A prospective, randomized clinical trial to compare vestibular incision supraperiosteal tunnel access (VISTA) and sulcular tunnel access root coverage procedures with coronally advanced flap and acellular dermal matrix (ADM) to treat teeth with gingival recession and lack of adequate keratinized tissue. A pilot study.

Study Protocol & Statistical Analysis Plan

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A prospective, randomized clinical trial to compare vestibular incision supraperiosteal tunnel access (VISTA) and sulcular tunnel access root coverage procedures with coronally advanced flap and acellular dermal matrix (ADM) to treat teeth with gingival recession and lack of adequate keratinized tissue. A pilot study.

1. Study Protocol 1. Objectives/Specific Aims:
This investigator-initiated study will compare two commonly used soft tissue grafting techniques [vestibular incision supraperiosteal tunnel access (VISTA) vs. sulcular tunnel access root coverage procedures with the uses of acellular dermal matrix (ADM)] to achieve coronal flap advancement and root coverage as well as augmentation of soft tissue at intraoral tooth sites. Research data and daily clinical observations reveal that teeth with gingival recession and a lack of adequate keratinized tissue (KT) are more prone to persistent gingival inflammation, dentinal sensitivity, radicular (root) caries (tooth decay), faster periodontal attachment loss, and compromised plaque control. Soft tissue grating (by various techniques) aims at changing the quality, quantity and placement of the soft tissue around teeth by covering exposed root surfaces and creating or increasing the zone of keratinized mucosa (KM) surrounding the affected teeth. Both techniques tested have shown good clinical outcomes with regard to root coverage, but clinical reports of the VISTA technique and other similar techniques suggest that patients experience a decrease in site morbidity and discomfort post-operatively. To our knowledge, these 2 types of grafting techniques have not been compared in a prospective trial for differences in clinical (percentage of root coverage, amount of KT increase, tissue thickness increase, and practitioner-assessed esthetics) and patient-centered outcomes (pain, swelling, change in daily activities, and patient-assessed esthetics) in a controlled study.

2. Materials and Method:
Study population:
A total of 40 patients seeking treatment at the UAB SOD Graduate Periodontology clinics will be recruited to participate in this study. The potential candidates will be approached during the treatment planning and/or pre-surgical visit in the periodontal clinic. The investigator/research staff will give the IRB approved consent form to the potential participants, explain the study, and obtain the patient demographics if the patient participate in the study.

Procedures:

Normal dental appointment: Patients that are seen at the school of dentistry for regular dental care and evaluation may be identified as plausible participants for the study based on the inclusion criteria, they will be scheduled for a screening appointment to determine eligibility for inclusion within the study. Screening/baseline visit: patient's electronic records will be reviewed to assess radiographic documentation. If the x-ray is at least one year old a new radiograph will be obtained. Two trained and calibrated examiners will conduct clinical and radiographic evaluations to determine eligibility according to the above criteria. Study visits and objectives will be explained to all participants. IRB approved written informed consent will be obtained from all the participants. Photos will be obtained at the screening visit and at each subsequent visit (1-7) to evaluate healing of the tissue.

Clinical parameters that will be captured include:

- Probing depth (PD) measurements
- Bleeding on probing (BOP)
- Plaque Index (PI, Silness & Loe): A modification of the Silness and Loe Plaque Index will be used full mouth. Categories 2 and 3 from the original index will be collapsed into a single

category so that examiners only have to distinguish between visible plaque and plaque that cannot be seen but is detectable with the probe. A single score will be recorded for each tooth. A single score 0 to 2 will be recorded for buccal and lingual/palatal surface of each tooth examined as follows:
0 = No plaque
1 = A film of plaque adhering to the free gingival margin and adjacent area of the tooth which cannot be seen with the naked eye. But only by using disclosing solution or by using probe.
2 = Moderate accumulation of deposits within the gingival pocket, on the gingival margin and/ or adjacent tooth surface, which can be seen with the naked eye.

