

## THE RELATIONSHIP BETWEEN BURNING MOUTH SYNDROME AND TREATMENT FOR THYROID DISEASES

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### Abstract

The study aims to evaluate a possible association between the characteristics of pain symptoms and thyroid disorders with specific thyroid replacement medication. Our results indicate a statistically significant association between the presence of thyroid disorders and a change in pain intensity over time. Thus, in 42.86% of all patients with associated thyroid disorders, pain intensity increased over time. We also found a correlation between the increase in the frequency of dysgeusia and the increase in the intensity of the pain symptoms. The administration of drugs for thyroid disorders was significantly associated with the presence of dysgeusia. Also, analysing whether there is a significant correlation between the medication administered for thyroid disorders and the evolution of pain intensity over time, it was observed that in 51.72% of patients with thyroid medication, the pain intensity increased from the onset of the disease *versus* 20.51% of patients without thyroid medication in whom the intensity of the symptom increased. In conclusion, endocrine disorders and specific medications may be responsible for changes in the taste system. The increase in the frequency of dysgeusia is correlated with the increase in pain intensity in patients with thyroid disorders.

### Rezumat

Scopul studiului a fost de a evalua o posibilă asociere între caracteristicile simptomatologiei algice și afecțiunile tiroidiene cu medicația substitutivă tiroidiană specifică. Rezultatele prelucrării statistice indică o asociere statistic semnificativă între prezența afecțiunilor tiroidiene și modificarea în timp a intensității algiei. Astfel, la 42,86% din totalul pacienților cu afecțiuni tiroidiene asociate, intensitatea algică s-a accentuat în timp. De asemenea, particulară studiului personal a fost constatarea existenței unei corelații între creșterea frecvenței disgeuziei și creșterea intensității simptomului algic. Administrarea de medicamente pentru afecțiuni tiroidiene este asociată statistic semnificativ cu prezența disgeuziei. De asemenea, analizând dacă există corelație semnificativ statistică între medicația administrată pentru afecțiunile tiroidiene și evoluția în timp a intensității algiei s-a observat că, la 51,72% din pacienții care prezintă medicație tiroidiană, intensitatea algiei a crescut de la debutul afecțiunii *versus* 20,51% din pacienții fără medicație tiroidiană la care s-a accentuat intensitatea simptomului. În concluzie, tulburările endocrine și medicația specifică pot fi responsabile de modificările sistemului gustativ, simptom frecvent prezent la acești pacienți. Creșterea frecvenței disgeuziei este corelată cu creșterea intensității durerii.

**Keywords:** burning mouth syndrome, thyroid disease, thyroid replacement medication, dysgeusia

### Introduction

Burning Mouth Syndrome (BMS) is a chronic condition with controversial etiopathogenesis, the diagnosis of which requires a systematic, multidisciplinary medical approach and an attitude of exclusion of other oral conditions with similar clinical manifestations [1-5]. BMS manifests as chronic localized pain in the oral cavity. It has been described by the International Headache Society (IHS-2018) as a recurrent "painful, burning intraoral sensation" that reappears daily for

more than 2 hours a day for more than 3 months and without noticeable causal lesions or modified laboratory tests [6-9].

It is more common in women in the pre-menopausal and menopausal period, with the ratio of women to men being 7/1 [7]. These symptoms are most commonly located in the lingual mucosa, especially in the anterior area. Patients most often complain, in addition to the burning sensation, of subjective xerostomia and altered taste sensation (dysgeusia) [10].

Although many experts have focused on it, non-specific oral pain still remains an entity that raises issues in terms of etiopathogenesis, diagnosis and treatment [11-15].

The International Association for the Study of Pain supports the neuropathological origin of oral pain along with the complex interaction between “local, systemic and psychogenic factors” with a probable cumulative and contributing effect (IASP, 2016). Possible causal systemic factors include endocrine disorders: diabetes, thyroid disease, menopause, hormone deficiencies and a number of classes of drugs (angiotensin-converting enzyme inhibitors, certain benzodiazepines, anti-thyroid drugs, antiretrovirals, anti-hyperglycaemics and chemotherapy) [16-19].

