts to characterise the oral pain based on the quality and/or location of pain [5, 6]. The International Classification of Headache Disorders (ICHD-3β), third edition, beta version, describes Burning Mouth Syndrome [7] as an "intraoral burning or dysaesthetic sensation, recurring for more than 2 hours per day over more than 3 months, without clinically evident causative lesions". The International Association for the Study of Pain (IASP) defines BMS as a chronic intra-oral burning sensation that has no identifiable cause in the form of either a local or systemic condition or disease [8]. It has been suggested that there may be discrepancy in ICHD-3β and IASP classification criteria of BMS [9]. Furthermore, there is a debate among researchers and clinicians as to whether burning mouth is a syndrome or a disorder [10-12]. A disorder, by definition, is a condition that manifests symptoms of other diseases and this occurs in some cases of BMS [12], whereas a syndrome is a collection of several simultaneous signs and symptoms of varying intensity, which also holds true for BMS [6, 13]. In this thesis (**Papers I-III**), the term BMS is treated as syndrome and the diagnostic criteria of BMS according to ICHD-3β criteria were applied.

2.2 The various classification systems of BMS

Scala *et al.*, classified BMS into primary and secondary BMS [5]. Primary BMS was when the pain was idiopathic and no local or systemic cause could be found for the oral mucosal pain and secondary when the pain resulted from possible precipitating factors [5]. According to Scala *et al.*, once such factors are treated, the symptoms of BMS would improve or disappear. Lamey and Lewis, on the other hand, have classified BMS into three different subtypes according to the diurnal pattern of oral symptoms [10, 14-16]. According to Lamey and Lewis, in Type I BMS, symptoms should be absent upon awakening but gradually increase in severity as the day progresses, and it has been reported to occur in about 35% of the cases of BMS. About 55% of the patients experience Type II BMS, with a burning sensation in the oral mucosa experienced everyday, being present already in the morning. Type III BMS was experienced by about 10% of the patients involving intermittent pain with pain-free intervals [17]. Type I BMS has

been reported to be linked to the nutritional deficiencies and endocrine disorders [14], Type II BMS to chronic anxiety, and mood changes [18], and Type III BMS to allergic reactions to food-related products [17].

2.3 Epidemiology of BMS

Women are much more frequently affected by BMS than men [19] and the prevalence increases with age [20, 21]. BMS is most commonly seen in middle-aged and elderly women [20, 22] (**Paper I**). The prevalence of BMS has been reported as little as 0.1% but also large as 40% [22-25]. This huge span in prevalence may be due to several factors e.g., different criteria used for the diagnosis of BMS, variations in the age group and gender of the participants included in the study, variation between population and countries and different methods used. In an epidemiological study carried out in Sweden, the prevalence of BMS was 3.7% in a population of 1,427 persons in the age range of 20-69 years [20]. Another Swedish study of middle-aged and elderly women reported a prevalence of 4.6% [26]. In a study carried out in US on 45,000 households, the prevalence of BMS was reported to be 0.7% based on self-reported symptoms [27]. A large retrospective Brazilian study carried out with more than 3,000 patients reported a BMS prevalence of 1% [28]. The incidence of BMS in individuals <50 years has been reported to be 3 per 100,000 as compared to 23 per 100,000 for persons in the age range of 50-59 years [22]. In the same study, the highest incidence range was among persons in the range of 70-79 years of age (47 per 100, 000). A brief overview of the prevalence data reported in studies on BMS is given in Table 1.

Table 1. Prevalence of BMS reported in epidemiological studies

Reference	Prevalence (%)	Study Population
Ben Aryeh *et al* [24]	10-40	154
Hakeberg *et al* [26]	4.6	1017
Bergdahl and Bergdahl [20]	3.7	1427
Thorstensson and Hugosson [29]	3.4	533
Tammiala *et al* [30]	14.8	431
Lipton *et al* [27]	0.7	45000
Netto *et al* [28]	1	3243
Suzuki *et al* [31]	3	2599
Kohorst *et al* [22]	0.11	482*

*Incidence-based study

2.4 Clinical BMS features

BMS represents a symptomatic triad with pain, xerostomia and taste disturbances being the most common clinical features [21] as illustrated in Figure 1. In addition, there are no detectable changes in the oral mucosa. Pain and taste disturbance are discussed below, while xerostomia will be discussed in the section on saliva (3.7).

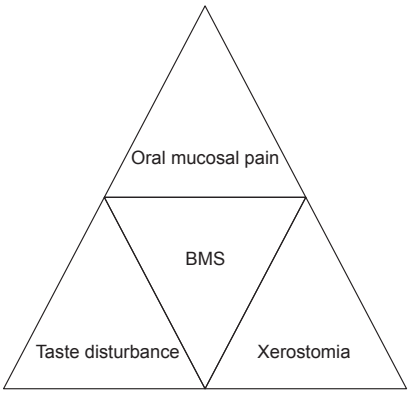


Figure 1. Symptomatic triad associated with BMS

2.4.1 Pain in relation to BMS

The sensation of pain is a subjective perception and every persons vocabulary contains nuanced connotations regarding pain such as burning, stinging, and stabbing, to name a few. Oral pain is one of the cardinal features of BMS [5]. The pain is experienced usually at the tip and anterior two-thirds of the tongue, followed by the anterior hard palate and gingivae, lower lip, and the pharynx [32]. The pain is usually bilateral and symmetrical [21, 33]. Thus, pain measurement is an essential component of the disease assessment, including initial diagnosis [21]. Pain management and relief of symptoms are often significant goals of the treatment. The Visual Analogue Scale (VAS) and Pressure Pain Threshold (PPT) are commonly used measures to evaluate sensitivity to pain [34] (**Paper I**). In **Paper I** sensitivity to pain was measured both by using an electronic pressure algometer, and on a VAS by asking about perceived pain when taking a blood sample from the figure tip (ranging from 0= ”no pain at all” to 100= ”terrible pain”).

2.4.1.1 Type of pain

In a patient with BMS, the type of pain described by the patients includes burning, scalding, tingling, itching, swelling and/or a numb sensation [4, 23, 35-37] (**Paper I**). The pain in BMS is usually described as being similar to toothache, although with a distinctive sensation of superficial oral burning [9]. A combination of burning and scalding was reported as the most common symptom in **Paper I**. The onset of pain in BMS can be idiopathic or related to previous events such as dental procedures and other diseases [21]. The intensity of pain may vary from mild to severe [38] and is usually within the range of 30-80 on a 100 mm VAS [14, 20, 39, 40] (**Paper I**). About 36% of the patients in **Paper I** scored ≥80 mm.

2.4.1.2 Duration and intensity of pain

BMS symptoms can persist for years or can be life-long [13, 41] (**Paper I**). The intensity of BMS pain is usually low or zero in the morning and gradually increases during the day [35, 39]. The symptoms may be present throughout day and night [33] (**Paper I**). None of the patients in **Paper I** reported the pain being present during the night only. The pain described by patients with BMS is usually long-lasting, although intermittent daily pain is also reported by the patients [42]. Some symptoms of BMS were reported to be eased by the usage of, for example, chewing gum (**Paper I**), mineral/tap water [39] (**Paper I**), and saliva substitute gel (**Paper I**). BMS patients are reported to have a higher threshold for pain in the oral cavity [43, 44], although this feature did not differ between the patients and controls in **Paper I**. In a recent study, patients with BMS showed a slightly higher PPT in the tongue [45].

2.4.1.3 Interaction of pain and sleep

A lack of proper sleep has been postulated to increase anxiety, and depression, cause a loss of concentration [46], and affect the pain threshold, resulting in increased sensitivity to pain [47]. A study has shown that pain and poor sleep lead to a decreased quality of life and decreased social functioning [48]. There have been conflicting reports on the relationship between BMS and sleep. Some studies have reported that BMS pain affects sleep in general [39, 41, 49, 50]. Data from our BMS project (not presented in the attached papers) reveal that that 71% of the patients who were suffering from BMS reported having significant sleep disturbances, as compared to 37% of the controls. For chronic pain conditions such as BMS, it is not surprising to find disturbed sleep as comorbidity. Sleeping disturbance may also be related to the psychological factors associated with BMS [51]. The cause and effect of BMS pain and sleep phenomena have not

yet been established [50] and require further consideration. Psychological aspects of BMS are discussed separately on section 2.5.4.

2.4.2 Taste disturbances

Taste disturbance in the general adult population has been reported to have a prevalence of 0.6%-11% [29, 52-54]. The taste sensation is detected using five different modalities: sweet, salty, sour, bitter, and umami. Taste receptors located around the tongue react to all kinds of taste-active stimuli, and they are not restricted to the theory of a tongue map, which is based upon the heterogeneity of receptor fields in the mouth [55]. In contrast, individual sensitivities to different tastes can vary [56], and taste sensitivity has been suggested to decrease with aging [55].

Altered taste sensation is one of the prominent features experienced by the patients suffering from BMS [6, 21, 54, 57, 58] (**Paper I**). Taste disturbances have been reported by 11%-69% of the patients [20, 21, 39] (**Paper I**). The most common taste disturbances reported are metallic, bitter or both taste [21, 59]. In **Paper I**, metallic and sour taste was the most common taste disturbances followed by salty, bitter, and sweet sensation reported by the patients. Measurements of taste perception in BMS have shown that the patients with BMS have a higher threshold for sourness but are indifferent to sweet, salty, umami and bitter stimuli [60]. In other studies, the detection thresholds for a sweet stimulus and for salty and bitter taste were found to be higher for patients with BMS than for the controls [61, 62]. Another study revealed BMS patients to be less sensitive than the controls for sweetness, sourness, saltiness and bitterness [43]. Thus, there have been discrepancies in the perception of the taste in the previous studies, which are plausibly attributed to the different methods used for taste tests and for the diagnosis of BMS. In an unreported study (unpublished own data), the whole mouth intensity test using VAS scales (0 = no sensation, 10 = extremely strong) for sour, sweet and metallic taste sensation was used and the results revealed that the patients were more sensitive than the controls to sour taste in lower concentrations (Figure 2). The sensation of sweet and metallic taste did not differ significantly between the patients with BMS and the controls.

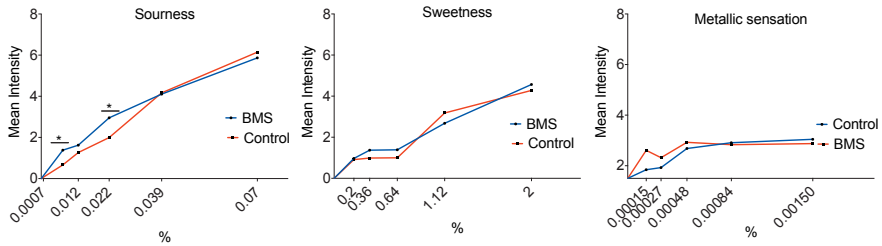


Figure 2. Profiles of intensity testing for patients with BMS (N=51) and controls (N=51). Different concentrations of citric acid (modelling sourness) ranging from 0.07%-0.7%, sucrose (modelling sweetness) ranging from 0.2%-2% and copper sulphate (modelling metallic sensation) ranging from 0.00015%-0.0015% were used. Plots A) Sourness; B) Sweetness; C) Metallic sensation. The y-axis represents mean intensity (scale 0-10 anchored both numerically and verbally) and the x-axis represents the concentration of stimulus.

Patients with BMS who have a higher density of fungiform papillae [63], as compared to the controls, are known as 'supertasters' [64]. However, another study found out that there was no difference in the density of fungiform papillae between patients with BMS and controls [65]. Being described as a taster or a non-taster could be due to differences in taste sensitivity, which varies between individuals. Recently, human clusters for sweetness, saltiness, bitterness, umami and sourness have been defined based on tasting tests [56]. A classical example of distinguishing individual differences in taste sensitivity is the genetically inherited insensitivity to compounds such as phenylthiocarbamide (PTC) [66]. The sensitivity to PTC and other thiourea compounds, such as 6-*n*-propylthiouracil is dictated by genetic variations (for e.g. single nucleotide polymorphism) in the TAS2R38 taste receptor gene [67, 68].

2.5 Factors associated with BMS

Of the factors most commonly associated with BMS (Figure 3), some will be discussed in the following section with an emphasis on saliva and clinical characteristics.

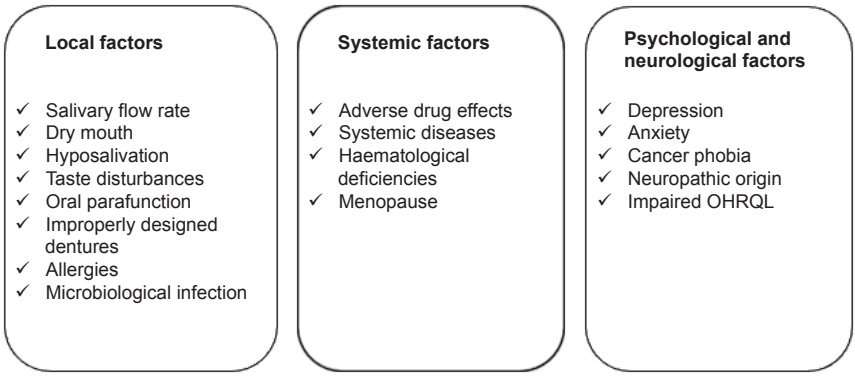


Figure 3. Factors commonly associated with BMS

2.5.1 Oral parafunction

Parafunctional habits are performed unconsciously, and are the activities of the stomatognatic (anatomic system comprising teeth, jaws, and associated soft tissues) system. Oral parafunctional habits, such as tongue thrusting, bruxism, and tooth clenching have been associated with the cause of burning pain in BMS [14, 69, 70]. BMS comorbidities, such as headache and pain in the temporomandibular areas, have also been reported [71]. Night bruxism has been noted in an observational study of patients with BMS [72]. While it has been proposed that parafunctional habits are associated with BMS [14, 70], this association was not evident in **Paper I**. No statistical significant differences were found for dental wear, tongue impressions, cheek strips or lip impressions between the patients and the controls, only more active bruxofacets (atypical facets on teeth, with flat, smooth shiny areas) in the patients with BMS. However, in the multiple logistic regression analysis, bruxofacets was not included in the final model suggesting minor influence. This was further confirmed in an unpublished study based on eight intra-oral photographs per patient and control subject, respectively (Table 2). The photographs, which were examined in a blinded fashion, showed more tongue impressions and cheek strips among the controls, and no significant differences were found for the dental wear and lip impression (Table 2). These findings suggest that parafunctional habits are not a triggering factor for BMS.

