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The 9th International Meeting of the Asian Pacific Society of Periodontology (APSP), organized by the Faculty of Dentistry of The University of Hong Kong on the special occasion of celebrating the 100 year anniversary of the University, and co-hosted by Guangdong Provincial Stomatological Hospital Southern Medical University as well as the Hong Kong Society of Periodontology & Implant Dentistry, was successfully held in the L’Hotel Nina et Convention Centre, Hong Kong on 9-10 September 2011. Over 360 delegates from 21 countries attended the APSP meeting with its theme “Multi-disciplinary management of periodontal diseases”.

The meeting was opened by Professor Lijian Jin (Chairman of the Local Organizing Committee) with welcome speeches by Dr KM Cheung (APSP President, 2009-2011) and Mr Masakazu Nakamura (CEO, Sunstar Corporation). The two-day program was very full, with 20 presentations contributed by speakers from 17 different countries. In addition, 78 posters were scheduled for presentation.

Over the two days 9 keynote speakers and 11 representatives from many countries in the Asian Pacific region presented lectures on a wide range of topics including:

- Periodontal inflammation and care strategies
- Periodontal / restorative interrelationships
- Periodontal / implant interrelationships
- Tissue regeneration around teeth and implants
- Periodontal and systemic health interrelationships

This volume serves as a record of all of the presentations made at this meeting. I am sure you will agree with me that the materials presented are not only very interesting but represent many contemporary concepts and excellent overview of multidisciplinary and multi-faceted nature of periodontics.

The generous support of our Diamond Sponsor: Sunstar; Gold Sponsor: Johnson & Johnson; Silver Sponsors: Nobel Biocare, Procter & Gamble (Crest & Oral-B); and Bronze Sponsors: GlaxoSmithKline, Advance Dental Consulting, Straumann and Henry Schein (Hong Kong) is very gratefully acknowledged. The kind support from the Faculty of Dentistry of The University of Hong Kong in organizing the meeting and financial support for production of this publication is also greatly appreciated. Without this support the 9th APSP meeting and the publication of the proceedings would not have been possible. I would like to acknowledge the contribution of my Co-Editor Professor Lijian Jin (APSP President, 2011-2013) to the publication of the proceedings. As in previous years I also thank the presenters for providing their manuscripts for publication. Finally this publication would not have eventuated had it not been for the excellent and efficient production editing of Ms Catherine Offler.

P. Mark Bartold
April 2012
Chapter 1

Pre-restorative periodontal surgery

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Introduction

The theme of the 2011 Asian Pacific Society of Periodontology meeting was ‘Multi-disciplinary Management of Periodontal Disease’. In the comprehensive management of patients with periodontal diseases, restorative dentistry often has a role. To facilitate restorative dentistry procedures surgical manipulation of periodontal tissues is often indicated. ‘Crown lengthening surgery’ is a poor term for such procedures. Crown lengthening surgery is performed to expose a greater height of tooth structure above the gingival margin. Often not only is coronal tooth tissue exposed through this surgical procedure but tooth roots may also be exposed. ‘Crown lengthening’ is also a negative term from the patient’s point of view because in a patient’s eyes what has been performed is in effect ‘gum shortening’.

Crown lengthening may also be performed for aesthetic reasons in order to remove excessive gingival covering of anatomical tooth crowns, without any restorative treatment being performed. Pre-restorative crown lengthening periodontal surgery is performed to facilitate the performance of restorative therapies and to enhance the aesthetic outcomes of restorative therapies. Such approaches are often required in the comprehensive care for patients with periodontal disease.

Crown lengthening surgery

As a topic, surgical crown lengthening, both for aesthetics and prior to restorative dentistry, is popular in dental journals aimed at general dental practitioners. For example, over recent years at least one article each year has appeared in the journal Dental Update published in the United Kingdom (Zaida et al. 2007, Cunliffe & Grey 2008, Bateman et al. 2009, Malik & Tablat-Pour 2010). In 2010 an article on contemporary crown lengthening therapy appeared in the Journal of the American Dental Association as a preview of a key presentation at the American Dental Association’s 151st Meeting, indicating the appeal of this topic in America (Dominici 2010).

An American Academy of Periodontology Practice Profile Survey in 2003 revealed that crown lengthening was one of the most common forms of periodontal surgery performed by its members. It is also a periodontal surgical procedure undertaken by general dental practitioners as revealed by a study in the United States of America and in Hong Kong one as yet unpublished survey has shown similar results (Lanning et al. 2007).
restorative therapies.

Gingival enlargement, sometimes as a result of medication, may interfere with restorative dentistry. Some form of pre-restorative periodontal surgery can expose sufficient tooth structure above the gingival margin or expose caries, restorations requiring replacement or fractured margins which, due to the gingival enlargement, are positioned subgingivally. However, if time is not of the essence, and if immediate restorative dentistry is not indicated, many drug influenced gingival enlargements can be resolved through thorough personal plaque control and nonsurgical periodontal therapy.

In restoring endodontically treated teeth, incorporation of a ferrule effect delivered by a fabricated crown surrounding a collar of prepared dentine extending coronally from the prepared cervical seat is considered by many to be advantageous (Sorensen & Engelman 1990). Pre-restorative periodontal therapy can allow for sufficient tooth structure above the gingival margin to be available for this ferrule effect to be delivered by the fabricated crown. However, some argue that by moving the entire restorative componentry in an apical direction, the tooth to be restored may in fact be weakened (Gegauff 2000).

If restorative procedures such as crowns, veneers or fixed dental prostheses are to be placed in areas in which uneven gingival margin positions may compromise an aesthetically pleasing outcome, then pre-restorative periodontal surgery may be employed to produce more regular gingival margins to enhance the aesthetic outcomes and this may provide challenges in the management of patients with periodontal diseases.

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**Table 1. Pre-restorative periodontal surgery indications**

- Subgingival caries
- Subgingival pre-existing restorative margins
- Subgingival tooth fractures
- Reduced crown heights (tooth wear)
- Reduced crown heights (gingival enlargements)
- Lack of a ferrule effect
- Uneven gingival margins of teeth to be crowned

**Pre-restorative periodontal surgery indications**

The principal indications for the performance of pre-restorative periodontal surgery are given in Table 1. Subgingival extension of dental caries, either coronal caries or root surface caries, on a tooth which is restorable, is a common indication for fairly localized pre-restorative periodontal surgery. Pre-existing subgingival restorative margins often require exposure when replacement restorations are indicated. This can be achieved through pre-restorative periodontal surgery which is often localized to the area to be restored. Subgingival fractures of teeth which can be restored are another common indication for pre-restorative periodontal surgery, which may also be quite limited in extent, obviously depending on the clinical situation.

Tooth wear, through erosion, abrasion or attrition, either alone or more usually acting in combination, may result in short unsightly teeth for which restorative treatment by crowns or veneers may be indicated. Due to the loss of tooth tissue, sufficient residual structure for retentive tooth preparations for the crowns or veneers above the gingival margin is often not available at the stage at which rehabilitation is indicated. Pre-restorative periodontal surgery can produce sufficient tooth structure above the gingival margin to allow for retentive tooth preparations to be produced for the intended
Contra-indications to pre-restorative periodontal surgery

Situations which may constitute absolute contraindications to pre-restorative periodontal surgery are listed in Table 2A. If a tooth cannot be restored then pre-restorative periodontal surgery \textit{per se} is wasteful. It can be argued that sometimes the subgingival extent of caries or fracture cannot be ascertained until the surgical exposure is underway. In these circumstances the surgical procedure is more of an exploratory surgery than a surgery which precedes any other form of dental treatment, other than extraction. A tooth which has lost so much periodontal attachment such that it is hopeless from a periodontal standpoint could not withstand the further reduction in support which would inevitably result from pre-restorative periodontal surgery.

What are often given as contraindications for pre-restorative periodontal surgery, yet which in reality are not so, are listed in Table 2B. It is often stated that if the pre-restorative periodontal surgery is likely to result in a furcation involvement, then pre-restorative periodontal surgery is contraindicated. Yet if the outcome of avoiding crown lengthening surgery is tooth extraction, because pre-restorative periodontal surgery is contraindicated, then such an approach can be seriously challenged. For mandibular molars the parameters likely to result in furcation involvement from such surgery have been established (Dilbart \textit{et al} 2003). The furcation involvements created are invariably Degree I. A systematic review of periodontal therapy of multirooted teeth with furcation involvement has shown that Degree I furcation involvements can be successfully managed by non-surgical periodontal therapy alone without any other periodontal interventions (Huynh-Ba \textit{et al} 2009). Maintaining teeth with reduced periodontal support, and thus altered crown-root ratios, is the everyday work of periodontists, general dentists and dental hygienists, alone or in combination. If crown lengthening surgery were to result in altered crown-root ratios, then affected teeth can be maintained in the long term and tooth extraction can be avoided.

Alternatives to pre-restorative periodontal surgery

The Asian Pacific Society of Periodontology directs itself towards discussing and reporting on matters relating to or impacting periodontology. However it must be acknowledged that in recent years alternatives to pre-restorative periodontal

- Adhesive build-ups
- Orthodontic extrusion
- Relative axial tooth movement

Table 3. Alternative strategies to pre-restorative periodontal surgery
surgery are often undertaken, such as adhesive additions to worn teeth, orthodontic extrusion of teeth to provide sufficient tooth structure coronal to the gingival margin and relative axial tooth movement to align gingival margins (Table 3). Similarly the absolute need for the provision of sufficient tooth structure for the establishment of a ferrule effect in restoring endodontically treated teeth has been altered by more recent development of materials for posts and advances in approaches to cementation.

**Biologic width - Classic understanding**

Any discussion of pre-restorative periodontal surgery must consider “a concept in periodontics and restorative dentistry” (Ingber et al 1977). Perhaps because of a renewed interest in the tenets underlying the performance of pre-restorative periodontal surgery issues relating to ‘biologic width’ have received scrutiny in the past decade, but an understanding of the classic description must first be established.

The biological width is defined as the distance from the coronal margin of the junctional epithelium to the alveolar bone crest. The biological width allows for the attachment to the tooth of the junctional epithelium and the connective tissue attachment of the dentogingival fibres, and interdentally the transeptal fibres and the circular fibres which may not be inserted into the cervical cementum. All of these fibre groups are part of the gingival apparatus and must be physically accommodated in a sufficient tissue volume.

The dimensions of this tissue compartment in humans were first described on the basis of post-mortem human histology (Gargiulo et al 1961). Careful study of this classic paper reveals some important considerations. Firstly, only the mean measurements were reported. Secondly, from the historic description of the different dentogingival arrangements encountered in the material studied, it is apparent that the dimensions reported were derived from specimens with a variety of periodontal conditions.

The dimensions of the biological width from that study were determined to be 2.04 mm. Add to that a gingival sulcus depth of at least 0.5 mm and building in a safety margin, a distance of 3 mm from the gingival margin to the alveolar bone crest was assumed. This came to be enshrined as the “3 mm rule”, whereby to maintain an inviolate biologic width there had to be 3 mm distance allowed from the alveolar bone crest to the intended gingival margin as a consequence of any crown lengthening surgery (Nevins & Skurow 1984).

Despite the knowledge that formaldehyde fixation, paraffin wax embedding, section cutting and mounting all contribute to unsupported tissue distortion of about 15% shrinkage, a further post-mortem histological study of the biologic width was reported (Boonstra et al 1983, Vacek et al 1994). This study produced similar mean values to the earlier histological investigation. Yet careful reading of this report reveals that the specimens studied had been subjected to a range of restorative procedures in life, possibly involving pre-restorative periodontal surgical procedures. However, this study reported a wide range of values in the tissue dimensions under investigation, showing that a “one size fits all” for biologic width could no longer be supported, yet the 3 mm rule was still perpetuated (Padbury et al 2003). A more discriminatory approach to its consideration did appear which introduced a new perspective (Lanning et al 2003).
Biologic width – Current understanding

The delay in measurement of the parameters related to the biologic width in healthy living humans, unaffected by previous restorative therapy, by clinical researchers is only a matter of conjecture.

A wide range of widths have been reported, leading to the recommendation from another study that the rule that standard tissue manipulation in pre-restorative periodontal surgery conform to the 3 mm rule be reviewed (Perez et al 2008, Barboza et al 2008). To gain an understanding of tissue dimensions coronal to the alveolar bone crest (the supraosseous gingivae in American terminology, supracrestal gingiva in international terminology) prior to pre-restorative periodontal surgery, it is imperative to perform trans-sulcular probing to the alveolar bone crest, after anaesthesia has been secured, and to record the measurements at a minimum of six sites around each tooth to be treated. The ‘crown lengthening” then has to be tailored to the results. Applying the “3 mm rule” may often result in the removal of more tooth support than is necessary to achieve the therapeutic goal (Nevins & Skurow 1984). Furthermore it has been shown that the dimension of the supraosseous/supracrestal gingiva can be reduced following pre-restorative crown lengthening surgery, indicating a need for further caution in the amount of tooth supporting tissue to be removed and gingival resection to be performed (Perez et al 2007). The biologic width following periodontal attachment loss by periodontitis and following successful periodontal treatment may well show wide and unexpected variations from what has previously been reported (Novak et al 2008).

Encroachment on the biologic width

There appears to be a minimum tissue volume coronal to the alveolar crest required to accommodate the dentogingival, circular and, interdentally, the transepithelial fibres and additionally the junctional epithelium and the gingival sulcus. Restorative margins which encroach upon the space required for the gingival apparatus set in motion adaptive changes to accommodate to any such incursion. Two factors influence the tissue reactions, one being the quality of margin, and the second being the gingival (and indeed the underlying and supporting alveolar process) morphotype, more commonly now termed biotype.

The better the margin, the less any inflammatory response evoked. The poorer the margin, the greater the gap between the restoration and the tooth, the larger and more extensive the overhang, the greater the opportunities for plaque retention and in consequence plaque induced inflammation.

The difference in behaviour of the periodontal tissues depending upon the gingival biotype is summarized in Table 4. In

<table>
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<th>Thin gingival biotype</th>
<th>Thick gingival biotype</th>
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<td>Inflammation</td>
<td>Inflammation</td>
</tr>
<tr>
<td>Loss of attachment</td>
<td>Loss of attachment</td>
</tr>
<tr>
<td>Recession</td>
<td>Pocket formation</td>
</tr>
<tr>
<td>Possible resolution of inflammation</td>
<td>Persistence of inflammation</td>
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Table 4. Results from encroachment on the biologic width by restorative margins
situations in which the gingiva and the underlying alveolar process are thin, then encroachment upon the biologic width is more likely to result in inflammation, which in turn produces gingival recession, an apical shift of the entire gingival apparatus, and basically a self-corrected adaptation. However when the gingival biotype is thick, encroachment upon the biologic width is more likely to induce inflammation which results in pocket formation, with no or only minimal recession and a self-perpetuating inflammatory condition without apical migration of the gingival margin away from the plaque retentive incursion. For patients, the ensuing and lasting gingival bleeding, oral malodour and discomfort, especially during personal plaque control efforts, can be distressing. These untoward by-products of encroachment upon the biologic width can offset any improvements in oral health related quality of life brought about by the restorative treatment itself.

General guidelines for performance of pre-restorative periodontal surgery

The use of clear acrylic stents to indicate the location of the intended restorative, or indeed gingival margins, can very usefully guide the tissue removal required during the surgical procedure. Trans-sulcular probing can determine the dimensions of the suprasseous/supracrestal gingiva and the alveolar crestal height and thus can guide the appropriate resection of gingival tissue and the sufficient removal of alveolar bone to allow for re-establishment of the biologic width with appropriate accommodation for the planned restorative margins. Bone removal should be accomplished in such a manner as to avoid damaging the teeth and bony outlines produced after bone removal should be without abrupt changes in direction. In areas of aesthetic concern, papillary preservation in the design and execution of flap incision and elevation can be of assistance in maximizing the aesthetic outcomes of this type of periodontal surgery. Periodontal dressings can be of assistance in maintaining the position of the surgically created flaps in order to cover the newly created bone outline.

Stability of gingival margin positions after pre-restorative periodontal surgery

An overview of ten selected studies on crown lengthening surgery, for all indications, reveals a range of periods at which the gingival margin position becomes stabilized. The shortest period reported was 4 weeks (Pruthi 1987). 6 weeks was given in two reports and a range from these short periods of up to 12 months has appeared in the dental literature (Maynard & Wilson 1979, Brägger et al 1991, Pontoriero & Carnevale 2001).

To investigate this from the perspective of those who perform crown lengthening surgery, a very useful questionnaire survey was conducted (Wyatt et al 2004). In asking those who perform this therapy when they consider the gingival margin to become stable, there was a range suggested from 4 weeks to longer than 12 months. 60% of respondents thought that within 3-6 months the gingival margin would be stable. However 11% replied that the position of the gingival margin would not

- Rebound more likely in thick biotypes
- Rebound of interdental papilla affected by restorations
- Rebound more likely after localized procedures
- Early restorative dentistry when feasible
- May need to accept eventual subgingival margins

Table 5. Implications of gingival tissue rebound after pre-restorative periodontal surgery healing
necessarily be stable even after 12 months. A classic 15-year follow-up study on dental bridges noted that the gingival margin positions relative to the abutment teeth never really fully reached stability and that gingival recession was the most common presentation (Valderhaug et al. 1993).

The gingival margin positions may either shift in a coronal direction, which is a rebound, or in an apical direction, where it exposes root surface or what would be root surface were it not covered by dental restorations. The implications arising from gingival tissue rebound are summarized in Table 5 and those from gingival margin recession are summarized in Table 6.

Anticipated tissue rebound may suggest that the restorative therapy be performed as soon as it is possible to do so, which depends on the circumstances. Tissue rebound is likely where localized apical shift of the gingival margin is expected, yet where adjacent teeth may have much fuller periodontal attachment, and bone heights, which are not reduced during the surgery so as to preserve their pristine states. Rebound is also more likely in circumstances in which pre-restorative surgery is performed around teeth with thick gingival biotype (Pontoriero & Carnevale 2001). Rebound more likely occurs sooner, rather than later, after pre-restorative periodontal surgery (Wise 1985). The result on the interdental papillae in terms of rebound or not, is not only affected by the thick versus thin biotype issue, but also depends upon the application or otherwise of papillary preservation, and the contour of the restoration and contact area location of the subsequent restorative dentistry relative to the postsurgical interdental papilla height. Rebound may mean that restorative margins will come to be positioned subgingivally, but at least these margins should be as well adapted as can be achieved, in that the pre-restorative surgery allowed for decent restorative dentistry during the period in which the margin was accessible. Recession, or apical shift in circumstances in which no root surface or covered by restorative material root surface is exposed, is more likely where the gingival biotype and its underlying alveolar process are thin (Pontoriero & Carnevale 2001). Recession or apical shift of the gingival margin may not become apparent until 6 to 12 months after the pre-restorative periodontal surgery, indicating a need for awareness in areas of aesthetic concern after the initial healing (Pontoriero & Carnevale 2001, Brägger et al. 1992). Often in areas of high aesthetic concern it is wise to fit well-made temporary restorations until the position of the gingival margin has become more established and papillae have fully reformed, at which stage the long-term restorations can be delivered.

**Table 6. Implications of gingival tissue recession (or apical shift of gingival margin) after pre-restorative periodontal surgery healing**

- Recession more pronounced in thin biotypes
- Recession may show 6 to 12 months after surgery
- Beware of recession in areas of aesthetic concern
- Delay final restoration

**Table 7. Timing of restorative dentistry procedures after pre-restorative periodontal surgery**

<table>
<thead>
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<th>Timing of Procedure</th>
<th>Description</th>
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<td>Early (1 – 3 months)</td>
<td>Where rebound likely</td>
</tr>
<tr>
<td>Routine (3 – 6 months)</td>
<td>Where aesthetics are not critical</td>
</tr>
<tr>
<td>Delayed (6 – 12+ months)</td>
<td>Where aesthetics are critical</td>
</tr>
</tbody>
</table>
Chapter 1

Guidelines for the timing of restorative dentistry following pre-restorative periodontal surgery

Given the range of periods reported from studies of crown lengthening surgery, some recommendations need to be made to guide those dentists who undertake the restorative dentistry for which pre-restorative periodontal surgery is performed, in order to facilitate the performance and the outcome.

Table 7 summarizes recommendations that arise principally from the study with the longest duration (Pontoriero & Carnevale 2001). In circumstances in which gingival rebound after pre-restorative periodontal surgery can reasonably be anticipated, early restoration, often as soon as feasible is indicated. In areas in which aesthetics are not of high concern, the long-term restoration can be placed after a healing period of 3 to 6 months. Where aesthetics are of high concern and where the pre-restorative surgery has been performed for an aesthetic indication then a delay of up to 12 months or more may be required.

These evidence-based guidelines should be communicated by periodontists to those responsible for the post-surgical restorative and prosthodontic care.

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Chapter 2

Effect of periodontal treatment on patients with periodontitis and type 2 diabetes mellitus

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Introduction

Periodontitis, a common chronic inflammatory disease, is caused by gram-negative infection and characterized by periodontal pocket formation, loss of connective tissue attachment and alveolar bone, which ultimately results in tooth loss. It affects periodontal health in a high percentage of the population worldwide (Albandar & Rams 2002). Diabetes mellitus (DM) has emerged as an increasingly common disease over the last decade worldwide. It is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids and proteins with hyperglycemia as a main feature. A new large Chinese national survey indicates that type 2 diabetes mellitus has become a serious public health threat in China, suggesting that China is overtaking India and becoming the epicenter of diabetes in the world (Yang et al 2010).

Diabetes has been unequivocally confirmed as a major risk factor for periodontitis (Khader et al 2006, Salvi et al 2008, Chavarry et al 2009). Although people with well-controlled diabetes do not seem to be at increased risk of periodontal disease than people without diabetes, those with poorly controlled diabetes (who are also at risk for retinopathy, nephropathy, neuropathy and macrovascular diseases) have an increased risk for periodontitis and progressive bone loss (Tervonen & Oliver 1993, Karjalainen et al 1994, Taylor 2001). The risk of periodontitis is increased approximately threefold in diabetic individuals compared with non-diabetic individuals (Mealey & Ocampo 2007). The level of glycaemic control is of key importance in determining increased risk. For example, in the US National Health and Nutrition Examination Survey (NHANES) III, adults with an HbA1c level of >9% had a significantly higher prevalence of severe periodontitis than those without diabetes (OR 2.90; 95% CI 1.40, 6.03) after controlling for age, ethnicity, education, sex and smoking (Tsai et al 2002). The significance of diabetes as a major risk factor for periodontitis became apparent in the 1990s after a number of cross-sectional and longitudinal studies of the Pima Indian population. The prevalence and incidence of periodontitis were greater in Pima Indians who had type 2 diabetes mellitus compared with those who did not (Nelson et al 1990, Taylor et al 1998).

In the past few years, there has been emerging evidence to support the existence of a two-way relationship between diabetes and periodontitis, with diabetes increasing the risk for periodontitis and periodontal inflammation negatively affecting glycaemic control (Grossi
Effect of periodontal treatment on patients with periodontitis and type 2 diabetes mellitus

& Genco 1998, Taylor 2001, Stewart et al 2001). In other words, periodontitis may have some adverse effect on diabetes which in turn worsens the gum disease (Diabetes Control and Complications Trial Research Group 1993, UKPDS Group 1998). Unfortunately, authoritative studies on diabetes such as Diabetes Control and Complications Trial (1993), UK Prospective Diabetes Study (1998) and Stratton et al (2000), did not collect data on periodontal disease or oral health in general. If a bi-direction relationship between periodontitis and diabetes exists, then periodontal treatment should have ameliorative effect on diabetes mellitus. In this review, the effects of periodontal treatment on the patients with both type 2 diabetes mellitus and periodontitis are discussed.

Effect of non-surgical periodontal treatment on the clinical periodontal parameters in patients with periodontitis and diabetes

Dentists have long been aware of the importance of a diagnosis of diabetes in their patients because of the possible influence of diabetes on the outcome of therapy. Researchers have studied the effectiveness of periodontal treatment on periodontal conditions for periodontitis patients with diabetes. Chen et al (2012) recruited 140 patients with periodontitis and diabetes from November 2008 to October 2009. A total of 134 qualified patients were randomly allocated into two treatment groups and one control group. Treatment group 1 underwent non-surgical periodontal treatment at baseline and additional subgingival debridement at 3 month follow-up. Patients in treatment group 2 received non-surgical periodontal treatment and supragingival prophylaxis at 3 month follow-up and those in the control group received no intervention throughout the study. All participants were reexamined 1.5, 3 and 6 months after initial treatment. The results showed that non-surgical periodontal treatment significantly reduced the periodontal parameters. Plaque index (PI), bleeding on probing (BOP), clinical attachment loss (CAL) and mean periodontal depth (PD) decreased at the 1.5, 3 and 6 month intervals compared with baseline. In the control group who only received oral education, PI and BOP reduced significantly during the study period; however the other parameters did not show a significant difference. This suggested that patients with equal mean PD and lower mean gingival recession (GR) (i.e. greater inflamed pocket epithelium) had a better clinical response to non-surgical treatment than their counterparts. These findings have been supported by other studies. Other researchers reported that non-surgical periodontal treatment reduced the number of sites with bleeding on probing by half at the 3 month interval (Koromantzos et al 2011, Li et al 2011). Li et al (2011) found that after 3 month of treatment sites with probing pockets >4 mm were reduced but sites with attachment loss >5 mm remained.

Effect of periodontal treatment on the metabolic parameters

Hyperglycaemia is the primary characteristic of diabetes mellitus. Prolonged hyperglycaemia is associated with complications such as retinopathy, peripheral neuropathy, macrovascular disease (coronary heart and cerebrovascular disease), foot disease (arising from a combination of vascular and neuropathic disease) and renal failure. Interestingly, Williams and Mahan (1960) reported a reduction in the insulin requirement for 7 of 9 patients after periodontal therapy in a non-controlled study. Rodrigues et al (2003) found that fasting plasma glucose (FPG) was not reduced in patients with type 2 diabetes mellitus and
periodontitis at 3 months after periodontal treatment.

Reports from the Diabetes Control and Complications trial (1993) and The United Kingdom Prospective Diabetes Study (1998) have demonstrated that intensive treatment of hyperglycaemia can reduce the risk of long-term complications. These reports also demonstrated that a decrease in HbA1c can reduce the relative risks of 21% for any diabetes-related endpoint, 21% for diabetes-related death, 14% for myocardial infarction and 37% for microvascular complications.

Recent meta-analyses by Teeuw et al (2010) and Simpson et al (2010) found that scaling and root planing reduced HbA1c by 0.39% after 3 month of the periodontal treatment. Stewart et al (2001) also found that HbA1c decreased from 9.5 to 7.6 (17.1%) after non-surgical periodontal treatment, although HbA1c also decreased from 8.5 to 7.7 in a control group. Koromantzos et al (2011) found that the decrease occurred 1.5 months after the treatment and was maintained for a long time. Chen et al (2012) reported that a significant reduction in HbA1c was seen at 6 months in the treatment group (P<0.05) and a significant lower FPG was observed in treatment group 1 at 6 months (P <0.05) but not in treatment group 2 or the control group (P >0.05).

Some of the complications of diabetes are related to lipid metabolism disorders, therefore, the change of lipid metabolism before and after the periodontal treatment was investigated. Chen et al (2012) found that low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were reduced at 6 months (p<0.05), although these parameters were not significantly different to the control group. Kiran et al (2005) reported total cholesterol (TC), triglyceride (TG) and LDL-C levels decreased in the treatment group whereas these values increased slightly in the control group. A decrease in TG levels is an expected outcome of improvement in metabolic control. Chen et al (2012) reported lipid metabolic levels, including TC, TG, HDL-C and LDL-C, in all three groups had a tendency to decline during the whole study period, but comparisons among the three groups showed no significant difference in these variables at any time point (P>0.05). Li et al (2011) had similar findings in that both Apo-lipoprotein A1 and B showed no significant differences between the treatment group and control group.

**Effect on the inflammatory parameters**

Recent findings have indicated that chronic low-grade inflammation is closely involved not only in the pathogenesis of type 2 diabetes mellitus and its complications, but also in the pathogenesis of periodontal diseases, whereby cytokines play a central role in the host’s response to the periodontal biofilm (Genco et al 2005, Salvi et al 2008, Mealey & Rose 2008). It has been suggested that periodontal treatment may improve glycemic control through a reduction in CRP, a significant risk indicator for both the development of cardiovascular disease and the progression of diabetes in patients with diabetes and periodontal disease.

Sun et al (2011) found that TNF-α, IL-6, hs-CRP and adiponectin were improved at 3 months after periodontal treatment. Emerging evidence showed that periodontal treatment could significantly improve endothelial function, although the improvement was not correlated with the change of inflammatory biomarkers like hs-CRP and interleukin-6 (IL-6), and the related mechanism is still not clear (Nibali et al 2007, Piconi et al 2009). Katagiri et al (2009) stated that a change in hs-CRP level at 1 month after periodontal treatment correlated significantly with the reduction of HbA1c 6 months after periodontal treatment.

Chen et al (2012) reported that, in
association with significant improvements in periodontal measures, hsCRP level declined markedly over time in both intervention groups, suggesting that non-surgical periodontal treatment contributed to improved systemic inflammatory status, which in turn helped to lower the risk for the development of microvascular complications in patients with diabetes. Furthermore, the two regimens of supportive periodontal care (supragingival prophylaxis and subgingival debridement) were equally effective in lowering hsCRP level as no significant difference was found between them. Because this intervention study was conducted with patients of both sexes, various ages (38-81 years), differing levels of glycemic control and a broad spectrum of periodontal infection severity, these outcomes also suggest that the general population of diabetic patients with periodontitis would benefit from periodontal treatment with respect to hsCRP level. Thus, it is suggested that periodontal treatment for patients with diabetes and periodontitis would reduce the risk of diabetes complications through reduction of hsCRP level.

CD34+T cells are involved in vascular inflammation and repair. Li et al. (2011) found that circulating CD34+T cell count decreased 3 months after periodontal treatment, although no significant difference in hsCRP was found. To date, the role of TNF-α in diabetic patients with periodontitis remains controversial. Some intervention studies have reported that periodontal treatment could improve glycemic control in diabetics by reducing peripheral TNF-α concentrations, whereas other studies have failed to find such a reduction in serum TNF-α level after periodontal therapy in patients with diabetes or systemically healthy populations (Al-Mubarak et al. 2001, Yamazaki et al. 2005, Lalla et al. 2007, Di’Aiuto et al. 2007, O’Connell et al. 2008, Kardesler et al. 2010). During the longitudinal study, Chen et al. (2012) showed that TNF-α did not differ by time point in each group, nor did it differ among the three groups at any time point, indicating that non-surgical periodontal therapy had no significant impact on serum TNF-α concentration in these patients with type 2 diabetes. These findings, combined with previous cross-sectional investigations showing little impact of the severity of periodontal inflammation on serum TNF-α levels suggest that increased circulating TNF-α concentrations, caused by periodontal infection, are too minor to play a major role in any adverse effect of periodontitis on diabetes (Chen et al. 2010).

**Conclusion**

Numerous studies have confirmed that diabetes is a significant risk factor for periodontitis, the risk of periodontitis is greater if glycaemic control is poor and that people with poorly controlled diabetes (who are also at risk for other macrovascular and microvascular complications) are at an increased risk of periodontitis and alveolar bone loss. Emerging evidence suggests that resolution of periodontal inflammation can improve metabolic control, however randomized controlled trials of a large sample size are needed to further validate these findings. Given the predicted increases in the prevalence of diabetes over the next few decades, oral health care should be promoted in people with diabetes as an integral component of their overall diabetes management. Prevention and control of periodontal disease should be considered an integral part of diabetes control.

**References**


Interdental oral hygiene: The evidence

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Introduction

There is increasing public awareness of the value of personal oral hygiene. People brush their teeth for a number of reasons: to feel fresh and confident, to have a nice smile, and to avoid bad breath and disease. Oral cleanliness is important for the preservation of oral health as it removes microbial plaque, preventing it from accumulating on teeth and gingivae (Choo et al 2001). Maintenance of effective plaque control is the cornerstone of any attempt to prevent and control periodontal disease. The benefits of optimal home-use plaque-control measures include the opportunity to maintain a functional dentition throughout life. Self care has been defined by the World Health Organization as all the activities that the individual takes to prevent, diagnose and treat personal ill health by self-support activities or by referral to a healthcare professional for diagnosis and care (Claydon 2008).

There is substantial evidence showing that toothbrushing and other mechanical cleansing procedures can reliably control plaque, provided that cleaning is sufficiently thorough and performed at appropriate intervals. Evidence from large cohort studies has demonstrated that high standards of oral hygiene will ensure the stability of periodontal tissue support (Axelsson 2004, Hujoel et al 2006).

Interdental plaque control is essential to every patient’s self care program. Several dental conditions result from infrequent or ineffective interdental cleaning, including caries and periodontal diseases. These two, in combination, suggest a need for effective interdental cleaning. It is therefore important that the effectiveness of these interdental oral hygiene products be assessed and understood. The present review was undertaken to provide the dental professional with the available scientific evidence.

Interdental devices

There is confusion in the literature with respect to the definitions of approximal, interproximal, interdental, and proximal sites. Commonly used indices are not suitable for assessing interdental plaque (directly under the contact area), and thereby limit interpretation of interdental plaque removal. The European Workshop on Mechanical Plaque Control in 1999 proposed the following definitions: approximal (proximal) areas are the visible spaces between teeth that are not under the contact area. In health these areas are small, although they may increase after periodontal attachment loss. The terms
**Interdental oral hygiene: The evidence**

*interproximal* and *interdental* may be used interchangeably and refer to the area under and related to the contact point.

The interdental gingiva fills the embrasure between two teeth apical to their contact point. This is a ‘sheltered’ area that is difficult to access when teeth are in their normal positions. In populations that use toothbrushes, the interproximal surfaces of the molars and premolars are the predominant sites of residual plaque. The removal of plaque from these surfaces remains a valid objective because in patients susceptible to periodontal disease, gingivitis and periodontitis are usually more pronounced in this interdental area than on oral or facial aspects (Løe 1979). Dental caries also occurs more frequently in the interdental region than on lingual and buccal smooth surfaces. A fundamental principle of prevention is that the effect is greatest where the risk of disease is greatest. Toothbrushing alone does not reach the interproximal areas of teeth, resulting in areas of teeth that remain unclean. Good interdental oral hygiene requires a device that can penetrate between adjacent teeth.

Many different commercial products are designed to achieve this goal, including floss, woodsticks, rubber-tip simulators, interdental brushes, single-tufted brushes, and recently introduced electrically powered cleaning aids (i.e. oral irrigators). Flossing is the most advocated method since it can be performed in nearly all clinical situations. While picking teeth may be one of humanity’s oldest habits, not all interdental cleaning devices suit all patients or all types of dentition (Galgut 1991). Factors such as the contour and consistency of gingival tissues, the size and form of the interproximal embrasure, tooth position, and alignment and patient ability and motivation should be taken into consideration when recommending an interdental cleaning method.

**Dental floss**

Reports of the benefits of flossing date back to the early 19th century, when it was believed that irritating matter between teeth was the source of dental disease (Hujoel *et al* 2006, Parmly 1819). Over the years, it has been generally accepted that dental floss has a positive effect on removing plaque (Waerhaug 1981, Darby & Walsh 2003, Axelsson 2004, Wilkins 2004). Even subgingival plaque can be removed, since dental floss can be introduced 2 to 3.5 mm below the tip of the papilla (Waerhaug 1981) (Figure 1). The ADA (1984) reports that up to 80% of plaque may be removed by this method. As dental plaque is naturally pathogenic and dental floss disrupts and removes some interproximal plaque, it has been thought that flossing should reduce gingival inflammation (Waerhaug 1981). Flossing as the sole form of oral hygiene has been shown to be effective in preventing the development of gingival inflammation and reducing the level of plaque (Barendregt *et al* 2002).

![Figure 1. Floss can be introduced 2 to 3.5 mm subgingivally relative to the tip of the interdental papilla.](image-url)
Berchier and co-workers (2008) conducted a systematic review of scientific literature to investigate the efficacy of dental floss as an adjunct to toothbrushing on plaque and parameters of gingival inflammation, in adults with periodontal disease. Eligible studies provided a test group that used dental floss as an adjunct to toothbrushing and a control group that used toothbrushing only. The MEDLINE and CENTRAL databases were searched through December 2007 to identify appropriate studies. Plaque and gingivitis were selected as outcome variables. Independent screening of titles and abstracts resulted in 11 publications that met the eligibility criteria.

The majority of these studies showed that there was no benefit from floss on plaque or clinical parameters of gingivitis (Table 1). From the collective data of the studies, it appeared possible to perform a meta-analysis of plaque and gingival index scores. Table 2 provides a summary of the outcomes of the meta-analysis. In both instances, baseline scores were not statistically different. Comparing brushing and flossing against brushing only, the plaque index WMD was -0.04 (95% CI: -0.12; 0.04, P = 0.39) and the gingival index WMD was -0.08 (95% CI: -0.16; 0.00, P = 0.06). End scores also showed no significant differences between groups for plaque (WMD: -0.24, 95% CI: -0.53; 0.04, P = 0.09) or gingivitis (WMD: -0.04, 95% CI: -0.08; 0.00, P = 0.06). The heterogeneity observed at the end point for the plaque scores ($I^2 = 76.4\%$) indicates that the WMD should not be used as the exact measure of results. Based on the individual papers in this review, a trend that indicated a beneficial adjunctive effect of floss on plaque levels was observed. However, this could only be substantiated as a non-significant trend in the meta-analyses. The dental professional should therefore determine, on an individual patient basis, whether high-quality flossing is an achievable goal. If this is likely to be the case, daily flossing may be introduced as the oral hygiene

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Table 1. Descriptive overview of the results of the dental floss and toothbrush group compared to the toothbrush only group.
+ = significant difference in favor of toothbrush & floss group, 0 = no significant difference, ^ = no data available, ? = unknown. (Berchier et al 2008)
tool for interdental cleaning. Routine recommendation to use floss is not supported by scientific evidence as established by Berchier et al (2008) in their comprehensive literature search and critical analysis.

One may critically ask why the review by Berchier et al (2008) does not substantially show dental floss as a co-operative adjunct to toothbrushing. The advocacy of floss as an interdental cleaning device hinges, in large part, on common sense. However, common sense arguments are the lowest level of scientific evidence (Sackett et al 2000). A possible explanation is that the previous narrative reviews were not been conducted systematically. These reviews also lack meta-analysis or descriptive analysis based on extracted data.

The fact that dental floss has no additional effect on toothbrushing is apparent from more than one review. Hujoel et al (2006) found that flossing was only effective in reducing the risk of interproximal caries when applied professionally. High-quality professional flossing performed in first-grade children on school days reduced the risk of caries by 40%. In contrast, self-performed flossing failed to show a beneficial effect. The lack of an effect on caries and the absence of an effect on gingivitis in the review by Berchier and coworkers (2008) are most likely the consequence of plaque not being removed efficiently, as established in the present meta-analysis. Flossing does also not effectively clean wide interdental spaces, root surfaces or concavities. Such periodontally involved dentitions are more common with advancing age when reduced dexterity and visual acuity further impede flossing.

**Woodsticks**

Toothpicks are one of the earliest and most persistent “tools” used to “pick teeth.” The toothpick may date back to the days of the cave people, who probably used sticks to pick food from between their teeth. Originally, dental woodsticks were advocated by dental professionals as ‘gum massagers’ used to massage inflamed gingival tissue in the interdental areas to reduce inflammation and encourage keratinization of the gingival tissue (Galgut 1991).

Woodsticks are designed to allow the mechanical removal of plaque from interdental surfaces. The friction of the sides rubbing against the interproximal tooth surfaces removes the bacterial biofilm. They
are fabricated from soft wood to improve adaptation into the interdental space and to prevent injury to the gingiva. They should not be confused with toothpicks, which are meant simply for removing food debris after a meal (Warren & Chater 1996). The round toothpick is too thick and too blunt to reach the lingual half of the tooth when trying to angle it, while the curved surface of the toothpick provides only point contact with the tooth surface. The rectangular woodstick is also designed inappropriately for interdental cleaning as the device is too pliable to be able to clean lingually (Bergenholtz et al 1974). However, a triangular woodstick seems to have the correct shape to fit the interdental space (Waerhaug 1959). Woodsticks are inserted interdentally with the base of the triangle resting on the gingival side (Figure 2). The tip should point occlusally or incisally and the triangles against the adjacent tooth surfaces. The tapered form makes it possible for the patient to angle the device interdentally and even clean the lingually localized interdental surfaces. Unlike floss they can be used on the concave surfaces of the tooth root.

The tapered form of a triangular woodstick makes it possible for the patient to angle the device interdentally and even clean the lingually localized interdental surfaces (Morch & Waerhaug 1956). From the results of Bergenholtz et al (1974), it may be concluded that triangular woodsticks with low surface hardness and high strength values are preferred for interdental cleaning. From studies performed in vivo and from autopsy material, it was shown that a triangular pointed woodstick inserted interdentally can maintain a subgingival plaque-free region of 2 to 3 mm (Morch & Waerhaug 1956). The resilience of the gingival papilla allows cleaning apical to the subgingival margins of fillings (risk surfaces for recurrent caries). For open interdental spaces, common among adults, woodsticks seem most appropriate (Lang & Karring 1994). In periodontitis patients, the woodstick will depress the papilla, which may help in recontouring the interdental tissues and consequently preclude the need for periodontal surgery (Baer & Morris 1977). Woodsticks can only be used effectively where sufficient interdental space is available. Woodsticks have the advantage of being easy to use and can be used throughout the day without the need of a bathroom or mirror (Galgut 1991).

How effective is the woodstick in maintaining oral health? Does it offer any particular advantage over flossing or interdental brushes? Hoenderdos and coworkers (2008) performed a systematic review to evaluate and summarize the available evidence on the effectiveness of using triangular woodsticks in combination with toothbrushing to reduce both plaque and clinical inflammatory symptoms of gingival inflammation. The MEDLINE and CENTRAL databases were searched through February 2008 to identify appropriate studies. Studies were screened independently by two
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reviewers. Randomised controlled trials and controlled clinical trials were selected if they were conducted in individuals of over 18 years of age who were in good general health, and which used plaque, bleeding or gingivitis as outcome measures. Case reports, letters, and narrative or historical reviews were excluded and only English-language papers were considered. Independent screening of the titles and abstracts yielded seven publications with eight clinical experiments that met the eligibility criteria.

The heterogeneity of the data prevented quantitative analysis. A qualitative summary is presented in Table 3 which summarizes the differences between woodsticks and other devices. In seven studies, the improvement in gingival health represented a significant incremental benefit realized by the use of triangular woodsticks. Seven publications describing eight clinical experiments met the inclusion criteria. The improvement in gingival health observed in the studies represented a significant reduction of bleeding realised by the use of triangular woodsticks. None of the studies that scored plaque demonstrated any significant advantage of the use of woodsticks over alternative methods of plaque removal in people who had gingivitis.

A series of histological investigations in patients with periodontitis has shown that the papillary area with the greatest inflammation corresponds to the middle of the interdental tissue. It is difficult to clinically assess the mid-interdental area, as it is usually not available for direct visualization (Walsh & Heckman 1985). When used on healthy dentition, woodsticks depress the gingivae by up to 2 mm and therefore clean part of the subgingival area. Thus, woodsticks may specifically remove subgingivally located interdental plaque that is not visible and therefore not evaluated by the plaque index. This physical action of woodsticks in the interdental area may produce a clear beneficial effect on interdental gingival inflammation (Finkelstein 1990).

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<tr>
<th>Author(s)</th>
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Table 3. Descriptive overview of the results for woodsticks compared to other interventions.  
^ = significant difference in favor of test group, - = significant difference in favour of the comparison,  
0 = no significant difference, ^ = no data available, ? = unknown. (Hoenderdos et al 2008)
Interdental brushes

Interdental brushes were introduced in the 1960s as an alternative to woodsticks. The interdental brush consists of soft nylon filaments twisted into a fine stainless steel wire. This ‘metal’ wire can prove uncomfortable for patients with sensitive root surfaces. For such patients the use of plastic-coated metal wires may be recommended. The support wire is continuous or inserted into a metal/plastic handle. Interdental brushes are manufactured in different sizes and forms. The most common forms are cylindrical or conical/tapered (like a Christmas tree). The length of the bristles in cross section should be tailored to the interdental space. Appropriate interdental brushes are currently available for the smallest to the largest interdental space which ranges from 1.9 to 14 mm in diameter. Interdental brushes have the added advantage of serving as vehicles for the local application of antibacterial agents or desensitizing agents to exposed sensitive root areas.

Interdental brushes are frequently recommended by dental professionals to patients with sufficient space between their teeth. Interdental brushes are small, specially designed brushes for cleaning between the teeth (Figure 3).

Upon examination of extracted teeth from individuals who habitually used interdental brushes, Waerhaug (1976) showed that the supragingival proximal surfaces (the central part of the interdental space and the embrasures) were free of plaque, and that some subgingival deposits were removed up to a depth of 2 to 2.5 mm below the gingival margin.

Slot and coworkers (2008) systematically reviewed the literature to determine the effectiveness of interdental brushes used as adjuncts to toothbrushes in terms of plaque and clinical parameters of periodontal inflammation in patients with gingivitis or periodontitis. This situation was compared to toothbrushing alone or toothbrushing in combination with floss or woodsticks. The MEDLINE and CENTRAL databases were searched through November 2007 to identify appropriate studies. Two independent reviewers assessed studies for inclusion, aiming to identify appropriate randomised controlled clinical trials and controlled clinical trials. Studies were selected if they were conducted in humans, and included subjects of over 18 years of age in good general health with sufficient interdental space to use an interdental brushes. The articles were limited to English-language publications. Case reports, letters and narrative or historical reviews were excluded. Clinical parameters of periodontal inflammation such as plaque, gingivitis, bleeding, and pockets were selected as outcome variables. Independent screening of the titles and abstracts resulted in nine publications that met the eligibility criteria.

Table 4 summarizes differences between interdental brushes and various intervention strategies. All three studies that compared...
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Interdental brushes as an adjunct to brushing showed a significant difference in favor of the use of interdental brushes for plaque removal. The majority of the studies showed a positive significant difference on the plaque index when using interdental brushes relative to floss. No differences were found for the gingival or bleeding indices. Two out of three studies showed that interdental brushes, when compared to floss, had a significant positive effect on pocket reduction in patients with periodontitis. Interdental brushes remove more dental plaque than woodsticks, as shown by one of the two comparative studies.

From the collective data of the studies, a meta-analysis appeared to be possible for the comparison of interdental brushes or floss as adjuncts to toothbrushing. Table 5 provides a summary of the outcome of the meta-analysis. In all instances, baseline scores were not statistically different. End scores only showed a significant effect with the Silness and Löe plaque index in favor of the interdental brush group relative to the floss group (WMD: -0.48, 95% CI: -0.65; -0.32, p <0.00001). Comparisons using the other indices (Quigley and Hein plaque index, bleeding on probing and pocket depth) were not statistically significant. The heterogeneity observed with the Silness and Löe index (P = 0.001, I² = 85.4%) reflects the different behaviors of the study populations to the study product, differences in study designs and other factors that may influence outcome. Again, the reader should therefore exercise caution when using this WMD as an exact measure of outcomes. Within the limitations of the search and selection strategy of the review, Slot and coworkers (2008) showed that interdental brushes are a useful device to complement toothbrushing. The evidence suggests that interdental brushing is the most effective method to remove plaque.

