Treatment and Quality of Life Outcomes Following Guided Bone Regeneration Procedure

Thesis

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By

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Abstract

**Objective:** The purpose of this study was to determine the effects of a guided bone regeneration (GBR) procedure on general and oral health-related quality of life. Changes in patient stress, depression, anxiety and coping levels during early wound healing were also evaluated.

**Material and Methods:** Sixteen non-smokers (mean age 60±4 yrs; 9 males), treatment planned to receive GBR for a single large size (≥2 adjacent missing teeth) defect (total of 17 sites), were recruited. Ridge width (RW) and ridge relative height (RRH), flap thickness (FT), keratinized tissue width (KTW) and clinical evaluation of the wound were recorded at surgery, 1 week, 1 month and 4 months. Wound fluid was collected and its content was studied for various wound healing related mediators. Pre- and post-surgical evaluation of perceived stress, depression, anxiety, coping and general health assessments were conducted as well as General Health (GHQ-12) and Oral Health Related Quality of Life (OHIP-49) questionnaires.

**Results:** Size of the wounds at various anatomical locations was similar. A slight but statistically significant gain in RW was noted (7.5±0.7 mm versus 8.6±0.6 mm; p=0.02). The difference detected at RRH was not statistically significant (12±0.6 mm versus 10.7±0.8 mm; p=0.057). Mean FT was 1.3±0.1 (0.6-2.5) mm. KTW remained unchanged. Primary wound closure was obtained in all cases except one. Eighty-eight and 35 percent of the sites had clinical wound exposure at 1 week and 1 month, respectively. Actual
exposure was 3.8±0.7 mm and 2±0.8 mm at 1 week and 1 month, respectively. Wound fluid volume decreased 2 fold by 1 month. Interestingly, most of the pro-inflammatory mediators reached picked levels at 1 month and not earlier. GHQ-12 and OHIP-49 scores were stable throughout the study. Eighty-eight and 44 % of the patients reported some pain at surgical site at 1 week and 1 month. Baseline mean Depression Scale (CES-D) score was 7±2 with only two patients having ≥16. A statistically non-significant increase was noted in CES-D at 1 week after surgery (mean 11±2; with an additional 5 subjects reaching ≥16). The decrease observed in CES-D following 4 months of healing to baseline levels was statistically significant (p=0.02). Similarly, a decrease was noted in PSQI levels (6±1 versus 4±1; p=0.08) as well as an increase in health survey (SF-36 total; specifically in SF-energy fatigue [62.3±4 versus 75.4±3.3 p=0.02]) at 4 months compared to baseline values. Other perceived stress and sleep quality related scores as well as SF sub-surveys showed similar decrease and increase patterns during early healing with differences between various observation times not reaching statistically significant levels (p>0.05).

**Conclusion:** Within the limits of this study, it appears that GBR outcomes to treat large size defects are predictable for ridge width and height preservation. Various clinical parameters can be routinely used to evaluate early healing following GBR. Local pro- and anti-inflammatory responses are delayed compared to clinical parameters at GBR.
wound. Pain intensity and discomfort levels are parallel to wound exposure. Some, but not all, quality of life scores are affected.
Dedication

Dedicated to my Family, Teachers, and Ming Chien
Acknowledgments

I would like to express my special appreciation and thanks to my advisor Dr. Binnaz Leblebicioglu for her insight, help and guidance throughout my Masters. I also would like to thank Dr. Dimitris Tatakis for his help and guidance. I also wish to thank Dr. Lisa Christian for her assistance through the psychological analysis portion of the study. I would like to thank Dr. Tim Eubank for his assistance with the cytokines data in his research laboratory facilities and Mr. Vedat Yildiz for his help in analyzing the data. My sincere thanks also goes to Dr. Lamees Alssum, Lo-Shen Chen, and Nicole Scheckelhoff for their hard work and dedication to assist me throughout the project period. Lastly, I would like to thank all of the Graduate periodontology residents for their support. The Division of Periodontology, The Ohio State University-College of Dentistry, supported this study.
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CHAPTER 1
INTRODUCTION

Wound healing within the oral cavity has distinct characteristics specific to oral mucosa. Etiology of the wound (surgery, trauma, infectious diseases or pathological growth) may induce the initiation of different types of wounds. It is well known that scar formation which generally accompanies fibrosis, occurs less within oral mucosa compared to dermal wound. Nevertheless, scarring may occur at various levels within the lining and masticatory oral mucosa. Despite the continuous bacterial challenge originated from oral flora, and the continuous wetness, saliva and its content are generally beneficial for wound healing. In addition, wound healing occurs around a relatively avascular surface; edentulous site, implant device or denuded root. Thus, even though cellular and biological factors may be similar, the source for these mediators may represent differences within oral cavity itself and also, when one compares a wound within oral cavity to a dermal wound. This, in turn, may differentially affect various phases of wound healing as well as treatment outcome.

**Guided Bone regeneration**

Guided Bone Regeneration (GBR) procedure is one of the surgical protocols where the outcome heavily depends on various phases of wound healing. The principle of specific cell types having access into a given wound space determines the type of newly
regenerating tissues forms the basis of GBR procedure.\textsuperscript{5, 7} GBR generally requires the placement of a barrier membrane occluding the space and some type of bone graft material to maintain the space and to induce surrounding cells to migrate and regenerate bone.\textsuperscript{7} Other than the resorption mechanism and rate, possible biological mediators within the biomaterials placed into bony defect, the wound closure and stability play major role in the quality and quantity of the regenerated bone.\textsuperscript{7, 8, 9} Blood supply necessary for the various phases of wound healing is provided from bone marrow as well as from angiogenesis occurring between flap and newly forming tissues.\textsuperscript{10, 11, 12}

GBR is indicated in cases where there is insufficient bone size/volume for implant placement; in most cases, bone augmentation is needed in horizontal and/or vertical dimensions. It can be performed prior or simultaneous to implant placement. Although it is not ideal, GBR protocol can also be applied to selected cases to improve tissue volume, contour and esthetics around implant or tooth supported prosthesis.\textsuperscript{13, 14} Naturally, approximately 50\% alveolar ridge width reduction is expected within 12 months following tooth extraction.\textsuperscript{15} Studies comparing grafted extraction sites with non-grafted counterparts report statistically significant differences in both bone quality and quantity, although there are significant variations among various studies in relation to study methodology, applied surgical protocol, biomaterials used and selected factors to explore as possible predictors of the outcome.\textsuperscript{16, 17, 18, 19, 20, 21, 22, 23} In general, the preservation of the ridge width can be accomplished but preservation of the ridge height is not as
predictable with GBR protocol. A recent study by Leblebicioglu et al., has evaluated alveolar ridge preservation outcomes in posterior maxilla and mandible. The study results have shown that GBR procedure have notably prevented alveolar ridge height loss. However, ridge width was significantly reduced by 2.5 mm following ridge preservation surgeries with anatomical location being a possible predictor affecting the outcome.

Based on existing evidence, GBR applied to regenerate combination type (bone loss in horizontal and vertical direction) large size defects (e.g more than one missing tooth) does not have a predictable outcome. Tinti & Parma-Benfenati have concluded that GBR procedures attempting to vertically augment alveolar bone ridges remain a challenge. A review paper by Rocchietta et al. (2008) also mentioned that negative bone height values with soft tissue dehiscences when non-resorbable barriers were used. Hence, a conclusion was drawn that vertical ridge augmentation can be accomplished successfully using GBR; however, it is a highly technique-sensitive approach. Another review by Hammerle and Karring reported that vertical bone augmentation outcomes remain controversial where different amounts of bone can be gained depending on the surgical protocol. In addition, Lang et al. have proved that non-resorbable membranes are capable of creating 90-100% bone fill; however, these results were compromised when complications such as infection or membrane exposure occurred.

A wide range of complication occurrence was reported in the literature, ranging
The most common problems that clinicians encounter after GBR surgeries are barrier membrane collapse, exposure, local infection, and incomplete bone formation underlying the used barrier membrane. Barrier membrane exposure is the most common complication. The significance of early membrane exposure on GBR outcomes is controversial. Machtei et al. conducted a meta-analysis that involved 60 sites from 2 studies. The results of this review have shown the non-exposed membranes of GBR sites resulted in 6 times greater new bone formation than exposed membrane sites. The authors also concluded that early membrane exposure has a significant effect on GBR outcomes around dental implants. Nevertheless, other investigators have reported that GBR surgery outcomes might not be jeopardized by early membrane exposure. Mellonig and Triplett have shown that 53% of the sites that received GBR surgeries were not affected by early membrane removal. Additionally, Shanaman suggested that early membrane exposure does not affect GBR outcomes, when the patient maintains an adequate oral hygiene.

Gingival thickness has also been shown to impact the course of GBR wound healing. According to several reports, the thickness of the gingival flap covering the membrane is a significant factor affecting regenerative therapy outcomes. Some reports have suggested 1.5 mm gingival thickness as a prerequisite for GBR therapy.
Oral Health-Related Quality of Life: The effect of surgical wounds on quality of life

Patients’ Quality of life (QoL) is defined as “individuals’ perceptions of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns”. Researchers have been investigating the effect of oral health on patients’ quality of life, hence several instruments have been advocated to measure oral health-related quality of life (OHRoL). Among various behavioral characteristics, compliance of patients with actual treatment protocol, home care and routine controls and their effect on outcomes of several non-surgical and surgical treatments have been intensively studied in Dentistry. However, the possible effect of a large intra-oral wound on daily functions and patients’ quality of life have not been investigated in depth. Similarly, there is significant amount of evidence reporting direct association between psychological stress levels and delayed wound healing, in general. Unfortunately, patients’ pre-surgical depression, anxiety, and coping levels and their effect on an oral surgical intervention and large wound site healing and, vice versa, the effect of a such wound on quality of life have not been studied.

Stress and Wound Healing

Psychological stress is defined as “the process through which environmental demands exceed an individual’s perceived ability to cope, thereby resulting in affective,
behavioral, and physiological changes. There is strong evidence from the medical literature concluding that well-known systemic factors such as age, sex hormones, diabetes, obesity, medications, smoking, systemic disorders, and psychological stress can be related to delayed wound healing. The possible mechanisms involved are the effects of psychological stress in modifying immune response, increase susceptibility to infections and reactivation of viruses. Stress can directly stimulate the hypothalamic-pituitary adrenal and the sympathetic-adrenal medullary axes, resulting in several hormonal and immunological responses. Similarly, it can indirectly affect patient’s health by negatively modifying his/her behavior and emotions.

Almost all of the studies related to stress and its effect on wound healing focus on dermal wound healing. Limited information is available for oral wound healing; In one study, oral wound was induced in healthy students using punch biopsy technique during exam and non-exam periods. Oral wounds created during examination period healed 40% slower than other wounds created during non-exam periods or summer vacation.

The effect of surgical and non-surgical periodontal therapy on patients’ stress, depression, anxiety, and perception of pain levels was evaluated by Kloostra et al. The results of this study suggest that periodontal surgical therapy is associated with higher psychological burdens and poorer well-being than non-surgical therapy on the day of the treatment. In another study, surgical patients reported higher level of pain, use of
medication, and poorer wound healing; hence the quality of life of these patients was negatively affected.\textsuperscript{62} Similarly, higher stress levels were found to slow patients’ recovery from surgical periodontal treatment.\textsuperscript{63} Moreover, healing outcomes of periodontal surgery were negatively affected by patients’ inability to utilized effective stress coping strategies.\textsuperscript{64}

Compared to surgical periodontal treatment, tooth extraction and GBR procedures are surgical manipulations that may create additional trauma, increased post-surgical discomfort and the need to wear some type of provisional restoration. Limited information is available on how advanced oral surgeries such as GBR may affect everyday’s quality of life. Related studies are mostly concentrating on outcomes following restorative phase of the treatment.\textsuperscript{65, 66, 67, 68} Recently, the patients perspective at various phases of treatment, from tooth loss through to implant placement, has been questioned.\textsuperscript{69}

\textbf{The purpose of this study} was to determine pre- and post-surgical oral health- and general health-related quality of life, stress, depression, anxiety, and coping levels and their effect on surgical treatment outcome following GBR. The \textbf{working hypothesis} of this study was that advanced GBR protocol performed to regenerate bone at a site that has more than one missing tooth affects quality of life measured by Oral Health Impact Profile (OHIP) and General Health Questionnaire (GHQ) in addition to its short term effect on an individual’s anxiety, depression levels and coping skills. The \textbf{specific aims} of this study were:
1. To develop a clinical scale to evaluate each phase of GBR healing outcome.

2. To study wound fluid content for specific mediators related to healing.

3. To investigate pre-surgical psychological stress and coping mechanisms within a specific patient population with tooth loss and a need for advanced regenerative surgery in the oral cavity.

4. To determine whether psychological stress levels and coping mechanisms are differentially affected during GBR wound healing.

5. To determine the short-term effects, if any, of GBR procedure on OHIP and GHQ, as well as individual’s anxiety, depression levels and coping skills.
CHAPTER 2
MATERIALS AND METHODS

Patient Selection and Study Design:

This study is a prospective observational clinical trial that recruited twenty adult patients from the patient pool of the Graduate Periodontology Clinics at the Ohio State University between July 2012 and May 2014. Patients who were scheduled to have guided bone regeneration (GBR) surgery with particulate bone graft and resorbable/non-resorbable membrane of at least one sextant with two or more adjacent missing teeth were recruited for this study.

