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RESEARCH ARTICLE

PERI-IMPLANTITIS – UNRAVELLING THE MYSTERY

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ABSTRACT

Research has now established that a thorough understanding of the implant related complications is essential if implant retained restorations are to be employed predictably. Biological complications in implant dentistry are referred to as peri-implant mucositis and peri-implantitis. Peri-implantitis, if not successfully treated, may lead to complete disintegration and implant loss. Bacteria, mainly Gram-negative anaerobes are an essential factor for the onset and progression of peri-implantitis. However, the disease is probably the result of interplay of several factors that may influence the host inflammatory response, including smoking, stress, genetic variation in relevant genes (polymorphism), occlusal overload, impaired healing, poor surgical technique, poor bone quality and poor prosthesis design. Diagnosis is based on changes of colour in the gums, bleeding and probing depth of periimplant pockets, suppuration, x-ray and gradual loss of bone height around the tooth. Therapeutic objectives focus on correcting technical defects by means of surgery and decontamination techniques such as abrasion with carbon particles, citric acid solution, topical tetracycline application and laser surgery.

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INTRODUCTION

Osseointegrated implants have revolutionized modern dentistry with reports of continually high survival rates in the 90th percentile. (Esposito *et al*., 1998) As a result of scientific and technological advances in the field of implants, they have become a more preferable alternative to fixed or removable prosthetic appliances. Despite high success rates, implant fixture failure may occur and is defined as the inability of the host tissue to establish or maintain osseointegration. Many soft and hard tissue complications are encountered around the inserted implants which become the cause of implant failure. Of these complications, the progressive loss of alveolar bone surrounding the implant is perhaps the most salient. (Bobia and Pop, 2010) Biological complications in implant dentistry are referred to as peri-implant mucositis and peri-implantitis. (Leonhardt *et al*., 1999; Mombelli and Lang, 2000; Roos-Jansaker *et al*., 2006) The consensus report from the 6th European Workshop on Periodontology described peri-implant mucositis as the presence of inflammation in the mucosa at an implant site with no signs of supporting bone loss.[6] Peri-implantitis is defined as 'an inflammatory process affecting the tissues around an osseointegrated implant in function, resulting in loss of supporting bone'. (Mombelli and Lang, 2000)

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Prevalance, extent and severity of peri-implantitis

The prevalence of peri-implant mucositis has been reported in the range of 8–44%, while the prevalence of peri-implantitis has been reported in the range of 0–14.4%. The wide ranges reported may partly be owing to differences in defining the two entities, and different lengths of the studies conducted. (Romeo *et al*., 2004)

In a systematic review by Berglundh *et al*. (2002), a 2.5-mm peri-implant bone loss, probing depth (PD) >6 mm and bleeding on probing (BOP) / suppuration were proposed as diagnostic criteria of peri-implantitis. The reported rate of peri-implantitis by the authors varied between 0 – 4.4% depending on the type of prosthesis in use. When using a bone loss ≥1.8 mm as a threshold value, Roos-Jansåker *et al*. (2006) identified 7.7% of the implants to suffer from progressive bone loss after 9-14 years from the 1-year control. Koldsland *et al*. (2010) assessed levels of severity of peri-implantitis as: 1) radiographic peri-implant bone loss ≥2.0 mm and BOP/suppuration at PD ≥4 or ≥6 mm; and 2) radiographic peri-implant bone loss ≥3.0 mm and BOP/suppuration at PD ≥4 or ≥6 mm. They found a substantial variance in prevalence i.e. 11.3% to 47.1% in the study population. Mir-Mari J *et al* (2012), suggested that the criteria for diagnosis of peri-implantitis as: 1).

In health - Bone Level (BL) < 2 threads without BOP, 2). Clinical stability - BL ≥2 threads without BOP, 3). a). Peri-implant mucositis - BL < 2 threads with BOP. b). Peri-implantitis - BL ≥ threads with BOP or suppuration. The authors concluded that implant and patient-based peri-implantitis prevalences were 9.1% and 16.3% respectively. Mucositis affected 21.6% of the studied implants and 38.8% of the patients. (Mir-Mari *et al*., 2012) The proceedings of Sixth European Workshop on Periodontology established that peri-implant mucositis occurs in about 80% of subjects (50% of sites) restored with implants, and peri-implantitis in between 28% and 56% of subjects (12–40% of sites). (Lindhe and Meyle, 2008)

