***CATeR*:**
Comprehensive Alveolar and Tooth Esthetic Replacement

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LIST OF ABBREVIATIONS

COI	Conflict of Interest
CRF	Case report form
HIPAA	Health Insurance Portability Acountability Act
ICD	Informed Consent Document
IRB	Institutional Review Board
OHIP	Oral Health Impact Profile
OHRP	Office of Human Research Protections
OPRS	Office for the Protection of Research Subjects
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event
UIC	University of Illinois at Chicago

1.0 Project Summary/Abstract

Recent studies suggest a positive association between the volume of the peri-implant mucosa ("*gum" tissue*) surrounding a dental implant and the ultimate health and appearance of a dental implant supported crown ("implant"). The use of a gum allograft (e.g., PerioDerm®) at the time implant placement has been advocated to increase the volume of mucosa to avoid the morbidity of autogenous soft tissue grafting from the patient's palate [1]. However, the evidence supporting this is limited and properly controlled, prospective trials are lacking. Despite this, many clinicians already use gum allografts during implant therapy.

The purpose of this study is to prospectively evaluate whether including an gum allograft during implant therapy enhances the implant health and appearance.

2.0 Background/Scientific Rationale

An alveolar ridge is the part of the jaw bone which immediately surrounds and anchors the tooth socket ("*alveolus*"). Similar to any bone or muscle atrophying when not used, the alveolar ridge will shrink ("*resorb*") following tooth extraction. The volume of an alveolar ridge can be measured by 3D intraoral scanning, and is used clinically as a metric of oral health.

A **dental implant** is a titanium screw shaped implant placed into the healed alveolar bone or tooth socket following tooth extraction. It replaces the tooth root and supports the crown that is attached to an abutment. The abutment is surrounded by peri-implant mucosa that protects underlying bone and provides esthetic contour for the artificial tooth.

An **abutment** is a titanium or zirconia transmucosal component that is screwed onto the implant and is designed to connect the crown to the implant. A **crown**, also referred to as a "dental cap", is an artificial tooth generally made with porcelain or surgical grade metals such as gold or titanium.

Osseointegration is the development of a functional and structural connection between the alveolar ridge of the jaw and the dental implant. Implant success requires both sufficient bone volume for osseointegration and sufficient mucosal tissue to protect against biofilm mediated inflammation, assure functional comfort and contribute to dental implant esthetics. Our own research has demonstrated that following dental implant placement in healed ridges or extraction sockets, the alveolar ridge continues to resorb approximately 0.5 to 1.0 mm during the first year of healing [2]. Healed ridges are also often volumetrically deficient, having lost approximately 30% of their horizontal volume following tooth extraction [3].

To account for this loss in peri-implant architecture, peri-implant mucosal bone grafting has been proposed and is currently part of dental implant therapy. Both autogenous grafts (*mucosal connective tissue from the roof of the patient's own mouth or "palate"*) and allogeneic grafts (*collagen-rich grafts derived from a genetically non-identical human donor*) are used for these purposes, but there is controversy regarding the effectiveness of this supplemental graft during implant treatment [4-7]. Xenograft mucosal materials are grafts from non-human donors. Popular

in Europe where allograft materials are not widely used and used for soft tissue augmentation at implants, xenografts have successfully increased soft tissue thickness and volume in a stable manner [8]. These studies have typically employed linear (2D) measures to study outcomes. When volumetric (3D) measures have been employed, positive effects were not observed [9]. Using 3D measurement to assess outcomes of soft tissue augmentation at the time of implant is viewed as essential to the proper architectural evaluation of this clinical intervention [10].

The studies cited above attest to the safety and efficacy of soft tissue grafting at implants. These studies have not indicated that soft tissue grafting at implants increases the risk of implant failure. Further, there is evidence that increased thickness of soft tissue enhances the patients' comfort when performing oral hygiene and reduces associated signs of inflammation such as bleeding on probing. These cited studies further revealed no incidence of untoward morbidity or associated complications.