BMS can begin in various clinical settings, most often in the presence of systemic or local contributing factors. General ailments have an important predisposing role in the onset, manifestation and evolution over time of pain symptoms. Studies in the literature indicate that systemic pathology is involved to varying degrees in the occurrence of BMS: hypertension (33% of cases), gastroesophageal reflux (29%), hypercholesterolemia (22%), autoimmune diseases (22%), thyroid disease (14%) and anaemia (2%) [20]. Various studies have also attempted to examine the correlation between adverse drug reactions and BMS as a possible etiopathogenic factor [18, 21-23].

Many medicines induce taste disorders, but the mechanisms by which they alter the sense of taste are not well known. Anti-thyroid drugs can induce taste disorders due to their negative influence on the maturation of the taste buds and a reduction of taste receptors [24, 25].

The aim of this study was to evaluate a possible association between BMS and thyroid disorders and specifically associated medication, as well as to analyse the characteristics of the pain syndrome in these patients.

## Materials and Methods

The study was conducted within the Department of Oral Pathology Department, Faculty of Dentistry, “Carol Davila” University in Bucharest, Romania, between October 2014 and October 2018, on a group of 263 patients diagnosed with BMS. Thyroid disorders were present in 42 of the patients included in the study (15.97% of the total), mainly hypothyroidism, hyperthyroidism, and the presence of thyroid nodules.

At the time of the first consultation, only one sample of 29 patients (11.03%) was receiving specific medication for associated thyroid disorders. The difference (13 cases) was represented by those who were at that time under specialized medical observation.

The patients underwent a complex evaluation and met the established inclusion criteria.

Following the evaluation, which included anamnesis, general examination, oral clinical examination, laboratory

investigations and paraclinical tests, demographic and clinical data, as well as the results of paraclinical and laboratory investigations were collected in a standardized form (observation sheet).

Two “standard systems” for assessing the severity or intensity of pain, the Verbal Rating Scale (VRS) and the Visual Analog Scale (VAS), were used to assess pain intensity.

The descriptive verbal scale (VRS) is another method of pain self-assessment, which includes 5 qualitative steps, nominated by grades and more correctly by assessment areas using standardized adjectives: mild pain, moderate pain, severe pain, very severe pain (Figure 1).

None	Mild	Moderate	Severe	Unbearable
(0)	(1-3)	(4-6)	(7-9)	(10)

**Figure 1.**

Verbal description scale

For this determination, the patient selects/nominates the word that best describes the pain, not the marks (notification fields).

The visual analogue scale was represented by a 10 cm ruler, at the ends having indicated in writing the absence of pain and severe pain, respectively. The patient was instructed to put a sign on the line in the spot where he thought the level of his painful sensation would be (Figure 2).

No pain 1 -----10 Extreme pain

**Figure 2.**

Visual Analog Scale (VAS)

These scales allow a simple and effective determination of pain intensity (level 0 means no pain; level 10 indicates pain of unbearable intensity).

Dysgeusia was assessed by the following questionnaire: “Did you experience any changes in taste regardless of its type: sweet, salty, sour or bitter?” If the answer was yes to any of these, the patient was considered to have a impaired sense of taste.

The assessment of salivary flow (xerostomia) was performed using a questionnaire consisting of the following 3 questions: 1. Do you feel any burning sensation in any part of your mouth?; 2. Does your mouth feel dry during the day?; and 3. Do you notice any change in taste?. This last question was also useful in identifying the presence/absence of dysgeusia.

Patients were categorized with xerostomia when they answered yes to any of the above questions.

In addition, xerostomia was assessed on a graded colorimetric scale analogous to the visual one. The scale also uses the subjective method, through the grades given from 0 - 10, measuring dryness, mouth discomfort (pain/burning in the mouth lining), difficulty

in chewing/swallowing and speech caused by lack of saliva.

The data obtained using the colorimetric scale was correlated, by quantifying it, with the values identified by using the visual analogue scale. Thus it was established that: 0 = no, 1 - 3 = mild, 4 - 7 = moderate and 8 - 10 = severe [6].

In the clinical staging of BMS, depending on the clinical symptoms of oral pain (BMS type 1, 2 and 3) we used the modified Lamey and Lewis classification.