Two out of the three studies that assessed probing pocket depth showed that reduction was more pronounced with interdental brushes than with floss (Christou *et al* 1998, Jackson *et al* 2006). Only Ishak and Watts (2007) could

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</tr>
<tr>
<td>Bassiouny &amp; Grant (1981)</td>
<td>?</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>Woodstick</td>
</tr>
</tbody>
</table>

*Table 4.* Descriptive overview of the results for interdental brushes and other interventions. + = significant difference in favor of test group, 0 = no significant difference, ^ = no data available, ? = unknown. (Slot *et al* 2008)
not support this finding. A possible reason that the meta-analysis does not support this advantage is the large difference between the interdental brush and floss groups in these studies at baseline. To overcome this imbalance, an elegant approach would be to use the difference between baseline and end scores as a measure of effect. Only one study provides this information (Christou et al. 1998). Jackson et al. (2006) proposed that the reduced pocket depth may have been related to the reduction in swelling with concomitant recession. However, with a lack of effect on signs of gingival inflammation (Table 5), the reason for the effect on pocket depth cannot readily be explained by a reduction in the level of gingival inflammation. As an explanation for the observed effect, the proposition by Badersten et al. (1984) seems conceivable. They suggested that a mechanical depression of the interdental papilla is induced by interdental brushes, which in turn causes recession of the marginal gingival. This, together with good plaque removal, could be the origin of the improved reduction in pocket depth.

**Oral irrigators**

Additional oral hygiene aids have been developed in an attempt to augment the effect of toothbrushing on reducing interdental plaque (Warren & Chater 1996). The oral irrigator was introduced in 1962. This device has been demonstrated to be safe and likely provides a particular benefit for gingival health to a large portion of the general public that does not clean interproximal spaces on a regular basis (Cobb et al. 1988, Lobene 1969, Frascella 2000). Oral irrigation has been a source of controversy within the field of periodontology. The adjunctive aid of the oral irrigator is designed to remove plaque and soft debris through the mechanical action of a jet stream of water (Figure 4). Oral irrigator devices can also be used with antimicrobial agents (Lang & Räber 1981). Patients report that the oral irrigator facilitates the removal

<table>
<thead>
<tr>
<th>Studies included</th>
<th>Index</th>
<th>WMD (random)</th>
<th>95% CI</th>
<th>Overall effect</th>
<th>Test for heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jackson et al. (2006)</td>
<td>Plaque index;</td>
<td>-0.01</td>
<td>-0.08; 0.06</td>
<td>P=0.84</td>
<td>P=0.97</td>
</tr>
<tr>
<td>Rösing et al. (2006)</td>
<td>Silness &amp; Löe (1964)</td>
<td>-0.48</td>
<td>-0.65; -0.32</td>
<td>P&lt;0.00001</td>
<td>P=0.001</td>
</tr>
<tr>
<td>Christou et al. (1998)</td>
<td>Plaque index;</td>
<td>-0.01</td>
<td>-0.28; 0.26</td>
<td>P=0.94</td>
<td>P=1.0</td>
</tr>
<tr>
<td>Jared et al. (2005)</td>
<td>Quigley &amp; Hein (1962)</td>
<td>-0.25</td>
<td>-0.57; 0.06</td>
<td>P=0.12</td>
<td>P=0.74</td>
</tr>
<tr>
<td>Christou et al. (1998)</td>
<td>Bleeding on probing</td>
<td>0.01</td>
<td>-0.04; 0.06</td>
<td>P=0.62</td>
<td>P=0.86</td>
</tr>
<tr>
<td>Ishak &amp; Watts (2007)</td>
<td>Base</td>
<td>-0.04</td>
<td>-0.10; 0.02</td>
<td>P=0.17</td>
<td>P=0.74</td>
</tr>
<tr>
<td>Jackson et al. (2006)</td>
<td>End</td>
<td>-0.14</td>
<td>-0.19; 0.47</td>
<td>P=0.39</td>
<td>P=0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.04</td>
<td>-0.28; 0.21</td>
<td>P=0.77</td>
<td>P=0.77</td>
</tr>
</tbody>
</table>

Table 5. Meta-analyses between interdental brushes and floss. Negative value favors interdental brushes. (Slot et al. 2008)
of food debris in posterior areas, especially in cases of fixed bridges or orthodontic appliances, when the proper use of interdental cleaning devices is difficult (Burch et al 1994).

Since its introduction, the oral irrigator has at times been a popular device (Newman et al 1994). However, there has been considerable controversy regarding the appropriate use and efficacy of this instrument (Astwood 1975, Newman et al 1994). Studies using an oral irrigator have reported both positive and negative results in terms of periodontal inflammation and plaque (Toto et al 1969, Fine & Baumhammers 1970, Lobene et al 1972, Hugoson 1978, Aziz-Gandour & Newman 1986, Walsh et al 1989). This inconsistency causes confusion on the efficacy of oral irrigators.

Husseini and coworkers (2008) performed a systematic review to evaluate the effectiveness of oral water irrigation as an adjunct to toothbrushing on plaque and clinical parameters of periodontal inflammation relative to toothbrushing alone or regular oral hygiene. Papers in the MEDLINE and CENTRAL databases up to January 2008 were searched to identify appropriate studies. Papers were assessed for inclusion independently by two reviewers and only those published in the English language were chosen. Randomized controlled clinical trials or controlled clinical trials conducted in adults with good general health were selected. Clinical parameters of periodontal inflammation such as plaque, bleeding, gingivitis and pocket depth were selected as outcome variables. Independent screening of the titles and abstracts of 809 PubMed and 105 Cochrane papers resulted in seven publications that met the eligibility criteria.

The heterogeneity of the data prevented quantitative analysis. Table 6 shows a descriptive analysis of the selected studies. None of the selected studies showed a significant difference between toothbrushing and use of an oral irrigator and only toothbrushing. When the oral irrigator was compared to regular oral hygiene, there were some significant differences for the clinical parameters of periodontitis. With respect to plaque, no significant differences were observed. All three studies that presented data on bleeding scores showed significant reductions in the oral irrigator group compared to the regular oral hygiene group (Flemmig et al 1990, Newman et al 1994, Flemmig et al 1995). When observing visual signs of gingival inflammation, three out of four studies found a significant effect with use of an oral irrigator as an adjunct to regular oral hygiene (Flemmig et al 1990, Newman et al 1994, Flemmig et al 1995). Two of the four studies showed a significant reduction in probing depth as a result of using an oral irrigator as an adjunct to regular oral hygiene (Newman et al 1994, Flemmig et al 1995).

Plaque reduction is a prerequisite for an oral hygiene device to be considered valuable (Newman et al 1994). The selected papers for this review reported no statistically significant reduction in plaque with use of an oral
irrigator. Despite a lack of effect on the plaque index, studies did find a significant effect on the bleeding index. The mechanisms underlying these clinical changes in the absence of a clear effect on plaque are not understood. Different hypotheses have been put forward by the authors to explain the results. One of the hypotheses is that when patients with gingivitis perform supragingival irrigation on a daily basis, the population of key pathogens (and their associated pathogenic effects) may be altered, reducing gingival inflammation (Flemmig et al 1995). There is also the possibility that H₂O pulsations may alter the specific host-microbial interaction in the subgingival environment and that inflammation is reduced independent of plaque removal (Chaves et al 1994). Another possibility is that the beneficial activity of the oral irrigator is at least partly due to removal of food deposits and other debris, flushing away of loosely adherent plaque, removal of bacterial cells, interfering with plaque maturation and stimulating immune responses (Frascella et al 2000). Other explanations include mechanical stimulation of the gingiva or a combination of previously reported factors (Flemmig et al 1990, Frascella et al 2000). Irrigation may reduce plaque thickness, which may not be easily detected using 2-dimensional scoring systems (Jolkovsky et al 1990). This may be the reason for an absence of an effect on plaque but a positive effect on gingival inflammation (Table 6).

Husseini and coworkers (2008) concluded that the effectiveness of an oral irrigator as an adjunct to toothbrushing does not have a beneficial effect on reducing plaque scores. However, there is evidence that suggests a positive tendency toward improved gingival health when using an oral irrigator as an adjunct to toothbrushing as opposed to regular oral hygiene (that is self-performed oral hygiene without any specific instruction).

### Discussion

Clinicians have choices and make decisions everyday as they provide care for patients. Some of the options may be evidence based, some not. This paper summarizes the highest level of evidence that is currently available. The systematic reviews included here attempt to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. They use explicit, systematic methods that are selected to minimize bias, providing more reliable findings from which conclusions can be drawn.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Plaque score</th>
<th>Gingival score</th>
<th>Bleeding score</th>
<th>Pocket depth</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frascella et al (2000)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>^</td>
<td>Toothbrush only</td>
</tr>
<tr>
<td>Hoover et al (1968)</td>
<td>?</td>
<td>^</td>
<td>?</td>
<td>^</td>
<td>Toothbrush only</td>
</tr>
<tr>
<td>Walsh et al (1989)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>Toothbrush only</td>
</tr>
<tr>
<td>Flemmig et al (1995)</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Regular oral hygiene</td>
</tr>
<tr>
<td>Flemmig et al (1990)</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>Regular oral hygiene</td>
</tr>
<tr>
<td>Meklas et al (1972)</td>
<td>0</td>
<td>^</td>
<td>0</td>
<td>^</td>
<td>Regular oral hygiene</td>
</tr>
<tr>
<td>Newman et al (1994)</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Regular oral hygiene</td>
</tr>
</tbody>
</table>

Table 6. Descriptive overview of the results of the toothbrush and oral irrigation group relative to the toothbrush only or regular oral hygiene only group.

+ = significant difference in favor of test group, 0 = no significant difference, ^ = no data available, ? = unknown. (Husseini et al 2008)
and decisions can be made (Antman et al 1992, Oxman & Guyatt 1993). Systematic reviews of randomized controlled trials are seen as the gold standard for assessing the effectiveness of healthcare interventions. The method of collecting information from a systematic review provides a solid base for clinical decision-making (Newman et al 2003). The Cochrane Collaboration declares in the Cochrane Handbook for Systematic Reviews that reviews are needed to help ensure that healthcare decisions throughout the world can be based on informed, high-quality, timely research evidence (Higgins & Green 2006). Using meta-analyses, systematic reviews can provide a quantitative distillation of apparently conflicting clinical data or identify a trend that might not be evident in a narrative review. As valuable as systematic reviews can be, their usefulness depends on the focus and quality of the previously published studies. It is important to interpret results of all research in the context it was performed. In the case of a systematic review, a lack of high quality, homogeneous evidence can result in lack of conclusive findings. In the presented reviews, the high levels of heterogeneity between study designs poses problems in reaching clear clinical recommendations.

According to the American Dental Association, evidenced-based dentistry is an approach to oral health care that requires judicious integration of systematic assessments of clinically relevant scientific evidence, relating the patient’s oral and medical condition and history with the dentist’s clinical expertise and the patient’s treatment needs and preferences (ADA 2009). Best care for each patient rests neither in clinician judgment nor scientific evidence but rather in the art of combining the two through interaction with the patient to find the best option for each individual. Considering the results established following the systematic review on floss, the conclusions have disappointed many dental professionals and believers in the use of floss. The fact that floss does not appear to be effective in the hands of the general public does not preclude its use. For instance, in interdental situations that only allow the penetration of a string of dental floss, this would be the most suitable tool. Although floss should not be the first tool recommended for cleaning open interdental spaces, if the patient does not like any other tool, flossing could still be part of oral hygiene instruction. The dental professional should, however, realize that proper instruction, sufficient motivation of the patient and a high level of dexterity are necessary to make the flossing effort worthwhile.

While most patients brush at least for a short period of time, fewer use interdental devices. Adjunctive aids, including interdental brushes, floss, and mechanical devices, are available to remove interdental plaque. Dental hygienists and their clients are faced with myriad products designed for interproximal tooth cleansing (Asadoorian 2006). The range is overwhelming, from simple dental floss or tape, through woodsticks and brushes (single or multi-tufted). However, what is apparent is that the choice of interdental cleaning method should be tailored to the size and shape of each interdental and proximal space. Furthermore, in order to gain maximum effectiveness, the level of oral hygiene advice delivered to the patient must contain enough information to enable the patient to be able to identify each site in turn, select a device and effectively clean the whole interdental surface (Claydon 2008). Ongoing patient education is also an integral part of patient compliance. The patient’s ability to remove plaque from all areas, including interproximal areas, is an essential part of every patient’s self care program.
Research shows that few individuals floss correctly (Lang et al. 1995). The inability to floss correctly may cause a lack of motivation (Tedesco et al. 1991). Historically, compliance with regular flossing has been far less than ideal and only a minority of patients are compliant flossers (Ciancio 2003). The routine use of dental floss has consistently been shown to be dramatically low (e.g. approximately 7% of the Dutch population flosses on a regular basis). The reasons for this lack of compliance apparently encompass two issues: a lack of patient ability and a lack of motivation (Christou et al. 1998, Van der Weijden et al. 2005). Studies are inconsistent in their ability to demonstrate that educational attempts to influence floss frequency can be successful (Asadoorian 2006). However, it has also been shown that flossing is like any other skill in that it can be taught, and those who are given appropriate instruction will increase their flossing frequency (Stewart & Wolfe 1989, Segelnick 2004, Asadoorian 2006). The difficulty in flossing likely makes application of this technique less than universal.

Patient acceptance is a major issue to be considered when it comes to the long-term use of interdental cleaning devices (Warren & Chater 1996). Patient preferences were evaluated in three studies (Kiger et al. 1991, Christou et al. 1998, Ishak & Watts 2007). Comparing interdental brushes and dental floss, patients preferred the interdental brushes. The interdental brushes were considered to be simpler to use, despite their tendency to bend, buckle and distort which made the procedure somewhat complicated at times (Ishak & Watts 2007). Interdental brushes were considered to be less time-consuming and more efficacious than floss for interdental plaque removal, which is consistent with previous reports (Bergenholtz & Brithon 1980, Christou et al. 1998).

Patients need interdental brushes of various sizes. Schmagne et al. (1999) assessed the relationship between the interdental space and the position of teeth. Most interproximal spaces in anterior teeth were small and suitable for the use of floss. Premolars and molars have larger interproximal spaces and are accessible by interdental brushes. Most studies do not discuss the different interdental brush sizes, nor do they indicate if the interdental brushes were used in all available approximal sites. This need to account for different sizes of interdental spaces makes a ‘true’ random assignment of interdental brushes in clinical trials difficult.

The available studies from the Hoenderdos and coworkers (2008) review show that changes in gingival inflammation, as assessed by the gingival index, are not as apparent as bleeding as an indicator of disease. Numerous studies have shown that sulcular bleeding is a very sensitive indicator of early gingival inflammation. Bleeding following the use of woodsticks can also be used to increase patient motivation and awareness of their gingival health. Several studies have shown the clinical effectiveness of gingival self-assessment (Kallio et al. 1990, Kallio et al. 1997, Walsh et al. 1985). The presence of bleeding provides immediate feedback on the level of gingival health. The dental professional can also easily demonstrate the gingival condition to the patient by using the interdental bleeding index for this obvious clinical manifestation. This monitoring device may encourage patients to include woodsticks as part of their own oral hygiene regimen (Bergenholtz & Brithon 1980).
Plaque accumulation is greater between molars and premolars than anterior teeth. The wider the interdental space, the more protected the bacterial biofilm will be. Molars and premolars provide the perfect interdental space for bacterial biofilm formation and maturation, without disruption by chewing or toothbrushing. Research has shown powered toothbrushing to have improved efficacy in approximal plaque removal compared with manual toothbrushing (Van der Weijden et al 1993, Van der Weijden et al 1994). The findings are based on relatively young study subject and extrapolation to a general population should be undertaken with caution.

Irrigation devices may increase the delivery of fluid beneath the gingival margin (Flemmig et al 1990). Greater penetration of a solution into periodontal pockets is achieved by patient-applied supragingival irrigation relative to mouthrinising (Flemmig et al 1995). Studies that evaluated the ability of supragingival irrigation to project an aqueous solution (H2O or medicinal fluids) subgingivally determined that supragingival irrigation with a standard irrigation tip was capable of delivering H2O or a medicinal fluid 3 mm subgingivally or to approximately half the probing depth in a 6 mm pocket (Eakle et al 1986, Larner & Greenstein 1993). Two studies demonstrated that H2O irrigation had little effect on the composition of the subgingival flora in sites with pocket probing depths of 4 mm or less (Sanders et al 1986, White et al 1988). An accessory of an oral irrigator device, the Pik Pocket® subgingival irrigation tip (WaterPik Technologies, Fort Collins, CO, USA), facilitates subgingival penetration of irrigants to 90% of 6 mm pocket depths when placed 1 mm subgingivally (Braun & Ciancio 1992). Supragingival irrigation applies considerable force to the gingival tissues. Irrigation was shown to have the potential to induce bacteremia relative to brushing, flossing, scaling and root planing, and chewing (Cobe 1954, Felix et al 1971, Sconyers et al 1973, Wampole 1978, Silver et al 1979, Carrol & Sebor 1980). Given the collective evidence, it appears that irrigation is safe for healthy patients.

**Conclusion**

Based on the available literature with respect to interdental cleaning, the best available data suggest the use of interdental brushes. These brushes should therefore be the first choice in patients with open interdental spaces. Meta-analysis shows a superiority of the interdental brush to floss with respect to plaque removal.

**Acknowledgments**

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Interdental oral hygiene: The evidence


Sniehotta FF, Araújo Soares V, Dombrowski SU.


Chapter 4

Multidisciplinary dentistry: Taking dentistry to the next level

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Introduction

Present dental practices are extensively different from what they have been in the past. Recently, dentistry has moved into an era of specialization and an interdisciplinary approach for any clinical condition for which specialist skills are required. At present, this kind of practice is desired not only by patients, but also by dentists who want to ensure optimal treatment results (Shetty 2011).

An interdisciplinary team consists of specialists from several dental fields combining skills and resources to formulate the most accurate diagnosis of a condition and provide the necessary treatments. The concept of interdisciplinary dentistry is the basis for further quality patient care. The team usually includes not only the various dental specialists (periodontist, endodontist, prosthodontist, restorative dentist, oral surgeon, orthodontist or paedodontist) but also medical doctors who can also collaborate to ensure the case is effectively managed and treated.

This is truly a challenging but rewarding way to do comprehensive dentistry. Involving other clinicians who can help direct and drive the case to its fundamental goal of giving the patient the best investment in time, effort and money. This arrangement avoids the frustrations that one may encounter when working alone and being limited to one’s own knowledge and experience.

This chapter will discuss how interdisciplinary or multidisciplinary dentistry through united efforts can affect treatment outcomes as well as provide the utmost care for patients. In the interdisciplinary model, the patient is seen by all practitioners involved, and a treatment plan is created through consultations between these clinicians (Speare 2005). This approved treatment plan is laid out by the group, presented to the patient and agreed upon with the general practitioner usually acting as the leader of the team.

The following cases have been treated using the multidisciplinary approach with the patient’s welfare as the primary goal.

Case 1 - Periodontally involved case: Periodontist, Oral Surgeon, Orthodontist, Prosthodontist & General Dentist

A 48 year old female patient presented to the clinic with a chief complaint of “My front teeth are moving. I cannot bite anymore. I do not want my teeth pulled out. Please help me.” Her past dental history consisted of irregular visits to the dentist. About 5 years prior to the visit she had orthodontic treatment. She was left with an open bite, since her orthodontist
did not see the need to correct this at that time. During orthodontic treatment she experienced occasional swelling. Her general dentist performed scaling and root planing for her and constructed a composite wire-splint on the palatal of teeth 21 and 22. A few weeks following this treatment she noticed increased mobility with pain on biting. She sought a second opinion from another general dentist and thus was referred for full periodontal evaluation.

Upon clinical and radiographic examination, she was diagnosed with:
1. Isolated localized advanced/severe chronic periodontitis particularly in relation to teeth 17, 21, 22, 26, 27, 37 and 47.
3. Anterior open bite (Figure 1).

The patient specifically expressed her desire not to have teeth extracted and accepted whatever compromises may result. With this in mind, a team of periodontist, orthodontist, oral surgeon and general dentist was assembled and several treatment plans were presented to the patient, involving extractions, bone grafting procedures, orthodontic treatment and periodontal treatment. After much discussion, and the patient again stressing that she preferred no extractions at that time, the following treatment plan was agreed upon.

Figure 1. Initial clinical and radiographic presentation of Case 1.
Treatment plan

1. Oral hygiene instruction and initial debridement.
2. Periodontal treatment with 4 quadrants of periodontal surgery, with bone grafting where indicated (Figure 2).
4. Fabrication of gum mask (Figure 3).
5. Re-evaluation: Assess response to treatment, if the condition stabilizes, patient will not need any further treatment. However, if the condition does not stabilize, the patient was informed that extraction will be required with fixed partial dentures or bone/soft tissue grafting and dental implant treatment as possible options to replace the extracted teeth.
6. Cosmetic treatment, limited bonding procedures (Figure 4).
7. Recall visits every 3 months.

This particular treatment plan was a compromised treatment plan for her as the primary factor was that the patient did not want to have her teeth extracted. Thus, the patient was willing to cooperate and compromise some functions such as not being allowed to bite or use her anterior teeth. The patient was also made to understand that at any point she traumatizes this area, the splint may give way and can become an ongoing problem for her. This option was a viable option for her since she has an anterior open bite, thus, the only load that can affect her teeth is biting/incising food.

With the severe bone loss that teeth 21 and 22 suffered, a severe ridge defect would be expected once these teeth are extracted. Ridge preservation was not an option as interdental bone between teeth 21 and 22 was not present and there was no vertical bone height that could be maintained. Most likely this would result in a Type III ridge defect as described by Seibert (1983a). Type III defects are
described as a combination of loss of the bucco-lingual width and the apico-coronal height of the ridge. Treatment usually comprises a staged approach, with hard tissue regeneration in the first stage and then soft tissue augmentation at another stage later on. Hard tissue regeneration either involves bone graft techniques that can be taken from autogenous intraoral and/or extraoral sources, autologous grafts and xenografts (Misch 1996, Shwartz-Arad et al 2005). Soft tissue augmentation involves a number of procedures including, the “roll procedure”, pouch procedures, onlay grafts and connective tissue grafts, among many other procedures (Abrams 1980, Langer & Calagna 1980, Seibert 1983b, Miller Jr 1986, Genco et al 1990). If extraction was chosen the patient would have to sacrifice time, effort and finances in order to rebuild the hard and soft tissues that were lost. If the tissues are not rebuilt after extraction, the patient will be left with a huge defect that will be hard to restore with good esthetics and will be hard to maintain long term.

Currently, as esthetics is of major concern to many patients, it has also become one of the primary considerations in multidisciplinary approaches. If the treatment planning sequence proceeds from biology, to structure, to function and finally to esthetics, the eventual esthetic outcome may be compromised. Therefore, we proceeded in the opposite direction: we commenced the treatment planning process with esthetics and proceeded to function, structure and, finally, biology. None of the important parameters were excluded, the planning process is simply sequenced from a different perspective (Spear 2006).

For Case 1, after exploring the advantages and disadvantages of keeping or extracting her
teeth and performing implant therapy or constructing a fixed partial denture, the patient opted to save her teeth with acceptance of some compromises. If and when these teeth go downhill, then she is prepared for any eventuality.

The sequence of treatment required the periodontal disease to be controlled which included initial debridement, followed by four quadrants of periodontal surgery. The gingiva healed as expected with the return of gingival stippling but loss of papilla was inevitable (Figure 5). Thus, fabrication of a gum mask or prosthesis was done. Orthodontic consultation was also suggested but the patient declined. Re-evaluation was done after 6 months, 12 months and the patient was found to be periodontally stable. The patient attends every 2 months for recall visits instead of 3 months and is a very motivated patient at this point.

Wilson et al (1987), documented 162 maintenance patients over 5 years, who were divided into compliant and erratic subjects. Results showed that all recorded tooth loss occurred in the erratic group, while patients who are compliant are less likely to have tooth loss. Studies of this kind should encourage all dentists that provided patients are made aware of the rationale for retaining teeth, dentists should strive for retention of teeth over other treatment options.

Case 2 - Esthetically involved case: Periodontist, Restorative Dentist/Prosthodontist, Oral Surgeon & Endodontist

A 40 year old female patient was referred by her general dentist with the chief complaint of “My tooth fractured while eating candy and I would like my teeth restored properly. Please help me regain my smile and confidence”. The past dental history showed multiple restorations which have been performed over the years on teeth 11, 21 and 22. These included root canal fillings on tooth 11, 21, 22, a large post and core restoration on teeth 11 and 21 and porcelain fused to metal crowns on teeth 11, 21 and 22 which has caused some weakening of the tooth structures. Tooth 11 had fractured subgingivally. Upon clinical examination, obvious signs of infection (presence of fistula) on the area between tooth 21 and 22 were found. Likewise, the loosening of the full veneer crowns on tooth 21 and 22 were noticed. This resulted in the removal of the old crowns on teeth 12, 21 and 22.

A multidisciplinary group composed of a general dentist, a periodontist, oral surgeon, and an endodontist were assembled to examine and diagnose this highly esthetic case.

Upon clinical and radiographic evaluation of the case, the conditions of each of the involved teeth were recorded as follows (Figure 6):
1. Tooth 22 – presence of periapical radiolucency, absence of root canal treatment, poor crown to root ratio, subgingival margins and the presence of a fistula which was confirmed by radiographic gutta percha point tracing (Figure 6c).
2. Tooth 21 – adequate root canal treatment, large post and core, symmetrical margins, weak tooth but restorable.
3. Tooth 11 – subgingival fracture, inadequate root canal treatment, poor crown to root ratio, crown margins subgingivally located.
4. Tooth 12 – tooth was found to be restorable.

**Treatment Plan**

1. Plan for temporization.
2. Atraumatic extraction of teeth 11 and 22 with ridge preservation (Figure 7).
3. Implant placement for teeth 11 and 22 using the flapless technique to preserve the hard and soft tissues.
4. Temporization at time of implant placement.
5. Final restoration of implant crowns on teeth 11, 22 and single crowns on natural teeth 12 and 21.

The collaboration for this case focused on the esthetic rehabilitation, noting that the periodontium should be preserved at all cost to attain a good final restorative outcome. Crown lengthening for teeth 11, 21 and 22 was ruled out since the amount of osseous reduction will compromise the support of these teeth, as well as that of the adjacent teeth.

Other considerations discussed by the team were the unfavorable crown to root ratio, and the possibility of retreated root canal teeth becoming very weak, and thus being prone to fracture. A common agreement was reached to atraumatically extract teeth with poor
prognosis, namely teeth 11 and 22, by an oral surgeon. Ridge preservation was performed for both teeth in order to preserve bone for implant placement later on (Figure 7) (Lekovic et al 1997, Lekovic et al 1998).

After waiting for four months for healing, a fistula was again noticed and radiographic tracing was not an option as the gutta percha barely entered it (Figure 8). An exploratory procedure was done and the fistula was observed to be coming from the apex of tooth 21 which was considered to be a very important tooth in this case. Thus, an apicoectomy procedure was performed on tooth 21 (Figure 9). Restoring adjacent implants is much more challenging than doing single anterior implants. (Tarnow et al 2000, Tarnow et al 2003) as when two adjacent teeth are extracted, there is loss of the interdental bone which houses the peak of the interdental papilla. Thus, with no interdental bone maintenance of the papilla becomes very difficult (Tarnow 1992, Tarnow et al 2003). Additionally, the level of interproximal papilla of the implant is independent of the proximal bone level next to the implant, but is related to the interproximal bone level next to the adjacent teeth (Kan et al 2003b). Thus tooth 21 was considered a pillar for this case and it was decided that it was in the patient’s best interest to keep tooth 21.

7 months after extraction and 3 months after apicoectomy, noting the good healing of the extraction sites at 11 and 22 where adequate bone height and width were maintained, a flapless approach was chosen for stage 1 implant placement in order to preserve the hard and soft tissues (Figures 10 & 11). It is well-known that flap reflection alone can lead to bone resorption up to 1 mm (Wood et al 1972, Moghaddas et al 1980). Likewise, reflection of a full thickness flap compromises the blood supply and can result in marginal bone loss (Pennel et al 1967). The resultant bone loss from flap surgery may cause gingival recession and the loss of interdental papillae (Kois 1994, Salama et al 1998). Thus, performing flapless surgery preserves the bone and soft tissue for the development of optimal aesthetics (Kan 2000). The specific criteria determined by Kan

Figure 7. Ridge preservation following extractions.

Figure 8. Presence of fistula at four mouths after extractions.
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(2000) were:
1. The presence of 6 mm of buccolingual bone.
2. At least 10 mm vertical bone.
3. An adequate band of keratinized gingiva.

Provisionalizations were done immediately to guide the soft tissues during healing and preview the final restoration. This is very critical for the development of the subgingival emergence profile (Kan et al 2003a) Final restorations were delivered 5 months following implant placement (Figure 12).

It has been almost three years since the case was completed and the patient has remained very satisfied and happy. Because of the presence of the large post in tooth 21 the patient was instructed not to bite nor apply pressure on the front teeth as this may cause this tooth to fracture. To further reassure the patient, she was advised of treatment options

Figure 9. An apicoectomy was carried out on tooth 21.

Figure 10. Healing of sites 11 and 22 following extraction and apicoectomy.
Figure 11. Implant placement in sites 11 and 22.

Figure 12. Final result.
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Discussion

Interdisciplinary dentistry is about a special relationship amongst clinicians who share a special goal of giving the patient the utmost care. Spear has developed a set of criteria as follows (Spear 2005):

1. The team should agree that quality patient care is paramount. The understanding that giving the best treatment possible, even though this may entail repeating and modifying certain procedures, is part of the discipline. Financial gain should not determine the level of care that the team collectively provides the patient.

2. As in any health care system, there are variations in the final result. Because many factors can contribute to an end result, such as patient’s healing response, attitude, patient compliance and the clinician’s skill, it should be understood that these factors may bring about either an outstanding result or “the best we can do” result.

3. Another crucial factor is acknowledging expectations right from the onset of the case. These will prevent any frustrations and disappointments that may occur in the process of the treatment. Likewise, this guides the overall sequence of therapy that the patient goes through. One must remember that some of these cases may run up to several years, thus duration of treatment is discussed from the beginning.

4. Some team members may have more expertise of the case than the others have. This allows free discussion of the best available procedures/techniques for the patient. There is a saying “An expert is one who knows more and more about less and less.” (Anonymous)

5. Each team member should accept responsibility for their own personal area of treatment. If there are any concerns with the work, the specialist should be called to manage the work.

6. Upon discussion of the different options in the treatment plan, negotiations are an accepted reality that shows any opinion from any team member is welcome and carefully assessed by the group.

7. Lastly, there should be respect for each other as well as commitment to the multidisciplinary approach team. He further explained that should complications arise discussions should be undertaken so that these can be avoided in subsequent cases.

Conclusion

This multidisciplinary relationship should be nurtured and cared for just like any relationship. This removes the frustration one experiences without the reliance of a team, especially with comprehensive cases that requires the utmost dental care. It directs the sequence of therapy so that its well-planned result is achieved. It always starts with ONE challenged dentist. From this one dentist, arises a team of qualified clinicians that can provide full commitment to the practice of dentistry that leads to successful and outstanding treatment outcomes (Spear 2005).

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with shared responsibility. Also, I would like to thank Dr Nanette Vergel De Dios for her sincere help in editing the manuscript.

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Chapter 5

Gingivitis revisited

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Introduction

Gingivitis is one of the most common dental conditions that exist in humans. Research has helped us to understand it better, yet significant unanswered questions remain. At present, gingivitis is often overlooked, with a corresponding tendency to ignore its management. However, a more recent ‘explosion’ of new findings has begun to challenge traditional concepts and perspectives of gingivitis, thereby arousing a renewed interest. Adding to this is the growing popularity of dental implants, along with the “gingivitis equivalent” of peri-implant mucositis. Clinicians may need to reconsider how to assess and manage this plaque induced inflammatory condition. This chapter presents an overview of recent findings, current concepts in plaque-induced gingivitis and additionally the implications and clinical significance for both clinicians and our patients.

Dental plaque

Dental plaque is a type of biofilm comprising a complex aggregation of microorganisms. It is characterized by an extracellular matrix of polymeric substance, structural heterogeneity, genetic diversity, complex community interaction, and possesses the ability to resist action of both detergents and antibiotics. The formation of a dental plaque biofilm begins when the pellicle, which is a thin layer of salivary proteins, attaches to the tooth surface. This occurs within minutes after cleaning of the tooth. The pellicle serves as a sticky surface that allows bacterial to be attached. This develops into an irreversible attachment of bacteria and proceeds with growth and development of bacteria leading to exopolymer production and biofilm formation. As the biofilm matures it begins to disperse bacteria. Examining dental plaque, there is a need to understand how it relates to oral health and conversely contributes as an etiologic factor to potential oral diseases. In health, there is an ecological balance between dental plaque and the host.

Our understanding of dental plaque and the role it plays in our mouth has evolved in response to new knowledge derived from continuing research using the latest advances and innovative applications of investigative techniques. At present, several parameters have been identified to have a role in the balancing equation between oral health and disease. Other interactive factors include: host defense mechanisms, genetic factors, socioeconomic factors (including lifestyle, dietary factors, social habits and oral hygiene...
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As well as the range of interactions between the microflora and host. There is also evidence to suggest that the geographical location of the plaque (i.e. the position of the tooth) influences the proportion of certain species being present (Haffajee et al 2009). It is conceivable that each host may interact in a unique manner with an oral microflora ecosystem at the species and strain level to the extent of individualized uniqueness like a fingerprint (Dethlefsen et al 2007). Thus it is potentially possible for oral microflora communities to have a greater impact in regulating the oral environment than previously thought. However, the evidence available today is rather limited when proving that plaque is indeed person-specific, but the door is wide open for more research and this poses an exciting challenge for the future in this ‘new’ field of microbial ecology based on the ecological plaque hypothesis first proposed by Marsh (Marsh 1991, Diaz et al 2006).

Plaque-induced gingivitis

The study of dental plaque would invariably involve gingivitis. Chronic gingivitis has been described as one of the most common and prevalent dental diseases globally (Albandar & Rams 2002). Gingivitis and periodontitis are the two major forms of periodontal disease. While much investigation and research has been centered on periodontitis in view of its potential impact on tooth morbidity, there has been less interest in gingivitis. Gingivitis is characterized by chronic inflammation of the marginal tissue of the gingiva and is induced by dental plaque. The American Academy of Periodontology website provides the following definition; “Gingivitis is the mildest form of periodontal disease. It causes the gums to become red, swollen, and bleed easily. There is usually little or no discomfort at this stage. Gingivitis is reversible with professional treatment and
good oral home care” (AAP 2012). However in the absence of treatment, gingivitis may progress to periodontitis, which is a major cause of tooth loss in adults aged 40 years and above. Unlike tooth decay, gingivitis is painless with little to no discomfort and therefore many tend to ignore its early signs and symptoms. An adult oral health survey conducted in 2003 revealed that 81% of subjects were aware of the causes of dental caries but only 43% knew the cause of gum disease (Singapore National Adult Oral Health Survey 2003). Of the 1,500 adults examined, 85% displayed mild to moderately severe forms of gum disease. The findings of the study suggested that in Singapore, there was a decrease in the prevalence of tooth decay but an increase in prevalence of gum disease. Taken together, the evidence concerning gingivitis indicates that this very common dental condition should be given more attention by both patients and clinicians. Additionally, both gingivitis and periodontitis have a commonality in gingival inflammation.

Inflammation and the processes involved have been studied and fairly well elucidated. The complex cascade of cell and molecular events that occur during gingival inflammation, accompanied by distinct histological changes in gingival tissue, have been described. However, we are only beginning to understand how various biodynamic interactions occur in the microbial aggregates (planktonic biofilm) found in saliva, and their interaction with dental plaque development and its heterogeneity within the mouth (Filolche et al 2010). A recent study of the changes in gingival crevicular fluid inflammatory mediator levels in an experimental gingivitis model revealed that while similar clinical responses were observed amongst study subjects there was considerable variability in the pattern of biomarker expression (Offenbacher et al 2010). This seems to suggest that the variability of host response via specific inflammatory biomarkers may reflect a potentially unique host response to an oral biofilm challenge to oral health. This study also showed that there was considerable variability of the phenotype of bacteria communities involved when clinical gingivitis develops. Thus it is plausible that in experimental gingivitis the dental plaque make-up/build up would vary from individual to individual, however the small sample size of the study presents limitations in further analysis and conclusions.

### Associated host responses

The way in which host inflammatory processes respond to an oral biofilm-based challenge has a significant influence on the outcome. A variety of factors participate interactively in determining whether disease occurs or health will prevail. The host susceptibility or disease risk profile of the individual will depend on genetic factors like gene polymorphism, systemic conditions like diabetes and social factors like smoking (Raunio et al 2009, Salvi et al 2010). The recent European Workshop on Periodontology reported in a review of papers that there is evidence to suggest a direct relationship between the properties of the host and composition and activity of resident microbiota. The resident microbes are affected by changes to the host environment whereby gene expression and composition changes are effected as a result of disruption of the normal symbiotic relationship, causing a reorganization of the biofilm community structure (Marsh & Devine 2011).

In a study by Deinzer et al (2007), where experimental gingivitis was compared to persistent gingivitis, significant differences in host inflammatory response were noted. After 4 weeks, levels of crevicular fluid IL-1 were found to be higher in experimental gingivitis whilst conversely, IL-8 was found in higher
concentrations in persistent gingivitis. It was also demonstrated that more fluctuations in clinical and immunological parameters occurred during the 4 weeks of experimental gingivitis as opposed to smaller fluctuations in the persistent gingivitis sites. The authors conceded that limits to this study included that subjects were students with chronic moderate gingivitis of undeterminable period of time and that in the experimental gingivitis group, baseline immunological values were obtained 7 days after prophylaxis, which may be an insufficient time to ascertain that these values have stabilized. However, the results lead us to consider that if persistent gingivitis reflects a steady state of inflammation that is different from acute gingivitis, then would this allow gingivitis to be distinguished by virtue of the inflammatory signature?

A recent study by Offenbacher et al (2009) involving 18 subjects demonstrated that genes which are transiently active in response to experimental gingivitis involved a relatively small subset (11.9%) of all the immune response genes and vice versa when resolution to experimental gingivitis occurs. This suggests a rather specific immune response is activated during gingivitis. An interesting observation was the discovery of novel cellular and molecular pathways that have not been previously linked to gingivitis responses, in particular that the pathway associated with neural processes was the second most dominant cellular activation pathway. However, due to the small sample size, it was not possible to draw firm conclusions.

Changes in the periodontium occur in response to hormonal changes during pregnancy, puberty and menopause in women have been studied for some time (Amar & Chung 1994, Mariotti 1994). While definitive evidence to suggest a significant influence of female hormones on gingival tissue is not available, a recent investigation compared 25 healthy females with 25 having gingivitis demonstrated that of the inflammatory biomarkers only IL-6 levels were higher in the gingivitis group during pre-menstruation, menstruation and ovulation period compared to the healthy group. Percentage sites with bleeding upon probing were also higher. Becerik et al (2010) found that changes in sex hormones may have a limited transient effect on gingival inflammation as reflected by bleeding on probing. In another study, Gursoy et al (2010) analyzed salivary samples from 30 pregnant women with good periodontal health taken at five time points (three times for each trimester, 4 to 6 weeks after delivery and after lactation) and compared them with 24 periodontally healthy non-pregnant women. Clinical parameters of plaque index, bleeding on probing, probing depth and clinical attachment levels were measured as well as, salivary biomarkers (elastase, matrix metalloproteinase-2, -8, -9, myeloperoxidase and tissue inhibitor of matrix metalloproteinease-1). The results revealed that MMP-8 and myeloperoxidase levels varied inversely to the presence of pregnancy gingivitis and associated clinical parameters. The lowest levels were recorded during the second trimester where there is most gingival inflammation, before increasing post-partum, and reaching normal levels after lactation.

The management of inflammation has seen significant developments, with the discovery of how the failure of resolution pathways of inflammation may impede the restoration of tissue homeostasis. With improved understanding of the pathways in inflammatory processes, studies by Van Dyke et al (2007) have focused on proresolving lipid mediators that have the ability to restore tissue homeostasis thereby resolve inflammation. It is currently understood that during the late inflammation stage a “class switch” located within neutrophils may, when activated, result in the synthesis of proresolving molecules along distinct resolution pathways via cell-cell
interactions. The result is production of 15-S-hydroxy-(p)-eicosatetraenoic acid from the oxidation of arachidonic acid by 15-LO which induces the subsequent synthesis of lipoxins A<sub>4</sub> and B<sub>4</sub>, which act as agonists to promote resolution restoration of tissue homeostasis (Kantarci & Van Dyke 2003, Van Dyke 2008). Other mediators like resolvins and protectins that are derived from omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexanoic acid have been elucidated and are known to act as proresolving lipid mediator agonists to stimulate the resolution of acute inflammation (Serhan & Chiang 2008). Resolvin E series (RvE1) has been shown in experimental periodontitis animal studies to prevent the onset and progression of periodontitis (Hasturk et al 2006). In addition, Hasturk et al (2007) demonstrated that topical application of RvE1 in a rabbit experimental periodontitis model using P. gingivalis and ligature has shown the ability to effect a bacterial shift of the oral biofilm where P. gingivalis concentrations were reduced to negligible levels.

**What is peri-implant mucositis?**

The definition provided by the 1994 European Workshop on Periodontology was that of a soft tissue inflammatory reaction that was reversible. More recently, peri-implant mucositis has been defined as the condition of the presence of inflammation in the mucosa around an implant with no signs of the loss of supporting bone (Zitzmann & Tord 2008).

**How prevalent is peri-implant mucositis?**

Studies have indicated that prevalence rates range from 50% of implants to as high as >90% (Roos-Jansaker et al 2006, Fransson et al 2008). A review by Lang et al (2011) concluded that gingivitis and peri-implant mucositis are not fundamentally different from a pathogenesis and diagnostic point of view. However, is this the entire picture? A recent study may appear to suggest otherwise. Salvi et al (2011), in a study with 15 subjects revealed that experimental gingivitis and peri-implant mucositis can be reversed from the biomarker perspective. However, at 3 weeks following resumption of plaque control, clinical peri-implant health around implants was yet to reach pre-investigation levels. In addition, the associated inflammatory response as measured via biomarkers like MMP-8, IL-1β and bacterial profiling were more severe when compared to natural teeth. Another recent study compared two methods of full mouth disinfection for 13 partially edentulous subjects with treated chronic periodontitis but with 36 dental implants with peri-implant mucositis. Both methods were equally effective in producing a reduction in probing depths after 8 months. However, the initial reduction of bacteria around both teeth and implants 24 hours after treatment was not sustained, and returned to approximately previous levels after 8 months (Thone-
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Muhling et al (2010). Thus, it would appear that the micro-environment would tend to revert back to an unhealthy state and taking into consideration the available evidence, it would be prudent to institute strict maintenance reviews for dental implant patients.

Treatment implications for gingivitis

The ability to ‘reverse’ gingivitis has not received as much attention in comparison to periodontitis, where there has been considerable interest in investigating the interaction between periodontal disease and systemic conditions including diabetes mellitus, chronic heart disease, stroke and rheumatoid arthritis. Although evidence to prove a stronger association is not yet available, there is a body of knowledge and findings to suggest such a link does exist. Research continues to provide a better understanding of periodontal disease. At the recent 7th European Workshop on Periodontology, the Consensus on understanding cellular and molecular mechanisms of host-microbial interactions reviewed the accumulated body of knowledge. In considering periodontal disease biomarkers classified under susceptibility, diagnostic, prognostic, predictive and therapeutic, limited evidence has been reported that salivary concentrations of myeloperoxidase and MMP-8 can be used as a diagnostic measure to distinguish between gingivitis and periodontitis (Kinane et al 2011). Perhaps, in time, we may be able to begin to see beyond clinical gingivitis and consider the host-response as well as various relevant biomarkers. In this way, we can manage gingivitis from a preventive perspective by assigning risk factors that may indicate a potential progression towards periodontitis.

Conclusion

It may be timely to re-examine how clinicians manage gingivitis, given how our latest understanding and current body of knowledge is leading us to change our perception. We must take cues from our medical colleagues who are managing chronic heart disease/heart attack from a preventive approach. The drive to advance research should be a multi-perspective approach that goes beyond just host-microbial interaction to include genetic factors and a socioeconomic angle. This, in turn, will help us identify specific risk factors present in specific patient groups so that appropriate preventive maintenance measures can be instituted to specifically target, prevent and manage periodontal disease. With exciting research that leads us to new knowledge, the future is bright for dentists to examine a common oral condition, gingivitis, and manage it more effectively for the benefit of our patients.

References


Chapter 6

Smoking and periodontal disease

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Introduction

It has long been recognized that tobacco smoking is one of the major public health concerns. In a seven billion world population, there are approximately 1.3 billion smokers (Esson & Leeder 2004). Each year, approximately 5 to 6 million people die from lung cancer and other smoking-related illnesses such as heart disease and stroke (World Health Organization 2008). Smoking-related illnesses also include oral cancer and periodontal disease.

It is well recognized that cigarette smoke can alter cell function and promote disease development and severity (Masubuchi et al 1998, Su et al 1998, Laan et al 2004, Oltmanns et al 2005, Vassallo et al 2005). Epidemiological investigations indicate that cigarette smoking is a leading risk factor for periodontitis. Smokers exhibit a greater number of diseased sites than non-smokers, as well as greater loss of alveolar bone and increased tooth loss (Grossi et al 1994, Grossi et al 1995). Disease severity increases with the intensity and duration of smoking exposure (Haber et al 1993, Papapanou 1996, Bergstrom et al 2000). It is thought that the immune modulating effect of smoking on the host response to bacterial plaque is associated with a more aggressive periodontal breakdown (Ryder 2007).

The effects of cigarette smoking on the innate immune response of human gingival epithelial cells

The oral epithelium is the first tissue in the oral cavity exposed to cigarette smoke. There is a lack of knowledge of the effect of smoking on gingival epithelial cells, although it is well recognized that these cells play an important role in innate immune defense. To recognize invading pathogens, gingival epithelial cells express innate sensing receptors. These cells not only serve as a physical barrier, but actively respond to microbes by producing pro-inflammatory cytokines such as IL-1, IL-8, TNF-α, as well as the important inducible antimicrobial peptide-human beta defensin 2 (hBD-2) (Ouhara et al 2006). The aims of this study were to characterize innate sensing receptors including Toll-like receptor (TLR) and non-TLR expression of primary human gingival epithelial cells (HGEC) and examine their responses to specific ligands. In addition, the modulating effect of cigarette smoke extract (CSE) on epithelial cells was investigated. Figure 1 briefly reviews the effects of smoking on cells in periodontal tissues, including both residential cells and immune infiltrates.
Innate sensing receptors in HGEC

Recent evidence suggests the emerging roles of innate sensing receptors (TLRs and non-TLR) in periodontitis (Sugawara et al 2006, Mahanonda et al 2011). The recognition by these receptors leads to the release of mediators which limit and contain microbial invasion.

