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4. Amounts of BMP-2, BMP-4, BMP-7 and TGF-B1 contained in DBM particles and DBM extract. Kay, JF; Khaliq, SK; King, E; Murray, SS; Brochmann, EJ. Isotis Orthobiologics, Irvine, CA (white paper/abstract).
Peri-implantitis is characterized by bone destruction around dental implants due to the host immune-inflammatory response induced by biofilm accumulation. Several approaches have been proposed to treat peri-implantitis, including mechanic debridement, antimicrobial therapy, and resective or regenerative surgical therapy. The present case report describes a peri-implantitis case treated by a surgical open flap debridement, decontamination of the implant surface with povidone-iodine and fill of the adjacent osseous defect with autogenous bone graft. After 20-month follow-up, the pocket depth reduction and radiographic fill of the defect could be observed. Therefore, it can be concluded that this therapeutic approach could promote clinical and radiographic improvements to the patient. However, more randomized controlled clinical trials are necessary for further understanding about the best approaches for the treatment of peri-implantitis.

**KEY WORDS:** Peri-implantitis, dental implants, guided bone regeneration

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INTRODUCTION
Peri-implant diseases are characterized by inflammatory lesions that involve tissues around dental implants, which is a result of biofilm accumulation. They can be classified into peri-implant mucositis or peri-implantitis. Peri-implant mucositis corresponds to an inflammatory reaction in the implant surrounding soft tissues, whereas peri-implantitis is the inflammation of the soft tissues and involves the loss of supporting bone around an implant. Clinically, this inflammation is detected by the presence of bleeding on probing; other clinical signs (e.g., suppuration, redness, and swelling) may be observed. Radiographs may be required to evaluate bone loss around implants due to peri-implantitis and differentiate it from the normal bone remodeling. In studies about peri-implantitis prevalence, the reported estimate is that it occurs in about 28% to 56% of individuals and between 12% and 43% of the implants. Therefore, the peri-implantitis treatment is a topic of increasing interest. However, only a few studies have provided data on the prevalence of peri-implant diseases; therefore, these data may be underestimated.

For treating peri-implant mucositis, the non-surgical mechanic therapy is effective in reducing the tissue inflammation; the adjunctive use of antimicrobial mouth rinse can improve the results of this therapy. With respect to peri-implantitis, the non-surgical mechanic therapy has not demonstrated to be equally effective. Therefore, surgical therapies have been proposed for treating peri-implantitis, including open flap debridement as well as resective or regenerative approaches.

Although some studies are aimed at establishing protocols treatment for peri-implantitis, there is no consensus about the best way to perform the implant surface debridement, decontamination, and regeneration of the bone defect. In this context, the aim of the present paper is to report a case of peri-implantitis treated with a surgical approach of open flap debridement for implant surface decontamination with iodine solution associated with a regenerative approach using autogenous bone graft.

CASE REPORT
A 43-year-old white male, presenting a good general medical condition was referred to the Graduate Clinic of the Piracicaba Dental School reporting bad breath as chief complaint. He also reported he had difficulty maintaining hygiene on a dental implant placed 2 years before, as well as bleeding in this area. Clinical examination revealed a dental implant (replacing the inferior left first molar) that has never received crown reconstruction; the implant presented a probing depth (PD) of 5 mm and bleeding on probing (BoP). Additionally, there was a bridle that made proper implant cleaning very demanding (Figure 1). Radiographs showed a crater-like peri-implant bone defect (3 mm) involving three implant screws (Figure 2). Thus, the diagnosis of peri-implantitis was established. The patient was informed about his problem and all the treatment options for the case; thereafter, he consented for the treatment as follows.

The initial treatment consisted of oral hygiene instructions, mechanical treatment with intrasulcular brushing and subgingival 10% povidone-iodine Riodeine® (Rioquimica™, São José do Rio Preto, SP, Brazil) irrigation,
which was performed during 5 to 7 minutes in a single session. Despite the improvement of the general oral hygiene observed afterwards, the dental implant still showed inflammation signs after 1-month of follow-up. Then, a surgical approach was proposed for implant surface decontamination and filling of peri-implant defect with autogenous bone graft. Under local

**Figure 1:** Initial clinical aspect of the dental implant that was diagnosed with peri-implantitis.

**Figure 2:** Initial radiographic aspect of the dental implant that was diagnosed with peri-implantitis.

**Figure 3:** Peri-implant defect visualization after mucoperiosteal flap elevation. Note the presence of extensive granulation tissue.

**Figure 4:** Peri-implant defect visualization after granulation tissue removal.
anesthesia Alphacaine® (DFL™, Rio de Janeiro, RJ, Brazil), two incisions were made mesially and distally to the dental implant; a muco-periosteal flap was raised to allow implant and bone defect visualization (Figure 3). After complete granulation tissue removal, the implant surface and bone defect could be observed (Figure 4). The implant surface decontamination was performed using gauze soaked with 10% povidone-iodine. Afterward, autogenous bone graft was obtained from an adjacent area and placed into the peri-implant defect to cover all implant screws (Figure 5). The flap was then repositioned and sutured (Nylon 5.0, Ethicon™, São José dos Campos, SP, Brasil). After this surgical procedure, the patient was instructed to take analgesics (500 mg sodium dipyroine every 6 h for 2 d) and to discontinue toothbrushing around the surgical site for 15 days after surgery. During this period, plaque control was achieved with a 0.12% chlorhexidine rinse twice a day. After this period, gentle toothbrushing with a soft-bristle toothbrush was allowed. Sutures were removed after 7 days; the patient was enrolled in a periodontal maintenance program (i.e., professional plaque control and oral hygiene instruction) weekly during the first month, then monthly during the consecutive months. After 20-month follow-up, a reduction of probing depth to 3 mm and radiographic bone fill could be observed (Figure 6).

**DISCUSSION**

Because of the similarities between the inflammatory diseases induced by biofilm accumulation on teeth and implants, some approaches that have been proposed to treat peri-implant diseases were initially based on previous evidences for treatments of periodontal diseases. In this context, the primary goal of
peri-implant disease treatment is the reduction of microbial challenge and control of the inflammatory reaction to re-establish a healthy peri-implant tissue. The therapeutic modalities for peri-implantitis comprise a non-surgical approach and surgical approach. The non-surgical approach includes mechanical debridement alone or combined with anti-septic agents or laser devices. The surgical approach includes open flap surgery that may be associated with resective or regenerative techniques. Although the non-surgical therapy could be effective for treating peri-implant mucositis, it does not seem to be as effective for peri-implantitis as it is for teeth. In peri-implantitis, the surgical approach has shown to perform better than non-surgical techniques.