*The inclusion criteria for the study* were: the presence of localized pain in the tongue or oral mucosa, manifested for at least 4 - 6 months, present throughout the day or only part of the day (for type 3 BMS), always without paroxysms (evolution in the plateau). The oral mucosa is clinically normal or associated with other lesions or changes that are considered normal anatomical variants. The patients agreed to participate in this study, signed informed consent and subsequently showed up for further investigation. *The exclusion criteria* were: pain in the oral cavity lasting < 4 months, disorders of the temporomandibular joint (TMJ), post-herpetic neuralgia, maxillary sinusitis, paroxysmal hemicranial pain, and other types of headache. The final diagnosis is established only after all other conditions with similar charges are ruled out.

The Ethics Commission for Scientific Research of the "Carol Davila" University of Medicine and Pharmacy in Bucharest approved the Study Protocol and the informed consent in accordance with the Helsinki Declaration.

*Statistical analysis*

The data collected were analysed using the StataIC 14 program (StataCorp. 2015. Stata Statistical Software:

Release 14. College Station, TX: StataCorp LP). Possible associations between the measured categorical variables were assessed using the Pearson Chi-squared test. The exact Fischer's test was used when the number of observations corresponding to a cell in the contingency table was less than 5.

Intergroup analyses for continuous variables were performed using the t-Student test. The level of statistical significance was set at 0.05.

**Results and Discussion**

*Demographic data of the patients with thyroid disease included in the study*

*The gender distribution of patients* highlighted the predominance of female patients. Out of 42 patients with thyroid disease included in the study, 34 patients (80.95%) were female, the number of male patients being 8 (19.05%). The F/M ratio (sex ratio) in the case of the batch was 80.95/19.05 = 4.24/1.

*The distribution by age groups of the patients.* Concerning the age group, most patients (n = 14/35%) were in the age range between 60 - 69 years, followed by the range of 70 - 79 years with 25%. The 50 - 59 years age group represented 22.5% of the analysed cases (n = 9). The age groups under 40 (2.5%) and over 80 (5%) were the least represented.

The results of the analysis of the number of cases by age period, biological gender and average age are recorded in Table I.

From the analysis of the number of patients according to age and gender, we can see that most patients, both female 26.19% (11/42) and male 7.14% (3/42), are in the 60 - 69 decade (Table V).

**Table I**

Distribution of the lot by age and gender

No. of cases	Gender		< 40	40 - 49	50 - 59	60 - 69	70 - 79	> 80	Average age
34 (80.95%)	Female	Number	1 2.38%	4 9.52%	7 16.66%	11 26.19%	9 21.42%	2 4.76%	60.43 years
		The average age of the group	38	47.80	56.62	63.52	74.69	82	
8 (19.05%)	Male	Number	-	2 4.76%	2 4.76%	3 7.14%	1 2.38%	-	58.71 years
		The average age of the group	-	43	53	64.86	74	-	
42 100%	Total	Number	1 2.38%	6 14.28%	9 21.42%	14 33.33%	10 23.8%	2 4.76%	59.79 years
		The average age of the group	38	45.4	54.81	64.19	74.34	82	

The patients in the study group had an age limit between 38 and 82 years, the average being 59.79 years (with a standard deviation of ± 14.32 years). The average age of female patients with NOP was 60.43 years (with a standard deviation ± 13.66 years and age limits of 38 - 82 years), while the average age of male patients in the study group was 58.71 years (with a standard deviation ± 16.05 and age limits between 43 - 74 years).

The results are similar to the data in the speciality literature. In a study conducted at the University of Naples on a group of 75 patients with BMS, the average age of the group was 61.17 years (± 11.75). The ratio of women/men was 3/1, which confirms that the prevalence of BMS is higher in women, especially those around the age of 60 (Adamo *et al.*). In a similar study of 65 patients who attended the School of Dentistry, Aichi University - Gakuin, Nagoya, Japan, the average age of the patients was 60.0 ± 9.9 years.

The ratio of women/men was 5.5/1, which confirms that BMS frequently develops in middle-aged and elderly women (Tokura *et al.*).

*Distribution of patients according to the job status*

In relation to job status, out of the total of the 42 patients under study at the time of the first visit, 57.41% (n = 19) were retired, 31.94% (n = 12) were employed, 7.22% (n = 5) unemployed and 3.42% (n = 6) homemakers (Table II).

