

Candida-induced stomatopyrosis and its relation to diabetes mellitus

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Abstract

Background: Glycaemic disorders and oral candidosis can be accompanied by burning mouth sensations. However, no clear relation between all three disorders is known.

Methods: Seventy-two native Upper-Austrians with burning mouth sensations were examined and smears for *Candida* estimation were taken from the spots where the sensations were felt. All patients with previously unknown diabetes mellitus (DM) were subjected to an oral glucose tolerance test (OGTT). Use of glucocorticoid-containing anti-asthmatic sprays and the body mass index (BMI) were determined.

Results: Of the examined non-inhalers of sprays, 52% had increased candidal density. A correlation between that increase and type 2 DM was found. The burning sensations in all patients with increased candidal density subsided completely after anti-mycotic therapy.

Conclusion: The perception of burning sensations was hypothesised to occur via stimulation of the capsaicin (vanilloid) receptor by *Candida* metabolites. The *Candida*-induced stomatopyrosis should be regarded as a single symptom indicating (predisposition to or established) type 2 DM in non-inhalers of the concerned population.

Key words: burning mouth sensations; *Candida*; type 2 diabetes mellitus

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Burning mouth sensations are associated with various local, systemic, and psychological factors. The large differences amongst the putative aetiological reasons make it doubtful to regard the burning mouth sensations as a nosological entity. Either *Candida* multiplication or candidosis (1–4), oropharyngeal candidosis in spray inhalers (5) and *Candida*-associated denture stomatitis (6,7) can be accompanied by burning mouth sensations which could causally be related to the multiplication of *Candida*. Similar to the relation between *Candida*-associated denture stomatitis and glycaemic disorders (6, 7) a relation between glycaemic disorders and the burning mouth sensations was also suggested (8–11). At this point, the question arises whether certain cases of burning mouth sensations are related with candidosis and glycaemic disorders.

The aim of this study was to examine the possible relationship between burning mouth sensations, candidosis, and glycaemic disorders.

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Materials and methods

Seventy-two patients (58 female and 14 male) in the age group 29–88 years (mean 60 years) with burning mouth sensations were examined. Patients were recruited for this study consecutively when attending the Upper Austrian Voecklabruck Dental Clinic. All patients had suffered from burning sensation located within the oral cavity (hard palate, pharynx, lips, mouth corner or tongue) for at least 3 months. The patients were questioned about mouth and denture hygiene, modus of denture wearing, eating habits and use of glucocorticoid containing anti-asthmatic sprays.

To estimate the candidal density, smear was taken with swabs (Biotest Transportsystem; Biotest AG, Dreieich, Germany) from the mucosal spots (about 1 cm²) where the sensations were felt (hard palate, pharynx, lips, mouth corner or tongue). The sampling took place between 09.00 and 12.00 hours, at least 2 h after the patient's breakfast. In addition, samples were taken in the same way from a control group of 20 female and 20 male denture wearers. To estimate the candidal density in them, smear was taken under the same conditions from about 1 cm² of the denture-bearing mucosa. The control group were not HIV positive and had not been treated with immunosuppressive drugs, radiotherapy or antibiotics in the last 6 months. They were in the age group 26–83 years (mean 59 years) and had neither diseases of the oral mucosa nor angular cheilitis. All samples were evaluated semiquantitatively by inoculating agar plates (Albicans ID; BioMérieux, Marcy l'etoile, France) aerobically incubated at 37°C for 48 h after the following count procedure: negative growth was characterised by 0–4 colonies per agar plate; increased candidal density was identified by the growth of at least 5 colonies per agar plate.

All patients with previously unknown DM were subjected to an OGTT. For that reason, drug intake affecting blood sugar levels (12) was stopped by the family physicians 3 days before the examination. An unrestricted diet rich in carbohydrates was recommended for at least 3 days before the OGTT and normal physical activity was advised. After a fasting period of 10–12 h, baseline blood glucose was measured. The patients were required to drink 75 g of glucose as a 25% solution within 5 min and to remain seated before and during the 2-h test. The results from the test were interpreted according to the WHO criteria (Table 1) (13). The diagnosis DM was confirmed per a second OGTT a week later. Patients' height and weight were measured in light clothing without shoes, and the BMI was calculated as weight(kg)/height(m²). For evaluation in our study, diabetic patients with a BMI over 25 kg/m² were classified overweight and those with a BMI below 25 kg/m² as lean or normal weight

Table 1. Diagnostic criteria for the interpretation of OGTT results

Capillary whole blood	Fasting (mg/dl)	2 h after oral glucose challenge (mg/dl)
Normal	<100	<140
Impaired glucose tolerance	<120	140–200
Diabetes mellitus	≥120	≥200

Table 2. Therapy (only in cases with increased candidal density)

Anti-mycotic therapy	Supporting measures
Nystatin (for 14 days)	Avoid frequent ingestion of sweets Improve oral hygiene for denture wearers only: avoid sleeping with the denture; reduce the time of denture wearing; reduce the size of the maxillary denture covering the palate, if justified from the prosthodontic point of view.

according to the American Diabetes Association criteria (14). Since the development of type 2 DM is tightly correlated with age (12, 15), the distribution of glycaemic disorders was analysed only in non-inhalers at an age over 50 years. Patients using corticoid-containing sprays were excluded from the evaluation.