Table 2. Descriptive data* on parafunction in patients with BMS and controls

	BMS		Control		p-value
	N	%	N	%	
Tongue impressions	18	32	30	54	0.035
Cheek strips	14	25	29	52	0.006
Dental wear	50	89	53	95	0.676
Lip impressions	7	13	10	18	0.600
Total localisations	89	41	122	55	0.003
Participants	53	95	54	96	1

* Number of patients and controls with different types of parafunction sites, total number of sites registered and total participants with one or more registered parafunction.

2.5.2 Allergy

Although a normal oral mucosa is a prerequisite for the diagnosis of BMS, allergic reaction has been known to cause an oral burning sensation [73]. Patients with BMS have reported being allergic to denture materials, food additives, flavouring components and fragrant substances [17, 74-77]. Furthermore, remission of an oral burning sensation after the removal of the allergen has been observed in some studies [78, 79]. However, no significant association has been observed between BMS and a positive patch test [80, 81]. In **Paper I**, patients with BMS reported being allergic to pollen, nickel and penicillin among others. However, allergies showed a weak influence on BMS when adjusting for other factors in a multiple logistic regression analysis. Allergy to denture and other dental materials has been reported to cause an oral burning sensation [14, 78]. In the present project, however, dentures were unusual, with only two patients having full denture in one jaw and one of them having a partial denture in the other jaw and, thus, denture is very unlikely the cause of the burning sensation. It also has been discussed that BMS is associated to possible allergy to amalgam fillings [71]. In **Paper I**, the patients with BMS were found to have fewer amalgam fillings than the controls. This mainly was due to replacement of amalgam with other dental materials. Ten of the patients with BMS had replaced their fillings but none of them reported to experience relief of symptoms after restorations were replaced.

2.5.3 Skin diseases

In **Paper I**, patients with BMS reported suffering more often than the controls from skin diseases such as rosacea, eczema, dry skin and psoriasis. Patients with BMS also reported more symptoms involving the genital mucosa, such as dry mucosa and lichen planus, as compared to the controls (**Paper I**). To the best of our knowledge, this association of skin diseases to BMS is a novel observation.

2.5.4 Psychological factors

As patients with BMS do not present visible signs in the oral cavity through clinical or laboratory investigations, has been suggested that the clinicians who are unfamiliar with BMS may regard patients being emotionally unstable and their complaint is often not taken seriously [33]. It has been reported that patients experience that they are mistrusted by the healthcare givers, as well as their family members, which in turn may increase the patient's anxiety, and ultimately their perception of pain [82, 83]. An inter-relationship between the chronic pain experienced by patients with psychological factors is presented in Figure 4. Patients with BMS often feel neglected; and experience depression, chronic anxiety, emotional sustainability, and anxiety in relation to cancer [83, 84]. A recent study investigating the psychological profiles of patients with BMS using SCL-R (Symptom Checklist-90- Revised questionnaire) revealed that BMS had significantly higher scores for somatisation, obsessive-compulsive disorder, depression, anxiety, and psychoticism than the controls [85]. The question of whether anxiety and/or depression are the causes or effects of BMS yet remains to be answered [33] A multidisciplinary approach to the patients suffering from BMS involving dentists, clinical psychologists and psychiatrist, thus was suggested in another study [83].

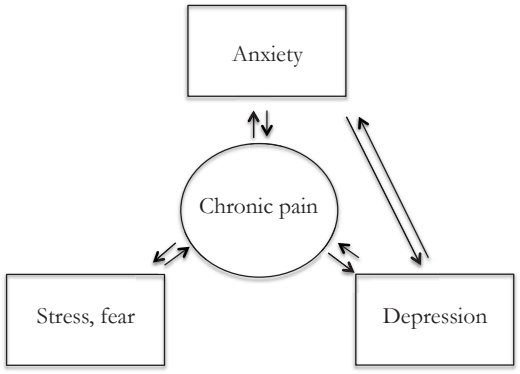


Figure 4: A generic schematic of inter-relationship between chronic pain, anxiety, depression and other emotions in patients with BMS. The greater intensity of pain may enhance anxiety, depression and other emotions and these factors may also aggravate the experience of chronic pain. Depression and anxiety are often found to be correlated to one another. Figure adapted and modified from [33].

2.5.5 Oral health-related quality of life (OHRQL)

Oral health is essential to general health and well-being at every stage of life. OHRQL captures both the clinical point of view and the individual's perception of oral health related factors [86]. OHRQL reflects four aspects of oral health: 1) functioning aspects such as mastication and speech; 2) pain and discomfort, both acute and chronic; 3) psychological aspects such as appearance and self-esteem; and, finally, 4) social aspects such as intimacy, communication and social interactions. Patients suffering from BMS reported poor OHRQL and experienced being affected in most of these areas [87, 88]. Patients with BMS were often less satisfied with their general [48] (**Paper I**) and oral health [89] (**Paper I**) and were dissatisfied with their quality of life/life situation (**Paper I**).

2.5.6 Menopause

Menopause is characterised by physiological ovarian failure and hormonal imbalances and a study showed that removal of ovaries resulted in oral burning sensations in 18% of the women [90]. This notion suggested the role of menopause on BMS as BMS occurs in peri-/postmenopausal women and the occurrence of BMS before the age of 30 is rare [21, 91] (**Paper I**). It has also been suggested that altered level of female sex-hormones may predispose women to BMS [5]. In one study [92], increased levels of hormones, such as 17-β oestradiol and progesterone, were noted, which suggests the role of hormones in BMS. However, the functional relevance of these hormones for the pathogenesis of BMS remains to be studied. The data from **Paper I** does not suggest an exacerbation of post-menopausal symptoms among BMS patients.

2.5.7 Neuropathic origin

As the pain described by patients with BMS is of burning nature, BMS has often been suggested to be associated with a neuropathic mechanism of pain, where the central and/or peripheral nervous system are suggested to play a significant role [9, 42]. Patients with BMS are reported to have significantly lower densities of epithelial nerve fibres in the tongue mucosa [93] and reported damage in the trigeminal nerve [9, 94]. Inter-relationship between the pain perception and taste disturbances also has been suggested [95]. Furthermore, patients with BMS exhibit decreases in synaptic dopamine levels similar to those seen in Parkinson's disease [96].

2.6 Current treatment strategies

The treatment of BMS is usually focused on relieving the symptoms. The pharmacological options to treat BMS include administration of local and systemic medications such as benzodiazepines, tricyclic antidepressants, anticonvulsant, capsaicin, and alpha lipoic acid [97-99]. Both topical [100-102] and systemic clonazepam [103] have been used in these patients for the relief of the symptoms. However, many of the above-listed drugs are known to decrease the salivary flow-rate [104]. Low-level laser therapy has also been used in treatment of BMS [95, 97]. Hormone replacement therapy and cognitive behavioural therapy (either alone or together with medication) have been used in the treatment of BMS in past studies [33, 105, 106]. However, none of the previous studies have described the optimally effective treatment for the management of patients with BMS.

3 Saliva

Saliva, salivary glands and the mechanism of saliva secretion are discussed in this chapter, as these distinct factors are known to be directly or indirectly associated with oral pain, feelings of dry mouth and taste [107, 108].

3.1 Salivary glands and saliva production

Saliva is a complex bodily fluid that that is often taken for granted until its quality or quantity deteriorates [109, 110]. Saliva is mainly produced by three major paired salivary glands known as the parotid, submandibular, and sublingual glands, which contribute approximately 90% of the total volume. The salivary glands are innervated and highly vascularised with a dense capillary network [111] providing the water for the saliva production. Most of the salivary components are produced by the glands, although certain molecules pass through the blood into the saliva through diffusion, active transport or ultra-filtration [112].

In addition to the major salivary glands there are 600-1000 minor salivary glands located in the labial, buccal and palatal regions. They range in size from 1-5 mm and contribute 6%-10% of the total 0.5-1.5 L of saliva produced in a 24-h period. In the oral cavity, the secretions from the different glands are mixed with gingival crevicular fluid, blood cells, microbes, cells and food debris along with naso-pharyngeal secretions [113]. In general, saliva secreted at rest is termed as "unstimulated whole saliva" (UWS) despite that this secretion is influenced by the nervous activity [113]. UWS flow is present in the mouth for 14-16 h/day [114]. It sustains the oral comfort and protection. Saliva is subjected to a circadian rhythm in terms of the flow-rate reaching peak flow in the mid-afternoon and a minimal flow in the early morning [115, 116] (Figure 5). Stimulated whole saliva (SWS) is secreted in response to masticatory or gustatory influence and is responsible for swallowing and oral clearance. Minor salivary glands secrete saliva spontaneously and they continue to secrete saliva at a low-rate even at night without the influence of any exogenous stimuli [113].

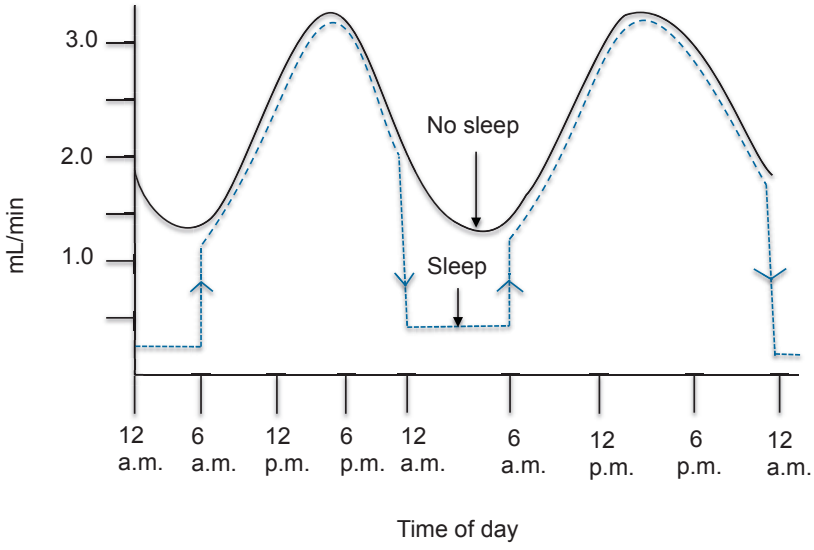


Figure 5. The circadian rhythm pattern of the unstimulated whole saliva (UWS) flow-rate showing the impacts of no sleep (solid line) and sleep (dashed line) (Adapted from [115]).

3.2 Mechanism of salivary secretion

The salivary gland is composed of polarised epithelial cells and consists of acinar cells and branched duct (intercalated, striated and excretory) cells that are surrounded by a dense network of capillaries. Saliva secretion is a two-stage process [117] (Figure 6). The acinar cells have bunch of grape-like structures that secrete an isotonic solution. The striated duct cells modify the composition of the secretion by reabsorbing sodium and chloride and secreting bicarbonate and potassium. Water does not pass through, as the apical membrane of the striated duct is water impermeable. This makes saliva hypotonic when passed through the ducts, before entering the oral cavity [108]. The saliva can be categorised as serous, mucous or mixed. Parotid gland acinar cells produce serous saliva, while the sub-mandibular and sublingual glands produce mixed mucous and serous secretions [118]. Saliva secretion is reflex-controlled via the autonomic nervous system, which gets activated by the higher centres of the brain, with the sympathetic and parasympathetic systems working synergistically (Figure 7). Salivary glands are innervated by parasympathetic nerves that use acetylcholine and a number of non-adrenergic, non-cholinergic transmitters, such as, vasoactive intestinal peptide (VIP) [108, 119]. Acetylcholine, via muscarinic receptors (M1 and M3), is mainly responsible for the fluid secretion, while VIP, via VIP receptors, is mainly responsible for the protein secretion. The sympathetic innervation causes the release of noradrenaline that acts on α_1-

adrenoreceptors and β_1-adrenoreceptors to evoke fluid secretion. It should be noted that although VIP is primarily responsible for protein secretion, it together with acetylcholine enhances both protein and fluid secretion (pathway not shown in figure 7). The secretory elements of minor glands are thought to lack a sympathetic innervation [113].

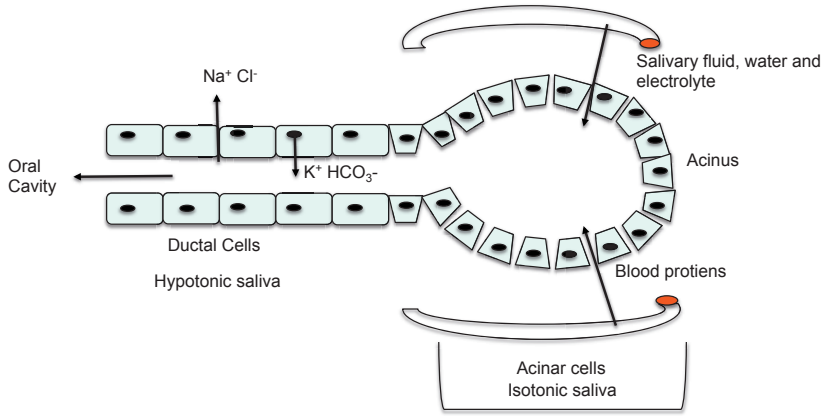


Figure 6. Schematic of salivary secretion (Adapted from [117, 119]). The secretion of saliva occurs in a two-stage process in which acinar cells secrete an isotonic solution. After passage of the isotonic solution through the ducts, the saliva becomes hypotonic, before being secreted into the oral cavity. The protein content of saliva comprises the salivary proteins secreted and synthesised by acinar cells. Proteins from the blood mainly enter the whole saliva in the oral cavity, mainly via the gingival crevicular fluid.

