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Titanium Ions Released from Oral Casting Alloys May Contribute to the Symptom of Burning Mouth Syndrome

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Purpose: Many metal ions released from dental casting alloys have been reported to influence the intraoral symptoms of oral lichen planus (OLP) and burning mouth syndrome (BMS). The aim of this study was to investigate the relationship between salivary metal ion levels and the prosthetic duration as well as to evaluate the time-dependent morbid effects of metal ions in OLP and BMS patients.

Methods: Three study groups consist of the following subjects respectively: 17 OLP patients, 12 BMS patients, and 12 patients without oral symptoms. The salivary concentrations of 13 metal ions (copper, cobalt, zinc, chromium, nickel, aluminum, silver, iron, titanium [Ti], platinum, tin, palladium, and gold) were measured by Laser Ablation Microprobe Inductively coupled Plasma Mass Spectrometry.

Results: The Ti ions had statistically significant differences among the groups with a prosthetic duration of less than 5 years. There were no significant differences between all ion levels among the groups wearing dental cast alloys for over 5 years. In the BMS group, the level of Ti ions in patients with prosthetic restorations less than 5 years old were significantly high ($p<0.05$).

Conclusions: In the BMS group, 3-60 months during which salivary Ti levels were higher were matched with the duration of burning symptoms (15.6±17.1 months). Furthermore, Ti ions were statistically high in the oral cavity of BMS patients fitted with dental casting alloys for 5 years. These results suggest that Ti ions released from dental implants and oral prostheses could attribute to burning sensation of BMS.

Key Words: Burning mouth syndrome; Metals; Saliva; Titanium

INTRODUCTION

Dental casting alloys placed in the oral cavity for a long time may cause adverse effects as a consequence of corrosion.[1-3] The release of metal ions into oral cavity may induce cytotoxicity, allergies, and mutagenesis. Oral lichen planus (OLP) and burning mouth syndrome (BMS) are some of the common complaints reported by patients to the oral medicine department and could be the result of metals.

OLP is a chronic immunological oral mucosal disease with many clinical manifestations.[4,5] The exact etiology of OLP is not known, but several factors have been proposed for the cause including genetic background, dental materials, drugs, autoimmunity, and food allergies.[5] Previous studies on OLP emphasized the role of contact allergy by documenting metal sensitivities in 0% to 62% of patients.[6]

These metals included amalgam (mercury), gold, cobalt, tin, and palladium.[6-10]

BMS is characterized by burning sensations of the normally visible oral mucosa.[11] Etiology of primary BMS remains unclear, but secondary BMS may be caused by lichen planus, candidiasis, hormonal disturbances, psychosocial stressors, vitamin or nutritional deficiencies, diabetes, dry mouth, contact allergies, galvanism, parafunctional habits, cranial nerve injuries and many other factors.[12,13] Previous studies have reported low salivary magnesium levels[14] and low serum zinc levels[15,16] in BMS patients.

The intraoral side effects from dental alloys were gingivitis, burning tongue, erythematous palate or tongue and lichenoid reactions.[17] These adverse effects could be influenced by types of casting alloys, amount of metal ions released from dental alloys, prosthodontic exposure time and so on. In vitro experiments on local toxicity of casting alloy, cell toxicity increases in time and dose-dependent patterns.[18,19] Alloys that release metal ions over longer periods tend to cause more toxic effects and clinically long-term released metallic ions may trigger intraoral toxic reactions at relatively low concentrations.[19,20]

The hypothesis of this study was that dental prostheses will release more metal ions over a longer period of time and that the ions will contribute to oral symptoms of OLP and BMS. Therefore, the relationship between salivary metal ion levels and the prosthetic duration in OLP, BMS and the control group were evaluated. An analysis of the concentration of salivary metal ions with the period of dental prostheses was also performed to explore the effects of metal ions in OLP and BMS.