The surgical approach allows better access to defects and provides a better access for implant surface decontamination. In this context, the literature reports that only mechanical debridement on roughened implant surfaces contaminated with bacteria may have limited effect; the adjunctive use of chemical agents is recommended to improve treatment outcomes. However, there is no evidence in the literature to demonstrate a superior decontamination method. In order to decontaminate the implant surface, a wide range of methods have been proposed in the literature, such as mechanical debridement, the use of antiseptics/antibiotics and laser therapy. In an experimental study, the influence of the non-surgical approach associated with non-submerged healing and the surgical approach associated with various implant surface decontamination methods (laser therapy; ultrasonic debridement; plastic curettes associated with local application of metronidazole gel) and submerged healing was evaluated in peri-implantitis lesions in dogs. The authors observed that all treatments resulted in improvement of clinical parameters; however, the surgical approach associated with implant surface decontamination and submerged healing leads to better radiographic improvement. Moreover, when the specimens were evaluated histologically, surgical approaches also demonstrated better bone–implant contact compared to non-surgical approach. In the present case, the surgical approach was performed and associated with decontamination of the implant surface using gauze soaked with 10% povidone-iodine solution. Povidone-iodine solution is considered an inexpensive and nonhazardous broad-spectrum antiseptic that has been used as an adjunct in periodontal therapy; it has demonstrated by a systematic review that it may improve PD reduction during scaling and root planing. The application of povidine-iodine with gauze was chosen to avoid damage to implant surface by metal curettes and ultrasonic tips or risk of surgical emphysema by air powder abrasives. Additionally, the correction of peri-implant defect should be one of the treatment objectives to allow efficient biofilm control by the patient and to eliminate micro-environments favorable for a pathogenic microbiota. The correction of these defects can be obtained by resective or regenerative techniques; however, the latter are preferable because the ultimate goal of peri-implantitis treatment is to regenerate lost tissue and re-establish the osseointegration along the previously contaminated implant surface. Autogenous...
bone, xenografts, alloplastic materials and membranes have been used in regenerative techniques, which demonstrate variable levels of bone fill and re-osseointegration.\textsuperscript{11,17,18}

In an animal model study, the regenerative treatments for bone defects around implants were evaluated. The defects were randomly assigned to receive the following: a bioabsorbable membrane; a mineralized bone xenograft; or a combination of both. The results showed non-significant difference regarding the range of bone fill among all the three treatments.\textsuperscript{19} In a clinical study, the treatment of peri-implantitis defects using autogenous bone grafts was evaluated in 25 implants diagnosed with peri-implantitis from 17 patients.\textsuperscript{18} During the observation period of up to 3 years, the use of autogenous bone graft demonstrated to be an efficacious treatment approach for restoring hard tissue lost by peri-implantitis. In another clinical study, three different techniques of bone regeneration in peri-implantitis lesions were compared: autogenous bone graft alone or associated with resorbable or non-resorbable barrier.\textsuperscript{20} At the 3-year follow-up evaluation, it was observed that all treatments revealed significant improvement of peri-implant probing depth from baseline; however, differences in surgical approach did not affect the treatment outcome. Therefore, this study concluded that the additional application of barrier does not improve the overall treatment outcome. This is in accordance with a case-control study comparing the use of a bone substitute alone or associated with a resorbable membrane with a follow-up over 3 years where no significant difference in defect bone fill was observed.\textsuperscript{21} The current literature demonstrates no additional beneficial effect on the use of membranes associated with grafts,\textsuperscript{11,19-21} membrane exposure as a frequent complication,\textsuperscript{11,20,22} and the use of autogenous bone graft is effective for treating peri-implant bone defects.\textsuperscript{18} Therefore, it was decided to use autogenous bone graft alone in the present case to avoid complications related to membrane exposure during the healing period.

Regarding the amount of defect bone fill, the chosen material as well as the peri-implant defect configuration are important and play a key role in treatment.\textsuperscript{11,23} A clinical study investigating the impact of defect configuration on the clinical outcome of surgical regenerative therapy using a xenograft in combination with a collagen membrane in peri-implantitis lesions demonstrated that intra-bony/circumferential defects tend to obtain higher improvements in probing depth reduction and clinical attachment level when compared with circumferential defects or semi-circumferential associated with buccal dehiscence at 6 and 12 month follow-up.\textsuperscript{23} In the present report, the peri-implant defect presented a favorable anatomical configuration. Despite a buccal bony dehiscence, the mesial, distal and lingual bone crest still remained in the level of the top of the implant, which could allow the autogenous graft placement and reposition of the mucoperiosteal flap in an adequate position. The radiographic examination after 20 month follow-up reveals the defect filling (Figure 6). However, the radiographic image cannot elucidate the type of healing or if re-osseointegration has occurred in fact. Nevertheless, this result does not discredit the clinical benefits obtained in this case by the regenerative approach, such as probing depth reduction and peri-implant
defect filling, which can promote better conditions for adequate hygiene and a less favorable environment for anaerobic pathogens.

**CONCLUSION**

The therapeutic approach for treatment of peri-implantitis using open flap debridement and iodine solution associated with autogenous bone graft was able to promote clinical and radiographic benefits in the case reported. However, it is not established in the literature which controlled clinical trials with long-term follow-up are necessary to elucidate this question.

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**Disclosure**

The authors report no conflicts of interest with anything mentioned in this article.

**References**


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En Masse Intrusion Of Maxillary Anterior Teeth Using Titanium Mini Implants As An Intraoral Anchorage: A Clinical Study

Rita Kashyap, MDS¹ • Pooja Chavan, MDS² • Ruchi Saxena, MDS³
Vijay Naik, MDS⁴

Abstract

Background: To evaluate efficacy of titanium mini implants as an effective means of anchorage for en masse intrusion of maxillary anterior teeth and to determine amount of intrusion achieved.

Materials and Methods: 10 subjects seeking orthodontic treatment in Department of Orthodontics, Institute of Dental Sciences, Belgaum, with deep bite requiring intrusion of maxillary anterior teeth. After initial alignment and leveling, the maxillary arch was divided into one anterior segment and two posterior segments using 19 x 25 stainless steel arch wire. Mini implants between lateral incisor and canine were placed bilaterally and loaded immediately using pre-stretched elastic chains. Central incisor and canine linear vertical movement, and central incisor angular movement were evaluated before and after intrusion using lateral cephalograms.

Results: The amount of intrusion achieved for incisors was 2.90 + 0.84mm and canine was 3.05 + 0.64mm with axial inclination of incisors being relatively stable. Intrusion achieved was statistically as well as clinically significant (p < 0.01). The average duration of intrusion was 3.75 + 0.85 months with a mean rate of intrusion of canine being 0.81mm/month and that of the incisors was 0.77mm/month.

Conclusion: Mini implants proved to be an efficient and stable source of anchorage for en masse intrusion of the six maxillary anterior teeth. The amount of intrusion of incisors and canine was statistically and clinically significant. However, long-term studies are required to evaluate the stability of the intrusion achieved during the post treatment period.

