Esthetic Outcomes Following Immediate Implant Combine with Soft Tissue Augmentation

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1. BACKGROUND AND RATIONALE

1.1. General Introduction

The concept of immediate implant was proposed about forty years ago (Schulte and Heimke 1976; Schulte et al. 1978). Over the past few decades, several clinical trials had demonstrated immediate implantation has high survival rate and stable interproximal bone levels (Becker et al. 1998; Chen et al. 2007; Lazzara 1989; Sanz et al. 2014; Schropp et al. 2003), similar to conventional delayed implant placement. Compared to delayed placement, immediate implantation is able to reduce the number of clinical visits and surgical procedures, by this diminishing patient morbidity, and in some cases, enabling immediate restoration (Lang et al. 2012). In addition to these advantages, it has been suggested that immediate implant preserves alveolar bone dimensions (Denissen et al. 1993; Lazzara 1989; Paolantonio et al. 2001; Watzek et al. 1995). However, several experimental studies and clinical trials demonstrated significant changes of bony ridge dimensions in the surgical site of immediate implantation (Botticelli et al. 2004; Botticelli et al. 2006).

Generally, the dimensional change of buccal site is greater than that of the lingual/ palatal site (Botticelli et al. 2004; Brownfield and Weltman 2012; Lee et al. 2014). The buccal bone(Lee et al. 2014) or buccal ridge dimensional alteration (Grunder 2011; van Kesteren et al. 2010) following immediate implant placement without placing any bone graft or tissue graft is about 1 to 1.5 mm within one year follow-up. The change of bone/ridge dimension also accompanies with gingival recession. The mean mid-buccal gingival recession is approximately 0.5 to 1mm within one year follow-up following immediate implantation and advanced mid-buccal gingival recession (>1 mm) sometimes happens (Cosyn et al. 2012). Many clinicians try to prevent the changes of soft tissue and hard tissue in the esthetic demanding sites by using different methods. The effect of placing bone grafts and/or immediate temporization has been proved on compensating soft tissue and hard tissue collapse (Cosyn et al. 2012; Tarnow et al. 2014). However, the use of autogenous tissue graft or alternative graft, such as collagen matrix and acelluar dermal matrix, combined with immediate implant is equivocal.

Some experimental studies (Berglundh and Lindhe 1996) and clinical studies (Linkevicius et al. 2009; Linkevicius et al. 2014; Vervaeke et al. 2014) showed tissue thickness is negatively associated with the resorption of alveolar bone following implant placement. Therefore, augmenting soft tissue by tissue graft or acellular dermal matrix in the immediate implantation site may prevent the resorption of bone. The limited change of alveolar bone level also prevents gingival recession. Additionally, soft tissue augmentation combined with immediate implantation can directly compensate the dimensional alteration of ridge following extraction (Grunder 2011) and also increases width of keratinized gingiva by two-stage approach (Covani et al. 2007; Jyothi et al. 2013).

Autogenous soft tissue graft has been utilized in ridge augmentation(Allen et al. 1985; Studer et al. 2000), root coverage(Cairo et al. 2014; Langer and Langer 1985), extension of keratinized gingival width (Cairo et al. 2014), gingival thickness augmentation(Muller et al. 1998), and as a barrier in wound healing (Ellegaard et al.

1974; Nelson 2001). Subepithelial connective tissue graft (SCTG) or free gingival graft (FGG) is usually harvested from palate (Langer and Langer 1985; Sullivan and Atkins 1968) given palate provides a large area of keratinized tissue. A number of studies have demonstrated clinical superiority of autogenous soft tissue grafts compared to the available substitutes used in procedures of root coverage (Chambrone et al. 2010; Oates et al. 2003) and keratinized gingiva augmentation(Thoma et al. 2009).

In implant therapy, soft tissue grafts are utilized in ridge reconstruction (Grunder 2000), coverage of crown margins or implant surface (Burkhardt et al. 2008; Lee et al. 2015a), and keratinized tissue extension (Stimmelmayr et al. 2011; Yan et al. 2006). Soft tissue grafts have also been employed to seal extraction socket following immediate implant placement and at the same time to increase the width of keratinized gingiva (Edel 1995; Evian and Cutler 1994; Landsberg and Bichacho 1994; Rosenquist 1997). Combination therapy of soft tissue and osseous grafting with or without a barrier in conjunction with immediate implantation has been proposed by several clinicians to address vertical and horizontal ridge dimensional reduction (Grunder 2011), gingival recession(Migliorati et al. 2015; Yoshino et al. 2014) and to increase width of keratinized gingiva (Covani et al. 2007; Jyothi et al. 2013). These procedures primarily aim to improve the esthetic outcomes following immediate implant placement.

A range of biomaterials, including acellular dermal matrix and xenogeneic collagen matrix, have been developed to replace autogenous soft tissue grafts and to reduce patient morbidity. AlloDerm® Regenerative Tissue Matrix (RTM) is one of the most widely used alternative tissue grafts in dentistry. It is an acellular dermal matrix (ADM) that is derived from donated human skin and is minimally processed to remove epidermal and dermal cells with nondenaturing detergent while preserving the extracellular matrix. The removal of viable cells and antigens during the decellularization process minimizes the risk of rejection and inflammation at the surgical site. Then, a cyropreservant is added to avoid crystal formation, and then resulting tissue matrix is freeze-dried. The remaining matrix serves as a framework for cellular infiltration and vascularization. ADM is indicated for soft tissue augmentation (Batista et al. 2001; Griffin et al. 2004; Park and Wang 2006), gingival recession defect coverage (Andrade et al. 2008; Tal et al. 2002), keratinized gingiva extension (Harris 2001; Yan et al. 2006), and extraction socket coverage (Fowler et al. 2000; Froum et al. 2004; Park 2011) for both teeth and implants. Basically, ADM can be used in all the procedures that the soft tissue graft is indicated for.

Although the application of soft tissue augmentation combined with immediate implant has been reported in some studies, there are only few studies directly comparing the esthetic outcomes of immediate implant combined with soft tissue augmentation to immediate implant alone (Lee et al. 2015b). The evidence regarding the clinical effects of placing acellular dermal matrix at the site of immediate implant is less. It is necessary to conduct a clinical trial evaluating the impact of immediate implant combined with or without soft tissue augmentation on preserving tissue contour.

1.2. Rationale and justification for the Study

a. Rationale for the Study Purpose

The results of a current systematic review indicated immediate implant combined with autogenous tissue graft is able to maintain the level of gingiva, increase gingival thickness and extend the width of keratinized gingiva (Lee et al. 2015b). However, there is lack of clinical trials directly comparing the esthtics-related clinical outcomes of immediate implant combined with or without soft tissue augmentation.