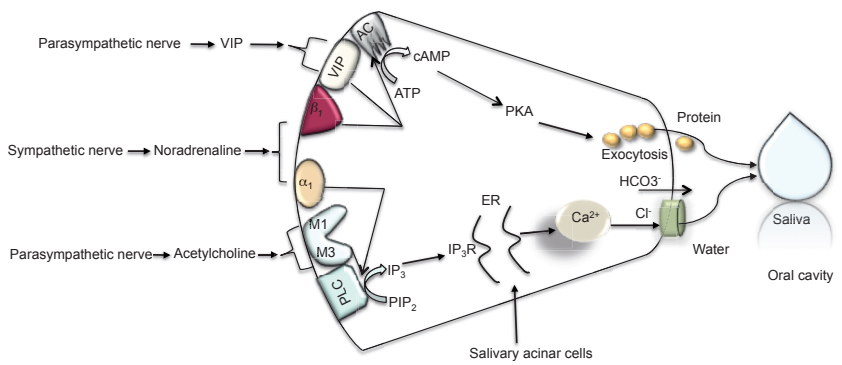


Figure 7. A simplified model showing the secretion of major gland saliva in acinar cells regulated by the autonomic nervous system (Adapted from [108, 117, 119, 120]). The fluid secretion of saliva is dependent mainly upon activation of the parasympathetic system. The parasympathetic transmitter acetylcholine stimulates the muscarinic cholinergic (M1 and M3) receptors on the cell surface. This activates the inositol phospholipid (IP3) pathway mediated via phospholipase C (PLC), which in turn increases intracellular calcium level in the endoplasmic reticulum leading to activation of the chloride release. The protein secretion of saliva is dependent mainly upon sympathetic stimulation by release of the transmitter noradrenaline and the vasoactive intestinal peptide (VIP) from parasympathetic nerves. The noradrenaline binds to both α_1- and β_1-adrenoreceptors. Activation of β_1-adrenoreceptors along with vasoactive intestinal peptide further induces activation of adenylyl cyclase (AC), followed by cyclic adenosine monophosphate that activates protein kinase A (PKA). This is followed by release of protein into saliva.

3.3 Composition of saliva

The saliva entering the oral cavity consists of 99% water containing both organic and inorganic components. The inorganic components include calcium, potassium, bicarbonate and magnesium among others [121]. The organic salivary components include urea, ammonia, fatty acids, amino acids, steroid hormones, proteins and peptides, mucins, amylases, agglutinins, proline-rich proteins, lysozymes, peroxidases, lactoferrin, secretory IgA (sIgA), cystatin, histatin, and defensins [121-124]. The salivary mucins will be discussed in a separate section below. In the mouth, the whole saliva also contains cells and particles such as epithelial cells, neutrophils, microorganisms (bacteria, viruses, yeasts and protozoa), DNA and RNA, and growth factors [119, 125]. Saliva also contains gingival crevicular fluid, which is produced at 2-3 μl/h per tooth and can be considered as a plasma transudate [126]. Some of the components of saliva described here generally occur in small amounts and may vary with flow-rate but these components provide important biological functions [124].

3.4 Functions of saliva

Saliva functions in: 1) moistening and lubrication; 2) taste; 3) swallowing; 4) protection of the oral mucosa and oesophagus; 5) protection of teeth against abrasion, attrition, erosion and dental caries; 6) oral clearance; and 7) antibacterial- and anti-viral functions, along with wound-healing functions [121, 127-131]. Saliva also facilitates speech and is an important mediator in social interactions [113]. Saliva is a non-newtonian fluid that easily spreads across the oral mucosal surfaces and is retained in the oral cavity [123]. Salivary flow is important for the removal of bacteria, buffering of saliva, and oral health generally. A variety of anti-microbial proteins and peptides keep the oral microbiota in homeostasis. The proteins in saliva aid formation of the pellicle, which acts as a protective layer on the oral tissues and e.g. reduces de-mineralisation of the teeth. Salivary constituents such as lactoferrin, amylase, calprotectin, proline-rich protein (PRPs), cystatin, histatin and sIgA have anti-microbial activities [132]. Saliva helps to break down food and is important for swallowing and lubrication [124, 133]. In the absence of saliva, the oral mucosa becomes susceptible to bacterial, viral and fungal infections. The lubricating properties of saliva, with the aid of the salivary mucins MUC5B and MUC7, help to ease the friction between tissue surfaces as well as mechanical wear [134]. Saliva also aids in taste perception by acting as a medium that dissolves food substances, and it prevents the taste receptors on the tongue from drying out [135].

3.5 Whole and oral mucosal saliva

3.5.1 Whole Saliva in relation to BMS

The oral mucosa of healthy individuals is constantly bathed in saliva, which protects the oral mucosa from drying. The range of normal UWS flow-rate has been reported as 0.2-0.5 mL/min and the SWS flow-rate as 1-1.5 mL/min [122, 124, 136-138]. Reported data on whole saliva in patients with BMS seems to deviate in different studies. Some studies have described a decreased salivary flow rate in patients with BMS [8, 14, 20, 139, 140] (**Paper II**) while others found no difference [21, 71, 141] compared to controls. In one study, a statistically non-significant increase in SWS and UWS in BMS was reported [30]. In **Paper II,** both UWS and SWS were found to be significantly reduced in BMS. Different from previous studies, factors that could affect the salivary secretion (for instance, medication, age, systemic disease) was thoroughly analysed statistically and controls were matched by age and gender in **Paper II**. The reduction in salivary flow may explain the decreased quality of life by interfering with daily activities such as chewing, swallowing and speaking (**Papers I and II)**. Reported UWS and SWS flow-rates in patients with BMS and controls are illustrated in Table 3.

Table 3. Whole saliva flow-rates in **Paper II** and in the literature.

Reference	UWS (mL/min)		p-value	SWS (mL/min)		p-value
	BMS (Mean±SD)	Control (Mean±SD)		BMS	Control	
Paper II	0.21±0.22	0.31±0.20	**<0.05**	1.46±0.79	1.84±0.80	**<0.05**
Imura *et al* [60]	0.32±0.20[1]	0.52±0.24[1]	<0.01	-	-	-
Poon *et al* [8]	0.30±0.18	0.52±0.26	<0.05	1.56±0.65	2.33±1.06	0.172
Nagler *et al* [142]	0.33±0.03	0.34±0.14	ns	-	-	-
YC Lee *et al* [143]	0.11±0.15	0.21±0.16	<0.05	1.17±1.25	1.21±0.73	0.875
Lundy *et al* [144]	-	-	-	0.54±0.37[2]	0.45±0.2[2]	-
Spadari *et al* [140]	0.18[3]	0.34[3]	<0.01	1.78	1.7	0.7
Soares *et al* [37]	0.13 ±0.09	0.16±0.13	-	1.25±0.67	1.27±0.73	-
Das *et al* [145]	0.40±0.27	0.59±0.13[4]	<0.001	0.87±0.47	0.94±0.51[4]	0.62

Saliva was measured in g/min[1], parotid-gland saliva[2], SD not mentioned in the article[3], patients with secondary oral burning[4], ns=not significant/p-value not mentioned in the article, -=value not given.

3.5.2 Oral mucosal saliva in relation to BMS

Saliva from the minor salivary glands is important for oral comfort, as it creates a protective lubricating layer on the mucous and contributes to the feeling of hydration. A correlation has been observed between the flow-rate of saliva from the minor salivary gland and the thickness of the residual saliva film remaining on the oral mucosa after swallowing, which suggests

that the minor salivary gland saliva secretion is important for sensation of dry mouth [146]. Oral dryness is experienced during reduced mucosal wetness, especially of the palate, or during salivary gland hypofunction [147]. Patients with hyposalivation often show reduced minor gland salivary secretion resulting in insufficient mucosal wetting [148]. The presence of saliva on the mucosal surfaces of the lips, tongue and cheeks of patients with BMS was first examined in **Paper II**. Buccal and labial saliva did not differ between the patients and controls, while the patients with BMS had less saliva on the lingual mucosa, which could be attributed to the use of saliva-affecting drugs (**Paper II**). Reduced palatal and labial salivary gland secretions has been reported to occur in individuals with subjective oral dryness [149]. However, this was not seen in case of saliva on the labial mucosa for the patients with BMS who reported dry mouth feelings. Differences in e.g., the study designs, saliva collection methods, inclusion and exclusion criteria for the patients, and selection of outcome measures may be the reason for deviating finding among studies.

3.5.3 Salivary constituents in relation to BMS

Salivary composition in BMS has been previously reported [21, 30] showing quantitative differences in total protein, sIgA [60], albumin and amylase between BMS patients and controls [141]. Initial explorative analysis (own unpublished data) showed no difference in salivary total protein, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), Interleukin-8 (IL-8) and sIgA between patients with BMS and the age matched controls. Immunological factors e.g. different cytokines and interleukins as well as endocrine has previously been reported to deviate between BMS patients and controls in some studies [150-152] but not in all [99, 153]. Sub-group of patients with BMS included in the thesis, revealed a higher concentration of cystatin SN, as compared to the controls suggesting a low-level oral inflammation (unpublished observation). Patients with BMS displayed increased heterogeneity in the level of inflammatory biomarkers compared to controls in **Paper III**. These findings need to be validated in a larger cohort.

3.6 Oral mucosal blood flow

The microcirculatory changes in the oral cavity have been relatively unexplored [154], and oral mucosal blood blow in BMS patients has been reported in two studies but only in relation to pain in the orofacial area [155] and in relation to saliva (**Paper II**). In **Paper II**, there was no significant difference in the oral mucosal blood flows on the labial, lingual and buccal mucosa in patients with BMS, as compared with the controls. A significant negative association between the mucosal blood flow and lingual mucosal

saliva and whole saliva was observed in the controls. Further studies are needed to reveal the relevance of this observation.

3.7 Xerostomia, hyposalivation and medication

3.7.1 Xerostomia and hyposalivation

Xerostomia is a subjective dry feeling in the mouth. It is derived from the Greek words xeros, meaning "dry" and stoma meaning "mouth" [156]. Chronic xerostomia is a significant burden for many individuals [157, 158]. The clinical manifestations that are present with xerostomia are difficulties in swallowing, chewing, and speaking, and halitosis [131, 159]. The assessment of xerostomia usually involves a patient history, a dry mouth questionnaire [160] (**Papers I and II**) that enquires about symptoms, and an assessment of the salivary secretion. VAS is a supplementary tool that reflects the severity of dry mouth experienced by affected individuals. Reported xerostomia is one of the common findings in patients with BMS [21]. The prevalence of xerostomia is in the range of 5.5%-46% in a general population [158], and 39%-75% in patients with BMS [5, 21] (**Papers I and II**). The xerostomia reported by patients in **Paper I** was more severe than that reported by the control subjects. The questions asked in relation to xerostomia are presented in Table 4 and are inspired from Fox *et al* [161].

Table 4. Assessment of xerostomia with a questionnaire and a VAS scale.

Number	Question about	Response alternatives and follow-up questions
29	Does the amount of saliva in your mouth seem to be too little?	Yes/no. If no, go straight to question 36
30	How often does your mouth feel dry?	Daily, many times/week, sometimes/week, sometimes/month
31	When diurnally do you experience dry mouth?	Always, nearly always, mostly at night, mostly in the morning, mostly during the day, mostly in the evening, varies
32	Rate your dry mouth experience	A VAS ranging from 0 mm to 100 mm where 0 corresponds to "no problem at all" and 100 to "unbearable"
33	How long have you been suffering from dry mouth?	Specify time period
34	Does your mouth feel dry when eating a meal?	Yes, no
35	Do you have difficulties swallowing dry foods?	Yes, no
36	Do you sip liquids to aid swallowing dry food?	Yes, no

Question number 29, was the primary basis for xerostomia in the **Papers I and II.**

Hyposalivation and xerostomia are not necessarily congruent phenomena. While xerostomia is a subjective term, hyposalivation is an objective measure of the salivary secretion, whereby the UWS is ≤0.1mL/min and the SWS is <0.7mL/min or ≤0.7mL/min [136]. In this thesis, a flow-rate of ≤0.7mL/min is considered hyposalivation. Patients with ≤0.1mL/min UWS and/or ≤0.7mL/min SWS were regarded as having hyposalivation, which was reported by some of the patients with BMS (**Paper II**). Hyposalivation is known to increase with age, which in turn has been related to the use of increased medications [158]. More patients with BMS than controls used prescribed medication and reported having diseases and disorders (**Papers I and II**). Patients with BMS also suffered from other comorbid diseases/disorders requiring medication [162] (**Paper I**). The controls were not allowed to have serious diseases and disorders in the inclusion criteria. Although the effect of medication, systemic diseases and the whole saliva flow-rate on xerostomia could be seen on the group level, these were not significant contributing factors for the patients with BMS, when analysing the patients only (**Paper II)**. On the contrary, although fewer controls experienced xerostomia compared to the patients, xerostomia experienced by the controls tended to be associated with the intake of medication and especially medication with reported-adverse effect on saliva in **Paper II**. It is also note-worthy that both patients and controls who were not taking medicines and who had normal salivary secretion also reported having xerostomia (**Paper II**). A brief overview of reported hyposalivation and xerostomia in patients with BMS is presented in Table 5.

Table 5. Prevalence of xerostomia and hyposalivation in patients with BMS

Study	Participants (Sex)		Age (±SD)		Hyposalivation				Xerostomia	
					UWS N (%)		SWS N (%)		N (%)	
	BMS	Controls	BMS	Control	BMS	Control	BMS	Control	BMS	Control
Paper II	56[1]	56[1]	67.8±8.82	67.7±8.48	26 (46.4)	13(23.2)	13(23.2)	2 (3.6)	42 (75)	11(19.6)
YC Lee *et al* [143]	27[1], 6[2]	27[1], 3[2]	(65±11.1)	(61.1 ±9.0)	23 (69.7)	-	15 (45.5)	-	10(30.3)	-
Imura *et al* [60]	15[1]	30[1]	(55±6)	(52 ±3)	-	-	-	-	10(66.7)	-
Grushka [21]	84[1],18[2]	36[1],7[2]	59.1±10.2[1] 52.2±11.5[2]	58.1±7.5[1] 47.7±13.8[2]	-	-	-	-	54(63)	27(19)
Soares *et al* [37]	37[1],3[2]	-	63±11.8		47.5%	50%	10%	12.5%	75%	45%
Das *et al* [145]	53[1],11[2]	-	61.63±10.77		-	-	-	-	40(62)	-
Bergdahl and Bergdahl [20]	42[1], 11[2]	-	-	-	-	-	-	-	35(66)	-

[1]Female, [2]Male

3.7.2 Effects of medication on xerostomia and hyposalivation

Dry mouth feelings linked to hyposalivation may result from the use of saliva affecting, xerogenic drugs [114, 163]. Many studies that have reported on medication-induced dry mouth feelings have only referred to subjective oral dryness experienced by the patients and have not taken into account the objective salivary flow-rate. Furthermore, medication-induced xerostomia has been associated not only with the type but also the number of medicines being taken. Medications such as anti-hypertensives (e.g. β-blockers), sedatives, tranquilizers and anti-psychotics are xerogenic [114]. Patients with BMS are commonly medicated [164] (**Paper I**). Xerogenic medication is known to reduce the salivary secretion by acting on the acinar cells [165]. The effect of medication on UWS in the patients with BMS has been described previously [8]. The number, type and dosage of medication are known to affect both the saliva flow-rate and the feeling of dry mouth [104, 114]. A systematic review has shown that the frequency of xerostomia is related to the dose and number of medications with a higher risk of xerostomia occurring at advanced age as a result of medication intake [163]. The same study reported medication-induced xerostomia as being more prevalent among women than men, which also holds true for BMS cases. The proportions and type of medicines taken by the patients with BMS and controls included in the current thesis are depicted in Figure 8.

