A randomized controlled Trial to Compare the Histomorphometric and Clinical Outcomes of Soft Tissue Augmentation at the Time of Lateral Ridge Augmentation Procedures.

Study Protocol & Statistical Analysis Plan

NCT03774888

May 3, 2023

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Study Protocol

1. Objectives/Specific Aims:

The purpose of this investigator-initiated study is to evaluate the effect of soft tissue autogenous vs allogenic grafts on the soft tissue quantity and quality at the time of Guided Bone Regeneration (GBR) in preparation for endosseous implant placement.

Autogenous Connective Tissue Grafting (CTG) and Acellular Dermal Matrix (ADM) soft tissue grafts are mainly used to alter the quality and quantity of soft tissue.

a) Core objectives of this study are to:

1) To evaluate the quality of soft tissue regenerated with the use of the two available soft tissue grafts via histological analysis.

2) To evaluate whether CTG or ADM influences the outcomes of Guided Bone Regeneration (GBR) procedures.

3) To quantify the soft tissue augmentation achieved by the two available soft tissue grafts by direct clinical measurements after the healing

b) Outcomes will be measured by an evaluation of the following:

1) The quality of soft tissue regenerated with the use of the two available soft tissue graft via histological analysis (attachment to bone and keratinization)
2) Keratinized tissue width (in mm) measured clinically with a periodontal probe from the implant collar to the mucogingival junction.
3) Vertical thickness of soft tissue (in mm) measured clinically with periodontal probe around the implant collar from soft tissue surface to bone contact.
4) Volumetric change of soft tissue dimensions around the implant collar evaluated by superimposition of pre- and post-grafting digital intra-oral scan.

2. Background

Dental rehabilitation of partially or totally edentulous patients with oral implants has become a routine treatment modality in the last decades, with reliable long-term results. Early loss of the teeth due to trauma or periodontitis often leads to deformities in these resulting edentulous ridges. Studies have demonstrated that bone resorption will occur secondary to tooth extraction. This tends to occur over a 12-month period, most notably in the first 4 months following extraction.

When a tooth or a group of teeth has been missing for a long time, the patient may present with a ridge that is deficient in thickness and/or height and inadequate for dental implant placement. In these cases, ridge augmentation using guided bone regeneration (GBR) is routinely used to regain the lost bone.

The concept of GBR is based upon the use of a barrier membrane to exclude rapidly growing soft tissue cells from a bony defect and, more importantly, to maintain a space for the slower process of bone formation. Bone grafts or bone substitutes are commonly used in GBR procedures to provide support for the barrier membrane, for additional space maintenance, and/or for their bone healing properties.

An important factor is flap closure during bone augmentation. The key to achieving wound closure is not only the clinician's ability to obtain tension-free release flap but also good soft tissue quality and quantity. In an attempt to achieve wound closure and hence graft stability, the buccal mucosa is often broadly released, and this often results in a severe apical translocation of the mucogingival line, loss of vestibule, and keratinized mucosa (KM). When the vestibule becomes shallow, it often leads to an esthetic challenge as well as a phonetics problem. Moreover, research has shown that areas with minimal KM often have a higher peri-implant plaque accumulation, inflammation, and attachment loss.

Various surgical techniques have been used to obtain adequate amounts of keratinized tissue around dental implants, including the gingival autograft, apically positioned flap (APF), coronally positioned palatal sliding flap, and acellular dermal matrix graft (ADM). Performing a free gingival graft (FGG) prior to im- plant surgery has been suggested when there is minimal keratinized tissue over the edentulous ridge and APF and FGG can be combined in shallow vestibules with minimal keratinized tissue. A recent systematic review demonstrated that the combination of apically positioned flap and free gingival graft (FGG) is the most successful approach to increase the width of keratinized tissue and deepen the vestibule. However, when comparing the use of epithelialized gingival grafts with free connective tissue grafts, their ability to promote keratinized tissue is similar.

These procedures are usually performed before implant placement or during the exposure of submerged implants, which can extend the healing period and result in patients suffering from pain and discomfort through several surgical stages. In addition, these can be time-consuming procedures in cases that already have good primary implant stability and do not need hard-tissue augmentation.

To our knowledge, the influence of soft tissue augmentation at the time of ridge augmentation procedure has not been tested in socket grafting (ridge preservation) and ridge augmentation (deficient healed site) defects. This study aims at evaluating the effects of soft tissue augmentation using CTG or ADM on the clinical (amount) and histologic (% vital bone) outcomes at time of lateral ridge augmentation.

