Comparison of Augmented Bone versus Pristine Bone by Monitoring Peri-implant Bone Level Changes

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ABSTRACT

Background

Bone augmentation, which also named as guided bone regeneration (GBR) procedure, is utilized in contemporary dentistry on implant related sites to get sufficient bone volume for implant placement to have better functional and esthetic outcome. The purpose of the present study was to compare the peri-implant bone levels changes of implants placed in augmented bone versus in pristine bone.

Materials and Methods

Twenty-nine submerged implants (11 from test group and 18 from control group) were placed in 26 human subjects. The test implants were placed in previously augmented ridge, whereas the control implants were placed in pristine alveolar ridge. All implants were placed in mandibular posterior arch. Customized radiographic stents were used to obtain standardized radiographs at the time of implant placement and stage II procedure. The mesial and distal peri-implant bone levels were measured from standardized radiographs by utilizing image-analyzing software. At the time of stage II procedure, the width of keratinized mucosa (wKM), thickness of soft tissue (ST) over the implant site and the classification of early implant exposure (eIE) were also recorded. Significantly statistical differences in mesial, distal and mean peri-implant bone level loss between test and control group were evaluated by using the mixed effects model with and without adjusting the potential cofounders (wKM, ST and eIE)

Results

The Mean peri-implant bone loss (ΔBL) was 0.74 ± 0.74 mm (Mean ± SD) for the test group and 0.25 ± 0.55 mm for the control group (P= 0.0007). The mesial peri-implant bone loss (ΔMBL) was 0.81 ± 0.85 mm for the test group and 0.30 ± 0.72 mm for the control group (P=0.0092). The distal peri-implant bone loss (ΔDBL) was 0.67 ± 0.77 mm for the test group and 0.20 ± 0.49 mm for the control group (P=0.0038). There was a statistically significant difference between test and control group for mesial, distal and mean peri-implant bone loss with adjusting the potential confounders.

Conclusions

With the limitation of the study, more bone resorption during the submerged implant healing period was observed in the test group compared to control group. Augmented bone may not perform as the same characteristic of pristine bone during the implant therapy, which could be a significant factor on peri-implant bone stability. Further studies with long-term follow up are recommended.

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I. Introduction:

Guided bone regeneration

Dental implants were widely used in dentistry to restore the integrity of the dental arch. In order to obtain favorable results, enough bone height and width were necessary for implant osseointegration. The atrophy of alveolar bone after tooth extraction had been documented in literatures.[1 2] The deficiency of sufficient residual ridge bone width and height may compromised the function and aesthetics of dental implants. In the late 1980s, the concept of guided bone regeneration (GBR) was developed and was utilized in contemporary dentistry to increase residual alveolar bone volume for placing implant in idea prosthesis driven position. [3-6 7] The concept of GBR was based upon maintaining a space on the surface of the bony defect to exclude rapid-growing soft tissue cell by using cell-occlusive barrier membrane. Bone grafts were used to support the membrane and assist new bone formation with their osteoconductive or osteoinductive properties. In 1996, Buser *et al.* used autogenous bone and non-resorbable expanded-polytetrafluoroethylene (ePTFE) membrane to augment the edentulous ridges of forty patients. After 7 to 13 months, the sites were re-entered and implants were placed. The mean ridge width was augmented from 3.5 mm to 7.1 mm.[8]

For bone augmentation, autogenous bone graft was still considered as the gold standard due to its biocompatibility and osteogenetic ability.[9] However, harvesting of autogenous bone required a secondary surgical site and might increase the post-operative discomfort and rate of complications.[10] Thus, other types of bone graft such as allograft and xenograft were often proposed as substitutes for autogenous bone

graft.

Allograft material had been used in periodontal therapy to restore the loss of periodontium for decades.[11] There were two forms of allograft materials which are generally used: freeze-dried bone allograft (FDBA) and demineralized freeze-dried bone allograft (DFDBA). Both FDBA[12-14] and DFDBA[15-17] had been used successfully to regenerate the attachment apparatus during periodontal treatment. Nevins *et al.* utilized mineralized, freeze-dried cortical bone allograft (FDBA) and non-resorbable ePTFE barrier membrane to augment severely resorbed edentulous ridges and successfully place implants in augmented bone 6 months after bone augmentation.[18] The same combination of FDBA graft and ePTFE membrane indicated the same beneficial effect in deficient alveolar bone ridge destroyed by advanced periodontitis and endodontic failure.[19]

