

Review Article

Dental implants in patients with oral autoimmune diseases

Theodora S. Tounta*Private Dentist, Athens, Greece***Abstract**

Oral mucosal autoimmune diseases include a variety of disorders, like oral lichen planus (OLP), pemphigus vulgaris (PV), mucous membrane (MMP) and bullous pemphigoid (BP), epidermolysis bullosa acquisita (EBA), systemic lupus erythematosus (SLE) and Sjögren syndrome (SS) and can cause painful erosions, blisters and ulceration at the oral epithelium. Such diseases complicate dental hygiene and can lead to tooth loss. When natural teeth are missing, dental implants can improve quality of life for these patients. Osseointegration is necessary for dental implant success and is not contraindicated for patients with oral mucosal autoimmune diseases. However, the clinical dentist must consider the possible impact of oral autoimmune diseases on the oral epithelium that might affect implant success, also due to the difficulty of everyday oral hygiene, leading to bone absorption around the implant. Moreover, medication approved for the therapy of such diseases, such as corticosteroids, immunosuppressants and non-steroidal anti-inflammatory drugs (NSAIDs) could provoke osseointegration, as it compromises bone quality and affects the patient's general health. However, the impact of these drugs on implant surgery depends on dose and duration of the drug and usually dental implantation is possible.

Keywords: Oral autoimmune diseases, Dental implants, Lichen planus, Pemphigus, Peri-implantitis

Introduction

An autoimmune disease is a condition in which the immune system reacts to antigens by producing autoantibodies or by activating cells such as lymphocytes, thereby producing a state of inflammation¹. Autoimmune diseases that affect the oral tissues are notably oral lichen planus (OLP), pemphigus vulgaris (PV), mucous membrane (MMP) and bullous pemphigoid (BP), epidermolysis bullosa acquisita (EBA) and systemic lupus erythematosus (SLE), which are characterized mainly by oral manifestations, such as erosions, blisters, papules and bullae² and Sjögren syndrome (SS), which causes severe xerostomia³. The lesions caused by these diseases are significantly painful and can be provoked by minimum pressure, as the patient talks, chews or performs dental hygiene. As a result, those patients avoid proper teeth brushing, in order to protect their wounded oral mucous membrane, or to avoid causing new lesions. Consequently, patients with autoimmune diseases that affect the oral cavity can easily lose their teeth by dental caries or periodontitis².

In the past, when the remaining teeth could not support a fixed prosthesis, the occlusion restoration could only be accomplished by removable partial or total dentures. However, the denture use is commonly problematic for

patients with oral autoimmune diseases, as erosions, ulcerations, bulla formation and blisters cause additional mucosal discomfort and pain, due to the tissue pressure from the dentures. Therefore, in order to improve quality of life for these patients, fixed oral restorations have to be used, which leads to the necessity of dental implant rehabilitation. Dental implants can support fixed prosthesis or removable dentures, which are particularly stable, in contrast to simple dentures. However, autoimmune diseases with oral manifestations, as well as the medication intended for these patients, can affect the oral epithelium, as well as the bone quality, which are both important factors of implant osseointegration and long term success⁴.

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Corresponding author: Theodora S. Tounta, DDS, 29 K. Varnali Street, N. Erythrea, 14671, Athens, Greece

E-mail: theodoratounta@gmail.com

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Impact on periodontal and peri-implant tissues

In order to be successful, implant placement must be followed by osseointegration. Osseointegration is described by Branemark as the state when the implant and the alveolar bone are in contact, without the involvement of fibrous connective tissue⁵. Osseointegration is affected, amongst other aspects, by the quality of the bone, as well as the atraumatic healing of the surgery site⁵. Normally, the oral mucosa acts as a barrier and protects the alveolar bone from the oral cavity's bacteria. However, if the oral mucosa is problematic, as when the patient suffers from autoimmune diseases with oral manifestations, the sealing may be disturbed and there is a higher possibility of tissue infection, which can undermine the long-term implant survival⁶. Successful mucosal protection is achieved by the unhampered connection between the epithelial cells, as well as between the basement membrane and the connective tissue. The connection is accomplished by desmosomes in the former and hemidesmosomes in the latter⁷.

