



Evaluation of the Effects of Dental Implants on Oral Lesions

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ABSTRACT

Objective: To determine whether dental implants impress oral lesions, and to evaluate the nature of their effect on the lesions.

Materials and methods: A comprehensive search was done via Google and PubMed for articles (including case reports and literature reviews) containing the keywords 'oral squamous cell carcinoma' (OSCC), 'oral lichen planus' (OLP), 'lichenoid contact reaction' (LCR), 'osseointegrated implants', and 'dental implants', in the last 10 years (2002-2012).

Results: The study included 24 articles involving patients with dental implants, and some oral lesions (e.g. oral lichen planus and oral squamous cell carcinoma) or with a history of lesions. In these publications, there is evidence suggesting the possibility of emergence, exacerbation, recurrence, or even malignant transformation of the oral lesions after implant placement in some cases.

Conclusion: Based on our review of the literature, implant treatment does not seem to be completely safe under any circumstances, but may have some complications in subjects with certain diseases (e.g. oral lesions, autoimmune diseases, malignancies, allergic reactions, etc.). Therefore prior to treatment, patients should be fully informed of the risks.

Clinical significance: Implant treatment is best done with caution in patients with cancer or mucocutaneous disorders.

Keywords: Dental implant, Oral lichen planus, Oral squamous cell carcinoma.

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INTRODUCTION

Oral rehabilitation, and replacement of missing teeth, has always been valued in all societies. There are different methods of tooth replacement, each having its advantages and disadvantages. Over recent decades, the application of dental implants to replace missing teeth has gained popularity. In applying this method, clinicians usually consider just the quality and quantity of alveolar bone, without regard to the oral mucosa condition; if the alveolar bone is adequate, they utilize this replacement method.¹⁻³

Some researchers found that the quality of oral mucosa is also important in placing the dental implant, and they demonstrated that the capacity of oral mucosa to adhere to the implant can change in patients with oral lesions.^{2,4} The studies revealed that the oral lesions may be intensified after the implant placing, and even the benign lesions may be transformed to malignancy. Also, after the implant placing in some patients with a history of malignancy, the clinicians may face the recurrence of malignant lesion that appears as a benign lesion in association with the implant. Moreover, some studies reported the emergence of oral lesions for the first time after the implant placing, and others mentioned the rise in cases of oral lesions following implant placing.^{3,5-13} So, it appears that implant placing to replace the edentulous areas is not inherently safe, and it should therefore be better explained to patients (especially high-risk individuals) the risks involved with this method of treatment.

The purpose of this study is the evaluation of several lesions that occurred or recurred following dental implant placement.

MATERIALS AND METHODS

In this study, a comprehensive search was done via Google and PubMed for articles (including case reports and literature reviews) containing the keywords 'Oral squamous cell carcinoma' (OSCC), 'oral lichen planus' (OLP), 'lichenoid contact reaction' (LCR), 'osseointegrated implants', and 'dental implants', in the last 10 years (2002-2012).

Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma accounts for approximately 90% of oral malignancies.^{14,15} According to the World Health Organization (WHO), oral cancer is the sixth most common cancer worldwide.^{16,17} The cancer can affect the quality of life and be very debilitating, and it has negative effects on chewing, swallowing, speech, and the patient's appearance.^{15,17}

Because oral cancer is usually painless in its early stages, referral of the patient to a dentist usually occurs a long time after the onset of the lesion, although sometimes the lesion may be discovered randomly during a routine examination.

Progress in the treatment of oral cancer has been slow, so the identification of each of the factors which plays a role in the development of the disease, and the avoidance of those factors, are very important.¹⁷

Many cases of oral cancer occur in a clinically normal mucosa, while some develop in premalignant lesions, such as leukoplakia, erythroplakia, and OLP.^{5,11} Therefore, precancerous lesions should be biopsied to confirm the existence or absence of malignant transformation.

Oral Squamous Cell Carcinoma and Dental Implants

Three contributing factors in the development of cancer are daily diet, smoking, and infection/inflammation. Of these three factors, infection/inflammation is definitely involved in carcinogenesis.¹⁸ Although acute inflammation is part of the host's defense to environmental stimuli, chronic inflammation can be an important factor in the development of cancer.^{19,20} Almost all tumors are associated with inflammatory cells. Chronic inflammation from mild and persistent viral, bacterial and chemical factors accelerates formation of pre-malignant foci and development of tumor.²¹ Today, there is sufficient evidence that chronic inflammatory process is able to provide an environment based on cytokine that can impress cell survival, growth, proliferation, and differentiation, and so, it may be involved in initiation, progression, invasion and metastasis of cancer.²²