The denture wearers were instructed to clean the dentures by hygiene-foam (Corega 1 Minute[®], Block Drug Company Inc., Ratingen, Germany) according to the instruction of the manufacturer at least once a day. The patients with increased candidal density were treated topically with a suspension (100,000 units/ml) of nystatin (Mycostatin-orale Suspension[®], Squibb-von Heyden, Munich, Germany). They were instructed to apply a thin layer of the suspension to the oral mucosa and in case of denture wearers to the fitting surface of the dentures three times a day before reinserting the denture into the mouth. This therapeutic scheme had to be carried out for 14 days. The entire treatment of the patients with increased candidal density only is listed in Table 2. Microbiological examination on day 15 after the beginning of the nystatin therapy was also performed to estimate the change in candidal density in each patient.

Results

The results of the oral, glycaemic, and microbiological examination are presented in Table 3. Unlike the control group in which only negative candidal growth was registered in 53% of patients with burning sensations, an increased candidal density could be found by microbiological examination. Nine patients with increased candidal density tended to eat sweets frequently. Burning sensations in denture stomatitis coincided in 10 patients

Table 3. Distribution of patients with burning mouth sensations

Spray use	Candidal density	Denture wearers	Patients with stomatitis
69 non-spray inhalers	ICD in 36 patients	27 DW	16 DS
		9 non-DW	11 no DS
3 spray inhalers	No ICD in 33 patients	33 DW	3 DS
		1 DW	30 no DS
3 spray inhalers	ICD in 2 patients	2 DW	2 OC, no DS
		No ICD in 1 patient	1 DW
			1 no OC, no DS

ICD: Increased candidal density. DS: Denture stomatitis. OC: Oropharyngeal candidosis. DW: Denture wearers.

with exacerbation of the inflammation and formation of thrush. Two married couples with increased candidal density declared that within a week after appearance of burning sensations in the first spouse, the second one also obtained them. The burning sensations were described as strong till unbearable by the first spouses, and as weak by the second ones. The distribution of glycaemic disorders and BMI in non-inhalers with increased candidal density is presented in Fig. 1 and in non-inhalers without

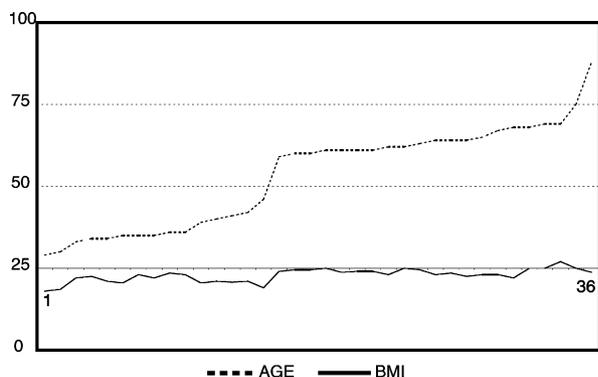


Fig. 1. Distribution of age and BMI in non-inhalers with increased candidal density ($n = 36$). Patients are predominantly normal or slightly underweight ($BMI < 25 \text{ kg/m}^2$).

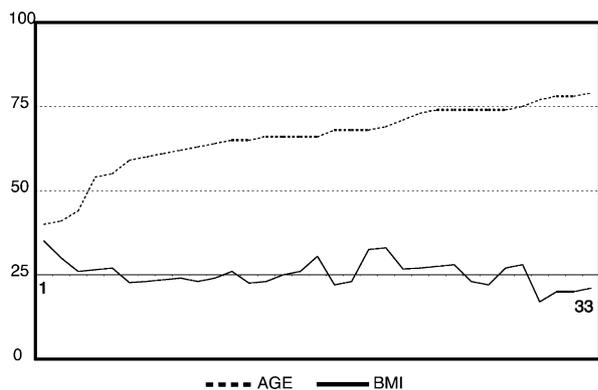


Fig. 2. Distribution of age and BMI in non-inhalers without increased candidal density ($n = 33$). Patients are underweight, normal, overweight or obese.

