

Increased Copper Level in Oral Mucosal Tissue of Patients with Submucous Fibrosis and who Chew Areca Nut Products

The Editor,

Sir,

Oral submucous fibrosis (OSMF) is a crippling disease that impedes the normal functions of the oral cavity. It is a slowly progressive disease characterized by epithelial atrophy, abnormal accumulation of collagen fibres in the sub-epithelial tissues leading to severe restriction of mouth opening and movement of the tongue. The disease is believed to be a localized collagen disorder.

Chewing areca nut alone, or as a component of betel quid, is widespread in the Indian subcontinent. Areca nut chewing is also causally linked to OSMF (1). Areca nut has a high copper content (302 nmol/g), a substantial amount of which is released into saliva while chewing (2). The role of copper in submucous fibrosis is not clearly understood although it is known that the copper dependent enzyme, lysyl oxidase, secreted by the fibroblasts, facilitates the cross-linking of collagen, thereby inhibiting its degradation (3).

The aim of this study was to determine the copper level in serum and buccal mucosa of OSMF patients who are habitual chewers of areca nut-containing products such as gutka, pan and pan masala. (Gutka is a commercially available preparation containing areca nut, tobacco, small quantities of slaked lime and catechu in a dry form).

This study was carried out on 40 patients with OSMF who attended the Department of Oral Medicine, College of Dental Sciences, Dharwad, India. The mean ages of these patients ranged from 17 to 44 years (23.40 ± 6.25 years). A detailed case history, with specific reference to their chewing habits (type, brand, duration, frequency) was recorded. Seven patients were cigarette smokers, eight consumed alcohol occasionally and twenty-two consumed excessive quantities of chilies. All patients complained of burning sensation in the mouth, especially in the cheeks, tongue and floor of the mouth. None of the patients had received any kind of treatment for OSMF and none was suffering from any systemic diseases. The selection of these patients was based on the following clinical criteria: positive history of areca nut chewing, burning sensation in the mouth on eating normal spicy food, history of gradual restricted mouth opening, blanched, mottled and pearly appearance of buccal mucosa with presence of fibrous bands, difficulty in protruding the tongue, involvement of uvula, soft palate, lips, faucial pillars, clinically palpable fibrous bands on the buccal mucosa and other areas of the oral cavity.

Normal healthy controls ($n = 31$) were selected in the age group of 17 to 44 years (23.09 ± 5.96 years). The

control group did not chew areca nut nor consume tobacco in any form. They had normal healthy looking mucosa and did not have any systemic disease.

Copper levels in the serum and buccal mucosa were estimated by atomic absorption spectrophotometry. Tissue specimen from the buccal mucosa was taken by incisional biopsy from the area that showed maximum involvement.

The serum level of copper in the OSMF patients and healthy control subjects was 75.6 ± 10.6 micrograms/100 ml and 80.5 ± 11.9 micrograms/100 ml, respectively. Copper level in the oral mucosal tissue in the OSMF patients and healthy control subjects was 1.71 ± 0.49 micrograms/100 mg ($n = 40$) and 0.69 ± 0.22 micrograms/100 mg ($n = 31$), respectively. No significant difference in serum copper level was observed between the OSMF patients and control subjects ($p > 0.05$), whereas the difference in copper level in the tissue was significant ($p < 0.01$), the level being 2.47-fold higher in the patients. There was no correlation between the copper level in serum and tissue of the two groups and the extent of mouth opening ($r = 0.3103$ and $r = 0.0961$, respectively).

The only report of tissue copper level in healthy and OSMF patients, determined by quantitative X-ray microanalysis, was that of Trivendy *et al* (4) who reported a mean copper level of $6.5 \mu\text{g/g}$ in OSMF cases ($n = 7$) and $2 \mu\text{g/g}$ in the non-areca nut-chewing controls ($n = 2$). The high amount of copper in areca nut along with the high exposure to the oral tissues during chewing could have increased the local absorption and accumulation.

It may be hypothesized that the extent of absorption of copper into the systemic circulation is reduced due to the fibrosis and reduced vascular supply. It is also possible that the denatured proteins like amyloid and β -proteins, which have a low turnover rate, may bind bivalent metal ions such as copper and could cause a net accumulation. The increased copper level in the tissue, which is already damaged by the chronic irritation, could predispose, initiate or perpetuate the disease or the accumulation may be the after effect of OSMF following alterations of tissue morphology. Other controls such as areca nut users without OSMF may be used to further study the relationship between copper and OSMF. A mean increase of 247.8% copper level in the oral mucosal tissue of OSMF patients in the present study is significant and warrants further research.

From: KG Pillai¹, KN Burde², School of Dentistry¹, Faculty of Medical Sciences, The University of the West Indies, Mount Hope, Trinidad and Tobago, West Indies and College of Dental Sciences², Dharward, India.

Correspondence: Dr KG Pillai. School of Dentistry, Faculty of Medical Sciences, The University of the West Indies, Mount Hope, Trinidad and Tobago, West Indies. Fax: 868-662-1447, e-mail: gopal@trinidad.net.

REFERENCES

1. Maher R, Lee AJ, Warnakulasuriya KA, Lewis JA, Johnson NW. Role of areca nut in the causation of oral submucous fibrosis: a case control study in Pakistan. *J Oral Pathol Med* 1994; **23**: 65-9.
2. Trivedy C, Baldwin D, Warnakulasuriya S, Johnson N, Peters T. Copper content in areca catechu (betel nut) products and oral submucous fibrosis. *Lancet* 1997; **349**: 1447.
3. Ma RH, Tsai CC, Sheih TY. Increased lysyl oxidase activity in fibroblasts cultured from oral submucous fibrosis associated with betel nut chewing in Taiwan. *J Oral Pathol Med* 1995; **24**: 407-12.
4. Trivendy C, Warnakulasuriya S, Baldwin D, Peters TJ, Hartley R, Senkus R et al. High copper levels in tissues from oral submucous fibrosis (OSF) patients may be related to the consumption of areca nut and be important in the pathogenesis. *Oral Dis* 1997; **3**: 39.