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# Elimination of oral candidiasis may increase stimulated whole salivary flow rate

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ABSTRACT

*Objectives:* *Candida* infections are frequently encountered fungal infections in the oral mucosa. This study aimed to evaluate the effect of eliminating *Candida* spp. on stimulated whole salivary flow rate (SWS) in patients with oral candidiasis.
*Subjects and methods:* This study involved 66 patients with oral candidiasis. Fifty-two consecutive patients, successfully treated by antifungal therapy, were available to examine the effect of elimination of oral *Candida* spp. on SWS (success group); the 14 patients who tested positive for *Candida* after therapy were retrospectively included (control group). SWS were used to measure saliva production. Moreover, tongue pain and xerostomia were evaluated using visual analog score (VAS).
*Results:* By eliminating oral *Candida* spp., SWS significantly increased in the success group after antifungal therapy [SWS: mean value $0.89 \pm 0.51$ ml/min (median 0.82 ml/min: 0.15–2.14) to mean value $1.16 \pm 0.58$ ml/min (median 1.05 ml/min: 0.2–2.93), $P < 0.001$]. Furthermore, VAS scores for subjective tongue pain and xerostomia were significantly decreased compared with those before therapy in the success group [xerostomia: mean value $52.5 \pm 28.8$ (median 53: 9–100) to $24.2 \pm 1.6$ (median 17: 0–70), tongue pain: mean value $52.6 \pm 27.2$ (median 56: 1–93) to $15.3 \pm 18.0$ (median 9: 0–62). $P < 0.001$]. There was no significant difference in SWS, subjective tongue pain, or xerostomia in the control group after antifungal therapy. [SWS: mean value $1.08 \pm 0.83$ ml/min (median 0.69 ml/min: 0.2–2.7) to $0.98 \pm 0.59$ ml/min (median 0.8 ml/min: 0.45–2.5), $P = 0.65$], [xerostomia: mean value $62.8 \pm 5.3$ (median 62: 28–70) to $64.0 \pm 8.8$ (median 64: 56–73), $P = 0.58$, tongue pain: mean value $64.3 \pm 18.6$ (median 67: 31–87) to $58.4 \pm 20.0$ (median 8: 20–78), respectively; $P = 0.24$]
*Conclusion:* Our study demonstrated that SWS may increase by eliminating oral *Candida* spp. in patients with oral candidiasis.



## 1. Introduction

*Candida* infections are the most frequently encountered fungal infections in the oral mucosa. Symptoms of oral candidiasis vary, and three types have been reported (Lynch, 1994; Osaki, Yoneda, Yamamoto, Ueta, & Kimura, 2000; Terai & Shimahara, 2005, 2007): atrophic, pseudomembranous, or hypertrophic. Atrophic oral candidiasis induces tongue pain and denture-associated stomatitis with few objective manifestations (Altarawneh et al., 2013; Hoshi et al., 2011; Salerno et al., 2011).

Xerostomia is mainly caused by decreased salivary secretion and is known to be a high-risk factor for oral candidiasis (Cassolato & Turnbull, 2003; Epstein, Pearsall, & Truelove, 1980; Navazesh, Wood, & Brightman, 1995). Signs and symptoms of xerostomia are closely related to changes in the oral microbial community. A reduction of stimulated whole salivary flow rate (SWS) may alter the oral microbiota; thus, may increase the risk of oral candidiasis (Torres et al., 2002). We routinely encounter cases where antifungal therapy relieves pain, flaring, and atrophy of the tongue papillae and buccal mucosa. In addition, we sometimes encounter patients with oral candidiasis whose salivary volume increases by eliminating *Candida* spp. However, any association between the

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effects of elimination of oral *Candida* on saliva production has not been extensively evaluated clinically. We conducted a clinical study to investigate the effect of elimination of *Candida* spp. on SWS, subjective intensity of xerostomia, and tongue pain after antifungal treatment.

## 2. Material and methods

### 2.1. Subjects

This study was conducted at the Department of Oral Medicine, Hokkaido University Hospital, from December 2008 to September 2010. All patients underwent an oral examination. The Institutional Review Board (IRB) of Hokkaido University Hospital approved the study (013–0209), and all participants provided written informed consent.

All patients with oral candidiasis were eligible for investigation and were enrolled in the study if they met the inclusion criterion of a positive Candida culture. Cultures were considered positive for oral candidiasis if a growth of >10 CFU was observed in CHROMagar medium. Exclusion criteria were as follows: pregnancy, <20 years of age, use of any drug that is contraindicated in combination with an antifungal of azole origin (e.g., warfarin or triazolam), previous antifungal therapy, and head and neck cancer patients.