3. Study Population, Protocol Procedure, and Method:

Approximately 60 adults determined to need ridge augmentation graft of any ethnicity or gender with established UAB School of Dentistry Records may be enrolled in the study.

Participants must be at least 18 years old with demonstrated ability to understand and consent to the proposed study procedure. Decisionally-impaired adults and/or minors who cannot consent for themselves will not be enrolled. Women who report a current pregnancy or patients who are not systemically healthy enough to receive out-patient elective dental care at the time of enrollment will be excluded.

All attending faculty and residents in the UAB Department of Periodontology will be notified of this study. Patients seeking dental implant therapy routinely present to the Periodontal clinic to have a consultation regarding ridge augmentation. Upon completion of the exam by the periodontal resident faculty members will confirm the appropriate treatment plan (bone grafting). If the patient is considered potentially eligible the PI will be asked to explain the study procedures and confirm eligibility based on the clinical and radiographic findings (inclusion criteria). Candidates will be provided an unsigned copy of the consent form to take with them. Participants will be given a minimum of 24 hours to decide upon participation. Upon agreement for study entry patients will be scheduled by the research team for a screening visit, signing of the Informed Consent document and scheduling of the surgical procedure.

Screening/baseline visit: Upon enrollment into the study the patient's medical history and electronic records will be reviewed. Clinical examiners will conduct clinical and radiographic review/exams, the data will be used to determine eligibility according to the inclusion criteria. Study visits and objectives will be explained to all participants. IRB approved written informed consent will be obtained from all the participants.

Surgical visit (Visit 1): Patients will be randomized like the flip of a coin to one of the three groups listed on the day of surgery. Randomly generated treatment groups will be printed on note cards and placed in sealed envelopes. Envelope will be opened during the visit.

Group 1: Connective tissue graft (CTG) at time of lateral ridge augmentation, or

Group 2: Acellular Dermal Matrix (ADM) at time of lateral ridge augmentation.

Group 3: Control group (no soft tissue augmentation at time of lateral augmentation)

During bone augmentation procedure, just before suturing the flaps that were reflected, a CTG (Harvested from the patient's palate) or ADM (donor tissue that is FDA approved) will be sutured to the membrane that covered the bone graft.

Visit 2: The sutures will be removed after two weeks. Surgical sites (CTG, ADM or Control group) will be evaluated for healing status and postoperative instructions on resuming oral hygiene measures will be instructed to patients. Review medical history and assess for adverse events experience.

Visit 3: Six months post-ridge augmentation, For the research purposes a soft tissue biopsy will be taken at the center of the augmented site after elevating the flap using a 2 mm tissue punch. It is noteworthy that this soft tissue specimen would have been typically drilled away (automatically discarded in the suction system) with the initial implant site preparation drill if a biopsy were not planned (regular clinical setting). Hence, the biopsy procedure will not affect in any negative way the likelihood of implant placement. One Soft tissue biopsy per every participant in each group will be harvested from the site that was augmented and each tissue sample will be labelled a unique set of numbers and/or letters.

The soft tissue biopsy will be harvested and fixed in special solution overnight at 4°C. Fixed tissues will be dehydrated through an ethanol gradient, cleared in xylene, and embedded in paraffin. Embedded Tissues will be sagittal sectioned at 7mm thickness and mounted on Superfrost Plus slides (Fisher Scientific, Hampton, NH, USA). Serial sections of biopsy containing epithelia and connective tissue will then be cleared in xylene, rehydrated, and stained with hematoxylin and eosin (H&E) according to

standard protocol. The samples will be store to the laboratory located in the Institute of Oral Health Research at UAB School of Dentistry for the analysis of the tissue samples.

4. Inclusion/Exclusion Criteria:

Inclusion Criteria	Exclusion Criteria
English speaking	Non-English speaking
At least 18 years old	Less than 18 years old
Must be a patient of the UAB Dental School	Smokers/tobacco users (>10 cigarettes/day)
Able to read and understand informed consent document.	Patients with systemic pathologies or conditions contraindicating oral surgical procedures or adversely affecting wound healing.
Need for implants to replace missing tooth or teeth in at least one quadrant of the mouth.	Patients with significant medical conditions or habits expected to interfere with bony healing.
Insufficient alveolar ridge width for endosseous implant placement defined as 5mm or less as determined by bone sounding and cone beam computed tomography (CBCT) scan.	Patient is a poor compliance risk (i.e., poor oral hygiene, history of alcohol or drug abuse).
Patient and/or guardian is willing and able to comply with the preoperative and postoperative diagnostic and clinical evaluations required.	Bone dehiscence of >4mm following tooth extraction or Vertical loss of bone at edentulous ridge.
Patient not pregnant or not breastfeeding.	Patient pregnant or breastfeeding.