Adamo *et al.*, in a study analysing the relationship between the socio-demographic characteristics and the clinical features of patients with pain, found that the prevalence of BMS was higher in female patients (74.7%) without a job (80%). Comparatively, inactive people are more affected by this condition in both studies. Still, while in the case of our research, they are retired people, in the study conducted at the University of Naples, they are unemployed people.

**Table II**

Distribution according to the job status of the patients in the studied group

Statistical parameters	Total patients		Female gender		Male gender	
	absolute no.	%	absolute no.	%	absolute no.	%
<b>Job status</b>						
Employee	12	28.57	9	21.42	3	3.14
Retired	19	45.23	16	38.09	3	3.14
Unemployed	5	11.90	3	7.14	2	4.76
Homemaker	6	14.28	6	14.28	0	0

\* of the total number of patients included in the study group

*Correlations of BMS symptoms with thyroid disorders*

*Analysis of the evolution over time of pain intensity in patients with thyroid disorders*

Correlating the evolution of BMS symptoms over time with thyroid disorders, a statistically significant

association was established between the 2 variables: in 18 patients (42.86% of this subgroup), the pain intensity strengthened/increased over time (Table III).

**Table III**

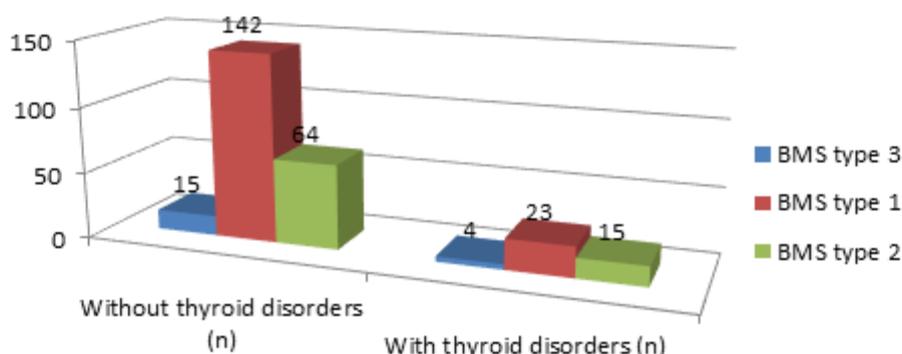
The evolution over time of pain intensity in thyroid disorders

Thyroid gland disorders	The degree of evolution of intensity over time					
	Constant		Lower		Higher	
	No. of cases	%	No. of cases	%	No. of cases	%
Absent	114	51.58	62	28.05	45	20.36
Present	18	42.86	6	14.29	18	42.86
Statistical significance	Chi2 test, p = 0.005 Fisher's exact test = 0.007					

*Correlation of thyroid disorders with the BMS type (Lamey and Lewis classification)*

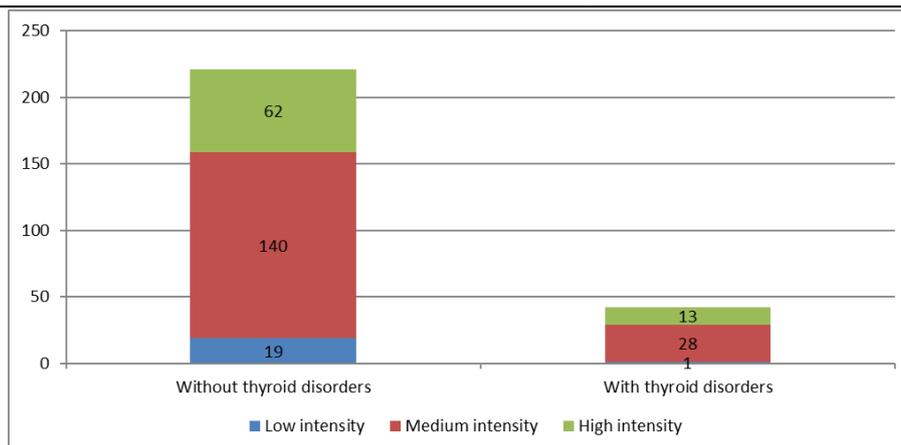
Statistical analysis indicated that 23 (54.76% of patients with thyroid disorders) had type 1 BMS, with no statistically significant association between the 2 variables (Pearson chi2 test, p = 0.494, Fisher's exact test = 0.451) (Figure 3).