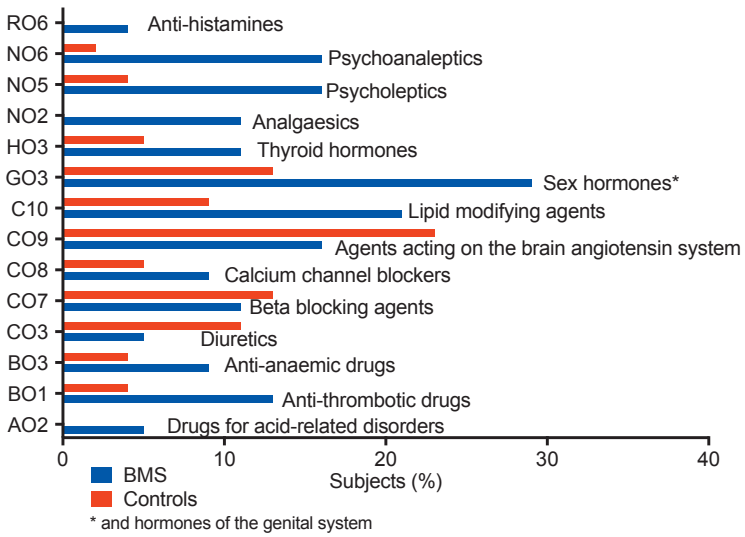


Figure 8. Proportions of different categories of drugs taken by the patients with BMS and by the controls included in the work of thesis. The three-digit code presented here is the ATC (Anatomical Therapeutic Chemical Classification System) code for the registered drugs.

3.8 Mucins and the oral cavity

The epithelial surfaces of the body including the oral epithelium are covered by a protective secretion known as mucous, which plays a key role in the host mucosal defence [166]. The mucous is highly hydrated and contains prominent macromolecules known as mucins. Mucins in saliva are contributed by submandibular and sublingual glands and most importantly by the minor salivary glands located in the oral cavity [134]. The mucous and serous cells from the submandibular glands secrete 30% of the salivary mucins, while sublingual, labial and palatal glands that mainly contain mucous cells secrete 70% of the mucins [167, 168]. Dryness of the oral mucosa, burning sensation in the mouth, difficulty with speaking, and formation of a food bolus have all been associated with qualitative or quantitative alterations in salivary mucins [169]. Mucins, in general, are high-molecular-weight glycoproteins that have a bottlebrush structure (Figure 9). The bottlebrush structure is due to the presence of the carbohydrate chains that are often clustered into highly glycosylated domains.

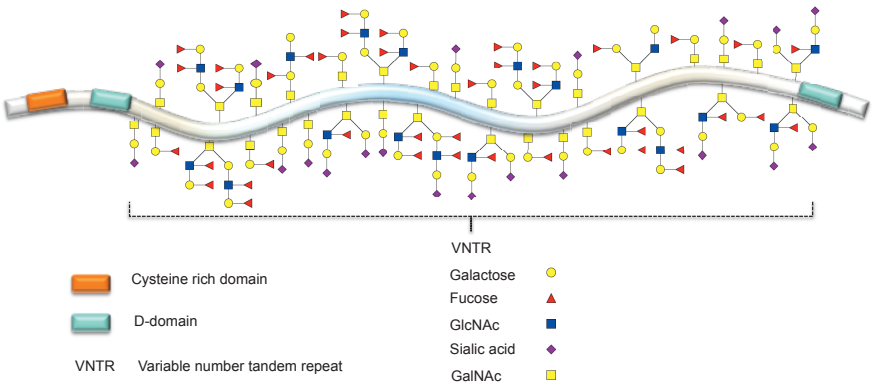


Figure 9. A generic schematic of bottlebrush structure of secreted gel forming mucin glycoprotein. The VNTR region is rich in serine, threonine and proline (STP) that is highly *O*-glycosylated. There is also the cysteine-rich region that aid in the formation of disulphide bonds and the D domains help in polymerisation for gel formation. Figure adapted and modified from [170].

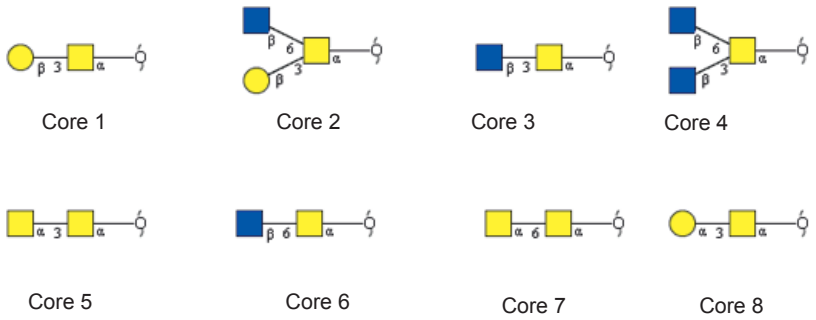
The mucins are categorised as: secreted (gel-forming and non-gel forming) and cell-surface bound mucins [171]. The mucins play a role in maintaining the viscoelastic properties of saliva and they actively participate in the bacterial aggregation and clearance from the oral cavity [169]. The lubricating property of mucins has been associated with the carbohydrate portion of the molecule [167], which facilitates the formation of a hydration shell [169]. The human salivary mucins comprise two structurally distinct species:

MUC5B (in-soluble, gel-forming), which was known as MG1; and MUC7 (soluble), which was known as MG2 previously [169]. The gel-forming MUC5B mucins are the main lubricating components of saliva [172]. MUC5B has been characterised as a high-molecular-weight mucin of more than 1 million Daltons (1MDa), consisting of about 78% carbohydrate [173]. MUC7 is smaller than MUC5B with molecular weight 150-200 kDa and contains about 68% carbohydrate [173]. Besides these classical mucins, salivary agglutinin is a mucin-like glycoprotein in the saliva that contains 45% carbohydrate, with 6% sialic acid and 12% fucose [174].

3.8.1 Mucin glycosylation

Glycosylation is a posttranslational modification that is highly conserved and almost 50% of all human proteins are glycosylated [175]. In the current thesis, sugar, glycan or carbohydrate would be used interchangeably where single carbohydrate units are termed, as monosaccharide and chain of 3-10 monosaccharide units constitute oligosaccharides. The salivary mucins are highly glycosylated glycoproteins that contain a wide variety of oligosaccharides [176]. There are two different types of glycosylation: a) *N*-linked glycosylation, whereby glycans are attached to the amide nitrogens of asparagine side-chains and b) *O*-linked glycosylation, whereby glycans are attached to the proteins via the hydroxyl group on serine or threonine residues. The *O*-linked oligosaccharides have three distinctive parts: the core, backbone, and peripheral regions [177]. The *N*-acetylgalactosamine (GalNAc) residue attached to the serine or threonine of the protein backbone and other sugar residues, directly linked to it constitute the core structure. The backbone region consists alternating Galβ1-3 and GlcNAcβ1-4/6 units that constitute i (linear) and I antigens (branched) [171]. *O*-linked glycans are highly heterogeneous and can vary in length with a range between 1-20 residues [171]. The peripheral regions of mucins contain individual monosaccharide such as galactose (Gal), fucose (Fuc), GalNAc, *N*-acetylglucosamine (GlcNAc) and sialic acid (NeuAc). The mucin structures can be further substituted with histo-blood-group antigens such as A, B, H, Lewis^{a} (Le^{a}), Lewis^{b} (Le^{b}), Lewis^{x} (Le^{x}), Lewis^{y} (Le^{y}), Sialyl-Lewis^{a} (Si-Le^{a}) and Sialyl-Lewis^{x} (Si-Le^{x}) structures [178, 179]. Sulphate is present linked to either Gal or GlcNAc. Sialylated and sulphated residues confer mucins a negative charge, which makes the mucin water-retentive together with the hydrophilic -OH groups of other monosaccharide residues [180]. In humans the expression of ABH and Lewis$^{y/b}$ antigens is found only in the secreted mucins (for e.g. in saliva) of "secretor" persons [171]. The *O*-linked glycans are highly variable in structure and the mammalian glycoproteins have at least eight different core structures. The most common core structures reported in saliva are core 1 and core 2 [181] (**Paper III**). A schematic of core structures along with different terminal glycan structures is presented in Figure 10 A and B respectively.

A



B

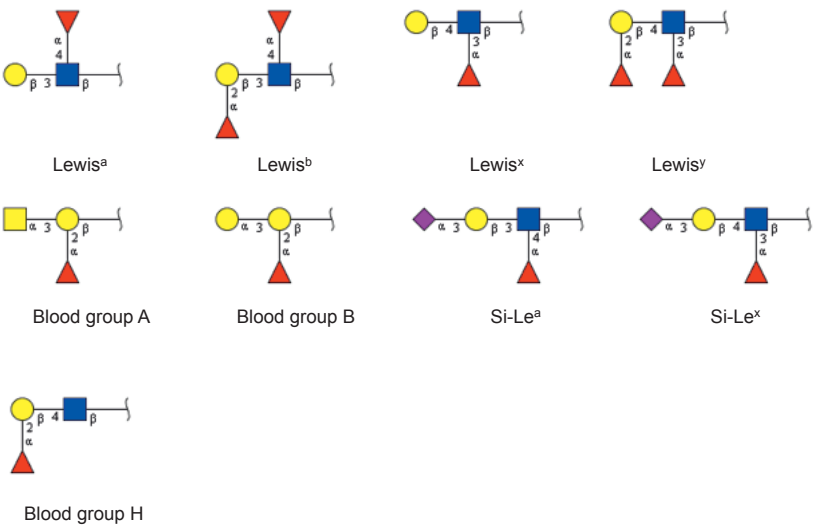


Figure 10. A schematic of: A) the eight different core structures B) terminal glycan epitopes.

Changes in glycan structure can occur through incomplete glycan formation during synthesis or through enzymatic degradation and may thus impact different disease processes. Protein glycosylation has a fundamental role in conditions such as inflammation and cancer [182] In Sjögrens syndrome, reduction in sulfo-mucin was observed and this may have affected the hydration property as the loss of negatively charged structures has been linked with reduced hydration along with altered rheological properties [183].

In **Paper III**, similar types of MUC7 oligosaccharides in patients with BMS patients and controls were found. The most common core structures found in both groups were core 1 and core 2 structures. The core 2 structures terminated with fucose or sialic acid. The presence of Si-Le^x, one of the terminal glycan in MUC7, was confirmed in **Paper III**. The levels of terminally fucosylated and sialylated oligosaccharide structures, especially, Si-Le^x were different between the patients with BMS and the controls (**Paper III**). The MUC7 mucin acts as a receptor for bacterial binding and Si-Le^x works as a ligand for selectins. Therefore, an individual who fails to express or expressed at a reduced level Si-Le^x in MUC7 may display a decreased leukocyte adhesion, presumably making this individual more prone to oral infection. Reduced Si-Le^x has been implicated in ulcerated conditions in the oral mucosa, such as RAS [184]. Morever, the reduced levels of sialylated structure could impair the rheological property of mucins in the patients with BMS. Thus, the altered terminal sugar epitope has a regulatory function and entails biological consequences.

3.8.2 Neutrophils and oligosaccharides

The oral ecosystem maintains homeostasis through an interplay that involves the oral microbiota, salivary biochemistry, and host immune factors [185, 186]. Neutrophils are a major component of the innate host response, constituting 40-60% of the white blood cells [187]. Neutrophils in the peripheral circulation can be diverted towards the mucosa and are an important component in maintaining oral homeostasis. Neutrophils are efficient phagocytes and deploy additional host-defence mechanisms by extruding DNA fibres in the process called as NETosis [188]. The extravasation (from the circulation into tissues) of polymorphonuclear leukocytes (neutrophils plus basophils and eosinophils) during inflammatory episodes involves a complex series of cellular adhesive interactions and signalling events [189]. Si-Le^x plays an important role in the leukocyte extravasation into inflamed tissues by serving as the ligand for E- and P-selectins [190, 191]. The role of neutrophils in oral mucosal diseases has been studied in diseases such as RAS and Behcet's disease [192]. Mohanty *et al* observed a reduction in the amount of Si-Le^x, and the ability of to form NETs associated with periods of ulceration in RAS [192]. Reduced levels of Si-Le^x in RAS [184] and in BMS (**Paper III**) was found. Saliva has been suggested to produce NETs *via* Si-Le^x stimulation [192]. In our study, Si-Le^x standards failed to induce NETs, indicating that in our case Si-Le^x are taken up by neutrophils by endocytocis after binding to Siglec [193] in a pathway to actually supress NETosis.

4 Main methodologies

This section provides an overview of the inclusion and exclusion criteria for the patients and controls participating in this thesis and the rationale behind the choice of methods used.

4.1 Ethical considerations

Ethical considerations for studies involving human subjects are pivotal. The participants need to have the freedom to drop out at anytime during the study without any reason being given. Therefore, one needs to consider that there is a risk that participants will dropout, which must not affect the implementation of the study. The present study did not provide treatment measures for the patients with BMS, although they were grateful that their problems were taken seriously and that someone wanted to find an explanation for their problems. All the studies included in the thesis **Papers** (**I-III**) were approved by the Regional Ethical Review Board in Gothenburg, Sweden (Dnr. 368-19) and followed the ethical guidelines of the Helsinki Declaration. The participants were given written and oral information about the project and written informed consent was obtained from all of them. The identities of the patients with BMS and the controls were kept anonymous and the confidentiality of their data was respected throughout the studies.