By using RT-PCR, HGEC derived from healthy periodontal tissues expresses a variety of TLRs: TLRs 1, 2, 3, 5, 6, 9, and 10 but not TLRs 7 and 8 (Figure 2). They minimally expressed TLR4. In addition, they expressed non-TLR which included RIG-I (retinoic acid-inducible gene-I) and MDA5 (melanoma differentiation associated gene 5) which play a role in viral detection. Peripheral blood mononuclear cells (PBMC) were used as positive control. PBMC expresses all the TLRs 1 to 10, as well as RIG I and MDA5 (Figure 2).

HGEC responses via TLR stimulation

In line with the observed expression of their respective TLRs 2, 3, and 5, P. gingivalis LPS, poly(I:C), and S. typhimurium flagellin induced hBD-2 and IL-8 in the epithelial cells (Figure 3A, B, and C). E. coli LPS, a TLR4 ligand, did not induce either hBD-2 or IL-8, which is consistent with our observation of only minimal expression of TLR4. Additionally, the epithelial cell culture medium did not contain serum, a source of LPS-binding protein. On the contrary, CpG ODN 2006, a potent TLR9 activator, had no effect, even though HGEC clearly expressed TLR9 mRNA. The reason for this observation remains unclear and requires further investigation.

CSE suppresses epithelial hBD-2 but stimulates IL-8 expression

The immune modulating effect of CSE was evaluated in HGEC that had been stimulated with the combination of P. gingivalis LPS and
Chapter 6

Figure 2. mRNA expression of innate sensing receptors: TLRs and non-TLRs in HGEC derived from healthy periodontal tissues. Abbreviations: GAPDH, Glyceraldehyde 3-phosphate dehydrogenase; HGEC, human gingival epithelial cells; MDA5, melanoma differentiation associated gene 5; PBMC, peripheral blood mononuclear cells; RIG-I, retinoic acid-inducible gene-I; TLRs, Toll-like receptors.

TNF-α. As depicted in Figure 4A and B, the combination of TLR2 ligand-\textit{P. gingivalis} LPS and TNF-α exerted an enhancing effect on both hBD-2 and IL-8 expression when compared to those of individual stimulations ($p < 0.05$). This may be due up-regulation of TLR2 by TNF-α (Figure 4C). Figure 4D shows that treatment of stimulated HGEC with a non-toxic concentration of CSE (1:2 dilution) led to a statistically significant reduction in hBD-2 mRNA expression, as compared to the response in stimulated cells with no CSE treatment ($p<0.05$). These data strongly suggest that smoking reduces ability to kill bacteria, and may thereby allow overgrowth and invasion of periodontal pathogens. \textit{P. gingivalis} and \textit{Tannerella forsythia} have been shown to colonize a larger proportion of tooth sites in smokers than the non-smokers (Wendell and Stein 2001). In contrast, CSE at the same concentration significantly enhanced IL-8 production ($p < 0.05$) (Figure 4E). These data support the in vivo study of elevated IL-8 in the gingival crevicular fluid of smokers (Giannopoulou et al 2003). In addition, our results are consistent with previous observations of heavier cellular infiltration in the epithelial cell layer in periodontitis lesions of smokers as compared to non-smokers (Haffajee & Socransky 2001). Furthermore, this simultaneous enhancing and suppressing effect of CSE on mediator production in HGEC suggests that the expression of these two mediators may be controlled by different pathways.

Conclusion

In conclusion, further insights into the immune modulating effect of cigarette smoking are provided. Tobacco smoking could serve as a risk factor of periodontitis by suppressing anti-microbial hBD-2 and increasing IL-8 production. Under these conditions susceptibility and severity of periodontal disease may be increased.

Acknowledgement

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Figure 3. TLR activation in HGEC. HGEC were stimulated with the following ligands: \textit{P. gingivalis} LPS (TLR2 ligand), poly(I:C) (TLR3 ligand); \textit{E. coli} LPS (TLR4 ligand); \textit{S. typhimurium} flagellin (TLR5 ligand); loxoribine (TLR7 ligand); poly(U) (TLR8 ligand); CpG ODN 2006 (TLR9 ligand). Control and stimulated HGEC were harvested after 24 h and (A) mRNA expression of hBD-2 was analyzed by RT-PCR. TNF-\(\alpha\)-stimulated HGEC were used as a positive control. GAPDH mRNA was used as an internal control. (B) Data represent the mean ratio of hBD-2:GAPDH \(\pm\) SEM (n=4, *, \(p<0.05\), compared with unstimulated control). (C) For assessment of IL-8 production, culture supernatants of control and stimulated HGEC were harvested after 24 h and then assayed by ELISA. Data shown are mean \(\pm\) SEM of four separate experiments (*, \(p<0.05\), compared with unstimulated control).
Figure 4. The effect of CSE on expression of hBD-2 and IL-8 in HGEC upon stimulation with \textit{P. gingivalis} LPS plus TNF-α. The combination of TLR2 ligand-\textit{P. gingivalis} LPS and TNF-α enhanced (A) hBD-2 and (B) IL-8 expression. Data shown are mean ± SEM of four separate experiments (*, \( p < 0.05 \), compared with single stimulator). (C) Treatment of TNF-α with HGEC overnight up-regulated TLR2 expression. (D) HGEC were stimulated with \textit{P. gingivalis} LPS plus TNF-α in the presence or absence of non toxic concentration of CSE (1:2 dilution). For quantitative analysis of hBD-2 expression, stimulated HGEC with or without CSE treatment were harvested after 24 h and mRNA expression of hBD-2 was analyzed by real-time PCR. GAPDH mRNA was used as an internal control.
References


Chapter 7

Regeneration and plastic surgery

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Mucogingival surgery was introduced in the late fifties and is defined as surgical procedures to preserve gingiva, to remove aberrant frenulum or muscle attachment and to increase the depth of the vestibule. The main procedure developed was the free gingival graft which was used to solve most mucogingival problems. In that era, many patients were treated based on the dogma of an ideal width of masticatory mucosa.

Since the 1970’s, the requirement for a minimum width of gingiva in order to maintain periodontal health has been investigated in several studies. The conclusions showed that:
1. The requirement for a minimum width of gingiva around teeth is not scientifically proven;
2. Periodontal health can be maintained independent of gingival width; and
3. A small band of gingiva seems to have the same resistance to attachment loss, even in the presence of plaque.

In the course of time, mucogingival surgery has moved away from the traditional problems of pocket surgery and evolved into a surgical method to treat periodontal and peri-implant problems relating to both hard and soft tissues. Therefore the term “mucogingival surgery” has now been replaced by “periodontal plastic surgery”.

Two of the most investigated treatment modalities in modern periodontal plastic surgery are guided tissue regeneration and the coverage of buccal root recessions. Both have been proven to be effective and to improve the corresponding clinical conditions. However, randomized controlled multicenter clinical studies show a huge variability in outcomes, which indicates that these interventions are technically sensitive and clinician related factors can influence the results.

The aim of this chapter is to investigate the influence of flap tension and its effect on the desired results. The first human study in the coverage of recession evaluated the outcome of flap tension in a split-mouth design. A tension reduction from 6.5 to 0.4 g improved complete coverage from 17 to 45% and mean coverage could be substantially improved by applying lower tensions.

Based on these results, flap adherence to different wound bed configurations was further evaluated in animal studies. The findings showed that the stability of the blood clot between flap and dentine surfaces compared to the interface between flap and bone differed significantly. The latter was more stable throughout the whole observation period and forces of almost three times higher had to be applied after one week of healing to
detach a flap from its underlying wound bed in these sites. These findings supported the importance of wound stability and the need for an appropriate flap design and corresponding suturing.

The influence of flap tension related to wound dehiscences has been further investigated in another clinical study. The outcome showed that dehiscences do occur. These numbers were low whilst low tension forces were applied. Once the tension to the wound margins exceeded the threshold of 0.1 N, a marked increase of adverse wound healing effects were noticed. Flap thickness influenced the percentage of wound dehiscences but only when higher forces were applied. This confirmed that flap tension seemed to be the greater risk for wound dehiscences than flap thickness.

Many in vitro and in vivo experiments document the influence of mechanical forces on the healing characteristics of soft tissues. It has been shown that forces in the macro scale can be directly transferred via the extracellular matrix to the cytoskeleton of the fibroblasts by transmembrane proteins. These result in a change of the form of the cell and define its fate. A good example of this kind of mechanical influence is the lumen formation of new capillaries during angiogenesis. Studies show irregular growth of endothelial cells without morphogenesis if there is insufficient mechanical stability of the blood clot. Finally, we must be aware that the stability of the blood clot is mainly influenced by the ability of the surgeon to create a stable wound environment.

The process of capillary ingrowth during wound healing is mainly driven by the wound bed. This means that, besides the influencing factors of clinician's abilities, the focus on the vascularity of the wound bed plays an important role in surgical procedures. This seems to be more pronounced when parts of the wound bed consist of an avascular surface as found in recession coverage around implants and teeth, or in guided tissue regeneration procedures. In these sites the presence of the periodontal ligament may additionally improve the early capillary ingrowth and improve the prognosis of the intervention.

The above mentioned factors confirm that the role of the clinician has been badly underestimated. In technically sensitive interventions particularly, a meticulous presurgical evaluation, a proper treatment plan with careful, minimally traumatic execution define the success of the final result.
Chapter 8

Maintenance and treatment of peri-implant mucosal diseases in patients with implant-supported overdentures

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Introduction

The use of dental implants to support and retain overdentures has been described as “the minimum standard of care” for fully edentulous patients (Feine et al 2002, Payne et al 2003). Within the Sir John Walsh Research Institute at the University of Otago, the interdisciplinary Biomechanics and Oral Implantology research group has focused on early loading protocols for implant-supported overdenture (ISOD) patients. Implant survival, osseous and mucosal changes and prosthodontics complications for various clinical protocols and a range of implant systems over periods ≥10 years have been documented (Ma et al 2010).

The first series of clinical studies considered mandibular two-implant ISOD in 106 completely edentulous participants. All gave a history of poor adaptation to their conventional complete dentures. Inclusion criteria included a requirement for 8 to 15 mm of residual anterior mandibular bone. Four different implant systems were used; all patients received two implants placed in the anterior mandible using a one-stage protocol (Table 1). The full mandibular ISOD prostheses were functionally loaded using different protocols, ranging from two to 12 weeks after implant placement. Outcome variables included implant success and survival rates, implant stability (resonance frequency analysis), radiographic measurement of marginal bone level, peri-implant mucosal parameters, prosthodontics maintenance requirements and patient satisfaction (Payne et al 2001a, Tawse-Smith et al 2001, Payne et al 2002, Tawse-Smith et al 2002a, Watson et al 2002a, Watson et al 2002b, Payne et al 2003).


Mucosal overgrowth and ISOD

The early healing periods for many of the patients were generally successful, with marginal bone loss within established criteria for success. However, approximately 40% of patients experienced problems with mucosal overgrowth beneath their ISOD (Payne et al 2001b). It was also apparent that even with removable overdentures these patients experienced difficulty with self-performed
oral hygiene. A crossover trial of electric and manual tooth-brushing was conducted in a subgroup of 40 ISOD patients; 45% had surfaces with persistent plaque and 35% had persistent mucosal bleeding, irrespective of the type of device used for cleaning (Tawse-Smith et al. 2002). Moreover, analysis of the plaque samples from these patients using DNA-DNA hybridization detected both *P. gingivalis* and *A. actinomycetemcomitans*, even although some subjects had been fully edentulous for 50 years, and this microbial flora persisted despite focused home-care (Duncan et al. 2002a). Thus, it is possible to ascribe the presence of mucosal overgrowth in these patient groups to the persistence of periodontal pathogens.

Other theories for mucosal overgrowth have been suggested. Palmer et al. (2002) stated that the creation of a so-called “dead space” beneath overdentures results in soft tissue proliferation and overgrowth, in particular beneath the bar of an implant-supported bar overdenture. However, the exact mechanism behind this “dead space” effect was not discussed.

Payne et al. (2001) tabulated reports from 27 papers in a literature review of peri-implant mucosal enlargement around ISOD. They advocated the term “mucosal enlargement” for this clinical entity, and noted the consensus of opinion that this enlargement occurs more commonly beneath maxillary overdentures. Two potential aetiological factors were identified: plaque-induced inflammation and the development of a “negative pressure gradient” in the “dead space” beneath an ISOD that has a good peripheral seal (Ekfeldt et al. 1997). Again, the physiological mechanism underlying the latter has yet to be defined.

Payne et al. (2001) concluded, based on anecdotal evidence alone, that the incidence
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of mucosal overgrowth ranged from 4 to 35%. They also commented that both mechanical trauma due to misfit of the overdenture, as well as poor oral hygiene, were likely to play a part in mucosal overgrowth.

**Peri-implantitis and ISOD**

Whilst mucosal enlargement may be one manifestation of plaque-induced inflammation beneath ISOD, peri-implantitis is a potentially more catastrophic event, characterized by progressive loss of the supporting peri-implant alveolar bone. This is particularly the case when the overdenture is fixed to the supporting implant as this exacerbates the hygiene challenge for the patient. In an extension of the original removable ISOD experiments at the University of Otago, a project was commenced where upper and lower acrylic fixed prostheses were fitted to fully edentulous patients and supported using the Nobel Biocare “All-on-four” treatment concept. In order to reduce the cost of the prosthodontic superstructure, all-acrylic prostheses were fixed directly to the implants, without a metal substructure. It became clear that the acrylic dentures needed considerable bulk in order to provide sufficient strength under load. The project was abandoned after 15 patients had been treated. Three years into the project, 67% of the patients have had major prosthodontics complications (fracture and loss of teeth from the prosthesis) and 40% have radiographically evident peri-implant bone loss (Figure 1).

The problems caused by an over-extended superstructure are further illustrated by the

![Figure 1](image1.png)

**Figure 1.** Clinical case demonstrating “all-on-four” protocol with full acrylic fixed dentures, after one year loading. (a) Radiographs showing peri-implant alveolar bone loss after one year; (b) bulky acrylic flanges impede hygiene procedures; (c) prosthodontic complications (white arrows); (d) mucosal enlargement, candidiasis and peri-implant pockets with bone loss around maxillary implants.
Maintenance and treatment of peri-implant mucosal diseases in patients with implant-supported overdentures

Figure 2. Transitioning a chronic periodontitis patient to a fixed, full maxillary ISOD. (a) Pre-implant radiography showing chronic periodontitis in the maxillary arch; (b) four Straumann implants placed in the maxilla; (c) one year after delivery of the prosthesis, showing peri-implant bone loss around all four implants; (d) maxillary prosthesis in situ. The buccal ridge-lap impedes hygiene access; (e) prosthesis removed, showing peri-mucositis; (f) prosthesis modified to permit cleaning prior to surgical treatment of peri-implantitis.
case of a patient with chronic periodontitis who was transitioned to a fixed complete maxillary denture supported by four Straumann implants (Figure 2). One year after delivery of the prosthesis, peri-implant bone loss was apparent radiographically and bleeding peri-implant pockets were detected clinically. The patient reported that she was unable to perform adequate home care beneath the superstructure, which was then extensively modified to permit access for oral hygiene. The patient subsequently received peri-implant therapy with laser-assisted debridement of the implant surfaces and is now enrolled in an appropriate maintenance program.

A number of conclusions may be drawn from this brief literature review and case reports. The aetiology of mucosal enlargement beneath implant supported full dentures, both removable and fixed, remains contentious. Whilst there is strong evidence for the role of peri-implant bacterial flora, the relevance of a low-pressure “dead space” and the mechanisms by which this causes mucosal enlargement have yet to be fully investigated. Whilst there is strong evidence for the role of peri-implant bacterial flora, the relevance of a low-pressure “dead space” and the mechanisms by which this causes mucosal enlargement have yet to be fully investigated. It is clear that inappropriate prosthodontic rehabilitation preventing adequate access for home care is a major factor; close cooperation between the periodontist and prosthodontist during the planning stages of ISOD therapy is needed to avoid this. Furthermore, enrolling the patient into a preventative maintenance regime would seem prudent, in order to avoid the risk of the bacterial-induced mucosal inflammation progressing to peri-implantitis. This may be even more important when the patient has a previous history of chronic periodontitis, since it is clear that the periodontal flora is not eliminated from the oral cavity when the teeth are extracted and thus may colonise the peri-implant sulcus (Karoussis et al 2003, Fransson et al 2005, Roos-Jansåker et al 2006c).

### Peri-implant titanium particles

The prevalence and cause of peri-implant bone loss remains contentious. Recent work has given a range for prevalence from 12 to 56% of patients (Karoussis et al 2003, Fransson et al 2005, Roos-Jansåker et al 2006b, Zitzmann & Berglundh 2008). In a recent rebuttal to this, Albrektsson et al (2009) referred to the orthopedic literature and suggested that adverse loading and compromised healing/adaptation may also play a part in peri-implant bone loss. Recent work suggests that other aspects of the orthopaedic literature regarding so-called “sterile” or non-infective peri-prosthetic inflammatory bone loss may also be of relevance to the dental implant situation. The evidence for this comes from both preclinical animal experimentation and human clinical work.

### Animal models

In a series of experiments using the edentulous mandible of domestic sheep, it was established that osseointegration, as measured by percent bone-implant contact (%BIC), shows a linear relationship to the roughness of the implant surface, with the exception of titanium plasma-sprayed (TPS) surfaces (Duncan 2005, Duncan 2006). An incidental finding was the presence of titanium particles within the dense cortical bone surrounding the implants (Figure 3.) This phenomenon has been previously reported, in association with an enhanced inflammatory reaction around TPS-coated implants placed into a sheep radial bone model (Lill et al 1992). Martini et al (2003) reported similar phenomena around TPS-coated implants in sheep femoral and tibial diaphysis without associated inflammatory reaction or reduction in osseointegration, however only two animals were studied. In a sheep mandible model, the
Maintenance and treatment of peri-implant mucosal diseases in patients with implant-supported overdentures

Association between titanium particles and peri-implant inflammation with reduced %BIC seemed particularly marked in animals that had naturally-occurring periodontitis; the presence of periodontal pathogens in these animals was confirmed by DNA-DNA hybridization (Duncan et al 2002b, Duncan et al 2003). Titanium particle loss was not found around implants from other manufacturers that had been placed into the same animal model (hydroxyapatite-coated SteriOss, machined or blasted-surface Southern Implants, machined-surface Branemark, SLA-surface Straumann).

A subsequent experiment using blasted-surface implants that had been subjected to anodic oxidization and then placed into a sheep maxillary sinus model, also revealed titanium particle loss as well as poor bone-implant contact (Figure 4); this was especially marked around titanium alloy (TiAl6Nb7) implants (Park et al 2008, Duncan et al 2008, Duncan et al 2010a). When the same implants were placed into the sheep mandible and sheep femoral epicondyle models, no titanium particle loss was seen and bone-implant contact appeared to be enhanced (Duncan et al 2008, Duncan et al 2010b). It is speculated that the loss of particles from the very rough TPS-coated implants was caused by the friction generated in placing these implants into the dense cortical bone of the mandible,

Figure 3. (a) Titanium plasma-spray (TPS)-coated implant successfully osseointegrated in sheep mandible after 12 weeks; (b) TPS implant with failing osseointegration in sheep mandible after 12 weeks (c) magnified view of a thread of implant shown in (a); (d) detail a thread near the apex of implant shown in (b), showing titanium particles within marrow space (white arrow); (e) scanning electron micrograph at 125K magnification of TPS surface, consisting of fragile, easily-detached titanium beads; (f) (g) (h) magnified views of TPS implants in the sheep mandible after 12 weeks, showing large and small titanium particles detached from the implant surface (red arrows labeled “p”).
Figure 4. Resorbable-media-blasted (RBM) cp-titanium or titanium alloy implants placed into a sheep maxillary sinus model for 4 weeks (a) Low-power micrograph of control RBM cp-titanium implant; (b) inset shows clinical picture of two implants in situ in the sheep maxillary sinus; (c) RBM cp-titanium implant with hydrothermally-anodized surface; (d) RBM titanium alloy (TiAl\textsubscript{6}Nb\textsubscript{7}) with hydrothermally-anodized surface; (e) scanning electron micrograph (SEM) at 3K magnification of RBM control surface; (f) SEM at 3K of RBM anodized cp-Ti surface; (g) SEM at 3K of RBM anodized Ti-alloy surface; (h) high-power micrograph of anodised Ti-alloy implants showing titanium particle migration (red arrows) and poor-quality bone-implant contact.
whereas the loss of titanium particles from the oxidized additive surface of implants placed in the sheep sinus may be related to the low volume of supporting bone and subsequent fretting and wear of unstable implants.

Titanium particles in human patients

The presence of titanium particles in an animal model had seemed of little relevance with respect to implant healing in human subjects, until a recent finding by a group of colleagues who were treating peri-implantitis in ISOD patients. Tawse-Smith and co-workers (2012) excised inflammatory tissue from these patients during surgical peri-implantitis therapy and found histological evidence of titanium particle migration associated with the inflammatory reaction (Figure 5). The presence of titanium was confirmed by scanning electron microscopy (SEM) and energy dispersive spectroscopy (EDS) analysis.

Two subsequent cases from my own practice appear to support these findings. The first patient (Figure 6A–C) had a pair of SteriOss TPS-coated implants that have been supporting a fixed partial denture in her posterior mandible for 20 years. Although clinically immobile, the anterior implant presented with bone loss near to the apex. A biopsy of the peri-implant inflammatory tissue

Figure 5. (a) Implants and bar supporting a mandibular over-denture: peri-implantitis around anterior Nobel TiUnite implant after flap elevation and prior to laser debridement; (b) H&E-stained histology of soft-tissue biopsy from peri-implant inflammatory tissue with titanium particulate material (black arrowheads); (c) energy dispersive spectroscopy (EDS) of histological specimens confirm that the particles are titanium.
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demonstrated many small titanium particles embedded within the fibrous connective tissue and surrounded by an intense infiltrate of mixed chronic and acute inflammatory cells. The patient reported that the implant had never been subjected to scaling or manipulation of the surface, but that the implant had been painful and felt “tight” when initially placed. Therefore mechanical friction (similar to that suggested for TPS-coated implants placed in the sheep model) might account for the loss of titanium surface material.

The second case was a patient with a single-tooth anterior maxillary implant that had been in situ for five years (Figure 6D-F). In this case a hygienist had previously instrumented the Nobel TiUnite-surface implant, in an attempt to resolve chronic suppuration. Again, the histology report noted a marked infiltrate of chronic inflammatory cells associated with particulate material that was later identified as titanium.

Although there has been little discussion of titanium particulate matter in the dental literature, this is not the case in the orthopaedic literature. It must be acknowledged that hip prostheses are very different to dental implants with respect to both loading and exposure to surface fretting and wear. The orthopaedic literature distinguishes between septic and aseptic loosening of prostheses, with the latter defined as “inflammation induced by polymeric and metallic wear particles derived from implant components in the absence of any clinical signs of infection” (Greenfield et al 2010). Phagocytosis of titanium wear-

Figure 6. Case 1. (a) Radiograph of TPS-coated implants supporting a fixed bridge; red arrows indicate peri-implant bone loss; (b) after replacing the bridge with healing abutments, a flap was raised and the implant debrided; white arrow indicates extent of peri-implant bone loss; (c) histology shows titanium particles (white arrowhead); Case 2. (d) Radiograph of implant supporting single anterior crown; red arrows indicate extent of bone loss; (e) clinical image shows location of chronic suppurring sinus on the labial of implant 21; (f) histological confirmation of the presence of titanium particles (white arrowhead).
particles by macrophages results in up-regulation and increased production of pro-inflammatory cytokines as well as stimulation of osteoclast differentiation and local osteolysis (Taira et al 2010). Osteoblasts show a similar response to titanium particles, although this is reduced when the particles consist of oxidized titanium (Vallés et al 2008). Phagocytosis of titanium particles by osteoblasts resulted in increased cell death, and the release of products cytotoxic to other nearby osteoblasts (Pioletti et al 1999). Furthermore, the repair potential of osteolytic defects is impaired, since titanium particles have a detrimental effect on human mesenchymal stem cells, suppressing their differentiation down the osteogenic pathway (Wang et al 2002, Wang et al 2003). Of note is the fact that zirconium oxide, proposed as an alternative to titanium for dental implants, does not have this effect on stem cells (Wang et al 2002, Wang et al 2003, Siddiqi et al 2011).

**Relevance of titanium particles**

A local role has also been proposed for titanium particles found within inflammatory osteolytic lesions. Titanium wear-particles appear to have the ability to localize circulating lipopolysaccharide (LPS) and lipotechoic acid (LTA) from gram-negative and gram-positive infections (respectively). These bacterial products may originate from subclinical or clinically apparent infections at sites remote from the orthopaedic prosthesis and are often accompanied by an increased expression of Toll-like receptors, TLR-4 (a primary receptor for LPS) and TLR-2 (LTA). Both of these toll-like receptors are considered highly important in the mediation of inflammatory and immune responses and both have been demonstrated in inflamed orthopaedic peri-prosthetic tissue (Greenfield et al 2010). These authors showed that both TLR-2 and TLR-4 contribute to the biological activity of titanium particles with adherent bacterial debris, and concluded that low levels of anaerobic gram negative and aerobic gram positive bacterial colonization may contribute to aseptic loosening of orthopaedic implants.

To date the association of TLR with dental implants and peri-implantitis has not been investigated. In a recent review, Berglundh et al (2011) noted that two authors have examined the expression of toll-like receptors in periodontitis but that this has not been attempted with peri-implantitis (Ren et al 2005, Beklen et al 2008). The presence of TLR-4 in peri-implantitis tissue has been suggested, but not investigated, in a study examining the response of LPS-coated titanium discs to laser treatment (Gianelli et al 2009).

**Conclusions**

The presence of titanium particles within peri-implantitis inflammatory tissue has been confirmed. The ramifications of this require further investigation, in particular whether these particles are associated with a localized up-regulation of toll-like receptors. Were this to be so, it would be possible to hypothesize that clinical and subclinical infections at a remote site from the dental implant might result in a sterile, localized osteolysis around the dental implant, which might account for some of the contradictory findings regarding peri-implant bone loss. The mechanism(s) causing the loss of titanium from the implant surface also require further investigation.

Definitive treatment protocols for peri-implantitis have yet to be elucidated and treatment thus remains mostly empirical. At the moment, the primary weapon in the treatment for peri-implantitis remains prevention, through control of bacterial
colonization of the implant surface. Appropriate prosthodontic restorations that permit professional and personal oral hygiene procedures, and the institution of a regular maintenance regime, are the mainstays of prevention.

Acknowledgments

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References


Greenfield EM, Beidelschies MA, Tatro JM, et al. Bacterial pathogen-associated molecular patterns stimulate biological activity of orthopaedic wear particles by activating cognate


Chapter 9

Effect of periodontal intervention on periodontal disease and diabetes mellitus

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Introduction

Periodontal diseases, including gingivitis and periodontitis, are common infections which if left untreated can ultimately lead to tooth loss. Periodontal diseases are bacterial infections that affect the supporting structures of teeth. The bacteria in dental biofilms cause gingival inflammation, culminating in gingival redness, oedema, bleeding, changes in contour, loss of tissue adaption to teeth and increased flow of gingival crevicular fluid (Page 1986). Gingivitis is reversible with professional treatment and meticulous home care. Untreated gingivitis may lead to periodontitis. With time, the dental biofilm can spread subgingivally and toxins produced by the bacteria stimulate a chronic inflammatory response in which the body in essence turns on itself and the periodontium undergoes destruction. As the disease progresses, the pockets deepen and more periodontal tissues and bone are destroyed (Listgarten 1986).

The main etiological agent of periodontal disease is the dental biofilm (Theilade et al 1966). However, factors like smoking/tobacco use, genetics, hormonal changes, stress, medications, diabetes, poor nutrition and systemic diseases that interfere with the body’s immune system also affect periodontal health (Butler et al 1987, Sooriyamoorthy & Gower 1989, Michalowicz 1994, Vroostos & Vrahopoulos 1996, Genco et al 1999, Mealey 2000, Nishida et al 2000, Johnson & Slach 2001). The American Academy of Periodontology treatment guidelines stress that periodontal health should be achieved in the least invasive and most cost-effective manner. This is often accomplished through non-surgical periodontal treatment, including oral hygiene instruction, scaling and root planing of the root surface to remove plaque, calculus and bacterial toxins from periodontal pockets. Adjunctive therapy, such as antimicrobial therapy and host modulation can be incorporated into the treatment regimen as required on a case-by-case basis.

Periodontal disease has been implicated in relation to several disease processes in the body such as pre-eclampsia and preterm birth, cardiovascular events, respiratory disease, chronic renal disease, rheumatoid arthritis and diabetes (Scannapieco 1999, Mealey 2000, Al-Katma et al 2007, Xiong et al 2007, Craig 2008, Tonetti 2009). Data obtained from several studies strongly suggest diabetes as a risk factor for gingivitis and periodontitis (Mealey & Oates 2006). Evidence also suggests that periodontal changes are the first clinical manifestation of diabetes (Lamster et al 2008). From the other perspective, increases in the severity of periodontal disease were
closely related to the development of glucose intolerance (Saito et al 2004). It has been reported that diabetics with severe periodontal disease are six times more likely to have poorer glycemic control and longitudinal studies have reported that infections of periodontal origin have an adverse effect on glycemic control (Taylor et al 1996, Taylor & Borgnakke 2008).

Type 2 diabetes is quickly becoming a pandemic and is predicted to affect more than 300 million people by 2025 (Preshaw 2009). To date, the United Nations estimates the number of people globally affected by diabetes to be 246 million with approximately half of those are residing in India, China, Nepal and other Asian countries. Epidemiological studies in India have shown that the prevalence of diabetes is high and is increasing, especially in the urban population. It has increased from 5% in 1986 to 8.2% in 1992 and 11.4% in 1997 among the adults in urban areas (Ramachandran et al 1988, Ramachandran et al 1992, Ahuja 1996, Ramachandran et al 1997). In China, the prevalence of diabetes increased from 1% in 1980 to 5.5% in 2001 (Gu et al 2003). Nearly 10% of Chinese adults residing in affluent Hong Kong and Taiwan have diabetes (Jia et al 2007). About two-thirds of diabetics in Mainland China and half in Hong Kong and Taiwan remain undiagnosed (Wong & Wang 2006).

In Singapore, the Indian population was found to have the highest prevalence of diabetes (12.8%), followed by Malays (11.3%) and Chinese (8.4%) in a 1998 study (Lee 2000). This finding is similar to the age-group specific prevalence reported in the 2004 National Health Survey in Singapore (Ministry of Health Singapore). However, in this National Health Survey 2004, the crude prevalence of diabetes was highest in Indians (15%), followed by Malays (11%) and Chinese (7%). The Nepal Diabetes Association reports that among people aged 20 years and older living in urban areas, 15% are affected by this condition whereas among people aged 40 years and older in urban areas, this number rose to 19%. This condition is also reflected in the population of Mauritius, where 13% of the population is living with Type 2 diabetes mellitus (Morton et al 1995). In the United Arab Emirates, 25% of the population is affected by diabetes, the second highest prevalence of diabetes worldwide.

In Malaysia, there are nearly 1.2 million people who have diabetes, out of whom, 98% suffer from the Type 2 variety (Bakri 2007). Based on ethnicity, Indians had the highest prevalence of diabetes (19.9%), followed by Malays (11.9%) and Chinese (11.4%) (Zanariah et al 2007). In an epidemiological survey conducted in a semirural community in Malaysia in 1993 comprising 1417 subjects, the prevalence of diabetes was high, reportedly being 10.7% and a further 10% probably undiagnosed based on the measured fasting plasma glucose of \( \geq 7 \text{ mmol/L} \) (Bakri 2007). This is consistent with the Third National Health & Morbidity Survey of Malaysia 2006 where diabetes prevalence in adults was reported to be 14.9% (Zanariah et al 2007). This is in stark contrast to developed countries, both US and Europe, where the prevalence of diabetes is much lower and varies between 6% and 8% (Dabelea 2007). The prevalence of diabetes has increased worldwide and, in particular, in the Asia-Pacific region and it is believed that 60% of the world’s population with diabetes will come from Asia, as it is and will remain the most prevalent region (King et al 1998, Cockram 2000).

There has also been a generally held view that Asians are particularly susceptible to periodontitis (Corbet 2006). This opinion appears to have originated from epidemiological studies which compared immigrant Asians and Caucasians from industrialized nations. A classic longitudinal study comparing Norwegian males and Sri Lankan Tamil males showed far worse
periodontal conditions in the Asian males (Loe et al 1978a, Loe et al 1978b, Loe et al 1978c). In 2003, it was reported that the Thai population may have more widespread and severe periodontal destruction than other Asian populations (Baelum et al 2003). In 2000, a National Oral Health Survey for Adults (NOHSA) was carried out in Malaysia (Oral Health Division 2004). It showed that out of the total 9.7 million individuals screened, only 9.8% had healthy gingiva while the remaining individuals had periodontal problems of various severity including gingivitis (4.5%), moderately deep probing pockets of 4 to 5 mm (20%) and deeper probing pockets >6 mm (5.2%). Half of the population had calculus present. Out of the various ethnicities in Malaysia, Malaysian Indians appeared to have the highest proportion of deep probing pocket depths of more than 6 mm (7.1%), followed by Kadazans and Ibans (5.9% each) and Malays (5.6%), while Chinese had the least (3.9%) (Said 2005).

Intervention trials have assessed the potential effects of periodontal therapy on glycemic control in subjects with diabetes. Stewart et al (2001) suggested that there was a marked improvement in glycemic control in type 2 diabetes mellitus patients following periodontal therapy. They reported a 17.1% improvement in metabolic control in the test group after periodontal therapy and a 6.7% improvement in the control group. Kiran and co-workers (2005) reported on 44 Turkish patients with type 2 diabetes and moderate periodontal disease. A statistically significant reduction was seen in periodontal parameters and 0.86% reduction in HbA1c for test group 3 months after non-surgical treatment, whereas the control group recorded a slight increase in HbA1c levels. Similarly the test group in a study of 52 Thais with uncontrolled type 2 diabetes and severe periodontitis recorded slight improvements in HbA1c and fasting plasma glucose levels 3 months post treatment (Promsudthi et al 2005). These results are similar to observations from several other clinical trials that have reported reductions in the inflammatory challenge to the body and improvements in periodontal parameters and metabolic control following non-surgical periodontal therapy (Navarro-Sanchez et al 2007, Singh et al 2008, Dag et al 2009, Correa et al 2010, Koromantzos et al 2011).

The aim of the present study was to determine if improving periodontal health leads to improved glycemic control and reduction of a systemic inflammatory marker among selected diabetic Malaysians with periodontitis.

**Materials and methods**

This study was a longitudinal, randomized controlled clinical trial. Subjects with moderate to advanced chronic periodontitis were selected.

**Selection of subjects**

112 type 2 diabetic patients between 30 to 70 years of age were screened from the patient pool of the Diabetic Clinic of the University Malaya Medical Centre and a total of 60 patients who fulfilled the inclusion criteria were recruited for the study. The recruited patients were then brought to the Periodontology Clinic at the Faculty of Dentistry for thorough clinical examinations. Patient information sheets regarding the study and verbal explanations were given to all patients. Informed consent was obtained from all recruited patients with the understanding that they could withdraw from the study at any time. All patients included had moderate to advanced periodontal disease, with at least 12 teeth present, 5 or more pockets of 5 mm or more present and probing attachment loss
of 4 mm or more in at least 2 different quadrants which bled on probing. Patients were not included in the study if they had a history of systemic antibiotic usage over the previous 4 months, had received non-surgical periodontal treatment within the past 6 months or surgical periodontal treatment within the past 12 months. Those who were pregnant, current smokers or had a cerebrovascular or cardiovascular event within the past 12 months were also excluded. Patients who changed their diabetic medication during the course of the study were excluded as well.

Based on an expected mean difference in the reduction of HbA1c between the two groups of around 1%, it was calculated at least 15 patients would be needed in each group to detect this difference with 80% power. All patients were distributed to 20 age-matched pairs who were randomly assigned to test and control groups. Patients in the test group received oral hygiene instructions combined with non-surgical periodontal therapy whereas patients in the control group received oral hygiene instructions only.

**Treatment protocol**

All recruited patients underwent full periodontal assessment at baseline, 2 months and 3 months after assigned treatment. The clinical examination included Visible Plaque Index (Ainamo & Bay 1975), Gingival Bleeding Index (Ainamo & Bay 1975), Probing Pocket Depth (PPD) and Probing Attachment Loss (PAL) measured with an electronic constant-force probe (Florida Probe®). All patients were motivated and instructed in oral hygiene methods (MOHI) using the modified Bass technique with a soft bristled toothbrush, and customized interdental cleansing with compact-tuft toothbrushes, interdental brushes and dental floss. Participants in both groups were re-motivated at recall visits. Full mouth debridement, consisting of scaling and root planing, was done in a single visit for all subjects in the test group using an ultrasonic scaler and Gracey curettes. Additionally, all patients in the test group were given 0.12% Chlorhexidine mouthrinse (Hexipro®). They were instructed to rinse three times a day using 15 ml each time for a period of 14 days commencing immediately after completion of full mouth debridement. At each recall visit, all patients in the test group received professional prophylaxis.

**Measurement of glycated haemoglobin and CRP**

15 ml of venous blood was collected from each patient at baseline prior to treatment and at 3 months after assigned treatments. Levels of glycosylated haemoglobin (HbA1c) and systemic C-reactive protein (CRP) were assessed from the venous blood samples. CRP levels were assessed using tests for high sensitivity CRP (hs-CRP). All blood investigations were done at a private laboratory with no affiliation to the Department of Periodontology.

**Statistical analysis**

Comparisons of changes in plaque index, bleeding index, probing depth (%) and probing attachment loss (%) both within and between the groups were performed using the chi-square test. Intragroup comparison for mean PPD, mean PAL, mean HbA1c and mean hs-CRP were assessed with the paired sample t-test whereas intergroup comparison for the same variables was accomplished using independent sample t-test.
### Table 1. Socio demographic data of study sample.

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<th>Control group n=17</th>
<th>p-value</th>
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<td>Ethnicity</td>
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<td>Malay</td>
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<td>Chinese</td>
<td>4 (26.7%)</td>
<td>4 (23.5%)</td>
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<tr>
<td>Indian</td>
<td>6 (40.0%)</td>
<td>9 (52.9%)</td>
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<td>Gender</td>
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<td>9 (52.9%)</td>
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<td>Female</td>
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### Table 2. Distribution of periodontal parameters at baseline.

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</thead>
<tbody>
<tr>
<td>Visible plaque index (%)</td>
<td>40.06%</td>
<td>32.70%</td>
<td>0.346</td>
</tr>
<tr>
<td>Gingival bleeding index (%)</td>
<td>20.81%</td>
<td>21.56%</td>
<td>0.908</td>
</tr>
<tr>
<td>Sites with PPD &lt;4mm (%)</td>
<td>81.14%</td>
<td>87.14%</td>
<td>0.219</td>
</tr>
<tr>
<td>Sites with PPD 4-6 mm (%)</td>
<td>16.51%</td>
<td>10.99%</td>
<td>0.138</td>
</tr>
<tr>
<td>Sites with PPD &gt;6 mm (%)</td>
<td>2.36%</td>
<td>1.54%</td>
<td>0.633</td>
</tr>
<tr>
<td>Mean PPD (mm) (±SD)</td>
<td>6.14±4.85</td>
<td>7.20±4.74</td>
<td>0.535</td>
</tr>
<tr>
<td>Sites with PAL &lt;4mm (%)</td>
<td>63.45%</td>
<td>75.91%</td>
<td>0.101</td>
</tr>
<tr>
<td>Sites with PAL 4-6 mm (%)</td>
<td>28.62%</td>
<td>19.59%</td>
<td>0.081</td>
</tr>
<tr>
<td>Sites with PAL &gt;6 mm (%)</td>
<td>7.93%</td>
<td>4.29%</td>
<td>0.260</td>
</tr>
<tr>
<td>Mean PAL (mm) (±SD)</td>
<td>3.35±0.83</td>
<td>2.79±0.96</td>
<td>0.089</td>
</tr>
<tr>
<td>Remaining teeth (mean±SD)</td>
<td>22.97±6.15</td>
<td>24.06±5.97</td>
<td>0.583</td>
</tr>
<tr>
<td>(% of 28)</td>
<td>(71.46%)</td>
<td>(75.18%)</td>
<td></td>
</tr>
</tbody>
</table>
Results

Periodontal parameters

The sociodemographic data of the study sample is shown in Table 1. There were no significant differences (p>0.05) in the variables between the test and control subjects. There were also no significant differences (p>0.05) in the periodontal parameters at baseline between the two study groups (Table 2). The baseline plaque index score (PS) for the test group was 40% (Figure 1). At 2 months the score reduced by more than 80% and at 3 months it further reduced by more than half. The reduction from baseline to 2 months and 3 months were statistically significant (p<0.001) and large effect sizes indicated a significant improvement. In the control group, the baseline score was 33% and it reduced to 12% at 2 months and about 5% at 3 months. The reduction in PS seen in the control group was also statistically significant (p<0.001) and the effect sizes were large at all time intervals.

In Figure 2, the gingival bleeding scores (GBS) for the test group improved from 21% at baseline to 3% at 2 months (p=0.006) but from 2 months to 3 months the change was not significant. For the control group, there was an improvement in GBS from 22% at baseline to 6.4% at 2 months (p<0.001). However, at 3 months, the GBS increased 2.5 times, but the change was not statistically significant (p=0.466). Overall, both the test and control groups showed improvements but the GBS at 3 months for the control subjects (14.85%) did not show a statistically significant difference when compared to baseline scores (21.56%).

Figures 3 and 4 depict the changes in Probing Pocket Depths (PPD) and Probing Attachment Loss (PAL) respectively over the period of 3 months. There were significant reductions in both groups with PPD of 4-6 mm between all time periods (p<0.005) and for mean PPD between all time periods (p<0.004). There was also significant reduction for the test group with PPD of >6 mm from baseline to 2 months and 3 months (p=0.012). However there was no significant reduction for control groups with PPD of >6 mm (p>0.05). The effect sizes in both groups were large at all time periods, indicating significant clinical changes. As for PAL, the changes between all time periods were statistically significant (p<0.001) for both groups with PAL of 4-6

![Figure 1. Plaque index at baseline, 2 months post-treatment and 3 months post-treatment.](image-url)
Effect of periodontal intervention on periodontal disease and diabetes mellitus

Figure 2. Gingival bleeding index at baseline, 2 months post-treatment and 3 months post-treatment.

Figure 3. PPD at baseline, 2 months post-treatment and 3 months post-treatment.

Figure 4. PAL at baseline, 2 months post-treatment and 3 months post-treatment.
mm. For those with PAL >6 mm in the test group, the reduction was significant at all time intervals also. In the control group, the change from baseline to 2 months was also statistically significant (p<0.001) for subjects with >6 mm PAL but there was no significant reduction thereafter from the 2 to 3 months interval. The effect size in both groups recorded a considerable improvement in mean PAL during the course of the study (p<0.002). There was significant reduction in mean PAL for both groups between all time intervals (p<0.002). There were no statistically significant differences between the two groups.

Table 3 shows the distribution of systemic parameters at baseline and 3 months post treatment. At the end of the trial more subjects were categorized as well controlled.

**Serum HbA1c and CRP levels**

Table 4 shows the mean systemic levels of glycated haemoglobin (HbA1c) and C-reactive protein (CRP). At baseline, HbA1c levels between test and control subjects were not significantly different (p=0.79). The same observation was noted at 3 months. However, within the test group, there was a statistically significant reduction in levels of HbA1c from baseline to 3 months (p=0.038). Within the control group, there were similar reductions as observed in the test group, which almost reached significance (p=0.053). Clinically relevant improvement (moderate ES) in HbA1c was detected for both groups after 3 months.

For serum CRP levels, the mean value at baseline for the test group (10.51) was almost twice as high compared to the control group (5.64) but was not statistically significant (p=0.24). The reductions observed within both the test and control groups at the 3 months interval did not reach statistical significance (p>0.05). However for CRP reduction in the test group, the effect size was moderate (ES=0.506) which indicated that the improvement was of clinical significance. For the control group, the mean CRP at baseline and at 3 months was almost equal.

**Changes in serum HbA1c and CRP for subjects with good periodontal response to treatment**

As indicated in Table 5, participants with a plaque score reduction of ≥50% recorded a clinically relevant reduction in HbA1c as indicated by the effect size (ES=0.853) but no significant changes in hs-CRP levels (ES=0.17). For those participants with ≥50% reduction in gingival bleeding sites, neither HbA1c nor hs-CRP reached statistical significance (p=0.205 and p=0.289 respectively) but both had large effect sizes (ES=2.12 and ES=1.45 respectively), indicating a clinically significant reduction. On the other hand, out of the total sample population (n=32), 16 participants demonstrated a ≥50% reduction in PPD as an effect of periodontal intervention, be it just MOHI or MOHI plus scaling and root planing. These participants also demonstrated a statistically significant reduction in HbA1c levels (p=0.004) as well as hs-CRP levels (p=0.012). Concomitantly, the effect sizes for both systemic markers were large.

Periodontal parameters for all subjects with a reduction in HbA1c of ≥1% at the end of the 3 months trial are shown in Table 6. There were statistically significant reductions for PI (p=0.001), BS (p=0.008), mean PPD (p=0.005) with large effect sizes.

**Discussion**

In this current study all periodontal parameters showed significant improvements in the test group receiving full mouth debridement. Other studies have reported
### Table 3. Distribution of systemic parameters at baseline and 3 months post-treatment.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Variable</th>
<th>Test group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>HbA1C (%) - number of diabetics (n) &amp; %</td>
<td>&lt;7% 5(33.3%)</td>
<td>6(35.3%)</td>
<td>0.462</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-7.9% 2(13.3%)</td>
<td>5(29.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥8% 8(53.3%)</td>
<td>6(35.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean CRP (±SD)</td>
<td>10.51±15.75</td>
<td>5.64±5.15</td>
<td>0.238</td>
</tr>
<tr>
<td></td>
<td>HbA1C (%) - number of diabetics (n) &amp; %</td>
<td>&lt;7% 8(53.3%)</td>
<td>10(58.8%)</td>
<td>0.952</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7-7.9% 4(26.7%)</td>
<td>2(23.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥8% 3(20.0%)</td>
<td>36(17.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean Hs-CRP (±SD)</td>
<td>6.98±13.41</td>
<td>5.55±5.34</td>
<td>0.687</td>
</tr>
</tbody>
</table>

### Table 4. Characteristics of monitored systemic markers at baseline and 3 months after treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>n=15</td>
<td>n=17</td>
<td>p-value</td>
</tr>
<tr>
<td>Baseline (mean±SD)</td>
<td>7.75±1.54</td>
<td>7.61±1.45</td>
<td>0.791</td>
</tr>
<tr>
<td>3 months (mean±SD)</td>
<td>7.07±1.20</td>
<td>7.07±1.19</td>
<td>0.995</td>
</tr>
<tr>
<td>P value</td>
<td>0.038*</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>Effect size</td>
<td>0.593</td>
<td>0.495</td>
<td></td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>n=15</td>
<td>n=17</td>
<td>p-value</td>
</tr>
<tr>
<td>Baseline (mean±SD)</td>
<td>10.51±15.77</td>
<td>5.64±5.15</td>
<td>0.238</td>
</tr>
<tr>
<td>3 months (mean±SD)</td>
<td>6.98±13.41</td>
<td>5.55±5.34</td>
<td>0.687</td>
</tr>
<tr>
<td>P value</td>
<td>0.076</td>
<td>0.783</td>
<td></td>
</tr>
<tr>
<td>Effect size</td>
<td>0.506</td>
<td>0.068</td>
<td></td>
</tr>
</tbody>
</table>

*Significant reduction in HbA1c in the test group after 3 months (p<0.038)
similar findings with the greatest improvements seen in the intervention of test groups (Correa et al 2010, Karamantzos et al 2011). Lalla and co-workers (2007) recorded a 50% reduction from baseline of clinical parameters. It is evident that non-surgical periodontal treatment is, and always has been, the gold standard of periodontal treatment and the results of this study and of those in the past have demonstrated its effectiveness even in diabetics. It is interesting to note that the control group which received oral hygiene instructions alone also displayed significant improvements in clinical parameters. The practice of proper plaque removal leads to a significant degree of disease resolution, albeit not as quickly or as extensively as that seen in the test group. Two prior studies have corroborated this finding with improvements in the plaque index (by as much as 47%) as well as significant reductions in the gingival index with meticulous oral hygiene practice (Almas et al 2003, Lee et al 2009).