The inclusion criteria were:

1) Adults between 18 and 75 years old
2) Scheduled for GBR procedure with particulate bone graft and resorbable/non-resorbable membrane on a sextant (two or more adjacent missing teeth with GBR indication)
3) Periodontally healthy
4) Non-smokers
5) Systemically no health problems that may affect wound healing

Exclusion criteria were:

1) Additional pre-GBR surgeries such as soft tissue grafting
2) Active (untreated) periodontal disease
3) Permanent restorations covering surgical site

4) Smokers

5) Pregnant women

6) Uncontrolled health problems that may affect wound healing

7) Patients who refuse to be treated with allograft placement

8) Patients taking medications that affect wound healing

The study protocol and consent forms were approved by the Institutional Review Board of the Ohio State University (protocol #2012H0208). All participants signed a written consent prior to entry into the study and they were provided with a copy of the consent forms.

The healing of the patients’ wound was followed at both clinical and molecular levels by documenting several clinical parameters and collecting gingival crevicular fluid (GCF) samples prior to surgery and at 1 week, 1 month and 4 months post-operative control appointments.

Psychological evaluations were also conducted to determine patients’ stress, depression, anxiety and coping levels by evaluating their response to specific questionnaires prior to surgery and at 1 week and 4 months post-operative control appointments.
Patient Medical, Dental, and Socioeconomical Status

Medical and dental data were collected from each patient’s clinic chart. The collected information were:

- Age
- Gender
- Ethnic background
- Systemic health related issues
- Medications used to control systemic health problems
- Reasons for tooth extraction, timing of tooth extraction, complications following tooth extraction
- Periodontal health and related treatment in the past
- Dental health and related treatment in the past

In addition, information related to education, income, and marital status was collected through specific questionnaires.

Clinical Protocol

Patients’ clinical data was collected at baseline and clinical measurements were repeated at 1 week and at 1 month post-operative appointment as well as at 4 months. Photographic documentation was done at each visit. The following collected data were recorded:
- Relative ridge height dimensions (RRH): Alginate impressions were taken during consultation and a stent was prepared. This surgical stent was fabricated with inserted standardized 3” aluminum tubes\(^1\) integrated into a 0.060” thermo-forming material and was used to standardize the measurements of ridge height (Figure 1). A total of 6 measurements were taken at the surgical site by using a periodontal probe inserted into the aluminum tubes. The 6 tubes were selected based on the location of the measurement (mesiobuccal, midbuccal, distobuccal, mesiolingual, midlingual, and distolingual), and the same tube was used for the same recorded RRD for each location at each visit. The measurements were taken at baseline and were repeated at each follow-up appointment. The mean for the 6 measurements calculated and assigned for each surgical site.

- Ridge Width: Measured using caliper. For each surgical site, 3 measurements were taken at mesial, mid and distal by using a caliper. The caliper was placed at a point 1 mm below the highest bone of the bone crest at each location. A mean score was calculated and assigned to each surgical site (Figure 1).

- Soft tissue thickness was measured following flap elevation.

- Details of the surgery including the use of conscious sedation, difficulty in wound closure, and type of the membrane/grafting materials used were also recorded.

- Gingival Crevicular Fluid samples were obtained from adjacent teeth prior to surgery and from the incision line at 1 week, 1 month and 4 months post-operative appointments.

\(^1\) K & S Engineering, Chicago, IL, USA
\(^2\) Periopaper, Proflow Inc. Amityville, NY, USA
by using a sterile paper strips (Periopaper®)\(^2\). A total of six GCF samples were collected both from teeth and wound sites. Teeth GCF samples were taken from randomly assigned teeth sites (3 buccal and 3 lingual sites) immediately adjacent to the surgical site (no more than 3 teeth past the surgery site). One patient received full maxillary teeth extraction and provided teeth GCF samples only for the baseline and not for the follow-up visits. Wound fluid samples were collected by inserting the strips into the incision line (mesial, mid, and distal locations). Cotton rolls and 2X2 gauze were used to isolate the site. Supragingival plaque was removed using a periodontal probe and soft tissue was gently air-dried using an air/water syringe without disturbing the gingival margin. Paper strip was gently introduced into the gingival sulcus (or between the wound edges) until a mild resistance was felt. The sampling time was 30 second for each strip. Samples that were contaminated with blood or saliva were discarded. GCF volume was determined by using a previously calibrated electronic volume quantification unit (Periotron 8000®)\(^3\). Samples were stores in sterile vials and kept in ice until the end of each visit, and then vials were transferred and stored at -20C for future multiplex assays to determine inflammatory cytokine content within wound fluid.

- Clinical wound closure immediately after surgery was documented through clinical observation; Clinical wound healing scores (0=Mature wound healing, 1=Erythema,

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\(^2\) Periopaper, Proflow Inc. Amityville, NY, USA

\(^3\) Periotron 8000, Ora Flow Inc, Plain View, NY, USA
2=Bleeding, 3=Graft mobility, 4=Suppuration, 5=Necrosis) were used for this purpose (modified from Kloostera et al.\textsuperscript{70}). Each category was given either a score of 0 if absent or a score of 1 if present. Mature wound healing was defined as complete wound closure with no other significant findings/complications. Erythema was defines as increase of redness compared to adjacent non-operated sites. Bleeding was given a score of 1 whenever spontaneous bleeding was detected at the wound site. Graft mobility was evaluated by gentle palpation and evaluation of any loose sub-gingival material by using a periodontal probe. Suppuration was evaluated by indication the presence or absence of pus or discharge at the wound site. Any visual soft and/or hard tissue necrosis detected was given a score of 1.

-Similarly, hydrogen peroxide test was used to determine complete wound closure.\textsuperscript{60} The amount of any possible wound exposure was measured with a periodontal probe by selecting the largest exposure area and measuring the farthest distance from the two flap margins.

-Clinical parameters before the surgery and at each post-operative visit were collected from 2 adjacent teeth to the surgical site. Those parameters were:

- Pocket depths (PD): pocket depth measurements were calculated by introducing the periodontal probe in between the gingiva and tooth surfaces. The probe was held as parallel to the tooth long axis until a resistance was felt. The measurements were taken at mesial, mid, and distal of buccal and lingual surfaces
of each tooth (total of 6 measurements per tooth = 12 sites). A mean score was calculated for both teeth. Same teeth were used for PD measurements were also used for GM and KT measurements.

- **Gingival margins (GM):** GM were measured using a periodontal probe by calculating the distance from the CEJ (cementoenamel junction) to the highest point of the tooth gingival margin. Similar to the PD measurements, a mean GM score was also calculated and assigned to adjacent teeth.

- **Keratinized tissue (KT):** The KT of the 2 adjacent teeth to the surgical site was calculated by measuring the distance from the mucogingival junction to the mid buccal gingival margin level of the tooth. One score was given for each tooth and a mean score was calculated and assigned to the adjacent teeth area.

- **Plaque and Bleeding on Probing (BOP) percentages were calculated at each appointment. A total of 6 adjacent teeth to the wound site were used. Each surface was given a score of 0 if plaque or gingival bleeding were absent or a score of 1 if they were present. Then, the total surfaces with a score of 1 were added and divided by the total number of surfaces (36 surfaces). Plaque and bleeding percentages then assigned for each patient.**

**Preparation of Wound Fluid Samples and Multiplex Assays**

Extraction of crevicular fluid from paper strips was accomplished. The following steps
were followed:

- PCR microtubes were prepared by creating small holes at the bottom of each then they were sterilized.
- Then, these tubes were placed into sterile 2 ml Eppendorf tubes.
- A sterile scissor was used to separate the paper strips from the waxed part of the strips.
- Then, they were transferred from cryovials into PCR microtubes, soaked in 200 µl cold sterile PBS, and incubated on ice for 15 minutes with occasional vortexing.
- Samples then were centrifuged at 13,000 rpm for 10 min.
- Supernatant was collected from the bottom of the tubes.
- Approximately 160 µl elution volume was recovered from each tube and 40 µl of this sample was loaded into multiplex bead-based assay plate.
- The multiplex bead-based assay\(^4\) was used to detect the presence and the amount of several cytokines within crevicular fluid samples. Those cytokines were: IL-1β, IL-1ra, IL-6, IL-7, IL-8, IL-10, IL-12, Eotaxin, FGF-b, G-CSF, GM-CSF, TNF-α, MIP-1α, MIP-1β, VEGF, IP-10, PDGF-bb, RANTES.
- Briefly, the assay uses Luminex multi-analyte profiling (xMap) technology, to allow the detection and quantitation of multiple RNA or protein targets concurrently. This technology combines flow cytometer, fluorescent-dyed microspheres (beads), lasers, and digital signal processing to allow multiplexing of up to 100 unique assays within a single

\(^4\) Bioplex™ Cytokine Assay. Bio-Rad Laboratories, Inc.
sample.
-The cytokine reagent kit includes assay buffer, antibody diluent, streptavidin-PE, and a 96-well filter plate.
-Specific kit\(^5\) designated as human cytokine group (Group I) was used for cytokines and growth factors.

**Psychological Data**

Psychological evaluation through questionnaires was performed and the purpose of this psychological evaluation was two fold:

- Determine baseline psychological stress, depression, anxiety and coping levels prior to GBR.
- Determine whether GBR procedure affect patient’s well-being as far as his/her perception of oral health and general health.

The following questionnaires were used to evaluate perceived stress, depression, anxiety, coping and evaluation of general health (Appendix A):

-Perceived Stress Scale\(^7\) (PSS-10): is a 10-items survey used to determine perceived stress. Each item is scored 0 – 4, where Very often = 4, Fairly often = 3, Sometimes = 2, Almost never = 1, and Never = 0. Total can be from 0 to 40. Higher scores indicate higher levels of perceived stress and there are no “cut-offs”.

\(^5\) Bio-Rad laboratories, Life Science Research, Hercules, CA
The Center for Epidemiologic Studies Depression Scale\textsuperscript{72} (CES-D): is a 20-items measuring assessing depressive symptoms. Each item is scored 0 – 3. The total score can range from 0 – 60. Items 4, 8, 12, & 16 are reverse scored. The total score equals the total of all 20 items, after reverse scoring applied. Higher scores indicate greater depressive symptoms. Scores \( \geq 16 \) indicate clinically significant depressive symptoms.

Clinically Useful Anxiety Outcome Scale\textsuperscript{73} (CUXOS): is developed to be useful in the management of depressed patients, who often report high levels of anxiety, and to monitor patients with diagnosed anxiety disorders. The CUXOS items were derived from clinician rating scales such as the Hamilton Rating Scale for Anxiety and DSM-III-R and DSM-IV descriptions. The scoring of each item is based on a 5-point Likert scale, including: 0 = not at all true; 1 = rarely true; 2 = sometimes true; 3 = usually true; 4 = almost always true. The anxiety severity is scored according to the following:

<table>
<thead>
<tr>
<th>Anxiety Severity</th>
<th>CUXOS Score Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonanxious</td>
<td>0-10</td>
</tr>
<tr>
<td>Minimal Anxiety</td>
<td>11-20</td>
</tr>
<tr>
<td>Mild Anxiety</td>
<td>21-30</td>
</tr>
<tr>
<td>Moderate Anxiety</td>
<td>31-40</td>
</tr>
<tr>
<td>Severe Anxiety</td>
<td>41 and above</td>
</tr>
</tbody>
</table>

Brief COPE Questionnaire\textsuperscript{74}: is a multidimensional coping inventory to assess the different ways in which people respond to stress. This inventory contains 28 items, which measure 14 subscales for coping reactions. Each subscale contains 2 items and each item is scored from 0 (I haven’t been doing this at all) to 3 (I have been doing this a
lot) following the 4-point Likert scale format. The higher score represents greater coping strategies used by the patients.

- General Health Questionnaire$^{75}$ (GHQ-12): is a measure of current mental health of the patient. It focuses on two major areas: the inability to carry out normal functions and the appearance of new and distressing experience. It contains 12 items and the scoring is based on Likert Scale (0-3). The total score ranges between 0 and 36. Scores between 11-12 are considered typical, scores of >15 show evidence of distress, and scores of >20 suggest severe problems and psychological distress.

- Oral Health Impact Profile$^{36}$ (OHIP-49): It consists of 49 items that are subdivided into seven domains: functional limitation, physical discomfort, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Responses to the items are recorded in a 5-point Likert scale. Three methods can be used to score the 49 items of the OHIP: OHIP Additive, OHIP Weighted Score, and OHIP Simple Count. OHIP Additive is the most frequently used method for scoring and is the method used in this study. Simply, the total score is calculated by summing the 49 responses, and the higher the score, the poorer oral health-related quality of life of the patient.

- Pittsburgh Sleep Quality Index$^{76}$ (PSQI): is a 9 item survey used to determine sleep quality. The total score range between 0-21. Higher numbers mean more sleep difficulties. Each component of this survey has certain scoring instructions. The total
score represents the total all of the components. A total score of higher than 5 is a sensitive and specific cut-off to indicate poor sleep quality relative to clinical and laboratory measures. Subscales of this survey include:

1. Subjective Sleep Quality
2. Sleep Latency
3. Sleep Duration
4. Habitual Sleep Efficiency
5. Sleep Disturbance
6. Use of Sleep Medication

-The Short-Form Questionnaire\textsuperscript{77} (SF-36): This questionnaire is designed to measure the functional health and well-being from the patient’s point of view. It has physical and mental components. It also has 8 domains that contain specific items. Each item is scored on a scale from 0 to 100. The scores from those questions that address each specific area of functional health status are then averaged for each domain. A final total score is then calculated by averaging all of the 8 domains. Higher scores represent higher levels of functioning.