4.2 Participants

The participants included in the studies of this thesis were women who had been diagnosed with BMS, mostly at the clinic of Oral Medicine in Gothenburg, Sweden. Men were not included since at start of BMS project, there were only three male patients diagnosed with BMS, which was too few to allow the analyses of gender-related differences. The detailed inclusion criteria for the female patients and controls are described in the **Papers I** and **II**. The control group consisted of age-matched women (±3 years) who were recruited from public and private dental clinics and staff working at the Institute of Odontology, Gothenburg. The exclusion and inclusion criteria for the patients with BMS and controls are briefly mentioned in Figure 11.

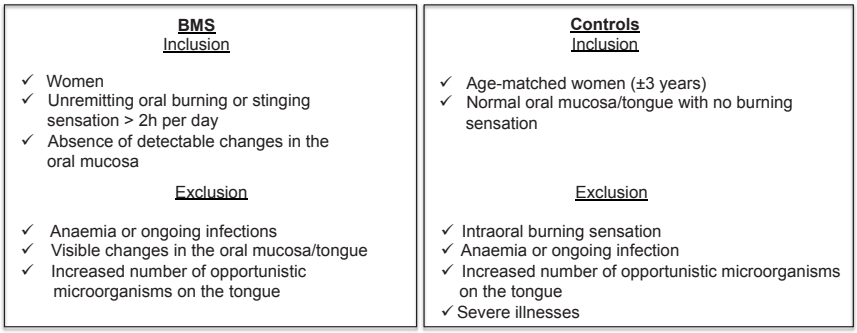


Figure 11. Inclusion and exclusion criteria for the patients with BMS and controls included in the studies of this thesis.

4.2.1 Haematological examination

All the women underwent a complete blood count (CBC) analysis to exclude abnormal blood values. CBC analysis usually involves counting the numbers of leukocytes (white blood cells) and erythrocytes (red blood cells) per unit volume in a sample of venous blood. CBC was performed to avoid any blood related anomalies for e.g anaemia or inflammatory marker changes. For instance, a high white blood cell count may indicate an infection. The subjects' laboratory results were compared to reference values, usually consisting of upper and lower limits. Abnormally low or high count of these leukocytes or erythrocytes may indicate signs of inflammation or even disease. Clinical signs of inflammation include increased serum levels of acute phase proteins such as C-reactive protein (CRP), which was also measured in all the participants. The parameters examined for haematological examination is presented in Appendix 1.

4.2.2 Microbiological examination

Scraping samples from the tongue were collected and analysed to exclude any opportunistic pathogens in high numbers that could contribute to the symptoms of BMS. Opportunistic organisms, such as *Candida spp*., *Staphylococcus aureus*, enterococci, *Pseudomonas spp*., and enteric rods occasionally occur in low numbers in the oral cavity of healthy individuals [194]. The presence of such opportunists in high numbers in relation to the oral-resident microbiota and especially to viridans streptococci, suggests dysbiosis, giving symptoms that mimic those of BMS. The presence of opportunists was evaluated, and low numbers were detected in some patients and controls (Table 6).

Table 6. Opportunistic pathogens detected in 14 patients with BMS and 6 controls subjects

Microorganisms	Patients with BMS	Controls
Candida *spp*	4	3
Enterococci	-	1
Enteric rods	8	5
S. aureus	1	1
H. influenzae	1	-

Candida was found together with enteric rods in two controls and together with *S. aureus* in one control subject. Enteric rods together with enterococci were found in one control subject.

After the fulfilment of the diagnostic criteria a total of 56 patients and 56 controls (**Papers I and II**) was included in the thesis work. The strategy for inclusion of patients and controls in the study is illustrated in Figure 12. All the patients included in the project were diagnosed by an expert in Oral Medicine. In order to study a group of patients like those of BMS, the diagnosis and inclusion and exclusion criteria is of importance since they could affect the results even in explorative studies such as these.

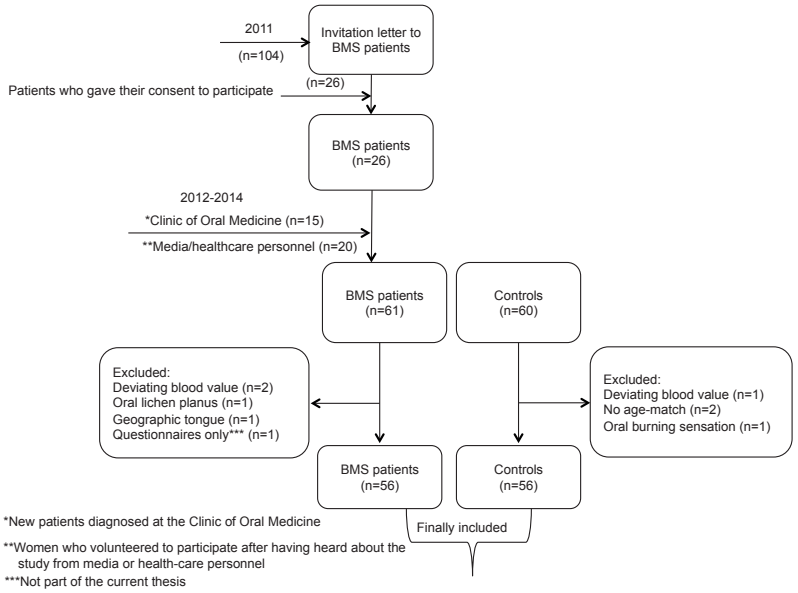


Figure 12. Flow-chart showing the selection process for the patients with BMS and the controls after adjustment for the inclusion and the exclusion criteria

4.3 Questionnaires

All cases and controls included in this thesis completed a general questionnaire and five psychometric instruments. There were two extra questionnaires for the patients with BMS, one concerning BMS-symptoms and one psychometric index regarding pain. In the current PhD project, which is a part of a larger BMS project, the general questionnaire, the BMS specific-questionnaire and one psychometric instrument (OHIP-14) were used (**Papers I and II**).

4.3.1 General questionnaire

The general questionnaire contained 39 questions often followed by supplementary questions related to how, when, why and which. Questions regarding socio-demographic status, physical activity, relationship status, medications, and diseases were included. The specific questions taken from the general questionnaire asked to the patients with BMS and controls are presented in Appendix 2 (in English) and the full general questionnaire is presented in Appendix 3 (in Swedish).

4.3.2 BMS questionnaire

The questionnaire specifically applied to the patients with BMS included 16 questions regarding the symptoms, associations connected to the debut of the symptoms, and other factors related to the syndrome. The questions that were posed to the patients with BMS were inspired by and modified from Bergdahl *et al* questionnaire [195]. The BMS questionnaire is presented in Appendix 4 (in English) and 5 (in Swedish).

4.3.3 OHIP

One of the psychometric instruments used today for measuring Oral Health Related Quality of life (OHRQL) is the Oral Health Impact Profile (OHIP-49) including 49 items [196, 197]. The OHIP-49 is divided into seven subscales that provide a comprehensive measure of functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. A short form of OHIP-49, known as OHIP-14 including 14 items to assess the OHRQL was used in the BMS project (**Paper I**). The Swedish version of OHIP-14 has been validated and found reliable [198, 199]. The responses to OHIP-14 are scored on a Likert scale (always, often, sometimes, seldom, never) resulting in a score of 14-70, with higher scores indicating poorer OHRQL. Given that BMS is a painful oral condition responses of the patients with BMS reflected a generally poorer OHRQL than the controls (**Paper I**). The OHIP questionnaire is presented in Appendix 6 (in English) and 7 (in Swedish).

4.4 Collection of whole and mucosal saliva

4.4.1 Whole saliva

The importance of saliva in health and disease is not disputed. The whole saliva, consisting of saliva, gingival crevicular fluid and the epithelial transudate has a rich content of biological substances. Saliva has therefore been used to study diseases such as cancer as well as autoimmune and endocrine diseases [200]. The role of saliva in oral mucosal diseases has been studied for Sjögren's syndrome, RAS, geographic tongue, and especially in studies related to pain [201, 202], but to a lesser extent for BMS. Here, the whole and mucosal saliva of patients with BMS were examined and compared to those of age-matched controls (**Papers II and III**).

The collection of whole saliva has not been standardised and is bound to limitations. The saliva secretion rate has a circadian rhythm [115, 203] with peaks during the late afternoon and drops to almost zero during sleep (Figure 3). Furthermore, *O*-glycosylation in human saliva significantly differed during the day [204]. It may therefore be important to standardise the time of day at which saliva is collected. To reduce any effects of diurnal variation, saliva was collected between 9 am and 1 pm and the participants were prohibited from eating or drinking 1 hour prior to saliva collection [205] (**Paper II**).

4.4.2 Mucosal saliva

The collection of saliva from the oral mucosa is rather complicated, as the saliva is viscous and secreted in small amounts. Methods using micropipettes, capillary tubes, and synthetic discs, and measuring coloured spots on chromatographic papers have been applied [206, 207]. The Periotron® instrument, which was originally designed to measure gingival crevicular fluid and later minor gland salivary flow and thickness [148, 208, 209] (**Paper II**), is considered to be reliable for minor fluid measurements in the clinical setting [210]. This method makes it possible to measure small volumes of fluids collected using absorbing paper, regardless of osmolarity and viscosity [211]. The Periotron instrument creates a voltage between two plates and measures the resistance of the salivary molecules in the filter paper. The volume collected in a 1-cm^2 pre-cut absorbing filter paper is determined from a standard curve obtained using known volumes of water added to the paper. For saliva measurements, the instrument was adjusted to zero using a dry filter paper, which was then placed on the oral mucosa after drying the mucosa with cotton swabs. The mucosa was dried so as to remove previously secreted saliva. However, it cannot be excluded that saliva remains even after drying and especially on the tongue with its crypts. Therefore we chose to report the mucosal volume of saliva rather than the

secretion rate (1/cm²/min) in the oral mucosa reported in other studies [208].

4.5 Proximity Extension Assay

The Proximity Extension Assay (PEA) was used to examine inflammation-related biomarkers, which could suggest an on-going inflammation processes that could differ in the patients with BMS and controls [212-214] (**Paper III**). PEA is based upon a pair of antibodies that are linked to unique oligonucleotides (proximity probes) that have affinity for one another. Upon binding the respective target protein, the probes come in close proximity and hybridise to each other. The hybridising oligonucleotides can be extended by use of DNA polymerase, and finally detected and quantified using quantitative Real-Time PCR. A schematic of the procedure for the PEA assay is given in Figure 13.

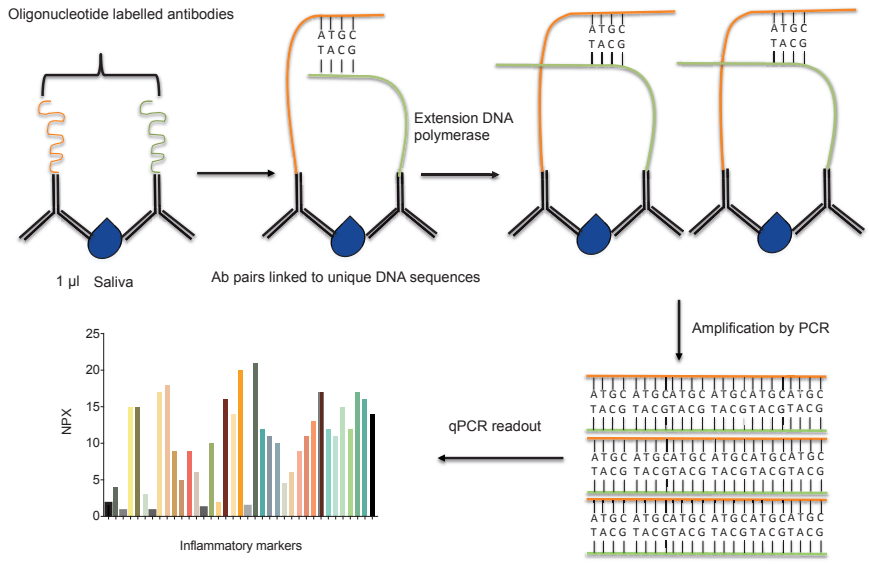


Figure 13. Schematic representation of the PEA assay. One microliter of saliva is incubated with the PEA probes, which have affinity for each other. The oligonucleotide probes hybridise, and are further extended by DNA polymerase and amplified by Polymerase Chain Reaction (PCR).

4.6 Oligosaccharide analysis

In this thesis, (**Paper III**) MUC7 glycosylation was compared between the patients with BMS and the controls using stimulated whole saliva samples. MUC7 oligosaccharides and not MUC5B analysis was prioritised as different MUC5B glycoforms can occur in the same glandular secretion reflecting extreme inter- and intra-molecular heterogeneity [215, 216]. Salivary MUC5B is also affected by the blood group and secretory status besides being heterogeneously glycosylated, making the analysis even more complex [217]. In contrast, salivary MUC7, is homogeneously glycosylated [218] (**Paper III**). In addition, MUC7 has been previously found to be similar in the SWS and UWS [219].

Glycans are one of the most structurally diverse molecules that are extensively being studied over the last few years [220] Carbohydrates also known as glycans consist of different monosaccharide units. The analysis of glycans, in analogy to genomics and proteomics is glycomics, which provides a comprehensive study of glycan composition and structure. Unlike proteins and nucleic acids the glycan biosynthesis is non-template driven, which means that the glycan structure is extremely heterogeneous [221, 222]. The carbohydrate part of the glycoprotein is responsible for the stability, activity, binding affinity, and specificity for other biomolecules, making analyses of the structures of carbohydrate analysis important in the field of glycoscience [222, 223]. The structural determination of carbohydrates (glycans) is challenging and demands highly sensitive methods. Isolation techniques such as Sodium dodecyl sulphate agarose polyacrylamide gel electrophoresis (SDS-AgPAGE) followed by electroblotting onto polyvinylidene fluoride (PVDF) membranes and staining by Alcian Blue allow the analysis of salivary mucin glycoproteins [184, 224] (**Paper III**). The MUC7 oligosaccharides can be released from the glycoproteins using chemical or enzymatic methods, and one of the common methods to release *O*-glycans uses reductive β-elimination (**Paper III**). Methods such as nuclear magnetic resonance (NMR) and X-ray crystallography can be used for large scale determination of oligosaccharides [225], while the highly sensitive method mass spectrometry [226] (**Paper III**) allows detection of small amount of released oligosaccharides. The released oligosaccharides can be desalted and analysed using Liquid Chromatography Mass Spectrometry (LC-MS) [227]. The analysis of derived glycans using the Xcalibur™ allows data visualisation for peak identification and quantification of relative glycan abundance [184, 227]. Manual interpretation of MS/MS as well as comparisons of the spectra can be done using the freely available UniCarb-DB software [228] (**Paper III**). A schematic of the glycomic workflow is given in Figure 14.