The difference between the test and control groups in this study was not statistically significant except for the plaque score index at week 8, where the test group had significantly better plaque scores than the

<table>
<thead>
<tr>
<th>Reduction of periodontal parameters after treatment</th>
<th>HbA1c</th>
<th>CRP</th>
<th>HbA1c</th>
<th>CRP</th>
<th>P1</th>
<th>P2</th>
<th>ES1</th>
<th>ES2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with 50% reduction in plaque index scores (n=7)</td>
<td>8.23 ±1.14</td>
<td>5.30 ±3.61</td>
<td>7.41 ±1.56</td>
<td>4.93 ±3.58</td>
<td>0.065</td>
<td>0.666</td>
<td>0.853</td>
<td>0.171</td>
</tr>
<tr>
<td>Subjects with 50% reduction in gingival bleeding scores (n=2)</td>
<td>9.00 ±0.28</td>
<td>10.00 ±0.42</td>
<td>7.658 ±0.35</td>
<td>8.05 ±0.92</td>
<td>0.205</td>
<td>0.289</td>
<td>2.121</td>
<td>1.452</td>
</tr>
<tr>
<td>Subjects with 50% reduction in mean PPD (n=16)</td>
<td>7.66 ±1.35</td>
<td>9.61 ±14.56</td>
<td>6.78 ±0.84</td>
<td>8.17 ±12.91</td>
<td>0.004*</td>
<td>0.012*</td>
<td>0.859</td>
<td>0.710</td>
</tr>
</tbody>
</table>

Table 5. Changes in mean HbA1c and CRP for subjects with good periodontal response to treatment.
*Significant reduction in HbA1c and hs-CRP levels for all subjects with mean PPD reductions of ≥50% (p=0.004 and p=0.012)

<table>
<thead>
<tr>
<th>Periodontal parameter</th>
<th>Baseline</th>
<th>3 months</th>
<th>p-value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque index (%±SD)</td>
<td>31.97±24.25</td>
<td>4.45±8.15</td>
<td>0.001*</td>
<td>1.369</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingival bleeding (%±SD)</td>
<td>18.70±17.64</td>
<td>1.60±1.92</td>
<td>0.008*</td>
<td>0.997</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPD (mean±SD)</td>
<td>6.59±4.46</td>
<td>1.79±0.25</td>
<td>0.005*</td>
<td>1.094</td>
</tr>
<tr>
<td>(n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Periodontal parameters for all subjects with a reduction in HbA1c (%) of ≥1 at the conclusion of the trial.
* Significant reductions for plaque index for all patients (p=0.001). Significant reductions for bleeding scores for all patients (p=0.008). Significant reductions for pocket depths for all patients (p=0.005).
Effect of periodontal intervention on periodontal disease and diabetes mellitus control. This could be due to the absence of plaque retentive factors in the test group which made plaque control easier and the repeated professional debridement provided. The most significant reductions in the percentage of sites with moderate to deep probing pocket depths in the test group seemed to take place within the first 8 weeks. This correlates with the healing period after non-surgical periodontal therapy. From the 2nd month to the end of the 3rd month, residual healing occurred but at a slightly slower rate. The same result was not observed in the control group, where reduction in sites with moderately deep pockets occurred more in the 2nd to 3rd month period. This could possibly be due to the slower response of the periodontium in the control group participants who did not receive any professional mechanical debridement. The response for sites with PPD >6 mm in the control group was also marginal & not significant as opposed to the test group who had no sites >6 mm at the end of the study.

In the current study, the test group showed a mean reduction in HbA1c of 0.68% and the control group showed a reduction of 0.54%. These results seemed to concur with findings by Darre and colleagues (2008) who reported a reduction of 0.79% following non-surgical periodontal therapy. Other researchers have also reported the same phenomena (Stewart et al 2001, Kiran et al 2005). HbA1c reductions as high as 17.1% have been reported (Stewart et al 2001). An improvement in glycemic control seen in the test group was accompanied by a reduction in the mean levels of CRP as indicated by a moderate effect size, but this observation did not reach statistical significance. Reports in the literature have been contradictory. It has been noted that the reduction in serum CRP was greater in treatment regimes combining systemic or local antibiotics with standard periodontal treatment (D’Aiuto et al 2005). Since no antibiotics were used in this study, it may explain the lack of an association. However, the present study does indicate that participants who responded well to periodontal therapy also recorded clinically relevant reductions in levels of HbA1c and CRP.

**Clinical implications**

As observed in the current study and findings of previous other studies, periodontal therapy was able to improve metabolic control in patients with type 2 diabetes mellitus and periodontal disease. Similarly, motivation and oral hygiene instructions (MOHI) only, were also able to reduce the HbA1c level in the control group diabetic participants as well as improving the periodontal parameters. The effects brought about by MOHI in this study are of great value. The mere act of educating diabetics in the proper techniques of plaque control may lead to clinically relevant improvements in metabolic control. Early to moderate periodontal disease can be effectively addressed with proper home care, whereas patients with advanced periodontal disease with deep pockets can be treated with non-surgical treatment or minimally invasive periodontal therapy, to further improve their diabetic status. This can all be done with relatively low cost and is not labor intensive. The same methods that are used to deliver MOHI to school children can be used to deliver it to the diabetic masses. The provision of an oral hygiene education room in diabetic clinics could be an added bonus to those who are unable to cope with frequent visits to the dental clinic.

**Conclusions**

Non-surgical periodontal therapy comprising of motivation, oral hygiene instructions as well as scaling and root planning significantly improved metabolic control in patients with type 2 diabetes
mellitus and periodontal disease. Additionally, motivation and oral hygiene instructions alone were also able to improve metabolic control in diabetic subjects. This may have important implications in public health promotion alongside diet counselling in the diabetic population at large.

A statistically significant improvement in HbA1c levels was not mirrored by a significant change in hs-CRP levels possibly due to inflammatory processes in other parts of the body which are common in diabetics. Type 2 diabetics with a good periodontal response to treatment showed clinically significant improvements (as indicated by effect size) in levels of HbA1c and hs-CRP. Periodontal intervention therapy contributed to improved metabolic control in type 2 diabetics and also to an overall reduction of the systemic inflammatory challenge. The converse was also observed. Hence it can be advocated that in the approach to management of either type 2 diabetes or periodontal disease, integration of interdisciplinary care should be considered in these individuals.

**Recommendations for further considerations**

A longer duration of observation (6 months and beyond) is needed to evaluate the long term response to periodontal treatment and the effect and importance of maintenance therapy in the diabetic population. Non-surgical periodontal therapy may be of benefit in controlling the Type 2 diabetes pandemic in Asia, together with concerted integrated population-wide preventive approaches such as diet counselling, early detection of disease, OHI and smoking cessation. In addition, clinical practice guidelines should be developed to facilitate interaction between medical and dental specialties to address the consequences of the interrelationship between diabetes and periodontal disease. This has been attempted by the Scottsdale Project, which brought together a wide range of medical and dental experts to discuss the association between diabetes, periodontal disease and cardiovascular disease and proposed a trans-disciplinary model of care. These propositions could be adapted and implemented into a similar approach in the Asian region for the well-being of affected individuals.

**Acknowledgments**

The authors are grateful to University Malaya for providing funding for the project and to the diabetic participants and auxiliary staff of the Diabetic & Dental Clinics.

**References**


Effect of periodontal intervention on periodontal disease and diabetes mellitus


Mealey BL. Diabetes and periodontal disease: Two
Chapter 10

Management of chronic periodontitis associated with cardiovascular disease, diabetes and adverse pregnancy outcomes

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Introduction

The term periodontal medicine, as first described by Offenbacher (1996a), is a broad term that defines a rapidly emerging branch of periodontology focusing on the wealth of new data establishing a strong relationship between periodontal health or disease and systemic health or disease. This means a two-way relationship in which periodontal disease may be a powerful influence on an individual’s systemic health or disease, as well as the more customarily understood role that systemic disease may have in influencing an individual’s periodontal health or disease.

Over the centuries, writings from the ancient Egyptians, Hebrews, Assyrians, Greeks, and Romans have all noted the importance of the mouth in overall health and well-being. Thus, one could say that the concept linking systemic disease and periodontitis can be traced back to the beginning of recorded history and medicine. In a paper entitled “The human mouth as a focus of infection”, Miller (1891) argued that oral flora caused osteitis, osteomyelitis, septicemia, pyemia, disturbances of the alimentary tract, noma, diphtheria, tuberculosis, syphilis, and thrush. William Hunter, a physician from the London Fever Hospital, remarked that the crowns, bridges and partial dentures he saw in his patients in London were built on teeth surrounded by a “mass of sepsis”. Indeed, this oral sepsis could explain why most individuals developed chronic diseases (Hunter 1900).

The term “oral sepsis” used by Hunter was replaced with the term “focal infection” in 1911 (Billings 1912). Focal infection implied that there was a nidus of infection somewhere in the body, such as periodontitis, which could affect distant sites and organs via the bloodstream. Therapeutic edentulation was common as a result of the popularity of the focal infection theory. Since many teeth were extracted without evidence of infection, thereby providing no relief of symptoms, the theory was discredited and largely ignored for many years. Recently, it has become increasingly clear that the oral cavity can act as the site of origin for dissemination of pathogenic organisms to distant body sites, especially in immunocompromised hosts such as patients suffering from malignancies, diabetes, or rheumatoid arthritis or receiving corticosteroid or other immunosuppressive treatment.

The incidence of bacteremia following
dental procedures such as tooth extraction, endodontic treatment, periodontal surgery and root planing has been well documented. Bacteremia after dental extraction, third molar surgery, dental scaling, endodontic treatment and bilateral tonsillectomy has been studied by means of lysis filtration of blood samples with subsequent aerobic and anaerobic incubation (Heimdahl et al 1990). Bacteremia was observed in 100% of the patients after dental extraction, in 70% after dental scaling, in 55% after third molar surgery, in 20% after endodontic treatment, and in 55% after bilateral tonsillectomy. Anaerobes were isolated more frequently than facultative anaerobic bacteria. Another study involving 735 children undergoing treatment for extensive dental decay found that 9% of the children had detectable bacteremias before the start of dental treatment (Roberts et al 1997).

Page proposed that periodontitis may affect the host’s susceptibility to systemic disease in three ways; by shared risk factors, by subgingival biofilms acting as reservoirs of gram-negative bacteria, and through the periodontium acting as a reservoir of inflammatory mediators (Marcus & Hajjar 1993, Page 1998).

**Cardiovascular disease and periodontal infection**

Cardiovascular disease (CVD) is the leading cause of death worldwide, killing 16 million people annually (WHO 2001). In developing countries it is responsible for 16% of all deaths, while in developed countries it accounts for 50% of all deaths, with coronary heart disease (myocardial ischaemia) representing about half of the sequelae. Classic risk factors for CVD include elevated serum lipids, in particular low-density lipoprotein (LDL), hypertension, smoking, male gender and low socioeconomic factors (Keil 2000).

Patients with periodontal disease share many of the same risk factors as patients with CVD including age, gender (predominantly male), lower socioeconomic status, stress, and smoking (Beck et al 1998). Additionally, a large proportion of patients with periodontal disease also exhibit CVD (Umino & Nagao 1993). These observations suggest that periodontal disease and CVD share similar or common etiological pathways.

One of the first researchers to indicate a relationship between orofacial infections and atherosclerosis was Mattila et al (1989). Other studies have shown a positive correlation between CVD and periodontal disease and stroke and periodontal disease, these are listed in Tables 1 and 2 respectively.

Considering the results of epidemiological studies, a search was started for mechanisms to elucidate the association between chronic periodontitis and the atherosclerotic and thrombotic components of cardiovascular disease. Various hypotheses have emerged which seem to complement one another. The theory of bacterial invasion assumes the direct action of bacteria and their toxins on the endothelium. Using polymerase chain reaction (PCR), Haraszthy et al (2000) demonstrated the presence of genetic material from gingival pocket bacteria in 44% of atheromatous plaques examined. The most frequently identified microorganisms were *Bacteroides forsythus* (30%) and *Porphyromonas gingivalis* (26%). Stelzel et al (2002) reported similar results based on the examination of human aorta specimens.

Konopka (2003) proposed the initiation of platelet aggregation by platelet aggregation-associated protein (PAAP) expressed on the cell surface of *Streptococcus sanguinis* as a mechanism that promotes atherosclerosis development. According to the cytokine theory, inflammatory mediators released by the cells of the immune system play a key role
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Population</th>
<th>Periodontal outcome or exposure</th>
<th>Cardiovascular outcome</th>
<th>Findings &amp; conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simonka et al 1988</td>
<td>Case Control</td>
<td>Yugoslavia; 211 cases and 336 controls.</td>
<td>DMF index, CPITN index</td>
<td>Previously diagnosed myocardial infarction (MI)</td>
<td>Significant difference in CPITN and demand for periodontal surgery in patients &gt; 50 years old with heart attack. No difference in DMF between case and controls.</td>
</tr>
<tr>
<td>Matilla et al 1989</td>
<td>Case Control</td>
<td>Finland; 100 cases and 102 controls.</td>
<td>Dental Severity Index</td>
<td>Evidence of MI from ECG and elevated enzyme levels</td>
<td>Dental health significantly worse in patients with MI versus controls after adjusting for smoking, social class, serum lipids, and diabetes.</td>
</tr>
<tr>
<td>Matilla et al 1993</td>
<td>Case Control</td>
<td>100 subjects. No controls.</td>
<td>Sum of the number of vertical bone defects, furcation lesion, periocoronitis.</td>
<td>Extent of coronary artery occlusion by angiography</td>
<td>Significant association between dental infections and severe coronary athermatosis in males. No association between females.</td>
</tr>
<tr>
<td>Emingil et al 2000</td>
<td>Case Control</td>
<td>60 cases with acute MI. 60 controls with chronic coronary heart disease.</td>
<td>Missing teeth, restorations, PD and BOP.</td>
<td>AMI subjects admitted to the hospital for treatment of AMI, verified by ECG and serum enzymes levels</td>
<td>% sites with BOP, number of sites with PD &gt;4, number of restorations, smoking status and triglyceride levels were significantly increased in AMI subjects. Results suggest that periodontal disease may be associated with acute MI.</td>
</tr>
<tr>
<td>Matilla et al 2000</td>
<td>Case Control</td>
<td>85 cases with proven cardiovascular disease. 53 controls.</td>
<td>Indices based on sum scores from periodontal probing, furcation lesions; radiographic examination enumerating vertical bone defect.</td>
<td>Subjects with diagnosed clinically or angiographically proven MI</td>
<td>Dental indices were higher among CHD than controls but not significantly associated.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design</td>
<td>Population</td>
<td>Periodontal outcome or exposure</td>
<td>Cardiovascular outcome</td>
<td>Findings &amp; conclusions</td>
</tr>
<tr>
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</tr>
<tr>
<td>Beck et al 2001</td>
<td>Cohort</td>
<td>United States; clinical attachment loss</td>
<td>Severe periodontitis; ≥3 mm at 30% of sites</td>
<td>Carotid artery intima media wall thickness (IMT) ≥1 mm</td>
<td>Periodontitis may influence atheroma formation (OR=1.3).</td>
</tr>
<tr>
<td>Beck et al 2005</td>
<td>Cohort</td>
<td>United States; 15,792 subjects (ARIC Study)</td>
<td>Serum antibodies to periodontal pathogens</td>
<td>Carotid artery IMT ≥1 mm</td>
<td>Presence of antibody to C. rectus was associated with carotid atherosclerosis (OR=2.3).</td>
</tr>
<tr>
<td>Hung et al 2004</td>
<td>Cohort</td>
<td>United States; 41,407 males from the HPFS and 58,974 females from the NHS</td>
<td>Self-reported tooth loss at baseline</td>
<td>Incident fatal and nonfatal MI or stroke</td>
<td>For males with tooth loss, the relative risk for coronary heart disease was 1.36. For females with tooth loss, the relative risk was 1.6.</td>
</tr>
<tr>
<td>Engebretson et al 2005</td>
<td>Cohort</td>
<td>United States; 203 subjects from INVEST</td>
<td>Radiographic alveolar bone loss</td>
<td>Carotid plaque thickness via ultrasonography</td>
<td>Severe periodontal bone loss was independently associated with carotid atherosclerosis (OR=3.64).</td>
</tr>
<tr>
<td>Pussinen et al 2004</td>
<td>Cohort</td>
<td>Finland; 6,950 subjects in the Mobile Clinic Health Survey</td>
<td>Serum antibodies to P. gingivalis or A. actinomycetemcomitans</td>
<td>Incident fatal or nonfatal stroke</td>
<td>Seropositive subjects had an OR of 2.6 for stroke.</td>
</tr>
<tr>
<td>Abnet et al 2005</td>
<td>Cohort</td>
<td>China; 29,584 rural subjects</td>
<td>Tooth loss</td>
<td>Incidence of fatal MI or stroke</td>
<td>Tooth loss was associated with increased odds for death from MI (RR=1.29) and stroke (RR=1.1).</td>
</tr>
<tr>
<td>Pradeep et al 2010</td>
<td>Case Control</td>
<td>500 subjects with AMI in Indian population</td>
<td>PDI (Ramfjord’s), OHI-S</td>
<td>Subjects diagnosed as AMI</td>
<td>Patients with PDI scores of 5-6 were 7 times more likely to have AMI than controls.</td>
</tr>
</tbody>
</table>

Table 1. Case control and cohort observational studies supporting association between periodontal disease and cardiovascular disease.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Population</th>
<th>Oral Assessment</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>Syrjanen et al 1989</td>
<td>Case control study of 40 patients with ischemic cerebral infarction under the age of 50, and 40 randomly selected community controls.</td>
<td>Total dental index that measured N carious lesions, of periodontitis, N periapical lesions and pericoronitis. The presence of subgingival calculus or suppuration in the gingival pockets was measured.</td>
<td>Poor oral health was more common in subjects with ischemic cerebrovascular disease in patients &lt;50 years of age.</td>
</tr>
<tr>
<td>Loesche et al 1998</td>
<td>Cross-sectional study of 401 veterans ≥60 years of age.</td>
<td>N teeth (0-14 and 15-28); PD, attachment level, gingival recession; plaque index; gingival bleeding; evaluation of salivary flow and xerostomia.</td>
<td>21% of the teeth in subjects with CV had attachment loss &gt;6 mm compared to 12% in subjects without CVA (P=0.028). Dentate subjects with CVA had more plaque and gingival bleeding than dentate subjects without CVA. The presence of 15-28 teeth and increased proportion of teeth with attachment loss &gt;6 mm were significantly related to CVA.</td>
</tr>
<tr>
<td>Mendez et al 1998</td>
<td>Assessment of a relationship between PVD and periodontal disease by analyzing data from the Normative Aging Study and Dental Longitudinal Study of the US Department of Veterans Affairs; 80 individuals with PVD were compared with 1,030 control subjects. Multivariate logistic regression analysis was used.</td>
<td>Radiographic measures of alveolar bone loss estimated by analyzing data from intraoral periapical films taken at baseline using Schei ruler.</td>
<td>Periodontal disease emerged as a significant independent risk factor for PVD in a multivariate analysis that adjusted for other established risk factors.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Population</td>
<td>Oral Assessment</td>
<td>Conclusions</td>
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<tr>
<td>Wu et al 2000</td>
<td>9,962 participants enrolled in NHANES-I and follow-up study.</td>
<td>Periodontal status was grouped into one of the following: 1) no periodontal disease</td>
<td>Compared with no periodontal disease, the relative risks (95% confidence intervals) for incident non hemorrhagic stroke were 1.24 (0.74-2.08) for gingivitis, 2.11 (1.30-3.42) for periodontitis, and 1.41 (0.96-2.06) for edentulousness.</td>
</tr>
<tr>
<td>Grau et al 2004</td>
<td>Case control study; 303 patients, 300 population controls, and 168 hospital controls with non vascular and non inflammatory neurological diseases, German population.</td>
<td>Mean CAL measured at 4 sites per tooth.</td>
<td>Subjects with severe periodontitis (mean CAL &gt;6 mm) had a 4.3 times higher risk of cerebral ischemia than subjects with mild or without periodontitis (&lt;OR=3 mm).</td>
</tr>
<tr>
<td>Sim et al 2008</td>
<td>Case control study; 265 cases, 214 control in Korean population.</td>
<td>CAL and interview assessed 17 sociodemographic, behavioral, systemic/oral health-related possible confounders.</td>
<td>Stroke was strongly associated with periodontitis (presence of CAL &gt;6 mm), the OR was 4.0.</td>
</tr>
<tr>
<td>Pradeep et al 2009</td>
<td>Case control study; 100 cases, 100 controls in Indian age and gender matched population.</td>
<td>Plaque index, gingival index, PPD, CAL, PPD &gt;4.5 mm was significantly associated with stroke (OR=8.5, CI 95%).</td>
<td>Data proposed the link between periodontitis and CVA.</td>
</tr>
<tr>
<td>Kim et al 2010</td>
<td>Case control study; 165 cases, 214 control in Korean population.</td>
<td>Clinical periodontal examination, CAL and structured questionnaires.</td>
<td>CAL ≥6 mm was significantly associated with stroke (OR=2.5, CI 95%; 1.1-5.6)</td>
</tr>
</tbody>
</table>

Table 2. Studies supporting association between periodontal disease and stroke.
in the damage to the vascular wall endothelium. Kinane & Lappin (2002) found that a decisive role belongs to the toll-like receptors (TLRs) present on the surfaces of immune system cells, including macrophages, monocytes and granulocytes. These receptors recognize bacterial endotoxin molecules, initiate intracellular signaling, and mediate the transcription of a factor responsible for the release of proinflammatory and proaggessiv aggres aggregative cytokines such as PGE₂, IL-1, IL-12, and TNF-α. These activate an arachidonic acid cascade and initiate further synthesis of prothrombotic agents, such as leukotrienes (LTB₄ and LTC₄ by erythrocytes and granulocytes), prostaglandins (PGE, and PGE₂ by leukocytes and myocytes of the vascular wall), and thromboxanes A₂ (TXA₂ by platelets). The compounds stimulate monocyte/macrophage chemotaxis and adhesion to endothelial cells, which leads to intracellular lipid accumulation and the formation of foam cells (Kinane & Lappin 2002). The autoimmunization theory emphasizes the significance of heat shock proteins (HSP65) expressed on oral pathogens such as Porphyromonas gingivalis, Prevotella intermedia, and Actinobacillus actinomycetemcomitans. The above mentioned reports suggest the existence of an autoimmune process where antibacterial antibodies show cross-reactivity with endothelial HSP-60, leading to endothelial cell damage and exposure to inflammatory factors.

**Periodontal management of a CVD/stroke patient**

The following treatment options may assist in the management of a patient with cardiovascular disease:

- Patient education and motivation regarding the potential role of periodontal infection as a risk factor for cardiovascular disease.
- Periodontal therapy including complete subgingival debridement with scaling and root planing under local anesthesia using hand and ultrasonic instruments with continuous irrigation with water.
- Intensive periodontal therapy may enhance inflammatory responses and may impair vascular functions and therefore should be avoided (Persson & Persson 2008).
- Extraction of teeth with hopeless prognosis, such as those with deep furcation involvement and tooth mobility, as tooth eradication may also reduce systemic inflammatory burden of individuals with cardiovascular diseases.
- Removal of plaque retentive areas like overhanging restorations, carious lesions, irregularities on the root surfaces, correction of restorative and prosthetic irritating factors and occlusal therapy.
- Strict plaque control measures such as regular and proper tooth brushing technique, 0.12% chlorhexidine mouthwash, regular flossing, etc.
- Local drug delivery should be performed in pockets with a residual probing depth more than 4 mm after the scaling and root planing. Subgingival minocycline microspheres, subgingival doxycycline, tetracycline containing fibres or the subgingival placement of periochip (chlorhexidine gluconate containing chip) can also be used as an adjunct to periodontal therapy.
- Periodic recall and check up and reinforcement of oral hygiene instructions should be carried out. The number of visits should be reduced by performing full mouth scaling instead of quadrant wise and accomplishing numerous procedures at each appointment depending on patients’ treatment needs.
- For patients on oral anticoagulants the anticoagulant regimen may need
<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of subjects</th>
<th>Treatment</th>
<th>Outcomes measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Couper et al 2009</td>
<td>303 subjects with periodontal disease and a history of blockage of coronary artery or a coronary event, including MI, coronary artery bypass graft surgery, or coronary transluminal angioplasty with or without a stent.</td>
<td>Full-mouth scaling and root planing</td>
<td>Dental outcomes: periodontal probing depth, bleeding on probing, and periodontal attachment level, GCF IL-1β. CVD outcomes: serum hs-CRP.</td>
<td>Improved periodontal status in treatment group. No reduction in GCF IL-1β or serum hs-CRP in treatment group.</td>
</tr>
<tr>
<td>Gunupati et al 2011</td>
<td>72 subjects with AMI in Indian population</td>
<td>PD, CAL and periodontal phase I therapy</td>
<td>Serum anti-cardiolipin antibodies</td>
<td>The phase I periodontal therapy alters serum IgG and IgM anti cardiolipin antibody levels in AMI patients associated with chronic periodontitis.</td>
</tr>
</tbody>
</table>

**Table 3.** Effects of periodontal therapy on CVD outcome.
adjustment in consultation with the cardiologist when undertaking procedures like periodontal surgery or tooth extraction.

**Cardiac conditions and antibiotic prophylaxis for periodontal treatment**

There are certain group of patients who require antibiotic prophylaxis before periodontal treatment (Dajani *et al* 1997). These high risk patient groups are those with prosthetic cardiac valves including bioprosthetic and homograft valves, previous infective endocarditis, even in absence of heart disease, complex congenital cardiac malformations and surgically constructed systemic/pulmonary shunts. Moderate risk patient groups are rheumatic and other acquired valvular dysfunction even after valvular surgery, hypertrophic cardiomyopathy, mitral valve prolapse with valvular regurgitation and non-complex congenital cardiac malformations. Patient groups who do not require antibiotic prophylaxis are isolated secundum atrial septal defect, surgical repair of secundum atrial septal defects, ventricular septal defects or patent ductus arteriosus after 6 months and without residua, previous coronary artery bypass graft surgery, mitral valve prolapse without valvular regurgitation, physiologic, functional or innocent heart murmurs, previous rheumatic fever without valvular dysfunction, previous Kawasaki disease without valvular dysfunction, cardiac pacemakers or implanted defibrillators and transplants.

**Future prospects for the management of periodontal diseases in cardiovascular patients**

The statin group of drugs are routinely used in the management of CVD patients. Atorvastatin has been found to be able to prevent alveolar bone loss seen in a ligature-induced periodontitis model (Goes *et al* 2010). A greater decrease in gingival index and PD and more CAL gain (1.63 ± 1.99 mm in the control and 4.36 ± 1.92 mm in the experimental group) with significant intrabony defect fill with locally delivered 1.2 mg simvastatin in patients with chronic periodontitis was observed (Pradeep & Thorat 2010). Patients on statin medication exhibit fewer signs of periodontal inflammatory injury than subjects without statin treatment (Lindy *et al* 2008). Metformin is extensively used for the management of type 2 diabetes. It was also demonstrated that metformin exerts an osteogenic effect on osteoblasts (Cortizo *et al* 2006). The effect of metformin on alveolar bone loss in ligature-induced periodontitis and osteoblast, osteoclast, and adipocyte differentiation and it has been found that metformin may exert a beneficial effect on alveolar bone in periodontitis by increasing osteoblast differentiation (Bak *et al* 2010). Therefore, this can be proposed that these agents can also be used as a local drug delivery in the periodontal pockets with a minimal invasive procedure.

Recently, it has been found that the combination therapy of omega-3 plus low-dose aspirin has demonstrated a successful reduction of gingival inflammation, reduction of pocket depth and attachment level gain and modulation of the cytokines profile in gingival crevicular fluid (Elkhouri 2011). Thus new avenues for treatment of chronic periodontitis patients both with and without cardiovascular diseases are created. It can be proposed that the role of such newer agents should be assessed in the management of periodontal diseases in cardiovascular patients. Similarly various other drugs like systemic clarithromycin, locally delivered 0.5% azithromycin and locally delivered 1%
alendronate gel which have been proven to be beneficial in the non surgical treatment of chronic periodontitis can also be considered potential candidates for the management of periodontal diseases in such patients (Pradeep et al 2008, Pradeep & Kathariya 2011, Pradeep & Sharma 2011). Therefore, further well designed studies are required to assess their role in periodontal management of such high risk patients.

The relationship between effects of periodontal therapy on CVD outcome

While there are no interventional trials directly investigating the impact of periodontal treatment on the risk of CVD or stroke, a number of studies have examined correlations between periodontal disease and traditional and emerging risk factors for CVD or stroke. Recent longitudinal studies suggest that controlling periodontal disease results in a reduction in the concentration of serum markers of inflammation and improved endothelial function. While molecular measures of inflammation and endothelial function are not routinely used in measuring risk for CVD or judging treatment outcomes, recent consensus statements published by the American Heart Association recognize their predictive value (Pearson et al 2003). It is not yet clear according to the consensus statement whether or not therapies aimed at reducing systemic inflammation and endothelial dysfunction result in a reduced risk of CVD, but some studies that have been published do support this view (Pearson et al 2003).

Periodontal disease and adverse pregnancy outcomes

It is universally accepted that acute inflammation is responsible for a substantial fraction of preterm births, particularly in early cases. Much of this inflammation is caused by intrauterine infection. There is also evidence that infection and perhaps inflammation remote to the genitourinary tract can trigger preterm labour. Several studies have suggested that periodontitis during pregnancy increases the risk of preterm birth (Table 4), however some studies have not found this association (Table 5). The findings of such studies would argue against a specific need to improve the periodontal health of pregnant women as a means of improving pregnancy outcomes.

Based on the available evidence, there appears to be an association between periodontitis and preterm birth but it is still not clear whether periodontitis is a cause or a confounding factor. Women who have poor dental hygiene may tend to have other unhealthy habits and behaviours that could be the real cause of preterm birth. However, the increase in risk of preterm birth among women with periodontal disease appears to be of greater magnitude than that associated with most unhealthy habits. It seems unlikely that confounding by lifestyle factors explains the association between periodontal disease and preterm birth. It is also possible that periodontitis is a marker for preterm birth women with periodontal disease may have an immune system that overresponds to low-virulence anaerobic infections. Perhaps when these women also happen to have abnormal genital tract flora, they hyperrespond to the genital infection, thereby causing preterm birth (Macones et al 2004). In that setting, the periodontitis serves to identify a hyperresponding woman, but is not itself a cause of preterm birth. Other possibilities are that intermittent low-level bacteraemia as a result of periodontitis leads to infection of the decidua and chorion that subsequently results in preterm birth; or that periodontitis releases
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Periodontal outcome or exposure</th>
<th>Adverse pregnancy outcome</th>
<th>Findings and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offenbacher et al 1996</td>
<td>United States; 93 cases &amp; 31 controls</td>
<td>≥60% of sites with clinical attachment levels ≥3 mm</td>
<td>Birth weight &lt;2500 g, gestational age &lt;37 weeks, preterm labor and/or premature rupture of membranes.</td>
<td>Significant association between periodontal disease and preterm low birth weight (PLBW) (OR=7.5)</td>
</tr>
<tr>
<td>Goepfert et al 2004</td>
<td>United States; 59 cases &amp; 44 controls</td>
<td></td>
<td>Spontaneous preterm birth &lt;32 weeks.</td>
<td>Significantly higher risk for preterm birth for mothers with periodontal disease (OR=3.4)</td>
</tr>
<tr>
<td>Radnai et al 2004</td>
<td>Hungary; 41 cases &amp; 44 controls</td>
<td>One or more sites with probing depth ≥4 mm and bleeding on probing ≥50%</td>
<td>Premature labor, spontaneous rupture of membranes and/or the birthweight of the newborn ≤2499 g</td>
<td>Significant association between periodontal disease and PLBW (OR=5.4)</td>
</tr>
<tr>
<td>Jarjoura et al 2005</td>
<td>United States; 83 cases &amp; 120 controls</td>
<td>Five or more sites with clinical attachment levels ≥3 mm</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>Significant association between periodontal disease and preterm delivery (OR=2.75, 95% CI,1.01–7.54)</td>
</tr>
<tr>
<td>Moliterno et al 2005</td>
<td>Brazil; 76 cases &amp; 75 controls</td>
<td>Four or more sites with pocket depth &gt;4 mm and clinical attachment levels ≥3 mm</td>
<td>Preterm delivery &lt;37 weeks and birthweight &lt;2500 g</td>
<td>Significantly higher risk for preterm LBW for mothers with periodontal disease (OR=3.48)</td>
</tr>
<tr>
<td>Bosnjak et al 2006</td>
<td>Croatia; 17 cases &amp; 64 controls</td>
<td>&gt;60% of sites with clinical attachment levels ≥4 mm</td>
<td>Spontaneous preterm birth &lt;37 weeks</td>
<td>Significant association between periodontal disease and preterm birth (OR=8.13)</td>
</tr>
<tr>
<td>Radnai et al 2006</td>
<td>Hungary; 77 cases &amp; 84 controls</td>
<td>One or more sites with probing depth ≥4 mm and bleeding on probing ≥50%</td>
<td>Preterm delivery &lt;37 weeks and birthweight &lt;2500 g</td>
<td>Significant association between periodontal disease and preterm LBW (OR=3.32)</td>
</tr>
<tr>
<td>Reference</td>
<td>Population</td>
<td>Periodontal outcome or exposure</td>
<td>Adverse pregnancy</td>
<td>Findings and conclusions</td>
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<tr>
<td>Contreras <em>et al</em> 2006</td>
<td>Colombia; 130 cases &amp; 243 controls</td>
<td>Pocket depth and clinical attachment loss ≥4 mm and bleeding on probing</td>
<td>Pre-eclampsia: blood pressure ≥140/90 mmHg and ≥2+ proteinuria</td>
<td>Significant association for periodontal disease and pre-eclampsia (OR=3.0)</td>
</tr>
<tr>
<td>Offenbacher <em>et al</em> 2001</td>
<td>United States; 1020 subjects</td>
<td>Moderate/severe disease: four or more sites with pocket depths ≥5 mm and clinical attachment levels ≥2 mm; progressive disease: one or more sites with clinical attachment loss ≥2 mm</td>
<td>Preterm delivery &lt;37 weeks; very preterm &lt;32 weeks</td>
<td>Moderate/severe periodontal disease (RR=1.6) and progressive disease (RR=2.4) are significant risk factors for preterm delivery</td>
</tr>
<tr>
<td>Jeffcoat <em>et al</em> 2001</td>
<td>United States; 1313 subjects</td>
<td>Severe/generalized disease: ≥90 sites with clinical attachment levels ≥3 mm</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>Severe or generalized periodontal disease is associated with preterm delivery (OR=4.5)</td>
</tr>
<tr>
<td>Lopez <em>et al</em> 2002</td>
<td>Chile; 639 subjects</td>
<td>Four or more teeth showing one or more sites with pocket depth ≥4 mm and with clinical attachment level ≥3 mm</td>
<td>Preterm delivery &lt;37 weeks and birth weight &lt;2500 g</td>
<td>Significant association between periodontal disease and preterm LBW (RR=3.5)</td>
</tr>
<tr>
<td>Boggess <em>et al</em> 2003</td>
<td>United States; 763 subjects</td>
<td>Severe disease: ≥15 sites with pocket depths ≥4 mm; progressive disease: four or more sites with increases in pocket depth ≥2 mm and resulting in pockets ≥4 mm in depth</td>
<td>Pre-eclampsia: blood pressure &gt;140/90 mm Hg and ≥1+ proteinuria</td>
<td>Significantly higher risk for pre-eclampsia among women with severe (OR=2.4) or progressive (OR=2.1) periodontal disease</td>
</tr>
<tr>
<td>Reference</td>
<td>Population</td>
<td>Periodontal outcome or exposure</td>
<td>Adverse pregnancy</td>
<td>Findings and conclusions</td>
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<tr>
<td>Moreu et al 2005</td>
<td>Spain; 96 subjects</td>
<td>Percentage sites with pocket depths $\geq$ 3 mm</td>
<td>Preterm delivery $&lt;37$ weeks and birth weight $&lt;2500$ g</td>
<td>Higher severity of periodontal disease among those having LBW infants</td>
</tr>
<tr>
<td>Boggess et al 2006</td>
<td>United States; 1017 subjects</td>
<td>Moderate–severe disease: $\geq$ 15 sites with pocket depths $\geq$ 4 mm</td>
<td>Small-for-gestational-age births: birth weight $&lt;10%$ for gestational age</td>
<td>Association between periodontal disease and small-for-gestational-age births (RR=2.3)</td>
</tr>
</tbody>
</table>

Table 4. Studies showing significant association between periodontal disease and adverse pregnancy outcomes.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Periodontal outcome or exposure</th>
<th>Adverse pregnancy outcome</th>
<th>Findings and conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davenport <em>et al</em> 2002</td>
<td>United Kingdom; 236 cases &amp; 507 controls</td>
<td>Mean pocket depth (mm)</td>
<td>Preterm delivery &lt;37 weeks and birthweight &lt;2499 g</td>
<td>No association detected for PLBW periodontal disease and (OR=0.83)</td>
</tr>
<tr>
<td>Buduneli <em>et al</em> 2005</td>
<td>Turkey; 53 cases &amp; 128 controls</td>
<td>Mean pocket depth (mm)</td>
<td>Preterm delivery &lt;37 weeks or birthweight &lt;2500 g</td>
<td>No statistically significant differences between the cases and controls with regard to clinical periodontal parameters</td>
</tr>
<tr>
<td>Moore <em>et al</em> 2005</td>
<td>United Kingdom; 61 cases &amp; 93 controls</td>
<td>Number of sites with pocket depth &gt;5 mm</td>
<td>Preterm delivery &lt;37 weeks</td>
<td>No association between periodontal disease and preterm birth</td>
</tr>
<tr>
<td>Skuldbol <em>et al</em> 2006</td>
<td>Denmark; 21 cases and 33</td>
<td>Pocket depth &gt;4 mm and bleeding on probing controls</td>
<td>Preterm delivery &lt;35 weeks</td>
<td>No difference in mean periodontal parameters between the two groups; no association between periodontal disease and preterm birth</td>
</tr>
<tr>
<td>Holbrook <em>et al</em> 2004</td>
<td>Iceland; 96 subjects</td>
<td>Pocket depth &gt;4 mm</td>
<td>Preterm delivery &lt;37 weeks or birth weight &lt;2500 g</td>
<td>No association between periodontal disease and PLBW</td>
</tr>
<tr>
<td>Moore <em>et al</em> 2004</td>
<td>United Kingdom; 3738 subjects</td>
<td>Percentage of sites with pocket depth &gt;4 or 5 mm</td>
<td>Preterm delivery &lt;37 weeks or birth weight &lt;2500 g</td>
<td>No association between periodontal disease case definitions and preterm delivery or LBW</td>
</tr>
<tr>
<td>Rajapakse <em>et al</em> 2005</td>
<td>Sri Lanka; 227 subjects</td>
<td>Pocket depth, bleeding and plaque scores &gt; median value in the total cohort</td>
<td>Preterm delivery &lt;37 weeks and birth weight &lt;2500 g</td>
<td>No association between periodontal disease and preterm delivery (OR=2.3)</td>
</tr>
<tr>
<td>Meurman <em>et al</em> 2006</td>
<td>Finland; 207 subjects</td>
<td>Community Periodontal Index for Treatment Needs</td>
<td>Preterm delivery &lt;37 weeks, birthweight &lt;2500 g, infant Apgar score &gt;7, caesarean section, gestational diabetes, hypertension, preeclampsia.</td>
<td>No association between poor periodontal health and pregnancy or delivery complications</td>
</tr>
</tbody>
</table>

Table 5. Studies not showing significant association between periodontal disease and adverse pregnancy outcomes
endotoxin or inflammatory mediators, such as cytokines, into maternal blood which initiate intrauterine inflammation.

Researchers from the University of Western Australia have found that gingival disease affects the time it takes women to become pregnant. For their study, the researchers monitored a group of 3,416 pregnant women and analyzed their pregnancy planning and outcome information. The findings, presented at the annual meeting of the European Society of Human Reproduction and Embryology, showed that women with gingival disease took an average of just over seven months to become pregnant, which was two months longer than the average of five months it took women without gingival disease to conceive (reported by Livescience 2011).

Xiong and co-workers (2006) reviewed all of the existing evidence that examines the influence of periodontitis on adverse pregnancy outcomes. 22 studies (13 case controlled and 9 cohort) focused on preterm low birthweight, low birthweight, preterm birth, birthweight by gestational age, miscarriage or pregnancy loss, and pre-eclampsia. 15 studies suggested an association between periodontal disease and increased risk of adverse pregnancy outcome (odds ratio ranging from 1.10 to 20.0) while 7 found no evidence of an association (odds ratio ranging from 0.78 to 2.54).

**Periodontal management of pregnant patients**

Good periodontal management of pregnant patients should include the following:
- Patients should be encouraged to achieve a high level of oral hygiene prior to becoming pregnant and throughout their pregnancy.
- Diagnosis and evaluation of patient periodontal condition and medical status.
- Patient education and motivation regarding the effects of periodontal infection on pregnancy outcomes and periodontal prevention and treatment options.
- Consultation with the patient’s gynaecologist regarding risk factors.
- Periodontal therapy include plaque control, 0.12 % chlorhexidine mouthwash, proper tooth brushing technique, flossing, and professional prophylaxis (scaling and root planing).
- Periodontal scaling and root planing or more involved periodontal treatment procedures are usually scheduled early in second trimester.
- Treatment of pregnancy gingivitis and surgical excision of pregnancy tumor (if present).
- The presence of acute infection, abscess, or other potentially disseminating sources of sepsis may warrant prompt intervention, irrespective of the stage of pregnancy.
- Pre-natal counselling about oral health.
- Periodic recall, check up and reinforcement of oral hygiene instructions.
- As the uterus increases in size during the II and III trimesters, obstruction of vena cava and aorta may occur if the patient is placed in supine position. This can be prevented by placing the patient on her left side or by elevating the right hip by 5 to 6 inches.
- Appointments should be short and the patient should be made to change her positions frequently.
- Use of dental radiographs should be kept to minimum.
- Medications should be prescribed carefully, considering their teratogenic effects.
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Obstetric parameters</th>
<th>Number randomized, number analyzed</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopez et al 2002b</td>
<td>PLBW: OR 5.49 (1.65–18.22)</td>
<td>PLBW</td>
<td>400 randomized, 351 analyzed</td>
<td>OHI, SRP</td>
<td>Periodontal therapy significantly reduced the rates of PLBW</td>
</tr>
<tr>
<td>Lopez et al 2005</td>
<td>PLBW: OR 2.76 (1.29–5.88)</td>
<td>PLBW</td>
<td>870 randomized (2:1 ratio of treatment to controls), 834 analyzed</td>
<td>Plaque control, scaling, daily 0.12% CHX rinse</td>
<td>Periodontal treatment reduced PLBW rate of women with pregnancy associated gingivitis</td>
</tr>
<tr>
<td>Sadatmansouri et al 2006</td>
<td>PLBW: 26.7% in controls, 0% in treated group</td>
<td>PLBW</td>
<td>30 randomized, 30 analyzed</td>
<td>SRP+0.2% CHX rinse for 1 week</td>
<td>Periodontal therapy results in a reduction in PLBW</td>
</tr>
<tr>
<td>Offenbacher et al 2006b</td>
<td>PTB incidence OR 0.26 (0.08–0.85)</td>
<td>PTB</td>
<td>109 randomized, 67 analyzed</td>
<td>SRP, OHI with power toothbrush</td>
<td>Periodontal treatment shows potential benefits on pregnancy outcomes</td>
</tr>
<tr>
<td>Tarannum &amp; Faizuddin 2007</td>
<td>SD between Tr/Co for PTB (p&lt;0.006) and LBW (p&lt;0.044)</td>
<td>PTB, LBW</td>
<td>200 randomized, 188 analyzed</td>
<td>SRP, OHI, 0.12% CHX rinse</td>
<td>Non-surgical periodontal therapy can reduce the risk for pre-term birth</td>
</tr>
</tbody>
</table>

Table 6. Clinical trials reporting statistically significant effect of periodontal treatment on adverse pregnancy outcomes
<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Obstetrical parameters</th>
<th>Number randomized, number analyzed</th>
<th>Intervention</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeffcoat et al 2003</td>
<td>PTB &lt;37 weeks:</td>
<td>PTB</td>
<td>366 randomized, 366 analyzed</td>
<td>Prophylaxis placebo; (n=123), SRP+placebo (n=123) SRP+metronidazole 250 mg/1 week (n=120)</td>
<td>Trend for reduction in PTB. No effect of adjunctive metronidazole therapy.</td>
</tr>
<tr>
<td></td>
<td>RR 0.5 (0.2–1.3), PTB&lt;35 weeks:</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>RR 0.2 (0.02–1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Michalowicz et al 2006</td>
<td>RR=0.93 (0.63-1.37)</td>
<td>PTB &amp; PLBW</td>
<td>823 randomized, 823 analyzed</td>
<td>SRP+monthly tooth polishing and OHI</td>
<td>Treatment of periodontitis improved signs of periodontal disease and was safe. No effect on PTB, LBW or FGR.</td>
</tr>
</tbody>
</table>

Table 7. Clinical trials not reporting statistically significant effect of periodontal treatment on adverse pregnancy outcomes
Periodontal treatment and adverse pregnancy outcomes

Several clinical trials have concluded that periodontal treatment during pregnancy may reduce the rates of preterm birth or the composite outcome of preterm birth and/or low birth weight while others have concluded that periodontal treatment did not result in significant reduction in preterm birth (Tables 6 and 7).

Thus, an association between maternal periodontitis and preterm birth has been proposed. Data on the mechanism of the association are sparse and inconsistent. Future studies using more sensitive tests to attempt to isolate oral organisms from decidua, membranes and placenta may provide further insights. In addition, measures of periodontal clinical and microbiological status, correlated with histological and biochemical measures of in utero inflammation may prove useful. Several clinical trials of the treatment of periodontitis to prevent preterm birth are continuing, but until those results are known there is currently little evidence to suggest that treatment of periodontitis during pregnancy reduces the incidence of preterm birth.