Chemokines are a group of cytokines, considered as acute and chronic inflammatory mediators. These proteins recruit leukocytes to the site of inflammation. Chemokines have both antitumor and protumor effects. Cancer, and the metastasis arising from it, are associated with expression of many chemokines.^{20,23-25} For example, Ammer et al conducted a survey on OSCC and expression of chemokines, and they demonstrated the relationship between expression of CXCR4 at the site of tumor, and metastasis to lymph nodes, invasion method, recurrence of the tumor and prognosis.²⁶ Parallel to this study, Ishikawa et al found a significant relationship between expression of CXCR4 and metastasis to lymph nodes in OSCC.²⁷ Ferreira et al gave a report on the role of CCL2 in OSCC metastasis to lymph nodes.²⁸ In another study, researchers also demonstrated that CCR7 is significantly associated with metastasis to lymph nodes, extensive tumors, local recurrence of the tumor and mortality from cancer.²⁹ It should be noted that some new research is being conducted to determine the exact mechanism of carcinogenesis from chronic inflammation caused by long-term stimulations and infections.

In the oral cavity, chronic inflammation can be caused by several factors, such as periodontal disease and OLP.^{30,31} Peri-implantitis is also a cause of chronic inflammation, and it can be a risk factor for developing OSCC. Jane-Salas et al demonstrated that in fact, implant placing is a cofactor for developing stimulation and inflammation, and it is able to develop OSCC. However, they could not prove a definite cause and effect relationship in this matter based on their study.³²

Periodic detailed examination of the tissue around the implant is important. The examiner should consider peri-implantitis, erosion or discoloration of mucosa, leukoplakia, pain, loosening of the implant, and bone destruction. Carcinoma may initially appear as peri-implantitis.^{11,33,34} Kwok et al reported that a non-healing ulcer in tissue around the implant (3 months after completion of implant treatment) in a 62-year-old male patient with a history of excessive alcohol and tobacco consumption (40 cigarettes per day for over 30 years until 2 months prior to his attendance to clinic) was diagnosed as SCC after histopathologic examination.⁵ In a study by Chimenos-Kustner et al of a 62-year-old woman with a history of moderate consumption of alcohol (consumption for 2 years prior to surgery), and tobacco (cessation of smoking 10 years previously), it was reported that squamous cell carcinoma (SCC) was detected around the implant as a rapid growth exophytic lesion a few weeks after the implant placing.³⁵

In some cases, the inflammation around the implant may persist over a long period without malignant trans-

formation. Gulati et al reported a case of a 62-year-old woman with a long history of smoking (20 cigarettes per day) with a white patch in the mouth that was diagnosed as SCC histopathologically. One year after the surgery of the lesion, dental implant was placed for the patient. During 7 years after implant placing, multiple episodes of inflammation were observed around the implant. Periodic biopsies revealed chronic inflammation without any evidence of dysplasia or malignancy, until 8 years after implant placement, one of the biopsy specimens was diagnosed as SCC.³⁶

Since factors, such as tobacco and alcohol consumption (as the most important factors), immune deficiency, nutritional deficiencies, and viral infections are implicated in SCC development,^{37,38} it can be considered that in people affected by one or more of these factors, emergence of OSCC following implant treatment can be an accidental phenomenon without any association with the dental implant. However, since dental implant is able to cause chronic inflammation and some changes in the human immune system, and also, since chronic inflammation and immune system disorder are underlying causes for development of malignancy, it seems that implant placing can be an explanation for OSCC development, and this issue needs more and closer evaluation.

Oral Lichen Planus

Lichen planus is a chronic inflammatory immune-mediated disease that affects the skin and mucosa. The prevalence of OLP is 0.5 to 2.2%, and the mean age at diagnosis is approximately 55 years. The disease is more common in women. It clinically includes reticular, erythematous (atrophic), and erosive (ulcerated, bullous) forms. Reticular lesions are usually asymptomatic, but some patients complain of annoying roughness of oral mucosa. Atrophic and erosive forms are usually symptomatic, and they can cause mild burning to severe pain that causes difficulty in swallowing and speaking.^{4,39-42}

The exact etiopathogenesis of OLP is unknown. It seems that several factors, including stress, genetics, environment, and lifestyle are effective in OLP development.^{4,43,44} The immunologic nature of the disease has also been accepted. In addition to the many autoimmune features in OLP, including chronicity, onset in adulthood, tendency to occurrence in females, association with other autoimmune diseases, and existence of cytotoxic T cells in the lesions, the role of autoimmunity has been confirmed in pathogenesis of the disease.⁴⁵ Cytotoxic T lymphocytes cause apoptosis of epithelial cells in OLP that lead to chronic inflammation. In fact, the above mechanism is a cell-mediated immunologic response that is developed against antigenic change of oral mucosa.^{41,46}