The general conclusion of a recent systematic review concerning the effects of soft tissue augmentation procedures on peri-implant health or disease were: 1) favorable peri-implant health, 2) increased keratinized mucosa, 3) reduced bleeding on probing, 4) less marginal bone loss with increased mucosal thickness. These advantages were reported in 10 articles, however, only 4 studies were randomized controlled trials [11]. Unfortunately, this review did not include any studies that have used allogeneic materials such as that proposed here. Thus, the present literature identifies both an important gap in knowledge regarding the use of allogenic materials for soft tissue augmentation at dental implants and relatively little volumetric assessment of any soft tissue augmentation procedure. The existing literature indicates that the placement of a submucosal connective tissue allograft is not associated with increased risks of implant failure or increased complications.

In this study, we will compare the clinical outcomes of placing a submucosal graft material in front of the dental implant immediately after placement of the implant (Figure 1). This soft tissue augmentation will be evaluated by comparision to implants placed without augmentation. An example of the significance of such a study is illustrated in Figure 2 that shows a healthy implant with sufficient soft tissue (top) and an unesthetic and inflammed implant with soft tissue recession (bottom). This can be prevented by increasing the thickness of the peri-implant mucosa using allogenic graft materials.

Figure 1

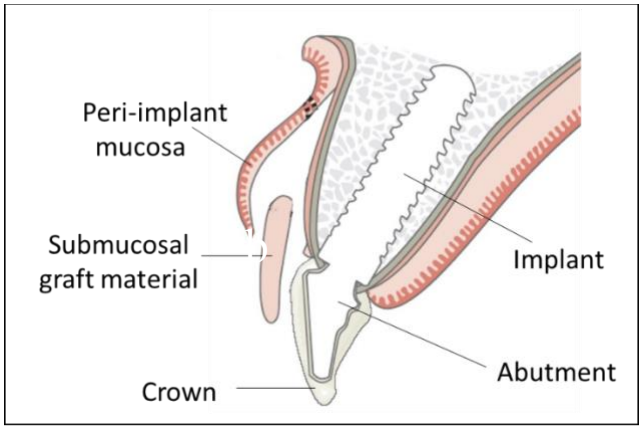

Figure 2

3.0 Objectives/Aims

The purpose of this research is to investigate changes in the health and appearance of oral tissues in patients receiving an artificial gum graft at the time of dental implant placement. Specifically, we want to know if adding a PerioDerm® allograft along with the dental implant will improve the health and appearance of a dental implant with a crown.

The anticipated study duration is approximately 18 months involving 6 months of recruitment and 12 months of treatment and evaluation.

4.0 Eligibility

The subject population will be:

a. Patients at the UIC Dental School who desire placement of a dental implant for an already missing tooth *or*
b. Patients at the UIC Dental School who desire placement of a dental implant for a tooth that will soon be extracted *or*
c. Patients in the community who desire placement of a dental implant for an already missing tooth or for a tooth that will soon be extracted.

Subject eligibility at UIC will be assessed and determined by the UIC PI with assistance from authorized UIC study co-investigators (Co-Is) and coordinators.

4.1 Inclusion Criteria

Patients within the UIC Dental School and the community who are:

- at least 18 years of age and
- willing and able to provide informed consent.
- in need of one implant to replace a missing tooth
- at least 20 teeth in good repair and occlusion
- Sufficient bone volume for dental implant placement without required bone augmentation

- Site development (soft and/or bone tissue) performed at least 5 months before implant placement, when required

4.2 Exclusion Criteria

- Implant cannot be placed without bone graft
- Unable to pay for crown
- Current smoker
- Untreated rampant caries and uncontrolled periodontitis
- Current alcohol or drug abuse
- Absence of adjacent (mesial and/or distal) natural tooth
- Uncontrolled diabetes
- Systemic or local disease or condition that would compromise post-operative healing and/or osseointegration
- Use of bisphosphonates
- History of radiation in the head and neck region
- Unable or unwilling to return for follow-up visits
- Unrealistic esthetic or functional demands
- Unlikely to be able to comply with study procedures
- Unwilling or unable to provide informed consent

4.3 Excluded or Vulnerable Populations

Vulnerable populations (minors, pregnant women, prisoners) will not be targeted in this study.