KEY WORDS: Orthodontics, anchorage, mini dental implants, occlusion

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INTRODUCTION

Deep overbite is a common component of malocclusion in adults and children. It can be corrected with various treatment modalities, but the best option will depend on the patient’s characteristics and the treatment objectives. Esthetic considerations are also important in deep bite treatment. Nonsurgical treatment alternatives include molar extrusion, incisor intrusion, or a combination of both.1

Correction of deep bite by extrusion of posterior teeth is both more difficult to accomplish and less stable especially when it is performed on non-growing patients. Also deep bite with gummy smile would be improved by maxillary intrusion.2 Hence, true intrusion is often a desirable orthodontic tooth movement but limited principally by inadequate dental anchorage. When an arch wire develops an active intrusion force against the anterior teeth, it simultaneously develops an extrusive force and tip-back moment against the anchor molars. This reactive force and moment are opposed mainly by occlusal forces. In some instances, for example high angle cases, occlusal forces may be inadequate and the reactive forces of the anchor molars may cause downward and backward rotation of the mandible. In other cases, such as adult patients lacking posterior teeth for anchorage, orthodontic intrusion may not be a viable option.3

All intra-oral appliances show some degree of anchor loss while extra-oral appliances, although efficient, require extensive patient cooperation. Aesthetics and social issues are also a matter of concern.4 Although endosseous implants, onplants, dental implants and miniplates have been used successfully for orthodontic anchorage, their clinical applications are still limited. Mini-screws have recently been introduced as simpler alternatives with advantages of smaller size, greater number of implant sites and indications, simpler surgical placement and removal, immediate loading and well tolerated by patients.5,6,7

When canines are in deep bite along with incisors, conventional methods cannot be used for intrusion of all the six anterior teeth, because en masse intrusion of six teeth is very difficult in terms of vertical anchorage as higher force values will be required. Thus incisor intrusion is done followed by separate canine intrusion. Various case reports have demonstrated the use of mini implants as a source of anchorage for maxillary incisor intrusion2,8,9 either for intruding four upper incisors or for intruding two upper incisors. It is also stated that to provide anchorage during incisor intrusion, mini-screws can be placed between upper lateral incisors and canines.10 In a case report, mini-implants are used in severe Class II division 2 malocclusion to intrude all maxillary anterior teeth en masse in a single step and implants remained stable throughout treatment.11 Similar clinical study is done using implants as a source of anchorage for intrusion of all the six teeth but had few limitations.12

Therefore, the present study was undertaken to evaluate whether titanium based mini-implants are really efficient as a rigid source of anchorage to achieve significant amount of intrusion of the six maxillary anterior teeth with the following objectives:

1. To evaluate the efficacy of titanium mini implants as an effective means of anchorage for en masse intrusion of maxillary anterior teeth.
2. To determine amount & rate of intrusion achieved of six anterior teeth.

MATERIALS AND METHODS

Ten subjects seeking orthodontic treatment in the Department Of Orthodontics And Dentofacial Orthopedics, Institute of Dental Sciences, Belgium
with deep bite requiring intrusion of maxillary anterior teeth were selected in the study with an informed consent. Patients with flared incisors were excluded.

The mini-implants were made by Denticon, Mumbai. They were self-drilling type, with 1.4mm diameter and 8 mm length. The site selected for the placement of implant was the alveolar bone between lateral incisor and canine at the level of attached gingiva. Availability of sufficient interdental bone and its density at implant site was assessed using panoramic x-rays, and intraoral periapical radiographs (IOPAs). A simplified stent\textsuperscript{13} for implant insertion was used with two L-shaped rectangular wires, facing each other, into the bracket slots adjacent to the mini-screw site. IOPAs were taken to confirm proper position of the stent and corrected if required, for avoiding contact with dental roots. Implants were placed under local anesthesia. An IOPA was taken to confirm the position of implant. Lateral cephalograph was taken as a pre-intrusion record after implant placement. Ethical clearance for the same was obtained from the institute.

**Clinical Set Up (Figure 1)**
The maxillary dental arch was divided into one anterior segment (including six anterior teeth) and two posterior segments. A 19 x 25 stainless steel arch wire was placed in all the three segments. In the anterior segment, three crimpable hooks were placed, two between lateral incisor and canine bilaterally and one in between two central incisors. Implants were loaded immediately using pre-stretched short clear rabbit force elastomeric chain, placed in the form of M-configuration (stretched from crimpable hook between canine and lateral incisor on one side to the implant head, then to the hook between two central incisors, further to the implant head on contralateral side and finally to third hook).

A Dontrix gauge was used to measure the amount of force being applied. A total of 90 gm of intrusive force was applied to the six anterior teeth. The pre-stretched elastomeric chains were also extended from the maxillary molar hooks to the tags incorporated in wire segment distal to canines which delivered 25 gm of Class I force per side to prevent flaring. The patients were recalled every 4 weeks to change elastic chains. Stability of implants and oral hygiene were also checked and all measures were taken to minimize the possibility of soft tissue coverage and inflammation which could directly affect the retention of mini implants.\textsuperscript{14} After achievement of required intrusion, another lateral cephalogram was taken and implants were removed. Method of evaluating treatment changes: Two Lateral cephalometric radiographs taken immediately after the placement of implants and after intrusion of anterior segment were analyzed using three variables.

**Cephalometric landmarks and planes used were as follows: (Figure 2)**
1. Anterior nasal plane (ANS)
2. Posterior nasal plane (PNS)
3. Incisor centroid (Ic)
4. Canine centroid (Cc)
5. PP- Palatal Plane- A line joining ANS- PNS
6. UL\textsubscript{1}: Long axis of the maxillary incisor

**Cephalometric measurements undertaken were:**
1. Maxillary central incisor vertical movement: 
   \(Ic – PP(\text{mm})\) - Perpendicular distance between the incisor centroid and palatal plane. (Fig 3)
2. Maxillary central incisor angular movement: 
   \(UL\textsubscript{1} – PP(\text{degree})\) - Angle between PP and long axis of the maxillary central incisor. (Fig 4)
3. Maxillary canine vertical movement:
   Cc – PP (mm) - Perpendicular distance between the canine centroid and palatal plane. (Fig 5)

   The difference between pre and post intrusion cephalometric measurements was calculated which provided data about linear intrusive movement of maxillary anteriors. The rate of intrusion was derived by dividing the mean amount of intrusion of the anterior segment by the mean treatment time recorded in mm/month.

   The data obtained from the cephalometric measurements, was analyzed using descriptive statistics such as mean, standard deviation and inferential statistic such as paired ‘t’ test.

   **RESULTS**

   The mean value of the difference of the pre and post intrusion value of variable $I_c – PP$ (mm), was $2.90 \pm 0.84$, which denotes the amount of incisor intrusion (Table 1), and for variable $Cc – PP$ (mm), the difference was $3.05 \pm 0.64$. The probability value and the ‘t’ value showed that the change in value was statistic-
Figure 2: Cephalometric Landmarks.

Figure 3: Maxillary central incisor vertical movement: \( Ic \) – PP(mm) Perpendicular distance between the incisor centroid and palatal plane.