- Gingival Index *(GI,* Loe and Silness) at surgical site(s). A periodontal probe will be swept around the tooth sulcus at a depth of 1-2 mm. The examiner will determine the status of tissue health. A single score will be recorded for buccal and lingual/palatal surface of each tooth examined as follows:
  0 = healthy tissue
  1 = mild inflammation but no bleeding
  2 = moderate inflammation with bleeding
  3 = severe inflammation with a tendency toward spontaneous bleeding

- Width of keratinized tissue (KT) will be measured at tooth site(s) at the mid-buccal aspect from the mucosal margin to the mucogingival junction.
- Width of attached tissue (AT) will be calculated by subtracting PD from KM
- Tissue Thickness (TT1 and TT2) at the buccal mucosa will be measured during the surgical visit by horizontal transmucosal probing (sounding the bone) using an endodontic reamer after local infiltration of anesthetic prior to surgical site preparation. TT1 and TT2 will be measured at 2 mm and 5 mm from the mucosal margin, respectively.

Clinical photographs of the tooth site (s) will be obtained with one digital SLR camera.

Randomization: two groups (Participants will be randomized like the flip of a coin to one of the two groups listed.) Randomly generated treatment groups will be printed on note cards and placed in sealed opaque envelopes. Once the patient consents to participate in the study an envelope is opened, and the patient is then offered the allocated treatment regimen.

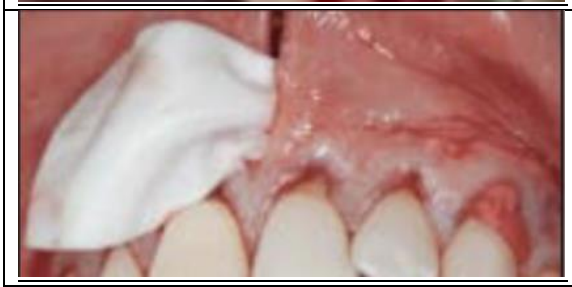
Group 1: will receive vestibular incision supraperiosteal tunnel access (VISTA) + Acellular Dermal Matrix (ADM) graft around teeth with gingival recession and lack of KT.

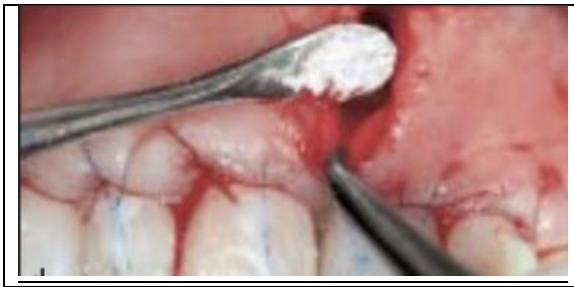
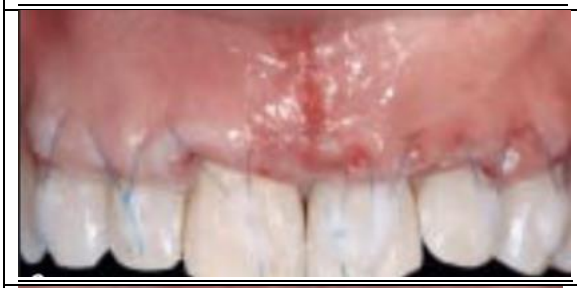
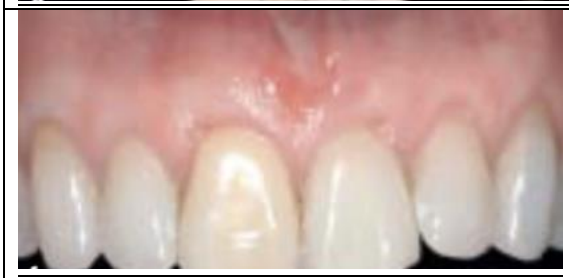
Group 2: will receive sulcular tunnel access + Acellular Dermal Matrix (ADM) graft around teeth with gingival recession and lack of KT.