The purpose of the randomized controlled trial is to evaluate the esthetic outcomes following immediate implant combined with the autogenous tissue graft or acellular dermal matrix compared to immediate implant alone. Changes of ridge dimension, gingival level, gingival thickness, width of keratinized tissue and bony structure will be assessed. SCTG is utilized instead of FGG because SCTG has less morbidity of the donor site and better esthetic outcomes than FGG (Del Pizzo et al. 2002). ADM is utilized because it is the one of the most widely chosen substitutes for autogenous tissue graft in all kinds of procedure and has many published clinical results (Gapski et al. 2005).

b. Rationale for Materials Selected

SCTG will be harvested from the palate and the required size depends on the size of the surgical site. Generally, the width of the tissue graft should be sufficient to cover the adjacent interproximal papillae, and the length could be standardized as 10 mm. The size of the tissue graft is able to cover the area usually having the most significant dimensional changes following extraction (Morimoto et al. 2015; Tarnow et al. 2014). The thickness of harvested tissue graft will be trimmed to the range from 1-1.5 mm (Hurzeler and Weng 1999).

The ADM is a commercial product and has multiple sizes available. One piece of 10mmx10mm ADM can be trimmed to an appropriate size defined by the criteria for SCTG. According to the manual instruction, the thickness of ADM ranges from 0.9-1.6mm which will be close to the thickness of SCTG utilized in this study.

c. Rationale for Study Population

The study will recruit subjects who have single unrestorable tooth planned for an implant placement. The tooth should have acceptable periodontal condition and locates in the oral esthetic zone, maxillary premolars to premolars. The surgical sites should have intact bony wall, but minor dehiscence or fenestration, up to 3mm, is allowed. These criteria justify the evaluation of esthetic outcomes in the site of immediate implantation.

d. Rationale for Study Design

The randomized controlled trail (RCT) is usually considered the gold standard for a clinical trial and it is able to provide the highest level of evidence within all the study designs (Howick et al. 2011). RCT can be used to test the efficacy or effectiveness of various types of medical/dental intervention. It is the most appropriate study design for the aim of the study.

2. HYPOTHESIS AND OBJECTIVES

2.1. Hypothesis

The hypothesis is that ridge dimensional reductions in the sites of immediate implant combined with autogenous tissue graft/acelluar dermal matrix are significantly less than the sites of immediate implant alone. Soft tissue augmentation is able to increase gingival thickness and limit resorption of bone by expanding the dimension of peri-implant mucosa. In addition to limited changes of ridge dimension and increased gingival thickness, stable gingival level and increased width of keratinized gingiva could also be found following soft tissue augmentation.

Placement of acellular dermal matrix has comparable clinical outcomes to placement of autogenous tissue graft because the clinical trials of mucogingival surgery, such as root coverage, show acelluar dermal matrix is as effective as autogenous tissue graft.

2.2. Primary Objectives

This randomized controlled trial aims to evaluate the esthetic outcomes following immediate implant combined with the autogenous tissue graft or acellular dermal matrix compared to immediate implant alone. Changes of ridge dimension, gingival level, gingival thickness, and width of keratinized tissue will be assessed.

2.3. Secondary Objectives

In addition to the esthetics-related clinical outcomes, the change of bony structure will also be measured. The alteration of bony structure around an implant is an important clinical parameter indicating the long term stability of the implant. The radiographic change of alveolar bone level will be measured on the images of periapical radiograph. The change of bone dimension will be measured on the images of cone beam computed tomography (CT)

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2.4. Potential Risks and Benefits:

a. End Points - Efficacy

All eligible patients have an unrestorable tooth planned for single implant placement. Therefore, all patients in different groups will at least receive the appropriate treatments. The patients will not have additional clinical benefits by participating in this clinical study, but the patients will have discounted treatments (extraction, implant placement, soft tissue augmentation, radiographic examination).

b. End Points - Safety

1) Study related risks:
Initial infection, pain or esthetically adverse outcome related to implant placement; inability to stabilize the implant due to poor quality of bone; implant failure and need for removal; discomfort in function and/or lack of satisfaction with the restoration for other reasons. If the implant has to be removed due to severe symptoms and unacceptable clinical outcomes, the patient will be immediately excluded from the

study and receive appropriate treatments. The patients will have the same risks if they receive the same treatment without participating in the study.
2) Protection against risks:
All efforts will be made to minimize risks to all and every participant: only sites with healthy or almost healthy bone levels will qualify for the study to avert esthetic concerns, restorative and functional expectations will be discussed and explained.

3. STUDY POPULATION

3.1. List the number of subjects to be enrolled.

The primary outcome is ridge dimensional alteration at six months after surgery while the secondary outcomes are changes of gingival level, gingival thickness, width of keratinized gingiva, alveolar bone level and bone dimension. Based on the preliminary results, 11 subjects per group need to be recruited to have 80% power to detect a 1 mm difference with 0.85 mm standard deviation in ridge dimensional change between groups. We plan to enroll 14 subjects in each group to account for potential dropout. The subjects will be recruited from the patients enrolled in the clinics of University of Texas Health Science Center at Houston School of Dentistry (UTSD) and Periodontal and Implant Surgeons of Houston (PISH). There will be no restriction on gender or race.

3.2. Criteria for Recruitment

The study aims to recruit patients enrolled in the clinics of UTSD and PISH. Therefore, all the patients will have basic dental examinations following the UTSD policy and PISH policy. The clinicians and dental students will be told the information of the study and they will be able to preliminarily screen the potential subjects based on the selection criteria. If the patients are potentially eligible and interested in participating the study, patients will be screened by one of the investigators (Chun-Teh Lee, Robin Weltman, Pedro Trejo); only these investigators will be obtaining the informed consent form. If additional investigators will be included in the study, we will apply for an IRB modification prior to their participation in the study. The qualified subjects will be asked to sign the informed consent form and attend the necessary appointments of the study.

3.3. Inclusion Criteria

Forty two subjects will be recruited among the patients attending the Clinic for Graduate Periodontics, UTSD, and the Clinic of PISH, who are in need of a tooth extraction at the maxillary premolar, canine and incisor region, and subsequent single implant placement. The reasons for extraction will include poor endodontic prognosis and/or unrestorable teeth (extensive caries, traumatic fractures, fractures of endodontically treated teeth, root perforation, root resorption with or without radiographic periapical lesion up to 3 mm in diameter). All subjects are ≥18 year-old and systemically healthy or with controlled common systemic conditions (controlled hypertension, controlled diabetes HbA1c up to 7 %). The adjacent teeth have to be present and the eligible tooth has esthetically acceptable buccal gingival margin position prior to surgery, compared to neighboring teeth and contralateral tooth, and adequate width of buccal keratinized gingiva(≥3mm). The level of radiographic bone

level has the distance from CEJ to interproximal crest up to 4 mm.