The analysis of pain intensity measured on a visual analogue scale (VAS from 1 - 10) in patients with thyroid disorders showed that over 1/2 of the patients included in the study group (n = 28/66.67%) reported moderate pain intensity, 13 (30.95%) high intensity and only 1 (2.38%) showed low intensity (Figure 4).



**Figure 3.**

Thyroid disorders vs. BMS type



**Figure 4.**

Prevalence of cases with/without thyroid disorders, depending on pain intensity

No statistical association was found between these parameters (Pearson chi2 test,  $p = 0.376$ , Fisher's exact test = 0.436).

*Analysis of the distribution of patients correlating dysgeusia with the intensity of the pain symptoms*

It was found that dysgeusia was significantly associated with a particularly high intensity of the pain symptom.

In particular, our study established a correlation between the increase in the frequency of dysgeusia and the intensity of the pain symptoms.

A percentage of 42.67% of patients with particularly high intensity developed dysgeusia, versus 27.98% of patients who reported medium intensity and 10% of subjects who showed low intensity (Table IV).

**Table IV**

Correlation of dysgeusia with the intensity of the pain symptoms

Dysgeusia	Pain intensity			Statistical significance
	Low	Moderate	High	
Present	2 (2.47%)	47 (58.02%)	32 (39.51%)	Pearson chi2(2) test $p = 0.008$ Fisher's test = 0.007
Absent	18 (9.89%)	121 (66.48%)	43 (23.63%)	

The correlation seems to be progressive. As the frequency of dysgeusia increases, so does the intensity of the pain.

*The association of subjective manifestations with medication for thyroid disorders*

The study group was divided into 2 subgroups: patients with BMS and without medication for thyroid disorders

(234 cases) and patients with BMS who were under treatment for thyroid disorders (29 cases).

Analysis of data showed that 81 patients with BMS had associated dysgeusia. Of these, 66 received no replacement medication for the treatment of hypo- or hyperthyroidism, and the remaining 15 were under treatment for thyroid disorders (Table V).

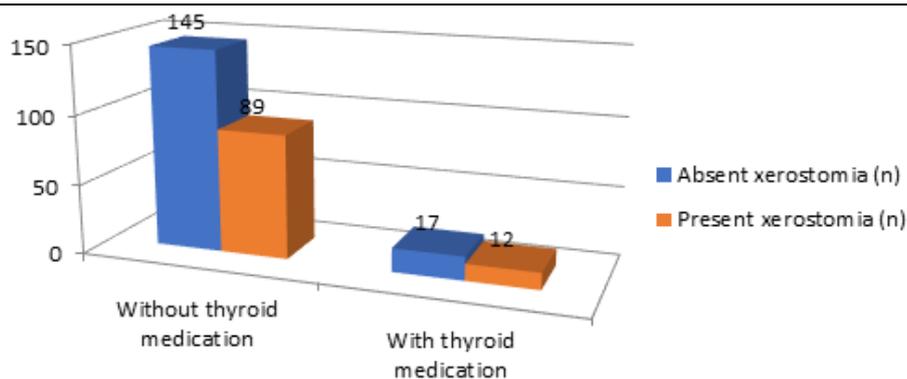
**Table V**

The correlation of medication for thyroid disorders vs. dysgeusia

Dysgeusia	Dual-purpose replacement medication: treatment of hypo- or hyperthyroidism		Statistical significance
	With medication	Without medication	
Present	15 (51.72%)	66 (28.21%)	Pearson chi2(1) test $p = 0.010$ Fisher's test = 0.017
Absent	14 (48.28%)	168 (71.79%)	
<b>Total</b>	29 (11.03% of the total group of 263 patients)	234 (88.97% of the total group)	

The analysis results showed that the administration of drugs for thyroid disorders was statistically significantly associated with the presence of dysgeusia. In this study group, 51.72% of patients with thyroid medication had dysgeusia as an associated symptom versus 28.21%

of patients without thyroid medication who had this associated symptom. This means that in patients with thyroid disorders under treatment, dysgeusia occurs in 1 in 2 patients, while in the absence of medication, the ratio is 1 to 4 (Figure 5).