Histological Analysis of Augmented Bone

Although bone grafts may gradually resorb with new bone formation in augmented site. The augmented bone did not completely occupied by pure, newly formed bone. Mordenfeld *et.al*, who harvested biopsies from subjects who had sinus been augmented with use of a mixture of 80% deproteinized bovine bone (DPBB) and 20% autogenous bone 6 months and 11 years after augmentation. The area fraction of the remaining DPBB particles was approximately 17.3% at 11 years and 14.5% at 6 months [20] That human histological finding showed residual bone graft amalgamation with newly formed bone even after long period of time. Feuille *et al*. did lateral ridge augmentation with e-PTFE membrane and FDBA. The histology analysis showed 47.6% of new bone formation and 52.4% of residual bone graft at 6 month after bone

augmentation.[21]

Many studies had been done to investigate the amount of vital bone presented in extraction sockets after grafting. Compare to the healing process of pristine bone, augmented site has slower healing rate and lower quality of new bone formation at 12 weeks. [22] In the study done by Artzi *et al*., bovine deprived bone graft was grafted in 15 fresh human extraction sockets and primarily covered by pedicle flap. 9 months after, histology showed lamellar bone in the apical region while abundance of cellular woven-type bone was only identified in the coronal area. More mean bone tissue area was found in apical part (63.9%) than in coronal part, which suggested the unmaturation of the coronal part in the grafted area. [23]

Fontana *et al*. analyzed samples from mandibular posterior edentulous ridge, which were treated with vertical bone augmentation by titanium-reinforced e-PTFE membrane and allogeneic bone matrix. Histomorphometric analysis revealed a mean 32.98 percent of mineralized bone. Corticocancellous chips of the allogeneic bone matrix were still visible after a submerged healing period varying from 24 to 32 weeks. In some specimens, the most coronal part of the implants were surrounded by a layer of connective tissue instead of bone cell nor residual grafts. [24]

Compared to pristine bone, the residual bone graft contained augmented bone might be more susceptible to bone remodeling or inflammation. Since in most of clinical situation, bone augmentation was mainly needed at the coronal level of future implant position, it might contribute to peri-implant crestal bone loss especially in

early healing phase.

Success and Survival Rate for Implants Placed in Augmented Bone

The long-term success and survival rate of implants placed in previously bone augmented area had been shown in many publications. [25,26] The success criteria proposed by Alberektsson *et al.* had been widely used in many literatures to define the success of implants: implant stability; absence of peri-implant radiolucency; absence of clinical symptoms; and less than 0.2 mm vertical bone loss per year after the first year of loading.[27] A prospective clinical study involving 61 ITI non-submerged implants showed a 5-year success rate of 98.3% and 100% survive rate with minimal bone loss for implants placed in bone horizontally augmented by autograft and ePTFE. [28] The result was comparable with other 5-year long-term studies on the same types of implants in non-regenerated, pristine bone. [29, 30]

Brocard *et al.*, Nevins *et al.*, and Fugazzatto *et al*. provided extensive data with survival rates of 92.5%, 97.5%, and 97.6%, respectively. [25, 31, 32] Nevins *et al.* followed 526 implants placed in horizontally augmented bone for average 23.4 month after loading. The survival rate was 97.5%.[25] Simion *et al.* monitored 123 Brånemark system implants placed in vertical augmented bone for 18-69 month after loading. The survival rate and success rate were 99.2% and 97.5% respectively.[33] In the study of Blanco *et al*., Juodzbalys *et al*. and Benić *et al*., implants were placed simultaneously with bone augmentation. The success rate ranged from 90% to 100%.[34-36] In the study done by Benić *et al*., the control group which consisted of implants placed in pristine, non-augmented bone showed 94.1% success rate.[36] In

general, implants placed in augmented bone have predictable success and survival rate comparable to implants in pristine bone.

Peri-Implant Crestal Bone Loss in Augmented Bone

Peri-implant Crestal bone loss was often observed at the first year after functional loading, and continually to loss less than 0.2 mm vertically per year in pristine bone. [37] [38] The coronal marginal bone loss might lead to gingival recession with compromised esthetic outcome and difficulty to maintain adequate oral hygiene which might increase the risk of peri-implant disease.