In addition to these well-established questionnaires, questionnaires and scales were used to evaluate pain/discomfort experience during post-operative wound healing period (Appendix A).\textsuperscript{78, 79}

The sequence of clinical data collection and study visits are illustrated in Figure 2.
**Statistical Analysis**

The data were analyzed using Statistical Analysis Software, version 9.3 (SAS Institute Inc., Cary, NC, USA). Prior to analysis, the data were examined for outliers; no extreme values were found. Descriptive statistics are reported as mean±se. Normality testing was performed for all the parameters. Logarithmic transformation was applied when it was needed. Repeated measure ANOVA was used to make the within the 1 week vs. 4 month comparisons at each time point. It is assumed that a non-zero correlation exists in data associated with the same subject regarding repeated measure in time. The spatial power (SP (POW) (TIME)) covariance structure was used due to the time points not being equally-spaced. Bonferroni correction was used to conserve the overall type I error at $\alpha=0.05$. Additionally, logistic regression analysis was performed to reveal the association between binary outcomes and other variables. Pearson correlation coefficients were calculated to reveal the association between various parameters.
CHAPTER 3
RESULTS

Study Population:

A total of twenty patients fulfilled the inclusion criteria and were recruited to the study. Three patients did not want to proceed due to compliance with the study protocol issues. One patient was excluded due to changes in the surgery treatment plan and failure to continue meeting the inclusion criteria after recruitment. Sixteen periodontally healthy, non-smoker patients completed the study. Information related to patient population is presented in Table 1. The mean age was 60 ± 4 years with a total of 9 males and 7 females. The study population involved 15 Caucasians and 1 Asian. The mean Body Mass Index (BMI) calculated prior to surgery based on reported weight and height of the patient was 28 ± 2. Only 5 patients reported health problems other than the currently experienced oral health issues. The reason for teeth extraction was mainly due to decay (53%); remaining cases were related to periodontal, endodontic, traumatic, functional, and/or restorative problems. All patients except one, who had two surgical sites, had one single surgical site providing a total of 17 available wound sites for the study. The socioeconomical status data of the patients, including yearly income, marital status, number of years being in a relationship, and educational level are shown in Table 1. Site-specific information and surgical details are provided in Table 2.

Distribution of anatomic location of wounds were similar, with 7 sites localized in
mandibular posterior, 6 sites localized in maxillary posterior and 4 sites localized in maxillary anterior sextants. All wounds were large size (59% of the sites had at least two adjacent teeth missing, the remaining sites being even larger). The bone graft material used in the GBR procedure was Freeze-dried bone allograft. In addition, Collagen membranes were used in 14 sites. The other three sites received collagen plug, Ti-reinforced membrane, or Titanium meshwork. Only 5 patients out of the 16 had GBR done at the time of teeth extraction. Surgery was performed under conscious sedation in 3 patients (2 patients under IV sedation, 1 patient with oral sedation).

**Clinical Outcomes**

**Site-specific Clinical Outcomes**

Changes in alveolar ridge width and relative alveolar ridge height were recorded as main outcomes of GBR surgery (Figure 3). The mesial, mid, and distal ridge width measurements recorded at each visit are presented in Appendix B. Initial ridge width determined before bone grafting procedure at the time of surgery was 7.5±0.7 mm. An increase at 1 week and 1 month was noted for this measurement (9.8±0.7 mm and

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8 CollaPlug®. ©2013 Zimmer Dental Inc. Carlsbad, California, USA
10 Titanium Augmentation Micro Mesh. © 2014 ACE Surgical Supply Co., Inc. Brockton, Maryland. USA
9.7±0.6 mm, respectively). This was followed by a slight decrease at 4 months (8.6±0.6 mm). The differences between baseline and various observation times were statistically significant (p ≤ 0.03) (Figure 3). Relative alveolar ridge height (RH) was documented by using a stent and occlusal plan as stable mark for repeated measures (Figures 1 and 3). Initial RH at the time of surgery before the grafting procedure was 12±0.6 mm. There was a gradual but not statistically significant decrease in this measurement from surgery to 1 week, 1 month and 4 months (11±0.5 mm, 10.4±0.4 mm and 10.7±0.8 mm, respectively; p > 0.05), which represents an actual gain in ridge height. The difference between baseline and 4 months was not statistically significant (p=0.057).

Changes in soft tissue characteristics during wound healing were documented by recording the initial thickness of the flap, the initial and final periodontal probing depths and the location of gingival margin on adjacent teeth and, the width of keratinized tissue through 4 months (Figure 3). The initial thickness of the flap was 1.3±1.1 mm. Initial probing depth on adjacent teeth was 2.5±0.1 mm and changed at 4 months (2.04±0.1 mm; p=0.005). The initial distance from cementoenamel junction to gingival margin was 0.3±0.1 mm and did not present significant change at 4 months (0.4±0.3 mm; p>0.05). The width of keratinized tissue at middle of the ridge was 4.5±0.4 mm prior to surgery and the changes observed during healing were negligible (5±0.4 mm, 4.5±0.4 mm, 4±0.4 mm at 1 week, 1 month and 4 months, respectively; p>0.05).
Plaque accumulation at wound site and bleeding upon probing in relation to plaque accumulation were recorded as possible factors that may differentially affect wound healing (Figure 4). Initial plaque accumulation at and/or adjacent to the surgical sites documented prior to surgery was 22±4 % and stayed at similar levels throughout observation time (25±4.4% at 1 week, 23±4.4% at 1 month and 18±4% at 4 months, respectively; p>0.05). Initial percentage of BOP on and/or neighboring teeth was 15±5% prior to surgery. Interestingly, a statistically significant decrease in BOP was noted up to 1 month which then started presenting an increase by 4 months (9.3±2.7% at 1 week, 3.1±1% at 1 month, 6.8±2% at 4 months, respectively; p=0.03 the difference between baseline and 1 month, p=0.04 the difference between 1 week and 1 month, p=0.08 the difference between 1 month and 4 months).

**Wound Healing Outcomes**

Characteristics of wound healing were determined by evaluating the presence or absence of open wounds (determined by naked eye but also by hydrogen peroxide [HP] test), erythema, bleeding at wound site, graft mobility and necrosis (Figure 5). Initial wound closure was complete in all except one patient at the time of surgery. However, 88% of the sites presented opened wound edges at 1 week. This percentage reached to 94% with HP test. Only 35% of the sites presented with clinically open wound edges by 1 month (53% with HP test). Two sites (12%) had clinically open wound edges by 4
months (one site [6%] with HP test). The difference observed between 1 week and 4 months was statistically significant for both evaluation of open wound edges and HP test (p<0.001, for both parameters).

As expected, all wound sites presented some levels of erythema during 1 week visit with 24% of these sites showing bleeding (Figure 5). This decreased to 41% for erythema and to 12% for bleeding by 1 month. Only two sites (12%) had erythema and none of the sites had bleeding by 4 months. These differences were not statistically significant following adjustment of p values for multiple comparisons.

Wound stability is an important factor affecting healing outcome following GBR. Graft mobility was clinically evaluated in addition to wound closure in order to clinically determine wound stability (Figure 5). No graft mobility was detected at 1 week. However, two sites (12%) had some graft mobility detected under soft tissue at 1 month as well as one of these same two sites (6%) having similar signs of graft mobility at 4 months. The differences between various observation times were not statistically significant (p>0.05).

Necrosis at the soft tissue level can be a sign of major healing complications such as trauma from surgery, lack of blood supply, lack of wound stability etc. Fifty-nine percent of the wound sites had some minor necrosis localized to wound edges at 1 week (Figure 5). Only 29% of these sites still presented some necrosis by 1 month with
no sites with the presence of necrotic tissue by 4 months. The differences between various observation times were not statistically significant (p>0.05).

**Severity of Wound Exposure and Experience of Pain During Wound Healing**

In parallel to clinical healing outcomes, a series of evaluations related to presence and absence of pain, discomfort and numbness at wound site was performed (Figure 6). Eighty eight percent of the patients reported some pain at surgical site at 1 week. This percentage decreased to 44% at 1 month and to 6% (1 patient) at 4 months. The difference between 1 week and 4 months was statistically significant (p<0.001). When the problem was defined as presence or absence of discomfort, only 50% of the patients reported presence of some discomfort at 1 week. This stayed about the same for 1 month observation period. Then, it decreased to 18% at 4 months. The differences between various observation times were not statistically significant (p>0.05). Only 3 patients (19%) reported some numbness related to surgical site at 1 week. This decreased to 1 patient (among the same patients who initially reported numbness) at 1 month as well as at 4 months. The differences between various observation times were not statistically significant (p>0.05) (Figure 6).

As reported earlier, there was only one site with clinically open wound edges at the end of the surgery, while 88% of the wounds were described as clinically open wounds by 1 week. Thus, a quantification of the amount of wound exposure was necessary as well as pain description and intensity (Figure 7). The mean wound
exposure was 3 mm at the time of surgery, 3.8±0.7 mm at 1 week, 2±0.8 mm at 1 month and 0.2±0.1 mm at 4 months. The differences between 1 week and 1 month were marginally statistically significant (p=0.058) and between 1 week and 4 months were statistically significant (p<0.001). By using a scale from 0 to 10, the mean pain description was 1.6±0.3 at 1 week, 0.7±0.2 at 1 month and 0.4±0.2 at 4 months. The difference between 1 week and 4 months was statistically significant (p=0.001).

Similarly, mean pain intensity was 5±0.7 at 1 week, 2±0.5 at 1 month and 1.3±0.6 at 4 months with statistically significant differences between 1 week and 1 month (p=0.001) and between 1 week and 4 months (p=0.001).

**Wound Fluid and Local Pro-inflammatory Cytokine Levels**

Samples were collected from the wound edges as well as from neighboring teeth as described in material and methods. All 17 pro-inflammatory/anti-inflammatory cytokines investigated as part of wound healing were detectable within fluid samples obtained from either wound or teeth. Related complete data is presented in Table 3 as concentration (pg/ml or ng/ml) and total amount of protein (pg or ng). Only wound healing related data is reported within this thesis since tooth related data was collected to determine background changes within oral cavity. However, tooth related data is presented in Table 3 as a reference to previous and future studies. The wound healing mediators included in the below text were detected at statistically significant levels at
various phases of healing (e.g. 1 week and 1 month compared to pre-surgical levels). Emphasis was given to those mediators with statistically significant differences at both concentration and total amount levels. It is also important to note that wound fluid samples at 4 months were only available from 4 sites due to complete wound closure. Thus, statistical analysis was not conducted. However, those that were detected at high concentration and total amount even at 4 months may be promising mediators as biomarkers for delayed wound healing and they were marked in red (namely, IL-1ra, IL-17, FGFB, GM-CSF, IP-10, TNF-α) (Table 3 and Figure 8).

As expected, wound fluid was highest at 1 week and gradually decreased throughout observation period (p<0.05) (Table 3 and figure 8).

Interleukin-1β (IL-1β) is a pro-inflammatory cytokine that is released from macrophages, is a mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. IL-1β concentration was 12±2 ng/ml at 1 week, which was slightly higher than baseline GCF levels (11±3 ng/ml) (p>0.05) (Table 3 and figure 8). Similarly, there was a 2-fold increase in total amount of IL-1β collected from wound at 1 week compared to baseline GCF total amount (35±8 pg), this difference was statistically significant (p= 0.005). In addition, the increase observed at 1 month for both IL-1β concentration and total amount was statistically higher than baseline GCF values (26±10 ng/ml and 41±10 pg,
respectively; p=0.04 and p=0.005) as well as 1 week wound fluid values (p=0.06 and p=0.009) (Table 3 and figure 8).

Interleukin-1ra (IL-1ra) is an IL-1 receptor antagonist and functions as an anti-inflammatory non-signaling molecule that prevents IL-1 receptor signaling by competitive inhibition. Wound fluid IL-1ra concentration and total amount were 516±109 ng/ml and 2835±550 pg at 1 week (Table 3 and figure 8). This was actually lower than baseline GCF levels (p>0.05 for concentration but p=0.022 for total amount). However, an increase in IL-1ra concentration and total amount was detected at 1 month wound fluid (2849±1014 ng/ml and 4664±642 pg, respectively). The differences observed between 1 week and 1 month were statistically significant both at concentration and total amount levels (p=0.011 and p=0.05, respectively) (Table 3 and figure 8).

Interleukin-6 (IL-6) is an immune modulation cytokine that is found at higher levels in inflamed gingival tissue compared to healthy gingiva. It has several functions, such as inducing B-cell maturation and neutrophils stimulation. Interleukin-6 can be considered as a pro-inflammatory cytokine that stimulates C-reactive protein and neutrophil elastase (MMP-9) secretion, or anti-inflammatory cytokine by indirectly causing the release of cytokines such as interleukin-10 (IL-10) and interleukin- (IL-4). A sharp increase in both IL-6 concentration and total amount was detected at 1 week wound compared to baseline GCF levels (17460±2954 pg/ml and 112±22 pg,
respectively; compared to 597±196 pg/ml and 2.4±1.1 pg pre-surgical levels; p≤0.001 for both values) (Table 3 and figure 8). Similarly, there was a sharp decrease in both concentration and total amount levels by 1 month (1909±897 pg/ml and 6±2 pg, respectively). The differences between 1 week and 1 month were statistically significant (p≤0.001 for both values).

Interleukin -8 (IL-8) is a pro-inflammatory, leukocyte chemo-attractant protein that plays a role in pathogenesis of periodontal disease and inflammation. The increase observed at 1 week IL-8 wound concentration and total amount was statistically significant compared to pre-surgical GCF levels (62±10 ng/ml and 354±45 pg, compared to 24±4 ng/ml and 83±13 pg, respectively; p≤0.002 for both) (Table 3 and Figure 8). The decrease observed at 1 month compared to 1 week was only statistically significant for total amount (77±21 pg; p≤0.001).