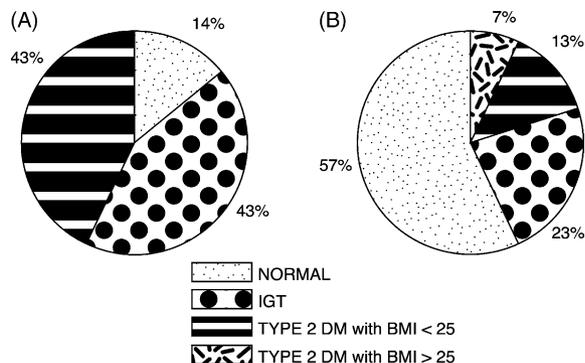


Fig. 3. Distribution of glycaemic disorders in non-inhalers with (A) increased candidal density ($n = 36$) and (B) without increased candidal density ($n = 33$) over 50 years of age.

increased candidal density in Fig. 2. Whereas the patients with increased candidal density were normal or slightly underweight ($BMI < 25 \text{ kg/m}^2$), the group without increased candidal density was completely heterogeneous with relation to BMI. The distribution of glycaemic disorders in non-inhalers with increased candidal density over 50 years of age as well as in non-inhalers without increased candidal density over 50 years of age is presented in Fig. 3. The exceedingly high coincidence (86%) with predisposition to or established type 2 DM and burning mouth sensations is evident in patients with a BMI below 25 kg/m^2 aged over 50. In overweight patients ($BMI > 25 \text{ kg/m}^2$) with impaired glucose tolerance (IGT) and type 2 DM, no increase in candidal density was found. The sex distribution of non-inhalers with increased candidal density and non-inhalers without increased candidal density (Fig. 4) was significantly different.

Microbiological examination on day 15 revealed reduction of the candidal density in eight of the patients and negative *Candida* growth in the remaining ones. All patients with burning sensations who had increased candidal density before the nystatin treatment became free from symptoms. Receding of both burning sensations and increased candidal density after 3 months

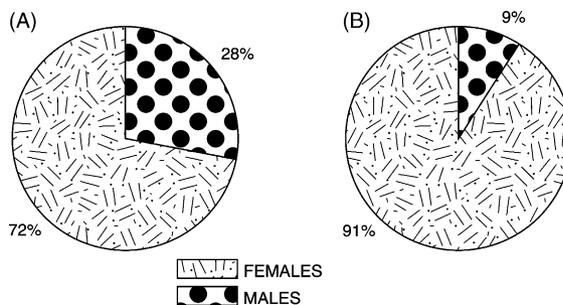


Fig. 4. Distribution of sex in non-inhalers with (A) increased candidal density and (B) without increased candidal density.

occurred in nine of the patients. They were treated again for 14 days with nystatin and became free from burning sensations after another 3 months.

Discussion

Burning mouth sensations might be regarded as a single symptom related to different causes. Although, in the presented cases as well as in the previously reported cases with (5) or without (3) mucosal inflammation where increased candidal density was registered, the reason for these sensation was *Candida* multiplication. The detection of painful stimuli occurs primarily at the peripheral terminals of specialised sensory neurons called nociceptors. These small-diameter neurons transduce signals of chemical, mechanical or thermal nature into action potentials and transmit this information to the central nervous system, ultimately eliciting a perception of pain or discomfort (16). In this way, capsaicin (17–19) as well as citric acid (17, 19) applied to the tongue causes reproducible burning sensations. Likewise, fungal products induce such sensations (20). All these agents act via the capsaicin (vanilloid) receptor, which is responsible for the detection of pain-producing chemical and thermal stimuli (16). The induction of burning sensations by fungal products indicates such a probability also in cases of *Candida* multiplication. Patients with burning mouth sensations could possibly have a reduced sensitivity threshold (3) to react to candidosis, respectively, to metabolic products of yeasts. The sensitivity threshold of burning sensations perceived via the capsaicin receptor is distinctly lower in women compared to men (21). Similar gender differences were found in the present work. The fact that anti-psychotic drugs and tricyclic anti-depressants act as capsaicin receptor antagonists (22, 23) could be the explanation for the alleviation of the burning mouth sensations by treatment with such drugs (24, 25).

Our finding that mouth burning sensations are a result of *Candida* multiplication confirms the findings of previous investigations related to burning sensations accompanying *Candida* multiplication (1–8). On the other hand, the high coincidence of increased candidal density and predisposition to or established type 2 DM in patients with a BMI below 25 kg/m² suggests a strong correlation. This result confirms the findings of previous investigations related to DM and *Candida* multiplication (6, 7, 9, 26–28). The relation between burning sensations and *Candida* multiplication on the one hand and between DM and *Candida* multiplication on the other hand, as well as the high coincidence

of *Candida* multiplication and type 2 DM in normal weight or lean patients aged over 50 suggest an overall correlation between DM and burning sensations. As the onset of type 2 DM takes place predominantly above the age of 40 years, *Candida*-induced burning mouth sensations in non-spray inhalers could precede or indicate type 2 DM in normal weight patients as previously suggested for *Candida*-associated denture stomatitis (7). Similarly, burning mouth sensations were estimated to be a sign of undiagnosed diabetes (9, 10).

In order to differentiate between burning mouth syndrome supposed to be predominantly of psychological genesis (29–31) and the burning mouth sensations related to candidal pathogenesis, the term *Candida*-induced stomatopyrosis has been introduced for the latter. *Candida*-induced stomatopyrosis can be considered as a symptom of *Candida* multiplication expressed in burning sensations and subsiding completely by treatment reducing the candidal density as previously reported (3, 5).

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