However, oral autoimmune diseases cause alternations in the oral epithelium and connective tissue, which may also disturb the connection between the mucosa and the dental implant surface and lead to infection and implant loss.

Oral lichen planus

Oral lichen planus is a chronic autoimmune disease that affects the oral mucosa, the skin, the genitals, the nails and the scalp. The prevalence ranges between 0.5-2.6%, in several countries worldwide⁸. White striations, blisters, erosions and atrophy are reported as clinical OLP features⁹. Figures 1 and 2 show lichenoid lesions on the buccal mucosa.

It has been suggested that osseointegration may be problematic in patients with oral lichen planus. Histologically, OLP causes degradation of the basal epithelial cells, as well as alternations of the basement membrane. As a result, the epithelium-connective tissue connection is affected, which leads to the creation of an empty space that can easily be infected⁹. Moreover, T-cells are increased in number and excrete cytokines, which leads to further epithelial cell apoptosis¹⁰. Therefore, it can be assumed that the implant survival is at stake if the implant is placed on damaged mucosal membrane¹¹. Moreover, Sugerma and Savage report increased levels of TNF- α in patients with oral lichen planus⁹. However, TNF- α is a major provoking periodontitis and peri-implantitis factor¹². Consequently, it is possible that peri-implant inflammation is more acute at patients with OLP compared to healthy subjects and could lead to quicker bone deformation and thereby also implant loss.

However, the majority of clinical studies referring to implant placement in OLP patients demonstrates promising results. Czerninski et al studied 29 OLP patients who had received 54 dental implants. The authors suggested that there is no correlation between lichen planus and implant

success¹³. Similar findings are reported by Hernández et

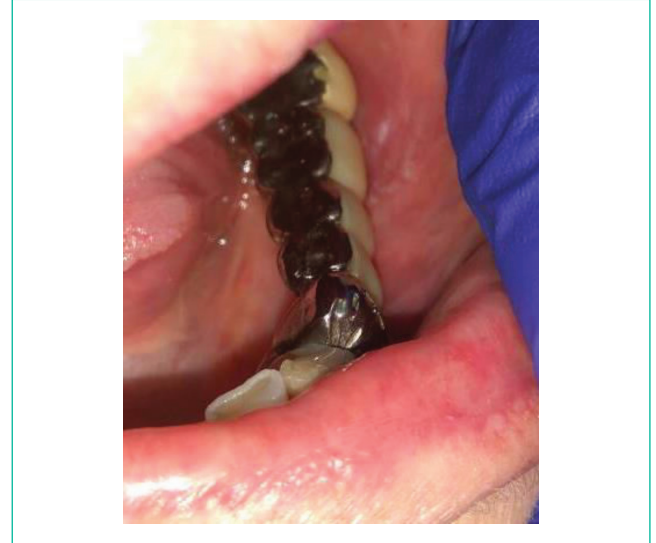


Figure 1. OLP lesions at a patient with active oral lichen planus. (Dr Foteinopoulou Elpida's archive).

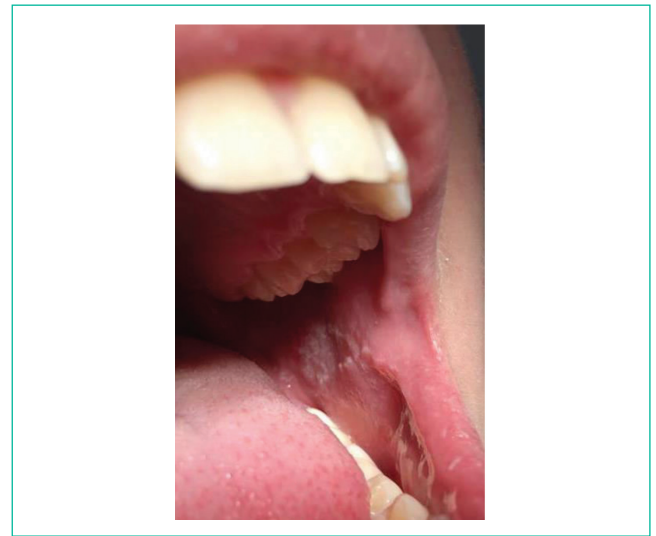


Figure 2. Lichenoid reaction in the buccal mucosa. (Dr Kartanos Euaggelos' archive).