Figure 4: Maxillary central incisor angular movement: \( UL_1 \) – PP(degree) Posterior-inferior angle between PP and long axis of the maxillary central incisor.

Figure 5: Maxillary canine vertical movement: \( Cc \) – PP(mm) Perpendicular distance between the canine centroid and palatal plane.
cally significant for both the variables (Table 2). The mean value of the difference of the pre and post intrusion value of variable UL$_1$ – PP (degree), was 0.2 ± 3.58, which denotes the angular changes in the incisor and % of change was 0.183. The probability value (0.8638) and Paired t-test value (0.1765) showed that the change in value was statistically not significant (Table 3). Average duration of intrusion was 3.75 ± 0.85 months. The rate of canine intrusion was 0.81mm/month and that of the incisors was 0.77mm/month.

**DISCUSSION**

Deep bite is one of the commonly encountered clinical situations and its correction is often a major component of orthodontic treatment.

---

### Table 1: Amount of Incisor Intrusion: Ic-PP (millimeters)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Std. Dv.</th>
<th>Mean Diff.</th>
<th>SD Diff.</th>
<th>% of Change</th>
<th>Paired t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intrusion</td>
<td>18.90</td>
<td>2.157</td>
<td>0.00</td>
<td>3.58</td>
<td>15.3439</td>
<td>10.8750</td>
<td>0.0000a</td>
</tr>
<tr>
<td>Post-intrusion</td>
<td>16.00</td>
<td>2.427</td>
<td>2.90</td>
<td>0.8433</td>
<td>0.1830</td>
<td>0.1765</td>
<td>0.8638</td>
</tr>
</tbody>
</table>

* Significant at 1% level of significance (p<0.01)

### Table 2: Amount of Incisor Angular Change: UL$_1$-PP (degrees)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Std. Dv.</th>
<th>Mean Diff.</th>
<th>SD Diff.</th>
<th>% of Change</th>
<th>Paired t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intrusion</td>
<td>16.70</td>
<td>2.137</td>
<td>0.00</td>
<td>2.90</td>
<td>18.2635</td>
<td>14.9919</td>
<td>0.0000b</td>
</tr>
<tr>
<td>Post-intrusion</td>
<td>13.65</td>
<td>2.014</td>
<td>3.050</td>
<td>0.6433</td>
<td>14.9197</td>
<td>15.3439</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

* Significant at 1% level of significance (p<0.01)

### Table 3: Amount of Canine Intrusion: Cc-PP (millimeters)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Std. Dv.</th>
<th>Mean Diff.</th>
<th>SD Diff.</th>
<th>% of Change</th>
<th>Paired t-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-intrusion</td>
<td>109.3</td>
<td>4.900</td>
<td>0.2000</td>
<td>3.5839</td>
<td>0.1830</td>
<td>0.1765</td>
<td>0.8638</td>
</tr>
<tr>
<td>Post-intrusion</td>
<td>109.1</td>
<td>6.367</td>
<td>0.0000</td>
<td>0.1765</td>
<td>0.1830</td>
<td>0.1765</td>
<td>0.8638</td>
</tr>
</tbody>
</table>
Review of the literature reveals a great controversy among the proponents of continuous arch and segmented arch leveling techniques. Various studies have shown that apart from some intrusion and flaring of the anterior teeth, the continuous arch wire treatment predominantly caused deep bite correction by extrusive movement in molar area, concomitant with posterior (bite opening) rotation of the mandible. Also, the high initial vertical force levels resulted in an overloading of the vertical anchorage. Incisor intrusion with little extrusive movement in the molar area, however, is found with the segmented arch technique as recommended by Burstone.15,16

True intrusion without axial inclination change can only be obtained by directing intrusive force through the center of resistance of six anterior teeth which is estimated to be halfway between the midpoint of the four incisors’ centers of resistance and the canines’ center of resistance.11,17 In the present study the implants were placed between the canine and the lateral incisor bilaterally so that the point of application of force is closer to the center of resistance of anterior segment.10 As intrusive force is applied anterior to the center of resistance of a segment, it results in tipping of teeth labially. To prevent this, about 25gm of class I force was applied with a pre-stretched elastic chain which altered the direction of the intrusive force so that true intrusion of the anterior teeth could be achieved along their long axes.11 (Fig 6) A very light force of 15-20 gm per tooth is recommended for intrusion.15 It has been documented that the use of heavier force will not increase the rate of intrusion. Instead it may lead to root resorption.18 In the present study, the intrusive force applied was 45 gm per side which was approximately 15 gm of per tooth. The force was provided by a pre-stretched elastic chain, extending from implants to three crimpable hooks in the wire, in the form of M-configuration. In a similar study, vertical forces were applied using two elastic chains stretched from implants to two crimpable hooks in the wire between lateral incisors and canines bilaterally. But bowing effect in anterior segment was observed with greater canine intrusion than incisors.12 Thus, M-configuration was used to distribute the force uniformly on all anterior teeth by changing the point of force application.

The incisors in this study were intruded to a mean value of 2.90 ± 0.84 mm which was clinically as well as statistically significant. The clinical result of one of the samples is shown (Fig 7). Vertical movement of the incisors was measured as a perpendicular distance from incisal centroid to the palatal plane. It is in accordance with a systematic review and Meta analysis, wherein it is specified that the incisal edge and root apex
are not good reference points because they are not independent of tooth inclination changes. The incisor centroid, defined as a point on the longitudinal axis of the tooth that is independent of any change in inclination, is the reference point of choice. Incisor intrusion achieved in present study is comparable with a study, where upper incisors were intruded in 15 patients to a mean value of 2.8 mm in mean time period of 3.3 months using an implant. However, the major advantage in the present study was that, all the six anterior teeth were intruded at a same time without taxing on the posterior unit, as was done in a case report and a similar study using implants which also showed comparable intrusion results.

The mean incisor angular change noted was 0.20 ± 3.58 which was not statistically significant. Labial tipping of incisors gives the clinical impression of deep bite correction because it influences the vertical incisal edge position. Thus, the change in angulation of incisors is an important parameter to assess true intrusion. Riedel suggested that a large interincisal angle at the end of treatment was associated with relapse of deep overbite. Therefore it is important to establish effective incisal stops and guidance between the maxillary and mandibular incisors. This also corroborates to the fact that the class I force applied in the present study was just sufficient enough to maintain the correct incisor angulations already achieved during aligning.

The canines were intruded to a mean value of 3.05 ± 0.64 which was clinically as well as statistically significant. The variable was however measured with limitations, as it is difficult to identify the canine on a conventional lateral cephalogram, because of superimposition of various structures. In a similar study, during en masse intrusion of all the six teeth, it was observed that the canines were intruded more than the central and lateral incisors. In the present study, this was avoided. The probable reason for this is distribution of the force uniformly on all anterior teeth by changing the point of force application which was closer to the canine in former study.