World Health Organization (WHO) has considered this disease as a precancerous condition, because many articles have substantiated the malignant potential of OLP and stated that patients with OLP are at increased risk of cancer.^{39,41,47-49} The prevalence of OSCC from this disease has been reported as 0.4 to 6.5%.⁵⁰

Oral Lichen Planus and Dental Implants

Oral lichen planus is a lesion that affects the quality of oral mucosa. Some researchers have demonstrated that, in addition to the quality and quantity of the bone, the condition of oral mucosa should be considered before application of dental implants. They found that the capacity of oral mucosa to adhere to the titanium surface of implant changes in patients with OLP.^{2,4} In a case reported by Reichart, a 63-year-old woman was treated by implant to replace her teeth, and 10 years later, the symptoms of OLP were observed. Later, dental implants were used again to replace other missing teeth. After some time, the clinical signs of OLP were observed again. In the same study, the case of a 68-year-old woman was also reported. The patient had been with OLP about 12 years previous to implant surgery. Sometime after surgery, the symptoms of OLP recurrence were observed.³

Among the patients with OLP that attended the Oral and Maxillofacial Diseases Department, Dental Faculty, Tehran Medical Sciences University, we faced with patients who have had dental implants. A 47-year-old man, who had been with OLP for 1 year, had undergone implant surgery 1 year previous to the diagnosis. A 62-year-old woman underwent implantation surgery about 1 year ago, and subsequently, OLP appeared as inflammation around the implant. None of these patients had a history of smoking and alcohol consumption.

After the implant placing, in addition to the likelihood of recurrence or exacerbation of OLP, there is the possibility of malignant transformation of the lesion, or development of malignancy in the patient with history of OLP. Czerninski et al reported a case of a 52-year-old woman who had a history of OLP and smoking (she had been a heavy smoker for over 20 years). The patient attended the clinic with severe manifestations of OLP. A few years previously, dental implants had been placed to replace missing teeth. In the oral examination, an ulcer and a red exophytic mass were observed around the implants that were clinically similar to peri-implantitis. Radiographic examination also showed bone destruction around the implants. Biopsy of the lesion established the diagnosis of SCC.¹¹

It could be assumed that the re-emergence of OLP after implant treatment is an accidental phenomenon, because

it is a naturally recurrent lesion. Alternatively, considering OLP is a chronic inflammatory immune-mediated disease and also considering the effect of implant on the immune system and development of chronic inflammation, it could be concluded that dental implant is probably effective in development or exacerbation of OLP and even, in malignant transformation of the lesion. However, more research is necessary to confirm this hypothesis.

Although the exact pathogenesis of OLP is unknown, nonspecific mechanism is one of the possible effective mechanisms in development of the lesion. This mechanism includes mast cell degranulation and activation of matrix metalloproteinase (MMP) in OLP lesions. Matrix metalloproteinase are a group of zinc-dependent extracellular enzymes (such as collagenases, gelatinases, stromelysins, and membrane-type MMPs) which are able to break down matrix extracellular proteins. These proteins (proteoglycans, glycoproteins, and adhesion molecules) are essential for mechanical connection of titanium implant to bone.^{45,51-53} Therefore, the above mechanism could explain the risk of implant failure increase in patients with OLP (due to activation of MMPs in OLP lesions and as a result, enhancement of these enzymes' effects on the matrix proteins).

Lichenoid Contact Reaction

Lichenoid contact reaction is a delayed hypersensitivity reaction to dental materials, including amalgam compounds. The clinical types of LCR are similar to OLP. The most significant clinical difference between LCR and OLP is extension of the lesions. Most LCR lesions are restricted to areas that are regularly in contact with dental materials (such as buccal mucosa and border of tongue). Some lesions, especially those that develop on the lateral border of tongue, may extend somewhat beyond the direct contact of dental materials. Lichenoid contact reaction is asymptomatic in most cases, but when there are ulcerative or erythematous lesions, hot and spicy foods may cause discomfort in the oral mucosa. The period of time that dental materials are in contact with the oral mucosa has a definite impact on development of the lesion.^{54,55}

Lichenoid Contact Reaction and Dental Implants

Some of the compounds in dental materials can cause allergic reactions. Previously, titanium in dental implants was considered an inert substance. It has been recently reported that titanium also can induce type I or IV allergic reactions (especially in subjects with a history of allergy to metals or jewelry), and these reactions can cause implant failure in some patients. There are several hypotheses to explain the sensitivity to titanium. It has

been reported that titanium activates macrophages. The activated macrophages are able to secrete cytokines and facilitate the inflammatory process.^{56,57}

Oral allergy signs include erythema, ulceration, gingivitis, geographic tongue, angular cheilitis, or local lichenoid reactions in the oral mucosa. Patients complain of burning sensation, dry mouth or lack of taste, and sometimes headache and joint and muscle pain.^{56,58,59}