To describe the extent and severity of the peri-implantitis lesion, the various clinical presentations of the disease need to be classified. Peri-implantitis can be classified on the basis of bone loss as follows:

- **Class 1:** Slight horizontal bone loss with minimal peri-implant defects (Fig. 1).
- **Class 2:** Moderate horizontal bone loss with isolated vertical defects (Fig. 2).
- **Class 3:** Moderate to advanced horizontal bone loss with broad, circular bony defects (Fig. 3).
- **Class 4:** Advanced horizontal bone loss with broad, circumferential vertical defects, as well as loss of the oral and/or vestibular bony wall (Misch, 2008) (Fig. 4).

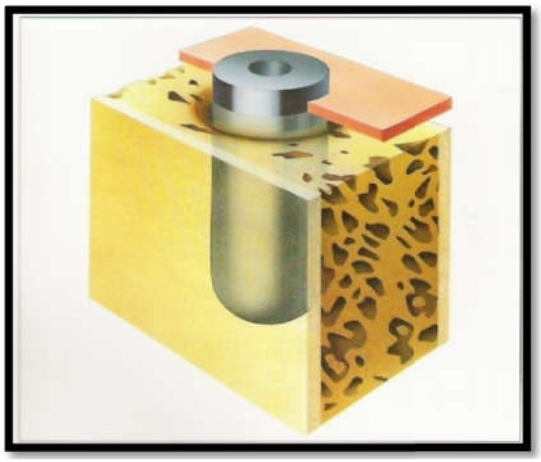

Fig. 1. Class 1 peri-implantitis

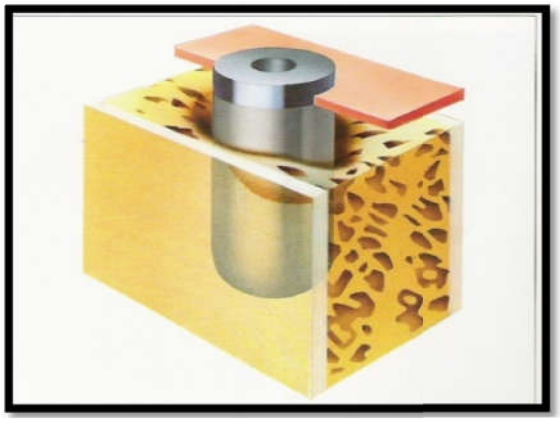

Fig. 2. Class 2 peri-implantitis

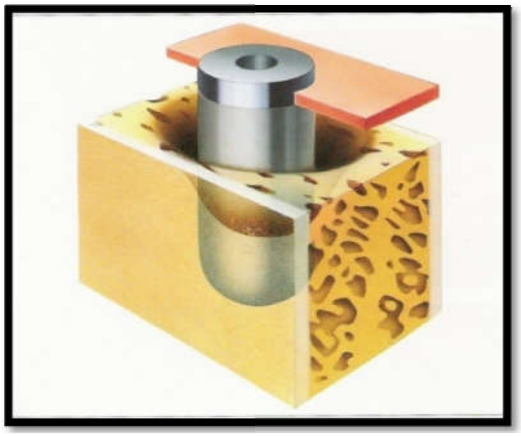

Fig. 3. Class 3 peri-implantitis

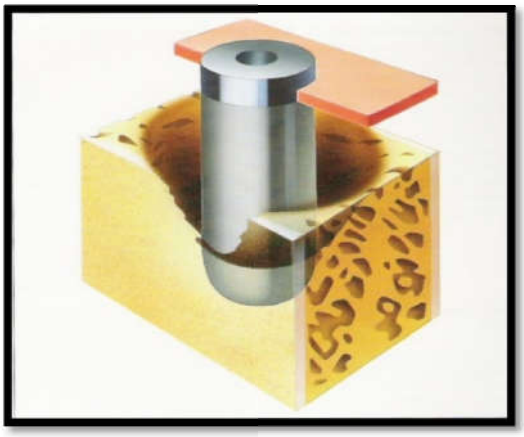

Fig. 4. Class 4 peri-implantitis

Froum SJ and Rosen (2012) proposed a classification of Peri-implantitis (Table 1) based on the severity of the disease:

Table 1. Classification of Peri-implantitis lesions (Forum & Rosen, 2012)

Early	•PD≥ 4 mm (bleeding and/or suppuration on probing) •Bone loss < 25% of the implant length
Moderate	•PD≥ 6 mm (bleeding and/or suppuration on probing) •Bone loss 25% to 50% of the implant length
Advanced	•PD≥ 8 mm (bleeding and/or suppuration on probing) •Bone loss > 50% of the implant length

Etiopathology

The peri-implant diseases are infectious diseases, having a microbial etiology. The occlusal overload does not initiate peri-implant tissue inflammation but exaggerates bone loss in a plaque induced peri-implantitis lesion.