Implants used in this study were Titanium mini-implants of 1.4 mm in diameter and 8 mm in length. According to Miyawaki et al. the length of the screw was not associated with its stability if the screw was longer than 5 mm, whereas
the diameter of the screw was significantly associated with its stability. Screws ranging from 1.5 - 2 mm in diameter and 4 - 10 mm in length can potentially be in inter-radicular locations. All the implants showed primary stability upon insertion and were loaded immediately. Although some authors recommend a waiting period of about 2 weeks for soft tissue healing before applying orthodontic force, recent studies have proved that immediate loading can be done with no compromise in their stability because they rely on mechanical retention for the anchorage which is sufficient to sustain normal orthodontic loading. In the present study one mini implant showed clinical mobility after 3 months of its insertion. Patients included were observed periodically for periodontal complications but none showed any sign or symptom. So vitality test was not required at the start or during intrusion. The displacement of implant can harm the adjacent vital structures. Hence in a tooth-bearing area 2 mm of safety clearance should be allowed. Extrusion of the posterior segment is a common side effect associated with conventional intrusion mechanics of the anterior teeth. Even with rigidly stabilized posterior units, only four teeth can be intruded at a time with conventional methods so as to keep undesirable forces and moments minimal. Since implants can withstand high forces of as much as 450g, the intrusion of all the six teeth was attempted without adversely affecting the molar position. This study has elucidated the clinical effectiveness of mini implants as a rigid source of anchorage for the purpose of en masse intrusion of maxillary anterior teeth in a single step. This approach not only eases the biomechanics involved, but also reduces the overall duration of intrusion.

Although implants can be used as anchorage during intrusion, yet this decision should be based on risk benefit ratio and individualized treatment plan. Sample size is one of the limitations of the study presented. In this study main focus was on the amount of intrusion achieved. However, long-term studies are required to evaluate the stability of the intrusion achieved during the post treatment period.

**CONCLUSION**

The following conclusions were drawn from the study:

1. Mini implants proved to be an efficient and stable source of anchorage for en masse intrusion of the six maxillary anterior teeth
2. The amount of intrusion achieved for both incisors (2.90 ± 0.84mm) and canine (3.05 ± 0.64) was statistically as well as clinically significant with axial inclination of incisors being relatively stable.
3. The average duration for intrusion was 3.75 ± 0.85 months, with the mean rate of canine intrusion at 0.81mm/ month and that of the incisors at the rate of 0.77mm/ month.

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Disclosure
The authors report no conflicts of interest with anything mentioned in this article.

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This brief review is an update about adult stem cells obtained from oral tissues and their therapeutic use through tissue engineering techniques in order to produce the tissues needed to repair/regenerate, from bone or tooth tissue lost to an entire bioengineered tooth.

**KEY WORDS:** Stem cells, dental progenitor cells, tissue engineering, periodontal regeneration.

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INTRODUCTION

The stem cell studies in recent years have been considered the most advanced type of medical-scientific research and early results have aroused great expectations.1 Also in dentistry many studies were performed with the final aim of obtaining new bone and new teeth.2 Tooth maladies are widespread in industrial countries; for example, approximately two thirds of German citizens suffer from periodontal disease, which is a frequent cause of tooth loss.3 When permanent teeth are damaged or lost, they do not regenerate therefore, compromises oral health. Although several clinical therapies to solve tooth loss problems, such as artificial denture and dental implants, there are consideration about safety and treatment time issues.4

Scientists in the field of regenerative medicine and tissue engineering are now applying the principles of cell transplantation, material science, and bioengineering to construct biological substitutes that will restore and maintain normal function in diseased and injured tissues.5 Tissue engineering aims to stimulate the body either to regenerate tissue on its own or to grow tissue outside the body which can then be implanted as natural tissue. The tooth tissue engineering field has evolved rapidly because of the advantages that would represent to health.4 Stem cell biology provides promising methods in vitro as well as in vivo in animal models which make speculation about a future application in human dentistry reasonable6 and is thought to be a promising way to replace the missing tooth.4 Stem cells are cells which divide to produce one stem cell and one cell capable of differentiation even as necessity demands.6

Figure 1a: Dental pulp.

Figure 1b: SHED is pointed by blue arrow.

Stems cells classified into embryonic and adult or post-natal. The use of embryonic stem cells which are pluripotent generates many ethical concerns regarding the consumption of blastocystes.7-9 This makes adult stem cells a more
viable approach for translation into clinical dental practice,\textsuperscript{10} although they are not pluripotent, still exhibit a limited differentiation potential from uni-, bi- to multi-potentiality.\textsuperscript{11} In this last category, dental tissues are classified and its stem cells have been isolated from the dental pulp, exfoliated deciduous teeth, the periodontal ligament (PDL), the dental follicle and the dental papilla. Stem cell markers such as STRO-1 were used for the characterization and isolation of stem cells.\textsuperscript{6} These mesenchymal stem cells (MSCs) are multipotent stem cells which can differentiate into a variety of cell types\textsuperscript{4} that might not be identical to the parent tissue.\textsuperscript{11} These adult dental stem cells are able to differentiate into many dental components, such as dentin, PDL, cement and dental pulp tissue, but not into enamel.\textsuperscript{6} The objective of this review is to give an overview on recent literature about dental-related stem cells for their respective use in regenerative medicine and dentistry.

**Stem cells origin**

The combination of cells, suitable biomaterials, and biochemical factors are important in tissue engineering to improve or replace biological functions. Isolated cells can be cultivated using tissue engineering in vitro prior to in vivo transplantation.\textsuperscript{12} The future goal is to regenerate human autologous functional teeth, analogous to the experimental animal model created 3 years ago by Ikeda et al.\textsuperscript{15}

Dental epithelial stem cells have an ectodermal origin and are able to arise ameloblasts to induce odontogenesis. Unfortunately, these cells are lost after eruption so they are not available for cell therapy.\textsuperscript{16} In animal models, epithelial stem cells have been obtained from third molars of newborn or juvenile animals.\textsuperscript{17}

Dental mesenchymal stem cells have an ectomesenchymal origin and are involved in odontogenesis forming almost all dental tis-
issues with the exception of enamel.\textsuperscript{9} Mesenchymal stem cells can differentiate into nerve, muscle, fat, cartilage or even bone cells.\textsuperscript{6} Non-dental stem cells are multipotent cells that can also regenerate dental tissue.\textsuperscript{18} They have been harvested from embryonic oral epithelium, human bone marrow, odontomas, hair follicles, adipose and dermal tissue.\textsuperscript{6}

**Dental Pulp Stem Cells – DPSCs**

These DPSCs display similar features as bone-marrow-derived mesenchymal stem cells (BMSCs). That is why both cell types adhere to plastic and are colony-forming cells. In contrast to bone-marrow-derived cells, DPSCs were found to differentiate into odontoblast-like cells. These cells also shared characteristics of osteoblast-like cells. Since 2008, BMSCs are being used in humans in sinus augmentation procedures,\textsuperscript{19} suggesting that DPSCs might work as well being less invasive when extraction is indicated according to the dental Implant treatment.