5.0 Subject Enrollment

Subjects will be screened by the UIC PI, UIC Co-I and/or authorized UIC study personnel at the UIC College of Dentistry Clinical Research Center. Dental AxiUm records may be reviewed for recruitment purposes. Patients attending the UIC Dental Clinic who desire implant therapy will be examined per standard of care; those found eligible for dental implant therapy will also screened for possible study inclusion.

Recruitment flyers may be posted on campus and on the websites of both UIC and the Chicago Dental Society. A recruitment email may be periodically be released on the UIC campus listserve. Interested patients will be instructed to contact the College of Dentistry Clinical Research Center (COD-CRC) to set up a screening appointment where the informed consent discussion and confirmation of study eligibility will occur. Target enrollment will be 40 subjects, but up to 60 subjects may be enrolled if needed to account for screening failures.

6.0 Study Design and Procedures

This will be a randomized interventional study of PerioDerm® gum allograft ("+Graft") plus standard dental implant with crown therapy versus standard dental implant with crown therapy alone ("-Graft").

Study Outcomes:

- Primary outcomes will be volume of the alveolar ridge at 12 months as measured by 3D intraoral scanning.
- Secondary outcomes will be implant survival, bleeding upon probing, marginal bone levels (MBLs) as measured by peri-apical radiographs and patient satisfaction as measures by the OHIP patient survey.

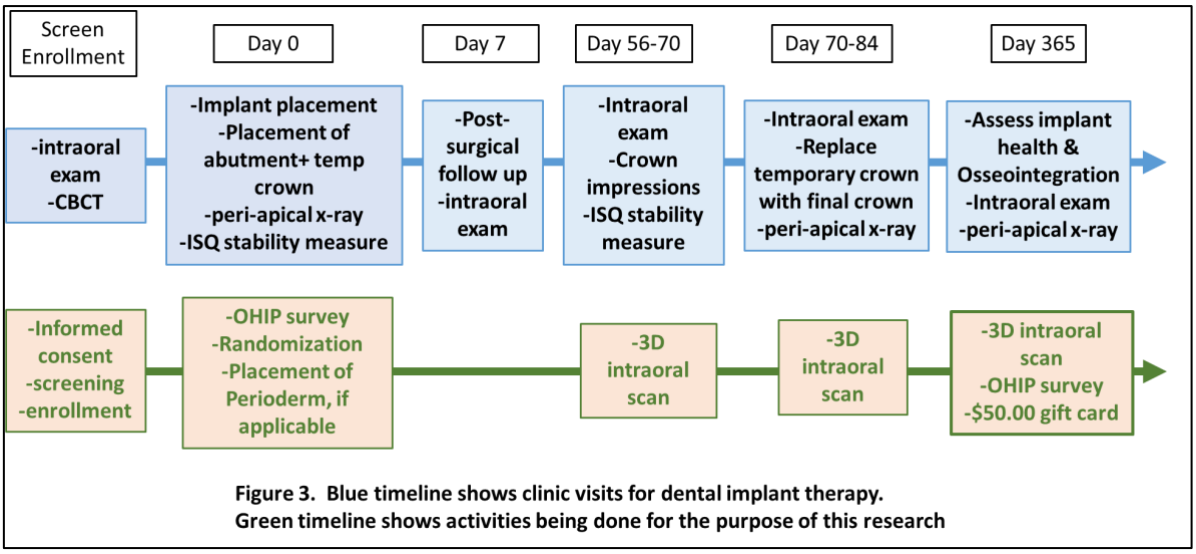

Figure 3. Blue timeline shows clinic visits for dental implant therapy. Green timeline shows activities being done for the purpose of this research