Surgical visit (Visit 1): Patients will be anesthetized via infiltration around recipient tooth/teeth site(s). Study surgeon will confirm measurements taken at baseline with relation to width of keratinized tissue (KT) and evaluate thickness of mucosa (TT1 and TT2) as described above. Surgeon will then measure the recipient site to determine the size of graft needed and ensure that surgical treatment will avoid any vital structures. Soft tissue grafting procedures will include local anesthesia, monitoring of vital signs (bp, HR, O2 sat). Study surgeons will follow standard-of-care procedures for soft tissue as follows:

- Group 1: vestibular incision supraperiosteal tunnel access (VISTA) + Acellular Dermal Matrix (ADM)
  The tooth/teeth site(s) will be prepared utilizing a vertical vestibular incision beyond the mucogingival junction and split-thickness flap elevated on buccal aspect leaving a thin periosteum as recipient bed. Extension of the flap to the gingival margin and laterally to allow for adequate coronal advancement and coverage of the ADM graft material will be insured. Mesio-distal and apico-coronal dimensions will be measured at recipient site the ADM material trimmed after hydration and washing per package instruction to equal dimensions and uniform thickness will be performed. Exact AMD graft dimensions will be measured with a calibrated UNC-15 periodontal probe and its thickness will be measured using a caliper prior to placement within the supraperiosteal pouch at the recipient site. ADM graft will be secured in position and overlying flap secured in a coronal position with multiple suture techniques.

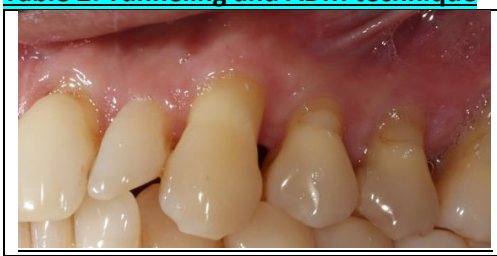
VISTA procedure:

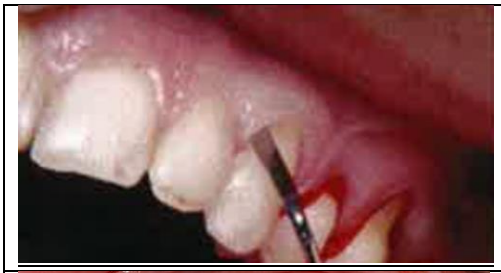
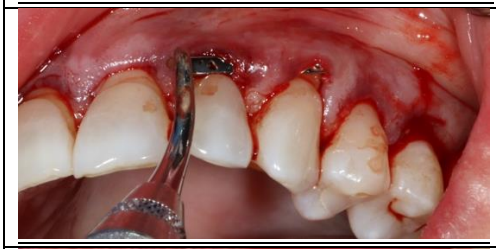
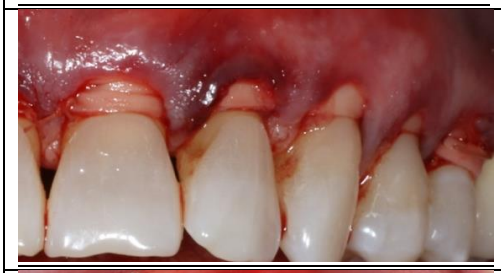
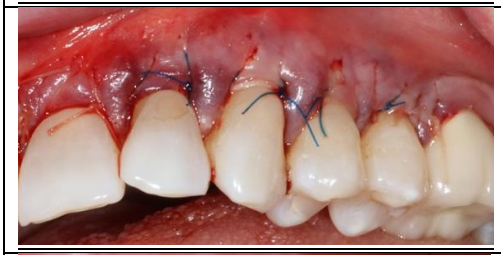
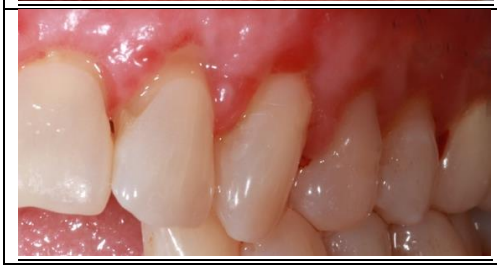
	Pt. presents with Miller Class I & II recession defects on upper front teeth.[12]
	Midline incision made and tissue released. [12]
	Release extended to include all involved teeth. [13]
	Acellular Dermal Matrix (ADM) is guided and manipulated to cover all root surfaces. [12]

	Tissue is repositioned at the desired level. Sutures bonded to the front of each tooth. [12]
	Midline incision sutured. [12]
	12 month follow up appt. [12]