A DNA microarray study could distinguish DPSCs from bone-marrow-derived mesenchymal stem cells,\textsuperscript{20} where DPSCs differentially express cell-cycle-associated genes.\textsuperscript{21} In other study, DPSCs were also found to differentiate into adipocytes or neural-like cells.\textsuperscript{22} Fascinatingly, dental stem cells are located in the perivascular niche and express the stem cell marker Stro-1.\textsuperscript{23} Recently, a special stem cell population was isolated from the dental pulp.\textsuperscript{24} These cells can be induced to undergo uniform differentiation into smooth and skeletal muscle cells, neurons, cartilage and bone cells under chemically defined culture conditions. Stem cells derived from the dental pulp are often mentioned in recent discussions about regenerative endodontology,\textsuperscript{25,26} inducing differentiation into odontoblasts similar to the therapy that induce tertiary dentin, giving a new approach to heal perforated roots.\textsuperscript{27} Dental pulp can be harvested from third molars or pulp-ectomized teeth left in situ,\textsuperscript{28} therefore some organ storage companies around the globe are taking advantage of these potential therapy alternative.

DPSCs while having an in vitro analysis may differentiate into osteo/dentinogenic, adipogenic, chondrogenic, myogenic and neurogenic cells.\textsuperscript{21,22} The ectopic tissue formation displayed in vivo is dentin-pulp-like complex, odontoblast-like cells\textsuperscript{29} and bone-like tissue with Haversian canals and living autologous fibrous bone tissue,\textsuperscript{30,31} besides promotes angiogenesis (Fig. 1a).\textsuperscript{32}

**Stem cells from Human Exfoliated Deciduous teeth – SHEDs**

SHEDs while having an in vitro analysis may differentiate into dentinogenic, adipogenic,
in vivo is PDL-like formation and cementum matrix formation (Fig. 1d)."6

**Periodontal Ligament Stem Cells – PDLSCs**
It can be harvested from the roots of extracted teeth."6 While having an *in vitro* analysis may differentiate into osteo/cementogenic, adipogenic, chondrogenic and neurogenic cells, but still the myogenic potential is not determined yet."1,39 The ectopic tissue formation displayed *in vivo* is PDL, cementum, bone and cartilage-like tissues."40 Combined with SCAP, a root and periodontal complex was formed in animal model."35 Recently, it was mentioned is time to apply stem cells from human periodontal ligament, but must take into account various factors (Fig. 2), such as appropriate delivery devices, immunogenicity, autologous cells vs. allogeneic cells, which tissues provide the most appropriate donor source, control of the whole process and cost-effectiveness are all important considerations that should not be overlooked."5

**STRO-1, an important stem cell marker**
This marker helps to identify, characterize and isolate stem cells and is one of the early surface markers of mesenchymal stem cells which is commonly used. Its expression diminishes gradually during its cultivation of the stem."1,34,42 There are more SC positive markers such as STRO-1 and CD44, and CD34.

**Future perspectives**
Over the years, titanium dental implants surface have improved by plasma sprayed, acid etch, hydroxyapate coats and combination of acid etched and grit blasted."43 There have
been even intentions to combine osseointegration with stem cells for humans by bioengineered periodontal tissue formed on titanium implants. In 2010 was reported the development of clinically relevant methods for autologous PDL regeneration on titanium implants.44

We might be close to accept the transition from xenodontics (titanium implants), which will be considered in the category of traditional dentistry, to biodontics (tissue-engineered tooth derived from SC).4,15,45,46

CONCLUSION

The adult dental stem cells can be used to regenerate different dental tissues. To regenerate dentin or pulp tissue, DPSCs, SHEDs and SCAPs are suitable. The periodontium can be generated from PDLSCs or DFSCs. In a near future, it is possible that clinicians use these forms of tissue engineering to regenerate lost portions of the periodontium and teeth based on these concepts of tissues development. These types of therapeutic approaches based on tissue engineering and stem cell biology for organogenesis have considerable potential; even an entire tooth could be developed. The time is now ripe to move from animal studies to human clinical trials.

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Disclosure

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Background: Preeclampsia is an obstetric complication that affects 7-10% of pregnant patients resulting in significant morbidity and/or mortality to the mother and fetus. Though the biologic basis for the development of preeclampsia is poorly understood, current research indicates that the disorder is a syndrome of excessive inflammatory immune responses. Recent studies have shown an association between periodontal disease and a number of systemic diseases including preeclampsia. The link between these maladies is thought to arise from immunologic responses to the chronic burden of endotoxin elicited inflammatory cytokines of periodontal disease. Previous studies examining the relationship between periodontal disease and obstetric complications such as preterm labor and preeclampsia have focused on inflammatory cytokines such as prostaglandin PGE2, interleukin-1β (IL-1β), and C-reactive protein. With current theories on the etiology of preeclampsia focusing on Th-1 cytokines such as interferon gamma (IFN-γ) and interleukin-12 (IL-12), the goal of this pilot study was to compare serum levels of IFN-γ and IL-12 in preeclamptic women with and without periodontal disease.

Materials and Methods: A study population of 8 total women, 5 with no periodontal disease and preeclampsia (Group 1) and 3 with periodontal disease and preeclampsia (Group 2) had peripheral venous blood sampled at the time of parturition. Serum IFN-γ and IL-12 concentrations were determined via enzyme linked immunosorbent assay (ELISA). Additional data such as gestational age, birth weight, and demographic data were also collected.

Results: The differences in p-value between Groups 1 and 2 for IFN-γ and IL-12 blood concentrations were statically significant. In all cases of this pilot study, preeclamptic patients with periodontal disease had elevated levels of both IL-12 and IFN-γ when compared to preeclamptic patients without periodontal disease (Figures 4, 5). In no case did the maximum Group 1 IFN-γ or IL-12 concentrations exceed the minimum IL-12 or IFN-γ concentrations of Group 2.

Conclusions: In this pilot study of 8 preeclamptic patients, serum concentrations of IL-12 and IFN-γ were elevated to statistically significant levels in patients with untreated periodontal disease. Although promising, the results of this pilot study must be critically examined. The small study population in this pilot study does not provide adequate statistical power to make definitive conclusions about the potential for elevated IL-12 and IFN-γ levels in periodontitis patients to contribute to the pathogenesis of preeclampsia. To confirm the results of this pilot study, additional studies with larger sample populations are warranted.