Currently, there was no consistent agreement on why peri-implant crestal bone loss happened and why the majority of bone loss happened at the first year after functional loading. Oh *et al*. summarized six possible etiology factors which might contribute to peri-implant crestal bone loss in pristine bone including surgical trauma, occlusal overload, peri-implantitis, microgap, biologic width, and implant crest module.[39]

For peri-implant crestal bone loss in augmented bone, many literatures showed there was no statistically long term differences about the amount of peri-implant bone loss between implants in augmented bone or in pristine bone: Simion *et al.* showed data of 1.35-1.87 mm peri-implant crestal bone loss around implants placed in augmented bone recorded at 18 to 69 months post loading by measuring radiographs.[33] Busar *et al.* found the mean distance from the platform of ITI non-submerged implant to the first bone to implant contact in augmented bone at 5 years after implant placement was 2.95 mm. Studies conducted by Blanco *et al.* and Juodzabalys *et al.* showed 2.03

mm and 2.01 mm peri-implant crestal bone loss respectively around implants with simultaneous bone augmentation over 5 years period by measuring standardized periapical radiographs. [34, 35] In a retrospective study, collagen membrane and bone grafts were used to augment bone simultaneously alone with implant placement. The data measured from regular radiographs showed the level of marginal bone below the implant shoulder was 1.33 mm in GBR group and 1.6 mm in control group for a mean of 57 observation months radiographs instead of standardized radiographs. [36] A recent randomized study done by Barone *et al.* compared the mean bone level around one-stage implants. In one group, implants were placed in previous xenograft preserved extraction socket, in the other group the implants were placed in natural healed socket. Standardized radiographs were obtained and the mean implant bone level loss was 1.00 mm in grafted site and 1.02 in natural healed site at 3 years post implant placement. [40] Authors concluded that the amount of peri-implant bone loss in augmented bone was similar to the amount of bone loss around implants in pristine bone, which were previously reported in published long-term studies. [41, 42] However, most studies were case series or retrospective studies with no control group and did not always use standardized radiograph to monitor the peri-implant crestal bone level. The result should be interpreted in a careful way.

A 5-year prospective longitudinal study conducted by Zitzmann *et al.* monitored the mean marginal bone loss around Brånemark endosteal implants. Total 153 implant sites that need simultaneous GBR along with implants placement were included in study. Among then, 112 implants had been placed with simultaneously bone augmentation using collagen membrane and xenograft; 41 implants had also been placed with simultaneously bone augmentation but using ePTFE non-resorbable

membrane and xenograft instead. Another 112 implants, which can be placed in pristine bone without any further bone augmentation procedure, were viewed as control group. Five year cumulative implant survival rate are 93.3% and 97.3% for implants with and without GBR. Regular periapical radiographs with proper parallel implant projection were utilized to measure the distance between the fixture-abutment junction to the first bone to implant contact. The marginal bone loss was found increased over time and there was statistically significant more bone loss in augmented site. The data showed 2.21 mm mean peri-implant marginal bone loss for the e-PTFE non-resorbable membrane group, 1.83mm for the collagen membrane group, and 1.73 mm for the control group. The difference of mean marginal bone loss between the three groups was statistically significant.[26]

Clinically, it was not uncommon to find peri-implant crestal bone loss at the time of Stage II procedure for implants placed in augmented bone. Fontana *et al*. did bilateral vertical ridge augmentation on posterior mandibles by using e-PTFE membrane and either allograft or autograft on 5 patients. 6 month after bone augmentation, Total 25 MR III implants were placed and healed submerged for 5 month. At the time of healing abutment connection (Stage II procedure), mean 1.26 mm marginal bone loss in allograft group and 0.84 mm in autogenous graft group were directly detected and measured by periodontal probe.[24] It indicated that the majority of peri-implant crestal bone loss in augmented bone happened at the phase of osseointegration. However, most studies use the time of prosthesis delivery as baseline for peri-implant bone level loss, which might miss the differences of peri-implant bone level changes between augmented bone and pristine bone.

Standardized Radiography

Radiography had been utilized in dentistry to evaluate alveolar bone height for a long period of time. The reliability of traditional radiographs in measurement of bone loss was not consistent due to angulation between the film and the long axis of teeth.[43] In order to get more reliable measurement outcome, standardized radiography by using customized stent was required. Hermann *et al*. compared measurement results from standardized periapical radiographs and from histometric evaluation. The clinical accuracy of standardized radiography was within 0.2 mm which was reliable to be one of the noninvasive clinical diagnostic methods.[44]

II. Significance of the present study

To the author's knowledge, despite many studies provided data on peri-implant crestal bone levels, most of them were retrospective studies, lack of control group and monitored the bone level changes from the time of prosthesis delivery instead of the time of implant placement. This study was a prospective clinical trial to monitor bone level changes of submerged rough surface taper implant with smooth machine collar in previously augmented ridge by using standardized radiography from the time of implant placement to Stage II procedure (Abutment connection) and to compare the result with implants in non-augmented, pristine alveolar ridge.