Interleukin -10 (IL-10) is anti-inflammatory cytokine is a key regulatory cytokine that has significant effects on both the innate and adaptive immune responses. It also stimulates the production of protective antibodies and down-regulates the pro-inflammatory cytokines. Wound fluid IL-10 concentration at 1 week was actually lower than pre-surgical GCF concentration (534±57 pg/ml compared to 1086±191 pg/ml, respectively; p>0.05) (Table 3). An increase in IL-10 concentration as well as total amount was detected at 1 month (1870±676 pg/ml and 2.8±0.3 pg, respectively; p=0.008 for concentration only).
Granulocyte-macrophage colony-stimulating factor (GM-CSF) is an important hematopoietic growth factor and immune modulator. In case of inflammation, IL-1, IL-6, and TNFα can stimulate the production of GM-CSF. Overexpression of GM-CSF can lead to severe inflammation. At one week, GM-CSF wound fluid level was actually lower than pre-surgical GCF levels for both concentration and total amount values (862±111 pg/ml and 5±0.5 pg compared to 3723 pg/ml and 8.2±1 pg, respectively; p≤0.001 only for total amount) (Table 3 and figure 8). A statistically significant increase was detected in wound fluid GM-CSF concentration and total amount at 1 months compared to 1 week values (6436±2192 pg/ml and 8.4±1 pg, respectively; p≤0.001 for both values).

Macrophage Inflammatory Proteins-1α (MIP-1 α) is a pro-inflammatory chemokine that plays a role in leukocytes chemotaxis, superoxide production and inhibits the proliferation of hematopoietic stem cells. The increase noted in MIP-1 α concentration and total amount at 1 week was statistically significant compared to pre-surgical GCF levels (1386±305 pg/ml and 9.2±2.4 pg compared to 231±44 pg/ml and 0.8±0.2 pg, respectively; p≤0.001 for both values) (Table 3 and figure 8). This increase was followed by a sharp decrease at 1 month, which was also statistically significant (428±100 pg/ml and 1±0.3 pg, respectively; p≤0.001 for both values).

Macrophage Inflammatory Proteins-1β (MIP-1β) is a chemotactic cytokine that activates granulocyte leading to acute inflammation status and severe periodontal
MIP-1β wound fluid levels at 1 week were also statistically significantly increased compared to pre-surgical GCF levels (7640±1712 pg/ml and 48±12 pg compared to 2898±511 pg/ml and 10±2 pg, respectively; p=0.012 for concentration and p<0.001 for total amount) (Table 3 and figure 8). A decrease in MIP-1β wound fluid levels were observed at 1 month (4728±1198 pg/ml and 10±2.3 pg; p<0.001 for total amount only).

Tumor Necrosis Factor (TNF-α) is a pro-inflammatory cytokine that stimulate bone resorption and protease production by fibroblasts and osteoblasts. There was a sharp increase in TNF-α wound fluid levels at 1 week (3294±658pg/ml and 21±5 pg compared to 1565±206 pg/ml and 5±0.6 pg, respectively; p<0.001 for total amount only) (Table 3 and figure 8). The increase detected at concentration reached statistically significant level at 1 month (p=0.03; difference between baseline and 1 month).

**Psychological Data**

Patients’ psychological evaluation and general health/oral health related questionnaires scores are presented in Tables 4 and 5. Questionnaires used to determine baseline levels of depression (CES-D), anxiety (CUXOS) and coping (COPE) were structured to study changes due to short-term events. Thus, they were applied for each observation time point. Baseline CES-D level was 7±2 for entire study population with only 2 patients recorded ≥16 (accepted threshold level for clinical depression). A four
units increase in CES-D was noted at 1 week following surgery, which was not statistically significant (p>0.05). However, an additional 5 patients scored CES-D ≥16 during the same time point. The decrease in CES-D from 1 week to 4 months observation period was statistically significant (11±2 and 5±2, respectively; p=0.02).

Baseline CUXOS score was 9.4±2 for entire study population with ranging scores from 1 to 37. A slight decrease in mean CUXOS score was noted at 1 week (8±2) with 11 subjects scored lower than their baseline CUXOS values at 1 week following surgery while 4 subjects scored higher than their baseline CUXOS values and only one subject stayed at the same score (higher score is interpreted as higher anxiety experience). This decrease continued throughout the observation time (5±1 at 4 months; p=0.06 between 1 week and 4 months). 73

The baseline COPE score was 18±3. A four-unit increase was noted at 1 week with 7 subjects reporting higher scores and 7 subjects reporting lower scores compared to their baseline values (higher score is interpreted as better coping skills). There was a decrease in COPE score back to baseline values by 1 month with no statistically significant differences throughout the study period. 74

PSQI questionnaires were used to evaluate changes in sleeping behaviors. The baseline PSQI score was 6±1 for entire study population ranging from 2 to 13 (A score of <5 is generally associated with good sleep quality with 21 reported as the maximum worse score for PSQI). A slight decrease in mean PSQI score was noted at 1 month
(5.3±2) with 7 patients reporting lower scores compared to their baseline values and 4 patients reporting higher scores compared to their baseline values (mean 4±1 for entire study population at 4 months; p=0.08 between baseline and 4 months).76

PSS-10 questionnaire was used to determine stress level at different point of time. Baseline PSS-10 score was 12±1 with negligible changes between baseline to 1 month (higher scores are interpreted as higher stress levels). A statistically non-significant decrease was noted at 4 months with 10 subjects reporting lower PSS10 scores compared to their baseline values (p>0.05).71

Based on health self-evaluation (Table 1), four subjects thought that they were in excellent health prior to surgery while 12 subjects defined their health as very good. GHQ-12 and OHIP-49 questionnaires were used to evaluate possible changes in general health and oral health during the study (Table 4). There were no changes in GHQ-12 scores throughout the study (p>0.05) (In general, higher score in GHQ-12 is interpreted as better mental health). A 5 units decrease was noted in OHIP-49 between baseline and 4 months with no statistically significant differences (p>0.05) (In general, higher score in OHIP-49 is interpreted as worse oral health75,36).

Short Form Health Survey was introduced to investigate in depth possible changes in quality of life. SF-36 score was increased approximately 6 units by the end of 4 months observation time (p=0.07). All other sub-questionnaires under SF reported increases at 4 months compared to baseline scores with statistically significant
differences for SF Energy Fatigue (p=0.02) and a 9-unit increase in SF-Social Function (p=0.08) (In general, lower scores in SF are interpreted as more disability\cite{77}).

**Post-operative Care Data**

The information related to post-operative care data is summarized in table 4. All patients reported taking prescribed antibiotics post-operatively. The average number of dates for the antibiotics consumption was 7.4±0.2 [8(5-8)]. All patients also reported post-operative analgesics intake. The average number of times patients had to take analgesic medications was 13.1±2 [11(2-26)]. Eight patients stated that they had to use other medications during the period of healing. All patients used prescribed mouthwash after the GBR surgical procedures. Fourteen out of 16 patients had no lip and/or check problems post-surgery. Only half of the sample population applied cold extra-ocrally. Only 3 patients were provided with temporary removable restoration following the GBR procedure. Regarding diet modification, almost all patients were compliant with post-operative instruction for soft diet consumption, avoiding hot/spicy food, and avoiding crusty food. Only one patient did not avoid spicy-hot food post-operatively. Diet modification practices applied by the patients were only for a maximum of 3 days. Moreover, 12 out of 16 had to avoid drinking alcohol for 3 days after the surgery. Only 6 patients followed their dentists’ instruction and avoided exercise after their surgical procedures.
Statistically Significant Correlations

Table 7 represents statistically significant correlations between different variables of collected clinical, psychological and pain-related data. Pain intensity reported by the patients was found to be statistically significant correlated to the presence of wound opening, as well as, wound size in mm (p=0.001, r=0.461). However, pain description scores reported by the study subjects showed statistical significant correlation with the presence of open wound (p=0.003, r=0.421). In addition, pain intensity and description scores were significantly correlated with CESD scores (p=0.001, 0.005; r=0.439, 0.39 respectively). Ridge width measurement scores were significantly associated with wound size in mm (p=0.02, r=0.329). Variables such as patient’s reported income, wound size in mm, and patient’s age were also found to exhibit statistically significant correlation with SF-36 fatigue and energy subscale scores (p=0.02, 0.006, and 0.003; r=0.554, 0.642, 0.668 respectively). Patient’s age was also correlated to PSQI sleep quality scores (p=0.02 and r=0.329) and BMI scores (p=0.003, r=0.668). Wound size was significantly associated with CESD scores (p=0.003, r=0.406).

Wound fluid cytokines were also investigated for significant associations with different psychological and pain parameters (Table 8). Wound fluid Granulocyte-macrophage colony-stimulating factor (GM-CSF) total amount and concentration were was significantly correlated with reported pain intensity, CUXOS, and SF-36 scores
(Table 8). However, pain description scores showed statistically significant correlation only with GM-CSF total amount scores. Vascular endothelial growth factor (VEGF) functions involve neovascularization as well as enhanced vascular permeability during wound healing. VEGF total amount was positively associated with CUXOS and CESD scores (p= 0.02, 0.03; r= 0.2). Platelet-derived growth factor (PDGF) is a regulatory protein that plays a significant function in angiogenesis during wound healing. A statistically significant negative correlation was found between PDGF total amount and concentration scores and PSQI sleep quality scores (p≤ 0.05, r= -0.2). Interferon gamma-induced protein 10 (IP-10) is a chemokine that functions as a chemo-attractant protein for several immune cells. Statistical analysis revealed a significant negative correlation between IP-10 scores (total amount and concentration) and social functioning subscale scores of the SF-36 questionnaire (p≤ 0.005, r= -0.3).
Figures and Tables

Figure 1- Clinical documentation of:

A: Relative Alveolar Ridge Height Measurements

B: Alveolar Ridge Width Measurements
<table>
<thead>
<tr>
<th>Appointment 1</th>
<th>Appointment 2</th>
<th>Appointment 3</th>
<th>Appointment 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline/Surgery</td>
<td>1 week Post-Operative</td>
<td>1 Month Post-Operative</td>
<td>4 Months Post-Operative</td>
</tr>
<tr>
<td>Control</td>
<td>Control</td>
<td>Control</td>
<td>Control</td>
</tr>
</tbody>
</table>

- Recording medical and dental histories of the patient and reviewing of treatment plan
- Patient psychological questionnaires delivery and collection
- Taking alginate impressions and stent fabrication for bone height measurements
- Photos documentation
- Segmental clinical exam
- GCF sampling from bounded teeth
- Ridge measurements with stent and caliper before and during surgery
- Evaluation of the wound
- Delivery of questionnaires related to the last 1 week and collection
- GCF sampling from wound edges and adjacent teeth
- Ridge measurements with stent and caliper
- Post-op care
- Evaluation of the wound
- Delivery of questionnaires related to for last month
- GCF sampling from wound edges and adjacent teeth
- Ridge measurements with stent/caliper
- Post-op care
- Evaluation of the wound
- Delivery of questionnaires related to the last four months
- Impressions taking and photo documentation
- Segmental clinical exam
- GCF sampling from bounded teeth (and wound if still exposed)
- Ridge measurements with stent/caliper

**Figure 2- Sequence of Clinical Data Collection**
**Figure 3-** Changes in Clinical Parameters During Wound Healing

- p≤ 0.03 (difference with baseline)
- p= 0.057 (difference with baseline)
Figure 4- Changes in percentage of plaque accumulation and Bleeding on Probing at wound site

★ $p \leq 0.04$ (difference from baseline and 1 week)
Figure 5- Characteristics of Healing Wound

☆ p< 0.001 (difference with 1 week)
Figure 6- Experience of Pain, Discomfort or Numbness During Wound Healing

p< 0.001 (difference between 1 week and 4 months)
Figure 7- Amount of wound exposure and pain description/intensity

- p= 0.001 (difference between 1 week- 1 month and 1 week- 4 months)
- p= 0.001 (difference between 1 week- 4 months)
- p= 0.058 (difference between 1 week- 1 month)
Figure 8 - Wound Fluid and Local Pro-inflammatory Cytokine Levels:  A GCF and Wound Fluid Volumes, B IL-1β expression within wound fluid, C IL-1ra expression within wound fluid, D IL-6 expression within wound fluid, E IL-8 expression within wound fluid, F GM-CSF expression within wound fluid, G MIP-1α expression within wound fluid, H MIP-1β expression within wound fluid, I TNF-α expression within wound fluid, J Mediators expressed at high levels at 4 months.
**Total Amount (pg):**

- ★ p = 0.005 (difference between Baseline - 1 week)
- ○ p = 0.03 (difference between 1 week - 1 month)
- ● p = 0.009 (difference between 1 week - 4 months)

**Concentration (ng/ml):**

- ○ p = 0.04 (difference between Baseline - 1 month)
- ▲ p = 0.06 (difference between 1 week - 1 month)
Figure 8 continued

*Total Amount (pg):

🌟 p = 0.005 (difference between Baseline - 1 week)

● p = 0.03 (difference between 1 week - 1 month)

*Concentration (ng/ml):

● p = 0.06 (difference between 1 week - 1 month)
Figure 8 continued

*Total Amount (pg):

- p = 0.005 (difference between Baseline - 1 week)
- p = 0.03 (difference between 1 week - 1 month)
- p = 0.009 (difference between 1 week - 4 months)

*Concentration (ng/ml):

- p = 0.002 (difference between Baseline - 1 week)
- p = 0 (difference between 1 week - 1 month)
- p = 0.004 (difference between 1 week - 4 months)
Figure 8 continued

*Total Amount (pg):
- p= 0.00 (difference between Baseline- 1 week)
- p= 0.0 (difference between 1 week- 1 month)
- p= 0.0 (difference between 1 week- 4 months)

*Concentration (ng/ml):
- p= 0.002 (difference between Baseline- 1 week)
- p= 0.004 (difference between 1 week- 4 months)
Figure 8 continued

*Total Amount (pg):

🌟 p = 0.00 (difference between Baseline - 1 week)

● p = 0.00 (difference between 1 week - 1 month)

◇ p = 0.00 (difference between 1 week - 4 months)

*Concentration (ng/ml):

◇ p = 0.00 (difference between Baseline - 4 months)

● p = 0.001 (difference between 1 week - 1 month)

◇ p = 0.004 (difference between 1 week - 4 months)