al¹⁴. López-Jornet et al studied 32 OLP patients compared to 16 healthy people. The study involved a total amount of 106 dental implants. The writers suggest that there is no significant relationship between lichen planus and peri-implantitis¹⁵. Reichart's study referred to 3 OLP patients treated with 10 dental implants and suggests that dental

Authors	Population	Number of implants	Results
Czerninski et al ¹³	14 OLP patients with implants and 15 OLP patients without implants	54	No correlation between OLP and implant success
Hernández et al ¹⁴	18 OLP patients and 18 healthy people	56 62	No correlation between OLP and implant success
López-Jornet et al ¹⁵	16 OLP patients with implants, 16 OLP patients without implants, 16 healthy people with implants	56-50	No correlation between OLP and peri-implantitis
Reichart ¹⁶	3 OLP patients	10	OLP patients can be treated with implants
Esposito et al ¹⁷	2 OLP patients with complete dentures	4	Better ability to masticate and fewer OLP flare-ups

Table 1. Relationship between oral lichen planus and dental implants.

implant rehabilitation is safe for lichen planus patients¹⁶. Finally, Esposito et al placed 4 dental implants in 2 OLP patients with complete dentures and report better ability to masticate and fewer OLP flare-ups¹⁷. All findings are additionally described in Table 1. A possible explanation of the high implant success rate may be that in most studies the autoimmune disease was under recession and the oral hygiene was excellent.

Pemphigus vulgaris

Pemphigus vulgaris describes a range of epithelial bullous diseases, in which IgG auto-antibodies are produced, provoking akantolysis¹⁸. *Pemphigus vulgaris* affects skin and mucous membranes and appears in 0.1-0.5/100000 persons per year. In the early stages, patients may only present oral alternations. More specifically, intra-epithelial bullae appear, which rapidly grow in size, burst and leave painful erosions². Dental hygiene is particularly inflexible and the use of dentures causes constantly new bullae, because of the rubbing¹⁹.

Patients with PV make auto-antibodies against the desmosomes that connect the epithelial cells¹⁸. The epithelium rupture enables the bacterial infection, as the protective barrier no longer exists. The infection can then easily advance to the inner tissues and lead to bone loss and implant failure⁶. Literature data referring to implant placement in patients suffering from PV, to the best of our knowledge, are scarce. Altin et al placed dental implants in a pemphigus patient in order to support overall denture. 32 months after, the results were still satisfying and the pemphigus symptoms were less intense after the implant rehabilitation¹⁹. However, the surgery was performed only after the disease's control with corticosteroid use for several months.

Mucous membrane and bullous pemphigoid

Mucous membrane and bullous pemphigoid are chronic autoimmune diseases that are characterized by the formation of sub-epithelial bullae, which burst and leave

erosions and scars when healed^{20,21}. The prevalence is reported 1.3-2 and 13.4-21.7/1000000 persons per year respectively²²⁻²⁵. In both MMP and BP, auto-antibodies against hemidesmosomes- which are necessary for the bond formation between epithelial cells and the implant surface- are produced²¹. As a result, hemidesmosome malfunction may prevent the formation of a protective epithelial barrier for the implant⁶.

Moreover, in bullous pemphigoid patients' serum, as well as the bullae liquid, an increase in cytokines, chemokines, interleukins and TNF- α has been found. These factors provoke bone absorption in active periodontitis and may also affect the bone tissue around the implants^{21,26}. References in the bibliography concerning the success of implantation in such patients are rare.

Epidermolysis bullosa acquisita

Patients who suffer from epidermolysis bullosa also present sub-epithelial blisters, as EBA leads to the formation of auto-antibodies against collagen type VII. Epidermolysis bullosa is a rare condition, with prevalence 0.2/100000²⁷. Usually, the bullae gradually decrease and leave erosions and scars, which may lead to microstomia²⁸. Collagen type VII is a major contributor to mucous membrane stability and well-functioning^{21,29}. As a result, collagen type VII destruction by the auto-antibodies may lead to problematic mucous membrane creation, which may enable infection by pathogens and prevent osseointegration⁶.