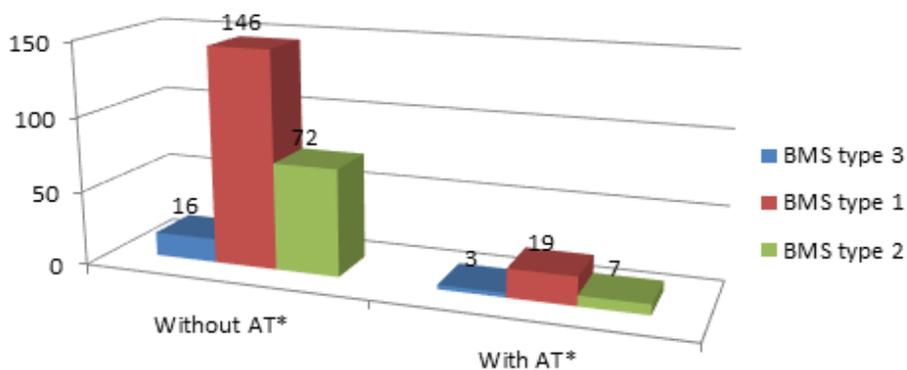
**Figure 5.**

The distribution of cases according to the combination of substitution medication for the treatment of hypo- or hyper-thyroidism xerostomia

The study results indicated that, in the subgroup of 29 patients with BMS who received thyroid replacement medication, a number of 12 had associated xerostomia. The ratio between the number of BMS cases with substitution medication-associated xerostomia and the number of BMS cases under specific treatment, but without xerostomia is  $12/17 = 0.71$ . From this statistical analysis, we noticed no statistically significant correlation between the administration of thyroid replacement medication and the presence of xerostomia as an associated symptom (Pearson chi2 test,  $p = 0.727$ , Fisher's exact test = 0.840) (Figure 3).

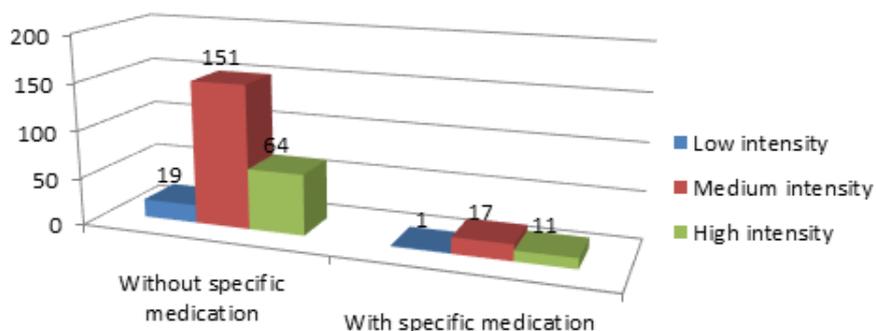
*Thyroid medication and the BMS type (after Lamey and Lewis classification)*

The analysis indicates no statistically significant association with BMS types 2 and 3. There is also no statistically significant association with type 1 BMS (Pearson chi2 test,  $p = 0.651$ , Fisher's exact test = 0.625). This is even though a number of 19 patients with thyroid disorders who receive specific medication (65.52% of this subgroup) have type 1 pain syndrome. In other words, 2 out of 3 patients with thyroid disorders under treatment get type 1 BMS (Figure 6).



**Figure 6.**

Statistical association of patients treated with anti-thyroid drugs and BMS type  
\*AT = thyroid replacement medication



**Figure 7.**

The distribution of patients according to the association of thyroid medication – pain intensity

*Pain intensity analysis (measured on the VAS scale from 1 - 10) in patients with thyroid replacement medication*

A number of 11 patients (37.93% of patients undergoing specific treatment) have a high pain intensity. A possible explanation for those who have hyperthyroidism is that, physiologically, they develop hypercatabolism with excess production of organic acids, which, once eliminated by saliva, change its pH.

This analysis indicates no statistically significant association in patients with thyroid disorders (Pearson

chi2 test,  $p = 0.388$ , Fisher's exact test = 0.455) (Figure 7).

*Analysis of the evolution over time of pain intensity in patients with thyroid medication*

Analysis of data shows that in 51.72% of patients with thyroid medication, the pain intensity increased from the onset of the disease *versus* 20.51% of patients without thyroid medication in which the intensity of the symptom increased. The analysis indicates a statistically significant association between the administration of thyroid medication and the change in pain intensity over time (Table VI).