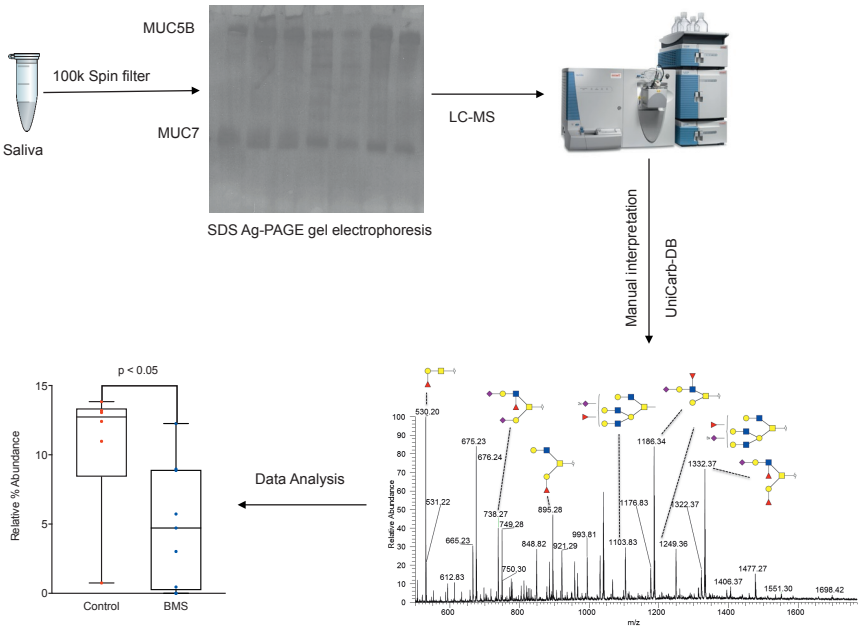


Figure 14. Schematic workflow for the analysis of *O*-glycans

4.7 Si-Le^x and release of NETs

The two common methods used to quantify NET release *in vitro* are DNA measurements of the supernatant fluids [229, 230] and visualisation of extracellular DNA by immunocytochemistry [229, 231, 232]. A study has shown that salivary neutrophils undergo saliva-induced NETosis *in vivo* elicited by Si-Le^x [192]. The results from **Paper III**, which includes reduced Si-Le^x level in BMS patients, encouraged us to test a method to determine if Si-Le^x standards could induce NETs. Si-Le^x standards did not induce NETs, which is in contrast to the findings from another study, where Si-Le^x from *N*-glycans stimulated released of NETs [192].

4.8 Data and statistical analyses

Data analysis is an important task in summarising the findings of scientific research into an understandable context. A power analysis for **Papers I-III** was not calculated and the studies may be regarded as power generating. The SPSS statistical package ver. 21.0 and ver. 23.0 (SPSS, Chicago, Illinois, USA) (**Papers I and II**), GraphPad Prism V.6.04 (GraphPad Software, La Jolla, California, USA) (**Paper III**) and SAS ver. 9.4 (SAS Institute Inc, Cary, NC, USA) (**Paper II**) was used for the descriptive statistics and the statistical

analyses. For the questionnaire data, full Likert scale was used in all the analyses, even when dichotomized. All the tests were two-tailed and the pre-chosen level of significance was $p < 0.05$.

An initial descriptive statistical analysis was done to find the difference between groups (**Paper I-III**). For the normally distributed data, i.e., following a Gaussians distribution that gives a bell-shaped curve, parametric tests, such as the Students *t*-test, were used for the continuous variables (**Papers I and II**). For the non-normally distributed data and ordinal scales, non-parametric tests (e.g., Mann-Whitney U-test) (**Papers I and III**) were used. The results are presented as percentages for the categorical variables (**Papers I and II**). For the continuous variables, the mean (standard deviation) or median (Min; Max) per group is presented (**Paper II**). For the purpose of comparison of proportions between groups, Fisher's exact test was applied. The Mantel Haenszel Chi square test was used for the ordered categorical variables in **Paper II**. For the purpose of comparison between more than two groups, one-way analysis of variance followed by Dunnett's multiple comparison *post hoc* test was applied (**Paper III**).

After completion of descriptive statistical analysis, further statistical analyses were carried out using multiple logistic (**Papers I and II**) and linear regression (**Paper II**), respectively. In **Paper I,** the multiple logistic regression group (BMS/Control) was used as the dependent variable and the significant variables from descriptive statistics were used as independent variables. In order to account for the potential confounders affecting salivary secretion and xerostomia, factors such as total number of drugs, use of drugs with a reported adverse effect on saliva (yes/no) and systemic disease, logistic regression was used with group as a dependent variable in **Paper II**. Multivariable linear regression was used to assess the variables that were significantly associated with UWS, SWS, buccal, labial and lingual saliva. Multiple logistic regression was used for the assessment of xerostomia in **Paper II**. The Odds Ratio (OR) and 95% confidence interval (CI) were calculated (**Papers I and II**).

5 Discussion

This part of the thesis explores the key findings from **Papers** (**I-III**), and simultaneously emphasises the relevance of the findings from our studies in context of other studies.

Paper I

This study included middle-aged to elderly women, in agreement with previous studies [22, 233]. The results from Paper I reveal that skin diseases and xerostomia are commonly associated with BMS. To the best of our knowledge, this is the first time that skin diseases have been associated with BMS. This finding adds to our existing knowledge on the characteristics of the patients with BMS. Xerostomia, on the other hand, is commonly associated with BMS [5, 21]. Almost half of the patients with BMS reported taste disturbances in agreement with other studies [5, 21]. BMS has often been associated with parafunctional habits such as lip and cheek biting, bruxism, and mouth breathing in many previous studies [14, 16, 70, 234]. However, in line with few other studies [89, 234], BMS was not found to be associated to parafunction, except for bruxism in the initial univariate analyses (Paper I). The discrepancy in the results regarding parafunctional habit may be explained by different methods e.g., diagnostic criteria used for BMS and parafunction, and lack of control group [14, 234]. In the univariate analysis, the patients with BMS reported having more allergies compared to the controls, which also has been addressed previously [17, 75]. In the multiple regression analysis, however, allergies were not found to have a significant impact on BMS. Patients with BMS in Paper I had less amalgam fillings compared to the controls as ten patients had exchanged their amalgam feelings with other dental materials. The symptoms prevailed even after the replacement, which suggests that amalgam fillings might not be a risk factor for development of BMS. This notion is supported in another study where, replacement of fillings did not relief the symptoms of BMS [71]. Patients with BMS also had more diseases and disorders, probably as a consequence of the inclusion criteria, and thereby also more medications. It is mostly likely that the cumulative effect of BMS symptoms and presence of other diseases and disorders is the reason why the patients rated their general and oral health poorer in comparison to the controls. The results from Paper I suggest that BMS is not a single entity disease but is instead comorbid with other associated factors. As the associations between comorbidities are not known, they warrant consideration in future studies.

Paper II

Saliva is of importance in maintaining the oral homeostasis. Therefore, saliva in BMS patients and factors affecting saliva was investigated in Paper II. Overall, lower levels of saliva on the lingual mucosa, UWS, SWS, and unaltered buccal and labial saliva was found in the patients with BMS, as compared to the controls. The lower levels of UWS and SWS were related to the usage of drugs and systemic diseases and not to BMS *per se*. More of the patients with BMS described to have subjective xerostomia than did the controls. The finding of less UWS accords with the results obtained in previous studies [8]. To the best of our knowledge, no previous studies have reported significantly reduced SWS in BMS. An increase in SWS has been reported in one study previously [30], which, however, included patients with fungal infection. Paper II revealed that significantly more patients with BMS had hyposalivation due to very low SWS secretion rate compared to the controls, which could not be explained by medication, age or systemic disease. It is well known that diseases, and especially medication, affect the salivary secretion, including the dosage and number of such medications [114]. Although medication was related to less saliva, it was not found to be a causative factor for xerostomia in the patients with BMS. On the contrary, drug usage tended to be associated with xerostomia in the controls. Other factors, for instance, psychological factors also need to be taken into consideration while assessing xerostomia. For instance, UWS hyposalivation and xerostomia were not only related to medication but also psychological factors such as anxiety, depression and stress [235].

Age

Old age and extent of medication are often related and they have important impacts on the quality and quantity of saliva [236, 237]. With increasing age come the consequences of, alteration in gland size. Both major and minor salivary glands undergo age-related structural changes, for instance loss of saliva producing acini cells. Some studies but not all have shown that the aging process leads to reduced salivary flow rate [237, 238]. According to a meta-analysis, aging results in a general decreased salivary flow-rate [239], which could always not be explained by medication. An age related reduced parenchyma of the salivary submandibular gland might implicate an impaired gland function resulting in reduced volume of saliva produced [237]. In Paper II, UWS (but not SWS) was affected by age in the patients. This differential effect may be due to SWS being mostly produced from the serous parotid glands. Aging might affect the salivary secretion in a gland specific manner where the more mucous submandibular and sublingual glands, which contribute most of the UWS, may be more affected by age [237]. Parotid gland, for instance remains stable in healthy non-medicated

people [240]. Saliva on the oral mucosa (labial, buccal and lingual) remained unaffected by age (Paper II) in contrast to other studies [239].

Comorbidity and medication

With increasing age, comes more ailments, such as diseases and disorders [241]. This in turn is indicative of a higher intake of medications, and even polypharmacy [242]. A previous study has shown that taking two more or medication can affect salivary secretion [8]. Additionally, it has been reported that some drugs might not have an affect on saliva when taken individually but exhibit xerogenic effect when used in combination [104, 242]. In our study, patients with BMS also took medicines, not prescribed by the physicians. Whether such preparations in combination with other drugs could affect the salivary flow-rate is not known. Patients with BMS used drugs such as psychoanaleptics, psycholeptics, diuretic and analgesics, which may decrease the saliva secreted. Furthermore, many of these patients with BMS used drugs, with a known reported adverse effect on the salivary secretion. The drugs with a reported adverse effect on saliva actually affected the salivary secretion in both patients and the controls, in agreement with other studies [104, 236].

Xerostomia

A feeling of oral dryness does not necessarily reflect reduced salivary output [37]. This was further confirmed in the present study, where there were patients with BMS and controls who had a normal salivary flow-rate but nevertheless complained of xerostomia. There were also patients and controls with hyposalivation who did not complain of xerostomia, which is in agreement with previous studies [37]. Even if the quantity of saliva could not explain xerostomia it is possible that the quality of saliva is of importance and especially the lubricating and protecting salivary mucins [183, 243].

Paper III

In Paper III, an analysis of the overall mucin MUC7 glycosylation was performed to see, if glycosylation differed between the patients with BMS and the controls. Overall, the types of MUC7 oligosaccharides were similar between the patients with BMS and the controls. However, a significant reduction in levels of terminal sialylated and fucosylated structures such as Si-Le^x was found in patients with BMS in comparison to the controls. Reductions in Si-Le^x and NeuAc may lead to ineffective bacterial aggregation and oral clearance [134]. Inflammatory markers in the patients with BMS and the controls were also compared but no difference in the overall level of the markers was revealed. However, careful analysis of data suggested that the

patients with BMS represented a heterogeneous group as the inflammatory markers varied more within the BMS group compared to the control group. This suggests that subgroup of the BMS patients could arise from low-level inflammation in some cases, while non-inflammatory driven in others. This may be an effect of the increased low level inflammation reported to occur at various level due to aging [244].

It is possible that the subjective dryness sensed by the patients with BMS condition could be due to an inefficient lubrication of the oral mucosa as a result of reduced mucins and especially MUC5B. Reduced levels of MUC5B have been observed in patients with severe xerostomia [245]. The higher molecular-weight mucin MUC5B contains carbohydrates and has terminal sialylated and sulphated structure that retains large amount of water. Since MUC5B was not analysed at the structural level, it can only be speculated that this larger mucin may contribute to the dry mouth feelings. A significant reduction in the level of MUC5B in the UWS was observed in patients with OLP and the severity of xerostomia was correlated to the level of MUC5B in sera of the patients with OLP [246]. Exploration of MUC5B oligosaccharides is a potential target in BMS research in addition to the decreased Si-Le^x on MUC7 as we report in Paper III. Overall, Paper III suggests that BMS patients are of heterogeneous in origin in terms of inflammatory markers they display. It further provides us the knowledge that in future studies, provided a reliable diagnosis, these patients can be stratified into further subgroups, to achieve personalised based therapy. Study III was done one a smaller subset of patients with BMS. However, studies like these with smaller number of patients are valuable in establishing a basis for further hypothesis-driven research and this in turn would enable to further carry out research in a larger cohort of patients and controls.

6 Main findings

The main findings of the studies developed in this thesis are listed below, and an illustration of the overall significant findings is presented in Figure 15.

1. The most common pain sensation was a combination of burning and scalding sensation described by 37% of the patients with BMS, and 45% reported to experience taste disturbances (**Paper I**).

2. The severity of BMS symptoms measured on a VAS scale on average was 66 (± 19.7 SD). About 80% of the patients reported their symptoms to be present "always" and 66% patients reported to experience BMS symptoms both day and night (**Paper I**).

3. Significantly fewer BMS patients than controls rated their general, oral health and life situation as satisfactory (**Paper I**).

4. Higher proportion of patients reported to have skin diseases and xerostomia compared to the controls and the aforementioned factors were strongly associated to BMS (**Paper I**).

5. Patients with BMS displayed less saliva on the tongue, less whole saliva, and more hyposalivation compared to the controls (**Paper II**).

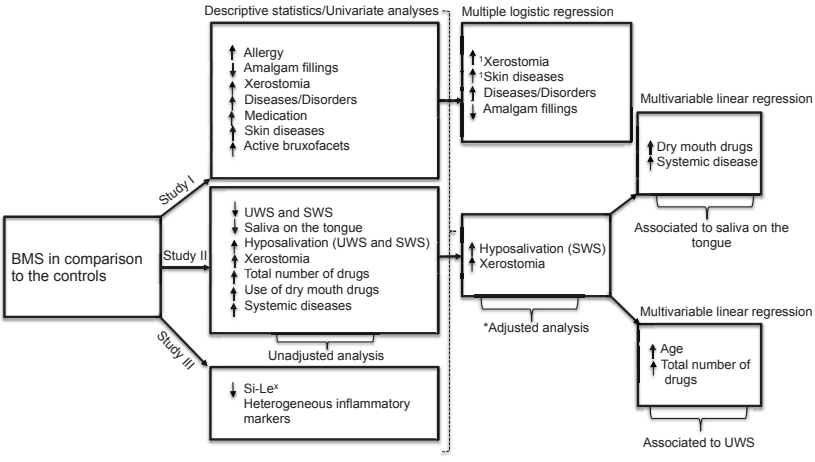
6. Less saliva in patients with BMS was related to more systemic diseases and medication (**Paper II**).