In contrast to the above, literature findings suggest that dental implantation is successful in such patients. Penarrocha et al placed 27 dental implants in 3 EBA patients, with 97.9% success. The writers suggest that dental implants are not contraindicated for patients suffering from epidermolysis bullosa, on the contrary implants can improve their quality of life³⁰. Letelier et al placed 11 dental implants in one EBA patient successfully and report better results than removable dentures³¹. Penarrocha-Diago et al placed a total of 15 implants in

Authors	Population	Number of implants	Results
Peñarrocha et al ³⁰	3 EBA patients, edentulous at the maxilla and/or the mandible	27	Dental implants are not contraindicated and improve quality of life
Letelier et al ³¹	1 31-year-old EBA patient with severe symptoms	11	dental implants are better than conservative removable dentures
Peñarrocha-Oltra et al ³³	4 EBA patients	23	Dental implants can be placed simultaneously with bone grafts in patients with EBA
Larrazabal-Moron et al ³⁴	1 52-year-old female EBA patient	2	Dental implants can be placed simultaneously with bone grafts in patients with EBA
Peñarrocha-Diago et al ³²	4 EBA patients, 1 man and 3 women, ages 26-35 years	15	Dental implants can be successfully placed in patients with EBA

Table 2. Relationship between epidermolysis bullosa and dental implants.

Authors	Population	Number of implants	Results
Binon ³⁸	67-year-old male SS patient	6	Implant success after 13 years
Isidor et al ³⁹	8 edentulous female SS patients	90	Functional and aesthetic amelioration in 87.5% of patients
Invernici et al ³	58-year-old SS patient	3	Implant success 3 years after
Chatzistavrianou and Shahdad ⁴⁰	Two female SS patients	Not available	Implant success after 18months and 2 years
Korfage et al ³⁷	50 SS patients with dental implants	140	impact on periodontal health but not on implant placement

Table 3. Relationship between Sjögren syndrome and dental implants.

4 patients and also suggest that dental implants can be a successful solution³². Penarrocha-Oltra et al placed 23 dental implants simultaneously with bone graft in 4 EBA patients and the results were successful³³. Similarly, Larrazabal-Moron et al claim that simultaneous bone graft and implant placement is possible for EBA patients³⁴. Table 2 summarizes findings from these studies.

Sjögren syndrome

Sjögren syndrome is a systematic disease that usually affects middle aged women. The prevalence of SS ranges between 0.5-1% of the population. Sjögren syndrome is characterized by mouth and eye dryness, caused by the presence of an inflammatory infiltrate of lymphocytes interfering with the function of the exocrine gland tissues^{3,35}. Oral dryness causes numerous problems and leads to tooth loss, as the saliva protects from dental caries and periodontal and peri-implant diseases. The oral epithelium is characterized by painful erosions and sometimes colonization by *Candida albicans*³⁶.

Numerous researchers refer to the use of dental implants in patients with Sjögren syndrome, as shown in Table 3. Korfage et al studied 140 cases of dental implants placed in 50 SS patients attending the University Medical Center Groningen. The writers concluded that the periodontal health indices reported were affected by the oral autoimmune disease, but the implant success rate was comparable to that concerning healthy people³⁷. Binon placed 6 dental implants in one patient suffering from Sjögren syndrome and report successful rehabilitation at a follow up of 13 years³⁸. Isidor et al placed a total of 90 implants in 8 women who suffered from Sjögren syndrome. All patients but one reported improvement in function and comfort 2 years after the surgery³⁹. Similar results were reported by de Mendonça Invernici et al, who placed 3 dental implants in a Sjögren female patient that ameliorated the patient's quality of life³. Finally, Chatzistavrianou and Shahdad report successful implant placement in two patients with SS after 18 months and two years follow-up respectively⁴⁰.