Periodontal disease and diabetes mellitus

Periodontitis has been identified as the sixth complication of diabetes and its prevalence in type 2 diabetic patients is more than twice that of non-diabetic patients (Loe 1993, Tsai et al 2002, Marugame 2003). Diabetic patients display an increased severity of periodontal disease with severity being related to diabetic control but unrelated to diabetic duration (Tervonen & Oliver 1993, Collin et al 1998, Tsai et al 2002). However, periodontitis appears to have a reciprocating negative impact on diabetic status and significant relationships between periodontitis and impaired glucose tolerance and diabetic retinopathy have been reported (Collin et al 1998, Noma et al 2004, Saito et al 2004). Furthermore, periodontitis patients have been reported to have higher resting plasma glucose levels than control patients and experimental periodontitis increases blood glucose levels in diabetic rats (Losche et al 2000, Pontes Andersen et al 2007). That periodontitis is a strong independent predictor of mortality from ischaemic heart disease and the development of diabetic nephropathy has been suggested by a prospective, longitudinal study of 628 type 2 diabetic subjects of the Pima Indian race (Saremi et al 2005, Shultis et al 2007). Support for this has come from several studies that have shown that improved periodontal health, achieved through periodontal therapy, improves the metabolic control of type 2 diabetes as measured by HbA1c levels (Table 8).

Metabolic dysregulation in diabetes as a result of prolonged exposure to chronic levels of glucose can lead to the glycosylation of long-lived proteins and lipids forming glycosylation products, referred to as advanced glycosylation endproducts (AGEs) (Brownlee 1994). AGEs were identified in 1912 by Louis Mallard (John & Lamb 1993). During normal states of metabolism, early reversible intermediates of AGEs, called Amadori products, are formed; with time and/or abnormal glucose metabolism, these products become irreversible (Monnier et al 1996). Subsequently, there is an increase in AGE deposition in matrix tissues as well as an increase in the number of receptors for AGEs on these tissues and on target cells (DeGroot 2004). Receptors for AGEs (RAGEs) is a multiligand receptor that propagates cellular dysfunction in several inflammatory disorders, in tumors, and in diabetes.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Diabetes type</th>
<th>Subjects</th>
<th>Periodontal therapy</th>
<th>Metabolic control outcome measure</th>
<th>Effects on metabolic control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldridge et al 1995</td>
<td>RCT</td>
<td>Type 1</td>
<td>16 subjects &amp; 15 controls</td>
<td>OHI, SRP, adjustment of restoration margins</td>
<td>Glycosylated hemoglobin, or HbA1c, fructosamine</td>
<td>No effect on change in HbA1c</td>
</tr>
<tr>
<td>Christgau et al 1998</td>
<td>Treatment study, non- RCT</td>
<td>Type 1 &amp; Type 2</td>
<td>20 subjects &amp; 20 controls</td>
<td>SRP, subgingival irrigation with CHX, OHI, extractions</td>
<td>HbA1c</td>
<td>No effect on HbA1c</td>
</tr>
<tr>
<td>Grossi et al 1996, 1997</td>
<td>RCT</td>
<td>Type 2</td>
<td>89 subjects &amp; 24 controls</td>
<td>Systemic doxycycline or placebo &amp; curettage + irrigation using water, CHX or PVP-I</td>
<td>HbA1c</td>
<td>Significant reductions (P ≤.04) in mean HbA1c at 3 months</td>
</tr>
<tr>
<td>Iwamoto et al 2001</td>
<td>Treatment study, non- RCT</td>
<td>Type 2</td>
<td>13 subjects</td>
<td>Mechanical debridement and local minocycline in each periodontal pocket once a week for 4 weeks</td>
<td>HbA1c</td>
<td>Significant improvement of HbA1c levels: reduction in TNF-α levels; decreased fasting insulin levels, HOMA-R in patients not receiving insulin</td>
</tr>
<tr>
<td>Miller et al 1992</td>
<td>Treatment study, non-RCT</td>
<td>Type 1</td>
<td>9 subjects</td>
<td>SRP, CHX rinses, systemic doxycycline</td>
<td>HbA1c, glycated albumin</td>
<td>Decrease in HbA1c and glycated albumin in patients with improvement in gingival inflammation</td>
</tr>
<tr>
<td>Seppala et al 1993, 1994</td>
<td>Treatment study, non-RCT</td>
<td>Type 1</td>
<td>38 subjects</td>
<td>SRP, periodontal surgery and extractions</td>
<td>Medical history for baseline control status, HbA1c and blood glucose for assessing response to treatment</td>
<td>Reported an improvement of the HbA1c levels</td>
</tr>
<tr>
<td>Smith et al 1996</td>
<td>Treatment study, non-RCT</td>
<td>Type 1</td>
<td>18 subjects</td>
<td>SRP with ultrasonics and curettes, OHI</td>
<td>HbA1c</td>
<td>No statistically or clinically significant change in HbA1c</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design</td>
<td>Diabetes type</td>
<td>Subjects</td>
<td>Periodontal therapy</td>
<td>Metabolic control outcome measure</td>
<td>Effects on metabolic control</td>
</tr>
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</tr>
<tr>
<td>Stewart et al 2001</td>
<td>Treatment, study, non-RCT, quasi experimental design</td>
<td>Type 2</td>
<td>36 subjects &amp; 36 controls</td>
<td>Full-mouth SRP, subgingival curettage, OHI, extraction of unsalvageable teeth</td>
<td>HbA1c</td>
<td>Significant reductions in levels of HbA1c in treatment and control groups</td>
</tr>
<tr>
<td>Williams &amp; Mahan 1960</td>
<td>Descriptive clinical study</td>
<td>Type 1</td>
<td>9 subjects</td>
<td>Extractions, scaling and curettage, gingivectomy, systemic antibiotics (intramuscular penicillin and streptomycin)</td>
<td>Insulin requirement, diabetes control (not operationally defined), blood glucose levels</td>
<td>7 of 9 subjects had significant reduction in insulin requirements and noticeable reduction in blood sugar levels</td>
</tr>
<tr>
<td>Wolf 1977</td>
<td>Treatment study, non-RCT</td>
<td>Type 1 &amp; Type 2</td>
<td>91 subjects</td>
<td>Scaling, intensive patient home care; periodontal surgery; extractions; endodontic treatment; restorations; denture replacement</td>
<td>Blood glucose, 24-hour urinary glucose, insulin dose</td>
<td>Subjects with improved oral inflammation and infection tended to demonstrate improved control of diabetic symptoms</td>
</tr>
</tbody>
</table>

Table 8. Effects of treating periodontal disease on glycemic control: Study design features and outcomes
The binding of AGEs to macrophages and other cell types contributes greatly to increased cytokine production, which can lead to vascular damage such as atherosclerosis or coronary heart disease, and a more severe and progressive form of periodontal disease (Lalla et al 2000). The accumulation of AGEs and monocyte hypersecretion provide a plausible explanation for enhanced periodontitis severity in this high risk group.

S100A12, also called EN-RAGE (extracellular newly identified receptor for AGE-binding protein) or calcium-binding protein in amniotic fluid-1, is also a ligand for RAGE (Miranda et al 2001). It has been shown that S100A12 induces adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in the vascular endothelial cell and mediates migration and activation of monocytes/macrophages through RAGE binding. Furthermore, infusion of lipopolysaccharide into mice causes a time-dependent increase of S100A12 in the plasma (Kosaki et al 2004). Results from that study suggest that plasma S100A12 protein levels are regulated by factors related to subclinical inflammation and glucose control in patients with type 2 diabetes.

Thus, current evidence points to a bidirectional interrelationship between diabetes and periodontitis. The precise nature of this interrelationship is unclear. An upregulated inflammatory state has been proposed as the common mechanism underlying both conditions with an increase in cytokines, including TNF-α, postulated as a possible link (Iacopino 2001, Duarte et al 2007, Engebretson et al 2007). Oxidative stress is a common factor in periodontal disease, type 2 diabetes and perhaps the ‘prediabetic’ condition and the imbalance in redox control resulting independently from these disease states acts synergistically, and amplifies in a bidirectional manner the biochemical and clinical course of these diseases.

Excess ROS generated by peripherally primed neutrophils in the periodontitis state and reduced peripheral antioxidant levels may further tax an already compromised local and peripheral antioxidant defence in the prediabetic/diabetic state (Fredriksson et al 2003, Chapple et al 2007). When both conditions coexist the balance is tipped towards stimulation of redox-sensitive pathways with downstream upregulation of inflammation and associated insulin resistance, compromising blood glucose control and contributing to the development of diabetic complications. On the other hand, the diabetic conditions of chronic hyperglycaemia and increased AGE formation may impair antioxidant capacity and enhance NADPH oxidase activity and ROS production by neutrophils, contributing to both direct and indirect oxidative damage to periodontal tissues in response to periodontal pathogens within the dental plaque biofilm (Opara et al 1999).

**Periodontal management and diabetes mellitus**

The glycated hemoglobin test (hemoglobin A1c) has been proposed as offering several advantages as a screening test for dentists (Piche et al 1989). In undertaking management of a known diabetic patient, detailed information regarding the type of diabetes, age of onset, any current medication, their administration and history of diabetic complication should be taken. Medical clearance should be undertaken prior to any extensive periodontal therapy. Supportive periodontal therapy, patient education and motivation regarding meticulous oral hygiene, mouth rinse and flossing should be routinely carried out.

Well controlled type I or type II diabetic
patients can be managed similarly to a healthy individual. Periodontal surgical procedures can be performed, although it must be assured that the patient can maintain a normal diet post-surgically. In uncontrolled or poorly controlled diabetic patients, prophylactic antibiotic therapy should be given for emergency periodontal procedures. Periodontal therapy other than emergency treatment is contraindicated unless metabolic control is achieved. Well controlled diabetics are often a good candidate for periodontal surgery and successful implantation has been undertaken in well controlled diabetes mellitus, but studies of uncontrolled diabetes mellitus in animals have suggested an altered pattern of bone formation in relation to implants (Gian-Grasso & Nagelberg 1997, Takeshita et al 1998).

**Future prospects in the management of periodontal diseases in diabetic patients**

Similar to cardiovascular patients, diabetic patients also represent a group of patients who require new avenues and frontiers in the management of periodontal diseases. Various drugs like simvastatin, clarithromycin, azithromycin and alendronate can also be used both as local drug delivery for the management of periodontal diseases in diabetic patients (Pradeep et al 2008, Pradeep & Thorat 2010, Pradeep & Kathariya 2011, Pradeep & Sharma 2011). Alphalipoic acid (ALA) has powerful antioxidant ability and ALA supplementation improves the antioxidant status of diabetics independent of glycaemic control (Borcea et al 2005). Application of the ALA homologue, N acetyl cysteine, decreases the intensity of the neutrophil oxidative burst by a direct scavenging action (Stolarek et al 2002). Aminoguanidine, a nitric oxide synthase inhibitor, decreased the levels of inflammation within the periodontal tissues of animals with artificially induced periodontitis (Di Paola 2004).

Other therapies under investigation include cross-link breakers, or AGE breakers, that react with and cleave the covalent AGE-derived protein cross-links. A study by Wolffenbuttel et al (1998) showed that treatment of rats with streptozotocin-induced diabetes with the AGE breaker ALT-711 for 1 to 3 weeks reversed the diabetes-induced increased large artery stiffness as measured by systemic arterial compliance, aortic impedance, and carotid artery compliance and distensibility. The effects of ALT have also been studied in a rat model of periodontitis; the results showed a reduction of measured inflammatory parameters and demonstrated a protective effect against tissue damage associated with periodontitis (Di Paola et al 2004). Future therapies such as ALT and aminoguanidine may prove useful in reducing complications such as coronary heart disease and periodontitis that are associated with diabetes.

**Conclusion**

Therefore, to conclude we can say that proper use of the knowledge of relationships between periodontal disease and systemic health requires the dental professional to expand his or her horizons, to step back from the technically demanding aspects of the dental art, and to recognize the oral cavity as one of the many interrelated organ systems.

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Chapter 11

Removable partial dentures in periodontally compromised patients

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Introduction

In developed countries, the current practice in dentistry is to prefer implant supported reconstructions over tooth supported reconstructions. In Indonesia, especially in public hospitals, dental implants are still too expensive for most patients and therefore the trend is to prefer removable partial dentures over implant dentures. As surgical procedures are not required and there is often a reduction in “chair time”, removable partial dentures should be considered in patients with poor general health. Gerstein and King (1975) suggested the use of partial denture splints in the treatment of postsurgical tooth mobility. As they permit the distribution of forces throughout the dental arch, removable partial dentures are suitable for use in periodontally compromised patients.

Bessade et al (1974) investigated the clinical and histological evidence of the gingival response to various types of removable partial dentures at 1, 6 and 12 month intervals following insertion. The results showed that dentures with no gingival relief had the highest levels of associated pathology and that metallic dentures caused less inflammation than resin dentures. Rissin et al (1985), in a six years longitudinal study of 1221 subjects over a three year interval, showed there was no difference between the periodontal health of fixed and removable partial denture abutment teeth, replacing missing teeth reduced mobility in either fixed or removable partial dentures and that oral hygiene instruction is a must.

The following guidelines should be considered by the practitioner prior to prosthodontic therapy:

1. Decisions regarding teeth to be retained, surgical procedure to be employed and restoration to be placed must be made with the ultimate design of the prosthesis in mind.
2. Initial and surgical therapy should be done before the prosthetic procedures, then continued with maintenance therapy after the prosthetic procedures are completed.
3. In the selection of a suitable design, the following approaches should be
considered: mobility, crown root ratio, the number and distribution of remaining teeth, the patient’s age, the type of opposing occlusion, the nature of the residual ridge, and the patient’s interest and desires (Newman et al 2006, Lang et al 2008).

**Selection of components for removable partial dentures in periodontally compromised patients**

**Major connectors**

A major connector joins the components on one side with those on the opposite side of the dental prosthesis. To function effectively and minimize potentially damaging effects, all major connectors must:

1. Be rigid.
2. Provide vertical support and protect the soft tissues.
3. Provide a means for obtaining indirect retention where indicated.
4. Provide a means for placement of one or more denture bases.

**Maxillary major connectors**

There are six types of maxillary major connectors used in removable partial denture therapy: palatal bar, palatal strap, anteroposterior palatal bar, horseshoe, anteroposterior palatal strap and complete palate (Figures 1-6). Structural requirements for maxillary major connectors are:

1. The distance between the borders and the gingival margin must be a minimum of 6 mm.
2. The anteroposterior palatal strap should be at least 8 mm in width.
3. The borders of a maxillary major connector should always cross the palatal midline at 90 degrees, never diagonally.
4. Maxillary major connectors should display *bead lines*; minor elevations at borders that slightly displace the palatal soft tissues to produce a mechanical seal and prevent food particles collecting under the major connector.
5. In periodontally compromised patients more of the palate should be covered, therefore a wide palatal strap or a complete palate is indicated (Phoenix et al 2003).

**Mandibular major connectors**

There are five types of mandibular major connectors used in removable partial dentures: lingual bar, lingual plate, lingual plate with “step back” design, double lingual bar, and labial bar (Figures 7-11). Structural requirements for mandibular major connectors are:

1. The lingual plate must completely close the interproximal spaces to the level of contact points; the inferior border of the lingual plate should be made thicker to ensure its rigidity, and must be supported by a rest located no further posterior than the mesial fossae of the first premolars. A lingual plate is indicated when there is insufficient vertical space for a lingual bar; or patient with mandibular tori.
2. A double lingual bar should be 2 to 3 mm in height and 1 mm thick; should have rests and be placed at each end of the upper bar and located no further posterior than the mesial fossae of the first premolars.
3. A labial bar is indicated when there is a gross uncorrectable interference that makes the placement of a lingual major connector impossible, i.e. lingually inclined teeth or large mandibular tori.
4. When the anterior teeth exhibit reduced periodontal support, a double lingual bar, lingual plate, or modified lingual plate, i.e.
step back design for large interproximal spaces, should be used (Phoenix et al 2003).

**Minor connectors**

The functions of minor connectors are to join the remaining components of a removable partial denture to the major connector and to distribute applied forces to the supporting teeth and oral tissues. Therefore rigidity is an essential characteristic of all minor connectors.

Components may be described as minor connectors when they join clasp assemblies to major connectors, joint indirect retainers or auxiliary rests to major connectors, joint denture bases to major connectors, or serve as approach arms for vertical projection or bar type clasps, the only minor connector not required to be rigid (Figure 12).

Structural requirements for minor connectors are:
1. To be strong, it must be broad buccolingually, but thin mesiodistally so as to not interfere with prosthetic tooth placement.
2. Positioned in a lingual embrasure to disguise its thickness.
3. Should be gently curved to promote patient comfort.
4. In maxillary prosthesis it should extend into the pterygomaxillary notch and extend beyond the most prominent portion of the tuberosity.
5. In mandibular prosthesis a distal extension base must cover the retromolar pad. Minor connectors should be two thirds the length of the edentulous to provide appropriate mechanical support (Phoenix et al 2003).

![Figure 12. Minor connectors (Phoenix et al 2003).](image-url)
Removable partial dentures in periodontally compromised patients

Rests and rest seats

The design of a rest and rest seat must ensure that forces transmitted from the prosthesis to an abutment are directed apically down the long axis of the tooth. The rest should serve as a vertical stop that prevents vertical movement of the prosthesis. A rest that is part of a retentive clasp assembly is referred to as a primary rest. A rest that is responsible for additional support is called a secondary rest and is used as an indirect retainer. When it is located on the mesial occlusal surfaces of the first premolars it provides adequate indirect retention in removable partial dentures (Phoenix et al 2003). Removable partial prostheses should always be constructed with an occlusal rest, but it sometimes omitted for reducing axial load on teeth with poor periodontal support (Bui 2011).

Direct retainers

Direct retainers are components of removable partial dentures that prevent displacement of the prosthesis, ensure prosthesis retention and minimize the transmission of forces to the abutments and supporting tissues. There are two types of direct retainers:

1. Intra coronal: direct retainers that reside within the normal contour of abutment teeth. These consists of a matrix, a metal receptacle contained within the clinical contours of a fixed restoration, and a patrix that attached to the associated removable partial denture.

2. Extra coronal: indirect retainers that reside outside the normal contour of an abutment teeth.

They are two subcategories of extra coronal direct retainers: extra coronal attachments, that derive their retention from closely fitting components termed matrices and patrices; and retentive clasp assemblies. All clasp assemblies must be designed following six requirements:

1. Retention that resists forces acting to dislodge components away from the supporting tissues. A retentive arm contacts on the facial surface of an abutment apical to the height of contour. There are two basic forms: suprabulge clasp arms that approaches the undercut from an occlusal or incisal direction (Figure 13), and

Figure 13. Suprabulge direct retainers (Phoenix et al 2003)
1. Infra bulge clasp arms that approach from an apical direction (Figure 14).
2. Support that resists the displacement force of the prosthesis in an apical direction, for example the rest.
3. Stability that resists displacement of the prosthesis in a horizontal direction, i.e. components that are rigid and contact vertically.
4. Reciprocation which counteracts lateral displacement of an abutment that harmful to the supporting periodontal tissues. The reciprocal element may be a cast clasp, a lingual plate, or a combination of mesial and distal minor connectors. It must contact on the lingual surface of the abutment tooth at, or occlusal to, the height of the contour.
5. Encirclement that prevents movement of an abutment away from the associated clasp assembly. The clasp assembly must contact the abutment tooth more than half the tooth’s circumference.
6. Passivity; when fully seated, a clasp assembly should be passive. (Phoenix et al 2003).

There are rules that apply to cast circumferential assembly (Phoenix et al 2003):
1. It should originate from a part of the framework lies above the height of contour;
2. The retentive terminus should be directed occlusally, not gingivally;
3. It should terminate at the mesial or distal line angle, not at the midfacial or midlingual;
4. The retentive arm should be positioned as far apically on the abutment.

Increased periodontal support can be achieved with a higher number of abutment teeth. Multiple abutments reduce injurious lateral and torsional stresses on abutment teeth and their use should be standard procedure in patients with reduced periodontal support. Multiple abutments can be made by clasping abutment and adjacent teeth in sequence. When the terminal tooth is periodontally weak, more than one adjacent tooth should be used for added support (Bui 2011).

**Indirect retainers**

The component of the framework that functions as indirect retention to resist rotational displacement of the denture away from the supporting tissues is called an indirect retainer. It also contributes to the overall support and stability of the denture and provides additional support and rigidity to the mayor connector. An occlusal rest is the preferred component for indirect retention, a

![Figure 14. Infrabulge direct retainers (Phoenix et al 2003)](image-url)
Cingulum rest and incisal rest can also be used as effective indirect retainers (Phoenix et al 2003). An investigation of the effectiveness of indirect retainers in removable partial dentures found that the effect of indirect retainer in preventing occlusal displacement of the denture base appeared to be limited, but the type of clasp had the greatest influence on the denture base movement. Proximal surface guiding planes were also important in preventing lifting of the denture base. Use of mesial instead of distal rests on the terminal abutment did not decrease indirect retention (Frank & Nicholls 1997).

Case Report

Case 1 - 59 year old female

The periodontal condition was recorded as follows: periodontal pockets of pocket depth between 3 to 7 mm; mobility of all teeth between grade II and III; some molar teeth missing; reduced alveolar ridge (Figure 15); Papillary Bleeding Index 0.5; Plaque Index 1.15; Calculus Index 2.1. The periodontal condition was diagnosed as generalized chronic periodontitis due to the presence of plaque and calculus; maxillary and mandibular incisor teeth were aggravated by trauma due to occlusal interferences in articulation; upper right first premolar aggravated by trauma from occlusion by disproportionate crown root ratio. The treatment undertaken was plaque control, scaling and polishing, occlusal adjustment, extraction of hopeless teeth, curettage of teeth with 4 to 5 mm pocket depth, and periodontal flap surgery on teeth with 6 mm or more of pocket depth. The dental prosthesis used was a Removable Metal Denture Splint for upper and lower teeth with a palatal strap and double lingual bar for the major connectors, a double Y/double T-clasp as the direct retainer for mobile teeth, Acher’s clasp as direct retainer for immobile teeth and an occlusal rest at mesio-occlusal of first and second premolars as the indirect retainer (Figure 16).

Case 2 - 47 year old male

The periodontal condition was as follows: periodontal pockets with pocket depth of 3 to 8 mm, all mandibular anterior and right premolar teeth having between grade II and

Figure 15. OPG of patient in Case 1.
Figure 16. Removable partial denture of patient in Case 1.

Figure 17. Radiographs of patient in Case 2.
Removable partial dentures in periodontally compromised patients

III mobility with the maxillary right first molar having III degree mobility; several teeth missing; reduced alveolar ridge (Figure 17); Papillary Bleeding Index 1.5; Plaque Index 1.45; Calculus Index 2.1. The periodontal condition was diagnosed as generalized periodontitis due to plaque and calculus and aggravated by trauma from edge to edge occlusion. The treatment done was plaque control; scaling and polishing; extraction of maxillary right first molar; endodontic treatment and permanent restoration of maxillary and mandibular left first molar; curettage of teeth with 4 to 5 mm pocket depth and periodontal flap surgery of teeth with 6 mm or more pocket depth. A Removable Metal Denture Splint was constructed for the upper and lower teeth: with a palatal strap and double lingual bar for the major connector, the direct retainers for mobile teeth were double Y/double T-clasp and for immobile teeth were Acher’s clasps, and an occlusal rest at mesial first and second premolars was used for the indirect retainer (Figure 18).

Figure 18. Removable partial denture of patient in Case 2.
Conclusion

There are many reports in the literatures that removable partial dentures are suitable for use in periodontally compromised patients. Appropriate design and good oral hygiene may decrease the occurrence of periodontal disease.

References


Chapter 12

Recent progress in periodontal regeneration using periodontal ligament cell sheets

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Introduction

The final goal of periodontal therapy is the regeneration of lost tissues including alveolar bone, periodontal ligament and cementum. Since the early 1980's, periodontal ligament (PDL) cells have been considered a reliable cell source for periodontal regeneration. Nyman et al (1982) reported the regenerative potential of the periodontal ligament in an experimental study in a monkey model. Based on this concept, several procedures have been introduced for the selective proliferation of periodontal ligament cells, such as guided tissue regeneration and enamel matrix derivatives. However, complete regeneration is still difficult to achieve, especially in severe periodontal defects. In order to overcome the limitation of current methods, PDL cells expanded ex vivo have been transplanted into defects as a stem cell replacement therapy (Dogan et al 2003, Nakahara et al 2004). These studies show that the transplantation of PDL cells is effective in regenerating the periodontal tissues. Several trials have been performed using not only PDL cells, but also bone marrow-derived mesenchymal stroma cells (BMMSCs), adipose-derived stromal cells (ADSCs), gingival fibroblast cells, and alveolar periosteum-derived stromal cells (APSCs) (Kawaguchi et al 2004, Mizuno et al 2006, Mohammad et al 2007, Tobita et al 2008). Their efficacy in periodontal regeneration has been reported (Tsumanuma et al 2011).

To apply cell therapy conveniently, a tissue engineering technique is used. Okano et al (1990) developed a new culture dish which is grafted with a temperature-responsive polymer; poly-N-isopropylacrylamide (PIPAAm). At lower temperatures (<32° C), PIPAAm is hydrated with an extended-chain conformation and at over 32° C it becomes dehydrated. Therefore, a dish grafted with PIPAAm allows cultured cells to be harvested as a monolithic cell sheet through low-temperature treatment without using enzymes, because cells generally and preferably can adhere to hydrophobic surfaces, but not to hydrophilic surfaces, as result of their intrinsic characteristics. Our group produced PDL cell sheets using temperature-responsive culture dishes and reported that the cell sheets have the potential to promote the regeneration of periodontal tissues containing bone, cementum, and PDL in vivo.

Previous progress in periodontal regeneration using cell sheet engineering

We investigated the application of cell
sheet engineering for a periodontal therapy and found that periodontal ligament cells can be harvested from a temperature-responsive culture dish as a monolithic cell sheet at low temperatures.

Hasegawa et al (2005) investigated the characteristics of human periodontal ligament cell sheets transplanted into a mesial dehiscence model in immunodeficient rats. Before transplantation, periodontal ligament cells were harvested from a temperature-responsive dish as a contiguous sheet containing abundant extracellular matrix including type 1 collagen, integrin, and fibronectin. The transplanted cell sheet of human periodontal ligament was found to survive and proliferate during the experimental period. Newly formed immature fibers were obliquely anchored to dentin surfaces in the experimental group. No fiber formation was observed in the control group at 4 weeks. These results suggest that the method based on cell sheet engineering can be useful and feasible for periodontal regeneration.

Akizuki et al (2005) studied periodontal healing after the application of periodontal ligament cell sheets in beagle dogs. Following the primary culture of dog periodontal tissue, a periodontal ligament cell sheet was obtained from a temperature-responsive cell culture dish. When the cells reached confluence, the medium was supplemented with 50 μg/mL ascorbic acid to increase production of type 1 collagen in order to strengthen the cell sheet. The PDL cells were then incubated for another 2 weeks. At the time of transplantation, hyaluronic acid sheets were used on the culture dishes as a reinforced carrier. Defects were surgically prepared on the buccal root surfaces of mandibular first molars. The cell sheets backed with hyaluronic acid sheet were transplanted to the deficient defect. Periodontal tissue healing with bone, cementum and periodontal ligament formation was observed in 60% of the experimental defects. Histomorphometric analysis indicated that the formation of new cementum in the experimental group was significantly higher than in the control group.

Flores et al (2008a) explored the possibility of cementum-periodontal ligament complex regeneration by improving two processes of periodontal cell sheet engineering. Firstly, an experimental group was cultured in minimum essential medium supplemented with 50 μg/mL of ascorbic acid, 10 nM dexamethasone and 10 nM β-glycerophosphate as an osteogenic differentiation medium. Dexamethasone has been known to induce the osteoblast differentiation of human bone marrow cells; Nagatomo et al (2006) reported that approximately 30% periodontal ligament cells show a calcifying differentiation in osteogenic differentiation medium. The cell sheets were multilayered by using fibrin gel. Multilayered sheets were then placed onto the dentin blocks and transplanted subcutaneously in the dorsa of immunodeficient rats. The multilayered constructs were left in situ for 6 weeks and then excised for histological investigation. Human periodontal ligament cells cultured with osteodifferentiation medium showed a marked increase in alkaline phosphatase and calcium deposition at 3 weeks in vitro. Newly regenerated cementum-like hard tissue on the dentin surfaces were observed in more than 60% of the periodontal ligament cell-dentin constructs. Many collagen fibers were found to be inserted perpendicularly into the newly formed cementum-like tissue, resembling native periodontal and Sharpey’s fibers.

Flores et al (2008b) transplanted a cell sheet onto the root surface of a defect created in the mandible of an immunodeficient rat, prepared following the method described in King et al (1997). This method allows regenerated cementum and periodontal ligament to be observed. Results showed that
Recent progress in periodontal regeneration using periodontal ligament cell sheets

the majority of the experimental group exhibited a new layer of cementum and new attachment of periodontal ligament fibers to the layer. Thus, periodontal ligament cells cultured in an osteogenic differentiation medium can regenerate both cementum and periodontal ligament.

Iwata et al (2009) performed periodontal regeneration with multilayered periodontal ligament cell sheets in a canine model. Periodontal marker genes were found in the cultured cells, and S-100 calcium binding protein A and periostin were also identified as markers. Three layered periodontal ligament cell sheets backed with woven polyglycolic acid were transplanted onto root surfaces in a 3 wall bony defect model. The bone defects were also filled with porous β-tricalcium phosphate. The experimental site of cell sheet transplantation exhibited regeneration of both new bone and cementum together with periodontal ligament fibers, while the control sites showed only a limited regeneration. Thus, the periodontal ligament cells on the sheet showed a multi-differentiation potential for regenerating all the necessary components of the periodontium in larger animals.

Preclinical study of periodontal ligament cell sheet engineering

An optimal protocol for the extraction, expansion, and characterization of human PDL cells was studied in pre-clinical trials, as periodontal ligament cells were a reliable source for periodontal regeneration (Iwata et al 2010). Human PDL (hPDL) tissues were obtained from 41 surgically extracted teeth and digested with enzymes. Human adipose-derived stem cells, bone marrow-derived mesenchymal stem cells, and gingival fibroblasts were also studied for comparison. All samples were examined individually for their proliferative activity, colony-forming ability, alkaline phosphatase activity, differentiation ability, the cell surface antigens, gene expression, and regeneration potential. Human periodontal ligament cells were more rapidly obtained with collagen/dispase (yielding 96.9%) than with conventional trypsin/EDTA (72.2%), and the cells exhibited an osteogenic potential both in vitro and in vivo. The proliferation activity of hPDL cells was stronger at a low cell density. Human PDL cells frequently differentiated into cementoblastic/osteoblastic lineage with an incidence of over 60%. On the other hand, the adipogenic and chondrogenic potential of hPDL cells was lower than those of human adipose-derived stem cells and human bone marrow-derived mesenchymal stem cells. S-100A4 and periostin were preferentially expressed in hPDL cells in comparison to those of bone-marrow-derived stem cells and gingival fibroblasts. Immunohistochemical stains also confirmed the expression of S100A4 and periostin in human periodontal ligament tissue.

Tanaka et al (2011) also investigated the characteristics of periodontal ligament cells obtained by two different methods (out growth and enzyme digestion). They reported that PDL cells cultured after enzyme digestion treatment show a higher proliferation rate, colony-forming activity and differentiation capacity into osteoblasts than those in PDL cells obtained by the outgrowth method. Washio et al (2010) assessed the safety and efficacy of a periodontal ligament cell sheet for use in future clinical trials. Periodontal ligament cells obtained from three donors were cultured with autologous serum in a cell processing center (CPC). The safety and efficacy of human periodontal ligament cell sheets were evaluated both in vitro and in vivo. The human PDL cell sheet was found to have a high ALP activity and periostin expression. In order to determine if the cell sheets were sufficiently free of contamination for clinical
use, the presence of bacterial or fungal contamination was investigated. The results from all samples showed the absence of contamination by mycoplasma, aerobic and anaerobic bacteria or fungi. In addition, the levels of endotoxins were found to be lower than 4.0 EU/mL. The human periodontal ligament cell sheets induced the formation of cementum and periodontal ligament-like tissue in immunodeficient mice.

To confirm the survival and proliferation of human periodontal ligament cells in immunodeficient mice after 4 week implantation, the expression of human vimentin (a mesenchymal marker) was investigated immunohistochemically. Anti-human vimentin antibody was positive only in the cells surrounding the dentin block which was wrapped in multilayered human PDL cell sheet and implanted subcutaneously in the mice. The tumorigenesis of human PDL cells was also studied by using a soft-agar colony forming assay and injecting them into mice. Both methods confirmed that the human PDL cells presented no evidence of malignant transformation. Finally, we developed a culturing process for autotransplantation of human PDL cells for clinical use (Figure 1).

Translational study of periodontal ligament cell sheet

The aim of this study was to produce PDL cell sheets applicable to clinics and to autotransplant them without any adverse effects. In 2006, the Japanese government announced new regulation of cell therapy including stem cells. The investigations of the autogenous transplantation of periodontal ligament cell sheets therefore had to follow the regulation. The regulations included two important controls in order to assure the quality of cell therapy; Good Clinical Practice (GCP) (Yoshida et al 2010). GCP is an international ethical and scientific quality standard applying to clinical studies, governing the study design and patient protection as shown in Table 1. GMP governs cell culture processes in cell therapies as shown in Table 2. The translational study of periodontal regenerative therapy using cell sheet engineering was prepared according to the guidelines of the Japanese Ministry of Health, Labour and Welfare. We chose an autologous cell transplantation procedure and cultured cells with the patient’s own serum to avoid any possible infection from other sources (Figure 2). To reduce the risk of tumor formation and to enhance hard tissue formation, periodontal ligament cells were cultured in medium that promoted calcifying differentiation, after seeding on temperature responsible culture dishes. We also established a culture protocol to manipulate the cell sheets.

- An international and scientific quality standard governing the design of clinical studies and ensuring patient protection
- Review of data and plans including the evidence, risk and benefit of the cell therapy
- The protection of patient rights
- Scientifically appropriate protocol
- Handling of information
- Approved by Institutional Review Board and an Independent Ethics Committee

<table>
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<th>Table 1. Components of Good Clinical Practice (GCP)</th>
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<td>GMP governs cell culture process in cell therapy</td>
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<td>GMP requires that materials, protocol, tools and environment used in cell therapy should be guaranteed safe and effective</td>
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<td>All culture procedures should be recorded and the records retained in the laboratory for traceability</td>
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| Table 2. Components of Good Manufacturing Process (GMP) |
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Figure 1. Culture process for human periodontal ligament cells.

Figure 2. Total working process of the translational study of periodontal ligament cell sheets
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The cell culture was performed in a clean room designated the “Cell Processing Center (CPC)” as shown in Figure 3. Controlled air flow and zoning ensured maintenance of strict cleanliness. All the work in CPC was carried out according to Standard Operating Procedure (SOP), a culture protocol that maintains the quality of cell sheets. All work was performed by two persons; one to perform the culture procedure and the other to direct and record the procedure to avoid human error.

The safety of cell sheets prepared according to the SOP was investigated. Verification of non-contamination from bacteria and mycoplasma was performed and showed that the cell sheets were free from infection by these microorganisms. We also verified that cells from the PDL cell sheet exhibited no tumorigenic properties. Karyotype testing revealed that no chromosomal abnormality related to tumors had occurred. A further tumorigenic test (soft agar test) indicated negative results (Figure 4).

All results were submitted to the Ethics Board.

Figure 3. Cell processing center (CPC)

**Tumorigenesis assay (in vivo)**

Method
1x10⁷ cells/200µl in serum free medium were injected into immunodeficient mice subcutaneously.
Observation; 3 and 12 weeks

Results / 3weeks
a. Negative control (medium only) → normal
b. Human PDL → some granulation tissue but not tumor
c. Positive control (HeLa S3 cells) → tumor formation (20x20x10mm)

**Soft agar colony forming assay (in vitro)**

a. Positive control: HeLa cells → colony (+)
b. Negative control: fibroblast → colony (-)
c. hPDL cells → colony (-)

Figure 4. Validation assay of non-tumorigenesis of periodontal ligament cells in vivo and in vitro (Modified from Washio et al 2010 with permission).
Committee of the Tokyo Women’s Medical University in June 2010. After several discussions and revisions, the Committee approved our project for clinical use in September 2010. The same protocol was submitted to the government authority in September 2010 and approved in January 2011 by the Ministry of Health, Labor and Welfare in order to proceed with a translational study of 10 patients within 2 years. This is the first official approval of a cell therapy procedure in the field of periodontal regeneration in Japan.

**Discussion and Conclusion**

A successful clinical trial using periodontal ligament cells in three patients was reported. Feng *et al* (2010) treated periodontal pockets of >6 mm with autogenous periodontal ligament progenitor cells. Periodontal ligament cells were obtained from third molars. Periodontal ligament cells were then cultured with α-MEM and 10% FBS and bone grafting materials (Calcitite 4060-2) are added to the medium. The PDL cells and Calcitite mixtures were inserted into the periodontal defect and sutured. The authors found that the periodontal tissues were regained several months postoperatively. They claim that periodontal ligament cell implantation may be a promising treatment in patients without inflammation or systemic disorder.

Similar efforts using tissue-engineered cultured periosteum with platelet-rich plasma and hydroxyapatite have used in treating 30 human infrabony periodontal defects. Yamamiya *et al* (2008) found that their treatment using a combination of human cultured-periosteum, PRP, and HA lead to a significantly favorable clinical improvement in infrabony defects. Park *et al* (2011) demonstrated that human periodontal ligament stem cells can be isolated during periodontal surgery from inflammatory granulation tissue attached to the base of the intrabony defect and that these cells have a potential to regenerate new cementum and related periodontal ligament tissue. Marchesan *et al* (2011) reviewed the implication of cultured periodontal ligament cells in a clinical and experimental setting. They claim that the periodontal ligament is a key contributor to the process of the regeneration in periodontics. Continued efforts will expand our understanding of cell behavior with the goal of optimal periodontal regeneration.

**Conclusion**

It has been demonstrated that the cell culture protocol maintains the quality of the cell sheet. Progress in the translational study of periodontal ligament cell sheets is ongoing.

**Acknowledgments**

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**References**


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Implant treatment in the anterior maxilla: Planning considerations, surgical concepts and changing techniques for esthetic success

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Introduction

In the pioneering Brånemark era of oral implantology, the goal of treatment was to simply restore function and therefore aesthetic outcomes were only a minor issue. The first totally edentulous patients wore a complete denture for a long time, the gingival architecture was completely flat and the main concern of the surgeon was solely placement of the fixture in the bone, without worrying about soft tissue integration and the position of the fixtures from a restorative perspective. These restorations, well known worldwide as the Toronto Bridge, are still in function after 30 or more years.

The reason for this long lasting success could be that the pink prosthetic flange was designed from the beginning not to contact the gingival tissues, and thus is not in what we know now as being a very critical zone for the longevity of implant supported restorations.

Currently implantology is considered to be a viable treatment, we can trust it and this is the reason for the widespread use of implants to restore not only full edentulism but also single or partial edentulism. The biomimetic need arose when we began placing implants close to natural teeth and patients began to compare the final aesthetic outcome of the implant supported restoration with the look of their own natural teeth and hence required a realistic outcome. Patient demands in modern implants have completely changed from the initial stages of implant dentistry (Table 1 & Figure 1).

As we are no longer in the pioneering era of implant dentistry, patients want a restoration that looks natural. In order to meet patient demands, we need to optimize the implant position, overcoming the traditional separation between the surgical and prosthodontic aspects that has existed since the beginning of implant dentistry.

The surgical and prosthodontic knowledge has to be blended together using a teamwork philosophy. A team approach is the key to achieving a natural restoration in the simplest way (Magne & Belser 2002). The hand of the surgeon has to be guided not only by the bone tissues, but above all by the final prosthetic outcome.

One of the most challenging situations in modern implant dentistry is the replacement of a lost tooth in the aesthetic zone (Gamborena & Blatz 2004, Sadan et al 2004a, Sadan et al 2004b).

Immediate implant placement into a fresh extraction socket offers functional and aesthetic advantages, by preserving the bone
and soft tissue architecture. The immediate provisionalization of such implants provides additional benefits to the patient from the aesthetic and functional perspectives, with improved speaking and chewing ability and shortening of the overall length of treatment (Barone et al 2006).

A systematic review of the scientific evidence on immediate implant placement supports such procedures as a safe and predictable protocol when certain guidelines are strictly observed (Esposito et al 2006). Furthermore the immediate restoration of dental implants is fully supported by the existing evidence, with clinical success rates reported to be comparable to conventional multi-step protocols (Esposito et al 2007). As well, the immediate loading procedure improves patient comfort in daily life following the surgery, avoiding the need for any kind of removable provisional appliance (e.g. retainer or partial denture).

**Figure 1.** The new high-tech approach to dentistry assists the restorative team in satisfying patient demands, improving the comfort and the quality of life and at the same time shortening the total treatment time.

1. AESTHETICS  
A restoration that looks natural.

2. FUNCTION  
Functionally comfortable with the new single, partial, as well as total restoration.

3. LONGEVITY  
A long lasting functional and aesthetic outcome.

4. MINIMALLY INVASIVE  
The minimally invasive philosophy in medicine requires that surgical and prosthetic comfort is essential as well as a shorter overall treatment time.

5. COST  
All the treatment has to be cost effective immediately and in the long-term.

| Table 1. Patient demands in modern implant dentistry. |
If the goals of implant treatment are optimal function and natural aesthetics, the traditional multistep protocol has to be shifted toward a modern multidisciplinary approach, in which the cutting edge surgical and prosthetic procedures are merged into one successful protocol.

The driving philosophy of this modern approach to implant treatment in the “aesthetic zone” is based on two main principles:

1. Preservation of the existing architecture of the gingival framework and the underlining bone tissue.
2. Enhancement of the long-term stability of the bone and soft tissue anatomy.

Careful case selection and comprehensive treatment planning are essential to achieve what patients require; a long lasting restoration that looks natural (Magner & Belser 2002).

**Minimally invasive and guided surgery**

Restorative-driven implant therapy requires accurate implant placement (Tarnow et al 1992, Grunder et al 2005). In highly challenging aesthetic cases, correct assessment of the bone conditions, planning of implant position and precise drilling into the bone according to simulation are essential in ensuring the successful placement of a dental implant according to prosthetic requirements. The purpose of computer-assisted, template-guided implantation is to ensure accurate preoperative planning and safe implant insertion. In our practice, template-guided placement of dental implants using NobelClinician™ software provides reliable transfer of preoperative computer-aided planning into surgical practice, reducing bone resorption due to a short and minimally invasive drilling protocol and preserving the existent soft tissue architecture (Figures 2-4).

The accuracy and reliability of this procedure has been demonstrated in a recent clinical study (Vasak et al 2011). The average deviations measured were 0.43 mm (bucco-lingual), 0.46 mm (mesio-distal) and 0.53 mm (depth) at the level of the implant shoulder, and 0.7 mm (bucco-lingual), 0.63 mm (mesio-distal) and 0.52 mm (depth) at the level of the implant apex which was slightly higher. A radiographic template of the tooth to be restored with an accurate prosthetic design which lies on the gingival tissue without any kind of flange is mandatory in order to match the bone data and the prosthetic needs.

**The immediate definitive zirconia abutment and provisional crown**

The immediate placement of a definitive zirconia abutment on the day of the surgery is a predictable treatment option which avoids repetitive mutilation of the fragile peri-implant soft tissue collar, which can occur whenever abutments are removed and reinserted during

**Figures 2-4.** New design of radiographic template without labial flanges. The template lies on the gingival tissue or fits on the remaining natural dies in order to customize the 3D implant positioning according to bone data and the ideal prosthetic emergence profile. The surgical template, due to the lack of labial flanges, is stabilized in the mouth with 2 anchor pins fixed in the palatal vault.
the prosthetic procedures. These repetitive prosthetic abutment movements compromise and disrupt the mucosal barrier around the implant supported restorations and result in a progressive apical shifting of the biological width, thus leading to marginal bone resorption (Abrahamsson et al. 1997). A customized CAD-CAM definitive zirconia abutment or a prefabricated zirconia abutment (NobelProcera™, NobelBiocare) should be inserted immediately after implant placement (Figures 5-7). Prosthetic abutments constructed from zirconium oxide ceramic have reliable clinical strength, excellent biological properties and natural aesthetic outcomes (Glauser & Sailer 2004, Jung et al. 2007). White and shaded zirconia abutments prevent the bluish discoloration of the peri-implant soft tissue. A natural looking prosthetic abutment is also beneficial should soft tissue recession occur in the long term. The CAD-CAM abutment can be designed before the surgery, customizing the final shape on the master cast poured from the surgical template. The abutment can be designed and produced by a full virtual workflow (digital wax-up) after the scan of the master cast, or through scanning the traditional wax-up of the abutment.

The NobelClinician™ software provides a digital library which allows the clinicians to choose a prefabricated zirconia abutment that is more suitable to the prosthetic requirements of the definitive restoration. These prefabricated zirconia abutments are available in various diameters, finish-line heights and angulations, although in most cases the final design is customized by chairside preparation. The abutment is prepared with diamond burs at a high speed with copious water, guided by a silicone index made from the diagnostic wax-up of the definitive restoration. The final reshaping of the prefabricated zirconia abutment is performed intra-orally after engaging the abutment into the implant connection. Care has to be taken to orient the implant connection so the scalloped design of the abutment fits the final prosthetic shape. Correct abutment placement is verified by periapical radiograph before the final reshaping. The soft tissue and the fresh extraction socket have to be protected from rotational injury and sealed with a cord and a block-out light-curing material to avoid penetration of zirconia particles (Figures 8-10). The provisional restoration, properly oriented with a silicone matrix, is relined chairside with a self-curing low shrinkage resin. The provisional crown is removed from the abutment after complete setting of the relining resin and the abutment is then removed from the implant. The dimensional

Figure 5-7. The implants are placed with a flapless or flap approach in order to preserve or improve the soft tissue architecture. The customized CAD-CAM definitive zirconia abutment or a prefabricated zirconia abutment (NobelProcera™, NobelBiocare) should be inserted immediately after implant placement. Prosthetic abutments fabricated from zirconium oxide ceramic provide reliable clinical strength, excellent biological properties and a natural aesthetic outcome.
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stability of this resin makes easier to fit the temporary crown to the abutment in the same intraoral relining position. The prosthetic unit, temporary crown and abutment are reconnected to a laboratory analogue for finishing and polishing. The remaining gaps are filled with the same resin in order to optimize the prosthetic emergence profile and create a smooth transition between the abutment and the provisional. Excess resin flashes are trimmed carefully to customize the final shape. Finally the customized zirconia abutment and the temporary are highly polished with silicone diamond disk and diamond paste to increase the biocompatibility of the prosthetic surface and reduce bacterial colonization (Scotti et al 2007).