KEY WORDS: Preeclampsia, periodontal disease, interleukin-12, interferon gamma

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BACKGROUND

Preeclampsia is an obstetric complication that affects 7-10% of pregnant patients resulting in significant morbidity and/or mortality to the mother and fetus.\(^1\)\(^-\)\(^7\) This pathologic condition is clinically diagnosed via the presentation of hypertension with proteinurea in mid to late gestation and may be associated with intrauterine growth restriction, preterm delivery, low birth weight, and/or maternal hypertensive crisis.\(^8\)\(^-\)\(^10\) Though the biologic basis for the development of preeclampsia is poorly understood, current research indicates that the disorder is a syndrome of excessive inflammatory immune responses.\(^11\)\(^-\)\(^24\) Recent studies have shown an association between periodontal disease and a number of systemic diseases including preeclampsia.\(^25\)\(^-\)\(^39\) The link between these maladies thought to arise from immunologic responses to the chronic burden of endotoxin elicited inflammatory cytokines of periodontal disease.\(^16\)\(^,\)\(^25\)\(^,\)\(^30\)\(^,\)\(^36\) Previous studies examining the relationship between periodontal disease and obstetric complications such as preterm labor and preeclampsia have focused on inflammatory cytokines such as prostaglandin PGE2, interleukin-1\(\beta\) (IL-1\(\beta\)), and C-reactive protein.\(^31\)\(^,\)\(^39\)\(^,\)\(^40\) With current theories on the etiology of preeclampsia focusing on Th-1 cytokines such as interferon gamma (IFN-\(\gamma\)) and interleukin-12 (IL-12), the goal of this pilot study was to compare serum levels of IFN-\(\gamma\) and IL-12 in preeclamptic women with and without periodontal disease.

MATERIALS AND METHODS

Study Population

The study protocol was reviewed and approved by the Responsible Conduct of Research Department and the Institutional Review Board of the National Naval Medical Center (NNMC) in Bethesda, Maryland. All participants were provided with a verbal explanation of the study and each signed a detailed consent form prior to enrollment. All study participants were diagnosed with mild preeclampsia by the NNMC Obstetrics-Perinatal Medicine Department prior to enrollment. Mild preeclampsia was defined by blood pressures of at least 140/90mm Hg obtained in two consecutive measurements at least 6 hours apart after 20 gestational weeks with concurrent proteinurea of at least 0.3gm/24 hours or greater than 30mg/dl in a single specimen. Study participants were considered systemically healthy prior to the onset of their pregnancy and all satisfactorily passed exclusion criteria standards. Exclusion criteria for this...
study included a history of diabetes, asthma, cardiovascular complications, chronic hypertension, renal disorders, gastric ulcers, chronic infectious diseases, and/or any condition that required antibiotic prophylaxis prior to dental treatment. Patients with severe preeclampsia, defined by blood pressures $\geq 160/110$ mm Hg obtained in two consecutive measurements at least 6 hours apart, serologic evidence of end organ damage, or $> 5$ gm of proteinuria in 24 hours, were also excluded as immediate delivery was typically indicated in such situations.

**Measurements of Periodontal Status**

Upon enrollment in the study, subjects received a full mouth periodontal examination (Figure 1) evaluating the following clinical parameters: probing depth (PD), clinical attachment loss (CAL), furcation involvement, tooth mobility, bleeding upon probing (BOP), and oral hygiene status. Oral hygiene was assessed by the percentage of tooth surfaces (4 per tooth) demonstrating plaque. Measures of supragingival plaque were made by staining the teeth with an Erythrosin disclosing tablet. PD, CAL, and BOP measurements were made by a single examiner (DH) at six sites per tooth using a 15mm UNC probe. CAL was measured using the cemento-enamel junction (CEJ) as a reference point and BOP was determined by the presence of blood within 30 seconds of probing. Patients with PD $\geq 5$ mm on 3 or more teeth with concurrent CAL $\geq 3$ mm and a bleeding index score of 33% were diagnosed as having periodontal disease. Patients not meeting these criteria were considered periodontally healthy.

**Study Group Assignment**

Upon determination of their periodontal health status, study participants were assigned to one
of two groups: (Group 1) Preeclamptic patients without periodontal disease or (Group 2) Pre-
eclamptic patients with periodontal disease.

Recording of Maternal Characteristics
Demographic data and maternal obstetric measurements such as blood pressure, gesta-
tional age and birth weight of the child at delivery were recorded. Parturition prior to
37 weeks was considered preterm labor while infants with a delivery weight under 2500gm
were considered to be of low birth weight.

Serum Sampling
Participants had peripheral venous blood sampled at the time of parturition (Figure
2). At each sampling, 20ml of blood was drawn into sterile plastic blood collection
tubes and centrifuged at a rate of 3,100 RPM for 10 minutes to separate serum. Separ-
ated serum samples were transferred to

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Participant Age</th>
<th>Gestational Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclamptic women without periodontal disease n=5</td>
<td>28.4 (±4.87) years</td>
<td>37.4 (±1.52) weeks</td>
</tr>
<tr>
<td>Group 2</td>
<td>Participant Age</td>
<td>Gestational Age</td>
</tr>
<tr>
<td>Preeclamptic women with periodontal disease n=3</td>
<td>35.6 (±2.08) years</td>
<td>31.0 (±7.21) weeks</td>
</tr>
</tbody>
</table>

| p Value | 0.0539 | 0.0902 |

Holtzclaw

Determination of Cytokine Concentration
Serum IFN-γ and IL-12 concentrations were determined via enzyme linked immunosorben-
t assay (ELISA) (Figure 3) using commercially available kits (R&D Systems, Minneapolis, Min-
nesota, USA). IFN-γ ELISA Kit #DIF50 and IL-12 Kit #D1200 were run according to the
manufacturer’s directions. Optical densities of the processed samples were determined
in a microplate reader with wavelength cor-
rection set to 550nm. Duplicates of each
serum sample were tested and the mean
value for each combination was reported.

Statistical Analysis
All data analyses were performed with the InStat statistical analysis program (GraphPad Soft-
ware, Inc., San Diego, California, USA). The
The data reported in this pilot study are presented as means ± standard deviation. Differences in meaned data were tested with a paired Student’s T test and a two-tailed p value of < 0.05 was considered to be statistically significant.

### RESULTS

A total of 8 women (Table 1) participated in this pilot study with 5 women comprising Group 1 (preeclamptic patients without periodontal disease) and 3 women comprising...
Group 2 (preeclamptic patients with periodontal disease). The mean gestational ages of infants delivered to patients in Groups 1 and 2 were 37.4 weeks (± 1.52) and 31.0 weeks (±7.21) respectively (p=0.09) while the mean birth weights of these same infants were 3,063 grams (±860.4) and 1,843 grams (±1,443.7) (p=0.16) (Table 2). The differences in p-value between Groups 1 and 2 for gestational age and birth weight were statically significant. Mean serum sample concentrations for IFN-ϒ and IL-12 are reported in Table 3. Again, the differences in p-value between Groups 1 and 2 for IFN-ϒ and IL-12 blood concentrations were statically significant. In all cases of this pilot study, preeclamptic patients with periodontal disease had elevated levels of both IL-12 and IFN-ϒ when compared to preeclamptic patients without periodontal disease (Figures 4, 5). In no case did the maximum Group A IFN-ϒ or IL-12 concentrations exceed the minimum IL-12 or IFN-ϒ concentrations of Group B.