MATERIALS AND METHODS

1. Participants

This study was conducted with 41 patients who visited the Department of Oral medicine, Pusan National University Dental Hospital (Yangsan, Korea) in 2014. There were 17 patients (mean age±standard deviation [SD], 56.8±12.8 year, 15 females and 2 males) in the OLP group, 12 patients (mean age±SD, 60.3±8.4 year, 9 females and 3 males) in the BMS group and 12 patients without oral symptoms (mean age±SD, 53.3±10.6 year, 9 females and 3 males) in the control group. Every patient had more than one prosthetic appliance on his or her teeth. There were 12 patients with amalgam restorations, 34 patients with gold crowns, 19 patients with porcelain-fixed metal crowns, and 13 patients with implants. There were 40 teeth with amalgam restorations, 141 teeth with gold crowns, 87 porcelain-fixed metal crowns, and 45 implants (Table 1).

The patients were asked how long they had been wearing their fixed prostheses. For those who had more than one casting alloy, the duration was calculated based on the oldest one because the first dental alloys had been intraorally corroded. This study focused on the relation between the concentration of oral metal ions and the exposure time. Thus, the type, number, surface area and thickness of dental alloys were not considered.

According to the duration of oral prosthetics, patients were divided into 6 groups; OLP (≤5) group (oral prosthesis for less than 5 years), OLP (>5) group (oral prosthesis for more than 5 years), BMS (≤5), BMS (>5), CON (≤5), and CON (>5) group. Clinical and histopathological criteria of OLP were applied to the inclusion criteria for OLP group in this study.[4,21] The inclusion criteria for BMS group consisted of complaints of a burning sensation in oral mucosa and tongue in the normal form, normal salivary flow rate (unstimulated whole saliva >0.1 mL/min and stimulated whole saliva >0.5-0.7 mL/min), and normal results in laboratory tests of complete blood counts, liver and renal function test (total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, and creatine), thyroid function tests (T3, T4, and thyroid stimulating hormone), vitamin B12, folate, serum iron, ferritin, and zinc levels.[22] In the control group, patients had mandibular torus, halitosis and masticatory muscle disorder that had no oral visible lesions or oral pain. The exclusion criteria for all three groups included having serious systemic diseases (e.g., uncontrolled medical conditions, cancer) or inability of communicating. The study protocol was approved by the Institutional Review Board of Pusan National University Dental Hospital (#PNUDH-2015-015).

2. Collection of Whole Saliva Samples

Patient's informed consents were obtained and saliva samples were accumulated from all patients at their first

Table 1. Characteristics of the OLP, BMS, and control groups

Characteristic	Control	OLP	BMS
Number of patients (gender)	12 (9 females, 3 males)	17 (15 females, 2 males)	12 (9 females, 3 males)
Age of patients (y)	53.3±10.6	56.8±12.8	60.3±8.4
Duration of the prosthetic appliance (y)	7.52±6.21	8.06±6.28	5.92±3.15
Severity of pain (NRS, 0-10)	NA	5.1±2.4	7.0±1.4
Duration of symptom (mo)	NA	20.0±22.4	15.6±17.1
Sites of symptom	Mandibular torus halitosis	Buccal mucosa 13	Anterior 1/3 of tongue 12
	Masticatory muscle disorder	Vestibule 13	Labial mucosa 3
		Gingiva 8	Lateral tongue 4
		Tongue 1	Buccal mucosa 1
Other features of symptom (% of patients)	NA	<Type of lesions>	<Related symptoms>
		Reticular 23.5	Dysgeusia 16.7
		Erosive 5.9	Hypoesthesia 16.7
		Atrophic 76.5	Xerostomia 23.5
Medication (% of patients)	No medication 58.3	No medication 47.1	No medication 33.3
	Diabetes 16.7	Diabetes 58.8	Diabetes 16.7
	Hypertension 25	Hypertension 35.3	Hypertension 25
	Hyperlipidemia 8.3	Hyperlipidemia 5.9	Hyperlipidemia 25
	Heart disease 16.7	Heart disease 11.8	Menopausal symptom 25
	Gastrointestinal disorder 33.3	Hyperthyroidism 5.9	
		Arthritis 5.9	

OLP, oral lichen planus; BMS, burning mouth syndrome; NRS, numerical rating scale; NA, not applicable.
Values are presented as mean±standard deviation.

dental visit. Subjects collected their unstimulated whole saliva in a polypropylene tube for 3 minutes. The saliva samples were immediately stored in −80°C deep freezer until assay.