The prosthetic units are disinfected in a 2% glutaraldehyde solution for 5 minutes and then rinsed with copious sterile saline solution. The zirconia abutment is fitted on the implant with a torque of 35 Ncm and the provisional is fixed with a mixture of definitive cement and Vaseline oil in order to ensure the stability of the restoration in the crucial soft and bone tissue recovering period. The absence of occlusal contacts during the excursions is verified by articulating paper. Follow-up visits are scheduled for 15 days, 1 month, 2 months and 3 months before final impression.

**The final restoration**

At the 3 month follow-up visit, final preparation of the abutment shoulder is performed in order to customize the scalloped design of the finish-line in the transmucosal area, in the same manner as the natural tooth with consideration given to periodontal support for the surrounding tissue. The concave-convex abutment design and the scalloped finish-line allow a natural prosthetic emergence profile from the gingival architecture (Figures 11-12). The finish-line

**Figures 8-10.** A chairside preparation of the abutment shoulder is performed in order to customize the scalloped design of the finish-line in order to support the surrounding tissue in the transmucosal area in the same manner as a natural tooth. An accurate impression of the prosthetic emergence profile is obtained after a slight tissue retraction, and the master cast is poured.

**Figures 11-12.** Pre-treatment view of the upper central incisors and post-treatment view 4 months after immediate implant placement with immediate zirconia abutment and loading.
is placed 1.5 to 2 mm below the gingival margin, a slight tissue retraction is obtained with cord in order to take an accurate subgingival impression of the prosthetic interface around the finish-line. A gentle conditioning of the per-implant tissue architecture with the provisional is mandatory in order to minimize mechanical injury during the impression procedure. A master cast is fabricated from the final impression of the implant abutment and a wax-up of the prosthetic framework is performed for production of a 0.4 mm customized shaded zirconia, alumina or lithium disilicate coping (NobelProcera™, NobelBiocare). The low translucency of zirconia copings is the treatment of choice as a prosthetic framework when there is the need to mask a discoloured natural tooth adjacent to the implant (Rutten & Rutten 2006). Conventional porcelain layering techniques are applied to finalize the shape and colour. A bisque-bake try-in is mandatory to customize the final prosthetic flaring in order to preserve and support the soft tissue architecture in the long term (Figures 13-21).

**Aesthetics, biotype and soft tissue integration**

The gingival morphology of the anterior region plays an important role in determining the final aesthetic outcome. Tissue biotypes affect the outcomes of periodontal therapy, root coverage procedures and implant aesthetics (Claffey & Shanley 1986, Huang et al 2005, Hwang & Wang 2006, Zigdon & Machtet 2008, De Rouck et al 2009). There are two main types of gingival morphology; the scalloped and thin, or flat and thick gingiva. The contour of the gingiva closely follows the contour of the underlying alveolar bone (Ochsenbein & Ross 1969). The term “periodontal biotype” was later introduced to categorize the gingiva into “thick-flat” and “thin-scalloped” biotypes (Seibert & Lindhe 1989). The thin tissue biotype has a gingival thickness of <1.5 mm, and the thick tissue biotype has a tissue thickness ≥2 mm (Claffey & Shanley 1986). In implant restorations, the thick-flat tissue biotype produces a more successful aesthetic treatment outcome (Kan et al 2003). In immediate single tooth implant restorations, patients with “thin-scalloped” mucosa often have more tissue recession, while patients with “thick-flat” mucosa tend to maintain the implant papillae height (Evans & Chen 2008, Romeo et al 2008). These observations suggest that tissue biotype might be a significant factor influencing aesthetic treatment outcomes (Fu et al 2010).

**Thick flat biotype**

The thick flat biotype offers a more predictable aesthetic outcome than the thin scalloped biotype due to the sturdy nature of the soft tissue and underlining bone structure. The thick flat biotype has a large keratinized band, the crown shape is almost square and the roots have a bulbous shape, the contact points are located apically and thus the gingival embrasure volume is minimal and the papillae completely fill the embrasure space. The crestal bone architecture, due to the bone and root topography, is nearly flat with minimal undulation between the interproximal bone peaks and the buccal walls and the bone peaks are wider than higher. The immediate implant placement in the thick flat biotype is not a serious clinical concern. Implants can be placed with a traditional approach as well as with a computer-assisted, template-guided implantation. We can use a wider implant diameter, in order to fill the gap between the implant and the alveolar socket walls, without increasing the risk of post-extraction resorption. The rationale in the thick flat biotype should be obtaining an optimal 3D implant positioning, keeping an optimal
Figures 13-15. A bisque-bake try-in of the ceramic is mandatory to customize the final prosthetic flaring in order to preserve and support the soft tissue architecture in the long term. A smooth customized transition between the zirconia coping and the ceramic profile mandate the final shape of the surrounding soft tissue.

Figure 16-17. A restorative driven philosophy and computer guided surgery ensure the perfect implant placement according to bone and soft tissue architecture and functional-aesthetic prosthetic needs.

Figures 18-19. A pre-treatment intraoral view and the final result at 4 year follow-up. Low translucency zirconia copings are the treatment of choice as a prosthetic framework where there is a need to mask a discoloured natural tooth adjacent to the implant.

Figures 20-21. Radiographic assessment on the day of final prosthesis insertion and at 4 year follow-up. The underlining bone crest stability is the key to obtaining satisfactory soft tissue architecture and aesthetics in the long term.
distance between the implant and the adjacent teeth without jeopardizing or infringing any biological areas. The flat bone and soft tissue architecture could mandate a deeper implant placement below the bone crest, in order to create two bone peaks beside the implant that could support the new thick scalloped soft tissue architecture (Figures 22-33).

**Thin scalloped biotype**

The thin scalloped biotype is characterized by a fragile nature and a reduced amount of keratinized tissue. The dental morphology is characterized by a triangular-cylindrical crown shape, with contacts point located more incisally than in the thick flat biotype; these influence the volume and the height of the gingival embrasures. The interproximal...
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Figure 27. Flat bone and soft tissue architecture mandate a deeper implant placement below the bone crest, in order to create two bone peaks beside the implant to support the new thick scalloped soft tissue architecture.

Figure 28. A standard titanium abutment has to be customized in order to have a scalloped design and a concave shape below the finish line.

Figure 29. CAD-CAM restoration. Virtual wax-up and final restoration composed of a concave shape zirconia abutment with an alumina coping designed as a preparation for veneering cemented on the top and a laminate made by feldspathic porcelain on a refractory die.

papillae are very thin and do not completely fill the whole embrasure space and this may affect the final outcome of the implant treatment (Figure 34). The roots have a narrow tapered shape, thus the bone architecture has a wave shaped undulation due to the distance between the interproximal bone peaks (that are higher but very thin) and the buccal walls. Replacing a missing tooth with an implant in a patient with a thin scalloped biotype might not be entirely predictable, because this biotype is more liable to slough when surgical procedures are being undertaken.

The sequence of losing the interproximal papillae and the surrounding gingival structures starts immediately after tooth extraction. The interdental papillae remodel in a sloping fashion and become depressed in comparison with the healthy adjacent marginal tissue (Engquist et al 1995). The scalloped design of the underlining bone tissue, with a great undulation between the buccal walls and the interproximal bone peaks, may lead to unsymmetrical bone resorption and thus to unsymmetrical peri-implant tissue margins, compared to the contralateral side (Wöhrle 2003). The lost interdental papilla usually cannot regenerate to its original dimension and
any additional osseous remodelling will result in further shortening of the already short papillae, thereby complicating the aesthetics.

**Clinical workflow in thin scalloped biotype**

The clinical recommendations for the implant treatment in the aesthetic zone of this fragile biotype range from minimally invasive surgery with very minimal soft tissue displacement or a flapless approach, in order to avoid postsurgical recession, to the use of new implant designs and concepts. Clinicians need to focus their attention on the platform size of the implant and on the prosthetic interface.

**Platform shifting**

The platform shifting concept is based on the observation that bone resorption does not occur, or is highly minimized, when the prosthetic interface between the abutment and the implant platform is moved away from the bone. This bone crest stability could be the result of distancing the contaminated prosthetic micro-gap from the bone tissue and limiting the resorptive effect of the implant-abutment junction associated inflammatory cell infiltrate. Platform shifting is a mismatch between the diameters of the implant and the prosthetic abutment (Baugarten et al 2005). Compared to restorations with an implant/
abutment matched diameter, which were typically reported to lose 1.5 to 2.0 mm of crestal bone after the first year of function, implants restored with platform shifting have noticeably less alveolar crestal bone remodelling (Fradeani 2004, Lazzara & Porter 2006, Huerzeler et al 2007). The biological width around the neck of a tooth or a dental implant constitutes a mucosal seal intended to offer protection to the underlying bone. It is generally formed apical to the prosthetic interface and requires a minimum of 1.5 mm of fibrous connective tissue between the bone and epithelial attachment of the gingival sulcus of tooth or implant.

Shifting the platform to a smaller diameter at the interface contributes a horizontal component to the establishment of the biological width that has mainly a vertical fashion. The development of the biological width mainly in a horizontal fashion instead of a vertical one, increasing the distance between the abutment and the bone crest, will minimize the short and long term bone resorption, helping to maintain stable soft tissue margins. Furthermore the platform shifting concept, providing a narrower diameter prosthetic component on a wider diameter implant platform, creates an exposed ridge on the implant platform for soft tissue development. The stability of crestal bone and peri-implant mucosa/papillae is strongly dependent on their volume and respective vascularisation and blood supply. A higher amount of tissue volume and vascularisation will lead to more stable crestal bone and interdental papilla. By increasing volume and vascularisation of hard and soft tissues, the platform shifting design is contributing to tissue stability and an aesthetic outcome of the gingiva and interproximal papilla.

A recent systematic review of 10 controlled clinical trials, comparing the outcomes of platform-switched dental implants with those of matched-diameter prostheses, demonstrated statistically significant less bone marginal level changes in the platform switching group (Cappiello et al 2008, Prosper et al 2009, Vigolo & Givani 2009, Atieh et al 2010, Canullo et al 2010). The range of the marginal bone loss in test and control groups was 0.055 to 0.99 mm and 0.19 to 1.67 mm respectively, with a follow-up period between 12 and 60 months. The meta-analysis concluded that marginal bone loss around platform-switched implants was significantly less than around platform-matched implants. In terms of failure rates, implants with or without platform switching performed similarly.

**Implant diameter**

The choice of correct implant diameter should be related to the diameter of the root at the bone level. For example, for restoration of an upper central incisor, the diameter at the bone level ranges from 4 to 6 mm, therefore a central incisor should be restored with an implant of 4 to 5 mm implant platform. For the thin scalloped biotype it is important not to exceed the root diameter size at the bone.

Figure 35. The use of an implant design with a tapered shape may reduce the risk of approximation of the adjacent roots, preserving the crestal bone from resorption due to surgical trauma injury and compromisation of the blood supply.
level in order to avoid crestal bone resorption (Figure 35).

**3D implant positioning**

The 3D implant positioning rationale requires an accurate positioning within the 3 dimensions of the space, whilst considering the three parameters which should be addressed in any implant procedures:

1. Osseous dimensions
2. Soft tissue dimensions
3. Restorative dimensions

An ideal balance between these key factors will allow the clinician to achieve complete biological integration of the implant-supported restorations.

The mesio-distal implant position in relation to the adjacent teeth and implants has a direct impact on the aesthetic outcome and hygiene maintenance, and thus on the long-term predictability of the entire implant treatment.

The implant should be positioned exactly in the middle of the available mesio-distal space in order to obtain a centrally positioned prosthesis, otherwise approximation or impinging of the interdental papilla with a blunting of the papilla and damage to the periodontium may occur. If the minimum distance is not observed it will jeopardize the tooth attachment, compromising the blood supply resulting in reduction or even the loss of the interproximal papilla. The optimal distance between an implant and a natural tooth should not be less than 1.5 mm (1 mm of sound bone and 0.25 mm the average measurement of the periodontal ligament). Is it possible to apply these guidelines in all the clinical situations? Is the safety zone concept valuable in each restorative space (Belser et al 2004)? In daily practice these guidelines are very often considered just sterile measurements; however every case should be approached on an individual basis, thorough a careful surgical and prosthetic evaluation (Figures 36-37).

**Implant design**

The use of an implant design with a tapered shape may reduce the risk of approximation

![Figures 36-37](image)

*Figures 36-37.* The implant should be positioned exactly in the centre of the available mesio-distal space in order to get a centrally positioned prosthesis. If the minimum distance is not respected this will jeopardize tooth attachment, compromising the blood supply, and will cause reduction or even loss of the interproximal papilla.
of the adjacent roots, preserving the crestal bone from resorption due to surgical trauma and the blood supply being compromised.

The rationale behind our treatment philosophy comes from the clinical experience of a variable thread implant design (NobelActive™, NobelBiocare), which has demonstrated significantly less bone loss (-0.16 ± 1.06 mm versus -0.85 ± 1.32 mm) and outstanding results in soft tissue integration with an overall improvement in papilla size and natural aesthetic outcome. This innovative implant design requires minimal osteotomy with reduced trauma to bone and the surrounding tissues (Figure 38). The osteotomy protocol is performed with smaller drills and only one drill is required in very soft bone or extraction sockets. The self-cutting feature and the reverse cutting flutes enable a gradual widening of the osteotomy. The variable thread design enhances bone expansion like sequential osteotomes, compacting the bone outwards. It is suitable for narrow ridges and condensing soft bone. Excellent primary stability is gained in the apical region and on the thread tips of the implant body, reducing the risk of bone overcompression. The distance between the thread tip and the narrow implant body creates an open space that enables high blood vascularization, and thus maximizes the volume of bone around the implant. The unique combination of design features enables easy insertion and high initial stability even in compromised bone situations, such as placement in extraction sites (Lang et al, 2007). The design features of the coronal portion are a back tapered coronal region and built-in platform shifting with a 0.25 mm wide flat shoulder and a dual-function internal tight prosthetic connection. The back tapered collar reduces stress in the upper cortical bone that may result in bone resorption. The coronal design allows bypassing of the cortical bone and elastic relapse of bone around the collar, which enables maximum alveolar bone volume around the implant for improved soft tissue support.

The clinical benefits due to a back tapered design and built-in platform shifting are:
1. Reduce high stress in the upper cortical bone.
2. Prevent cortical bone resorption.
3. Enable maximum bone volume.
4. Improve soft tissue support.
5. Increase volume into which soft tissue can grow.
7. Natural looking aesthetics.

The rationale behind the platform-shifting concept also needs to be applied in abutment shaping. The sub-gingival area of the

Figure 38. A variable thread implant design enables minimal osteotomy with minor trauma to bone and surrounding tissues.
The prosthetic abutment should have a concave shape, narrower compared to the shoulder area. Therefore the platform-shifting concept obliges to a wider flare of the prosthetic profile in order to compensate the difference between the medially shifted prosthetic interface and the cervical dimension of the missing tooth. The abutment should flare from the prosthetic interface with a concave fashion until reaching the final diameter of the cervical portion of the definitive restoration, being decided by the soft tissue contour (Rompen et al 2007) (Figure 39). The clinical behavior in the thin scalloped biotype mandates for a prosthetic emergence profile with smooth transition from the implant platform to the crown shape. The prosthetic conditioning of the peri-implant tissue has to be very gentle to avoid any kind of gingival recession (Figure 40). In the immediate post-extraction fashion application of the aforementioned guidelines will result in a free volume between the implant-abutment surfaces and the surrounding tissues that will be filled rapidly by new collagen. This minimally invasive approach will increase the soft tissue volume without the need for any kind of tissue grafting, but through enhancing the soft tissue recovering process around high

**Figure 39.** The abutment should flare from the prosthetic interface in a concave-convex fashion until reaching the final diameter of the cervical portion of the definitive restoration, being determined by the soft tissue contour.

**Figure 40.** In the thin scalloped biotype, prosthetic conditioning of the peri-implant tissue has to be very gentle in order to avoid gingival recession. In the immediate post-extraction method, the shape of the temporary and of the abutment will leave a free volume between the implant-abutment surfaces and the surrounding tissues that will be filled rapidly by new collagen. This minimally invasive approach will increase the soft tissue volume and 2 months after immediate loading the final prosthetic soft tissue conditioning can be commenced.
Implant treatment in the anterior maxilla

Figures 41-42. The fragile thin scalloped biotype is fully preserved at 3 years follow-up. The key to obtaining long term function and aesthetics is outstanding soft tissue integration of the implant supported restoration.

Figure 43. Bone crest stability at 3 year follow-up.

Figure 43. Bone crest stability at 1 year follow-up.

biocompatible surfaces. From the clinical perspective a highly tight and sealed connection reduces micro-movement and micro-leakage at the implant-abutment interface, avoiding contamination of the prosthetic interface. Therefore, the key to obtaining outstanding soft tissue integration, long term function and aesthetics is the biological seal that we can obtain around the collar of this new implant concept, which performs as a mechanical barrier against bacterial penetration and food impaction (Figures 41-44).

Conclusions

Demand is increasing for aesthetic restorations which challenge clinicians to recreate a state of harmony between natural teeth and implant supported restoration, which above all depends on the presence of healthy natural looking peri-implant soft tissue architecture. If the implants are considered a viable treatment option to prevent the sacrifice of sound tooth structure for fixed prosthodontics, a solely functional long-term outcome is no longer sufficient. Implant supported restorations, being the preferred treatment of choice, should have a result as aesthetically successful as or even better than that of conventional fixed prostheses. In order
to deliver a natural looking restoration

demands of clinicians are shifting toward a
more modern concept of implants focusing on
predictable osseointegration as well as soft
tissue integration.

A better understanding of the biological
features of periodontal tissue and an accurate
evaluation and assessment of the tissue biotype
will mandate the specific implant design and
surgical approach (Table 2).

<table>
<thead>
<tr>
<th>Biotype</th>
<th>Thick flat</th>
<th>Thin scalloped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gingival thickness</td>
<td>Thick</td>
<td>Thin</td>
</tr>
<tr>
<td>Keratinized tissue width</td>
<td>Wide</td>
<td>Narrow</td>
</tr>
<tr>
<td>Bone thickness SHAPE</td>
<td>Thick flat SHAPE</td>
<td>Thin scalloped SHAPE</td>
</tr>
<tr>
<td>Adjacent contact</td>
<td>Midcoronal (area)</td>
<td>Incisal point</td>
</tr>
<tr>
<td>Reaction to inflammation/injury</td>
<td>Periodontal pocket</td>
<td>Recession</td>
</tr>
<tr>
<td>Treatment outcomes</td>
<td>High predictability</td>
<td>Highly challenging</td>
</tr>
<tr>
<td></td>
<td>Low risk gingival recession</td>
<td>Soft tissue/more liable to slough</td>
</tr>
<tr>
<td></td>
<td>Traditional surgery</td>
<td>Minimally invasive guided surgery</td>
</tr>
<tr>
<td></td>
<td>Deep placement</td>
<td>Bone level</td>
</tr>
<tr>
<td></td>
<td>Optimal 3-D position</td>
<td>Optimal 3-D position</td>
</tr>
<tr>
<td>W/w</td>
<td>Platform shifting</td>
<td>Platform shifting</td>
</tr>
<tr>
<td>Immediate loading</td>
<td>Immediate loading</td>
<td>Immediate prosthetic conditioning</td>
</tr>
<tr>
<td>Immediate prosthetic conditioning</td>
<td>Concave/convex shape abutment</td>
<td>Concave shape abutment</td>
</tr>
<tr>
<td>W/w</td>
<td>Zirconia framework</td>
<td>Zirconia framework</td>
</tr>
<tr>
<td>Long term function &amp; aesthetic</td>
<td></td>
<td>Long term maintenance</td>
</tr>
</tbody>
</table>

Table 2. The effect of biotype on implant planning decisions.

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Chapter 14

The use of Minocycline-HCl ointment for root conditioning in periodontal surgery: A preliminary study

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Background

Root conditioning is a very important part of periodontal treatment and clinicians have begun to use many agents to treat root surfaces during periodontal surgery. The effect of periodontitis on root surfaces is detrimental to periodontal attachment, as the root surface structure is changed by the effects of toxic and other substances from periodontal pathogens (Aleo et al 1974, Polson & Caton 1982, Adriaens et al 1988). While mechanical root planing can effectively remove endotoxins from affected root surfaces, the smear layer created during the root planing will affect periodontal attachment (Jones & O’Leary 1978, Nishimine & O’Leary 1979, Polson et al 1984). Chemical root conditioning can be an adjunct to mechanical debridement. Microorganisms and toxins can be neutralized by antibiotics and reducing pH (Minabe et al 1994, Jeong et al 1994, Darhous et al 1995). Demineralization can then effectively remove the smear layer, expose dentinal tubules and part of the matrix proteins, which might improve the wound healing environment (Isokawa et al 1970, Garrett et al 1978, Polson et al 1984, Ririe et al 1980). Citric acid demineralization has also been reported to further remove remaining endotoxins from the root surface (Fine et al 1980). The classical root condition agents include citric acid, tetracycline and EDTA (Renvert & Egelberg 1981, Labahn et al 1992, Mayfield et al 1998, Kassab et al 2006).

Minocycline-HCl ointment is the paste form of minocycline and has both antibacterial and anticollagenase properties (Golub et al 1983, Greenwald et al 1987). The commercial preparation of minocycline ointment (Periocline®, Sunstar) has been used to treat dental diseases, such as recurrent periodontitis (Nakagawa et al 1991). Due to its ability to demineralize, it can be used as root conditioning agent and therefore may be a cost efficient and convenient adjunct to periodontal treatment.

This study aimed to investigate the effect of 2% minocycline-HCl ointment on root conditioning during periodontal flap surgery. A clinical trial was undertaken to observe the curative effect of periodontal flap surgery combined with root conditioning using minocycline ointment on periodontal healing.
Materials and methods

Patient selection

24 tooth sites were selected in this study after initial examination and informed consent was obtained. The patients selected were those with a diagnosis of chronic periodontitis and who had completed non-surgical treatment about 3 months prior. In each individual, the site was required to have probing pocket depth ≥6 mm, clinical attachment loss ≥5 mm and bleeding on probing. Tooth mobility was required to be less than degree III. The exclusion criteria were systemic diseases such as diabetes mellitus, allergy to tetracycline, smoker and pregnancy or lactation for women.

Experimental design

3 months following non-surgical periodontal therapy, tooth sites were randomly assigned to either a minocycline-HCl ointment (treatment) group or normal saline (control) group. Baseline measurements were made before surgery. All study sites underwent flap surgery with root conditioning using the prescribed agent before suturing. The periodontal parameters were measured again 3 months after surgery (Evaluation 1). The parameters measured were plaque index (PI; Silness & Löe), sulcus bleeding index (SBI; Muhlemann & Son), probing pocket depth (PPD), and clinical attachment level (CAL).

The process of this clinical trial is shown in Figure 1.

Surgical procedures

After local anesthesia and sterilization, the surgical sites underwent flap elevation, root and flap debridement, root surface conditioning, irrigation, suturing and dressing.

In order to protect the periodontal ligament, cotton floss was placed at the bottom of the bony defect. The root surface corresponding to the deep pocket was burnished with the prescribed agent (mino-ointment or normal saline) for 1 minute duration for 3 times, and irrigated sufficiently after each burnishing.

Figure 1. Clinical trial process
The use of Minocycline-HCl ointment for root conditioning in periodontal surgery: A preliminary study

Data analysis

All clinical parameters were entered into SPSS (17.0, USA) and Mean and SD value for the two groups were calculated. The difference between parameters before and after surgery was analyzed with Wilcoxon signed ranks test. The difference of parameter variation between treatment and control groups was analyzed with Mann-Whitney U test.

Results

This study included 24 surgical sites and of these, 20 sites (10 in treatment group and 10 in control group) have completed Evaluation 1.

Intra-group variations

Figure 2 presents the mean PI, SBI, PPD and CAL at baseline and Evaluation 1 in treatment and control groups. From baseline to Evaluation 1, the change of all parameters except PI and SBI in control group reached statistical significance, not only in the treatment group but also in the control group (Treatment group - PI: p>0.05, SBI: p<0.05, PPD: p<0.01, CAL: p<0.01; Control group - PI: p>0.05, SBI: p>0.05, PPD: p<0.01, CAL: p<0.05).

Inter-group differences

Figure 3 demonstrates the mean PI variation, BI, PPD and CAL reduction 3 months following flap surgery in the treatment and control groups. PI and BI changes between two groups were not significant. PPD reduction was 3.60±0.97 mm in the mino-ointment group and 2.40±0.84 mm in the normal saline group, with statistical significance (p<0.05); CAL reduction was 2.30±0.68 mm in the mino-ointment group and 0.80±1.03 mm in the normal saline group, also with statistical significance (p<0.01).

Discussion

The use of minocycline for periodontal treatment has been studied for years, but with a focus on non-surgical treatment. The use of minocycline as a root conditioning agent has been studied in only a few in vitro studies. Atilla and Baylas (1996) compared the demineralizing effect of citric acid, tetracycline-HCl and minocycline-HCl, and found that minocycline-HCl could demineralize Ca,P content and expose the collagen matrix on the root surface but showed less effectiveness than tetracycline-HCl and citric acid. Another study compared the efficacy of smear layer removal using tetracycline-HCl, doxycycline, minocycline, sumycin and saline, and found that tetracycline-HCl had the best effect, then doxycycline and minocycline which showed better results than sumycin and saline (Madison & Hokett 1997). The utilization of minocycline in flap surgery has not been reported in other literature.

The current study was carried out as a clinical trial. Minocycline-HCl ointment with a low PH value of 2.1 was selected in order to adequately demineralize the affected root surface. The clinical trial suggested that minocycline-HCl ointment can improve the clinical effect of flap surgery by increasing clinical attachment gain. Renvert and Egelberg (1981) found that flap surgery combined with citric acid root conditioning in intraosseous periodontal defects resulted in greater clinical attachment and bone levels (Renvert et al 1985). However, Erdinc and Efeoglu (1995) conducted a 4 week clinical trial in ten aggressive periodontitis patients and found that tetracycline conditioning of the root
Figure 2. Clinical periodontal parameters at baseline and Evaluation1. Each data set is represented as the Mean±SD (Mino-ointment group: n=10, Normal saline group: n=10; *P<0.05, #P<0.01, Non Parameters Wilcoxon signed ranks test.)

Figure 3. The inter-group differences of periodontal clinical parameters variations from baseline in Evaluation1. (Mino-ointment group: n=10, Normal saline group: n=10; *P<0.05, Non Parameters Mann-Whitney U test.)
The use of Minocycline-HCl ointment for root conditioning in periodontal surgery: A preliminary study

surfaces during flap surgery has no clinical detectable additional regenerative benefits. Another study has reported that citric acid conditioning may not be necessary in coronally positioned flap surgery with mandibular furcation involvement (Fuentes et al 1993). This difference might be related to the periodontal pocket type. The sites in the present study all included an intrabony defect discovered during flap surgery. Another possible reason is the low fluidity of minocycline-HCl ointment. The ointment form was convenient for operative purposes and the conditioned area was easily controlled, resulting in less damage to soft tissue and the periodontal ligament cells. Furthermore, cotton floss was placed at the bottom of intrabony defects to protect the periodontal membrane.

In the human oral environment, the two most important cell types for periodontal tissue healing are periodontal ligament cells (PDLC) and human gingival keratinocytes (HGK). PDLC creates new periodontal attachment which is called periodontal tissue regeneration and HGK leads to epithelial healing. A series study demonstrated that exposure of the collagenous matrix on the dentin surface can facilitate the attachment of a fibrin network that mechanically inhibited the downgrowth of gingival epithelium, which might lead to the formation of more new attachment (Polson & Proye 1982, Proye & Polson 1982a, Proye & Polson 1982b, Polson & Proye 1983). However, Vanheusden et al (1999) noted that conditioning the dentin with citric acid or minocycline promotes the attachment of human gingival keratinocytes and the reformation of a junctional epithelium (Vanheusden et al 1999). Therefore if root conditioning with minocycline ointment can improve fibroblast cell attachment and proliferation, it might also promote epithelial cells at the same time. So, in order to determine whether root conditioning with minocycline ointment can promote periodontal regeneration, co-culture with PDLCs and gingival epithelium is a future study direction.

Conclusion

The present study suggests that conditioning root surface with minocycline-HCl ointment tends to improve the curative effect of flap surgery. Considering the limited cases examined to date, the results should be confirmed by further study.

References


Chapter 15

Periodontal regeneration by FGF-2: Present status and future outlook

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Introduction

At present a variety of regenerative therapies are available in the field of periodontal therapy, such as bone grafts, guided tissue regeneration (GTR) and application of enamel matrix derivatives, all of which have achieved a measure of success. However, a number of issues with these techniques remain to be solved, including technique sensitivity, limitation of indications, predictability, and the longevity of outcomes.

In the 1990s, Langer and Vacanti (1993) developed the concept of tissue engineering, consisting three key elements: signaling molecules, scaffolds and stem cells (Figure 1). They proposed that the active introduction of one or more of the triad enables the induction of desirable tissue regeneration. In relation to periodontal regenerative therapy, the use of somatic tissue stem cells and/or progenitor cells within periodontal ligaments to act as “stem cells” has been demonstrated (Seo et al 2004). In order to enhance the outcomes of tissue regenerative therapy, it is crucial to stimulate the biological activities of these cells, and a physiologically efficient method for doing so is through the use of cytokines or growth factors. The ability of various recombinant cytokines to enhance periodontal tissue regeneration has been investigated in preclinical and clinical studies (Table 1). This chapter reviews the potential use of basic fibroblast growth factor (bFGF, FGF-2) to promote periodontal tissue regeneration, with a discussion of the current status and prospects of FGF-2 therapy.

In vivo analyses of effects of FGF-2 on periodontal regeneration

Fibroblast growth factor (FGF) was discovered in 1974 as a protein from bovine pituitary glands that strongly induces proliferative activity in fibroblasts (Gospodarowicz 1974). In 1984, two distinct proteins with different isoelectric points were fractionated from the pituitary extract using acidic and basic pHs, which became known as acidic FGF (aFGF, FGF-1) and basic FGF (bFGF, FGF-2), respectively (Bohlen et al 1984, Thomas et al 1984). A year later the entire amino acid sequence of bovine FGF-2 was determined, and the cDNA of human FGF-2 was cloned in 1986 (Esch et al 1985, Abraham et al 1986). FGF-2 has received particular attention in the field of regenerative therapy, as it stimulates various stem cells to proliferate while maintaining their multipotency and is a strong inducer of angiogenesis.

In order to evaluate the effectiveness of
1. PDGF-BB (platelet-derived growth factor) plus IGF-I (insulin-like growth factor-I)
2. BMP-2 (bone morphogenetic protein-2)
3. TGF-β (transforming growth factor-β)
4. OP-1 (BMP-7) (osteogenic protein-1)
5. BDNF (brain-derived neurotrophic factor)
6. FGF-2 (bFGF) (basic fibroblast growth factor)
7. PDGF-BB (platelet-derived growth factor) plus β-TCP (GEM21STM) (β-tricalcium phosphate)
8. GDF-5 (growth and differentiation factor-5)

Table 1. Periodontal regeneration by recombinant cytokines.
applying topical FGF-2 to induce periodontal tissue regeneration, a series of animal studies using beagle dogs and non-human primates were performed (Takayama et al 2001c, Murakami et al 2003c). The mandibular molars of beagle dogs and the first and second molars of non-human primates were utilized for experimentation. After elevation of mucoperiosteal flaps, class II furcation defects were surgically created and the exposed cementum removed by curettage, before vinyl polysiloxane impression material was placed in the defects to induce inflammation. Four weeks after the first surgery, a flap was raised to expose the inflamed furcation, granulation tissues were removed and the root surfaces curetted. A small round bur was used to make a horizontal groove on each root in order to indicate the base of the defect. Furcation defects were filled with a gelatinous carrier with or without FGF-2 and the wound was surgically closed. Periodontal tissue regeneration at the test sites was examined at 6 and 8 weeks respectively, after FGF-2 application to the defects.

As shown in Tables 2 and 3, topical application of FGF-2 significantly stimulated periodontal regeneration in both the beagle and the non-human primate models when compared to control sites (Figure 2). Histological observation revealed new cementum with Sharpey’s fibers, new functionally-oriented periodontal ligament fibers and new alveolar bone (Takayama et al 2001, Murakami et al 2003a). Interestingly, enhancement of angiogenesis and regeneration of peripheral nerve fibers at the FGF-2 treated sites were also observed one week after FGF-2 application (Murakami 2011a).

More importantly, no epithelial downgrowth, ankylosis or root resorption was

<table>
<thead>
<tr>
<th>Control site (n=6)</th>
<th>0.1% FGF-2-applied site (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBF (%)</td>
<td>35.4 ± 8.9</td>
</tr>
<tr>
<td>NTBF (%)</td>
<td>16.6 ± 6.2</td>
</tr>
<tr>
<td>NCF (%)</td>
<td>37.2 ± 15.1</td>
</tr>
<tr>
<td>0.1% FGF-2-applied site (n=6)</td>
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</tr>
<tr>
<td>NBF (%)</td>
<td>83.6 ± 14.3 *</td>
</tr>
<tr>
<td>NTBF (%)</td>
<td>44.1 ± 9.5 *</td>
</tr>
<tr>
<td>NCF (%)</td>
<td>97.0 ± 7.5 *</td>
</tr>
</tbody>
</table>

*: p<0.01, Control site - gelatinous carrier alone was applied.

Table 2. Efficacy of FGF-2 for periodontal tissue regeneration in animal models - Furcation class II model in beagle dogs (6-week follow up) (modified from Murakami et al 2003).

<table>
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<td>NBF (%)</td>
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<tr>
<td>NTBF (%)</td>
<td>31.6 ± 3.5</td>
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<tr>
<td>NCF (%)</td>
<td>38.8 ± 8.6</td>
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<tr>
<td>NBF (%)</td>
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<tr>
<td>NTBF (%)</td>
<td>48.7 ± 8.9 **</td>
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<td>NCF (%)</td>
<td>72.2 ± 14.4 **</td>
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</tbody>
</table>

*: p<0.05, **: p<0.01, Control site - gelatinous carrier alone was applied.

Table 3. Efficacy of FGF-2 for periodontal tissue regeneration in animal models - Furcation class II model in non-human primates (8-week follow up) (modified from Takayama et al 2001).
observed at the FGF-2 sites in any of the *in vivo* experiments, nor was any severe gingival inflammation or swelling observed at any of the sites examined throughout the experimental periods.

**In vitro analyses of effects of FGF-2**

It has already been demonstrated that FGF-2 promotes proliferation of fibroblasts and osteoblasts, and enhances angiogenesis. These activities are crucial in the process of periodontal tissue regeneration. However, periodontal ligament (PDL) cells also play an important role during periodontal tissue regeneration (Lekic *et al* 2001, Murakami *et al* 2003b, Shimono *et al* 2003, Seo *et al* 2004). To reveal the molecular and cellular mechanisms by which FGF-2 enhances periodontal tissue regeneration, a series of *in vitro* experiments using PDL cells were carried out.

RT-PCR experiments demonstrated that PDL cells express FGF receptor (FGFR) 1 and FGFR2 mRNA, and *in vitro* experiments revealed that FGF-2 regulates the proliferation, differentiation, migration and extracellular matrix (ECM) production of PDL cells (Takayama *et al* 1997, Takayama *et al* 2002, Shimabukuro *et al* 2005, Shimabukuro *et al* 2008, Terashima *et al* 2008, Shimabukuro *et al* 2010). FGF-2 also enhances the proliferative responses of PDL cells via the extracellular signal-regulated kinase (ERK) 1/2 signaling pathway, an important second messenger system downstream of FGFRs. Interestingly it was found that FGF-2 significantly decreased both ALPase activity and the formation of calcified nodules in PDL cells in a dose-dependent manner. However, the suppressive effect of FGF-2 on PDL cell differentiation into hard-tissue-forming cells such as osteoblasts and cementoblasts was reversible. Thus, when FGF-2 stimulated PDL cells were re-cultured in the absence of FGF-2, calcified nodule formation resumed. By temporarily inhibiting the differentiation of PDL cells, FGF-2 facilitates their proliferation while maintaining their multipotency, but once the influence of FGF-2 is biologically diminished immature PDL cells begin to differentiate into osteoblasts and

*Figure 2. Periodontal tissue regeneration by FGF-2 (furcation class II beagle model).* FGF-2 (0.1%) plus gelatinous carrier was topically applied to surgically-created class II furcation defects in the mandibular molars of beagle dogs. Representative images at (A) baseline and (B) 6 weeks after FGF-2 application are shown. Arrow indicates furcation (from Murakami *et al* 2003).
FGF-2 also stimulated significant migration of PDL cells, even when their proliferation was completely inhibited by mitomycin-C. Furthermore, it was shown that FGF-2 stimulates the biosynthesis of hyaluronan (HA) and the cell surface expression of CD44, and that the interaction between these molecules plays a crucial role in PDL cell migration (Shimabukuro et al. 2010).

This series of in vitro studies have facilitated the development of a hypothesis on the mode of action of FGF-2. Thus, during the early stages of periodontal tissue regeneration, FGF-2 stimulates proliferation of PDL cells while suppressing their differentiation (Figure 3). Then, during the subsequent healing process, when FGF-2 is no longer present at the administration site, PDL cells begin to differentiate into hard tissue-forming cells such as osteoblasts and cementoblasts resulting in marked periodontal tissue regeneration at sites of FGF-2 application. In addition, FGF-2 induces the angiogenesis that is indispensable in the regeneration of tissue and regulates the production of osteopontin, heparan sulfate and HA from PDL cells (Takayama et al. 1997, Shimabukuro et al. 2005, Shimabukuro et al. 2008, Terashima et al. 2008). Notably, FGF-2 specifically promotes the production of high molecular weight HA, which plays an important role in cell migration and the early stages of wound healing (Shimabukuro et al. 2005). Based on the results described above, we concluded that FGF-2 contributes to the overall regeneration of periodontal tissue by

Figure 3. Possible mode of action of FGF-2 in induction of periodontal regeneration. During the early stages of periodontal tissue regeneration, FGF-2 stimulates the proliferation and migration of PDL cells while maintaining their multipotent nature, and in later stages induces their differentiation into hard-tissue-forming cells such as osteoblasts and cementoblasts. Furthermore, FGF-2 induces angiogenesis and increases the production of osteopontin, HS and macromolecular HA from PDL cells, creating a local environment suitable for the regeneration of periodontal tissue.
creating a local environment that facilitates the function of this mechanism (Murakami 2011b).

**Clinical trial of FGF-2 for periodontal tissue regeneration**

**Phase IIA clinical trial**

Given the promise shown by FGF-2 as a periodontal regeneration agent, we performed a Phase II clinical trial. Using data from animal trials, we estimated that an effective FGF-2 concentration for periodontal tissue regeneration is 0.03 to 0.3%. This concentration range was therefore applied in the Phase IIA trial.

We prepared gel-like investigational drugs using 3% hydroxypropylcellulose (HPC) as a vehicle. We then designed a double-blinded clinical trial with approximately 80 periodontitis patients from 13 dental facilities in Japan. Patients displaying a two- or three-walled vertical bone defect ≥3 mm from the top of the alveolar bone were registered for this clinical trial and randomly divided into four groups: Group P (Placebo), Group L (0.03% FGF-2), Group M (0.1% FGF-2) and Group H (0.3% FGF-2). Patients underwent flap surgery during which we administered 200 μl of the appropriate investigational drug to periodontal tissue defects. For efficacy analysis, standardized radiographs of the region of investigation were taken before and 36 weeks after administration of the investigational drug. The rate of increase in alveolar bone height was independently measured by five specialist dental radiologists who were blinded to the treatment each patient had received. The median of five measurements taken from the same image was then selected for efficacy analysis.

We observed that the mean alveolar bone height in Group H (0.3% FGF-2) gradually increased for 36 weeks after application (Figure 4). After 36 weeks, a significant increase ($p=0.021$) in alveolar bone height was seen on standardized radiographs between Group P (23.92%) and Group H (58.62%) (Figure 4) (Kitamura et al 2008). No serious adverse effects were seen during the course of this clinical trial. The data obtained from this clinical trial suggest that topical application of FGF-2 is efficacious in regenerating periodontal tissue in patients with two or three wall intrabony defects.

**Phase IIB clinical trial**

Having obtained positive results from the Phase IIA trial, we progressed to a Phase IIB trial (Kitamura et al 2011). In this large clinical trial, approximately 260 periodontitis patients from 25 dental facilities in Japan were registered, and were randomly divided into four groups comprising a placebo group and three FGF-2 groups (0.2, 0.3 and 0.4%). Results, in terms of efficacy and safety, were similar to the Phase IIA trial (Kitamura et al 2011, Murakami et al 2011a).

However, in both the Phase IIA and IIB trials, no significant differences in the regain of clinical attachment loss (CAL) between Group P and the FGF-2 groups were found. This is in agreement with observations reported in a clinical trial showing the efficacy of PDGF-BB plus β-TCP for periodontal regeneration (Nevins et al 2005). We speculate that differences may exist between Group P and the three FGF-2 groups in the histological ratio of fibrous and epithelial attachments achieving CAL acquisition.

**Future Outlook of FGF-2 therapy**

“Tissue engineering” is a fundamental concept in tissue regeneration. As mentioned above, we observed that topical application of FGF-2 significantly induces periodontal tissue regeneration, including fibrous attachment...
Figure 4. Rates of increase in alveolar bone height in cases of 2- and 3-walled intrabony defects. We compared rates of increase in alveolar bone height at 36 weeks after FGF-2 administration among Group P (Placebo; n=19), Group L (0.03% FGF-2; n=19), Group M (0.1% FGF-2; n=19) and Group H (0.3% FGF-2; n=17). Graph shows mean rates of increase in alveolar bone height (%) ± standard deviation. While no significant difference was observed between Groups L, M and P, Group H showed significantly ($p = 0.021$) increased alveolar bone height in the bone defect region compared to Group P. (Modified from Kitamura et al 2008)

Figure 5. Ideal FGF-2 carrier for periodontal tissue regeneration. An FGF-2 carrier that could provide a formable and osteoconductive scaffold for undifferentiated cell types within periodontal ligament would dramatically increase the indications of an FGF-2-based drug.
and neogenesis of alveolar bone and cementum in animal models. It is also noteworthy that no gingival epithelial downgrowth was observed at sites to which FGF-2 was applied. In the clinical trials of 0.3% FGF-2, we observed significant differences in the rate of increase in alveolar bone height between the placebo group and the FGF-2 group (Kitamura et al 2008, Kitamura et al 2011). This suggests that FGF-2 is efficacious for periodontal regeneration of intraosseous bone defects such as two or three wall bone defects and probably furcation involvements. However, to treat severe bony defects such as one wall or horizontal bone defects with FGF-2, the FGF-2 carrier may require the function of a “scaffold” to reinforce/direct its actions. HPC, which was used in our clinical trials as a carrier, does not function as a scaffold. Development of an FGF-2 carrier that provides a formable and osteoconductive scaffold for undifferentiated cell types would dramatically increase the indications of FGF-2 drugs beyond dental applications and into the craniofacial field (Figure 5). We recently examined the combined effects of FGF-2 and β-TCP on periodontal regeneration in one wall bony defects in beagle models and found that the combination induced significant periodontal tissue regeneration, compared with β-TCP alone (Anzai et al 2010). This suggests that the combination of scaffold material(s) and bioactive molecule(s) such as FGF-2 could be useful for the treatment of severe cases.

The efficacy of “cytokine therapy” in periodontal tissue regeneration was first reported in the 1990s. Since then, various recombinant cytokines have been investigated for their efficacy (and safety) in stimulating periodontal tissue regeneration, however few have been approved for use in the dental field. Therefore, we need to evaluate carefully the usefulness and safety of cytokine therapy in stimulating periodontal tissue regeneration. We hope that our work, together with future investigations, will provide a framework within which to understand “cytokine therapy” and its application to periodontal regeneration and oral reconstruction. Furthermore, “stem cell therapy” may also assist in improving periodontal regenerative therapy. It has already been reported that transplantation of bone marrow-derived cells or adipose-tissue derived stem cells can enhance periodontal regeneration (Murakami 2011b). The combined effects of “cytokine therapy” and “stem cell therapy” still require investigation.

**Acknowledgments**

We would like to thank Dr M Takedachi and Dr H Oohara for their helpful discussion. We are grateful to all of the investigators and patients for their important contributions to the clinical trials. The studies in this review were supported in part by Grants-in-Aid for Scientific Research, Grants-in-Aid from the Ministry of Health, Labour and Welfare and research funding from Kaken Pharmaceutical Co Ltd.

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Chapter 16

Periodontal health status and quality of life

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Introduction

There has been significant interest in Quality of Life (QoL) in a medical context for its importance in the assessment and evaluation of health status. QoL usually refers to the total wellbeing of an individual and society. The World Health Organization (WHO) defined QoL as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns' (WHOQOL Group 1995).

The concept of health-related QoL (HRQoL) was developed in the healthcare field, where health was defined as 'a state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity' (WHO 1946). HRQoL is a multidimensional concept which includes physical, social, and psychological impacts related to a disease, a disability, or a disorder (Revicki 1989). Medical treatments can be effective in improving health status but not necessarily result in better HRQoL (Gill 1994). Some patients with chronic illness reported better QoL than healthy people (Allison et al 1997). Therefore, HRQoL is regarded as a dynamic concept with subjectivity and variability.

It has been reported that aging, illness, and physical disability play an important role in decreasing the level of wellbeing of older Americans (Larson 1987). Chronic diseases such as diabetes or hypertension are the leading causes of disability and mortality within the aging population (WHO 2003). A health policy for improvement of QoL seemed to reduce disability caused by chronic diseases in older people (Pusca et al 2002). The WHO emphasized the necessity of health promotion for older people and proposed “Active Ageing,” which minimized risk factors for chronic diseases and functional declines, and maximized protective factors (WHO 2002).

Common risk factors exist between chronic diseases and oral diseases. Oral diseases in the elderly can have a critical impact on general health conditions. Petersen et al (2005) stated that oral health status was closely related to nutritional conditions, infection, and prevention from injury. It was reported that 75% of adults in the United Kingdom perceived oral health as being important to QoL (McGrath et al 2004). It has been suggested that promotion of oral health could lead to improved QoL in the elderly through recovery of self-esteem, activation of social relationships and the restoration of working ability (Shtereva 2006).

Locker (1988) suggested the model of oral
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Oral diseases can lead to impairment such as tooth loss, which may lead to functional limitations such as difficulties in chewing, or discomfort and pain. This may cause a physical or psychological disability such as avoiding foods and subsequently to handicaps such as social isolation. This serial phenomenon may compromise the overall QoL.

Oral health can be considered as an independent factor for the wellbeing of the elderly, in addition to life circumstances and general health (Locker et al 2000). The cost of dental treatment can be an additional burden, especially in the elderly. The necessity of an individual-based assessment of oral health status led to the development of various instruments for measuring QoL related to oral health status, termed Oral Health-Related QoL (OHRQoL).

It has been suggested that the assessment of OHRQoL should be considered in evaluating the effects of periodontal treatments (Hujoel 2004). However, there have been limited studies on the relationship between OHRQoL and periodontal diseases (Needleman et al 2004, Ng et al 2006, Jang et al 2006, Jang 2007, Saito et al 2010). The results of these studies support the importance of periodontal health status in contributing to overall OHRQoL.