● p = 0.001 (difference between 1 month - 4 months)
Figure 8 continued

**Total Amount (pg):**
- ⭐️ p = 0.00 (difference between Baseline - 1 week)
- ⬜️ p = 0.00 (difference between 1 week - 1 month)
- ⭕️ p = 0.001 (difference between 1 week - 4 months)

**Concentration (ng/ml):**
- ⭐️ p = 0.00 (difference between Baseline - 1 week)
- ⬜️ p = 0.00 (difference between 1 week - 1 month)
- ⭕️ p = 0.016 (difference between 1 week - 4 months)
Figure 8 continued

*Total Amount (pg):

- p= 0.00 (difference between Baseline- 1 week)
- p= 0.00 (difference between 1 week- 1 month)
- p= 0.00 (difference between 1 week- 4 months)

*Concentration (ng/ml):

- p= 0.012 (difference between Baseline- 1 week)
- p= 0.02 (difference between 1 week- 4 months)
Figure 8 continued

*Total Amount (pg):
- $p = 0.00$ (difference between Baseline- 1 week)
- $p = 0.00$ (difference between 1 week- 1 month)
- $p = 0.00$ (difference between 1 week- 4 months)

*Concentration (ng/ml):
- $p = 0.08$ (difference between Baseline- 1 week)
- $p = 0.02$ (difference between Baseline- 1 month)
Figure 8 continued

- IL-17
- FGFB
- TNF-a

- BL (n=17)
- 4 MONTHS (n=4)

- GM-CSF
- IP-10

- BL (n=17)
- 4 MONTHS (n=4)
Figure 9- Examples of wounds:

A: Primary closure of a wound during surgery
B: an example of open wound at one month
C: an example of a wound with complete healing
### Table 1 - Demographics

<table>
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<td><strong>Age</strong></td>
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<td>No</td>
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continued
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<th>Very Good</th>
<th>Good</th>
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**Table 2-** Site-specific information and surgical details

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<td>five teeth</td>
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<th>Type of Bone Graft Material</th>
<th>FDBA</th>
<th>17</th>
<th>Others</th>
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<th>Type of Membrane Material</th>
<th>Collagen plug only</th>
<th>1</th>
<th>Biomed Extend</th>
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<tr>
<td></td>
<td>Ti-reinforced</td>
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<td>Ti-mesh</td>
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| GBR at the time of extraction | Yes | 5  | No | 12 |

| Conscious sedation during surgery | Yes | 3 (1 oral; 2 IV) | No | 13 |


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<th></th>
<th>TOOTH (17)</th>
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<th>WOUND (17)</th>
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<td>525±550</td>
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<td>35±45</td>
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Table 3- Cytokines Data
Table 3 continued

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**Table 4- Psychological Evaluation and General Health/Oral Health- Related Questionnaire**

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<th>1 WEEK</th>
<th>1 MONTH</th>
<th>4 MONTHS</th>
<th>p-values*</th>
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<td>CUXOS</td>
<td>9.4±2</td>
<td>8±2</td>
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*Difference between 1 week and 4 months (P<0.05)

†Difference between 1 week and 1 month (P>0.05)
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<th>p values</th>
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Table 5- Short Form Health Survey
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**Table 6-** Post-operative Care
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Table 7- Clinical and Psychological Data Correlations
Table 7 continued

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**Table 8-** Wound Fluid Cytokines and Psychological Data Correlations
GUIDED BONE REGENERATION (GBR) TECHNIQUES HAVE BEEN SUCCESSFULLY APPLIED FOR ALVEOLAR BONE AUGMENTATION PRIOR TO IMPLANT PLACEMENT.\textsuperscript{8, 97, 98} COMMON COMPLICATIONS THAT ARE ASSOCIATED WITH GBR PROCEDURES ARE BARRIER MEMBRANE COLLAPSE, EXPOSURE, LOCAL INFECTION, AND/OR INCOMPLETE BONE FORMATION.\textsuperscript{9, 28} IN ADDITION, PATIENTS RECEIVING SIMILAR PROCEDURES REPORT HIGHER LEVEL OF PAIN, USE OF MEDICATION, AND POORER WOUND HEALING, WHICH MIGHT NEGATIVELY AFFECT THEIR QUALITY OF LIFE.\textsuperscript{61} HENCE, THE PURPOSE OF THIS STUDY WAS TO DETERMINE THE EFFECTS OF GBR PROCEDURES ON GENERAL AND ORAL HEALTH-RELATED QUALITY OF LIFE. CHANGES IN PATIENT STRESS, DEPRESSION, ANXIETY AND COPING LEVELS DURING EARLY WOUND HEALING WERE ALSO EVALUATED.

WOUND SIZE IS GENERALLY A MAIN FACTOR IN INDUCING PAIN, DISCOMFORT AND RELATED COMPLICATIONS.\textsuperscript{99} LARGE SIZE DEFECTS (≥ 2 MISSING ADJACENT TEETH) WERE INCLUDED INTO THIS STUDY IN ORDER TO DETECT ANY DIFFERENTIAL EFFECT OF RELATED POSSIBLE DISCOMFORT ON VARIOUS ASPECTS OF QUALITY OF LIFE. THERE ARE SEVERAL OTHER FACTORS THAT COULD AFFECT WOUND HEALING AND GBR OUTCOMES, INCLUDING PLAQUE CONTROL, BACTERIAL INFECTION, PATIENT’S COMPLIANCE, PREGNANCY AND/OR SMOKING.\textsuperscript{100, 101} MOREOVER, AGE-RELATED EFFECTS ON WOUND HEALING HAVE BEEN DOCUMENTED IN THE LITERATURE.\textsuperscript{102, 103} WHETHER AGING BY ITSELF OR AGE RELATED MEDICAL CONDITIONS CAN DELAY ORAL WOUND HEALING REMAINS CONTROVERSIAL.\textsuperscript{102, 104, 105} IN THIS STUDY,
patients who had possible health-related risk factors that might affect wound healing were excluded. In addition, patients older than 75 years were not included. Nevertheless, the study population mainly includes older patients (60±4 yrs [61 (22-75)]). It is expected that there is a greater need for GBR procedures in older age group (older, failing dental restorations, age related dentition wear as well as bone loss due to longer exposure to periodontal disease), except for trauma cases. There was only one trauma case in this study who was the youngest patient (Table 7).

Smoking is another factor that has been reported to negatively affect regenerative periodontal therapy; smokers have higher rate of regenerative therapy failures and complications compared to non-smokers.\textsuperscript{106, 107} Smoking also can alter the revascularization process of both soft and hard tissues during wound healing.\textsuperscript{108, 109} Therefore, smoking was exclusion criterion in this study.

Hormonal changes during pregnancy have been shown to modulate gingival inflammatory reaction in; thus, pregnant women were also excluded from this project. In addition, performing GBR surgery on a pregnant woman might negatively impact her pregnancy.\textsuperscript{110}

Patients’ gender has been implicated as a factor in wound healing.\textsuperscript{102, 111} It has been reported that females exhibit slower oral wound healing.\textsuperscript{112, 113} Additionally, post-menopausal females are more prone to osteoporosis and bone loss due to estrogen deficiency.\textsuperscript{114} Consequently, to have a similar distribution between the two different
gender groups was crucial in order to minimize the gender-associated effects on wound healing.

Moreover, lower socioeconomic status has been shown to have a negative impact on patients’ stress level, general health, and psychological well-being.\textsuperscript{115,116} Collected socioeconomic data did not show any impact on measured clinical parameter. On the other hand, our data analysis suggests that patient’s income is positively correlated to the reported energy and fatigue scores of the SF-36 questionnaire (Table 7).

Another factor that has been documented to have an effect on wound healing is patient’s obesity and higher body-mass index (BMI), although this is not well documented for oral mucosal wounds. Patients with a higher body-mass index (BMI) (kg/m\(^2\)) took longer time to heal their wounds. The fact that obese patients might have an increased risk for having other health conditions, such as diabetes, might negatively impact wound healing.\textsuperscript{57,117} The mean reported BMI in this study was 28±2 (overweight), with a range of 14-41 kg/m\(^2\). It would be expected that this in turn might alter clinical wound healing outcomes, with patients having higher BMI presenting more complications and/or delayed wound healing. However, our statistical analysis did not conclude any significant association between BMI scores and psychological or clinical parameters examined (Table 7).

Similarly, patients with other health issues such as poorly controlled diabetes may suffer from delayed wound healing and/or higher incidence of complications. Patients
with poor metabolic control have been shown to experience tissue hypoxia, fibroblast dysfunction, impaired revascularization of wounds, high levels of metalloproteases, reduced host immune resistance, and neuropathy.\textsuperscript{57} Thus, patients with poor metabolic control were excluded from the study.

Questionnaires used for psychological assessments and perceived mental status may be differentially affected in patients using anti-depressant medications as well as chronic pain patients consuming significant amount of analgesics.\textsuperscript{118} Thus, emphasis was given to document the use of these types of medications and record them separately from general medications list. Final analysis revealed only one subject with chronic pain problem and three subjects reported using anti-depressant medications. It was impossible to conduct statistical analysis due to these small sizes. Nevertheless, inclusion of these patients may differentially affect the outcome results. Unfortunately, due to large percentage of the dental patients routinely using anti-depressants, our initial attempt to exclude these patients failed.

Differences in healing outcomes have been observed in different anatomical locations. Our group has reported in a previous study that the location and the size of the ridge defect could influence regenerative therapy outcomes.\textsuperscript{119} It has been observed that greater bone loss was noted in maxillary compared to mandibular sites, and in anterior compared to posterior sites following teeth extraction.\textsuperscript{120, 121} In this study, the distribution among different anatomical locations was similar as well as wound size at each
Complete wound closure was achieved after all GBR procedures, except one, in the current study. However, most of the wounds presented exposure by one week. Others have shown that the quantity of the regenerated hard tissue is affected if the primary closure of the covering soft tissue is jeopardized. In addition, healing by secondary intention by leaving open wounds results in slower healing and more scar formation. Nonetheless, the significance of early membrane exposure on the GBR outcomes remains controversial. Machtei et al. have conducted a meta-analysis that involved 60 sites from 2 studies. The results of this review shows the non-exposed GBR sites had 6 times greater new bone formation than exposed sites. On the other hand, other investigators have reported that GBR surgery outcomes might not be jeopardized by earlier membrane exposure. Mellonig and Triplett have shown that 53% of the sites that received GBR surgeries were not affected by early membrane removal. Additionally, Shanaman suggested that early membrane exposure does not affect GBR outcomes, as long as the patient maintains an adequate oral hygiene. Interestingly, our present data suggests a statistical significant correlation between the size of the wound exposure and initial ridge width measurements (Table 7).

Another factor that might impact wound healing behavior is gingival thickness and biotype. According to several reports, the thickness of the gingival flap covering the membrane is a significant factor affecting regenerative therapy outcomes. Some reports
have suggested 1.5 mm gingival thickness as a prerequisite for GBR therapy. 32,33 Although, mean flap thickness was 1.3±0.1 (range between 0.6 and 2.5 mm), our present data shows that 88% and 35% percent of the sites had clinical wound exposure at 1 week and 1 month, respectively. Wound exposure was not correlated with initial thickness of the flap tissue (p>0.05) (Table 7). Several other factors such as the control of flap tension, clinician experience, early loss of suture materials, and/or suturing technique could affect wound opening during healing.

Clinician experience might have an impact on the surgical therapy outcomes. The effect of clinicians’ experience on other periodontal therapies such as scaling and root planning have been reported in the literature.124 All clinicians in this study were either second or third year graduate students with significant experience in basic surgical techniques. They worked under board certified faculty supervision. Thus, expected outcome variations should be minimal.

In the literature, several reports have documented the use of both resorbable and non-resorbable barrier membranes in GBR procedures. It is required that the membrane used has certain characteristics; such as, biocompatibility, cell occlusion properties, soft tissue integration, space maintaining, and ease of manipulation by the clinician.7 The disadvantage of using non-degradable membranes is the need for a second surgery in order to retrieve them. Thus, demand for resorbable membranes has increased over the years by patients as well as clinicians.125 Strietzel et al. reviewed experimental and
clinical studies \(^{19, 20, 21, 22, 23}\) that evaluated the effectiveness of different membranes utilized for different GBR techniques. The conclusion of this review was that it is difficult to formulate particular indications for different membrane types, due to the small sample sizes and lack of comparative studies. They have also concluded that there is inadequate information regarding specific hard and soft tissue healing behavior in relation to different types of membranes used.\(^{16}\) There is increasing evidence from the literature that supports similar success rates of resorbable and non-resorbable membranes used in GBR surgeries for augmenting horizontal bony defects. However, vertical augmentation of bony defects remains a challenge for today’s clinicians.\(^{126}\) Notably, 14 out 17 sites received resorbable collagen membranes in this study. Factors affected material selections were clinician preference, membrane properties, and/or size/shape of the defect.

Regarding the bone grafting material, there is limited evidence in the literature to support the superiority of one type of material over another. Several reports have failed to draw a conclusion regarding the best material choice for GBR. Moreover, similar success rate was found of implants placed in regenerated sites, regardless of the grafting material used.\(^{127}\) All GBR procedures included in this study utilized freeze-dried bone allograft (FDBA\(^{\text{xi}}\)). Material selection was based on the availability of the product, patient’s selection, as well as, decreasing morbidity associated with autogenous graft.

\(^{\text{xi}}\) FDBA ©DENTSPLY Tulsa Dental. Tulsa, Oklahoma, USA
harvesting sites and the need for another surgical site.