Location of buccal alveolar crest has to be generally within 4 mm from the free gingival margin, verified after the extraction, before randomization; and fenestration, if present, up to 3mm in diameter at the apical part of the root and affecting less than 30% of the buccal socket wall.

3.4. Exclusion Criteria

Patients will be excluded if they currently smoke exceeding 10 cigarettes/ day, have severe parafunctional habits, malocclusion or intent of orthodontic therapy in the future and are pregnant. The teeth in the surgical site will be excluded if there is advanced periodontal disease or periapical lesion causing significant bony defects that are beyond the criteria mentioned at Section 3.3. The patient who is allergy to antibiotics contained in the ADM (Gentimicin, Cefoxitin, Lincomcin, polymixin B and Vancomycin) will not be included in the immediate implant combined with ADM group.

3.5. Withdrawal Criteria

A subject may be discontinued from participation in the study for any of the following reasons:

1. Withdrawal of consent
2. Subject noncompliance with the protocol, as determined by the investigator
3. Any event or condition that would make continued participation in the study not in the best interest of the subject, as determined by the investigator
4. Pregnancy
5. Development of any medical condition that might affect the treatment and clinical outcomes, as determined by the investigator.
6. Initiation of any treatment or exposure that might affect the outcomes of implant therapy, as determined by the investigator.
7. Investigator discretion

3.6. Subject Replacement

Subjects who withdraw from the study can be replaced. However, to complete the study within the time allocated, centers will not enroll subjects after 24 months from enrollment initiation.

4. TRIAL SCHEDULE

There will be eight appointments including the baseline appointment and seven follow-up appointments (2, 4, 8, 12, 24, 36, 48 weeks) after the surgery. The details of each visit will be mentioned in 6.3. Study Visits and Procedures.

5. STUDY DESIGN

5.1. Summary of Study Design

We propose to conduct a randomized controlled trial with three treatment arms: immediate implant, immediate implant combined with SCTG, and immediate implant combined with ADM. Patients (age≥18 year-old) need to have single maxillary unrestorable tooth which is planned to be replaced with an implant in the esthetic zone (maxillary premolar to premolar). The unrestorable tooth has adjacent teeth and acceptable periodontal condition (probing depth ≤4mm, gingival recession≤ 1mm at six sites: mesial-buccal, mid-buccal, distal-buccal, distal-palatal, mid-palatal, distal-palatal). The patients have to be systemically healthy or have controlled common systemic conditions (controlled hypertension, controlled diabetes HbA1c up to 7 %). Smokers having cigarettes ≤ 10/per day are eligible but they are encouraged to stop smoking 1 week prior to and up to 2 months after implant placement (Bain, 1996). The primary outcome of the study is the ridge dimensional alterations at six months and 12 months after surgery while the secondary outcomes are the changes of gingival level, gingival thickness, width of keratinized gingiva, alveolar bone level, and bone dimension.

6. METHODS AND ASSESSMENTS

6.1. Randomization and Blinding

Patient allocation to the three groups (immediate implant combined with SCTG, immediate implant combined with ADM, immediate implant alone) was performed by a blinded non-surgeon following tooth extraction, based on computer-generated randomization (MATLAB). The surgeon will be noticed the randomization results the date of performing surgery. Patients will not be blinded given the patients definitely know the treatments that they receive due to the characteristics of procedures.

6.2. Contraception and Pregnancy Testing

Pregnancy status of subjects who are women with childbearing potential will be orally confirmed at the screening. The pregnant subjects will be excluded from the study.

6.3. Study Visits and Procedures

a. Screening Visits and Procedures

Study protocol and consent forms will be approved by the Institutional Review Board at the University of Texas Health Science Center at Houston. The trial will be registered with ClinicalTrials.gov. The clinicians and dental students in UTSD and PISH will be told the information of this clinical trial. The potential subjects who are interested in participating in this project will be referred to the clinic of Department of Periodontics and Dental Hygiene, UTSD or the clinic of PISH for initial screening. The principal investigator will confirm the eligibility of these patients. All patients will have dental cone-beam computed tomography before the surgery given the implants will

be placed in the highly esthetic zone (Benavides et al. 2012). All patients will sign the consent forms and are informed of the details of study procedures as well as potential complications. After informed consent is obtained, and initial periodontal therapy and oral hygiene instruction, whenever indicated, the surgery will be scheduled as the first visit.

At the first appointment, all clinical measurements will be performed (probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI)) and the impression of maxillary and mandibular dentition will be taken. One periapical radiography of the surgical site will be taken after the surgery is finished. After verification that the local anatomical inclusion criteria are met, patients will be randomized to one of three treatment groups. All implants will be placed according to standard protocol at a subcrestal position (1 mm below the buccal crest) engaging the palatal wall without elevation of a mucoperiosteal flap. The gap between the implant and alveolar bone will be filled with xenograft (Geistlich Bio-Oss®) and covered by collagen dressing (CollaTape®). In the groups having soft tissue augmentation, intrasulcular incisions will be carried out to partially dissect the buccal flap from mesial papilla to distal papilla. The SCTG or ADM will be inserted into the dissected buccal flap. The SCTG will be subepithelially harvested from the palate of the patient. The width of tissue graft will be equal to the distance between the interproximal papillae on the level of buccal gingival margin. The length of SCTG will be standardized as 10 mm. The thickness of SCTG will be standardized as 1-1.5mm. The size of ADM will be standardized following the same principle. The SCTG tissue graft or ADM will be stabilized by sling suture (chromic gut 5-0).

In the three groups, the straight healing abutment will be delivered immediately after implant placement provided that the implant shows primary stability and has engaged in the bone with an insertion torque of 25 Ncm or more (Norton 2004). In case of a lower insertion torque, the protocol will be abandoned, a cover screw will be placed, and a two stage implant protocol will be followed. All patients will receive a permanent restoration at 6 months after surgery, if the implant is deemed to be successful (Misch et al. 2008). The placement of xenografts aims to optimize the esthetic outcomes.