**Instruments for OHRQoL**

The majority of instruments for measuring OHRQoL have been developed on the basis of a multi-dimensional concept of OHRQoL. The Social Impact of Dental Disease (SIDD) was one of the first socio-dental indicators developed for evaluating the social and psychological impacts of dental disease (Cushing et al 1986). It consisted of five categories with dental impact: eating restrictions, communication restrictions, pain, discomfort and aesthetic dissatisfaction. It simply indicated the presence or absence of each category, but it did not measure its severity.

![Diagram of locker's model of oral health](image)

Figure 1. Locker's model of oral health (Locker 1988)
The Geriatric Oral Health Assessment Index (GOHAI) is another simple measurement for estimating the degree of psychological impacts related to oral diseases in the elderly (Atchison et al 1990). It is composed of 12 questions grouped under three dimensions such as physical function, psychosocial function and pain or discomfort (Table 1). Subsequently, because of its reliability and validity in all age groups, it was renamed the General Oral Health Assessment Index (Atchison 1997).

The Oral Health Impact Profile (OHIP) was developed on the basis of Locker’s oral health model, which was based on the WHO international classification of impairments, disabilities and handicaps (WHO 1980, Locker 1988, Slade et al 1994a). Although prior to this there were no standard instruments for measuring OHRQoL, Robinson et al (2003) stated that OHIP expressed dental problems, pain and self-reported oral health status better than other instruments. OHIP provided comprehensive measurements for seven dimensions such as functional limitation, pain, psychological discomfort, physical disability, psychological disability, social disability and handicap.

### The General Oral Health Assessment Index

1. How often did you limit the kinds or amounts of food you eat because of problems with your teeth or dentures?
2. How often did you have trouble biting or chewing any kinds of food, such as firm meat or apples?
3. How often were you able to swallow comfortably?
4. How often have your teeth or dentures prevented you from speaking the way you wanted?
5. How often were you able to eat anything without feeling discomfort?
6. How often did you limit contacts with people because of the condition of your teeth or dentures?
7. How often were you pleased or happy with the looks of your teeth and gums, or dentures?
8. How often did you use medication to relieve pain or discomfort from around your mouth?
9. How often were you worried or concerned about the problems with your teeth, gums, or dentures?
10. How often did you feel nervous or self-conscious because of problems with your teeth, gums, or dentures?
11. How often did you feel uncomfortable eating in front of people because of problems with your teeth or dentures?
12. How often were your teeth or gums sensitive to hot, cold or sweets?

Table 1. Questions for GOHAI (Atchison et al 1990).
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OHRQoL can complement traditional epidemiologic surveys on clinical diseases, gives information about the personal burden of disease and informs the efficacy of health policy (Slade 1997). OHIP has been shown to have an appropriate reliability without showing cultural bias and to have acceptable validity in most countries (Slade 1994b, Allen et al 1997). The item weights and magnitudes of OHIP were compared among Australians, English-speaking Canadian and French-speaking Canadians (Allison et al 1999). Even though the magnitudes were quite different, the item weight rankings were similar. This result supported a reasonable degree of cultural consistency for OHIP. Slade (1997) introduced a short-form of OHIP with good reliability, validity and precision (Table 2).

Other instruments for evaluating OHRQoL such as the Dental Impact Profile, the Subjective Oral Health Status Indicators, the Oral Health-Related Quality of Life Measure

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**Table 2.** Questions for OHIP-14 (Slade 1997).

1. Have you had trouble pronouncing any words because of problems with your teeth, mouth or denture?
2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth, or dentures?
3. Have you had painful aching in your mouth?
4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth, or dentures?
5. Have you been self-conscious because of your teeth, mouth, or dentures?
6. Have you felt tense because of problems with your teeth, mouth, or dentures?
7. Has your diet been unsatisfactory because of problems with your teeth, mouth, or dentures?
8. Have you had to interrupt meals because of problems with your teeth, mouth, or dentures?
9. Have you found it difficult to relax because of problems with your teeth, mouth, or dentures?
10. Have you been a bit embarrassed because of problems with your teeth, mouth, or dentures?
11. Have you been a bit irritable with other people because of problems with your teeth, mouth, or dentures?
12. Have you had difficulty during your usual jobs because of problems with your teeth, mouth, or dentures?
13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth, or dentures?
14. Have you been totally unable to function because of problems with your teeth, mouth, or dentures?

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and the Dental Impact on Daily Living have been developed (Strauss et al. 1993, Locker et al. 1994a, Kressin et al. 1996, Leao et al. 1996).

The effects of socio-demographic factors on OHRQoL

Due to its subjectivity and variability, OHRQoL can be influenced by various social and environmental factors and it has been agreed that economic factors influence OHRQoL. Locker (1992) reported that a low income group suffered more psychosocial impacts after controlling for other variables. Poor financial status combined with poor oral health was proven to have more negative effects on OHRQoL (Locker et al. 1994b, Locker et al. 2000). In general, higher socioeconomic groups were found to have better OHRQoL than their counterparts (McGrath et al. 2000). In a study targeting elderly Koreans, economic ability was found to be a significant factor for OHIP-14 while age and gender failed to be significant factors (Jang et al. 2006).

Educational level is another factor which should be considered in measuring OHRQoL since it has been found to influence oral conditions (Paulander et al. 2003). However, John et al. (2004) reported that level of education had a negligible influence on OHRQoL compared to denture status.

The effect of age on OHRQoL has rather inconsistent results. Although older people often experience various daily problems in association with oral diseases, the significance of oral health is often ignored in daily living compared to other socioeconomic conditions (Locker 1992, Locker et al. 2000). McGrath et al. (2000) reported that younger people reported better OHRQoL in the United Kingdom, however Srisilapanan et al. (2001) stated that older people were found to have less dental impacts on daily performance in an older Thai population. This inconsistency may be the result of cultural differences between Thailand and the United Kingdom.

Cultural differences in OHRQoL have been examined. It was reported that edentulous patients in Hong Kong exhibited more restrictions on daily living such as diet but were less concerned about their appearance without dentures than those in the United Kingdom (Scott et al. 2001). Steele et al. (2004) concluded that cultural backgrounds were important factors in OHRQoL after comparing OHIP-14 between both Australian- and British-born groups.

Personal coping with stress was thought to be another predictor of OHRQoL. A person with a better coping style can manage daily problems effectively and perceive better QoL. Heydecke et al. (2004) reported that a coping style utilizing emotional support was a positive predictor of OHRQoL whilst other styles such as instrumental support, behavioral disengagement, substance abuse, denial or religion had negative effects on OHRQoL.

As the term ‘socio-dental indicators’ was used before the phrase OHRQoL was introduced, the effects of socio-demographic factors should be considered as essential factors in evaluation of OHRQoL for dental therapeutic outcomes.

OHRQoL in clinical dentistry

Traditional approaches to evaluate oral health status have utilized objective clinical outcomes related to oral health conditions. However, there is a move toward assessing non-clinical outcomes of dental treatments such as subjective self-reports or psychological impacts. Buck et al. (2001) stated that there were more than 1000 published articles during the 10 year period from 1988 to 1998 based on non-clinical outcomes in dentistry. Researchers became interested in the question of whether dental treatments were effective in the improvement
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In general, there are complex problems in longitudinal studies about OHRQoL. For example, tooth loss decreased masticatory function, but removed pain, resulting in a simultaneous improvement and decline of OHRQoL (Slade 1998). Cultural differences and other confounding factors may compromise reliability and validity of the studies. The results should be interpreted with caution.

There are several studies that have reported the effect of dental treatments on OHRQoL (Strassburger et al 2004). Edentulous patients with implant-supported overdentures reported better OHRQoL than those with conventional dentures (Awad et al 2000, Allen et al 2001, Heydecke et al 2003). New dentures could improve patient satisfaction but failed to increase OHRQoL (Forgie et al 2005). Intravenous antibiotic administration before third molar surgery was found to have little effect on HRQoL while it reduced clinical recovery (Foy et al 2004). It was reported that OHRQoL deteriorated immediately after third molar surgery and then gradually improved over months (McGrath et al 2003). While the numbers of studies on OHRQoL are still insufficient, most researchers agreed that it is necessary to assess what a patient really feels and experiences regarding ongoing dental treatment.

**Periodontal status and OHRQoL**

Like other fields of dentistry, OHRQoL involves the field of periodontology. Needleman et al (2004) reported the relationships between periodontal health status and OHRQoL among 205 periodontal patients in the United Kingdom. They used the UK oral health-related quality of life measure (OHIQoL-UK) developed by McGrath et al (2000) to assess OHRQoL. To evaluate subjective periodontal symptoms, subjects marked ‘yes’ or ‘no’ in seven categories such as swollen gums, sore gums, receding gums, loose teeth, drifting teeth, bad breath and toothache. OHQoL-UK was found to be negatively associated with the existence of subjective periodontal symptoms. Patients with deeper probing depths (≥5 mm) reported worse OHQoL-UK than those with shallower probing depths (≤4 mm). Periodontal maintenance patients were found to have better OHQoL-UK than new patients. The authors stated that the prevalence of the impact of periodontal health on OHRQoL was high and that the use of patient-orientated outcomes in periodontology might be necessary in the assessment and evaluation of periodontal care.

A study evaluated the effects of different treatment protocols for chronic periodontitis on oral health impacts (D’Avila et al 2005). The subjects were 60 periodontitis patients in Brazil. They were randomly assigned to one of following groups; Group 1, Scaling and Root Planing (SRP) plus systemic antibiotic (metronidazole) administration (SRP + Met); Group 2, SRP with periodic supragingival plaque removal (PP); Group 3, SRP plus Met with PP, Group 4, SRP plus placebo capsules (control group). Patients’ oral health impacts such as gingival bleeding, halitosis, sensitivity to cold or hot, aesthetic dissatisfaction and eating and social restriction were collected at baseline and 3 months after SRP. A similar reduction in the amount of psychosocial impacts were found after periodontal treatments regardless of treatment protocols, in addition to clinical improvements.

Ng et al (2006) investigated the relationship between OHRQoL and clinical periodontal attachment level (CAL) among 767 Chinese adults. The Chinese short-form of OHIP (OHIP-14S) was utilized as measurement for OHRQoL. Self reported periodontal symptoms were checked as per the previous study by Needleman et al (2004). Periodontal symptoms except drifting tooth
were significantly associated with OHIP-14S. Clinical periodontal attachment loss (CAL) was also found to be related to OHRQoL. The subjects with CAL \(<2\) mm were found to have better OHRQoL than those with CAL \(>3\) mm (Ng et al 2006). The subjects in that study were not regular dental patients and 75\% of them had not visited a dental clinic within a year. Despite not only cultural differences but a difference in study population between this study and the Needleman et al (2004) study, both studies clearly supported relationships between periodontal health and OHRQoL.

A series of studies targeting elderly Koreans aged 60 or older were conducted to evaluate the effect of periodontal health status on OHRQoL (Jang et al 2006, Jang 2007). The first study was a cross-sectional survey in which 421 elderly Korean from three different types of senior institutions were requested to undertake oral examinations and complete questionnaires on the OHIP-14 and current periodontal health status such as periodontal symptoms, self-rated periodontal health and periodontal treatment needs (Jang et al 2006). Seven periodontal symptoms were checked as a same manner as the previous studies (Needleman et al 2004, Ng et al 2006). Self-reported periodontal health was measured in a five point Likert scale and periodontal treatment need was marked ‘yes’ or ‘no’. The Korean version of OHIP-14 was utilized in order to assess oral health-related QoL (Bae et al 2007). Answers were presented with five point Likert scale; ‘never’ (0), ‘hardly ever’ (1), ‘occasionally’ (2), ‘fairly often’ (3), ‘very often’ (4). The summary OHIP scoring method was used, however item weighting was not used in calculating OHIP-14 score because of its nonsignificant effect (Allen et al 1997). There were significant differences in OHIP-14 scores between the presence and absence of each periodontal symptom such as swollen gums, sore gums, receding gums, loose teeth, drifting teeth, bad breath and toothache (Table 3). Lower OHIP-14 scores (signifying better OHRQoL) were found in those subjects who reported less number of periodontal symptoms, better self-reported periodontal health and no need of periodontal treatment (Table 4). After adjustment for age, gender, types of institution, financial security and number of teeth present, multivariate analysis revealed that numbers of periodontal symptoms, self-reported periodontal health and periodontal treatment need were significantly associated with OHIP-14.

In the second study, 83 chronic periodontitis patients, aged 60 or older, who had scaling and root planing (SRP) as non-surgical periodontal treatment in the Department of Periodontology at the Seoul National University Dental Hospital were examined (Jang 2007). Each subject completed the questionnaire at an initial examination and at least 30 days after SRP. The number of present teeth and Community Periodontal Index (CPI) were recorded through oral examination. The socio-demographic questionnaire included questions regarding gender, age, smoking behavior, alcohol drinking, diabetes, education, marital status, income and financial security. A modification of Leake’s index of chewing capacity was used to check the number of masticable foods among seven different types of food (Leake 1990). Campbell’s index of well-being was also used to measure general quality of life (Campbell 1981). All subjects reported their current periodontal health status and OHIP-14 in the same manner as the previous study (Jang et al 2006). Number of present teeth and masticable foods were both statistically associated with OHIP-14 scores at baseline. Tooth loss was reported to be an important factor which decreased QoL in other studies (Gilbert 2005, Wong et al 2005). Decreases in OHIP-14 scores after SRP were not statistically significantly different among each group when divided by various socio-
### Table 3. Self-reported periodontal symptoms and OHIP-14 (Jang et al 2006).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>OHIP-14* Mean (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen gums</td>
<td>Yes (n=163)</td>
<td>11.5 (10.2-13.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=192)</td>
<td>4.0 (3.2-5.3)</td>
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<tr>
<td>Sore gums</td>
<td>Yes (n=171)</td>
<td>12.2 (10.9-13.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=183)</td>
<td>3.6 (2.9-4.4)</td>
<td></td>
</tr>
<tr>
<td>Receding gums</td>
<td>Yes (n=122)</td>
<td>12.2 (10.2-13.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=232)</td>
<td>4.8 (4.0-6.2)</td>
<td></td>
</tr>
<tr>
<td>Loose teeth</td>
<td>Yes (n=135)</td>
<td>10.9 (9.0-12.2)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=216)</td>
<td>5.3 (4.0-6.2)</td>
<td></td>
</tr>
<tr>
<td>Drifting teeth</td>
<td>Yes (n=106)</td>
<td>10.2 (8.4-12.9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=247)</td>
<td>5.7 (4.8-6.7)</td>
<td></td>
</tr>
<tr>
<td>Bad breath</td>
<td>Yes (n=173)</td>
<td>10.2 (9.0-11.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>No (n=183)</td>
<td>4.4 (3.6-5.7)</td>
<td></td>
</tr>
<tr>
<td>Toothache</td>
<td>Yes (n=187)</td>
<td>9.6 (8.4-10.9)</td>
<td>&lt;.0001</td>
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<tr>
<td></td>
<td>No (n=163)</td>
<td>4.4 (3.6-5.7)</td>
<td></td>
</tr>
</tbody>
</table>

* Reversed to original OHIP-14 after being analyzed as square-root transformed scale.

### Table 4. Bivariate associations between OHIP-14 scores and periodontal health status (Jang et al 2006).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OHIP-14* Mean (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of Periodontal symptoms</td>
<td>0-1</td>
<td>3.2 (2.2-4.4)a**</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>5.2 (3.6-7.2)b</td>
</tr>
<tr>
<td></td>
<td>4&lt;</td>
<td>12.9 (10.2-15.2)c</td>
</tr>
<tr>
<td>Self-reported periodontal health</td>
<td>Good</td>
<td>3.2 (1.6-4.8)a</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>4.4 (2.8-5.7)a</td>
</tr>
<tr>
<td></td>
<td>Bad</td>
<td>11.5 (9.6-13.6)b</td>
</tr>
<tr>
<td>Periodontal treatment need</td>
<td>Yes</td>
<td>11.5 (9.6-12.9)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4.0 (2.8-4.8)</td>
</tr>
</tbody>
</table>

* Reversed to original OHIP-14 after being analyzed as square-root transformed scale.

** Different letters mean significantly different means at significance level 0.05
demographic characteristics. There was a statistically significant difference between the mean OHIP-14 scores before and after SRP. Patients reporting five or more periodontal symptoms, periodontal health above average and no need for periodontal treatments had significantly lower OHIP-14 scores than their counterparts at baseline. A similar result was reported by Slade et al (2004) who compared patients who were scheduled for third molar surgery. The patients with symptoms such as pain or swelling had more adverse impacts on OHRQoL than asymptomatic patients. After SRP, self-reported periodontal health status improved significantly and periodontal treatment need decreased significantly. Self-reported periodontal symptoms did not disappear significantly after SRP, except “sore gums” which decreased significantly. There was, however, a statistically significant decrease in total number of periodontal symptoms after SRP. The decrease in number of periodontal symptoms was statistically associated with the decrease in OHIP-14. CPI decreased significantly after SRP but did not have a statistically significant association with OHIP-14 before or after SRP. Periodontal treatment improved not only OHRQoL but also general QoL (Jang 2007). In addition, periodontal treatment needs decreased after SRP but did not influence subjective periodontal health status and periodontal symptoms.

Saito et al (2010) reported the effect of periodontal therapy on OHRQoL in Japanese periodontitis patients. They selected 58 patients (mean age = 53.6 years) who undertook initial periodontal therapy such as oral hygiene instructions and SRP. They measured OHRQoL using the oral health-related QoL model for dental hygiene (OHRQL) which was introduced by Williams et al (1998). OHRQL scores were improved significantly after initial periodontal therapy, regardless of baseline disease activity.

Self-reported periodontal symptoms were found to have significant association with OHRQoL (Needleman et al 2004, Jang et al 2006, Ng et al 2006). Cunha-Cruz et al (2007) reported that OHRQoL was negatively affected by perceived oral health in patients referred to a periodontist. From the validity study of self-reported periodontal health status, it was found that people who have periodontitis had statistically significantly more bleeding on probing and more periodontal pockets with probing depths 4 mm or greater than their counterparts (Buhlin et al 2002). Tooth mobility was not associated with clinical examination and self-reports. They suggested that self-reported periodontal status could be used for epidemiologic studies. Self-reported periodontal health was usually associated positively with clinical periodontal examinations (Glavind et al 1979, Joshipura et al 1996, Unell et al 1997). Some people were shown to be unaware of their oral health status (Gilbert et al 1999). This was explained by objective measurements such as dental caries or attachment loss not precisely reflecting the patient’s perception because of a weak association with a patient-orientated subjective evaluation of oral health status (Gooch et al 1989, Locker et al 1994). However, the effects of self-reported periodontal status seemed to correlate well with clinical periodontal examination data (D’Avila et al 2005).

It was indicated that OHRQoL varied with subjective periodontal health status (Jang 2007). Patients who needed periodontal treatment were shown to have lower OHRQoL. Other subjective periodontal health status indices such as self-reported periodontal health status and periodontal symptoms failed to show statistically significant differences from OHRQoL after adjusting for confounding factors. One possible explanation is that OHRQoL was influenced by patients’ perception of periodontal treatment need.
rather than simple awareness of their periodontal condition. That is, if patients need more periodontal treatment, they may experience worse OHRQoL regardless of their periodontal condition. Therefore, it can be assumed that their OHRQoL can be improved only after proper periodontal treatments are provided.

As socio-demographic factors were important factors in OHRQoL, the role of social factors such as ethnicity, education and socioeconomic environments were also found to be associated with periodontal health (Borrell et al 2006). These socio-demographic factors should be taken into consideration whenever the effects of periodontal health status on OHRQoL were evaluated. From the studies reviewed so far, there was an agreement of the effect of periodontal health status on OHRQoL regardless of socio-demographic factors. However, more studies are needed to verify the reliability and validity of periodontal effects on OHRQoL.

Conclusion

It can be concluded that periodontal treatments such as SRP can increase OHRQoL in elderly chronic periodontitis patients. While there are a lack of studies on periodontal status and quality of life in the elderly, the existing research on OHRQoL should be utilized as fundamental materials for establishing an oral health policy for older people. Moreover, health policy for prevention and treatment of periodontal disease should be developed in order to improve OHRQoL.

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A critical review of guided bone regeneration

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Principles of guided bone regeneration

The concept of guided bone regeneration (GBR) was first employed by Dahlin et al. (1988) to reconstruct the structure and function of lost bone tissue in critical sized mandibular defects in rats. Since then, it has been applied successfully to the treatment of different types of osseous defects in the maxilla and mandible, as well as the broader craniofacial region (Kostopoulos & Karring 1994a, Bosch et al. 1995, Donos et al. 2004, Donos et al. 2008, Retzepi & Donos 2010a). The biological rationale of GBR advocated the mechanical occlusion of undesirable soft tissues from proliferation into the osseous defect, thereby allowing osteogenic cells derived from the parent bone to repopulate the coagulum-filled osseous wound space (Dahlin et al. 1988, Nyman et al. 1991, Hammerle et al. 1995).

The ingrowth of soft connective tissue may inhibit osteogenesis in an osseous defect and lead to bone repair, rather than bone regeneration. It is imperative to distinguish the differences in the concepts of bone repair and regeneration. Bosch et al. (1995) defined bone repair as the reestablishment of tissue continuity in disrupted tissues by another tissue that is not able to fulfill the structural and functional characteristics of the lost tissues. On the other hand, bone regeneration requires a complete biological process that renews the architecture and function of lost bone (Melcher et al. 1969).

GBR therapeutic protocol

The GBR therapeutic protocol involves surgical placement of a cell occlusive membrane facing the bone surface, in order to physically seal off the skeletal site requiring regeneration (Dahlin et al. 1988). The membrane is able to create and maintain a secluded space, hence providing an environment for the osteoprogenitor cells where they are allowed to proliferate and differentiate into the osteoblastic cells (Karring et al. 1993, Lindhe et al. 1993a).

Currently, there are a wide range of membrane materials available to achieve successful GBR, either in the form of non-resorbable or resorbable materials. The desirable properties of barrier membranes used for GBR procedures should include biocompatibility, cell occlusion, integration by the host tissues, clinical manageability, limited susceptibility to complications and a space making ability (Karring et al. 1993, McAllister & Haghighat 2007). In addition, bioresorbable
membranes should not negatively influence regeneration during their degradation phase (Hammerle & Jung 2003).

**Non-resorbable membrane**

Expanded polytetrafluoroethylene (e-PTFE) has been the most frequently used material for periodontal and bone regeneration. An e-PTFE membrane is a non-resorbable, biocompatible and chemically stable polymer, which has sufficient porosity to allow nutrients and transudates through. It resists (up to a certain extent) microbiological and enzymatic degradation and does not elicit immunological reactions (Becmeur et al 1990). e-PTFE membranes have been widely and successfully applied in experimental and clinical regeneration studies, however the outcomes have been highly correlated with wound healing complications and post-operative microbial colonization and infection (Simion et al 1994, Zitzmann et al 1997, Donos et al 2002).

**Bioresorbable membrane**

Owing to the risk of early membrane exposure and the need for a secondary surgery for removal when using non-resorbable membranes, the use of bioresorbable membranes has been investigated. Several materials have been tested for periodontal and/or bone regeneration with varying success, including collagen type I, polyurethane, polyglactin 910, polylactic acid, polyglycolic acid, polylacto-hester and different copolymers of polylactic and polylactiglic acid (Sandberg et al 1993, Zellin et al 1995, Brunel et al 1998, Retzepī et al 2010). In addition to fulfilling all the basic characteristics of an occlusive membrane, the efficacy of the bioresorbable membrane depends on the degradation rate, which is influenced by many factors such as pH, temperature and polymer crystallization (Warrer et al 1992, Hammerle & Jung 2003). This, in turn, means that the duration of barrier function for the bioresorbable membrane is not strictly controlled, leading to possible negative effects on the wound healing and bone regeneration process. However several experimental and clinical studies demonstrated that GBR could be predictably accomplished using both bioresorbable and non-resorbable membranes (Zitzmann et al 2001, Donos et al 2002a, Donos et al 2002b, Donos et al 2004, Donos et al 2008)

**GBR treatment of critical size osseous defects**

The critical size osseous defect model has been used to evaluate the efficacy of different GBR related treatment modalities. It is defined as the minimum size of osseous defect that will not heal spontaneously with bone fill but instead with fibrous connective tissue (Schmitz & Hollinger 1986).

**Mandibular defects**

Dahlin et al (1988) were the first to apply the GBR principle in critical size mandibular bone defects in rats. Standardized 5 mm diameter transmandibular defects were created bilaterally, one serving as test and the other as control. The defects at the test sites were covered with e-PTFE membranes whilst on the contralateral control sites, no membranes were used. After 6 weeks of healing, histologic analysis revealed that the test sites had healed completely with bone fill, whereas the sham-operated controls showed partial healing of the periphery of the defects with bone, while the central portion of the defects healed mainly with connective tissue. These results indicated that the use of a membrane-like mechanical barrier isolates the osseous defects and hinders the invasion of the surrounding tissues, allowing bone forming mesenchymal cells to
repopulate and proliferate in the bone defects.

In another experimental animal study by Schenk et al (1994), similar results were reported. The study aimed to demonstrate the histological healing pattern of bone regeneration in membrane-protected mandibular osseous defects. In this study, saddle-type defects measuring approximately 8 x 12 x 10 mm were created 2 months after premolar extraction in dogs. Test defects were covered with e-PTFE membranes reinforced by polypropylene mesh and fixed with mini-screws. After healing periods of 2 and 4 months, the histological evaluation showed that membrane protection resulted in successful bone regeneration, whereas non-membrane protected sites showed a consistent repair pattern in which bone formation was restricted to the defect margins. It was also reported the maturation sequences of the regenerated bone closely resembled the pattern of bone development and growth (Schenk et al 1994).

An experimental model was developed in order to evaluate GBR treatment efficacy following application of a bioresorbable barrier membrane made of polyhydroxybutyrate (Kostopoulos et al 1994a). A 2 x 3 mm bone defect was created at the lower border of both mandibular rami of rats, and one side was covered with the bioresorbable membrane, while the contralateral side remained uncovered and served as control. The histological analysis showed gradual bone fill up to 85% of the initial defect depth at 180 days postoperatively in the test sites, whereas new bone formation in the non-GBR treated control sites was limited (Kostopoulos et al 1994a). In a subsequent study, it was reported that it is possible to produce significant amounts of bone in areas where bone has never existed before, and insufficient peripheral sealing of the membranes results in incomplete bone fill of the created space due to soft tissue invasion (Kostopoulos et al 1994b). The efficacy of the application of bioresorbable barrier membranes for the treatment of critical size mandibular defects has been further documented in various experimental models in rats and rabbits (Colangelo et al 1993, Sandberg et al 1993, Zellin et al 1995, Lundgren et al 1998).

**Calvarial defects**

The GBR principle has been further applied to promote bone regeneration in critical size calvarial osseous defects. Dahlin et al (1991) and Bosch et al (1995) demonstrated that the use of double layers of e-PTFE membranes protecting the bone edges of a parietal bone defect from the overlying and underlying soft tissues enhanced bone regeneration in experimental calvarial bone defects in rats. On the contrary, incomplete occlusion of the surrounding intracranial (dura mater) and extracranial soft tissues has been associated with impaired bone formation (Verna et al 2002). Similar observations were reported when only a pericranial non-resorbable membrane was used on calvarial defects of rabbits and rats (Hammerle et al 1992, Hammerle et al 1995). In addition, the effect of membrane collapse into the defects was studied and showed that diminished space availability for bone regeneration resulted in limited new bone formation (Lundgren et al 1998).

The use of bioresorbable membranes in calvarial defects also showed predictable bone regeneration in rabbits and rats (Lundgren et al 1992, Donos et al 2004). In the study by Donos et al (2004), the effect of GBR in combination with bone grafting materials and/or enamel matrix proteins (EMD) on the healing of critical size defects was investigated. The authors concluded that the predictability of bone formation depends mainly on the presence or absence of barrier
membranes.

In summary, bone regeneration is predictably achievable following GBR application in critical size mandibular and calvarial defects. Histologically, de novo bone formation process closely resembles bone development and growth pattern during intramembranous ossification (Schenk et al 1994).

**Neo-osseogenesis beyond the skeletal envelope**

Several preclinical studies and human investigations were carried out to investigate the possibility of augmenting and/or regenerating bone beyond the skeletal envelope (Lundgren et al 1995, Hammerle et al 1996, Stavropoulos et al 2001, Donos et al 2002a, Donos et al 2002b, Donos et al 2002c, Donos et al 2002d, Mardas et al 2003a, Mardas et al 2003b, Donos et al 2005, Mardas et al 2011). They demonstrated that new bone can be produced in areas beyond the skeletal envelope with the application of GBR principles, thereby inducing changes of the skeletal background in a controlled and predictable way (Mardas et al 2011). There are a number of factors to be considered when extra-skeletal osteogenesis is to be achieved with GBR, some of which are described below.

**Membrane characteristics (porosity)**

Lindhe et al (1993b) demonstrated various amount of extra-skeletal new bone formation under customized e-PTFE domes with a healing period of 9 to 16 weeks in rats. They concluded that the amount of bone neo-osseogenesis was dependent on membrane qualities, such as stiffness and porosity, and the length of the healing period. It was suggested that increased porosity of the membrane may enhance neogenetic bone formation (Lindhe et al 1993). A subsequent study by Zellin and Lindhe (1996) investigated the influence of membrane porosity (<8, 20 to 25, and 100 μm) on the GBR efficacy in rats, reporting that the e-PTFE membranes with the smallest porosity were less efficient than the others in that osteogenesis was somewhat delayed. However, at 12 weeks of healing there was no difference in the amount of newly formed bone among the experimental groups with different membrane porosities. The authors concluded that there is a porosity range within which osteogenesis beneath the membrane is optimal, tissue integration for stability is adequate, and soft connective tissue ingrowth is avoided (Zellin & Lindhe 1996). Another study by Lundgren et al (1998) investigated the effect of various barrier porosities on guided bone augmentation. They demonstrated that the placement of barriers with a porosity >10 μm promoted a faster rate of bone formation during the early healing period, but in a less predictable manner. On the other hand, the use of completely occlusive barriers resulted in the slowest rate of bone tissue augmentation but in a highly predictable manner. However, after 12 weeks of healing, similar amounts of mineralized neogenetic bone were observed.

**Development of the titanium dome model**

The necessity of creating a secluded space with a rigid support led to the development of various devices aiming at supporting the permeable and soft barrier membrane structure. Schmid et al (1991) reported substantial extra-skeletal new bone formation under a titanium solid structure (Supraplant) covered with e-PTFE membrane over the rabbit calvarium. Also, larger and more rigid Teflon membranes of various permeabilities and surface characteristics were produced.
However, Schmid et al (1994) disputed membrane permeability as a prerequisite for guided bone formation by demonstrating new bone formation after 8 months of healing in secluded chambers on the rabbit calvarium, irrespective of whether the chambers were sealed off by titanium or e-PTFE membranes. In a subsequent experimental study, Lundgren et al (1995) introduced and used prefabricated smooth surface titanium dome-shaped membranes to create a secluded space adjacent to the bone surface and ensured peripheral sealing between the borders of the barrier and the adjoining bone surface. After a healing period of 3 months they demonstrated complete bone fill in all domes with no signs of ingrowth of other types of tissues (Lundgren et al 1995). Most recently, Mardas et al (2011) demonstrated a predictable new bone formation beyond the skeletal envelope in rabbits with the use of pre-fabricated rough surface titanium dome barriers (SLA and SLActive) following the GBR application.

**Length of healing period**

The length of healing period following the GBR application is another critical factor affecting the amount of experimental neogenetic bone formation. In a pre-clinical study, Kostopoulos et al (1994) demonstrated augmentation of the mandibular bone beyond its skeletal envelope by the application of hemispherical non-porous teflon capsules in rats, which promoted a five to sixfold increase of the mandibular ramus width after 120 days of healing. A subsequent study using the same experimental model demonstrated that the newly formed bone beyond the skeletal envelope remained stable in the long-term following removal of the GBR device (Lioubavina et al 1999).

With regard to the healing period during the GBR procedure, similar observations to those found in pre-clinical studies were demonstrated in a clinical trial by Hammerle et al (1996). Hollow titanium cylinders covered with e-PTFE membranes were placed in the retromolar areas of healthy human subjects. The titanium devices were partly submerged by 1.5 to 2.0 mm in the mandible, whereas the remaining 2.0 to 2.5 mm extended past the level of the mandibular borders. The histological sections showed that the specimens harvested before 12 weeks were almost entirely comprised of soft tissue, whereas specimens with more than 4 months of healing period were composed of both soft and increasing amounts of mineralized tissue. It took 6 months before they could observe new bone formation beyond the skeletal border.

**Grafting materials**

By using the mandibular ramus animal model, Stavropoulos et al (2001) investigated whether osteoconductive materials may influence new bone formation when used as an adjunct to GBR. In the study, deproteinized bovine bone (DBB, Bio-Oss®) was selected as an osteoconductive material. The authors reported limited amounts of new extra-skeletal bone formation in the specimens with DBB under the teflon capsules, concluding that DBB used as an adjunct to GBR interferes with bone formation. A subsequent study by Mardas et al (2003) demonstrated similar results with the use of demineralized bone matrix (DBM) as an adjunct to the GBR treatment in rats. The authors concluded that DBM did not provide any additional effect on bone formation but increased the density of the newly formed bone. More recently, Donos et al (2005) evaluated whether the use of enamel matrix proteins (EMP), with or without the use of deproteinized bovine bone, influences bone formation when used as an adjunct to GBR in the mandibular ramus of rats. Similar results were observed as shown...
in the previous studies, suggesting that the use of adjunct materials does not result in enhanced amount of new bone formation in comparison with the GBR procedure alone.

**Factors influencing the efficacy of GBR**

**Systemic conditions**

*Diabetes mellitus*

Diabetes mellitus is defined as a clinically and genetically heterogeneous group of metabolic disorders manifested by abnormally high levels of blood glucose (Mealey & Ocampo 2007). This hyperglycaemia is a result of either absolute insulin deficiency (Type 1) or insulin resistance (Type 2) in the liver or muscle tissue, or a combination of both (Retzepi & Donos 2010). The pathophysiology of the cellular mechanism in impaired diabetic bone healing is not currently fully understood.

It is well documented in the literature that the presence of diabetes mellitus is associated with impaired bone healing and pathophysiological changes in the skeletal system as a whole. It has been suggested that a suppressed bone turnover may have contributed to the decreased bone mineral density in type 1 diabetes mellitus patients, which involves relative changes of osteoblast and osteoclast cellular activities (McCabe 2007). Furthermore, impaired intramembranous bone healing in the early healing phases has also been demonstrated in experimental type 1 diabetic animal models (Santana et al 2003, Follak et al 2004a, Follak et al 2004b, Follak et al 2005). Recently, Retzepi et al (2010) evaluated histologically and histo-morphometrically the effect of experimental diabetes on de novo bone formation via application of the GBR principle in animals. The authors demonstrated significant new bone formation even in the presence of uncontrolled diabetes. However, a poorly controlled metabolic state was associated with higher outcome variability and with increased rate of infectious complications. The authors concluded that in experimental diabetes neo-osteogenesis could be achieved via GBR to an extent comparable to the healthy condition (Retzepi & Donos 2010).

*Osteoporosis*

Osteoporosis is characterized by a reduction in bone mineral density and microarchitectural deterioration of the bone tissue, consequently leading to an increased risk of fracture (WHO 1994). The disease can be classified as primary type 1, primary type 2 and secondary (Alldredge et al 2009). The most common form of the disease is primary type 1 osteoporosis and it occurs mainly in the postmenopausal female population where an imbalance of calcium-phosphate equilibrium is caused by a decline of estrogen level. Primary type 2 osteoporosis refers to as one of geriatric syndromes characterized by a particular mineral deficiency; however the pathogenesis of this form of osteoporosis is not fully understood (Atik et al 2006).

Secondary osteoporosis occurs regardless of gender or age, and it is secondary to chronic predisposing medical conditions or prolonged use of drugs such as glucocorticoids. Both aetiology and therapy of osteoporosis (HRT, vitamin D and bisphosphonates) have been shown in several studies to have a negative impact on bone healing potentials and osseointegration (Fini et al 2004, Tsolaki et al 2009, Mardas et al 2011).

Mardas et al (2011) investigated the effect of the SLActive implant surface in guided bone formation in an osteoporotic-like condition with the use of a SLA and SLActive titanium dome model. In this pre-clinical study, it was demonstrated that an
osteoporotic-like condition per se negatively influenced extra-skeletal total bone formation under the SLA domes to a certain degree and the osseointegration of the newly formed bone was compromised in the group of animals which had been exposed to bisphosphonate at the early healing phases. Moreover, it was reported that the use of a modified hydrophilic titanium surface (SLActive) barrier membrane may promote bone healing and osseointegration in osteoporotic-like rabbits in the early healing period. The results of these animal trials, however, should be cautiously interpreted and cannot be directly extrapolated to clinical situations where GBR is attempted in patients with those systemic conditions.

**Implant surface characteristics**

There is strong evidence that both extent and speed of osseointegration are influenced by surface roughness (Wennerberg & Albrektsson 2009, Wennerberg & Albrektsson 2010). With regards to chemical modification of an implant surface, it has been suggested that chemical modification have a profound influence on the surface charge and wettability, which, in turn, may affect protein adsorption, cell adhesion and specific cell responses (Bosshardt et al 2011).

Whole-genome microarray analysis has been utilized to determine the mRNA expression profile, hence elucidating the biological mechanisms associated with bone healing and regeneration in vivo and the influence of surface topography on cell function in vitro (Hadijargyrou et al 2002, Rundle et al 2006, Wall et al 2009, Donos et al 2011, Ivanovski et al 2011). Several studies have been conducted using a microarray technique to assess transcriptional events associated with endochondral bone healing and calvarial “guided bone regeneration” in animals (Hadijargyrou et al 2002, Rundle et al 2006, Donos et al 2011, Ivanovski et al 2011). The latter studies have demonstrated that the transcriptome associated with a maturing GBR-treated craniofacial bone defect is characterized by down-regulation of the imuno-inflammatory response and up-regulation of skeletogenesis-, angiogenesis-, and neurogenesis-associated genes (Ivanovski et al 2011). These pro-osteogenic and pro-angiogenic influences were more pronounced at day 14 in a moderately rough SLA surface, compared with a smooth surface (Donos et al 2011).

**Clinical case**

The patient was a 57 year old, well-educated male in good general health, with initial complaints of periodontal diseases and missing teeth in the 22 and 23 sites. The teeth were lost due to restorative and endodontic failures, and replaced with a removable partial denture. Generalized chronic advanced periodontitis was diagnosed at the initial phase of the treatment plan and the periodontal health was successfully reestablished through non-surgical and surgical periodontal treatments. After 6 months of maintenance care, implant therapy was planned to replace the missing dentition (Figure 1). The reduced edentulous ridge dimension was evaluated in both soft and hard tissue aspects, requiring a simultaneous ridge construction procedure during the endo-osseous implant placement (Figure 2). Despite the scheduled hard tissue augmentation and implant placement, possible compromised aesthetics was discussed with the patient due to the presence of vertical osseous defects at the edentulous ridge.

**Treatment planning**

A restorative driven diagnostic wax-up procedure was done on a cast model to locate correct placement of the implant, aiming to achieve aesthetically and functionally
acceptable outcomes. Based on the wax-up, a radiological stent was fabricated and used in a cone-beam CT scan (CBCT) image as a guide. The CBCT revealed that there were enough residual ridge dimensions for both implant sites to achieve primary stability, hence a simultaneous surgical procedure (i.e. GBR and implant placement) was planned.

**Treatment**

4.1 mm diameter (23 site) and 3.25 mm diameter (22 site) rough surface implants (11.5 mm in length, 3i Osseotite Certain® parallel) were placed with the guidance of a surgical stent which was fabricated from the diagnostic wax-up (Figure 3A). Primary stability (>30 cmN) was achieved for both implants and a simultaneous GBR procedure was performed (Bio-Oss® and Bio-Gide®) to augment the horizontal ridge deficiency (Figure 3B & C). Primary wound closure was achieved with a coronally advancing flap positioning and the healing was uneventful. After 3 months of healing, a second stage surgery was performed to expose the implants and healing abutments were placed to remodel the soft tissue emergence profile (Figure 4A & B). To
Figure 3. 3i system used x2 and GBR planned to augment the horizontal osseous defects. (A & B) 3.25 mm (22) and 4.1 mm (23) diameter implants in length of 11.5 mm were placed using the GBR procedure. (C) Membrane placement (double membrane technique, Bio-Gide). (D) Post-op radiograph.

Figure 4. (A) Uneventful recovery and clinical presentation after 3 months of healing. (B) Second stage surgery.
evaluate the outcomes of the soft tissue profile, screwed retained temporary restorations were planned for placement prior to the final restorations.

Conclusions

Since its introduction, guided bone regeneration (GBR) has been widely applied and considered a predictable treatment modality in current implant dentistry to augment various osseous defects. However there are several crucial factors to be fulfilled in order to achieve successful GBR, such as appropriate qualities of membrane, length of post-operative healing period and control of any other systemic factors which may delay or interfere with the bone tissue healing capacity. Recently, in addition to moderately rough topography, chemically modified implant surfaces, e.g. those with hydrophilic characteristics (SLActive), have been introduced and several pre-clinical and clinical studies have demonstrated these promote superior osseous healing and osseointegration compared to conventional SLA surfaces. However continued research is required to confirm additional benefits of the hydrophilic implant surface since such a healing property in conditions where bone healing has been compromised might be of paramount importance.

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Chapter 18

Inter-relationships of rheumatoid arthritis and periodontal disease

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Introduction

Both periodontitis and rheumatoid arthritis are chronic destructive inflammatory diseases characterized by the accumulation and persistence of an inflammatory infiltrate in the periodontal and synovial tissues respectively causing the destruction of surrounding hard tissues.

The aim of this chapter is to consider the similarities between these two common chronic inflammatory diseases affecting humans. Not only do these conditions have similar patterns of natural history but their pathogenesis, dictated by immunogenetics, cellular infiltration, enzymes and cytokines, is similar. In addition, these chronic inflammatory conditions are also associated with many other systemic and inflammatory disorders. Not surprisingly, the treatment and management implications of both periodontitis and rheumatoid arthritis range from treatment of symptoms, modulation of the inflammatory response and surgical options.

Natural history of rheumatoid arthritis and periodontitis

Rheumatoid arthritis occurs worldwide and affects approximately 1 to 2% of the world population in a 3:1 female/male ratio (Arnett et al. 1988). It has a peak onset in women in the fourth and fifth decades of life (Harris 1997). About 50% of all patients diagnosed with rheumatoid arthritis must stop working within 10 years and 90% by 30 years due to this disease (Shanahan & Smith 1999). Rheumatoid arthritis is a progressive disease over 5 years or longer. The majority of patients show radiographic damage within the first few years with further radiographic progression over the next 5 to 10 years, severe functional decline and increased mortality rates (Kvien 2004). Most clinical studies of rheumatoid arthritis over periods of 10 years or longer indicate severe morbidity (Kvien 2004). Almost 50% of patients show evidence of radiographic joint space narrowing and/or erosion within the first year of disease and functional status declines in most patients with rheumatoid arthritis over periods longer than a decade (Scott et al. 1985, Fuchs et al. 1989, Sharp et al. 2005).

The periodontal diseases represent a group of heterogeneous conditions ranging from the relatively benign form of gingivitis to the more destructive forms such as chronic and aggressive periodontitis. While up to 95% of the population may suffer from gingivitis and up to 50% have some form of chronic periodontitis, only between 5 to 15% of the population appears to suffer from advanced...
and aggressive periodontitis (Albander & Rams 2002). Indeed, from many studies it is evident that the prevalence of severe periodontitis is confined to a minority of any population (Albander & Rams 2002). No longer is periodontitis considered universal and nor is it considered to be the major cause of tooth loss amongst adults (Chauncey et al 1989, Niesson & Weyant 1989). Notwithstanding this, if left untreated gingivitis may progress to periodontitis and ultimately tooth loss may be the end point if the disease process progresses. Alternatively the disease may become self-contained and not progress or may even enter into long periods of remission.

From studies of the natural history of periodontal disease and rheumatoid arthritis it is apparent that there are individuals who experience disease progression despite the best available treatment. Whether the individuals with rheumatoid arthritis progression refractory to treatment are the same as those who experience uncontrollable periodontitis remains to be established.

**Types of rheumatoid arthritis and periodontitis**

At least three types of disease manifestation can be observed in rheumatoid arthritis populations and these are termed self limited, easily controlled and progressive (Arnett et al 1988). However some degree of caution should be observed with this terminology depending on the cohort being studied. For example, based on epidemiological studies of the individuals originally presenting for rheumatoid arthritis according to the American Rheumatism Association criteria, more than 75% have no evidence of disease 3 to 5 years later (O’Sullivan & Cathcart 1972). In contrast, of those patients studied within clinical settings of rheumatology practice, fewer than 10% had a self-limited process (Scott et al 1984). Similar findings have been reported for those individuals within the easily controlled category. In an epidemiological-based study, it was reported that around 27% of those originally diagnosed with rheumatoid arthritis might belong to this category (O’Sullivan & Cathcart 1972). In contrast, 85% of the rheumatoid arthritis patients seen in clinical rheumatology practices took at least one second-line drug and fewer than 15% of patients were controlled only with non-steroidal anti-inflammatory drugs (Pincus et al 1992a). In clinical rheumatology practices, most patients who meet the criteria for rheumatoid arthritis have progressive disease that generally requires second-line drugs, which still do not fully control the disease (Wolfe et al 1990, Pincus et al 1992b). A number of clinical studies have shown substantial progression of disease in more than 90% of rheumatoid arthritis patients (Scott et al 1987, Fuchs et al 1989). Within this group of patients, only 2% of the patients who are prescribed second-line drugs undergo remission of longer than 3 years, while most of the patients still have progression of the disease while taking these drugs (Ianuzzi et al 1983, Wolfe & Hawley 1985, Wolfe & Cathey 1991). In general, these patients have a number of poor prognostic indicators such as the presence of rheumatoid factor, rheumatoid nodules, HLA-DR4 haplotype and number of affected joints in the early stages of the disease (Van Zeben et al 1991).

Similar to rheumatoid arthritis, longitudinal studies on the natural history of untreated periodontal disease in humans have indicated the presence of three distinct subpopulations: rapid progression (8%), moderate progression (81%), and no progression of periodontal disease (11%), despite the absence of any dental treatment and the presence of copious amounts of dental plaque (Löe et al 1986). In addition, studies
on treated populations have demonstrated remarkably similar proportions, with about 4 to 13% of the population having severe forms of periodontal disease despite comprehensive periodontal treatment (Hirshfeld & Wasserman 1978)

**Effector mechanisms of tissue destruction in rheumatoid arthritis and periodontitis**

There is no doubt about the importance of inflammation in the pathogenesis of rheumatoid arthritis and periodontitis (Figure 1). The task now is to identify the specific cytokines, their concentrations, the cells they affect *in vivo*, the stages in which they are active, and the role and concentrations of their inhibitors (Findlay & Haynes 2005). While the role of cytokines on normal cellular processes is important, it is their purported roles in disease that result in excessive production, dysregulation or inadequate inhibition which have gained most attention (Arend & Dayer 1990). Cytokines can be classified into functional groups based on the cells of origin. For example, interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), and interferon-gamma are the products of T-cells, and most of their recognized functions are related to the activation and amplification of cellular and humoral immune responses. In addition, IL-1, IL-6, colony stimulating factor-1 and tumor necrosis factor-α (TNF-α) are produced primarily by macrophages and fibroblasts. Although involved in the initiation of immune responses, these cytokines have broad effects on many cells, leading to cell proliferation, increased prostaglandin synthesis, matrix-degrading protease activity and bone resorption.