3. Analysis of Metal Ions

The 13 metal ions mainly contained in current dental prosthetic supplements were selected for this study.[19] These includes copper (Cu), cobalt (Co), zinc (Zn), chromium (Cr), nickel (Ni), aluminum (Al), silver (Ag), iron (Fe), titanium (Ti), platinum (Pt), tin (Sn), palladium (Pd), and gold (Au) ions. To evaluate the metal levels in saliva, samples were diluted with distilled water up to 3 mL. The ions in saliva were measured by Laser Ablation Microprobe Inductively coupled Plasma Mass Spectrometry (LAM-ICP-MS, Optima8300; Perkin-Elmer, Shelton, CT, USA). As the amount of crude saliva samples were around 0.3-2.5 mL, the data was revised by each diluted ratio.

4. Statistical Analysis

The data did not follow the normal distribution so nonparametric tests were used in this study. The Kruskal-Wallis test was used to find meaningful differences between the groups. The Mann-Whitney U test was used to determine significance of the OLP and BMS group compared to the control group. p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Prosthetic Durations of the OLP, BMS, and Control Patients

The mean±SD duration of prosthetic appliance was 8.06±6.28 years in OLP group, 5.92±3.15 years in BMS group and 7.52±6.21 years in control group (Table 1). The mean±SD duration of oral symptom was 20.0±22.4 months in OLP group and 15.6±17 months in BMS group. Prostheses were observed in the oral cavity before symptoms appeared in both the OLP and BMS groups. Information of other clinical features and medications is given in Table 1.

2. Metal Ion Concentrations according to Prosthetic Duration

The prosthetic time of each patient was based on the

duration of the oldest casting alloy on his or her teeth. Salivary Cu, Co, Zn, Cr, Ni, Al, Ag, Fe, Ti, Pt, Sn, Pd, and Au ions were used to check the relation between concentrations of metal ions and time. Ti ions showed statistical difference between groups ($p<0.05$) (Fig. 1). There was no correlation between other ions and prosthetic duration.

3. Ti Ion Concentrations from Saliva Samples

In comparison of 13 ions, only Ti ions show a clear difference among groups with prosthetic periods of less than 5 years (Table 2). Groups with oral dental cast alloys of over 5 years showed no difference in ion concentrations (data not shown). The Ti ions had statistically significant differences among the groups with below 5 years of prosthetic duration (Fig. 2). There was no significant difference among the groups wearing dental cast alloys of more than 5 years.

4. Ti Ion Concentration in BMS (≤5) Group

To distinguish OLP and BMS groups from control group by their levels of Ti ions, three groups were analyzed by the

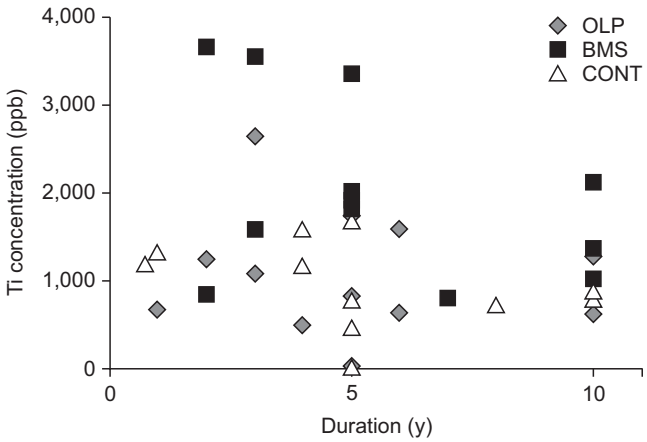

Fig. 1. The relationship between Ti ion concentrations and the prosthetic duration. Ti ions in BMS group displayed a tendency to exhibit higher levels compared to other groups ($p<0.05$). Ti, titanium; OLP, oral lichen planus; BMS, burning mouth syndrome; CONT, control.