All patients will receive Amoxicillin 500mg, t.i.d, (for penicillin allergic patients: Clindamycin 150 mg, q.i.d) for seven days following surgery. Patients will be instructed to use mouth rinse (Chlorhexidine 0.12%) twice daily during the first two weeks and avoid brushing the surgical area for two weeks. All patients will be seen at two weeks following surgery, remove suture, follow up of healing, and oral hygiene; at 4 weeks (supragingival prophylaxis) ; at 8 weeks (supragingival prophylaxis); at 3 months (prophylaxis and measurements); at 6 months (prophylaxis, measurements, periapical radiography, cone beam computed tomography, impression for the permanent restoration). The permanent restoration will be delivered within one month following the final impression taken. After the crown placement, the patients will be seen at 9 months (prophylaxis) and 12 months (prophylaxis, measurements, periapical radiography, impression).

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b. Study Visits and Procedures

A stent with reference notches made by #1/2 bur at a 2 mm distance from the gingival margin at the mesio-buccal, mid-buccal and disto-buccal sites will be fabricated. The stent will be made based on the patient's dental model to have the best fit. A new stent with the same design will be made after patients have permanent restorations and the stent will be used to measure the parameter at the 12-month follow-up

The following measurements will be carried out at the visits:
1) Soft tissue distance from each of the three notches (mesio-buccally, mid-buccally and disto-buccally, respectively): the distance is measured from the notch to the gingival margin at three sites; it is measured at implant placement visit (baseline), 3 months, 6 months, and 12 months.
2) Horizontal defect dimension (HDD) defined as horizontal distance from the implant shoulder to the buccal alveolar socket wall, measured in the mid-buccal site; it is measured only at implant placement visit (the first visit).
3) Vertical defect dimension (VDD) defined as vertical distance from implant shoulder to the apical contact with the socket wall, measured in the mid-buccal site; it is measured only at implant placement visit (the first visit).
4) Buccal soft tissue thickness will be measured following the extraction using the endodontic file and the digital caliper (one measurement/ mid-buccal/6mm apical to gingival margin); it is measured before and after implant surgery at the first visit, 6 months and 12 months.
5) Probing depth (PD): probing depth is defined as the distance from the gingival margin to the tip point of the probe (Williams probe). PDs will be measured at 6 sites per tooth (mesio-buccal, mid-buccal, disto-buccal, disto-palatal, mid-palatal, mesio-palatal); it is measured before surgery at the first visit, 3 months, 6 months and 12 months.
6) Bleeding on probing (BOP): the prevalence of bleeding on probing at six sites (mesio-buccal, mid-buccal, disto-buccal, disto-palatal, mid-palatal, mesio-palatal) of the tooth/implant will be documented at the first visit, 3 months, 6 months and 12 months.
7) Plaque index (PI): A periodontal probe will be swept along each site to all the teeth to identify the presence or absence of plaque accumulation at the first visit, 3 months, 6 months and 12 months. A dichotomous scoring system will be used with one (1) and zero (0) equaling presence and absence, respectively, of plaque.
8) Buccal-palatal dimension of the ridge at the site of implant placement: the dimension will be measured at different reference points (3 mm, 6 mm from the baseline gingival margin) on the study model. Impressions for study models will be taken at the first visit, at 3 months, 6 months and 12 months. The measurement will be done by the digital caliper and the computer assisted scanned images.
9) Buccal plate thickness: it will be measured on the images of dental cone beam computed tomography. The patients will have the images taken with a stent before the surgery and 6 months after the surgery. The stent will be made based on the patient's dental model. The midline of the implant site will be buccally and palatally marked with gutta percha.
10) Interproximal bone level: a film holder with silicon putty to aid in reproducibility of the radiograph position will be used. The mesial and distal crestal bone level will be measured using the MIPACS software. Implant platform will serve as the reference point. Vertical and horizontal changes (depth and width of the vertical defect on the mesial and/or distal aspect of the implant, if present) will also be measured from radiographs taken at the time of completion of surgery, at 6 and 12 months. Dose and frequency of x-rays in the study are standard of care for any implant patient in UTSD, PISH or in standard clinical practice, and are not altered for the purpose of the study. (Medical status is updated and recorded at each visit, including verification that female patients are not pregnant prior to x-ray taking; this is also standard of care).
11) The diameter of the apical radiolucency, when initially present, will be monitored radiographically. Any lesions present in the radiography will be assessed immediately after surgery and 6 months.
12) Blood flow of gingiva: The laser Doppler flowmeter is a noninvasive measure of capillary blood perfusion. The readings are obtained by placing the tip on the

surface of buccal gingival. It is measured before and after implant surgery at the first visit, 3 months, 6 months and 12 months.

c. Final Study Visit:

The 12-month follow-up will be the subject's last visit for this clinical trial. The patients will have clinical measurements (PD, BOP, PI), dental impressions taken, and periapical radiographic examination. All subjects will have periodontal maintenance in the periodontics clinic of UTSD or PISH in the future.

d. Post Study Follow up and Procedures

The subjects will continue having routine maintenance appointments to follow up the health and function of implants and teeth in the periodontics clinic of UTSD or PISH. If the patients have symptoms of inflammation and signs of progression bone loss, the necessary treatments, such as debridement, will be performed.

e. Discontinuation Visit and Procedures

Subjects are free to withdraw from participation in the study at any time upon request. A subject may be discontinued from participation in the study for any of the following reasons:

1. Withdrawal of consent
2. Subject noncompliance with the protocol, as determined by the investigator
3. Any event or condition that would make continued participation in the study not in the best interest of the subject, as determined by the investigator
4. Pregnancy
5. Development of any medical condition that might affect the treatment and clinical outcomes, as determined by the investigator.
6. Initiation of any treatment or exposure that might affect the outcomes of implant therapy, as determined by the investigator.
7. Investigator discretion

Any subject with a serious adverse event, such as life-threating diseases, hospitalization, that is ongoing at the time of discontinuation will be followed until the event returns to baseline, resolves, or stabilizes. If the serious adverse event does not meet these outcomes within 30 days after discontinuation or after study completion, the subject will be referred to an appropriate practitioner for continued care. If the study is discontinued, subjects will be referred back to the qualified clinicians for necessary dental care.

7. TRIAL MATERIALS

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7.1. Trial Product (s)

Implants, bone grafts (Bio-Oss) and collagen dressing (CollaTape®) will be used following the indications approved by Food and Drug Administration (FDA). Implants will be placed to support the crowns to restore patients' oral esthetics and functions. Bone grafts are placed to preserve the socket dimension following extraction. Collagen dressing is placed to cover the bone grafts and extraction wound.