The research study will be performed at the UIC Dental School Clinical Research Center and will involve multiple clinic visits. These clinic visits usually occur at the same time as the subjects clinic visits for implant therapy, to avoid any research-only visits. The schedule for obtaining a dental implant is shown above in Figure 1 in blue with research visits shown in green and is described below:

1. First visit: ("Screening/Enrollment")
Subject screening, enrollment and the informed consent discussion will occur at this visit. Upon obtaining consent, medical and dental history may also be obtained from subjects. A scanned image of the subjects jaw bones, called a "cone beam CT" (CBCT) in addition to a 3D intraoral scan, will be obtained for the purpose of standard of care. This visit will require 30 - 60 minutes.

2. Second visit: ("Implant surgery")
The second visit will be coordinated with usual and customary treatment for dental implant therapy. Prior to implant surgery, subject will be asked to complete the OHIP patient satisfaction questionnaire. This questionnaire is for research purposes only. Additionally, at the second visit, subjects will be randomized (+Graft vs. -Graft) by authorized study personnel and his/her implant, with abutment and temporary crown, will be placed (+/- Graft). The abutment and temporary crown will be placed onto the implant. If this implant is not stable, a healing abutment will be placed instead and a removable temporary will be provided within 24 hours. The experimental variable in this study is placement of a submucosal allograft in randomized patients. PerioDerm® is not an

experimental material and is available for sale and use within the USA (see Appendix A1). This visit will require approximately 2 hours.

3. Third visit: ("1 week followup")
Third visit is an approximately 1 week post-surgical follow-up and is standard of care. This visit will require approximately 15 – 30 minutes. Should any complication be observed at this time, appropriate standard of care interventions will be made.

4. Fourth visit: ("8 week: crown impression")
This visit is an approximately 8 week post-surgical followup and is standard of care. At this visit, the implant health and osseointegration assessed by tactile evaluation and impressions will be taken for a final crown. At this visit, a 3D intraoral scan will be performed for research purposes. This visit will require approximately 1.5 hours. Should any complication be observed at this time, appropriate standard of care interventions will be made. If the implant has failed to integrate, the implant will be removed (this is atraumatic and without discomfort) and the patient will be referred to the UIC college of dentistry dental clinics or their dentist for further treatment or retreatment and the subject may be discontinued from the study.

5. Fifth visit (10-12 week; crown delivery)
This visit is approximately 10-12 weeks post-surgery and is standard of care. At this visit, implant health and osseointegration will be assessed by tactile evaluation and the final crown will be placed. This visit will require approximately 1.5 hours. Should any complication be observed at this time, appropriate standard of care interventions will be made. If the implant has failed to integrate, the implant will be removed (this is atraumatic and without discomfort) and the patient will be referred to the UIC College of Dentistry dental clinics or their dentist for further treatment or retreatment and the subject may be discontinued from the study.

6. Sixth visit: ("1 year follow-up")
This final visit will be approximately 1 year post-surgical followup and is performed in accordance with standard of care. Additionally, a 3D intraoral scan will be performed, subject will be asked to complete the OHIP patient satisfaction questionnaire and will receive a $50 gift card for research purposes.
This visit will require approximately 30 – 60 minutes. Should any complication be observed at this time, appropriate standard of care interventions will be made at that time and the subject will be referred to the UIC College of Dentistry dental clinics or their dentist for further treatment or retreatment.

All 3D intraoral scans are light-based, are not x-ray scans, and utilize scanners sold to and used by dentists in replacement of conventional impressions

7.0 Expected Risks/Benefits

The risks of dental implant therapy are minimal but include complications such as bleeding and bruising after surgery, post-surgical pain, infection, delayed healing, temporary speech problems, bone fracture, temporary or permanent damage to the nerves of the jaw, loss of bone on the upper or lower jaw (including altered appearance of the gum line), infection in the bone, damage to the adjacent teeth, chronic pain, abscess, and infection of the gums.