Lymphocyte-associated cytokines are present in low concentrations in rheumatoid synovial membrane, whereas the levels of macrophage and fibroblast associated products are high (Firestein *et al* 1988, Miyasaka *et al* 1988). A study estimating the concentrations of mRNA for various cytokines in rheumatoid synovial membranes showed that IL-6 was found in the highest concentrations, followed by IL-1β, TNF-α, granulocyte-macrophage colony-stimulating factor, and IL-2 whose concentrations were half that of colony-stimulating factor (Firestein *et al* 1988). Such results should be interpreted with caution since the activity of IL-1/TNF-α per milligram is much greater than some of the other cytokines such as IL-6.

Although IL-1 is capable of a wide-array of systemic effects, it is the local effects of

![Figure 1. Histological appearance of normal (A & C) and inflamed (B & D) gingival (A & B) and synovial (C & D) tissues. Both inflamed gingival tissue (B) and inflamed synovial (D) tissue contain large numbers of leucocytes. The inflamed gingival tissue shows a loss of tissue architecture while the synovial lining of the inflamed synovial tissue is markedly thickened.](image-url)
IL-1 on both immune and inflammatory cells which are considered to be most important in rheumatoid arthritis (Kay & Calabrese 2004). These responses include augmentation of T and B lymphocyte function, chemotaxis of neutrophils, lymphocytes, monocytes, and proliferation of fibroblasts. IL-1 also stimulates the production of prostaglandin E₂ (PGE₂) and collagenase by synovial fibroblasts and chondrocytes (Evequoz et al 1984, Dayer et al 1985). In addition, IL-1 alters collagen production by chondrocytes, reduces production of type II collagen, and enhances synthesis of type I and III collagen (Goldring et al 1988). Since type II collagen is the predominant form in articular cartilage, these effects of IL-1 may result in a further weakening of the rheumatoid joint. Furthermore, IL-1 has been shown to have opposing effects on proteoglycans in cartilage, leading to both the inhibition of prostaglandin synthesis and the enhancement of prostaglandin degradation (Arner & Pratta 1989). The importance of IL-1 in rheumatoid arthritis has been corroborated by clinical studies which have demonstrated that levels of circulating IL-1β in rheumatoid arthritis patients can be correlated with clinical disease activity (Eastgate et al 1988). In recent years, inhibitors of IL-1 have been developed as a treatment for rheumatoid arthritis (Dayer et al 2005).

The main systemic pathologic role of TNF-α appears to be that of septic shock (Sherry et al 1988). However, locally TNF-α has been shown to stimulate PGE₂ and collagenase production in vitro by synovial fibroblasts and chondrocytes, as well as bone resorption and fibroblast proliferation (Dayer et al 1985). Intra-articular injection of TNF-α into rabbit knees did not lead to loss of cartilage proteoglycans, as was observed with IL-1 (Henderson & Pettipher 1989). Injection of both TNF-α and IL-1 produce greater inflammation than is observed with either cytokine alone, supporting the observation that TNF-α augments the damaging potential of IL-1 (Henderson & Pettipher 1989). As for IL-1, TNF-antagonists have been developed as a treatment aid for rheumatoid arthritis (Connell & McInnes 2006).

High levels of IL-6 are also present in inflammatory synovial fluids of rheumatoid arthritis patients (Punzi et al 2002). The biologic activities of IL-6 are similar to those of IL-1 and TNF-α except that IL-6 fails to stimulate PGE₂ and collagenase production in chondrocytes and synovial fibroblasts (Guerne et al 1989). IL-6 levels are correlated with the serum measures of inflammation, such as erythrocyte sedimentation rate and the presence of acute-phase proteins which are used as good markers of disease activity (Guerne et al 1989, Duff et al 1994).

IL-18, a novel cytokine with pleiotropic activities critical to the development of T-helper 1 responses, has been detected in rheumatoid arthritis synovial tissues (McInnes et al 2005). Furthermore IL-18 has been noted to promote production of granulocyte-macrophage colony stimulating factor (GM-CSF) and nitric oxide production by synovial tissues. It also induces TNF-α synthesis by macrophages in synovial cultures (Gracie et al 1999). These findings again emphasize the importance of synergistic actions of inflammatory cytokines in sustaining inflammation. Both interferon-γ (IFN-γ) and GM-CSF can stimulate HLA-DR and HLA-DQ expression by synovial tissue macrophages and fibroblasts. This may amplify the inflammatory cycle by enhancing lymphocyte stimulation and local immune response induction (Burmester et al 1987). GM-CSF, which may be stimulated by IL-1, TNF and IL-6, also stimulates IL-1 production, activates neutrophils, and induces HLA-DR expression on monocytes (Feldman et al 1996).

Analysis of cytokine mRNA and protein
expression in rheumatoid arthritis reveals that many proinflammatory cytokines including TNF-α, IL-1, IL-6, GM-CSF and chemokines such as IL-18 are abundant, regardless of therapy (Feldman et al 1996). This may be compensated to some degree by the increased production of anti-inflammatory cytokines such as IL-10, and cytokine inhibitors such as interleukin-1 receptor antagonists (IL-1ra) and soluble tumor necrosis factor-receptor (TNF-R) (Feldman et al 1996). These cytokine inhibitors can antagonize the ongoing inflammation and may induce the synthesis of collagen.

Tissue destruction in rheumatoid arthritis is ultimately carried out by enzymes released by resident and migrating cells. These effector molecules are able to degrade collagen and proteoglycans either through direct or indirect means. For example secretion of the arachidonic acid metabolite prostaglandin E₂ (PGE₂), as well as the release of neutrophil-associated enzymes such as neutrophil elastase b-glucuronidase and macrophage and synoviocytes associated matrix metalloproteinases (MMPs) contribute significantly to the pathogenesis of rheumatoid arthritis.

The major MMPs-producing cells in rheumatoid arthritis are synovial fibroblasts and monocytes/macrophages in the synovial lining layer. Both IL-1 and TNF-α may induce the production of collagenase and other neutral proteases in synovial fibroblasts and in chondrocytes located in the adjacent articular cartilage (Lotz et al 1995). These enzymes degrade proteoglycans and collagen, resulting in cartilage destruction. Chondrocytes respond to these cytokines with a decrease in collagen and proteoglycan synthesis and the synthesis of collagenase and stromelysin which can degrade type II collagen and proteoglycans (Lotz et al 1995).

Periodontitis has remarkably similar cytokine profiles to rheumatoid arthritis (Snyderman & McCarty 1982, Greenwald & Kirkwood 1999, Seymour & Gemmell 2001). In both diseases, progression consists of the continuing presence of high levels of pro-inflammatory cytokines including IL-1β and TNF-α and low levels of IL-10 and transforming growth factor b, cytokines that suppress the immunoinflammatory response. Furthermore, low levels of tissue inhibitors of metalloproteinases (TIMPs) and high levels of MMPs and PGE₂ secreted by macrophages, fibroblasts and other resident and inflammatory cells describe the active stages of both rheumatoid arthritis and periodontitis.

There is accumulating evidence that genetic heterogeneity determining the function of cytokines such as TNF-a, IL-1 and IL-10 is of importance (Fugger & Svejgaard 1997, Kajjzel et al 1998, Cantagrel et al 1999, Mu et al 1999). In both rheumatoid arthritis and periodontitis, tissue destruction is not unidirectional but an iterative process that is constantly being adjusted by the host response to inciting agents. The destruction of extracellular matrix in both diseases is determined by the balance of MMPs and their inhibitors. Bone destruction in periodontitis and rheumatoid arthritis is a result of the uncoupling of the normally coupled processes of bone resorption and bone formation, with PGE₂, IL-1, TNF-α and IL-6 as mediators of bone destruction. It is evident in both diseases that the host’s immune response is controlled by genes which regulate differences in the monocyte/T cell response traits to different antigens that determine both the nature of the protective antibody response and the magnitude of tissue-destructive inflammatory responses.

Since the primary mode of destruction in these diseases is the exuberant host response and the imbalance between pro-inflammatory and anti-inflammatory mediators, host-modifying agents and genetically engineered chemicals that can target specific pro-
inflammatory cytokines and enzymes are being developed for their possible role in the restoration of balance in the inflammatory mediators.

Environmental influences

The outcome of both rheumatoid arthritis and periodontitis is influenced not only by genetic factors but also by environmental factors. In its broadest context an environmental factor could be considered anything which might modify or alter the host response. In this context demographic, socioeconomic, lifestyle, diet, hormonal and psychological variables could all be considered environmental factors which could influence the outcome of these two diseases.

Age is considered to be an important variable for both rheumatoid arthritis and periodontitis with both diseases manifesting juvenile and adult forms. Interestingly age seems to play more of a key role in rheumatoid arthritis than periodontitis. For example it seems that younger onset rheumatoid arthritis patients have a higher incidence of entering spontaneous remission while older-onset patients tend to have more active disease and be more disabled (Corbett et al 1993, Tunn & Bacon 1993, Young 1995, Harrison et al 1996). The opposite seems to hold true for periodontitis whereby the early-onset forms of the disease tend to be more aggressive than the later adult-onset forms.

As noted above, females are more prone to suffer from rheumatoid arthritis than males and females also tend to have worse outcomes than males with males tending to be more likely to enter into spontaneous remission (Young 1995, Harrison & Symmons 2000). Gender does not appear to be a significant environmental variable for periodontitis.

Socioeconomic status is a significant factor influencing both incidence and severity of both rheumatoid arthritis and periodontitis (Callahan & Pincus 1988, Borrell et al 2006). While it is still not clear why this link with lower socioeconomic class exists it might be that such individuals are less compliant with regards to their general health care. Alternatively, it is possible that a low socioeconomic status leads to increased exposure to psychosocial stress, which activates primary allostatic mediators including catecholamines, glucocorticoids and cytokines. These mediators can lead to favorable host responses. However, repeated activation of this self-correcting system can produce inappropriate host responses which are not self-correcting. Under these conditions of increased allostatic load, primary allostatic dysregulation of diverse cellular functions occurs, leading to manifestation of disease (McEwen & Seeman 1999).

Smoking is well recognized as a significant environmental modifying factor for many conditions. Through its effect on the cardiovascular system, immune cell function and general tissue physiology it is not surprising that smoking is considered a risk factor for the development of both rheumatoid arthritis and periodontitis (Wilson & Goldsmith 1999, Johnson & Hill 2004).

Stress and other psychological factors such as depression and coping mechanisms have been well documented to influence inflammatory responses.

Psychoneuroimmunology has become an accepted paradigm for the modification of host responses to a variety of inflammatory conditions (MacFarlane & Brooks 1990). Both rheumatoid arthritis and periodontitis are influenced by stress and psychological factors (Sheiham & Nicolau 2005).

Hormonal factors have the potential to influence a wide range of physiological and pathological responses. Of these, hormonal changes associated with diabetes and pregnancy are two of the best documented. Diabetes is a well-documented modifying
factor in both rheumatoid arthritis and periodontitis. Interestingly, while pregnancy can exacerbate periodontal inflammation the converse hold true for rheumatoid arthritis with several reports demonstrating remission of rheumatoid arthritis in pregnant women (Barrett et al 2000).

Diet can have both a protective and destructive effect on rheumatoid arthritis and periodontitis. It is well recognized that malnutrition, vitamin and mineral deficiencies can significantly affect normal and pathological tissue physiology (Ritchie & Kinane 2003). Conversely, obesity may also be a significant risk factor for the development of both rheumatoid arthritis and periodontitis (Symmons et al 1997). A protective role for diet has also been proposed. Both theoretical and clinical trial evidence has shown that omega-3 fatty acids are natural anti-inflammatory agents which can significantly influence the outcome and progression of inflammatory disorders. There is accruing evidence to indicate that dietary supplementation with omega-3 fatty acids can have a beneficial effect on the outcome of rheumatoid arthritis (James & Cleland 1997).

Initial studies along similar lines for periodontitis are showing considerable promise (Rosenstein et al 2003).

Is there a role for bacteria in the aetiology and pathogenesis of rheumatoid arthritis?

The idea that rheumatoid arthritis is an infectious disease has been postulated for over 70 years and is still under consideration. An infection which induces an immune response in the synovial membrane may account for some of the clinical features of rheumatoid arthritis which includes the accumulation of immunocompetent T and B cells in the synovium. Although the early features of endothelial swelling and synovial hyperplasia are considered nonspecific, they could be a response to blood-borne pathogens (Stransky et al 1993). Within this context, bacteria, viral agents and mycoplasma have all been implicated in the aetiology and pathogenesis of rheumatoid arthritis (Nishioka et al 1996).

The association of mycobacteria with rheumatoid arthritis is of particular interest because these bacteria express heat-shock proteins similar to the arthritogenic factors of adjuvant arthritis in rats (van Eden et al 1988). It has been demonstrated that patients with rheumatoid arthritis have elevated levels of antibodies to heat-shock proteins from recombinant mycobacteria (Tsoulfa et al 1989).

Evidence consistent with the concept that bacterial stimuli can result in an anti-cartilage response was presented in a study by van Den Broek et al (1988). By priming mice in vivo with cell wall fragments of Streptococcus pyogenes or Eschrichia coli a cellular and humoral anti-cartilage response could be induced. Isolated T cells from these mice could be stimulated by small bacterial components and diverse antigens of cartilagenous origin. Antibodies from these bacteria-primed mice displayed reactivity to cartilage extract as well as reactivity to the priming bacteria. In addition a delayed type hypersensitivity reaction could be elicited in bacteria-primed mice by challenge with cartilage extract (van Den Broek et al 1988). From this study a mechanism was proposed for the pathology of chronic arthritis which was based on repeated challenges with different bacterial stimuli. The relevance of this to human rheumatoid arthritis remains equivocal.

Additional evidence supporting the role of exogenous bacterial antigens in rheumatoid arthritis comes from the observations that certain bacterial species cross-react with the immune response initially elicited by another bacterial species. Thus the response induced by one bacterial species can be reactivated by
Inter-relationships of rheumatoid arthritis and periodontal disease

Another non-related species or even by bacterial components like lipopolysaccharides (LPS), a cell wall structure of gram-negative bacteria (van Den Broek et al 1988). This response has important ramifications in terms of the maintenance and persistence of arthritis. For example, upon triggering anti-bacterium and anti-cartilage responses in a susceptible individual, subsequent exposure to other bacterial species, or structural components such as lipopolysaccharide, may reactivate not only the anti-bacterium but also the anti-cartilage response (van Den Broek et al 1988). Such a response may be induced by exogenous or endogenous bacteria such as those from the gastrointestinal tract.

Clearly another potential source of bacteria and bacterial by-products is from the oral cavity, especially when infected with the gram negative anaerobes associated with periodontitis. The role of gram-negative bacteria and their by-products (particularly lipopolysaccharide) has long been implicated in the aetiology-pathogenesis of rheumatoid arthritis. It has been demonstrated that four gram negative bacteria (Proteus, Serratia, Escherichia and Pseudomonas) possess sequences resembling the rheumatoid arthritis susceptibility sequence (Tiwana et al 1996). In another study bacterial lipopolysaccharide was shown to induce the formation of IgM rheumatoid factors (RF) in several strains of mice (Izui et al 1979). The rheumatoid factor induced by lipopolysaccharide reacted not only with murine IgG but also with IgG from cows, goats and humans (Izui et al 1979). The result of these experiments should be considered in relation to the pathogenic role of bacterial products in the development of rheumatoid arthritis. This concept is explored further in the section on rheumatoid factor.

The combined data from a number of animal models demonstrate that arthritis can develop secondarily to several different stimuli and through several different effector pathways including exogenous infections. If the observations in animal models are also applicable to human rheumatoid arthritis, we might anticipate that different types of infections as well as other environmental exposures with capacity to induce excessive pro-inflammatory cytokines in genetically susceptible individuals may contribute to disease either together with some autoimmune reaction or by themselves.

**Could periodontal pathogens provide an infective source for rheumatoid arthritis?**

Many of the so-called periodontal pathogens exhibit similar characteristics to those microorganisms suspected to induce rheumatoid arthritis in a genetically susceptible host (Table 1). Periodontal pathogens, which are organised in a biofilm with the other groups of bacteria, incite a chronic continuous infection within the periodontal tissues and also serve as an abundant supply of lipopolysaccharide. Interestingly there appears to be a local production of IgA and IgM rheumatoid factors in diseased periodontal tissues (Hirsch et al 1989, The & Ebersole 1991). Although the ability of lipopolysaccharide from periodontal pathogens to induce an immune response which cross-reacts with the cartilage components to cause an anti-cartilage response has not been demonstrated, it is plausible. In this sense, the aetiologic agents in periodontitis reasonably fulfill some of the requirements for a microorganism to trigger the inflammatory cascade seen in rheumatoid arthritis. Thus, the possibility that an ongoing periodontitis can trigger, or exacerbate rheumatoid arthritis (and vice-versa) in genetically susceptible individuals is biologically possible. Recently two reports have indicated that rheumatoid arthritis patients have elevated IgG levels to a number
of periodontal pathogens compared to non-rheumatoid arthritis controls (Yoshida et al. 2001, Ogrendik et al. 2005).

Until the causative agent for rheumatoid arthritis can be unequivocally identified these ideas remain speculative. Indeed, despite many investigative attempts, infectious agents have not been identified as the prime cause of rheumatoid arthritis and there appears to be no convincing evidence to support the concept that a single antigen drives the synovial inflammation. In light of this it remains possible that there is no single primary cause of rheumatoid arthritis and that a number of unrelated different mechanisms may lead to the initial tissue injury and subsequently precipitate synovial inflammation.

**Rheumatoid factor in rheumatoid arthritis and periodontal disease**

Rheumatoid arthritis is commonly associated with the presence of autoantibodies to antigenic determinants of the Fc receptor of IgG molecules, termed rheumatoid factors. Rheumatoid factors (RF) are found in more than two-thirds of adult patients with rheumatoid arthritis, but they are not specific to rheumatoid arthritis and are found in patients with a number of other chronic inflammatory conditions, including periodontitis (Geraci & Wilson 1982, Hirsch et al. 1989, The & Ebersole 1991). These autoantibodies are usually of the IgM isotype, although IgG and IgA isotypes have also been reported. The production of rheumatoid factor was originally thought to be the result of polyclonal B-cell activation. However, more recently rheumatoid factors are thought to arise following activation of B-cells by two signals, one from interaction with the B-cell receptor and the other from recognition of a pathogen-associated molecular pattern through a Toll-like receptor (TLR). These autoantibodies thus link the innate and acquired immune responses. While rheumatoid factors are not essential for the development of rheumatoid arthritis, they provide a mechanism for amplification of joint disease (Weismann 2004). Although serum

<table>
<thead>
<tr>
<th>Features of microbial induction of RA</th>
<th>Is this a feature of periodontal pathogens?</th>
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<tr>
<td>Induction of non-lethal low grade infection</td>
<td>Yes</td>
</tr>
<tr>
<td>Distribution should be common and universal in population</td>
<td>Yes</td>
</tr>
<tr>
<td>Express proteins which have shared epitopes with the third hypervariable region of HLA-DRB10401 and HLA-DRB10101, the part of the molecule that carries susceptibility to RA (e.g. EBV, E. Coli, mycobacteria)</td>
<td>Yes</td>
</tr>
<tr>
<td>Persist in the host to produce a chronic continuous LPS exposure and also be able to form complexes with antibodies</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibodies to pathogens must be able to cross-react with cartilage protein breakdown products and be able to produce an anti-cartilage response. Also, the pathogens must be able to continuously reactivate this cross-reactivity</td>
<td>Yes</td>
</tr>
<tr>
<td>Have the capacity to citrullinate proteins leading to autoimmune responses</td>
<td>Yes</td>
</tr>
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**Table 1.** Features of periodontal pathogens which could make them candidates to be involved in the initiation of rheumatoid arthritis
rheumatoid factor estimation has been used as a basic diagnostic aid some controversy still exists over its specificity and sensitivity. Nonetheless it still remains a mainstay in rheumatologists’ armamentarium as a prognostic indicator of disease activity and progression in adult forms of rheumatoid arthritis (Westwood et al 2006).

Rheumatoid factors have been reported in patients with periodontitis by several groups (Gargiulo et al 1981, Hirsch et al 1989, The & Ebersole 1991). Rheumatoid factor seropositive periodontal patients have been shown to have elevated IgM and IgG antibodies to a number of oral bacteria including Capnocytophaga gingivalis, Fusobacterium nucleatum and Actinobacillus actinomycetemcomitans (Hara et al 1996, The & Ebersole 1996). While IgM-rheumatoid factor from rheumatoid arthritis patients reacts with these bacteria it is believed to be a non-specific reaction towards shared epitopes between these bacteria and IgG (The & Ebersole 1996). The precise function, if any, of rheumatoid factors in periodontal disease is still unclear. Nonetheless, increases in IgM-rheumatoid factor seen in periodontitis seems to reflect a chronic antigenic stimulation by periodontopathic bacteria which have cross reactive epitopes which permit clearance of the IgG-coated bacteria (The & Ebersole 1996). Such a process reflects very closely the involvement and role of immune complexes in rheumatoid arthritis.

**Citrullinated proteins and autoimmunity**

Recognizing that rheumatoid factors are relatively non-specific markers for rheumatoid arthritis has led to investigations for more specific markers. One such group of markers/antigens are found in the anticyclic citrullinated peptide (CPP) autoantibody system. In this cascade, proteins become antigenic through the conversion of arginine to citrulline via deimination enzymes such as peptidyl arginine deaminase (PAD) (Masson-Bessiere et al 2001). With the accumulation of proteins such as fibrin within the synovium and their prolonged and complex degradation, which includes citrullination, leads to exposure of new epitopes to immunocompetent cells within the synovium (Masson-Bessiere et al 2001). In this context, anti-CPP antibodies have been reported to have a high predictive value for rheumatoid arthritis onset several years before it is evident clinically and are also associated with more severe clinical outcomes (Kroot et al 2000). Moreover, the presence of both rheumatoid factor and anticyclic citrullinated peptide autoantibodies is highly predictive of severe and progressive rheumatoid arthritis (Rantapaa-Dahlqvist et al 2003). Recently, peptidyl arginine deaminase enzymes have been reported to be synthesized by periodontopathic bacteria which have the capacity to citrullinate proteins within inflamed periodontal tissues (Travis et al 1997).

**Periodontal disease and rheumatoid arthritis have significant interrelationships with other systemic conditions**

In recent years there has been increasing evidence to suggest that periodontal diseases are associated with a large number of systemic conditions. Amongst the best studied of these are diabetes, preterm low birth weight infants, cardiovascular disease, pulmonary disease, obesity, and osteoporosis. Interestingly nearly all of these diseases have also been associated with individuals suffering from rheumatoid arthritis (Table 2). While some of the association of rheumatoid arthritis with these conditions can be a result of the medications these patients take, many studies have been
able to demonstrate relationships between rheumatoid arthritis and systemic conditions after removal of the confounder of medications. A common feature appears to be dysregulated chronic inflammation in both periodontitis and rheumatoid arthritis.

**What is the evidence for a relationship between periodontitis and rheumatoid arthritis?**

In light of the above it is clear that an interrelationship between rheumatoid arthritis and periodontitis, as two remarkably similar chronic inflammatory conditions, is plausible. What then is the evidence for such an association?

A proposed association between rheumatoid arthritis and periodontitis is not new. Indeed, as early as 1926, Sachs commented that the relationship between “gelenkrheumatismus and paradentose” was a question of a constitution with a predisposition to both of these conditions (quoted in Helminen Pallala 1971). While several studies followed debating this relationship little consensus was achieved (Cecil et al 1938, Kerr 1962). More recently, results from several studies examining the association between rheumatoid arthritis and periodontal disease have continued to provide conflicting and confounding results. For example, a South African study determined that crippling joint conditions were not associated with any marked increase in dental disease (Blair & Chalmers 1976). Similar findings were reported for Japanese populations where serum antibodies against common periodontal pathogens were not found in rheumatoid arthritis patients and other clinical and immunological findings indicated that rheumatoid arthritis patients were not a risk group for advanced periodontal conditions (Yavuzyilmaz et al 1992, Yusof et al 1995). In a Scandinavian study of 204 rheumatoid arthritis patients and 204 controls, a tendency toward better periodontal conditions was noted for the rheumatoid arthritis patients (Sjöström et al 1989). In the USA Eklund and Burt (1994) collected longitudinal data from 10,523 individuals initially seen during the first National Health and Nutrition Examination Survey (NHANES I) of 1971-75 and concluded that there was no correlation with self-reported arthritis and the number of missing teeth.

On the other hand, many studies have reported a significant association between rheumatoid arthritis and periodontal disease. Simple analyses of self reported illnesses have indicated the likely interrelationship between periodontitis and rheumatoid arthritis (Mercado et al 2000, Lagervall et al 2003, Georgiou et al 2004). A number of case/control studies have also reported a significantly higher incidence of tooth loss and alveolar bone loss (Malmström & Calonius 1975, Albander 1990, Tolo & Jorkjend 1990, Kaßer et al 1997, Mercado et al 2000, Al-Shammari et al 2005, Zhang et al 2005, Bozkurt et al 2006). In addition, other studies which have addressed cytokine profiles, HLA-DR shared epitopes and antibody titres to periodontopathic bacteria have contributed to our body of knowledge strongly suggesting an interrelationship between periodontitis and rheumatoid arthritis (Bozkurt et al 2000, Moen et al 2003, Havemose-Poulsen et al 2005, Ogrendik et al 2005, Marotte et al 2005, Bozkurt et al 2006, Havemose-Poulsen et al

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**Table 2.** Systemic conditions reported to be associated with both periodontitis and rheumatoid arthritis.

- Cardiovascular Disease
- Diabetes
- Obesity
- Obstetric Problems
- Pulmonary Conditions
2006). Of particular interest have been several studies which have reported that periodontitis may serve as a risk factor or severity factor for rheumatoid arthritis and that periodontal treatment might even have a beneficial effect on rheumatoid arthritis (Mercado et al 2000, Riberio et al 2005, Riberio et al 2006). From a recent laboratory study it was reported that following induction of adjuvant experimental arthritis in rats, there was subsequent evidence of periodontal breakdown characterized by alveolar bone loss and increased matrix metalloproteinase activity in adjacent gingival tissues (Ramamurthy et al 2005).

Notwithstanding these conflicting reports the evidence seems to weigh in favour of an association between these two diseases. From all of these studies a number of important observations can be made. Interestingly, despite current dogma, there is no evidence to support the notion that rheumatoid arthritis patients have impaired oral hygiene (judged by plaque and bleeding scores). In addition, individuals with severe rheumatoid arthritis are more likely to suffer from advanced periodontitis and vice versa. The role of medications is interesting but may confound the clinical picture. For example, while most rheumatoid arthritis patients take medications which can reduce inflammation (i.e. NSAIDs and immunosuppressants), we have noted significant periodontal destruction can still be seen in these patients (Mercado et al 2001). This indicates that prior to the development of rheumatoid arthritis symptoms, the periodontitis was most likely developing and not detected. Thus, disease duration is a critical factor. Thus to fully appreciate the associations between periodontitis and rheumatoid arthritis it is necessary to document the disease on the basis of both severity and duration (i.e. type of disease).

**Current hypotheses**

**Rheumatoid arthritis as a product of the humoral immune response to oral bacteria**

In a recent review, Rosenstein et al (2004) proposed a novel hypothesis for the development of rheumatoid arthritis via the humoral response to oral bacteria found in periodontitis. It is proposed that the development of autoimmune disease (e.g. rheumatoid arthritis) can arise due to infectious agents (e.g. periodontal pathogens) inducing immune responses to altered self-antigens in genetically susceptible individuals. This hypothesis recognizes the importance of the production of rheumatoid factors and anticyclic citrullinated peptide autoantibodies in the development of rheumatoid arthritis. Since Porphyromonas gingivalis produces deimination enzymes such as peptidyl arginine deaminase that can then induce autoantibodies, a link between periodontal infection and development of rheumatoid arthritis has been proposed (Figure 2).

**Clinical relevance of an association between periodontitis and rheumatoid arthritis**

While disease associations may be of academic interest they would be far more valuable if there were to be a clinical outcome or value to such an association. In this context an association between advanced rheumatoid arthritis and advanced periodontal destruction appears to have clinical implications with respect to the management of rheumatoid arthritis patients at risk of periodontitis. Even though most clinical protocols for rheumatoid arthritis patients include an assessment for oral pathology such as the known effects of xerostomia associated with Sjögren’s disease...
and drugs used in the treatment of rheumatoid arthritis (cyclosporin-A-induced gingival overgrowth and oral signs of lichenoid drug reactions), the signs and symptoms of periodontitis are painless and subtle and may advance rapidly without the patient being aware of the problem. Accordingly, if studies can demonstrate that individuals suffering from rheumatoid arthritis are at higher risk of developing periodontal problems then early intervention to prevent significant periodontal destruction occurring in these individuals could be put into effect.

**Conclusions**

It has been recognized for some time now that periodontitis and rheumatoid arthritis share many common pathologic features. Recent case control studies indicate that a strong relationship exists between disease severity and extent for individuals suffering from both rheumatoid arthritis and periodontitis. It is recognized that causality between the two diseases is unlikely although a number of possibilities exist which should be investigated such as the potential for periodontal infection to lead to production of antibodies capable of reacting with autoantigens from the synovial tissues leading either to initiation or modulation of the synovial tissue reaction seen in rheumatoid arthritis. Alternatively these diseases exist as a result of a generalized systemic dysregulation of the immune and inflammatory responses and thus could be considered extensions or manifestations of the same disease process manifesting in different parts of the body. Whether this represents one in the same disease as suggested by Greenwald and Kirkwood (1999) remains to be established.

![Diagram](image.png)

**Figure 2.** The humoral immune response to oral bacteria provides a stimulus for development of rheumatoid arthritis.
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Inter-relationships of rheumatoid arthritis and periodontal disease


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Ramanurthy NS, Greenwald RA, Celiker MY, Shi EY. Experimental arthritis in rats induces biomarkers of periodontitis which are ameliorated by gene therapy with tissue inhibitor of matrix metalloproteinases. *J Periodontol* 2005;76:229-233


Inter-relationships of rheumatoid arthritis and periodontal disease


The following is a record of the posters presented at the 9th Meeting of the Asian Pacific Society of Periodontology
Peri-implant conditions and their relationship with periodontal conditions in Chinese patients: A cross-sectional study

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2Dental Center, School of Stomatology, Peking University, China
3School of Dentistry, University of Hong Kong, Hong Kong SAR, China
4Peking University School of Stomatology, China

**Background:** Clinical studies have documented that peri-implantitis may lead to implant failure and loss. Few studies in Chinese populations have provided data on peri-implant conditions. It appears that a history of chronic periodontitis may predispose an individual to the development of peri-implantitis, however the body of evidence supporting this conclusion is limited.

**Objectives:** To describe the peri-implant condition after at least one year following implant surgery in Chinese patients and to analyze the relationships between peri-implant conditions and periodontal conditions.

**Methods:** Patients who received dental implant surgery at least one year ago from a public hospital in China were recalled. Demographic information of the patients was collected. Clinical examinations and radiographic examinations were performed around the implants. The clinical examinations included: plaque index, gingival index, probing depth (PD), bleeding on probing (BOP), suppuration, attachment level, and mobility. Periapical radiographs were taken using the long cone technique and radiographic bone level was measured. Periodontal condition of the natural teeth were also recorded; percentage of BOP and percentage of sites with PD >4 mm were calculated. Comparison of the peri-implant conditions were performed between the patients with different periodontal conditions by t-test.

**Results:** 86 patients (Mean age = 41 years) who received placement of 148 dental implants after a mean period of 25 months (ranged 12 to 66 months) responded to recall. On a subject level, the prevalence of peri-implant mucositis and peri-implantitis were 77% and 14%, respectively. On an implant level, the prevalence of peri-implant mucositis and peri-implantitis were 80% and 9%, respectively. In patients who had inferior periodontal conditions (≥5% of sites with PD ≥4 mm and ≥30% sites with BOP) the mean peri-implant gingival index was significantly higher (P≥0.001), the probing pocket depth around the implants was significantly deeper (P=0.002), and the percentage of bleeding on probing sites around the implants was significantly higher (P≥0.001) compared with patients who had superior periodontal conditions (<5% of sites with PD ≥4 mm and <30% sites with BOP).

**Conclusions:** The prevalence of peri-implant disease was high in this group of Chinese subjects. Peri-implant BOP and PD was significantly related to the full mouth BOP score and the percentage of deep pockets (PD ≥4 mm) around natural teeth.

*Recipient of Poster Presentation Award - 1st Place*
Association of FcγRIIB-nt645+25A/G gene polymorphism with preeclampsia and periodontitis in pregnant Japanese women

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Background: FcγRIIB (CD32b) is a human type II low-affinity receptor for immunoglobulin G (IgG). FcγRIIB contains a unique immunoreceptor tyrosine-based inhibition motif (ITIM) and functions as a negative feedback regulator of leukocytes activation and antibody production. We have previously reported FcγRIIB-nt645+25A/G gene polymorphism to be associated with periodontitis, FcγRIIB expression level on peripheral B lymphocytes and the serum IgG level against periodontopathic bacteria. Preeclampsia is a pregnancy condition with hypertension and proteinuria. Previous studies reported maternal periodontal disease as an increased risk for preeclampsia. Therefore, FcγRIIB-nt645+25A/G gene polymorphism may affect immune response to periodontopathic bacteria in pregnant women, and be associated with preeclampsia.

Objectives: To elucidate whether FcγRIIB-nt645+25A/G gene polymorphism has associations with preeclampsia and/or periodontitis in pregnant Japanese women.

Material and Methods: Subjects were 119 pregnant Japanese women who had no systemic medical problems before pregnancy. We collected clinical periodontal parameters and bacterial data of A. actinomycetemcomitans, P. gingivalis and Prevotella intermedia in subgingival plaque from all subjects within 5 days of delivery. FcγRIIB genotypes were determined from genomic DNA. Maternal serum IgG antibody levels specific for each bacteria were determined by enzyme-linked immunosorbent assay. The pregnant women who had preeclampsia or pregnancy induced hypertension (PIH) were determined from obstetric data. The relationships between periodontitis, the number of these bacteria, preeclampsia and FcγRIIB-nt645+25A/G were analyzed statistically.

Results: The frequency of the FcγRIIB-nt645+25AA genotype was higher in preeclampsia group compared to non-preeclampsia group (P=0.007), in PIH group compared to non-PIH group (P=0.041). The ratio of serum IgG antibody level against A. actinomycetemcomitans to the number of subgingival A. actinomycetemcomitans was lower in FcγRIIB-nt645+25A allele carriers than in non-carriers (P=0.010). Regarding P. gingivalis and P. intermedia, the ratio of antibody levels/bacterial counts showed no difference between the genotypes. The number of A. actinomycetemcomitans in subgingival plaque was shown to be higher in preeclampsia group (P=0.017). Prevalence of periodontitis or clinical periodontal parameters showed no association with preeclampsia.

Conclusions: FcγRIIB-nt645+25A/G polymorphism was significantly associated with the IgG antibody response against subgingival A. actinomycetemcomitans and the prevalence of preeclampsia in pregnant Japanese women.

*Recipient of Poster Presentation Award - 2nd Place
Effect of periodontal treatment on glycemic control and inflammatory biomarkers in type 2 diabetes patients with chronic periodontitis

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**Background:** Type 2 diabetes and periodontal disease are known to be biological linked, although the temporality and mechanism of this association has not been firmly established. Clinical trials are needed to determine the long-term efficacy of periodontal care in improving glycemic control in diabetes.

**Objectives:** To investigate the effect of periodontal therapy on the circulating levels of inflammatory biomarkers and on the glycemic control in type 2 diabetes mellitus patients with chronic periodontitis.

**Methods:** A total of 134 qualified subjects were randomly allocated into two treatment groups and one control group, respectively. Both treatment groups underwent non-surgical periodontal treatment at baseline. Treatment group 1 received additional subgingival debridement at 3-month follow-up, while subjects in treatment group 2 have supragingival prophylaxis. And those in control group received no periodontal intervention throughout the study. Full-mouth periodontal assessment was evaluated for all the participants. Blood analyses were carried out for glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), high-sensitivity capsule-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α) and lipid profiles. All parameters were assessed at baseline, at 6 weeks, 3 and 6 months after the first visit. Repetitive measure analysis of variance was used to analyze clinical parameters at different time points.

**Results:** A statistically significant effect could be demonstrated for periodontal parameters for treatment groups. Both them had a significantly lower hsCRP level following therapeutic periodontal improvement (Group 1, F=4.181, P=0.027; Group 2, F=3.119, P=0.023). Compared to control group, hsCRP levels in treatment groups were significantly decreased in 6-month follow-up (F=3.242, P=0.042). A significantly lower FPG was observed in treatment Group 1 at 6 months (F=3.750, P=0.013), but not in treatment group 2 (F=2.831, P=0.051) or the control group (F=1.098, P=0.348). Although HbA1c declined significantly in treatment group 2 (F=5.257, P=0.004), inter-group difference for HbA1c, FPG, TNF-α and lipid profiles did not reach significance after therapy (P>0.05).

**Conclusions:** Non-surgical periodontal treatment can effectively improve periodontal and systemic inflammatory status. Despite lack of strong evidence, trends in some results are in favor of improvement in glycemic control after periodontal treatment in type 2 diabetic patients.

*Recipient of Poster Presentation Award - 3rd Place
Pattern of attachment loss and expression of biomarkers in experimental diabetic periodontitis

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Background: Diabetes can mediate the inflammatory response and augment periodontal breakdown. The pattern of attachment loss and related biomarkers expression in diabetic periodontitis has not been clarified yet.

Objectives: To compare the dynamic change of periodontal characteristics between physiologically-healthy (PH) and diabetic (DB) animals.

Materials and Methods: 64 male Sprague-Dawley rats were utilized, and experimental diabetes was induced by injection of streptozotocin (STZ) in half of animals. After 3 weeks, periodontal breakdown was initiated by placing a silk-ligature surrounding the tooth. The animals were sacrifice at days 7, 14 and 21. The treatment outcome was evaluated by blood chemistry, micro-computed tomography (micro-CT), histology, and stains for collagen alignment, tartrate-resistant acid phosphatase (TRAP), proliferating cell nuclear antigen (PCNA), advanced glycation end products (AGEs), and receptor for AGEs (RAGE).

Results: Significant elevation of blood glucose, glycated hemoglobin (HbA1c), and reduced body weight was noted in STZ-injected animals throughout the study. Significant attachment loss was noted in the ligature-placed periodontal area from day 7, and DB rats tended to show more rapid loss from day 7 to 14. Inflammation was noted at day 7, gradually augmented at day 14, and resolved at day 21 in PH rats, whereby evident inflammation persisted until day 21 in DB rats. Irregular alignment of collagen fibers can be seen in days 7 to 21 in both groups. TRAP, AGEs, and RAGE expressions were evident on the surface of alveolar crest and periodontal ligament space in all ligature-placed sites, and in DB rats the TRAP expression was gradually increased and persisted until day 21. DB rats also showed a weaker expression of PCNA and occasionally extensive expression of AGEs in the gingival epithelium. However, the expression of AGEs and RAGE did not demonstrate significant difference between PH and DB rats.

Conclusions: The diabetic condition can augment periodontal attachment loss from extending osteoclast activity and reducing proliferating capability. The presence of AGE-RAGE axis without diabetes implies it roles in regulating inflammation.

*Recipient of Poster Presentation Award - 4th Place
Awareness of periodontal risk and oral health practices among diabetic patients in Hospital Kuala Lumpur: A preliminary study
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Effect of the new herbal preparation, Akhizunber, on younger and older adults with recurrent aphthous stomatitis
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Multidisciplinary integrated treatment to patients with advanced chronic periodontitis: a case report
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Effects of platelet-rich-plasma and calcium sulphate in socket preservation procedures
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Periodontal conditions of Hong Kong Chinese adults with essential hypertension: A cross-sectional study
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The effect of Epigallocatechin-3-Gallate on periodontal disease in rats: A pilot study
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Poster Presentations

**In vivo cleansing effect of two interdental brushes on interproximal tooth and implant surfaces: A randomized controlled, double-blind cross-over study**

Chongcharoen N*, Lulic M, Lang NP
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**P. gingivalis LPS stimulates LPS-binding protein expression through NF-κB and p38 MAPK pathways in human oral keratinocytes**

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**Is there a higher risk for oral diseases in psoriatic patients? A single-blinded comparative study**

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**Identification of lipid mediator profiles in aggressive periodontitis patients**

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**Patient’s expectation and perception of initial periodontal treatment outcome**

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**Bone formation of synthetic block type bone graft on rabbit calvaria**

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**Osteoinductive activity of biphasic calcium phosphate with different rhBMP-2 doses in rats**

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Anti-inflammatory effect of green tea polyphenol epigallocatechin-3-gallate on human periodontal ligament fibroblasts
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Porous carbonate apatite with bFGF regenerates class III furcation defects.
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Bone morphogenetic protein-2 regulation of bone sialoprotein gene transcription
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Surface topography of a Thai dental implant
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Biomarkers’ profile around implant during different osseointegration periods
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The comparative study of the effects of various membranes combined with porous titanium membrane on exophytic bone formation in rabbit calvaria
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Comparison of telomere length of periodontal cells according to periodontal status
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The effects of pure honey on the wound healing process of Sprague Dawley rats
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A systematic review on survival and success rates of implants placed immediately into fresh extraction sockets after at least one year
Lau KY*, Pun L, Wong CM, Li KY, Lang NP
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Clinical and histological study on the bone regenerative efficacy of synthetic oligopeptide-coated bone (Ossgen-X®) in socket preservation
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Bone response of Escherichia coli-derived recombinant human bone morphogenic protein-2 coated commercial dental implants in the rabbit
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Effects of osteogenic induction culture on bone marrow mesenchymal stromal cells’ ability to repair grade II root furcation lesions
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A study of gene-enhanced tissue engineering on periodontal tissue regeneration
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Different *in vitro* potential in periodontal tissue regeneration between PDLCs and BMSCs
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Effect of the Health Belief Model on OHI outcome in periodontal patients
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Postmenopausal osteoporosis and its therapies on periodontitis-associated bone loss
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Intra-oral clinical finding of tuberculosis (TB) patients in Balai Besar Kesehatan Paru Makassar
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Effects of melatonin on human bone sialoprotein gene transcription
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Iron acquisition of *A. actinomycetemcomitans* with JP2 type leukotoxin isolated from Japanese periodontitis patients in Hokkaido
Nagasawa T, Kato S, Shimizu S, Hidaka T, Kado T, Mori M, Furuichi Y
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The effects of systemic sitafloxacin on microbiological and clinical parameters in supportive periodontal therapy
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Biostimulation effects of GaAlAs diode laser on human gingival fibroblast and periodontal ligament fibroblast
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Periodontal treatments in a case with acatalasemia and periodontitis
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Effect of gingival depigmentation by Er:YAG laser and CO₂ laser treatment
Nishida E, Yoshinari N
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Effect of simvastatin on exophytic bone formation in rabbit calvaria
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A comparative study of biphasic calcium phosphate ceramics as a carrier for human alveolar-bone-derived mesenchymal stem cell
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A case report of generalized aggressive periodontitis followed by periodontal regenerative therapy using enamel matrix derivative
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The relationship between OHI and periodontal disease disorder of tuberculosis (TB) patients in Makassar
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The impact of periodontal disease and its intervention on the oral health related quality of life among Type 2 diabetics
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Oral health related quality of life among diabetic patients following non-surgical periodontal intervention
Peh CE, Ting DL, Renukanth PCR, Saub R, Taiyeb-Ali TB, Vaithilingam RD*
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The combination effect of HMGB1 and lipopolysaccharide of Porphyromonas gingivalis on RANKL and OPG expression in human gingival and periodontal ligament fibroblast
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Effect of the periodontal dressing containing 10% catechins from green tea leaves on wound healing in rabbit gingiva
Putra PA, Wulandari F, Baskara AT, Prayitno, Murdiastuti K*
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Implant replacement with simultaneous guided bone regeneration with a combination of autogenous and equine origin graft materials for management of congenitally missing lateral incisors
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Insulin-like Growth Factor-II regulates bone sialoprotein gene expression
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Severely generalized periodontitis treated effectively with non-surgical therapy
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Anti oxidant activities of minocycline in the saliva of chronic periodontitis patient using DPPH assay
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Profilng biomarkers in the gingival crevicular fluid using a multiplex bead immunoassay
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Establishment ligature-induced experimental periodontitis in metabolic symptom rat model
Su Y, Ni J, Xuan DY, Zhang JC
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Porphyromonas gingivalis lipopolysaccharide extraction using Tri-Reagent®
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Level of calprotectin in gingival crevicular fluid of periodontitis with diabetes mellitus patients
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A systematic review of post-extraction alveolar bone dimensional changes in humans and animals
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Subepithelial connective tissue graft for gingival recession defects
Tengkawan M*, Oktawati S
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Glycine powder air-polishing as an adjunct to non-surgical periodontal therapy
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Concerns and views of Hong Kong dentists on extraction of periodontally-involved teeth
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Crestal bone loss measurements in implants with internal conical connection (Astra) one year after loading
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The management of gingival enlargement with and without Er,Cr:YSGG laser
Tunru D*, Oktawati S
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A randomized control trial of Mastic usage in periodontal treatment
Watanabe H*, Hagiwara S, Izumi Y
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Implant-supported overdenture and telescope denture for an advanced chronic periodontitis patient with cross bite
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Animal experiment of using collagen-hydroxyapatite artificial bone plus collagen membrane in the reconstruction of periodontal defect
Wu W, Sun W, Ge J
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Interleukin-8-251 gene promoter polymorphism in Chinese patients with aggressive periodontitis
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The systemic treatment of severe chronic periodontitis depends on the multidisciplinary cooperation: A case report
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Therapy for a patient with generalized progressive periodontitis and rheumatoid arthritis: A 17-year follow-up case
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Analysis of a novel gene, FLJ25143 identified by human periodontal ligament cDNA library
Yamada S*, Ozaki N, Fujihara C, Murakami S
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A feasibility study of acellular dermal matrix as a transplantation scaffold for bone marrow stromal cells of Beagle dogs
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Change in the periodontium after extraction of periodontally diseased teeth: In vivo study in rats
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Observation of laser-assisted treatment of systemic disease with periodontal disease
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Link between serum amyloid A and atherosclerogenesis in ApoE efficient mice
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Effect of bone marrow derived mesenchymal stem cells and platelet-rich plasma on bone regeneration of calvarial defects in rabbits
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Clinical outcomes of treatment periodontal intra-bony defects with a reconstituted bovine porous bone mineral containing bone morphogenetic proteins
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Combined therapy in a patient with Papillon-Lefèvre syndrome: A 20-year follow-up
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The methanol extract effectiveness of Lawsonia inermis Linnaeus leaf on gingivitis healing in Sprague Dawley rats
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