AlloDerm® Regenerative Tissue Matrix (RTM) is the one of the most widely used substitutes for autogeneous tissue graft in dentistry. It is an acellular dermal matrix (ADM) that is derived from donated human skin and is minimally processed to remove epidermal and dermal cells with nondenaturing detergent while preserving the extracellular matrix. The removal of viable cells and antigens during the decellularization process minimizes the risk of rejection and inflammation at the surgical site. Then, a cyropreservant is added to avoid crystal formation, and then resulting tissue matrix is freeze-dried(Wang et al. 2015). The remaining matrix serves as a framework for cellular infiltration and vascularization. ADM is indicated for soft tissue augmentation (Batista et al. 2001; Griffin et al. 2004; Park and Wang 2006), gingival recession defect coverage (Andrade et al. 2008; Tal et al. 2002), keratinized gingiva extension (Harris 2001; Yan et al. 2006), and extraction socket coverage (Fowler et al. 2000; Froum et al. 2004; Park 2011) for both teeth and implants. Basically, ADM can be used in all the procedures that the autogenous tissue graft is indicated for.

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7.2. Storage and Drug Accountability

Implants, bone grafts, collage dressing, and AlloDerm® Regenerative Tissue Matrix will be stored at room temperature in its original packaging following the manual instruction. The expiration date for the product is recorded on the product container labeling as year (4 digits) and month (2 digits) and the product expires on the last day of the month indicated. Expiration date printed on the labeling is valid as long as product is stored at room temperature and in an unopened foil pouch/packaging. Once the product is expired, the material will be discarded.

8. TREATMENT

8.1. Rationale for Selection of Treatments

Although subjects will be assigned to different experimental groups, all treatments are conducted following general clinical principles. The details of procedure are mentioned in section 6.3.

8.2. Specific Restrictions / Requirements

Subjects will be instructed to discontinue brushing the surgical area, to use mouth rinse (Chlorhexidine 0.12%) twice daily during the first two weeks and to avoid biting at the surgical area for at least two months.

8.3. Blinding

The surgeons and patients cannot be blinded because the surgeons will be told which procedure to perform at the first visit and patients will be aware of the procedures that they received after surgery. The patients will be informed of benefits of all the procedures and realize all procedures are supported by scientific evidence.

9. SAFETY MEASUREMENTS

9.1. Definitions

All unanticipated problems will be reported in this study. The Committee For the Protection of Human Subjects (CPHS) considers unanticipated problems to be any incident, experience, or outcome that meets all of the following criteria:

[redacted] unexpected in terms of nature, severity, or frequency given a) the research procedures that are described in the IRB-approved research protocol and informed consent, and b) the characteristics of the subject population being studied;

[redacted] related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

[redacted]laces subjects or others at a greater risk for physical, psychological, economic, or social harm than was previously known or recognized.

An incident, experience, or outcome that meets the 3 criteria above will generally warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others. Examples of corrective actions or substantive changes that might need to be considered in response to an unanticipated problem include the following:

[redacted]hanges to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects

[redacted]odification of inclusion or exclusion criteria to mitigate newly identified risks

[redacted]mplementation of additional procedures for monitoring subjects

[redacted]uspension of enrollment of new subjects

[redacted]uspension of research procedures in currently enrolled subjects

For this study, an severe adverse event (SAE) is defined as an unanticipated problem occurring during the study that fulfils 1 or more of the following criteria:

1. Results in death
2. Is immediately life-threatening†
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect
6. Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

Hospitalization for elective procedures or surgeries will not be considered SAEs, nor will inpatient hospitalizations for convenience.

Pregnancy in women with childbearing potential should not be reported as an SAE, but if pregnancy occurs, it must be reported in accordance with the procedures described in Section 6.2. Pregnancy will not be regarded as an SAE unless there is suspicion that a study intervention may have interfered with the effectiveness of a contraceptive medication and the event meets the criteria for an unanticipated problem. If the pregnancy results in an outcome other than a normal birth or elective abortion of a healthy fetus, it will be reported as an SAE.

9.2. Collecting, Recording and Reporting of Adverse Events

Examination and close follow-up of parameters capturing subjects' oral health will be collected on case report forms (CRFs). These will be completed at every study visit, and data will be compiled into a pre-specified format and reviewed monthly by

the PI for safety oversight.

Serious adverse events (as defined in Section 9.1) will be collected from the time of enrollment until the last clinic visit and will be recorded in the electronic health records (EHR) system. At each study visit, the study staff will inquire about the occurrence of SAEs since the last assessment. The investigator will review all source documentation related to study procedures for evidence of SAEs. Events will be followed for outcome information until they return to baseline or stabilize, or until 30 days after study completion or subject discontinuation. Subjects who have an SAE that is ongoing 30 days after study completion or discontinuation will be referred to an appropriate practitioner for continued care.

Upon learning that a subject has experienced an SAE, the investigator must report the event to CPHS within 24 hours after becoming aware of the event.

On a monthly basis, the following events will be reported to every PI:

[redacted]umber of subjects meeting criteria for implant failure and number of subjects enrolled.

[redacted]uration of observation of subjects meeting implant failure criteria and duration of observation of subjects enrolled

[redacted]or subjects having failed implants:

- Criteria for failure implants
- Baseline enrollment and interim visit information

[redacted]ny tooth loss, abscess, or other adverse oral health development requiring therapy or other intervention and the etiology (as captured in the dental history)

Every PI will review the monthly reports for any safety signals.

9.3. Safety Monitoring Plan

The purposes of the clinical monitoring activities are to ensure that the rights of human subjects are protected, the study is implemented in accordance with the protocol, and the integrity of study data is maintained.

All subjects will be monitored for postoperative healing and tissue response at a regular interval while the entire oral health will be maintained throughout the study period.

10. DATA ANALYSIS

10.1. Data Quality Assurance

Data and measurements will be checked by two separate sub-investigators (Chun-Teh Lee, Robin Weltman) as well as analyzed statistically to ensure that the data obtained is accurate, complete and reliable.

10.2. Data Entry and Storage

Case report forms (CRFs) will be completed and stored in a locked file cabinet in the PI's office located at UTSD. Data will be entered electronically in excel spreadsheets, and images will be stored electronically; both will be stored on the PIs work computer in a locked office and password protected.

11. SAMPLE SIZE AND STATISTICAL METHODS

11.1. Determination of Sample Size

Hypothesis:
H1: Ridge dimensional reductions in the sites of immediate implant combined with autogenous tissue graft/acelluar dermal matrix are significantly less than the sites of immediate implant alone.

Null hypothesis:
H0: Ridge dimensional reductions in the sites of immediate implant combined with autogenous tissue graft/acelluar dermal matrix are not significantly less than the sites of immediate implant alone.