Risks of a PerioDerm® allograft include local or systemic infection, dehiscence (*wound rupture along the line of incision*) and/or necrosis (*death of tissue*) due to poor revascularization or allergic response to some component(s) of the graft material.

In accordance with the graft manufacturer's instructions, tissue recipient records for subjects receiving PerioDerm® will be maintained for the purpose of post-transplant tracing. This may increase the risk to the privacy of subjects randomized to +Graft.

CBCT and other 3D intraoral scanner capture light-generated images which are compiled by the appropriate software into a 3 dimensional geometric image. Since these scanners does not utilize xray technology, the medical risks of use are minimal and include mild fatigue of the facial muscles.

Subjects will be encouraged to contact the PI in the event of medical emergencies related to his/her dental care and will be provided a 24-hour emergency contact number. Subjects experiencing complication may require additional (>5) clinic visits during the course of this study. This is clearly indicated within the consent document.

If implant integration fails or the implant site is infected, the implant will be removed or the site infection treated using standard dental therapies. The subject will be excluded from this study and referred to UIC College of Dentistry for care.

Restoration of the oral cavity is likely to benefit all subjects, irrespective of study group. The potential for an enhanced restoration in the +Graft study group, as compared to the –Graft group, is the focus of this study.

Results from this research may lead to modifications in standards of care which may benefit future patients receiving dental implant therapy.

8.0 Data Collection and Management Procedures

Each subject will be assigned a unique study ID. Study data will be collected following each clinic visit and recorded on the applicable case report forms (CRFs). Data will be coded to the subject study ID. The Enrollment Log, needed to link a subjects study code to identifiers, will be stored separately. Hard copies of CRFs and the Enrollment Log will be stored in locking file cabinets within the UIC College of Dentistry Clinical Research Center. Electronic documents will be stored on a secure departmental server. Only authorized UIC research personnel will have access.

9.0 Data Analysis

Data analysis will be performed by the UIC PI in collaboration with the Co-I's using SPSS, SAS or similar software. A biostatistician may be consulted for statistical analysis, if required. Data will be de-identified prior to release to any statistician not listed as study personnel on Appendix P.

10.0 Quality Control and Quality Assurance

The UIC investigators are clinicians who are trained to perform dental implant therapy (both with and without allografts) at the UIC College of Dentistry. Only trained UIC personnel will participate in the clinical care of UIC subjects.

Study data, including photographic records, hard copy CRFs and the electronic patient records of treatment, will be reviewed periodically by the PI and Coordinator. All investigators will be calibrated to the study protocol in an initiation meeting(s) before undertaking study intervention (visit #2; implant surgery). Outcomes regarding quality of care and records will be reviewed in monthly research team meetings.

11.0 Data and Safety Monitoring Plan

11.1 Data Monitoring

UIC data will be checked for errors and omissions by the UIC PI and authorized UIC research personnel and corrected on the CRFs in a timely fashion by authorized UIC research personnel.

11.2 Safety Monitoring Plan

This protocol will be presented to the UIC Institutional Review Board for review and approval before the study commences. The IRB will be responsible for human subject protection oversight through annual periodic review of the research. All personnel participating in research activities at UIC will meet UIC IRB requirements for human subjects research, including completion of an approved CITI human subjects training and refresher courses at required intervals.

Each year, the UIC PI will submit a continuing review to the UIC IRB, which will review progress and re-approve the protocol. As part of these reviews, the UIC PI will report how many subjects have been recruited and if there have or have not been any adverse reactions reported by study participants.