7. Hyposalivation with very low SWS secretion rate in the patients with BMS was not associated to diseases and medication (**Paper II**).

8. Xerostomia reported by BMS patients (**Papers I and II**) was not related to systemic diseases and medication (**Paper II**).

9. Similar MUC7 oligosaccharides but significantly decreased fucosylated and sialylated oligosaccharide (e.g. Si-Le^x) classes was seen in BMS (**Paper III**).

10. The level of inflammatory markers was more heterogeneous in BMS compared to the controls (**Paper III**).



[1]Strongest impact on BMS

*Adjusted for total number of drugs, use of dry mouth drugs and systemic diseases using multiple logistic regression

UWS= Unstimulated whole saliva; SWS= Stimulated whole saliva

Figure 15. A schematic of the most significant findings from the work of this thesis **Papers (I-III).**

7 Conclusion and future perspectives

This thesis explores three aspects of BMS: patients' described and clinical characteristics, saliva secretion, and mucin component in saliva. BMS is a condition of diagnosed through exclusion, and therefore elucidating the clinical and socio-demographical/background characteristics of patients with BMS arms us with a better understanding of the condition. The findings from the explorative studies in this thesis provide the basis for defining the clinical and salivary parameters in BMS, which may contribute to a future model for BMS. Xerostomia and skin diseases are significant findings in this study. Another interesting finding is that BMS was not related to parafunction.

Accounting for potential confounding factors, such as age, total number of drugs, and drugs having a reported adverse effect on the salivary secretion and oral mucosal blood flow, allowed a comprehensive comparison of the saliva of patients with BMS and controls. Although xerostomia was strongly associated to BMS, the factors such as medicines and systemic diseases did not have an impact in BMS group. Further studies are needed to elucidate whether other factors than objective salivary flow-rate, medicines and systemic diseases would affect xerostomia. Salivary constituents from the minor salivary glands, e.g., MUC5B and sIgA, are important for mucosal hydration/lubrication and mucosal immunity, respectively, and they are of interest to examine in patients with BMS and controls. In addition, results from work described in current thesis encourages us to carry out the inflammatory biomarker analysis on a larger cohort of patients with BMS with a wider age range, that in the future may aid in the classification of inflammatory and non-inflammatory driven BMS. This could increase our knowledge on the effect of inflamm-aging in BMS. Furthermore, reduced sialylated structures, such as Si-Le^x, may suggest ineffective hydration of the oral mucosal surfaces.

While not life threatening, BMS is a debilitating condition for the patients and different group of people show different symptoms. A thorough understanding of the pathogenesis and aetiology of BMS, along with novel diagnostic methods and development of therapeutic interventions is necessary for the management of BMS. Even if the present studies are well designed in terms of using age- and sex-matched case-controls, the results cannot be applied to a general population because men were excluded. Thus, the findings presented in this thesis not only provide new knowledge, but also raise new and interesting questions in the field of BMS.

8 Acknowledgements

I would like to thank everyone who have accompanied in my PhD journey. I have thoroughly enjoyed this "roller-coaster" ride of my PhD studies and I am grateful for this learning process both on scientific and personal level.

Special thanks goes to my enthusiastic supervisors: **Niclas Karlsson** and **Anette Carlén** for the support and guidance. **Niclas** thanks for giving me the scientific freedom but at the same time continuing to provide me your valuable feedback, advice, encouragement and for all the social activities in our "Glycogroup". I truly admire your problem-solving skills and your way to view science from different angles. Thank you so much for sometimes pushing me outside my "comfort zone". It has moulded me to get ready for new scientific adventures. **Anette**, thank you for all the scientific support you have provided throughout these years and always having the time for my queries. Your door has always remained open to my petty queries to major ones. I truly value your eye for details and effectiveness. I am very thankful to my co-supervisor **Catharina Hägglin** for the mentorship and valuable suggestions throughout my PhD studies and for your warm and welcoming personality. In addition to our academic collaboration, I greatly value the "outside" academia activities that we have forged over these years. I would like to extend my gratitude to my co-supervisor **Mats Jontell**, for sharing your knowledge and valuable advice. You view on BMS project has widened my horizon. Thanks to all my four supervisors for "putting me back to track" whenever my scientific journey derailed.

My profound gratitude goes to my co-authors **Jörgen E**, **Bengt W** and **Johan B**. You all have put on your valuable input in one way or the other to the work presented in my thesis. I appreciate all of your advices. **Jörgen**, thanks for sharing your expertise in saliva/drugs and your willingness to answer all my queries. **Bengt**, thanks for your guidance during algometer and Laser Doppler measurements. **Johan,** thank you for your top-notch and most importantly very constructive feedback on my all queries. I feel like I come out much "wiser" after every conversation with you no matter what the topic of conversation is about.

I am grateful to **Mari S**, for introducing me to the whole new world of human taste perception and your tremendous hospitality during my stay in Turku. I admire your enthusiasm for sensory science and I am deeply moved by your intellectual and team-building skills.

Dozens of people have helped and taught me immensely at both Institute of Odontology and Institute of Biomedicine. I am truly inspired by office mate and a great friend **Halla B**. I am so lucky to have met you. I am motivated by your work skills and your positive/calm attitude in every situation and surrounding. You are a very down to earth person in my eyes and have been truly influential in my academic journey. **Karin C** and **Agnes D.R.** you have been such great office mates providing me cheerful environment in the room. I admire our laughs from talking about "Påse", "pöse" jokes, "scissor" and "Tape" to all our lunch session in lyktan ;), and of course I thoroughly enjoy our discussion trying to "decode" mysterious dessert recipes at lyktan. I have truly enjoyed sharing office and enjoyed our scientific as well as non-scientific discussions with you. Three of you really made my work-days exciting. Thanks for bearing with my sometimes "stupid adventures/jokes". My days at work are filled with fun and positivity and there's nothing more I could have asked for.

Heartfelt thanks to **Amina B**, whom I got know since I started my PhD studies. Thank you for sharing kind offer to help whenever I needed and for the social activities during the first years of my PhD studies. We surely had fun! My deep appreciation goes to **Anna-Karin Ö**, **Sara A**, **Anna A** and **Anna L** for all the *fika* moments and the positivity you spread. The academic journey wouldn't have been fun without all of your support. **Alicia B**, thank you so much for your generous support in the last months of my PhD. Your support and willingness to help definitely made these challenging days fun.

My sincere gratitude goes to **Peter L** and **Gunnar D**, you two have been so inspirational and positive and always answered my queries. Thank you **Ulf D**, for sharing some interesting discussion and of course sharing 100 movies to watch before I die and not to mention all the apple gadgets. Special thanks to **Annica A**, **Ulf Ö**, **Charlotte S**, **Birgitta L**, **Kerstin W**, **Felix K**, **Haidar H**, **Georgios C**, **Cajsa F**, **Cecilia J**, **Inger V.B**., **Harriet H**, **Firoozeh**, **Hulya C.A.**, **Lisa D**, **Erika P**, **Ulrika A**, **Sahal A**, **Heba H**, **Amal D** and **Ali A** for kindness you have bestowed upon me. You all have created beautiful environment in our lunchroom. I would like to further acknowledge **Susanne B**, **Lisbeth B**, **Gunilla H** and **Ann-Britt** for your generosity throughout these years. Thank you **Marie A**, **Elisabet R** and **Sandra S** for all the administrative support and **Johan T** for the IT support.

Special thanks to **Emma** and **Ebru**, it has been such a good experience getting to know you from the beginning of PhD studies to the final defence. Thanks for keeping in touch throughout these years. Our lunch sessions have been inspiring.

Maria, thank you for being so thoughtful and kind to me throughout these years. I hope to keep in touch with you no matter which part of the world I will be at ☺.

I am grateful to **Bengt H** for your valuable input and inspiring discussions in the journal club at Oral Medicine. You are so insipiring and positive person and it reflects in your personality from the journal club to simple "hi" in the corridor.

Thank you **Vincent Collins** for proof-reading the frame.

I would like to thank our *Glycogroup* for such amazing atmosphere scientfically and socially as well. I would like to thank my co-author and a true *glycoguru* **Jin** that taught me everything about the glycans. Your technical expertise is deeply appreciated. Thank you for your continuous support and patience for having me throughout the years. As I always say, there is no other Jin. Being so knowledgeable and remaining extremely humble is what I truly admire about you. A big thanks to *B1* and *B2* (**Barbara A** and **Varvara V**), *Jessfika* (**Jessica Ö**), **Shan H** for your continuous support academically and for the fun-times we shared. Dr. Sombrero (**Miguel R**), thank you for being there to help whenever I needed, especially the fun while introducing Mexican and nepalese way of making posters, and also for all those fun discussions regarding different cuisines. Thanks to, **Tina T**, **Yolanda M** and **Vignesh V** for your encouragement and tremendous support. I would also like to thank all of the members from **Sara L** and her group and **Gunnar H** and his group. Special thanks to **Claes W** for generously providing me MUC5B and MUC7 antibodies. I wish to express my gratitude to **Camilla G** for the support during my first months of meeting BMS patients. Special thanks to **Anna H** and **Emelie S** for the parafunction data presented in table 2 in this thesis.

I am indebted to my dear friends **Jessica** and **Kalle** who have made my stay in Sweden more like home. Thanks for all the support from my times in Örebro and never-ending friendship. Thanks for giving me "Lisebergs" experience in gruvan ☺. Our lovely team in Örebro: **Claudia P**, **David R**, **Axel G**, **Åsa W**, **Åsa L**, **Dawei**, **Camilla**, "**Kattis" M**, **Dana**, **Daniel**, **Oskar**, *Luka* (**Stefan**), **Florian**, *Autogrill* (**Artin**) and **Jenna D** ☺.

I am grateful to my lovely friends in "*Awesomeborg*"(Gothenburg) (you all know who you are). Thanks for all your support throughout these years.

To our nepalese (*ish*) group in Gothenburg: **Mani**, **Suvash**, **Ina**, **Ena**, **Niranjan**, **Suman** and **Sandhya**. Thank you for all those nepalese dinners for not making me miss home and those laughters.

I would like to express my gratitude to all the participants in the BMS project. Thank you for your patience during all the studies and your enthusiasm in participation.

To **TUA Research Funding** (TUAGBG-66851, TUAGBG-289931 and TUAGBG-627791)

I would like to finish my acknowledgement with thanking my family for their unconditional love and support and keeping the faith in me in all circumstances. Thank you *bunu* **Rija Acharya,** *buwa* **Thagendra Prasad Acharya** and *mommy* **Sarita Acharya**. Three of you are the source of inspiration in my life and my eternal sunshine ☺

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10 Appendices

Appendix 1. Complete Blood Count (CBC)

Component	Unit	Reference range
Reticulocytes	$x10^9/L$	20-100
Neutrophils	$x10^9/L$	1.8-7.5
Lymphocytes	$x10^9/L$	0.8-4.5
Monocytes	$x10^9/L$	0.1-1
Eosinophils	$x10^9/L$	0.04-0.4
Basophils	$x10^9/L$	0-0.1
Hb	g/L	117-153
LPC	$x10^9/L$	3.5-8.8
TPC	$x10^9/L$	165-387
EPC	$x10^{12}/L$	3.9-5.2
MCV	fL	82-98
MCH	pg	27-33
MCHC	g/L	317-357
S-CRP	mg/L	<5

Hb: Haemoglobin

LPC: Leukocyte particle count

TPC: Thrombocyte particle count

EPC: Erythrocyte particle count

MCV: Mean corpuscular volume

MCH: Mean corpuscular haemoglobin

MCHC: Mean corpuscular haemoglobin concentration

S-CRP: Serum C-reactive protein

Appendix 2. Specific questions asked to all the participants from the general questionnaire

Question no.	Question about	Response alternatives and follow-up questions	Paper
1.	Year of birth	-	I, II
2.	Relationship status	married, divorced, single, in relationship but living apart, cohabiting, widow	I
7.	Description of general health	very good, good, decent, poor, very poor	I
8.	Description of oral health	very satisfied, satisfied, neither/nor, unsatisfied, very unsatisfied	I
9.	Satisfaction with life situation	very good, good, decent, poor, very poor	I
11.	Diseases	yes, no. If yes, what diseases?	I, II
13.	Medication regularly	yes, no. If yes, which medicines?	I, II
14.	Menstrual periods regularly	no, has completely stopped; no, irregular; yes	I
15.	Postmenopausal symptoms	yes, have had; yes, have; no If yes, what type of symptoms?	I
16.	Have you been recommended oestrogen by your health-care giver?	no,yes; but haven't used, yes; but stopped using it, yes; I use it now	I, II
17.	Susceptible to infections	yes, no. If yes, what infections?	I
18	Skin diseases or skin problems	yes, no. If yes, which ones?	I
19.	Symptoms from genital mucosa	yes, no. If yes, which ones?	I
21.	Allergy	yes, no. If yes, to what are you allergic ?	I
23.	Smoking habits	never smoked, stopped (year), smoke sometimes, smoke everyday	I
24.	Physical activity at least 30 mins/day	days per week (1,2,3,4,5,6,7)	I
25	Sleep disturbances	yes, no. If yes, how often? Sometimes/month, sometimes/week, nearly every night, every night	I
37	Pain while taking blood from finger	0-100, where 0 corresponds to "no pain at all" and 100 relates to "terrible pain"	I, II

Appendix 3. Allmänt frågeformulär

1. Födelseår:_____

2. Civilstånd:

❒ Gift ❒ Skild ❒ Singel ❒ Särbo ❒ Sambo ❒ Änka/änkling

3. Har ditt civilstånd förändrats de senaste 10 åren?

❒ Ja ❒ Nej

4. Huvudsaklig sysselsättning de senaste 10 åren
(ex. typ av arbete/arbetslös/pensionär/sjukskriven)?

_____

5. Bytt sysselsättning de senaste 10 åren (ex. bytt arbete/ blivit arbetslös/ blivit pensionär/ blivit långtidssjukskriven)?