Significance Tests:
If significance tests generate 95% likelihood that the results do not fit the null hypothesis (H0), then it is rejected, in favour of the alternative (H1).

Otherwise, the null is accepted. These are the only correct assumptions, and it is incorrect to reject, or accept, H1.

Accepting the null hypothesis does not mean that it is true. It is still a hypothesis, and must conform to the principle of falsifiability, in the same way that rejecting the null does not prove the alternative.

Calculation of Sample Size:
Based on the data published in the articles and preliminary results, we have calculated that 11 subjects per group need to be recruited in order to have 80% power to detect a 1mm difference with 0.9 mm standard deviation in ridge dimensional change between the immediate implant alone group and the other two groups (Faul et al. 2009). We plan to enroll a total of 42 subjects (14 subjects in each group) to account for potential dropout.

11.2. Statistical and Analytical Plans

a. General Considerations

We will present means and standard deviations for completeness of the report. The statistical significance level to test the primary endpoint was set at $p<0.05$, a priori.

b. Safety Analyses

Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at Baseline and follow-up visits each month.

Adverse events will be classified as biological complications, such as severe inflammation, progressive alveolar bone loss>2mm, or prosthetic complications, such as lose of healing abutment and summarized for both baseline and follow-up visits.

All information pertaining to adverse events noted during the study will be listed by

subject, detailing verbatim given by the investigator, preferred term, , date of onset, date of resolution, severity, and relationship to procedure. The onset of adverse events will also be shown relative (in number of days) to the day of performing the surgery.

A tabulation of Serious Adverse Events (SAEs) will be provided by subject within treatment groups. The proportion of subjects in each treatment group reporting adverse events that occur in ~ 3% in either treatment group will be compared using Bayesian methods. The specific preferred terms analysed will be those that are reported by at least five percent of the subjects in either treatment group.

c. Statistical Analysis Plan:
Differences in the primary and secondary outcomes between the three groups will be examined using the one-way ANOVA analysis. Differences in the primary and secondary outcomes overtime within each group will be examined using paired t-test. The level of significance will be set at 0.05 and Bonferroni corrections for multiple comparisons will be carried out. All statistical analysis will be performed using SAS version 9.4 (SAS Institute, Cary NC). The data derived from withdrawn patients will be included in the analysis.

12. ETHICAL CONSIDERATIONS

12.1. Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of study participation will be provided to the subjects and their families. A consent form describing in detail the study interventions, procedures, and risks will be given to the subject. Consent forms will be IRB-approved, and the subject will be asked to read and review the document. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.
The consent process will be documented in the clinical or research record. This documentation will include the following:
[redacted] notation of the date that the consent was obtained
[redacted] statement that the consent was obtained prior to the initiation of study procedures
[redacted] statement that the subject had adequate time to review the consent and that all questions were answered prior to initiation of study procedures
[redacted] notation confirming that a copy of the signed consent was given to the subject

12.2. IRB review

The protocol, informed consent form(s), and all advertising and subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and informed consent form must be obtained before the enrollment of any subject. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the clinic.

12.3. Confidentiality of Data and Patient Records

The subject's name will appear only on the consent form and clinical record, both of which will be kept separate from collected study data. All subject files will be kept confidential and placed in a double-locked office. A unique coded study number will be assigned to each subject for data collection. The number will not contain any personal information (e.g., dates, age) to further ensure protection.
The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the PI. No subject names will be used in publications or presentations.

13. PUBLICATIONS

Following completion of the study, the investigator is expected to publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov (De Angelis et al. 2004), which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For grants and cooperative agreements, it is the institution's responsibility to register the trial in an acceptable registry.
The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase I trials), would be exempt from registering trials in a public registry such as ClinicalTrials.gov.

14. RETENTION OF TRIAL DOCUMENTS

Patients will be assigned identifying codes that will be linked to all collected study data, stored in secured database by Primary Investigator. All the electronic files will be encrypted and are stored in primary investigator's external drive, that will be locked in the PI's office cabinet. Models will be stored in a locked cabinet in the PI's office. The following individuals/ institutions will have access to the records: the Principal Investigator and coinvestigators, and the University of Texas Health Science Center at Houston, including the Institutional Review Board. Absolute confidentiality cannot be guaranteed because of potential need to share this information with the above parties. The aggregate results of this study, with preservation of patient confidentiality, may be used for teaching, meeting presentation or publishing purpose. Records will be maintained for at least 6 years from the starting date of each subject.

List of Possible Attachments

Appendix 1	**Case report form**
Appendix 2	**Flyer**
Appendix 3	**Informed Consent Form**
Appendix 4	**Schematic of Study Design**
Appendix 5	**Study Schedule**
Appendix 6	**Screening examination checklist**

References:

Allen EP, Gainza CS, Farthing GG, Newbold DA. 1985. Improved technique for localized ridge augmentation. A report of 21 cases. Journal of periodontology. 56(4):195-199.

Andrade PF, Felipe ME, Novaes AB, Jr., Souza SL, Taba M, Jr., Palioto DB, Grisi MF. 2008. Comparison between two surgical techniques for root coverage with an acellular dermal matrix graft. Journal of clinical periodontology. 35(3):263-269.

Batista EL, Jr., Batista FC, Novaes AB, Jr. 2001. Management of soft tissue ridge deformities with acellular dermal matrix. Clinical approach and outcome after 6 months of treatment. Journal of periodontology. 72(2):265-273.

Becker BE, Becker W, Ricci A, Geurs N. 1998. A prospective clinical trial of endosseous screw-shaped implants placed at the time of tooth extraction without augmentation. Journal of periodontology. 69(8):920-926.

Benavides E, Rios HF, Ganz SD, An CH, Resnik R, Reardon GT, Feldman SJ, Mah JK, Hatcher D, Kim MJ et al. 2012. Use of cone beam computed tomography in implant dentistry: The international congress of oral implantologists consensus report. Implant dentistry. 21(2):78-86.

Berglundh T, Lindhe J. 1996. Dimension of the periimplant mucosa. Biological width revisited. Journal of clinical periodontology. 23(10):971-973.

Botticelli D, Berglundh T, Lindhe J. 2004. Hard-tissue alterations following immediate implant placement in extraction sites. Journal of clinical periodontology. 31(10):820-828.

Botticelli D, Persson LG, Lindhe J, Berglundh T. 2006. Bone tissue formation adjacent to implants placed in fresh extraction sockets: An experimental study in dogs. Clinical oral implants research. 17(4):351-358.