The peri-implant microflora is established shortly after implant placement. Healthy peri-implant sites are characterized by high proportions of coccoid cells, a low ratio of aerobic/anaerobic species, a low level of Gram-negative species and low detection frequencies of periodontal pathogens. While implants with peri-implantitis reveal an increased amount of a complex microbiota encompassing conventional periodontal pathogen species such as *Prevotella intermedia, Prevotella nigrescans,*

Aggregatibector actinomycetemcomitans, Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, Peptostreptococcus micros, Campylobacter rectus and *Fusobacterium* spp. (Ata-Ali *et al*., 2011; Klinge *et al*., 2005) Other more unsusual species such as *Pseudomonas aeruginosa, Enterobacteriaceae, Candida albicans* and Staphylococci may be recovered from failing implants. (Khashu *et al*., 2012) So, the main cause of peri-implantitis is dental plaque. (Meffert, 1996) Shortly after implants are placed, glycoproteins from saliva adhere to exposed titanium surfaces with concomitant microbiological colonization. The implant's rough surfaces and those presenting greater surface free energy tend to accumulate more plaque. Initial bacterial adhesion starts in areas of high wettability (a characteristic of titanium) and inside the pits and grooves of the roughened surfaces, where from it is difficult to eliminate. It has also been demonstrated that periodontal pathogens like *Prevotella intermedia* can be transmitted from residual teeth to implants. (Mombelli and Lang, 1998) The description of the inflammatory process of peri-implant mucositis is quite similar to gingivitis around natural teeth.

Adhesion to host cells is an important first step for the establishment of a successful infection. *P. gingivalis* can adhere to epithelial cells, endothelial cells and fibroblasts in the peri-implant connective tissues through fimbriae, property of surface hydrophobicity and gingipains. Adhesion may proceed to invasion of the host cells and thereby offer protection to *P. gingivalis* from external pressures such as host immune factors and antibiotics. (Irshad, 2013) These Gram-negative organisms produce endotoxins, which initiate an acute inflammatory response in peri-implant tissues. (Meffert, 1996) It results in the release of certain inflammatory mediators and growth factors with the aim to eliminate the invading microorganisms and to repair the resulting tissue damage. The immune cells from the circulation including polymorphonuclear cells and mononuclear cells transmigrate through the peri-implant sulcular epithelium and further enhance the inflammatory reaction and local tissue damage.

Non-circulating cells such as gingival fibroblasts and gingival epithelial cells are also known to produce inflammatory mediators in response to microbial challenge. Progression of tissue damage in peri-implantitis depends on the high local production of pro-inflammatory mediators including IL-1β, IL-6, IL-8, monocyte chemotactic protein - (MCP) – 1, matrix metalloproteinases (MMPs) and prostanoids, accompanied by low local production of inhibitors of inflammation and growth factors. These inflammatory mediators play an important role in peri-implant bone resorption by promoting osteoclastogenesis and subsequently activating the differentiated osteoclasts. Furthermore, pro-inflammatory cytokines such as IL-1β and TNF- α induce the release of prostaglandin PGE-2 from monocytes and fibroblasts, thereby further enhancing tissue damage. (Irshad, 2013) Basically, similar markers are upregulated between peri-implantitis and periodontitis, including pro-inflammatory cytokines such as interleukin IL-1, IL-6, IL-8, IL-12, and tumor necrosis factor TNF-alpha.[18] Degradation of connective tissue is followed by epithelial migration and bone resorption, which marks the conversion of mucositis into peri-implantitis. (Klinge *et al*., 2005) The only barrier to epithelial invagination nearing the crestal bone lays in the tonus of the gingival tissues by means of the circular fibres in the supracrestal soft tissues. These circular fibres are only present in keratinized tissue. (Meffert, 2001) However, this attachment is fairly weak, and if destroyed, bacterial contamination spreads directly to the bone, leading to its rapid destruction. (Bobia and Pop, 2010) The aforementioned colonisation does not necessarily culminate into peri-implantitis with rapid loss of bone height. In addition to the presence of these periodontal disease-causing germs, other local, systemic and genetic factors that may influence the host inflammatory response, including smoking, stress, diabetes mellitus and genetic variation in relevant genes (polymorphism), must coexist in order for prolonged, active infection to actually take place. (Bobia and Pop, 2010; Prathapachandran and Suresh, 2012) Other contributing factors include, osteoporosis, long-term treatment with corticoids, radiation and chemotherapy. (Prathapachandran and Suresh, 2012)