- Group 2: sulcular tunnel access + Acellular Dermal Matrix (ADM) graft
  The tooth/teeth site(s) will be prepared utilizing a papilla-sparing, sulcular incision extending one tooth mesial and distal to the tooth/teeth site(s) to be treated and split-thickness flap elevated on buccal aspect leaving a thin periosteum as recipient bed. Extension of the flap apically and laterally to allow for adequate coronal advancement and coverage of the ADM graft material will be insured. Mesio-distal and apico-coronal dimensions will be measured at recipient site the ADM material trimmed after hydration and washing per package instruction to equal dimensions and uniform thickness will be performed. Exact AMD graft dimensions will be measured with a calibrated UNC-15 periodontal probe and its thickness will be measured using a caliper prior to placement within the supraperiosteal pouch at the recipient site. ADM graft will be secured in position and overlying flap secured in a coronal position with multiple suture techniques.

Table 2: Tunneling and ADM technique

	Pt. presents with Miller Class II and III recession defects.

	Incision made on the front of each tooth to be treated.
	Elevation of the flap with blunt dissection to necessary level.
	Insertion of acellular dermal matrix.[15]
	Positioning of acellular dermal matrix with sutures overlying root surfaces.
	Flap positioned at the desired level and sutured into place.
	One month post-operative evaluation of healing.

To help guard against possible infection, a pre-surgical antibiotic loading dose will be dispensed and prescriptions for relief of post-surgical discomfort, follow-up antibiotics and written home care instructions will be provided.

Follow up visits: The surgical sites will be examined at 1 week (visit 2) and 2 weeks (visit 3) after surgical visits and loose sutures will be removed. Exams will then be scheduled at 1 month (visit 4), 3 months (visit 5), 6 months (visit 6), and 1 year (visit 7).

During these follow up visits the following will take place:

1. Medical history review (all visits)

2. Assess for adverse events experience (all visits)

3. Intra-oral photographs: (all visits)

4. Clinical measurements:
   The width of keratinized tissue (KT) will be assessed at visits 4, 5, 6 and 7. Tissue thickness (TT1 and TT2) will be evaluated at visits 5, 6 and 7. Clinical measurements will be collected by calibrated examiners. Measurements from all visits will be compared to baseline in order to evaluate the progression of healing over time up to 12 months post-op.

5. Patient satisfaction survey
   This survey will be performed at visits 2 and 4 using a visual analogue scale (VAS) based questionnaire regarding esthetic appearance, pain, swelling, bruising, effects on daily activities. Esthetic evaluation by the patient will also be assessed at visits 6 and 7.

6. Pink Esthetics Score (PES)
   This standardized assessment of esthetics will be performed at visits 6 and 7 by blinded, calibrated examiners.

7. Study participation and satisfaction survey to be completed at final study visit (visit 7)

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.
One or more adjacent teeth (up to four) with Miller class I or II gingival recession defects and ≤ 2mm of KT at each site to be treated.	Presence of active periodontal disease or radiographic interproximal bone loss or tooth malposition, which would yield a Miller class III or IV categorization for the recession defect.
Presence of periodontally healthy, non-carious neighboring teeth, healthy implants, or edentulous ridges on either side of the involved site(s)	Presence of frenulae or other soft tissue anomalies at the site(s) to be treated that, in the opinion of the investigators, will interfere with successful access and treatment of the soft tissue defects.
No anticipated need for restorative care at the teeth to be treated during the study period.	Previous soft tissue grafting at the site(s) to be treated

Group Table:

Group	Treatment	Number of participants
Group 1	Vestibular incision supraperiosteal tunnel access (VISTA) + Acellular Dermal Matrix (ADM) graft	20
Group 2	Sulcular tunnel access + Acellular Dermal Matrix (ADM) graft	20

3. Study Background:

Soft tissue grafting for root coverage and alteration of the quality of gingival tissue surrounding teeth was originally described in 1956 using a Lateral Pedicle Flap.[1] Since that time, myriad techniques and materials have been described to improve clinical outcomes and patient acceptance.[2-6] Systematic reviews and meta-analyses have concluded that root coverage and KT gain at sites with Miller class I or II defects could be reliably achieved with the use of allogeneic donor tissue as well as autogenous connective tissue harvested from a patient's palate.[7-9] Use of a tunnel technique has also been shown to demonstrate decreased post-operative discomfort when compared with a standard coronally advanced flap.[10] Recently, there has been renewed interest in vestibular incisions, originally described in 1912[11], for the coronal advancement of gingival tissues with the use of graft materials due to purported decrease in post-operative discomfort and healing time.