Systemic lupus erythematosus

Systemic lupus erythematosus is an autoimmune disease with a wide range of symptoms, as most organs are affected. The prevalence ranges between 1.2-50/100000 worldwide⁴¹. The oral mucosa is affected in 40% of patients. Often, desquamative gingivitis, erosions and serious infections are present, as well as inflammation of the temporomandibular joint, that may complicate the opening of the mouth and pose difficulty in the implant surgery. Auto-antibodies against the nucleus and the cytoplasm antigens are created⁴¹. The immunological pathway of SLE resembles the one that develops during periodontitis and peri-implantitis⁴². Therefore, it is possible that SLE aggravates the periodontal and peri-implants diseases and may result in a higher possibility of implant loss compared to healthy people⁴³. Only one study referring to implant placement in patient suffering from SLE was found. Ergun et al placed 6 dental implants in a patient suffering from lupus erythematosus. The patient also suffered from dry mouth and difficulty in opening the mouth, because of the autoimmune disease, and was a corticosteroid user. The writers claim implant success 2 years after the implant placement surgery⁴⁴.

Oral autoimmune diseases and peri-implantitis

As mentioned above, oral lesions caused by oral autoimmune diseases impair proper oral hygiene as it is painful and may provoke new manifestations. In addition, patients with oral autoimmune diseases often avoid dental appointments, as they fear that their symptoms may aggravate. As a result, it is possible for them to suffer from gingivitis, periodontitis and peri-implantitis due to the plaque accumulation.

Peri-implantitis is an inflammatory disease that affects the tissues around the dental implant and leads to bone absorption and eventually implant loss⁴⁵. In order to prevent the severe peri-implantitis results, the dental clinician should pay close attention to patients with oral autoimmune diseases and implants. If peri-implantitis is identified at an early stage, it is easier to treat with the use of chlorhexidine, antibiotics and plaque removal⁴⁶.

In the bibliography, many studies support the correlation between oral autoimmune and periodontal diseases⁴⁷. Ertugrul et al showed that LP patients present a higher percentage of pathological bacteria in their saliva compared to healthy subjects, which may lead to more severe symptoms and quicker deterioration of periodontal and peri-implant disease⁴⁸. In accordance with the above, the Wang et al survey suggests correlation between the periodontal diseases and OLP⁴⁹. In addition, Thorat et al suggested that pemphigus vulgaris patients had higher plaque accumulation and pore pockets compared to healthy people. In fact, the pockets were deeper when the PV was more aggressive⁵⁰. Tricamo et al found that patients with mucous membrane pemphigoid had statistically significant augmentation of gingival inflammation compared to the control group⁵¹.

Similarly, it seems that a correlation between systemic lupus erythematosus and periodontal diseases exists⁵².

Oral autoimmune diseases and soft tissue regeneration

In some cases of severe bone deficiency, in order to insert dental implants, it is necessary to perform periodontal plastic surgery and soft tissue regeneration, with the use of grafts and membranes⁵³. However, oral autoimmune diseases may complicate such surgeries, as these specific disorders affect soft tissue healing. An additional problem for patients with oral autoimmune diseases is that the mucosa is thin and fragile and makes the surgery harder⁵⁴.

Available data in the published literature are scarce. Katz et al claim lichen planus appearance after periodontal surgery and suggest avoiding traumatic surgery in patients with OLP⁵⁵. In contrast, Toscano et al suggest that periodontal surgery may be performed after the proper pharmacological treatment of the oral autoimmune disease⁵⁶. Furthermore, corticosteroid use, which is a common autoimmune disease treatment, impairs healing. However, Shin-Yu Lu supports that successful soft tissue regeneration with grafts and resorbable membrane is possible despite systemic corticosteroid use⁵⁷.

Oral autoimmune diseases pharmacological therapy and implant rehabilitation

Systemic autoimmune diseases with oral involvement cause severe symptoms that range from discomfort and pain to organ failure and eventually death and require prompt action. Treatment is often challenging and medication may have severe side-effects and long duration. These drugs can also affect the implant osseointegration and long-term survival.

Corticosteroids

The most common therapeutic agent for the treatment of autoimmune diseases with oral manifestations is glucocorticosteroids, either topically or systematically². In mild cases oral lesions can be treated with topical ointments⁹, whereas patients with more severe symptoms may need systematic administration with doses up to 0.5 mg/kg per day for oral lichen planus⁵⁸ or even greater for pemphigus vulgaris (0.75-1.25 mg/kg/day)⁵⁹. However, the use of corticosteroids in such doses affects bone quality and can result in glucocorticoid-induced osteoporosis⁶⁰. More specifically, bone formation is diminished as osteoblasts are reduced in number and are less active and bone absorption is increased as osteocytes lead to apoptosis and osteoclasts are overactive^{61,62}. Glucocorticoids also affect calcium metabolism, thereby interfering to mineralization of new bone⁶³.