Risk factors for Peri-implantitis

A number of clinical studies have explored potential risk factors for peri-implantitis but, in the absence of long term prospective data that validate a cause - effect relationship, most of these factors are termed as "risk indicators". These can be: i). *Genetics* - IL-1RN gene polymorphism may be associated with peri-implantitis (Laine *et al*., 2005). ii). *Poor Oral Hygiene*- Poor plaque control may increase the risk for peri-implant disease by 2.5 times while regular prophylaxis can result in greater than 11 fold risk reduction for development of peri-implantitis. (Karnik and Pradhan, 2012) iii). *Smoking*- There has been found an increased risk of periimplantitis in smokers compared with nonsmokers (odds ratios from 3.6 to 4.6). (Heitz-Mayfield and Huynh-Ba, 2009) iv). *Diabetes*- The evidence regarding the association between diabetes and peri-implantitis is limited and it does not allow a definitive conclusion that diabetic patients have a higher incidence of peri-implantitis. (Lindhe and Meyle, 2008) However, high blood glucose level can impact tissue repair and host defence mechanisms, as diabetic control affects neutrophil function. (Rosen *et al*., 2013)

Recent research has indicated that delayed implant integration occurs among diabetics but with no significant increase in implant failure rates. (Turkyilmaz, 2010) v) *Occlusal overload* - Implants have been considered less tolerable to non-axial occlusal load compared to teeth because of a lack of a periodontal ligament. So, as suggested by finite element studies, occlusal load is concentrated at the implant marginal bone. Bone remodels in response to the strain and excessive stress can cause micro-fracture within bone and eventual bone loss. (Rosen *et al*., 2013) However, the current view is that in the absence of a biofilm, occlusal overload may actually increase bone density by functional stress shielding, but in the presence of a plaque induced inflamed peri-implantitis lesion, increased occlusal load causes rapid bone loss. (Chambrone *et al*., 2010) vi). *Implant surface*- With increasing roughness, implant surfaces attract and retain more bacteria. Current consensus is that there is limited and conflicting information, with respect to the impact of implant surface topography as a

risk factor for peri-implantitis (Karnik and Pradhan, 2012; Greenstein *et al*., 2010) vii). *Width of keratinised peri-implant mucosa*-Although implant survival has not been noted to be significantly different between keratinized and non keratinized peri-implant mucosa, but at some instances, more peri-implant mucositis and bone loss at implants in non keratinized mucosa has been noted when a high level of plaque control is absent.[28] So, techniques that preserve keratinized tissue should be preferred at implant site.[22] viii). *Potential emerging risk factors*- include rheumatoid arthritis with concomitant connective tissue disease, increased time of loading, alcohol consumption, long term treatment with corticoids, radiation and chemotherapy. Further research will determine the appropriateness of their inclusion in the risk factors for peri-implantitis. (Bobia and Pop, 2010; Rosen *et al*., 2013)

Typical clinical signs of peri-implantitis are suppuration and bleeding at the peri-implant margin upon insertion of a periodontal probe into peri-implant space, whereby the probe easily penetrates 5mm or deeper. Swelling and redness of the marginal tissues with raised levels of the peri-implant sulcular fluid (PISF) is seen, which is usually not accompanied by pain. The characteristic peri-implantitis bone defect is well demarcated and extends circumferentially around the implant. Bone destruction may proceed without any notable signs of implant mobility until osseointegration is completely lost. (Mombelli *et al*., 2012)

Diagnosis

Accurate diagnosis of peri-implant disease is mandatory for appropriate management. Comparing clinical and radiographic parameters with baseline data is the key to diagnosis of peri-implant diseases. Standard parameters for evaluating peri-implant tissue health may include the following:

Peri-implant Probing: Probing the peri-implant sulcus with a blunt straight plastic periodontal probe allows assessment of peri-implant probing depth, bleeding on probing, exudation and suppuration. In general, successful implants allow probe penetration of approximately 3 mm. (Mombelli *et al*., 1987) Probing may have to be done with the prosthesis removed as it may obviate probing along a parallel axis to the implant. The size (point diameter) of the probe, force applied and density of the peri-implant tissues affect the depth of probe penetration. A probing force of 0.25 N has been recommended for probing around oral implants because delicate and unique anatomy of the peri-implant mucosa.