Similar to what has been documented in previous studies\textsuperscript{128, 129, 130, 131}, our results have suggested that GBR outcomes to treat large size defects are predictable for ridge width and height preservation. According to Schropp\textsuperscript{15}, 50\% of alveolar ridge width reduction should be expected during the first 12 months following tooth extraction. It has been shown in 6-10 months follow-up trials that a mean of 1.5-5.5mm bone can be augmented using GBR therapies.\textsuperscript{132, 14, 133, 97} Comparably, a slight but statistically significant gain in ridge width was noted (7.5±0.7 mm at baseline versus 8.6±0.6 mm at 4 month; \(p=0.02\)). However, the difference detected at the relative ridge height scores was not statistically significant (12±0.6 mm at baseline versus 10.7±0.8 mm at 4 month; \(p=0.057\)). Although relative ridge height outcome did not significantly result in height gain, one could value the fact the GBR procedures can predictably preserve bone height and minimize bone loss following teeth extraction during 4 months of the study period.

Alveolar ridge preservation (ARP) is a GBR performed at the time of tooth extraction to control bone resorption. Although ARP technique follows the principles of GBR, the surgeries have different goals. GBR technique is applied in cases where bone remodeling/resorption after tooth extraction has already occurred; while ARP is performed immediately at the time of extraction when dealing with the original bone dimensions and fresh extraction sockets. In another words, ARP outcomes are expected to differ from GBR, since it is performed at fresh extraction sockets with higher original
bone volume. In addition, the outcome of these procedures is not always predictable, as the degree of bone loss varies among individual subjects and between anatomic sites.\textsuperscript{120} As mentioned above, according to Schropp et al.\textsuperscript{15}, bone volume loss within the first 12 months after extraction accounts for 50\% of the original alveolar bone width. Lekovic\textsuperscript{134} also documented 40\% loss in alveolar bone height and 60\% loss of alveolar bone width following in post-extraction sockets. This amount of reduction of bone volume, hence, would challenge GBR regenerative outcomes compared to ARP. Another challenge to the GBR surgeries is dealing with scar formation at the regenerative sites. Scarred wounds exhibit delayed wound healing compared to fresh wounds. Although scar formation-type of healing in the oral cavity is very rare, such trauma from GBR surgery might entail a significant restriction to the regenerative capacity of GBR wounds.\textsuperscript{135} In this study, 5 out 17 sites received GBR, or ARP, at the time of tooth extraction. The decision to include fresh extraction sites into this study was made based on size of the defect; significantly larger defect than single tooth extraction and performing ARP due to extraction of two or more adjacent teeth. Thus, the variations for clinical outcomes should be minimal since pre-grafting defect characteristics and surgical manipulations were similar.

Our results showed no change in KT during the follow up healing period with better PD and minimal recession of teeth adjacent to the surgical sites. Although GBR surgeries have been shown to preserve hard and soft tissues following teeth extractions in
several reports, there is limited data on soft tissue healing outcomes, specifically keratinized tissue width. Strietzel et al. reviewed experimental and clinical studies[^19] that evaluated the effectiveness of different membranes utilized for different GBR techniques. Their review failed to reach any conclusions regarding specific hard and soft tissue healing behavior following GBR surgeries, due to the lack of information regarding the outcomes of using different types of membranes.[^16] In agreement to our results, Ooestervald et al.[^136] have reported a small but statistically significant gingival recession and bone resorption observed on adjacent teeth at 12 months after GBR surgery. However, only 50% of these cases were related to GBR site. Figure 3 illustrates the clinical changes of the gingival margin from baseline to the end of the follow-up period.

For clinical evaluation of the GBR surgery site, this study has utilized several tools and parameters obtained from oral wound healing literature to objectively evaluate wound healing related outcomes. These parameters include clinical evaluation of wound[^61], wound opening, hydrogen peroxide test[^60], pocket depths, keratinized tissue width, gingival recession, gingival fluid volume and cytokines, graft mobility, percentage of BOP and plaque as well as defining soft tissue characteristics such as edema, necrosis, and bleeding. The medical literature is rich with standardized indices and tools that are being utilized efficiently to grade/score dermal wounds; however, there is limited number of tools, if there is any, reported in the dental literature that can predictably evaluate oral
mucosal wounds following guided bone surgery. The data reported in our study suggests that GBR wound healing outcomes can be predictably evaluated by employing wound-healing indices that are obtained from literature.

Plaque and bleeding on probing scores are commonly used in dental literature as a diagnostic tool to assess patients’ oral hygiene and inflammatory status. although the plaque percentage score remained constant throughout the follow up period, the BOP percentage scores were remarkably lowered by 1 month (Figure 4). The difference was statistically significant. This could be explained due to the effect of chlorhexidine 0.12% (CHX 0.12%) mouth rinse used post-surgically by patients. Several studies have proven that chlorhexidine 0.12% mouth wash use can significantly reduce gingivitis, bleeding, and plaque as well as, wound healing enhancement compared to other mouth rinses. Lang et al. performed a clinical study evaluated the clinical effects of one month use of 0.12% chlorhexidine solution. The study conclusions demonstrated that the use of 0.12% CHX rinses resulted in a significant enhancement of the periodontal status adjacent to extraction sockets. However, the results of studies reporting the effect of the drug on oral wound healing varied depending on the concentration of the drug; while the results for gingivitis and plaque prevention were more consistent on the positive effect of the mouthwash. Bassetti and Kellenberger have conducted an animal study where different concentrations of chlorhexidine were used. The study results showed that delayed wound healing was noted with increasing chlorhexidine concentrations,
especially in cases where bone exposure was performed. Other in vitro studies have reported that chlorhexidine is highly cytotoxic to cells and it might affect cellular proliferation, collagen gel contraction, and protein synthesis.\textsuperscript{145}

Our results have shown that wound fluid volume peaked at 1 week and gradually reduced as predicted throughout observation period (p<0.05) (Table 3). Contamination with blood, saliva, and/or plaque might affect protein concentration and evaporation of gingival crevicular fluid.\textsuperscript{138} This in turn might have an impact on GCF volume and content. In order to reduce these effects, careful manipulation of the GCF strips, strict moisture control measures, as well as, discarding any blood-contaminated strips were followed.

The hydrogen peroxide test is a conventional research tool to evaluate wound closure during healing.\textsuperscript{60, 147} This test involves the application of small amount of hydrogen peroxide, using a Q-tip, on the wound area. This will examine the seal of the epithelial barriers. If the wound is open where no epithelial seal exists, the catalase enzyme of the connective tissue will release oxygen and water from the hydrogen peroxide. This will result in a foaming effect, which indicates a positive result for an open wound. In addition, hydrogen peroxide has other uses as a mouth rinse that have been reported in the literature, such as in management of acute necrotizing gingivitis, promoting wound healing, plaque removal, and treatment of periodontal disease.\textsuperscript{148} In this study, a negligible amount of hydrogen peroxide was applied on the wound using a
Q-tip, to avoid the possible positive effects of this product on wound healing.

One of the main challenges that confronted our clinical evaluation of the wounds was the determination of graft mobility and wound stability at the surgical site. The only reliable measure in predicting graft mobility was to have a total loss of the grafting material, which did not occur at any of the studied sites. Gentle palpation and evaluation of any loose sub-gingival material by periodontal probe were used to determine any possible graft mobility. Alternatively, cone beam CT scan and/or impression materials could be utilized for a more precise analysis. However, each of these tests has site effects such as exposure to radiation as well as causing graft mobility during impressions.

Another challenge to our data collection was pain reported by subjects, as pain being a subjective measure that would differ from one patient to another and could be affected by several factors, including the use of pain medication. Only one patient reporting taking chronic pain medication was recruited in this study. Patients suffering from chronic pain are usually having other immune, inflammatory, and/or other systemic issues that might modify their course of healing as well. Another factor that might affect pain perception reported by our patient is psychological factors, that might also in turn affect wound healing.\textsuperscript{149, 150} The pain questionnaire that was used in this study was obtained and modified from another project performed by our department (Appendix A).\textsuperscript{78, 79} One of the major drawbacks of psychological data collection and pain reported by patients is that these are subjective measures that will largely depend on patient’s
reliability. The only way to measure pain is by using questionnaires that depend on patients reporting pain intensity and describing based on their on perception of pain. In our study, we used several tools and compared them to each other to determine if we are getting predictable consistent response from our recruited patients (Appendix A). In addition, our findings indicate that pain intensity scores were significantly correlated with CES-D depression scores, wound opening, and wound size. Pain description scores reported by the patients were also significantly associated with CES-D depression scores as well as wound opening (Table 7).

Gingival crevicular fluid (GCF) is a serum transudate or inflammatory exudate that can be collected from gingival crevice around teeth. Its constituents reflect the cellular responses of periodontium, as well as, components of serum.\textsuperscript{151,152,153} GCF can be collected by several techniques, such as absorbent paper strips or paper points, capillary tubes, and gingival crevicular washings.\textsuperscript{154-156} GCF volume can be indicative of inflammatory changes of the periodontium that can be triggered either by dental biofilms and/or trauma.\textsuperscript{157} Surgical manipulation of gingiva and oral mucosa induces an inflammatory/immune reaction, which is characterized by systemic and local production of cytokines. Concentrations of these proteins can be collected from periodontal sulcus (gingival crevicular fluid) or oral wounds (inflammatory exudates).\textsuperscript{158,159} Although cellular and biological factors may be similar between GCF and oral mucosa wound exudates, the source for these mediators might be different due to the structural
differences between the two. Hence, we might speculate differences in the wound healing progression as well.

Lamster et al.\textsuperscript{160} reported that the correspondence of data expressed in total enzyme quantity per standardized time period to the clinical parameters was more sensitive than presentation of the data as concentration. There is a controversy in the literature on whether the clinicians should report site-specific concentrations or total amount of proteins within GCF. As some investigators believe that it is more meaningful to report the total amount because of the changes in collected volume, others choose to report concentration together with collected amount.\textsuperscript{6} GCF sampling collects the entire volume of the fluid at the selected site, contrasting serum samples.

The disadvantages of sampling wound fluids are the possibility of sample contamination with blood, plaque, and/or saliva, as well as, fluid evaporation from the paper strips. As mentioned before, a strict moisture control and plaque removal measures were followed to minimize sample contamination and any contaminated strips were discarded.

As expected, a significant increase in several pro-inflammatory cytokines levels was observed during the first week of healing. Interestingly, some but not all cytokines reached peak levels at 1 month observation time. It is reasonable to think that that this may be due surgical trauma to blood circulation as well as the introduction of biomaterials between bone surface and soft tissue flap. This differential response
specific for certain but not all mediators requires additional investigation. Similarly, other cytokines that were detected at high concentration at 4 months were IL-1ra, IL-17, GM-CSF, IP-10, and TNF-α. Sample size was too small to reach any conclusion related to this observation. However, it appears that these mediators may be related to delayed wound healing.

There is a strong evidence to support the stress role in modifying immune response and slowing wound healing.\textsuperscript{56} In Marucha et al.\textsuperscript{60} study, oral wound were induced in healthy students using punch biopsy technique during exam and non-exam period of times. Oral wound placed during examination period healed 40% slower than non-exam periods or summer vacation. Moreover, current evidence has suggested that certain strategies that aimed to reduce stress can prevent delayed wound healing. For example, exercise, social support, and/or other strategies of coping can modify the level of stress.\textsuperscript{161} Contrarily, we aimed in this study to evaluate how our surgical therapy could possibly affect patients’ quality, stress, anxiety, and/or coping levels.

Researchers have documented the effect of psychological challenges in modifying immunity. The meta-analysis performed by Walburn et al.\textsuperscript{162} confirmed the relationship between stress and impaired wound healing or dysregulation of biomarkers related to wound healing. Studies done on students experiencing stress related to examination periods have shown increased interleukin-1 and decreased immunoglobulin A levels of the gingival crevicular fluids.\textsuperscript{163,164} In addition, It has been suggested that psychological
factors, including stress and anxiety, can affect patient’s behavior. The association between stressful life events and poor oral hygiene has been proven by several researchers.\textsuperscript{43, 44, 45, 46}

Researchers have explored the relationship between stress and coping responses in periodontal disease patients.\textsuperscript{41, 165} However, little is known about how periodontal therapy can affect patient’s psychological status and state of mind and how these psychosocial factors, in return, affect periodontal treatment outcomes such as wound healing, experienced pain, and the use of pain medications. In this study, our data suggests that GBR surgeries are associated with some negative effects on the patients’ quality of life such as depression (from 1 week to 1 month). On the other hand SF-36 post-GBR scores for energy and fatigue subscales were improved (from baseline to 4 months). Our data also suggest that pain intensity and discomfort levels are correlated, as mentioned above, to wound exposure (Table 7). However, only pain intensity scores are related to the amount of exposure. Which propose that patient’s negative psychological status can affect GBR wound healing.

One of the major weaknesses of questionnaire-base psychological evaluations is patient’s reliability and consistency in reporting their answers. Moreover, some of these questionnaires are designed for short term and others for long-term evaluation; which might affect the assessment consistency, sensitivity, and/or specify as an evaluation tool. Vining et al.\textsuperscript{166} utilized saliva cortisol levels in saliva to assess patients’ stress levels,
which might be a better objective tool that is not confounded by patients reliability in reporting psychological status. However, this technique might lack the ability to differentiate between different psychological symptoms, such as stress, depression or anxiety. It also can fluctuate significantly at different times of the day.

In our project, we were challenged by patients’ compliance and commitment to the research protocol. Study protocol was modified for two patients so that the subjects can complete questionnaires at home due to lack of an assigned clinical space that would provide privacy in answering personal questions as well as chair time and management related issues. Questionnaires were provided for those patients with a request of completing them within 5 days prior to next appointment. Nevertheless, not having a more strict control over who completes the questionnaire, where and when is a concern in this and similar studies.