Brownfield LA, Weltman RL. 2012. Ridge preservation with or without an osteoinductive allograft: A clinical, radiographic, micro-computed tomography, and histologic study

evaluating dimensional changes and new bone formation of the alveolar ridge. Journal of periodontology. 83(5):581-589.
Burkhardt R, Joss A, Lang NP. 2008. Soft tissue dehiscence coverage around endosseous implants: A prospective cohort study. Clinical oral implants research. 19(5):451-457.
Cairo F, Nieri M, Pagliaro U. 2014. Efficacy of periodontal plastic surgery procedures in the treatment of localized facial gingival recessions. A systematic review. Journal of clinical periodontology. 41 Suppl 15:S44-62.
Chambrone L, Sukekava F, Araujo MG, Pustiglioni FE, Chambrone LA, Lima LA. 2010. Root-coverage procedures for the treatment of localized recession-type defects: A cochrane systematic review. Journal of periodontology. 81(4):452-478.
Chen ST, Darby IB, Reynolds EC. 2007. A prospective clinical study of non-submerged immediate implants: Clinical outcomes and esthetic results. Clinical oral implants research. 18(5):552-562.
Cosyn J, Hooghe N, De Bruyn H. 2012. A systematic review on the frequency of advanced recession following single immediate implant treatment. Journal of clinical periodontology. 39(6):582-589.
Covani U, Marconcini S, Galassini G, Cornelini R, Santini S, Barone A. 2007. Connective tissue graft used as a biologic barrier to cover an immediate implant. Journal of periodontology. 78(8):1644-1649.
De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke AJ et al. 2004. Clinical trial registration: A statement from the international committee of medical journal editors. The New England journal of medicine. 351(12):1250-1251.
Del Pizzo M, Modica F, Bethaz N, Priotto P, Romagnoli R. 2002. The connective tissue graft: A comparative clinical evaluation of wound healing at the palatal donor site. A preliminary study. Journal of clinical periodontology. 29(9):848-854.
Denissen HW, Kalk W, Veldhuis HA, van Waas MA. 1993. Anatomic consideration for preventive implantation. The International journal of oral & maxillofacial implants. 8(2):191-196.
Edel A. 1995. The use of a connective tissue graft for closure over an immediate implant covered with occlusive membrane. Clinical oral implants research. 6(1):60-65.
Ellegaard B, Karring T, Loe H. 1974. New periodontal attachment procedure based on retardation of epithelial migration. Journal of clinical periodontology. 1(2):75-88.
Evian CI, Cutler S. 1994. Autogenous gingival grafts as epithelial barriers for immediate implants: Case reports. Journal of periodontology. 65(3):201-210.
Faul F, Erdfelder E, Buchner A, Lang AG. 2009. Statistical power analyses using g*power 3.1: Tests for correlation and regression analyses. Behavior research methods. 41(4):1149-1160.
Fowler EB, Breault LG, Rebitski G. 2000. Ridge preservation utilizing an acellular dermal allograft and demineralized freeze-dried bone allograft: Part ii. Immediate endosseous implant placement. Journal of periodontology. 71(8):1360-1364.
Froum S, Cho SC, Elian N, Rosenberg E, Rohrer M, Tarnow D. 2004. Extraction sockets and implantation of hydroxyapatites with membrane barriers: A histologic study. Implant dentistry. 13(2):153-164.
Gapski R, Parks CA, Wang HL. 2005. Acellular dermal matrix for mucogingival surgery: A meta-analysis. Journal of periodontology. 76(11):1814-1822.
Griffin TJ, Cheung WS, Hirayama H. 2004. Hard and soft tissue augmentation in implant therapy using acellular dermal matrix. The International journal of periodontics & restorative dentistry. 24(4):352-361.

Grunder U. 2000. Stability of the mucosal topography around single-tooth implants and adjacent teeth: 1-year results. The International journal of periodontics & restorative dentistry. 20(1):11-17.
Grunder U. 2011. Crestal ridge width changes when placing implants at the time of tooth extraction with and without soft tissue augmentation after a healing period of 6 months: Report of 24 consecutive cases. The International journal of periodontics & restorative dentistry. 31(1):9-17.
Harris RJ. 2001. Clinical evaluation of 3 techniques to augment keratinized tissue without root coverage. Journal of periodontology. 72(7):932-938.
Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, Moschetti I, Phillips B, Thornto H. 2011. Explanation of the 2011 oxford centre for evidence-based medicine (ocebm) levels of evidence (background document).
Hurzeler MB, Weng D. 1999. A single-incision technique to harvest subepithelial connective tissue grafts from the palate. The International journal of periodontics & restorative dentistry. 19(3):279-287.
Jyothi SG, Triveni MG, Mehta DS, Nandakumar K. 2013. Evaluation of single-tooth replacement by an immediate implant covered with connective tissue graft as a biologic barrier. Journal of Indian Society of Periodontology. 17(3):354-360.
Landsberg CJ, Bichacho N. 1994. A modified surgical/prosthetic approach for optimal single implant supported crown. Part i--the socket seal surgery. Practical periodontics and aesthetic dentistry : PPAD. 6(2):11-17; quiz 19.
Lang NP, Pun L, Lau KY, Li KY, Wong MC. 2012. A systematic review on survival and success rates of implants placed immediately into fresh extraction sockets after at least 1 year. Clinical oral implants research. 23 Suppl 5:39-66.
Langer B, Langer L. 1985. Subepithelial connective tissue graft technique for root coverage. Journal of periodontology. 56(12):715-720.
Lazzara RJ. 1989. Immediate implant placement into extraction sites: Surgical and restorative advantages. The International journal of periodontics & restorative dentistry. 9(5):332-343.
Lee CT, Chiu TS, Chuang SK, Tarnow D, Stoupel J. 2014. Alterations of the bone dimension following immediate implant placement into extraction socket: Systematic review and meta-analysis. Journal of clinical periodontology. 41(9):914-926.
Lee CT, Hamalian T, Schulze-Spate U. 2015a. Minimally invasive treatment of soft tissue deficiency around an implant-supported restoration in the esthetic zone: Modified vista technique case report. The Journal of oral implantology. 41(1):71-76.
Lee CT, Tao CY, Stoupel J. 2015b. The effect of subepithelial connective tissue graft placement on esthetic outcomes following immediate implant placement: Systematic review. Journal of periodontology.1-22.
Linkevicius T, Apse P, Grybauskas S, Puisys A. 2009. The influence of soft tissue thickness on crestal bone changes around implants: A 1-year prospective controlled clinical trial. The International journal of oral & maxillofacial implants. 24(4):712-719.
Linkevicius T, Puisys A, Steigmann M, Vindasiute E, Linkeviciene L. 2014. Influence of vertical soft tissue thickness on crestal bone changes around implants with platform switching: A comparative clinical study. Clinical implant dentistry and related research.
Migliorati M, Amorfini L, Signori A, Biavati AS, Benedicenti S. 2015. Clinical and aesthetic outcome with post-extractive implants with or without soft tissue augmentation: A 2-year randomized clinical trial. Clinical implant dentistry and related research. 17(5):983-995.