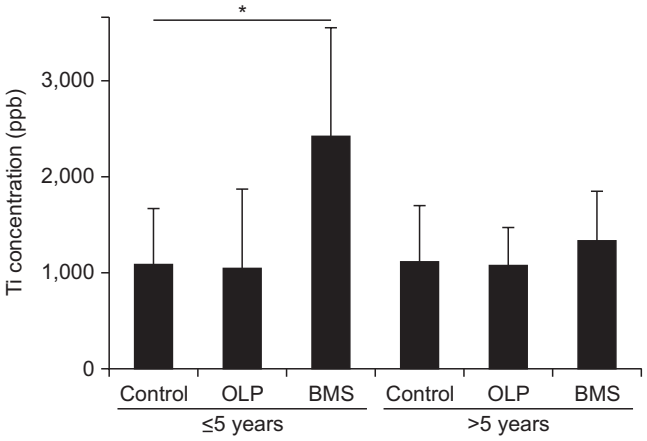

Fig. 2. Comparisons between Ti concentrations and period of prostheses based on 5 years. Statistically significant differences measured by Kruskal-wallis test. The Ti levels had meaningful differences among the groups with below 5 years of prosthetic duration (*$p=0.016$). There was no significant difference among the groups wearing dental cast alloys of more than 5 years ($p=0.565$). Ti, titanium; OLP, oral lichen planus; BMS, burning mouth syndrome.

Table 2. The concentrations of metal ions among the groups with below 5 years of prosthetic duration

Metal ion	Control (n=7)	OLP (n=8)	BMS (n=7)
Copper	20.87±16.69	12.86±6.33	39.61±50.70
Cobalt	0.25±0.22	0.25±0.14	0.50±0.38
Zinc	139.15±202.93	74.95±79.60	942.64±2271.66
Chromium	12.46±7.56	14.07±7.42	30.82±24.19
Nickel	8.65±8.57	3.41±3.37	8.00±9.31
Aluminum	19.51±17.91	9.31±5.23	127.97±207.87
Silver	0.39±0.34	0.42±0.31	0.68±0.74
Iron	100.63±81.38	118.29±82.67	158.90±85.66
Titanium*	1,094.15±564.36	1,050.34±805.97	2,401.69±1,111.12
Platinum	0.24±0.21	0.06±0.07	0.27±0.35
Tin	0.44±0.42	0.94±1.46	2.41±5.08
Palladium	10.11±7.66	3.13±1.82	9.04±10.45
Gold	22.59±35.10	8.66±7.29	68.09±140.79

OLP, oral lichen planus; BMS, burning mouth syndrome.
Values are presented as mean±standard deviation (ppb).
Kruskal-Wallis was performed to compare the concentrations of metal ion between groups.
*Significant difference between the groups ($p<0.05$).

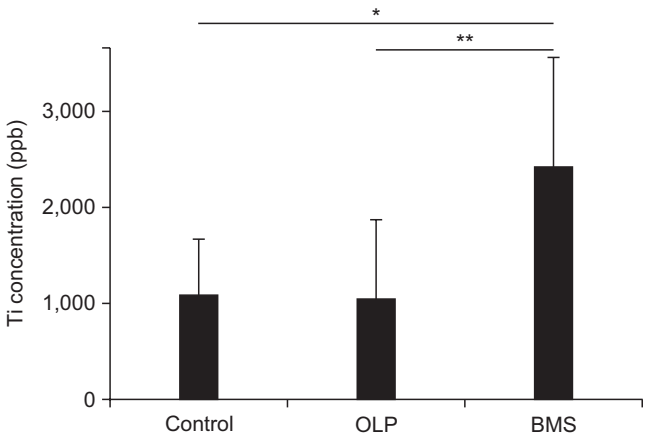

Fig. 3. The mean concentration of Ti ions in unstimulated whole saliva from OLP, BMS and control groups with fewer than 5 years wearing prosthetic appliances. The Mann-Whitney test was used for comparison (*p=0.017, **p=0.021). The Ti levels in BMS group were higher than the OLP and control groups. Ti, titanium; OLP, oral lichen planus; BMS, burning mouth syndrome.

Mann-Whitney U test. Ti ion concentration of the BMS (≤5) group was higher than that of the OLP (≤5) and control (≤5) groups ($p<0.05$) (Fig. 3).