However, when bone healing and remodeling is affected, implant placement may be difficult for those patients. The

findings in the literature are controversial. Petsinis et al suggest that glucocorticosteroid intake for systemic diseases does not have a significant impact on the osseointegration and should not be considered as a contraindication for dental implant surgery⁶⁴. In accordance, Lu and Huand (2007) presented a successful implant placement in a chronic corticosteroid user and proposed antibiotic prophylaxis, strict oral hygiene and frequent recall appointments as special caution measures⁵⁷. However, in Keller's survey (2004) osseointegration was affected in rabbits who received corticosteroids and it was suggested that this might jeopardize long-term implant stability⁶⁵. Similarly, Fujimoto et al worked with rabbits and showed that corticosteroids affect implant placement, but may have less impact on the osseointegration at the mandibular bone compared to the skeletal bone⁶⁶.

There is good evidence that glucocorticoids affect bone quality and can cause osteoporosis and implant failure. However, patients with autoimmune oral mucosa diseases differ amongst each other in medication agents, dose and duration, even when suffering from the same disease, so that care should be taken in an individual basis.

Immunosuppressive drugs

Very often immunosuppressants such as cyclosporine, azathioprine, mycophenolate and methotrexate are used for the treatment of autoimmune diseases with oral manifestations, especially when remission occurs^{2,67}. However, to the best of our knowledge there are no published data concerning the impact of immunosuppressive drug agents, used for autoimmune disease treatment, on dental implant surgery in humans. The only studies found referred to animals and suggest controversial results^{68,69}.

Therefore, there are no clear instructions on oral surgery for patients under such immunosuppressive agents. The clinician must bear in mind that soft tissue and bone healing are affected to some extent and the patient is more prone to infections.

Non-steroidal anti-inflammatory drugs

Patients who suffer from lupus erythematosus are sometimes recommended to use non-steroidal anti-inflammatory drugs (NSAIDs)⁶⁷, in order to control inflammatory arthralgia and myalgia, as well as fever⁷⁰. However, NSAIDs and especially COX-2 inhibitors are thought to impair osseointegration⁷¹, as they delay bone healing⁷², particularly when NSAIDs are used in large doses and for long periods⁷¹. This can be explained by the fact that non-steroidal anti-inflammatory drugs inhibit the COX-2 activity, which results in reduced prostaglandins and regulation of the inflammation. However, prostaglandins and especially E2 affect bone metabolism and may lead to problematic osseointegration^{71,73}. With regard to the above, caution should be taken when deciding if implant rehabilitation is suitable for patients with lupus erythematosus who use non-

steroidal anti-inflammatory drugs for long periods of time.

Conclusion

To sum up, the use of dental implants in patients with autoimmune diseases with oral manifestations is still currently under investigation. It is clear that the severity of the disease is the major factor that the dental clinician will take into consideration in order to decide the implant solution. Patients with severe symptoms are rather unlikely to refer to the dentist for dental implant rehabilitation, as it is not their priority. In mild cases, where the drug treatment may be exclusively local, or for short periods and in low dose, the implant success rates are similar to these of healthy people^{74,75}. On the contrary, patients with average disease severity should be treated on an individual basis⁵⁶. Implant placement should always be attempted after flare ups of the disease have been managed. The implant placement spot on the mucosa should be lesion free. The drug duration and dose is of paramount importance for the implant survival, as augmentation in the drug dosage impairs the bone and soft tissue quality⁵⁶.

Finally, dental clinicians should place emphasis on oral hygiene, which is often neglected by patients with oral autoimmune diseases. Successful oral hygiene ameliorates the soft tissue lesions, reduces the infection possibility and protects from periodontal and peri-implant diseases, that could lead to implant loss. Teeth brushing should be performed by applying low pressure and using a soft toothbrush and mild antimicrobial mouthwashes are recommended.

In the future, more studies concerning dental implant placement in patients with oral autoimmune diseases are needed, as well as studies discussing the potential and limitations of regenerative periodontal tissue techniques in these patients.

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