The goal of OHIP was to develop a tool that assesses the social influence of oral-related conditions. General Health Questionnaire (GHQ) is designed to measures general mental health and distress, which includes items on depression symptoms, such as enjoying daily activities, feeling under strain, and having difficulties. Both of these instruments were designed as screening tools to detect those likely to have or be at risk of developing psychological problems. GHQ-12 and OHIP-49 scores were stable throughout the study which might indicate that in general, GBR procedure does not affect general health as well as oral health.
Post-operative medications can affect wound healing by either assisting or interfering with wound healing phases. Antiplatelet drugs that are commonly used as analgesics, such as aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), can affect coagulation phase of the wound healing. Other drugs might interfere with the inflammatory phase of wound healing, such as NSAIDs by blocking arachidonic acid metabolism and platelet aggregation. Antibiotics also have anti-inflammatory properties. For example, tetracycline and erythromycin can act as anti-inflammatory drugs by inhibiting leukocyte chemotaxis, hence affecting wound healing. In addition, to this anti-inflammatory role, antibiotics play an important function in prophylaxis and fighting infections.

One of the limitations of this study is a small study population. Based on the literature, changes in alveolar ridge width were chosen as main parameter to evaluate GBR outcome. In order to detect 2 mm difference between pre- and post-surgical dimensions at \( \alpha=0.05 \) level a priori sample size determination test requirement was n=15. A predilection for psychological outcomes was not possible and was actually exploratory for this study. Nevertheless, we were able to detect differential responses at pain perception and depression at statistically significant levels as well as differential responses at anxiety and quality of sleep at near to statistically significant levels. Thus, despite the small sample size, it is possible to conclude that advanced surgeries such as GBR performed to regenerate bone in large size alveolar ridge defects induce short-term
changes in some aspects of psychological health status that may differentially affect quality of life.

Within the limits of this study, GBR surgeries outcomes are predictable for alveolar ridge preservation of large bony defects. Short-term wound healing outcomes following GBR surgery can be evaluated using several routinely used clinical parameters. Interestingly, several but not all local pro- and anti-inflammatory cytokine responses are delayed compared to clinical parameters at GBR wounds. In addition, pain and discomfort levels outcomes are parallel to wound exposure outcomes. Following GBR therapy, some of the parameters related to psychological health status are affected at least for short observation time period. This may differentially affect quality of life. Future research should be directed toward creating better psychological evaluation tools, as well as, implementing them in the dental clinical practice in order to protect patient’s well-being and to accomplish more predictable healing outcomes following advanced regenerative surgeries.
References


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Appendix A: Psychological Questionnaires

Demographic Data

Subject #: ___________________________ Date: ___________________________

General Information

1. What is your weight? _______________ pounds
2. What is your height? _______________ feet.
3. What best describes your race/ethnicity?
   - White/Caucasian
   - Black/African-American
   - Asian
   - Pacific Islander
   - Native American
   - Other, please specify: ____________________________
4. What is your total family income per year?
   - Less than $15,000
   - $15,000-$29,999
   - $30,000-$49,999
   - $50,000-$74,999
   - $75,000-$99,999
   - $100,000 and above
5. What is your marital status?
   - Married
   - Divorced
   - Unmarried but in a long-term relationship
   - Single, or not in a long-term relationship
   - Other, please specify: ____________________________
6. If you are married or in long-term relationship, how long have you been together?
   ____________ years
7. What is the highest level of education you have completed?
   - 7th grade
   - Junior High
   - Some High School
   - High School Graduate
   - Some College
   - College Graduate
   - Some Graduate School or Higher
**Health Behaviors**

1. How often do you engage in any vigorous physical activity long enough to build up a sweat? (This includes activities such as running, biking, and other aerobic activity).
   - Less than once per month
   - Once per month
   - 2-3 times per month
   - Once per week
   - More than once per week

2. On an average weekday (Monday-Friday), how many hours do you spend standing or walking?
   - Less than 2 hours
   - 2-4 hours
   - 5-8 hours
   - More than 8 hours per day

3. In general, would you say your health is:
   - Excellent
   - Very Good
   - Good
   - Fair
   - Poor
PSS-10

Subject #: ___________________  Date: ___________________

INSTRUCTIONS: The questions in this scale ask about your feelings and thoughts during the past month. In each case, please indicate how often you felt or thought a certain way by filling in the appropriate circle. The best approach is to answer each question fairly quickly. That is, don’t try to count up the number of times you felt a particular way, but rather indicate the answer that seems like a reasonable estimate.

1. In the last month, how often have you been upset because of something that happened unexpectedly?
   - Never
   - Almost Never
   - Sometimes
   - Fairly Often
   - Very Often

2. In the last month, how often have you felt that you were unable to control the important things in your life?
   - Never
   - Almost Never
   - Sometimes
   - Fairly Often
   - Very Often

3. In the last month, how often have you felt stressed?
   - Never
   - Almost Never
   - Sometimes
   - Fairly Often
   - Very Often

4. In the last month, how often have you felt confident about your ability to handle your personal problems?
   - Never
   - Almost Never
   - Sometimes
   - Fairly Often
   - Very Often

5. In the last month, how often have you felt that things were going your way?
   - Never
   - Almost Never
   - Sometimes
   - Fairly Often
   - Very Often

6. In the last month, how often have you found that you could not cope with all the things that you had to do?
   - Never
   - Almost Never
   - Sometimes
   - Fairly Often
   - Very Often
7. In the last month, how often have you been able to control irritations in your life?

Never   Almost Never   Sometimes   Fairly Often   Very Often

8. In the last month, how often have you felt that you were on top of things?

Never   Almost Never   Sometimes   Fairly Often   Very Often

9. In the last month, how often have you been angered because of things that happened that were outside of your control?

Never   Almost Never   Sometimes   Fairly Often   Very Often

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?

Never   Almost Never   Sometimes   Fairly Often   Very Often
**CES-D**

*Subject #: __________________  Date: _____________________*

**INSTRUCTIONS:** Please read each statement and then fill in the bubble which best describes how often you felt or behaved this way – DURING THE PAST WEEK:

1. I was bothered by things that usually don’t bother me.

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2. I did not feel like eating; my appetite was poor.

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3. I felt that I could not shake off the blues even with help from my family or friends.

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4. I felt that I was just as good as other people.

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5. I had trouble keeping my mind on what I was doing.

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6. I felt depressed.

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7. I felt that everything I did was an effort.

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8. I felt hopeful about the future.

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9. I thought my life has been a failure.

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10. I felt fearful.
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**11. My sleep was restless.**

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**12. I was happy.**

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**13. I talked less than usual.**

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**14. I felt lonely.**

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**15. People were unfriendly.**

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**16. I enjoyed life.**

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**17. I had crying spells.**

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**18. I felt sad.**

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**19. I felt that people disliked me.**

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**20. I could not “get going.”**

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<td>5-7 days</td>
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CUXOS

Subject #: __________________  Date: __________________

INSTRUCTIONS: Please read each statement and then fill in the bubble which best describes how often you felt or behaved this way DURING THE PAST WEEK.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little bit</th>
<th>A medium amount</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I felt nervous or anxious.</td>
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<tr>
<td>2. I worried a lot that something bad would happen.</td>
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<tr>
<td>3. I worried too much about things.</td>
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<tr>
<td>4. I worried too much about things.</td>
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<tr>
<td>5. I was jumpy and easily startled by noises.</td>
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<tr>
<td>6. I felt keyed up and on edge.</td>
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<tr>
<td>7. I felt scared.</td>
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<tr>
<td>8. I had muscle tension or muscle aches.</td>
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<tr>
<td>9. I felt jittery.</td>
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<tr>
<td>10. I was short of breath.</td>
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<tr>
<td>11. My heart was pounding or racing.</td>
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<tr>
<td>12. I had cold, clammy hands.</td>
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<tr>
<td>13. I had a dry mouth.</td>
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<tr>
<td>15. I had diarrhea.</td>
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<tr>
<td>16. I had hot flashes or chills.</td>
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<tr>
<td>17. I urinated frequently.</td>
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<tr>
<td>18. I felt a lump in my throat.</td>
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<tr>
<td>19. I was sweating.</td>
<td></td>
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<tr>
<td>20. I had tingling feelings in my fingers or feet.</td>
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</tr>
</tbody>
</table>
COPE

Subject #: __________________  Date: _____________________

INSTRUCTIONS: Please read each statement and then fill in the bubble which best describes how often you felt or behaved this way—DURING THE PAST WEEK.

1. I've been turning to work or other activities to take my mind off things.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
2. I've been concentrating my efforts on doing something about my situation.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
3. I've been saying to myself “this isn't real.”
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
4. I've been using alcohol or other drugs to make myself feel better.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
5. I've been getting emotional support from others.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
6. I've been giving up trying to deal with it.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
7. I've been taking action to try to make the situation better.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
8. I've been refusing to believe that it has happened.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
9. I've been saying things to let my unpleasant feelings escape.
   ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
10. I've been getting help and advice from other people.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
11. I've been using alcohol or other drugs to help me get through it.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
12. I've been trying to see it in a different light, to make it seem more positive.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
13. I've been criticizing myself.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
14. I've been trying to come up with a strategy about what to do.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
15. I've been getting comfort and understanding from someone.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
16. I've been giving up the attempt to cope.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
17. I've been looking for something good in what is happening.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
18. I've been making jokes about it.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
19. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.
    ○ Not at all  ○ A little bit  ○ A medium amount  ○ A lot
20. I've been accepting the reality of the fact that it has happened.
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<tbody>
<tr>
<td>21.</td>
<td>I've been expressing my negative feelings.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
</tr>
<tr>
<td>22.</td>
<td>I've been trying to find comfort in my religion or spiritual beliefs.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
</tr>
<tr>
<td>23.</td>
<td>I've been trying to get advice or help from other people about what to do.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
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<tr>
<td>24.</td>
<td>I've been learning to live with it.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
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<tr>
<td>25.</td>
<td>I've been thinking hard about what steps to take.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
</tr>
<tr>
<td>26.</td>
<td>I've been blaming myself for things that happened.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
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<tr>
<td>27.</td>
<td>I've been praying or meditating.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
</tr>
<tr>
<td>28.</td>
<td>I've been making fun of the situation.</td>
<td>○ Not at all</td>
<td>○ A little bit</td>
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GHQ-12

Subject #: __________________ Date: __________________

INSTRUCTIONS: Please answer each question by filling in the circle that correctly corresponds to how you have been feeling recently.

1. Have you recently been able to concentrate on whatever you are doing?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
2. Have you recently lost much sleep over worry?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
3. Have you recently felt that you are playing a useful part in things?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
4. Have you recently felt capable of making decisions about things?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
5. Have you recently felt constant strain?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
6. Have you recently felt you couldn't overcome difficulties?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
7. Have you recently been able to enjoy your normal day-to-day activities?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
8. Have you recently been able to face up to your problems?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
9. Have you recently been feeling unhappy and depressed?
   ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
10. Have you recently been losing confidence in yourself?
    ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
11. Have you been thinking of yourself as a worthless person?
    ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
12. Have you recently been feeling reasonably happy, all things considered?
    ○ Better than usual  ○ Same as usual  ○ Less than usual  ○ Much less than usual
OHIP-49

Subject #: __________________
Date: _____________________

INSTRUCTIONS: Please answer these questions pertaining to the last 12 months by filling in the appropriate circle. The best approach is to answer each question fairly quickly.

1. In the past twelve months, have you had difficulty chewing?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

2. In the past twelve months, have you had trouble pronouncing words?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

3. In the past twelve months, have you noticed tooth that doesn’t look right?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

4. In the past twelve months, have you felt your appearance was affected?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

5. In the past twelve months, have you had stale breath?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

6. In the past twelve months, have you noticed food didn’t taste as good?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

7. In the past twelve months, noticed food catching on your tooth?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

8. In the past twelve months, did your digestion worsened?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

9. In the past twelve months, have you noticed your dentures not fitting?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

10. In the past twelve months, have you had painful aching?
    - Never
    - Hardly Ever
    - Occasionally
    - Fairly Often
    - Very Often

11. In the past twelve months, have you had a sore jaw?
    - Never
    - Hardly Ever
    - Occasionally
    - Fairly Often
    - Very Often

12. In the past twelve months, have you had headaches?
    - Never
    - Hardly Ever
    - Occasionally
    - Fairly Often
    - Very Often

13. In the past twelve months, have you had sensitive teeth?
    - Never
    - Hardly Ever
    - Occasionally
    - Fairly Often
    - Very Often

14. In the past twelve months, have you had a toothache?
    - Never
    - Hardly Ever
    - Occasionally
    - Fairly Often
    - Very Often

15. In the past twelve months, have you had painful gums?
    - Never
    - Hardly Ever
    - Occasionally
    - Fairly Often
    - Very Often
16. In the past twelve months, have you noticed it was uncomfortable to eat?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

17. In the past twelve months, have you had sore spots?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

18. In the past twelve months, have you noticed your dentures were uncomfortable?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

19. In the past twelve months, were you worried by dental problems?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

20. In the past twelve months, were you self-conscious?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

21. In the past twelve months, have dental problems made you miserable?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

22. In the past twelve months, have you felt uncomfortable about your appearance?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

23. In the past twelve months, have you felt tense?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

24. In the past twelve months, have you had unclear speech?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

25. In the past twelve months, were you misunderstood by others?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

26. In the past twelve months, have you noticed less flavor in food?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

27. In the past twelve months, were you unable to brush your teeth?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

28. In the past twelve months, have you avoided eating?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

29. In the past twelve months, was your diet unsatisfactory?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

30. In the past twelve months, were you unable to eat due to dental problems?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

31. In the past twelve months, have you avoided smiling?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

32. In the past twelve months, has a dental problem interrupted meals?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

33. In the past twelve months, has your sleep been interrupted?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

34. In the past twelve months, were you upset?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

35. In the past twelve months, have you found it difficult to relax?
   ○ Never  ○ Hardly Ever  ○ Occasionally  ○ Fairly Often  ○ Very Often

36. In the past twelve months, were you depressed?
37. In the past twelve months, was your concentration affected?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

38. In the past twelve months, have you been embarrassed?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

39. In the past twelve months, have you avoided going out?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

40. In the past twelve months, were you less tolerant of others?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

41. In the past twelve months, did you have trouble getting along with others?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

42. In the past twelve months, were you irritable with others?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

43. In the past twelve months, did you have difficulty doing jobs?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

44. In the past twelve months, has your general health worsened?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

45. In the past twelve months, did you have a financial loss?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

46. In the past twelve months, were you unable to enjoy people’s company?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

47. In the past twelve months, have you found life unsatisfying?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

48. In the past twelve months, were you unable to function?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often

49. In the past twelve months, were you unable to work?
   - Never
   - Hardly Ever
   - Occasionally
   - Fairly Often
   - Very Often
# PSQI

**Subject #: __________________**  
**Date: __________________**

**INSTRUCTIONS:** The following questions relate to your usual sleep habits during the past month **only.** Your answers should indicate the most accurate reply for the **majority** of days and nights in the past month. Please answer all questions.