Bleeding on probing (BOP) is the reaction of the soft tissue seal following the penetration of a periodontal probe into the peri-implant sulcus or pocket by using a gentle force. BOP is always present in inflamed mucosa, but it will not always be absent in healthy mucosa. It is also important to consider that not all tissues presenting pathologic bone loss show clinical signs of inflammation. (Mombelli and Lang, 1998) The clinical aspect as well as the radiographic aspect must be always used as a diagnostic factor of periimplant disease, even if BOP is absent. Standardised probes, such as the Audioprobe, the TPS probe or the HAWE Click probe, may be recommended. Suppuration on probing is associated with disease activity and indicates a need for anti-infective therapy.

Mobility

Mobility is insensitive in detecting the early stages of peri-implant disease as implants may still appear immobile due to some remaining direct bone to implant contact even in advanced tissue destruction. It only serves to diagnose the final stage of osseodisintegration and confirms that an implant has to be removed. For interpretation of low degrees of mobility, an electronic device designed to measure the damping characteristics of the periodontium of natural teeth – (Periotest®, Siemens AG, Bensheim, Germany) is used. A new, non-invasive device based on the principles of resonance frequency analysis (RFA) has been developed to measure and monitor primary implant stability over time. An implant stability quotient (ISQ) is displayed as a number between 1 and 100. Research has shown that the ISQ value of a stable osseointegrated implant increases with time, suggesting an increase in the bone-implant contact area while crestal bone loss around implants has been correlated with loss of implant stability. This may allow detection of an increase in implant mobility before clinical signs are recorded. (Slavi and Lang, 2004)

Peri-implant Radiographic examination

For accurate assessment of bone level changes, longitudinal series of standardised radiographs are required. Vertical bone loss of less than 0.2 mm annually following the implant's first year of service has been proposed as one of the major criteria for success. In peri-implantitis, bony defect develops around the implant which is often the shape of a saucer or a rounded beaker and extends circumferentially around the implant. More recently, Cone Beam Computed Tomography (CBCT) images have been utilized to aid in evaluating the extent of facial, lingual and proximal bony lesions around implants. (Rosen *et al*., 2013)

Secondary Diagnostics

Bacterial culturing, inflammatory markers in peri-implant sulcular fluid (PISF), genetic diagnostics may be useful in diagnosis of peri-implant diseases.

Management

Since dental plaque is the key etiological factor for the development of peri- implantitis, management of these lesions must seek to reduce the microbial load, eliminate inflammation of the peri-implant mucosa and decontaminate the implant surface in order to preserve supporting bone and then, if possible, bring about regeneration of the lost bone. (Mellado-Valero *et al*., 2013) Both surgical and nonsurgical techniques have been developed to this effect.

Non surgical therapy

The goal of non-surgical therapy of peri-implant mucositis and peri-implantitis is to eliminate or significantly reduce the

amounts of oral pathogens in the pockets around implants to a level that allows healing and reestablishment of a clinically healthy condition.

a). Local Debridement

Its objective is the elimination of toxins from the implant surface in order to produce a surface compatible with health and to promote re-osseointegration. The implant should be cleaned by instruments softer than titanium, such as polishing with a rubber cup and paste, floss, interdental brushes, or using plastic scaling instruments which do not roughen the implant surface unlike metal and ultrasonic scalers. (Romanos *et al*., 2009) The main difficulty lies in the implant's surface roughness, which facilitates bacterial adhesion and colonization. One of the techniques proposed for dealing with this is *implantoplasty*, that is, the mechanical elimination of surface roughness together with the implant thread. Romeo *et al*. (2007) showed 100% of implant survival after 3 years, with improvements in clinical and radiological parameters compared with those without implantoplasty. The adjunct use of local antibiotics (chlorhexidine gels, minocycline spheres) to mechanical therapy has been shown to reduce bleeding on probing (BOP) and probing pocket depth (PPDs) in cases with peri-implantitis (Renvert *et al*., 2008).