The UIC PI or authorized UIC research personnel will obtain informed consent and will follow all protocols to assure compliance with standards of subject privacy. Data may be collected from the UIC subjects electronic dental record (AxiUm) and recorded on the appropriate Case Report Forms (CRFs) by the UIC PI, Co-I or authorized member of the UIC research team. Study data will be coded to a subjects ID and securely stored within the College of Dentistry Clinical Research Center. Data collection timepoints are: Screen/Enrollment, Implant, 1 week

follow up, 8 week follow up (Final Crown) and 12 month Follow-up. Access to UIC study data will be limited to the UIC PI, Co-Is and authorized members of the research team.

The UIC PI, assisted by the Co-Is, will monitor for adverse events occurring to UIC subjects.

An adverse event (AE) is defined as any untoward and unintended medical occurrence in a subject. A serious adverse event is defined as an unintended medical occurrence in a subject that: results in death, is life-threatening, results in hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability/incapacity or a congenital anomaly/birth defect.

There are a number of expected adverse events related to implant with crown surgery, including bleeding and bruising after surgery, post-surgical pain, infection, delayed healing, temporary speech problems, bone fracture, temporary or permanent damage to the nerves of the jaw, loss of bone on the upper or lower jaw (including altered appearance of the gum line), infection in the bone, damage to the adjacent teeth, chronic pain, abscess, and infection of the gums which may be unrelated to the study intervention (allograft).

A risk of implant treatment is failure of the implant prior to restoration or 'early' failure due to the lack of Osseointegration. This is associated with no pain or infection and the implant can be easily removed. Following 8 weeks of healing of the site, an implant can be replaced. In this study, if an implant is lost in the patient receiving the gum graft, the gum graft would not be removed.

Adverse events related to the PerioDerm® allograft include local or systemic infection, dehiscence (*wound rupture along incision line*) and/or necrosis (*death of tissue*) due to poor revascularization and allergic response to component(s) of the graft.

The UIC subject's treating clinician, who may or may not be a member of the research team, will attend to these adverse events until they have resolved and/or will refer the UIC subject to the appropriate provider as needed. These anticipated adverse events are described in the informed consent document and will be recorded on the appropriate CRF. Implant failure will result in dismissal of the subject and appropriate referral to the local dentist or UIC College of Dentistry clinics for further treatment.

Serious adverse events that are both unexpected and considered to be related to the study intervention will be reported to the UIC IRB in accordance with UICOPRS reporting guidelines. Anticipated adverse events that are not serious but occur at a frequency or intensity greater than anticipated by current clinical practice knowledge will also be reported to the UICIRB in accordance with UICOPRS reporting guidelines.

12.0 Statistical Considerations

A sample size of 40 subjects is based on previous studies. Our previous investigations of peri-implant mucosal levels have demonstrated that it is possible to distinguish differences of 0.5 mm among groups of 25 subjects. Here, we anticipate augmentation of approximately 1.0 mm – 1.5 mm and should readily determine significant differences between 20 subjects / group. A recent prospective clinical study comparing no graft to a autogenous connective tissue graft demonstrated a significant difference with 20 subjects / group [12]. This study utilized a similar set of inclusion/exclusion criteria and performed a similar intervention. Even a smaller study comparing 8 subjects with grafts to 10 without demonstrated significant 3D volume changes using a similar scanner-based analytic method [13]

13.0 Regulatory Requirements

13.1 Informed consent. UIC subjects participating in this study will provide informed consent and HIPAA authorization for the use of his/her personal health information in this research.

13.2 Subject Confidentiality. The privacy of the UIC study participants will be safeguarded by assigning each subjects a unique study code. Study data will be labeled with this code. An enrollment log, needed to link UIC subject identifiers to this study code, is stored separately. Only the UIC PI and authorized UIC study personnel will have access.

13.3 Unanticipated Problems. Unanticipated problems at UIC will be reported to the UIC IRB in accordance with UIC OPRS guidelines and as described above in section 11.2 Safety monitoring.

14.0 References

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