**DISCUSSION**

Multiple studies have proposed that abnormal activation of the maternal immune system plays an important role in the etiology of preeclampsia. The maternal immune system of normal pregnancies displays a Th2 cytokine profile composed of interleukin-4 (IL-
Figure 5: IFN-ϒ blood concentrations of study participants. Blood samples of preeclamptic patients with periodontal disease are circled in red.

4), interleukin-5 (IL-5), interleukin-10 (IL-10), and interleukin-13 (IL-13). The maternal immune system of preeclamptic patients, on the other hand, undergoes an immunity shift from a Th2 to a Th1 cytokine profile with the cytokines interleukin-2 (IL-2), IL-12, tumor necrosis factor alpha (TNF-α), tumor necrosis factor beta (TNF-β), and IFN-ϒ predominating. The Th1 cytokine IFN-ϒ has an intimate relationship with the immunoregulatory cytokine IL-12 as each factor regulates one another via feedback loops. In the placentas of preeclamptic women, IFN-ϒ is theorized to prime decidual macrophages to produce elevated levels of IL-12. IL-12, in turn, primes decidual natural killer cells to produce elevated levels of IFN-ϒ. A vicious cycle is established as each cytokine effectively upregulates on another. Through different mechanisms, both IFN-ϒ and IL-12 demonstrate potent suppressive properties that may have a deleterious effect on human pregnancies. During fetal development, invading cytotrophoblasts utilize matrix metalloproteinases (MMP) to degrade maternal decidual tissues in the placenta as they attempt to establish and maintain uteroplacental circulation. IFN-ϒ mediated inhibition of MMP’s 1, 3, 7, and 9 interferes with decidual trophoblast migration and may play a key role in the placental spiral
artery modification seen in preeclampsia.\textsuperscript{58-59} IL-12, on the other hand, may act as a regulator of preeclamptic placental angiogenesis via inhibition of vascular endothelial growth factor (VEGF).\textsuperscript{60-66} Decreased VEGF concentrations found in preeclamptic patients is theorized to result in endothelial cell dysfunction and subsequent incomplete trophoblast proliferation, invasion, and migration required for normal placentation.\textsuperscript{66-68} With multiple studies showing preeclamptic patients having elevated IFN-$\gamma$ and IL-12 concentrations, the altered cytokine profile may prove essential to the etiology of preeclampsia.\textsuperscript{69-74,105}

Reports on cytokine profiles for periodontal disease have been mixed with some studies showing periodontal disease to be associated with a Th2 cytokine profile and others showing a combination of Th2 and Th1 cytokine profiles.\textsuperscript{75-82} The explanation for these mixed results may lie in the fact that Th2 cytokines are predominant during active phases of periodontal destruction while a mix of Th1 and Th2 cytokines are present during quiescent stages of periodontal disease.\textsuperscript{46,83,84} Currently, there is no single test to distinguish between actively destructive or quiescent phases of periodontal disease. Depending on whether studies were conducted during times of actively destructive versus quiescent periods of periodontal disease, it is understandable that mixed results for periodontal cytokine profiles have been noted.

In spite of these mixed findings for periodontal cytokine profiles, one constant finding is that localized periodontal tissue and systemic serum concentrations of IFN-$\gamma$ are elevated during periods of periodontal inflammation.\textsuperscript{80-83} A reason for IFN-$\gamma$’s dual utilization may lie in the fact that it is an inhibitor of osteoclastogenesis and MMP production.\textsuperscript{94-97} During active phases of periodontal disease, increases in IFN-$\gamma$ may temper inflammatory destruction of the supporting tissues. In quiescent phases, increases in IFN-$\gamma$ may strike a delicate balance with destructive cytokines allowing for a tenuous reprieve from periodontal breakdown.

With both active and quiescent periodontitis producing elevated levels of IFN-$\gamma$, systemic distribution of this cytokine could have undesirable consequences, especially due to its intimate relationship with IL-12. Multiple studies have shown preeclamptic patients to have elevated IL-12 levels.\textsuperscript{20,41,42,70} While macrophages and monocytes represent the main source of IL-12 production in preeclampsia, their numbers are not statistically different between preeclamptic and non-preeclamptic patients.\textsuperscript{20,42} Such an observation suggests...
that the properties of monocytes and macrophages are altered in preeclamptic patients. A potential cause for altered monocyte properties in preeclamptic patients may be linked to IFN-\(\gamma\). It is well documented that IFN-\(\gamma\) has the ability to prime monocytic cells for excessive cytokine production and recent studies have proposed that in preeclamptic patients, macrophages are a likely source of increased IL-12 production.\(^{41,42}\) Because periodontal disease increases systemic IFN-\(\gamma\) levels, hematogenous dissemination of this cytokine may be a contributory monocyte/macrophage priming agent in preeclampsia (Figure 6).

Linking periodontal disease to an increased risk for preeclampsia has been accomplished with numerous comparative case controlled studies.\(^{25,27,36,39,97,98,99,100}\) While there is convincing evidence showing an association between the two diseases, the mechanism of action conjoining periodontitis with preeclampsia is poorly understood. A recent study by Politano et al.\(^{101}\) performed a case control analysis of 116 pregnant women, 58 with preeclampsia and 58 without. This study found a correlation between periodontitis and preeclampsia (adjusted odds ratio of 3.73, 95% confidence interval 1.32-10.58), but failed to demonstrate a link between the diseases via the cytokine profile of IL-6 and TNF-\(\alpha\). Multiple independent studies have demonstrated both disease processes have elevated IL-12 and IFN-\(\gamma\) levels and the results of this pilot study show trends in which periodontitis may contribute to the pathogenesis of preeclampsia via the IL-12/INF-\(\gamma\) pathway. In all cases of this pilot study, preeclamptic patients with periodontal disease had elevated levels of both IL-12 and IFN-\(\gamma\) when compared to preeclamptic patients without periodontal disease. In no case did the maximum Group 1 (preeclamptic patients without periodontal disease) blood concentrations IFN-\(\gamma\) or IL-12 exceed the minimum IL-12 or IFN-\(\gamma\) blood concentrations of Group 2 (preeclamptic patients with periodontal disease).

**CONCLUSIONS**

In this pilot study of 8 preeclamptic patients, serum concentrations of IL-12 and IFN-\(\gamma\) were elevated to statistically significant levels in patients with untreated periodontal disease. Although promising, the results of this pilot study must be critically examined. The small study population in this pilot study does not provide adequate statistical power to make definitive conclusions about the potential for elevated IL-12 and IFN-\(\gamma\) levels in periodontitis patients to contribute to the pathogenesis of preeclampsia. To confirm the results of this pilot study, additional studies with larger sample populations are warranted.

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Disclosure

The author reports no conflicts of interest with anything mentioned in this paper.

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References


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- 5 months postoperative

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