Misch CE, Perel ML, Wang HL, Sammartino G, Galindo-Moreno P, Trisi P, Steigmann M, Rebaudi A, Palti A, Pikos MA et al. 2008. Implant success, survival, and failure: The international congress of oral implantologists (icoi) pisa consensus conference. Implant dentistry. 17(1):5-15.

Morimoto T, Tsukiyama Y, Morimoto K, Koyano K. 2015. Facial bone alterations on maxillary anterior single implants for immediate placement and provisionalization following tooth extraction: A superimposed cone beam computed tomography study. Clinical oral implants research. 26(12):1383-1389.

Muller HP, Eger T, Schorb A. 1998. Gingival dimensions after root coverage with free connective tissue grafts. Journal of clinical periodontology. 25(5):424-430.

Nelson SW. 2001. Subperiosteal and intraosseous connective tissue grafts for pocket reduction: A 9- to 13-year retrospective case series report. Journal of periodontology. 72(10):1424-1435.

Norton MR. 2004. A short-term clinical evaluation of immediately restored maxillary tioblast single-tooth implants. The International journal of oral & maxillofacial implants. 19(2):274-281.

Oates TW, Robinson M, Gunsolley JC. 2003. Surgical therapies for the treatment of gingival recession. A systematic review. Annals of periodontology / the American Academy of Periodontology. 8(1):303-320.

Paolantonio M, Dolci M, Scarano A, d'Archivio D, di Placido G, Tumini V, Piattelli A. 2001. Immediate implantation in fresh extraction sockets. A controlled clinical and histological study in man. Journal of periodontology. 72(11):1560-1571.

Park JB. 2011. Immediate implantation with ridge augmentation using acellular dermal matrix and deproteinized bovine bone: A case report. The Journal of oral implantology. 37(6):717-721.

Park SH, Wang HL. 2006. Management of localized buccal dehiscence defect with allografts and acellular dermal matrix. The International journal of periodontics & restorative dentistry. 26(6):589-595.

Rosenquist B. 1997. A comparison of various methods of soft tissue management following the immediate placement of implants into extraction sockets. The International journal of oral & maxillofacial implants. 12(1):43-51.

Sanz M, Cecchinato D, Ferrus J, Salvi GE, Ramseier C, Lang NP, Lindhe J. 2014. Implants placed in fresh extraction sockets in the maxilla: Clinical and radiographic outcomes from a 3-year follow-up examination. Clinical oral implants research. 25(3):321-327.

Schropp L, Kostopoulos L, Wenzel A. 2003. Bone healing following immediate versus delayed placement of titanium implants into extraction sockets: A prospective clinical study. The International journal of oral & maxillofacial implants. 18(2):189-199.

Schulte W, Heimke G. 1976. [the tubinger immediate implant]. Die Quintessenz. 27(6):17 - 23.

Schulte W, Kleineikenscheidt H, Lindner K, Schareyka R. 1978. [the tubingen immediate implant in clinical studies]. Deutsche zahnarztliche Zeitschrift. 33(5):348-359.

Stimmelmayr M, Stangl M, Edelhoff D, Beuer F. 2011. Clinical prospective study of a modified technique to extend the keratinized gingiva around implants in combination with ridge augmentation: One-year results. The International journal of oral & maxillofacial implants. 26(5):1094-1101.

Studer SP, Lehner C, Bucher A, Scharer P. 2000. Soft tissue correction of a single-tooth pontic space: A comparative quantitative volume assessment. The Journal of prosthetic dentistry. 83(4):402-411.

Sullivan HC, Atkins JH. 1968. Free autogenous gingival grafts. 3. Utilization of grafts in the treatment of gingival recession. Periodontics. 6(4):152-160.

Tal H, Moses O, Zohar R, Meir H, Nemcovsky C. 2002. Root coverage of advanced gingival recession: A comparative study between acellular dermal matrix allograft and subepithelial connective tissue grafts. Journal of periodontology. 73(12):1405-1411.

Tarnow DP, Chu SJ, Salama MA, Stappert CF, Salama H, Garber DA, Sarnachiaro GO, Sarnachiaro E, Gotta SL, Saito H. 2014. Flapless postextraction socket implant placement in the esthetic zone: Part 1. The effect of bone grafting and/or provisional restoration on facial-palatal ridge dimensional change-a retrospective cohort study. The International journal of periodontics & restorative dentistry. 34(3):323-331.

Thoma DS, Benic GI, Zwahlen M, Hammerle CH, Jung RE. 2009. A systematic review assessing soft tissue augmentation techniques. Clinical oral implants research. 20 Suppl 4:146-165.

van Kesteren CJ, Schoolfield J, West J, Oates T. 2010. A prospective randomized clinical study of changes in soft tissue position following immediate and delayed implant placement. The International journal of oral & maxillofacial implants. 25(3):562-570.

Vervaeke S, Collaert B, Cosyn J, De Bruyn H. 2014. A 9-year prospective case series using multivariate analyses to identify predictors of early and late peri-implant bone loss. Clinical implant dentistry and related research.

Wang HL, Suarez-Lopez Del Amo F, Layher M, Eber R. 2015. Comparison of freeze-dried and solvent-dehydrated acellular dermal matrix for root coverage: A randomized controlled trial. The International journal of periodontics & restorative dentistry. 35(6):811-817.

Watzek G, Haider R, Mensdorff-Pouilly N, Haas R. 1995. Immediate and delayed implantation for complete restoration of the jaw following extraction of all residual teeth: A retrospective study comparing different types of serial immediate implantation. The International journal of oral & maxillofacial implants. 10(5):561-567.

Yan JJ, Tsai AY, Wong MY, Hou LT. 2006. Comparison of acellular dermal graft and palatal autograft in the reconstruction of keratinized gingiva around dental implants: A case report. The International journal of periodontics & restorative dentistry. 26(3):287-292.

Yoshino S, Kan JY, Rungcharassaeng K, Roe P, Lozada JL. 2014. Effects of connective tissue grafting on the facial gingival level following single immediate implant placement and provisionalization in the esthetic zone: A 1-year randomized controlled prospective study. The International journal of oral & maxillofacial implants. 29(2):432-440.