DISCUSSION

In the oral cavity, a temperature of 37°C and high humidity are maintained and electrolytes are always present in the saliva.[18] Also there are numerous chemical and physical reactions as well as metabolism of about 30 species of bacteria.[23,24] Therefore, it can be said that a dental prosthesis is always exposed to a corrosive environment influenced by salivary pH, glucose levels and local galvanism.[18,25-27] Corrosion of dental cast alloys produces the release of metal ions, which may cause toxic effects or allergic reactions.[2,19] The intraoral symptoms were gingival swelling and erythema, mucosal pain and lichenoid reactions.[28] Previous studies have reported the salivary metal concentrations in patients with oral diseases, but there is no data about in vivo changes of metal ion concentrations corresponding to time. This study provided more meaningful results because the concentrations of salivary metal ions were analyzed according to period of dental prostheses in the OLP, BMS, and control group.

The data from this study reported the levels of metal ions released from dental cast alloys according to the prosthetic duration. The Ti ion concentrations in the BMS group were significantly higher than other groups. Particularly, BMS group with prosthetic duration of lower than 5 years had significantly high Ti concentration. In BMS group, the increased section of 3-60 months coincided with the duration of burning symptoms (15.6±17.1 months). Many other studies support this suggestion. Patients with complaints or symptoms in the oral cavity in relation to dental cast alloys mainly reported burning mouth (72%), metal taste (56%), and electric sensation (44%).[17] In other studies, subjective oral complaints like burning mouth and metal taste were related to dental alloy components, too.[29-32]

When dental cast appliances were fitted in to the oral cavity for 5 years, salivary concentrations of Ti ions in the BMS group were statistically higher than those of the OLP and control groups. As Ti has high corrosion resistance compatible with physiologic conditions, it is widely approved as an excellent metal for in vivo implantation.[33-37] However, if the protective oxide layer of Ti is peeled, it can become corrosive like many other metals. The Ti ions and particles may function as an allergen that can cause a hyperactive reaction in adjacent oral tissue and even in other remote other organs and biological systems such as lymph nodes, lungs and serum.[38,39] The inflammatory response to metallic and polymeric debris in lymph nodes is followed by the immune activation of macrophages and the associated production of cytokines.[40] In sheep model, failed dental implants showed higher levels of Ti in lungs (2.2-3.8 times the mean of the controls) and regional lymph nodes (7-9.4 times the levels in controls).[33] In vitro studies using Memory Lymphocyte Immuno-Stimulation Assay (MELISA) demonstrate that Ti can induce clinically relevant hypersensitivity in some patients chronically exposed via dental or endoprosthetic implants.[41]

Systemic Ti ion levels in dental or endoprosthetic implants have been reported in various studies. It's concentrations in peri-implant tissues have been described as 100-300 ppm, often accompanied by discoloration or type IV hypersensitivity reactions.[23,35,42-44] Serum Ti ion levels in 52 preoperative patients were between 1.68-6.97 ppb, and 3-years after operation of mandibular dental implants, the concentration were between 1.03-4.98 ppb.[45] In other studies serum, Ti ion levels ranged from 2.1-7.9 ppb.[46,47] The data from this study shows a range of 7.7-3,654.9 ppb

(1,303.1±808.1 ppb) for salivary Ti ion concentrations. These values are higher than the known serum ones. The patients in this study had no systemic Ti implants such as those for total joint arthroplasty, endovascular intervention and bone substitution. The differences may be the cause of saliva directly contacting with Ti implants and casting alloys frequently containing acidic and sugared food, microbial plaque and prophylactic fluoride ions that have been reported as much more corrosive environments for Ti alloys.[48-50]

This study has several limitations. Since the prosthetic duration was determined by only patient's report, it might not be sufficiently validated. The sample number of patients was too small and having more patients would have given a more statistically significant result. Lastly, dental cast appliances were characterized by their type and duration of exposure, so their components, number, surface area, and thickness were not considered. To have information of the metal ion, particularly Ti's contribution to BMS, further studies would be needed using a large sample size, oral prosthetic components, and salivary conditions that could affect metal corrosion rate.

As time passes, dental casting alloys in oral cavity release metal ions that could be contributors of many intraoral signs and symptoms. This present research mentioned that in the BMS group, salivary metal ions from dental prosthesis have high concentrations compared to patients with no oral symptoms. Particularly, Ti ions from 5-year-old prosthetic restorations are statistically higher in the oral cavity of BMS patients. These results suggest that Ti ions released from old dental implants and Ti casting alloys could attribute to burning sensation of BMS patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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