5. Benefits

Following a conventional lateral ridge augmentation, a displacement of the alveolar mucosa will take place because of the periosteal release that is part of the ridge augmentation procedure to achieve passive closure. Usually, this soft tissue defect that is created on the ridge where it will receive implants is corrected by a free gingival graft before, or at the time or after implant placement in order to create attached tissue adequate for future implant success. Benefits of this project is to monitor the expected benefits of using soft tissue grafting at the time of lateral ridge augmentation in creating a thicker tissue and possible attached soft tissue on the sites that will receive implants after the bone graft healing potentially leading to higher implant survival. This will decrease the number of surgeries and patient morbidity as the two procedures are going to be performed at the same visit.

6. Risks

Regarding procedural risks, due to each subject's physical and dental conditions being unique, the success of soft tissue grafting cannot be guaranteed. Some discomfort after treatment can be expected.

This may include pain, bleeding, inflammation, and soreness. These discomforts can be expected to go away within approximately 48 hours. The treatment site could become infected. If an infection occurs, the study dentist will treat the area.

Risks in group 1, post-operative discomfort may be expected with harvesting of the CTG although there is a considerable variability in patient reported discomfort after having received the same treatment with either group.

Risks associated with use acellular dermal matrix (group 2) include a low, theoretical possibility of viral or prion contamination of the materials. No such contamination has ever been reported and ADM has been used in many medical and dental applications. ADM is processed from cadaveric donor skin and all donors are tested for nondetectable levels of HIV and HepC. Furthermore, it is processed using proprietary methods to removal all cells and cellular components (and this is histologically verified for each processing batch) to allow the collagenous and extracellular framework to remain without the cells which may produce antigenicity.

Regarding the randomization risk, patients will be assigned to a group by chance, which may prove to be less effective than the other. There is a chance that one procedure may have a risk of increased post-operative discomfort, although there is considerable variability in patient reported discomfort after having received the same treatment with either group.

There are no additional risks associated with the soft tissue biopsy in addition to those associated with the routine implant site preparation itself. The biopsy trephine will simply replace the initial implant drill, as it will have the same dimensions.

Other risks associated with this protocol involve potential loss of confidentiality. Precautions will be taken to ensure that patient confidentiality is maintained. All records will be assigned identifying alphanumeric codes and the list linking identifying PHI to patient data will be kept on a password protected computer and destroyed immediately after statistical analysis is completed. All consent documents will be assigned non-identifying, alpha-numeric codes and the list linking personal information and patient data will be kept on a password protected computer and destroyed immediately after data analysis have been completed.

There may be other risks that are unknown.

7. Data Analysis/Outcome measures

The null hypothesis is CTG and ADM materials will have the same soft tissue thickness and possible attached tissue (as demonstrated by histology) at time of implant placement. To reject the null hypothesis of equal means with a significance level (alpha) of 0.05 using a two-sided two-sample unequal-variance t-test, 22 patients in each group (total of 66) will reach 0.90 statistical power. Accounting for a 6-patient loss-to-follow up, 60 patients will be enrolled in the study.

Outcomes will be measured by an evaluation of the following:

1) the quality of soft tissue regenerated with the use of the two available soft tissue grafts via histological analysis (attachment to bone and keratinization)
2) Keratinized tissue width (in mm) measured clinically with a periodontal probe from the implant collar to the mucogingival junction.
3) Vertical thickness of soft tissue (in mm) measured clinically with a periodontal probe around the implant collar from soft tissue surface to bone contact.
4) Volumetric change of soft tissue dimensions around the implant collar evaluated by superimposition of pre- and post-grafting digital intra-oral scans

8. Confidentiality

Data will be stored in a password-protected study-specific computer database within the department of Periodontology. The computer is backed-up by UAB IT. Knowledge of passwords and access to the database will be strictly limited to study personnel who are working with the collected data.

9. Adverse Event Reporting

Participants will be interviewed and instructed to call if they experience any adverse events after study procedures. Such events will be recorded. In the event of a serious adverse event, the IRB will be notified per posted requirements and in full compliance with federal guidelines for research in human subjects.