All patients were consecutively included in the study. Before administration of antifungal therapy, fungal examination was performed.

Following *Candida* culture test to confirm the diagnosis, 66 consecutive outpatients with oral candidiasis were treated with antifungal drugs. Fifty-two consecutive patients (45 females, 7 males) with successful elimination of *Candida* spp. after antifungal treatment were included in the success group. Fourteen patients (10 females, 4 males) who still tested positive for *Candida* after the antifungal therapy were included in the control group (Fig. 1).

### 2.2. Fungal examination

The dorsal surface of the tongue was swabbed 10 times with a dental mirror, and swabs were directly inoculated onto Chromagar™ *Candida* agar (Kanto Chemical Co. Ltd., Tokyo, Japan). After 48 h of culture at 35 °C, CFUs were counted. The culture was considered positive for oral candidiasis if growth of ≥ 10 CFU was observed, in accordance with a previous study (Kimori, Nakagawa, Yamamoto, & Ohshima, 2009). Colonies of *C. albicans*, *C. glabrata*, and *C. parapsilosis* could directly be differentiated on chromogenic isolation plates, appearing as light to medium green, light or dark mauve, and flat colonies with a whitish border, respectively (Beighton et al., 1995). *Candida* tests were performed on day 0 and at 4 weeks for each patient. The criterion for success was having <10 colonies in the CHROMagar medium.

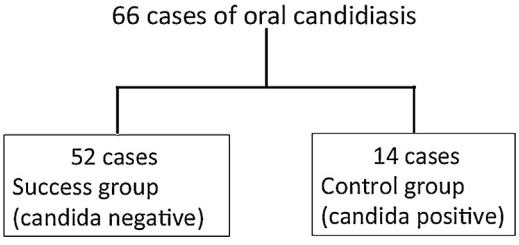


**Fig. 1.** Trial profile.

### 2.3. Antifungal therapy

Miconazol gel 25 mg (Frorid oral gel 2%: 5 g) was applied by the patients four times a day for 14 days. Patients were instructed to apply the gel on the tongue, spread evenly in the whole mouth, and retain it in the mouth after each meal and before going to bed.

### 2.4. Subjective evaluations

The subjective intensity of xerostomia and tongue pain was evaluated using a visual analogue scale (VAS) from 0 to 100 (no pain to extreme pain) before treatment and 4 weeks after treatment. The VAS values in the control group were only collected in 8/14 cases because the control group was retrospectively selected in this study.

### 2.5. Measurement of stimulated whole salivary flow (SWS)

All patients were instructed to not eat, drink, smoke, chew, or perform any oral hygiene measures for 1 h before saliva collection. Thereafter, they were asked to chew gum, one per second, which did not adhere to the denture, (3 g; Free Zone; Lotte, Tokyo, Japan) and expectorate whole saliva into a tube for 10 min, as previously reported. Normal SWS was defined as saliva flow rate of >ml/min. Hyposalivation was defined as a saliva flow rate < ml/min. The cutoff value for hyposalivation was defined as previously reported (Iwabuchi, Fujibayashi, Yamane, Imai, & Nakao, 2012; Sreebny, 2000). Secondary collection of SWS after antifungal therapy was performed at the same time point as with first gum test. We compared SWS between the success and control groups both before and after antifungal therapy.

### 2.6. Statistical analysis

Statistical analyses of results of all four tests were performed using Mann–Whitney *U* test, Wilcoxon signed-rank test. *P* values of <0.05 were considered statistically significant. All statistical analyses were performed using JMP software (version 9; SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Clinical findings

The mean age of the 52 patients (success group: 7 male, 45 females) with oral candidiasis was 70 years (range, 37–88). The chief complaints of patients in this group were tongue pain (58%), dysgeusia (14%), xerostomia (14%), coated tongue (5%), discomfort (3%), and others (6%). All patients had xerostomia and tongue pain, to a greater or lesser extent.

In the control group, the mean age of the 14 patients (4 males, 10 females) with oral candidiasis was 73.64 years (range, 54–87). The chief complaints of patients in this group were tongue pain (82%) and xerostomia (18%). The percentage of wearing denture was 79.6% in success group and 71.4% in control group.

*Identification of Candida species*

Various *Candida* species isolated from all success group (52 patients) and control group (14 patients) are summarized in Table 1. In success group, as a single species, *C. albicans* was the most frequently isolated strain in 30 patients (58%), and *C. glabrata* was the next most prevalent strain in 2 patients (4%). Further, *C. parapsilosis* was detected in 1 patient (2%). A mixture of *C. albicans* + *C. glabrata* was detected in 10 patients (19%), whereas *C. glabrata* + *C. parapsilosis* was identified in 3 patients (6%) (Table 1).