b). Implant Surface Decontamination

Four implant surface decontamination methods can be employed: (1) air-powder abrasive technique followed by citric acid application, (2) air-powder abrasive technique, (3) gauze soaked in saline followed by citric acid application, and (4) gauze soaked alternately in 0.1% chlorhexidine and saline. (Pikner, 2008) Air-polishing devices have used slurry of water and sodium bicarbonate ($NaHCO_3$) and pressurized air/water. A less abrasive method using an amino acid glycine has been proven to be effective in removing bacterial biofilm structures in deep periodontal pockets.

c). Decontamination Using Laser

Laser decontamination is based on its thermal effect, which denatures proteins and causes cellular necrosis. The use of Er:YAG (Erbium : Yittrium Aluminium Garnet) laser (Kreisler *et al*., 2002), CO_2 and diode lasers (Romanos *et al*., 2009) have been shown to be effective for biofilm removal, having bactericidal effects that do not damage implant surfaces.

d). Photodynamic Therapy (PDT)

This technique uses a photosensitizing substance that fixes itself to the bacteria of the biofilm, and when irradiated with laser, cytotoxic singlet oxygen is produced which is able to destroy the bacterial cells. The main photosensitizers found in the literature are hematoporphyrin derivatives (620–650 nm), phenothiazine, like toluidine blue and methylene blue (620–700 nm), cyanine (600–805 nm), phytotherapic agents (550–700 nm), and hytalocyanines (660–700 nm). (Kreisler *et al*., 2002) A review of *in vitro* studies, which aimed to analyze the effect of laser on titanium surfaces, has shown that it is possible to carry out photosensitization which is lethal to bacteria but does not damage the implant surface (Romanos *et al*., 2009).

e). Chemical Decontamination and Antibiotic Therapy

This involves localized use of anti-microbial solutions such as topical chlorhexidine, tetracycline or minocycline, citric acid, hydrogen peroxide or 35% phosphoric acid gel, in combination with mechanical debridement for eliminating hard and soft deposits. It has been concluded that 40% citric acid with pH 1 for 30-60 seconds is the most effective agent for the reduction of bacterial growth on HA surfaces. However, Consensus Report of the Sixth European Workshop on Periodontology on peri-implant diseases concludes that based on evidence, it seems that the outcome of non-surgical therapy is unpredictable. (Lindhe and Meyle, 2008)

Surgical therapy

The primary objective of surgical treatment in peri-implantitis lesions is to get access to the implant surface for debridement and decontamination in order to achieve resolution of the inflammatory lesion that persists despite the initial treatment provided and the application of bone regeneration techniques to restore the lost bone (Ata-Ali *et al*., 2011; Lawande, 2014). The surgical techniques can be divided into resection procedures and regenerative techniques, depending on the morphology and type of bone defect. (Roccuzzo *et al*., 2010) In peri-implantitis treatment, mechanical debridement of granulation tissue with teflon curettes and abrasive sodium carbonate air-powder, performing full thickness flap elevation, has been shown to produce clinical (plaque levels, marginal bleeding, bleeding on probing, suppuration, probe depth) and microbiological improvements.

a). Resection techniques

Resection techniques are used when there are moderate (< 3 mm) horizontal suprabony defects or vestibular dehiscences in a non-aesthetically compromised region. These procedures include ostectomy or osteoplasty, with the raising of an apical repositioning flap, degranulation and implantoplasty.

b). Regenerative surgery

Regenerative surgery is used when the implant is decisive for prosthetic preservation, or when aesthetic considerations are involved. Regenerative treatments require prior decontamination of the implant surface. Surgical therapy can be carried out using: (1) autogenous bone grafts covered by membranes, (2) autogenous bone grafts alone, (3) membranes alone. It has been shown that defects treated with membrane-covered autogenous bone demonstrated significantly larger amounts of bone regeneration and re-osseointegration than those treated with the other three procedures.

Conclusion

As with many inflammatory diseases, earlier the diagnosis and intervention, the better is the treatment outcome. To that end, routine monitoring of dental implants as a part of a

comprehensive periodontal evaluation and maintenance is essential. The ultimate success of implants is not only based on diagnosis, evaluation, treatment planning, but also on having a knowledge regarding the complications of implants and their fruitful management. In short, it is always better to remember "prevention is better than cure" and "a stitch in time saves nine".

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