**Table VI**

The correlation of thyroid medication – the evolution over time of pain intensity

Thyroid medication	Pain intensity			Statistical significance
	Constant	Lower	Higher	
Present	10 (34.48%)	4 (13.79%)	<b>15</b> <b>(51.72%)</b>	Pearson chi2(2) test $p = 0.001$ Fisher's test = 0.002
Absent	122 (52.14%)	64 (27.35%)	48 (20.51%)	

In the study we undertook, the results showed a statistically significant association between the pathological history of thyroid disorders in patients and a change in pain intensity over time. Thus, in the case of 18 patients (42.86% of all those with associated thyroid disorders), the pain intensity increased over time.

The results of a study conducted by Felice *et al.* in a group of 50 patients highlighted the possible association between thyroid disease and taste changes. A total of 30 patients with BMS reported an affliction for the bitter taste, and 2 patients had an affliction for the acid taste [26].

A more recent study (Talattof *et al.*) conducted on a group of 153 patients with Hashimoto's thyroiditis showed that the level of thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), thyroid peroxidase antibodies (TPOAb) and antithyroglobulin antibodies (AT) indices of patients were associated with the presence and severity of BMS. The conclusion of the study was that hypothyroidism may be responsible for a negative influence on taste and may cause an increase in tactile, thermal and painful sensations in the trigeminal nerve [27, 28].

It can be said that the same conclusion regarding the influence of thyroid diseases on taste change is valid in the case of our research.

In the current literature, different drug classes have also been reported as etiological factors of BMS [1, 13, 23, 29].

From a clinical point of view, it is absolutely mandatory to differentiate the form of secondary BMS, which may include different classes of drugs as possible etiopathogenic factors and the idiopathic form of BMS, which is described as a separate clinicopathological entity [23].

Anti-thyroid drugs may induce taste disturbances due to their negative influence on the maturation of the

fungal papillae and the decrease in taste receptors, resulting in a reduction in taste [25].

The hypothesis admits that the appearance of the characteristic symptoms of BMS is dependent on the therapeutic dose administered because experimental studies have shown that the burning sensation appeared when raising the dose of the drug, a decision taken in order to increase therapeutic efficacy [18].

Our study showed a correlation between the increase in the frequency of dysgeusia and the increase in the pain intensity symptoms. The explanation is provided by Su *et al.*, who postulated that due to the intersection of the gustatory reflex arc with that of pain management at the oral level, taste disturbances induce pain, even if it is atypical, in terms of subjective perception [30]. According to other authors, another general hypothesis is that BMS is the expression of damage on the nerves that serve the taste sensation [31-33].

The hypothesis that anti-thyroid medication would reduce the perception of taste is also supported by the results of our study. The administration of drugs for thyroid disorders was significantly associated with the presence of dysgeusia ( $p = 0.01$ ). Of the study group (263 patients), 29 had thyroid disorders and received specific medication, and 13 were diagnosed with thyroid disorders but were not receiving drug treatment accordingly. In this study group, 51.72% of patients with thyroid medication had dysgeusia as an associated symptom, *versus* 28.21% of patients without thyroid medication who had this associated symptom. This means that in the case of patients under medication for thyroid disorders, dysgeusia occurs in 1 in 2 patients, while in the absence of medication, the ratio is 1 in 4.

Also, analysing whether there is a statistically significant correlation between the medication administered for thyroid disorders and the evolution over time of the

pain intensity in the patients in the study group, we found that in 51.72% of patients ( $p = 0.001$ ) with thyroid medication the pain intensity increased from the onset of the disease, *versus* 20.51% of patients without thyroid medication whose pain intensity increased.

### Conclusions

Endocrine disorders and specific drugs may be responsible for changes in the taste system, a symptom frequently present in these patients. Future studies are needed to confirm these hypotheses.

The current medication for patients developing pain is a very important point that must exist in the investigation protocol.

The study confirms the importance of a multi-disciplinary approach in treating patients with BMS. We consider that an endocrinological consultation and the evaluation of the specific treatment are essential for the diagnostic protocol of patients with BMS.

### Conflict of interest

The authors declare no conflict of interest.

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