Sicilia et al performed a clinical study to test for titanium allergy on 1500 dental implant patients. In this study, 9 patients had sensitivity to titanium and displayed positive reactions to this metal.⁶⁰ In another study by du Preez et al the case of a 49-year-old female patient with allergy to implant was reported. After the implant placing, severe local reaction occurred in the tissue, leading to the removal of the implant, after which soft and hard tissues healed satisfactorily.⁶¹ Egusa et al reported another allergy case. In this patient, allergy to titanium appeared as facial eczema, and it disappeared after removal of the implant.⁶²

Other Oral Diseases and Dental Implants

Gingival tissue can react to local irritant factors and cause a lesion that is usually referred to as epulis in the clinic. Olmedo et al reported the case of a 75-year-old female patient who developed an exophytic lesion on her alveolar ridge, in the implant area 2 months after surgery. Radiographic view revealed no bone destruction, and there was no trauma of occlusion. The patient had a favorable oral hygiene and accumulation of microbial plaque was not seen. By histopathologic examination, the diagnosis of pyogenic granuloma was confirmed and also, multiple granular metal-like particles were observed in the tissue. In the patient follow up for 4 years after removal of the lesion, no sign of recurrence was seen.⁶³

Olmedo et al also presented the case of a 64-year-old woman with an exophytic lesion. The lesion was developed in the gingival vestibule 10 months previously. Implant treatment had been performed for the patient 12 years previously. Bone destruction was observed in radiographic examination. Oral hygiene was favorable and no accumulation of microbial plaque was seen. The lesion was diagnosed peripheral giant cell granuloma (PGCG) based on histopathological features and also, discrete metal-like particles were detected in the tissue. In the patient follow-up for 2 years after surgery of the lesion, no recurrence was observed.⁶³

Another 6 cases of PGCG following implant treatment have been reported across a number of articles.⁶⁴⁻⁶⁷

Since, the developing of reactive lesions is associated with a local irritant factor, and there are not any usual irritant factors (such as microbial plaque and calculus)

in the two patients above, the metal-like particles in the tissue can be considered as stimulus (these particles may be due to corrosion).

Ben Slama et al reported a case of osteoradionecrosis (ORN) around the implant. The patient was a 75-year-old woman who underwent implant treatment 10 years before radiotherapy. Forty months after radiotherapy, inflammation around the implant was observed that was associated with ORN and pathologic fracture. They concluded that high dose of radiation on the bone around the implant can cause ORN that is followed by pathologic fracture.⁶⁸

There are some reports indicating that in addition to SCC, other neoplastic lesions including osteosarcoma and plasmacytoma can also occur in association with dental implant. McGuff et al reported the case of a 38-year-old woman with maxillary osteosarcoma, where the lesion developed 11 months after the dental implant placing. The researchers stated that determining a definite cause and effect relationship between dental implant and cancer, based on just one reported case, is difficult or impossible; and they believe that the relationship between implant and developing of osteosarcoma may be accidental. However, clinical and scientific evidence supports the theory of malignancy development in association with implant and although rare, it is considered as a potential complication of implant application.⁶⁹ It should be noted that most reported sarcomas in association with implant are related to orthopedic implants. Researchers reported almost 49 cases of sarcomas in association with orthopedic implants over the past 50 years.^{70,71} Although implant is made up of non-toxic and histocompatible materials, researchers proved that many materials in implant, including titanium have potential oncogenic properties.^{69,70} Investigators also reported a case of dental implant failure in association with developing of plasmacytoma in a patient with a history of vertebral plasmacytoma.⁷²

Dib et al presented a case of breast cancer metastasis around osseointegrated implants. The patient was a 67-year-old woman with symptoms of severe pain, swelling and gum irritation in jaws, halitosis, and implant mobility in the maxilla. Radiographic examination revealed bone loss in maxilla, including around the implants. The histopathological features established the diagnosis of metastatic carcinoma from an adenocarcinoma of the breast (diagnosed at the same time) to the mandible and maxilla. It is assumed that the manipulation of the tissue during oral surgeries and placement of implants can be an important factor in the spread of tumors to the jaws.⁷³

CONCLUSION

Dental implant is routinely used as the best treatment for teeth replacement. However, caution should be used in its application, because of its role in the development of inflammation, and its effect on the immune system and therefore, possible adverse effects following treatment. This is particularly important in patients with a history of malignancy, or with one of oral mucosa lesions; and also, in patients with some systemic diseases, including autoimmune diseases. Patients should be informed about the possible consequences of implant treatment, including exacerbation or recurrence of these diseases.

If patients choose implant treatment to replace their missing teeth, oral mucosa should be checked regularly after implant placement (at least once every 3 months). It should also be noted that there is possibility of implant failure in patients with a history of allergy, so in some cases, it seems reasonable to perform titanium allergy test before implant placement.

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