Given the increase in the number of procedures performed, this study seeks to compare two established tunneling technique procedures with the use of allogeneic soft tissue graft materials to evaluate clinical and patient-centered outcomes to determine if there are any notable differences in post-operative healing and clinical outcomes associated with each technique.

4. Outcomes Measures

Outcomes will be measures by an evaluation of the following:

- Percentage previously visible root surface that has been covered by gingiva at 6- and 12-months following grafting with VISTA and sulcular tunnel access with ADM as compared to the baseline data.
- KT width as measured in mm by practitioner at 6- and 12-month following grafting with VISTA and sulcular tunnel access with ADM
- Change in tissue thickness evaluated with gentle intrasulcular probing and level of transparency of the grafted sites at 6 and 12 months.
- Practitioner-assessed esthetic outcomes using a standardized pink esthetic scale (PES) at 6 and 12 months postoperatively.
- Patient-assessed esthetic outcomes of root coverage and soft tissue appearance at 6 and 12 months post-operatively
- Patient centered outcomes including pain, bleeding, swelling, change in daily activities at 1 week and 1 month postoperatively, see attached Visual Analog Scale (VAS)
- Group sample sizes of 20 and 20 achieve 92% power to detect non-inferiority using a one-sided, two-sample t-test. The margin of non-inferiority is -1.0. The true difference between the means is assumed to be 0.1. The significance level (alpha) of the test is 0.025. The data are drawn from populations with standard deviations of 1.0 and 1.0.

- Regarding patient-centered outcomes, there is not adequate data available to complete an accurate sample size analysis to determine the proper N, therefore in this respect this study serves as a pilot study.

5. Benefits:

Benefits of this project for individual participants include enhancing periodontal soft tissue health and thus decreasing the risks of dentinal sensitivity, radicular (root) caries (tooth decay), and tooth root structure wear as well as a reduction in progressive recession and periodontal attachment loss at the tooth sites to be treated. Information gained from this research may be used by investigators to facilitate a healthier environment around teeth with gingival recession and a lack of keratinized tissue (KT) with therapies that are well-accepted with low post-operative morbidity.

6. Risks

The only risks associated with this protocol involve potential loss of confidentiality and randomization. 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 surveys and consent documents will have 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. Intra-oral photos will also be assigned alphanumeric codes that link with codes assigned to the demographic data collection form and consent documents. Photos will be stored as digital images on encrypted computers in the department of Periodontology. The photos will be used in the publication and presentations.

Regarding the randomization risk, patients will be assigned to a group by chance, which may prove to be less effective than the other. Both surgical techniques to be tested have been shown to result in clinical improvements in root coverage and soft tissue quality. 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.

Regarding procedural risks, due to each subject's physical and dental conditions being unique, the success of 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 associated with use acellular dermal matrix (both groups) 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.

Risks associated with dental anesthesia include injury to nerves, which may cause numbness or tingling of the lips, other teeth, chin, face, and tongue. This is usually temporary but could be permanent. The mouth, lips and tongue may remain numb for up to four hours after the treatment. During this time there may be difficulty eating, drinking, speaking, and smiling.

Some subjects may experience sensitivity or allergy to the anti-bacterial mouth rinse, the local anesthesia, the antibiotics given, or the post-treatment medications prescribed.

A major side effect of the anti-bacterial mouth rinse is staining of the teeth. This stain is similar to stains left by coffee or tea, or by smoking and may be removed by professional teeth cleaning. A less

frequent side effect may include temporary changes in taste. This will disappear once use of the rinse is stopped.

There may be other risks that are unknown.

7. Confidentiality
Data will be stored in a password-protected study-specific computer database within the department of Periodontology. Photographs of the teeth and gums will not be individually identifiable. 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.