**During the past month,**

1. **When have you usually gone to bed at night?**  
   _____ AM / PM

2. **How long has it usually taken you to fall asleep each night?**  
   _____ minutes

3. **When have you usually gotten up in the morning?**  
   _____ AM / PM

4. **How many hours of actual sleep did you get at night?**  
   _____ hours  
   (This may be different than the number of hours you spend in bed).

5. **How often have you had trouble sleeping because you:**

<table>
<thead>
<tr>
<th>A. Cannot get to sleep within 30 minutes.</th>
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</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>&lt;1 time/week</td>
<td>1-2 times/week</td>
<td>3+ times/week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Wake up in the middle of the night or early morning.</th>
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</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>&lt;1 time/week</td>
<td>1-2 times/week</td>
<td>3+ times/week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Have to get up to use the bathroom.</th>
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</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>&lt;1 time/week</td>
<td>1-2 times/week</td>
<td>3+ times/week</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>D. Cannot breathe comfortably.</th>
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</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>&lt;1 time/week</td>
<td>1-2 times/week</td>
<td>3+ times/week</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E. Cough or snore loudly.</th>
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</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>&lt;1 time/week</td>
<td>1-2 times/week</td>
<td>3+ times/week</td>
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F. Feel too cold.
   - Not at all: <1 time/week
   - 1-2 times/week
   - 3+ times/week

G. Feel too hot.
   - Not at all: <1 time/week
   - 1-2 times/week
   - 3+ times/week

H. Had bad dreams.
   - Not at all: <1 time/week
   - 1-2 times/week
   - 3+ times/week

I. Have pain.
   - Not at all: <1 time/week
   - 1-2 times/week
   - 3+ times/week

6. How would you rate your sleep quality overall?
   - Very Good
   - Fairly Good
   - Fairly Bad
   - Very Bad

7. How often have you taken medicine (prescribed or “over the counter”) to help you sleep?
   - Not at all: <1 time/week
   - 1-2 times/week
   - 3+ times/week

8. How often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
   - Not at all: <1 time/week
   - 1-2 times/week
   - 3+ times/week

9. How much of a problem has it been for you to keep up enough enthusiasm to get things done?
   - No problem at all
   - Only a very slight problem
   - Somewhat of a problem
   - A very big problem
INSTRUCTIONS: Please answer the 36 questions of the Health Survey completely, honestly, and without interruptions.

General Health

1. In general, would you say your health is:
   - Excellent
   - Very Good
   - Good
   - Fair
   - Poor

2. Compared to one year ago, how would you rate your health in general now?
   - Much better now than one year ago
   - Somewhat better now than one year ago
   - About the same
   - Somewhat worse now than one year ago
   - Much worse than one year ago

Limitations of Activities – The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

5. Lifting or carrying groceries.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

6. Climbing several flights of stairs.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

7. Climbing one flight of stairs.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

8. Bending, kneeling, or stooping.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

9. Walking more than a mile.
   - Yes, limited a lot
   - Yes, limited a little
   - No, not limited at all

10. Walking several blocks.
11. Walking one block.
   ○ Yes, limited a lot  ○ Yes, limited a little  ○ No, not limited at all

12. Bathing or dressing yourself.
   ○ Yes, limited a lot  ○ Yes, limited a little  ○ No, not limited at all

**Physical Health Problems** – during the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

13. Cut down the amount of time you spent on work or other activities.
   ○ Yes  ○ No

14. Accomplished less than you would like.
   ○ Yes  ○ No

15. Were limited in the kind of work or other activities.
   ○ Yes  ○ No

16. Had difficulty performing the work or other activities (for example, it took extra effort).
   ○ Yes  ○ No

**Emotional Health Problems** – during the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

17. Cut down the amount of time you spent on work or other activities.
   ○ Yes  ○ No

18. Accomplished less than you would like.
   ○ Yes  ○ No

19. Didn’t do work or other activities as carefully as usual.
   ○ Yes  ○ No

**Social Activities**

20. Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
   ○ Not at all  ○ Slightly  ○ Moderately  ○ Severe  ○ Very Severe

**Pain**

21. How much bodily pain have you had during the past 4 weeks?
   ○ None  ○ Very Mild  ○ Mild  ○ Moderate  ○ Severe  ○ Very Severe
22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
   ○ Not at all ○ A little bit ○ Moderately ○ Quite a bit ○ Extremely

**Energy and Emotions** – These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

23. Did you feel full of pep?
   ○ All of the time
   ○ Most of the time
   ○ A good bit of the time
   ○ Some of the time
   ○ A little bit of the time
   ○ None of the time

24. Have you been a very nervous person?
   ○ All of the time
   ○ Most of the time
   ○ A good bit of the time
   ○ Some of the time
   ○ A little bit of the time
   ○ None of the time

25. Have you felt so down in the dumps that nothing could cheer you up?
   ○ All of the time
   ○ Most of the time
   ○ A good bit of the time
   ○ Some of the time
   ○ A little bit of the time
   ○ None of the time

26. Have you felt calm and peaceful?
   ○ All of the time
   ○ Most of the time
   ○ A good bit of the time
   ○ Some of the time
   ○ A little bit of the time
   ○ None of the time
27. Did you have a lot of energy?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little bit of the time
   - None of the time

28. Have you felt downhearted and blue?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little bit of the time
   - None of the time

29. Did you feel worn out?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little bit of the time
   - None of the time

30. Have you been a happy person?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little bit of the time
   - None of the time

31. Did you feel tired?
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
DA Little bit of the time
O None of the time

**Social Activities**

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

O All of the time
O Most of the time
O Some of the time
O A little bit of the time
O None of the time

**General Health** – how true or false is each of the following statements for you?

33. I seem to get sick a little easier than other people.

O Definitely true  O Mostly true  O Don’t know  O Mostly false  O Definitely false

34. I am as healthy as anybody I know.

O Definitely true  O Mostly true  O Don’t know  O Mostly false  O Definitely false

35. I expect my health to get worse.

O Definitely true  O Mostly true  O Don’t know  O Mostly false  O Definitely false

36. My health is excellent.

O Definitely true  O Mostly true  O Don’t know  O Mostly false  O Definitely false
PAIN EXPERIENCE EVALUATION- 1 Week

SUBJECT ID#: ___________________________  Date Completed __________________

Please answer as best you can.

Did you have any pain at surgical site since your last visit (surgery day)?

Yes ______  No ______

If yes, please describe the pain as best you can (for example: throbbing, stabbing, sharp, dull, duration, etc…)

_______________________________________________________________________________

If you experienced pain at surgical site, how much pain did you have?  Please circle number, with ‘0’ being no pain and ‘10’ being the most severe pain imaginable

0     1      2     3     4     5      6     7      8     9    10
No Pain  Moderate Pain  Worst Pain Imaginable

3. Please circle the number that best describes the pain that you experienced at the surgical site and how it affected your activities

0 = No pain
1 = Tolerable and pain does not prevent any activities
2 = Tolerable and pain prevents some activities
3 = Intolerable and pain does not prevent use of telephone, TV viewing, or reading
4 = Intolerable and pain prevents use of telephone, TV viewing, or reading
5 = Intolerable and pain prevents verbal communication.

If you experienced pain that you rated 2 or higher, please list or describe all the activities that were prevented by the pain:

_______________________________________________________________________________

4. Did you use the prescribed mouth rinse since your surgery?

Yes ______  No ______

If yes, how much and how often did you use it?

_______________________________________________________________________________

5. Did you feel any discomfort (example: itching, pulling) from the stitches since your surgery?

Yes ______  No ______

If yes, please describe the discomfort, when and how often you felt it:

_______________________________________________________________________________
6. Did you experience any bleeding from the wound since your surgery?

   Yes     No

If yes, please describe when and how often you experienced it:
_____________________________________________________________________________
_____________________________________________________________________________

7. Did you have any swelling in the wound area since your surgery?

   Yes     No

If yes, please describe when did it start and whether it prevented you from any activities:
_____________________________________________________________________________

8. Did you experience any numbness in the wound area following since your surgery?

   Yes     No

If yes, please describe when and where it did start and whether you are still having the same sensation:
_____________________________________________________________________________

0    1    2    3    4    5    6    7    8    9    10
No Pain          Moderate Pain          Worst Pain Imaginable
PAIN EXPERIENCE EVALUATION- ONE MONTH

Subject ID#:___________ Date Completed ______________

Please answer as best you can.

Did you have any pain at surgical site since your last visit (following 1st week after surgery)?

_____Yes       _____No

If yes, please describe the pain as best you can (for example: throbbing, stabbing, sharp, dull, duration, etc…)
________________________________________________

If you experienced pain at surgical site, how much pain did you have? Please circle number, with ‘0’ being no pain and ‘10’ being the most severe pain imaginable

0 1 2 3 4 5 6 7 8 9 10
No Pain Moderate Pain Worst Pain Imaginable

3. Please circle the number that best describes the pain that you experienced at the surgical site and how it affected your activities

0 = No pain
1 = Tolerable and pain does not prevent any activities
2 = Tolerable and pain prevents some activities
3 = Intolerable and pain does not prevent use of telephone, TV viewing, or reading
4 = Intolerable and pain prevents use of telephone, TV viewing, or reading
5 = Intolerable and pain prevents verbal communication.

If you experienced pain that you rated 2 or higher, please list or describe all the activities that were prevented by the pain:
_______________________________________________________________________________

4. Did you use the prescribed mouth rinse following 1st week after surgery?

_____Yes       _____No

If yes, how much and how often did you use it?

5. Did your surgeon kept your sutures longer than one week? Or Did you have to have new sutures placed in place following first week after surgery?

_____Yes       _____No

If yes, did feel any discomfort (example: itching, pulling) from the stitches?

_____Yes       _____No

If yes, please describe the discomfort, when and how often you felt it:

6. Did you experience any bleeding from the wound following one month after surgery?

_____Yes       _____No

If yes, please describe when and how often you experienced it:
7. Did you have any swelling in the wound area following 1st week after surgery? _____ Yes  
     _____ No  
     If yes, please describe when it did start and whether it prevented you from any  
     activities:  

__________________________________________________________________  
__________________________________________________________________

8. Did you experience any numbness in the wound area following 1st week after  
    surgery? _____ Yes  _____ No  
    If yes, please describe when and where it did start and whether you are still  
    having the same sensation:  

__________________________________________________________________

0 1 2 3 4 5 6 7 8 9 10  
No Pain       Moderate Pain       Worst Pain Imagineable
PAIN EXPERIENCE EVALUATION - FOUR MONTHS

Subject ID#: __________   Date Completed __________

Please answer as best you can.

Did you have any pain at surgical site since your last visit (following 1st month after surgery)?
   ____ Yes   ____ No

If yes, please describe the pain as best you can (for example: throbbing, stabbing, sharp, dull, duration, etc…)
_______________________________________________________________________________
_______________________________________________________________________________

If you experienced pain at surgical site, how much pain did you have? Please circle number, with ‘0’ being no pain and ‘10’ being the most severe pain imaginable

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3. Please circle the number that best describes the pain that you experienced at the surgical site and how it affected your activities

   0 = No pain
   1 = Tolerable and pain does not prevent any activities
   2 = Tolerable and pain prevents some activities
   3 = Intolerable and pain does not prevent use of telephone, TV viewing, or reading
   4 = Intolerable and pain prevents use of telephone, TV viewing, or reading
   5 = Intolerable and pain prevents verbal communication.

If you experienced pain that you rated 2 or higher, please list or describe all the activities that were prevented by the pain:
_______________________________________________________________________________
_______________________________________________________________________________

4. Did you use the prescribed mouth rinse following one month after surgery?
   ____ Yes   ____ No

If yes, how much and how often did you use it?
_______________________________________________________________________________
_______________________________________________________________________________

5. Did you have to have new sutures placed in place following first month after surgery?
   ____ Yes   ____ No

If yes, did feel any discomfort (example: itching, pulling) from the stitches?
   ____ Yes   ____ No

If yes, please describe the discomfort, when and how often you felt it:
_______________________________________________________________________________

6. Did you experience any bleeding from the wound following one month after surgery?
1. Did you experience any pain in the wound area following one month after surgery?
   _____Yes      _____No
   If yes, please describe when and how often you experienced it:
   _______________________________________________________
   _______________________________________________________

7. Did you have any swelling in the wound area following one month after surgery?
   _____Yes      _____No
   If yes, please describe when it did start and whether it prevented you from any activities:
   _______________________________________________________
   _______________________________________________________

8. Did you experience any numbness in the wound area following one month after surgery?
   _____Yes      _____No
   If yes, please describe when and where it did start and whether you are still having the same sensation:
   _______________________________________________________
   _______________________________________________________

0 1 2 3 4 5 6 7 8 9 10
No Pain   Moderate Pain   Worst Pain Imaginable
### Appendix B: Ridge Width Measurements

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<th>Surgery Mesial (mm)</th>
<th>Surgery Mid (mm)</th>
<th>Surgery Distal (mm)</th>
<th>1 week Mesial (mm)</th>
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