❒ Ja ❒ Nej

6. Har du varit sjukskriven under den senaste 10-års perioden?

❒ Nej
❒ Ja, vid något enstaka tillfälle
❒ Ja, några enstaka dagar då och då
❒ Ja

7. Hur skulle du beskriva din allmänna hälsa just nu?

❒ Mycket god ❒ God ❒ Skaplig ❒ Dålig ❒ Mycket dålig

8. Hur skulle du beskriva din munhälsa just nu?

❒ Mycket god ❒ God ❒ Skaplig ❒ Dålig ❒ Mycket dålig

9. Hur nöjd är du med din livssituation?

❒ Mycket nöjd ❒ Nöjd ❒ Varken eller ❒ Missnöjd ❒ Mycket missnöjd

10. Anser du dig fullt frisk?

❒ Ja ❒ Nej

11. Har du någon eller några sjukdomar?

❒ Ja ❒ Nej

Om ja, vilken eller vilka?

12. Har du haft några allvarliga sjukdomar?

❒ Ja ❒ Nej

Om ja, vilken eller vilka?

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13. Tar du regelbundet mediciner (även naturläkemedel, östrogenpreparat, p-piller etc)?

❒ Ja ❒ Nej

Om ja, vilken eller vilka?

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14. Har du regelbunden menstruation?

❒ Nej, slutat helt ❒ Nej, oregelbunden ❒ Ja

15. Har du eller har haft övergångsbesvär?

❒ Ja, har haft ❒ Ja, har ❒ Nej

Om ja, vilken typ av besvär?

---

16. Har du av din vårdgivare blivit rekommenderad östrogenbehandling för övergångsbesvär?

❒ Nej ❒ Ja, men ej använt ❒ Ja, men slutat ❒ Ja, använder nu

17. Anser du dig vara infektionskänslig?

❒ Ja ❒ Nej

Om ja, hur yttrar det sig?

---

18. Har du några hudsjukdomar eller hudbesvär?

❒ Ja ❒ Nej

Om ja, vilken eller vilka hudsjukdomar? Om hudbesvär, hur yttrar det sig?

---

19. Har du några besvär i underlivets slemhinna?

❒ Ja ❒ Nej

Om ja, hur yttrar det sig?

---

20. Går du på regelbundna vårdkontroller?

❒ Ja ❒ Nej

Om ja, vilken form av vårdkontakt och hur ofta?

21. Är du allergisk mot något?

❒ Ja ❒ Nej

Mot vad? _____

22. Är du överkänslig mot någon medicin?

❒ Ja ❒ Nej

Om ja, vilken/vilka? _____

23. Vad har du för tobaksvanor?

❒ Jag har aldrig vanerökt
❒ Jag slutade röka år:_____
❒ Jag röker ibland
Antal cig./vecka om du inte röker dagligen?_____
❒ Jag röker dagligen
Antal cigaretter/dag?_____

24. Hur många dagar per vecka är du fysiskt aktiv i sammanlagt 30 min?
(t.ex. promenad i rask takt)

❒ 1 dag ❒ 5 dagar
❒ 2 dagar ❒ 6 dagar
❒ 3 dagar ❒ 7 dagar
❒ 4 dagar

25. Har du sömnproblem?

❒ Ja ❒ Nej

Om ja, hur ofta?

❒ någon natt/mån ❒ någon natt/vecka ❒ nästan varje natt ❒ varje natt

26. Snarkar du när du sover?

❒ Aldrig ❒ Sällan ❒ Ibland ❒ Ofta ❒ Alltid ❒ Vet ej

27. Andas du generellt sett mest genom munnen?

❒ Aldrig ❒ Sällan ❒ Ibland ❒ Ofta ❒ Alltid ❒ Vet ej

28. Upplever du att din urin är koncentrerad (stark lukt, kraftigt färgad)?

❒ Aldrig ❒ Sällan ❒ Ibland ❒ Ofta ❒ Alltid ❒ Vet ej

29. Händer det att det känns som mängden saliv i munnen är för liten?

❒ Ja ❒ Nej

Om du svarat "nej" så hoppar du till fråga 37:

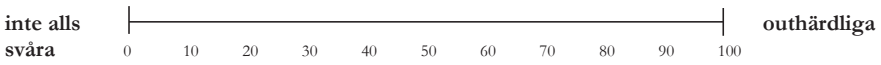
30. Hur ofta är du muntorr?

❒ Dagligen ❒ Flera ggr/v ❒ Någon ggn/v ❒ Någon ggn/månad

31. När på dygnet är du muntorr?

❒ Alltid
❒ Nästan jämt
❒ Mest på natten
❒ Mest på morgonen
❒ Mest mitt på dagen
❒ Mest på kvällen
❒ Varierar

32. Hur svåra är dina muntorrhetsbesvär? *Markera med kryss på linjen.*



33. Ungefär hur länge har du lidit av muntorrhet?_____

34. Upplever du att muntorrheten är ett problem när du intar en måltid?

❒ Ja ❒ Nej

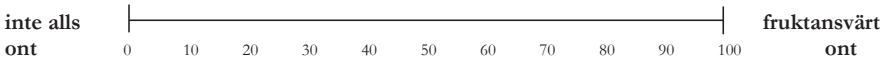
35. Har du problem att svälja föda som är torr?

❒ Ja ❒ Nej

36. Behöver du dricka för att kunna svälja?

❒ Ja ❒ Nej

37. Hur ont tycker du att det gör att ta ett blodprov i fingret? *Markera med kryss på linjen.*



38. (frågan kommer sist)

39. Hur ofta och hur länge har Du haft något av följande besvär?

	Aldrig eller sällan	**1-2 ggr per månad**	**Någon ggn i veckan**	**Några ggr i veckan**	**Dagligen**
A) Trötthets/stelhetskänslor i käkarna	❒	❒	❒	❒	❒
B) Käkledsknäppningar	❒	❒	❒	❒	❒
C) Skrapljud från käkleden	❒	❒	❒	❒	❒
D) Smärtor eller värk i ansikte och käkar	❒	❒	❒	❒	❒
E) Huvudvärk	❒	❒	❒	❒	❒
F) Smärtor vid rörelse av käken (gapa, tugga)	❒	❒	❒	❒	❒
G) Svårt att gapa stort, gäspa el. bita stor tugga	❒	❒	❒	❒	❒
H) Käken hoppar ur led, hakar upp sig el. låser sig	❒	❒	❒	❒	❒
I) Tandvärk	❒	❒	❒	❒	❒
J) Ilande och ömma tänder	❒	❒	❒	❒	❒
K) Migrän	❒	❒	❒	❒	❒
L) Yrsel	❒	❒	❒	❒	❒
M) Öronsusningar	❒	❒	❒	❒	❒
N) Tung- eller munsveda	❒	❒	❒	❒	❒
O) Besvär från nacken	❒	❒	❒	❒	❒
P) Ryggbesvär	❒	❒	❒	❒	❒
Q) Övrigt.: Vad?.....	❒	❒	❒	❒	❒

38. Hur ofta dricker du eller använder följande drycker och preparat?

	Aldrig eller sällan	1 gång/v	2-3 ggr/v	1 gång/dygn	2 ggr/dygn	3-5 ggr/dygn	>5ggr/dygn
Kranvatten	❒	❒	❒	❒	❒	❒	❒
Mineralvatten	❒	❒	❒	❒	❒	❒	❒
Saft	❒	❒	❒	❒	❒	❒	❒
Läsk	❒	❒	❒	❒	❒	❒	❒
Nyponsoppa	❒	❒	❒	❒	❒	❒	❒
Mjölk	❒	❒	❒	❒	❒	❒	❒
Äppeljuice	❒	❒	❒	❒	❒	❒	❒
Apelsinjuice	❒	❒	❒	❒	❒	❒	❒
Kaffe	❒	❒	❒	❒	❒	❒	❒
Te	❒	❒	❒	❒	❒	❒	❒
Vin	❒	❒	❒	❒	❒	❒	❒
Öl	❒	❒	❒	❒	❒	❒	❒

	Aldrig eller sällan	1 gång/v	2-3 ggr/v	1 gång/dygn	2 ggr/dygn	3-5 ggr/dygn	>5ggr/dygn
Annan dryck:……	❒	❒	❒	❒	❒	❒	❒
Saliversättnings-medel	❒	❒	❒	❒	❒	❒	❒
Tuggummi	❒	❒	❒	❒	❒	❒	❒
Sugtabletter	❒	❒	❒	❒	❒	❒	❒

Appendix 4. BMS questionnaire

Question Number	Question	Response alternatives and follow-up questions
1.	Describe your BMS symptoms	burning, scalding, numb, pricking
2.	Rate the severity of your BMS symptoms	VAS scale (0-100), where 0 corresponds to "no problem at all" and 100 corresponds to "extremely difficult to bear"
3.	How often do you feel your symptoms?	very rarely, rarely, very often, always (every now and then option in all cases)
4.	Diurnal symptoms of BMS	in the morning, during the day, in the evening, at night, during day and night
5.	Factors contributing to debut of BMS e.g. medicine, stress.	yes, no. If yes, what factors?
6.	Factors aggravating symptoms of BMS	yes, no. If yes, what factors?
7.	Factors relieving the symptoms	yes, no. If yes, which factors?
8.	Do you experience any taste changes?	yes, no. If yes, which ones?
9.	Do you have any other symptoms related to BMS?	yes, no. If yes, which ones?
10.	Debut of BMS symptoms	year
11.	Do you associate your BMS debut to any life situation?	yes, no. If yes, what/which situation?
12.	If BMS symptoms vary diurnally, when do they occur mostly?	in the morning, during the day, during evening, during night, both day and night, varies
13.	How long do the BMS symptoms last if you don't have them permanently?	hours, days, weeks, months or constantly
14.	How often do you have symptoms if not constantly?	times per day/week/month/year or constantly
15.	Did you receive any treatment for BMS that have had positive effect?	yes, no. If yes, which treatment?
16.	Do you have any family member/relative who suffers from BMS?	yes, no. If yes, who?

Appendix 5. BMS-frågeformulär

1. Hur yttrar sig dina BMS-symptom?

❒ Brännande ❒ Svidande ❒ Domnat ❒ Stickande

2. Hur svåra är dina BMS-besvär besvär (intensitet)? ***Markera med kryss på linjen.***

3. Hur ofta uppträder symptomen?

❒ Då och då, men mkt sällan
❒ Då och då, men sällan
❒ Då och då, men ofta
❒ Finns där alltid

4. När på dygnet brukar symtomen uppträda?

❒ På morgonen
❒ Under dagen
❒ På kvällen
❒ Under natten
❒ Både dag och natt

5. Är det några faktorer som kan starta symtomen ex föda, medicin, stress?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____

6. Är det några faktorer som kan förvärra symtomen ex föda, medicin, stress?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____

7. Är det några faktorer som kan lindra symtomen ex föda, medicin, stress?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____

8. Har du lagt märke till några smakförändringar?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____

9. Har du några andra symptom som du kopplar till din BMS?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____

10. När ungefär debuterade din BMS?

År: _____

11. Associerar du debuten av din BMS med någon speciell händelse (ex ny medicin, slutat röka, förändrad levnadsförhållanden, dödsfall)?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____ _____

12. Om symptomen varierar över dygnet, när på dygnet har du mest besvär?

❒ På morgonen
❒ Under dagen
❒ På kvällen
❒ Under natten
❒ Både dag och natt
❒ Varierar

13. Ungefär hur länge varar besvären om du inte har dem ständigt?

_____ timmar
_____ dagar
_____ veckor
_____ månader

❒ Jag har dem ständigt

14. Hur ofta har du besvär, om dina besvär inte är konstanta?

_____ gånger/dag
_____ gånger/vecka
_____ gånger/månad
_____ gånger/år

❒ Jag har dem ständigt

15. Har du fått någon behandling för dina besvär som haft positiv effekt?

❒ Ja ❒ Nej

Om ja, vilken/vilka?

_____

16. Har du någon anhörig eller släkting som lider av BMS?

❒ Ja ❒ Nej

Om ja, typ av släktskap? _____

Appendix 6. OHIP-14 questionnaire

Question no	During the past three months:	Response alternatives
1	Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
2	Have you felt that your sense of taste has worsened because of your problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
3	Have you had painful aching in your mouth?	never, hardly ever, occasionally, fairly often, very often
4	Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
5	Have you been self-conscious because of your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
6	Have you felt tense because of your problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
7	Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
8	Have you had to interrupt meals because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
9	Have you found it difficult to relax because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
10	Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
11	Have you been a bit irritable with other people because of your problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
12	Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
13	Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often
14	Have you been totally unable to function because of problems with your teeth, mouth or dentures?	never, hardly ever, occasionally, fairly often, very often

Appendix 7. **ENKÄT OM MUNHÄLSA OCH LIVSKVALITÉ (OHIP)**

Detta är frågor som syftar till att utvärdera i vilken utsträckning Ditt munhälsotillstånd påverkar Din allmänna livssituation.

Kryssa endast i ett alternativ per fråga. Exempel:	aldrig	sällan	ibland	ofta	mycket ofta
Har Du problem med att prata beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐

Under de senaste tre månaderna:		aldrig	sällan	ibland	ofta	mycket ofta
1.	Har Du haft svårigheter att uttala något/några ord beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
2.	Har Du känt att Dina smak-upplevelser har försämrats beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
3.	Har Du haft smärta från munhålan?	☐	☐	☐	☐	☐
4.	Har Du upplevt svårigheter att äta någon föda beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
5.	Har Du upplevt osäkerhet beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
6.	Har Du känt dig stressad beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
7.	Har Din diet varit otillfreds-ställande beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
8.	Har Du avbrutit måltider beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐

Vg vänd

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		aldrig	sällan	ibland	ofta	mycket ofta
9.	Har Du känt svårigheter att slappna av beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
10.	Har Du känt dig något genererad beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
11.	Har Du varit irriterad på andra människor beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
12.	Har Du haft svårt att genomföra Dina vanliga sysslor beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
13.	Har du känt att Din allmänna livssituation varit mindre tillfredsställande beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐
14.	Har det varit totalt omöjligt för Dig att fungera i det dagliga livet beroende på problem med Dina tänder, munhåla eller proteser?	☐	☐	☐	☐	☐

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