III. Specific Aims and Hypothesis

Aims

Evaluate and compare the peri-implant crestal bone change from the time of implant placement to Stage II procedure in previously augmented bone and in pristine bone by measuring peri-implant bone level on standardized radiography.

Hypothesis:

There is more peri-implant crestal bone loss measured on radiography around implants placed in previously augmented bone than implants placed in pristine bone.

IV. Research Design and Methods

Experimental Design: Controlled clinical trial

This prospective clinical study utilized a single center IRB-approved design to measure and compare the peri-implant bone level change of submerged dental implants placed in pristine bone and augmented bone from the time of implant placement to stage II procedure via standardized radiography. The study was graded as the level of IIB according to the classification of evidence-based medicine of Oxford study. Implants placed in previously augmented edentulous ridge via GBR procedure were in the test group, while Implants placed in pristine edentulous ridge were belong to the control group.

Subject Characteristics

The inclusion criteria of the study were:

1. 18 years of age or older
2. Non-smokers or former smokers (quit smoking at least 1 year before surgery).

3. Subjects must be healthy without uncontrolled systemic disease or condition which may interfere with periodontal surgery and would affect hard or soft tissue healing.
4. Subjects with mandibular posterior edentulous pristine ridge or with mandibular posterior edentulous ridge previously augmented by guided bone regeneration procedure in TUSDM periodontology clinic (at least 6 months prior).
5. Patients who treatment planned in the Tufts University School of Dental Medicine (TUSDM) periodontology clinic for implant placement and implant supported prosthesis over mandibular posterior edentulous ridge and who meet all medical and dental requirements of the TUSDM periodontology clinic for periodontal surgery (e.g., healthy subjects with no diseases contraindicating periodontal surgery).

The exclusion criteria of the study were:

1. A female subject who was pregnant or lactating at the time of screening.
2. A subject who had medical contraindication to dental surgery at the time of screening which not allow them to be treatment planned in the TUSDM periodontology clinic for surgical procedures (e.g., uncontrolled hypertension (more than stage II, ≥160/110) and/or poorly controlled diabetes (past three month HbA1c>7 %).
3. A subject who had a disease or condition that may affect hard and soft tissue healing (e.g., previous or current head and neck radiation therapy, long term steroid use (defined as more than two weeks in the past two years), and/or HIV/AIDS) at the time of screening.

4. A subject who had diseases that affect bone metabolism such as Osteoporosis and Osteopenia.
5. A subject who had socket/ridge preservation procedure done over the research related mandibular posterior edentulous ridge.
6. Implant placed less than 6 months post guided bone regeneration procedure for the augmented group.

Subject Withdrawal/Termination Criteria

1. Non-compliance.
2. Unwillingness to further participate.
3. Extra bone augmentation was required at the time of implant placement.

Sample Size calculation

A sample size calculation was performed using the statistical software package nQuery Advisor (Version 7.0). Based on the previous literatures[24,45], the anticipated peri-implant bone loss at the time of stage II procedure was 1.26 ±1.18 mm (mean±SD) for the test group and 0.123±0.52 mm (mean±SD) for the control group. Under these assumptions and account for an anticipated attrition rate of 20%, a number of 20 subjects for the test group and a number of 15 subjects for the control group would provide a Type I error rate of 0.05 and a power of 90%.

Randomization

Each subject could have up to two implants which were placed in the same research related edentulous ridge during the same surgery to be included in the study and then

used for data collection and analysis. A randomization scheme was created using the statistical package R Version 2.11.1. The scheme was used in the instance where a subject had more than two implants placed in the research related edentulous ridge to randomly decide which two implants to include. Randomization occurred during Visit 1.

Study approval

The Tufts Medical Center and Tufts University Health Sciences Institutional Review Board approved the study protocol before initiation of the study (IRB #10575).

Study Procedures

Visit 1

Patients treatment planned for implant placement and restoration in the TUSDM post-graduate periodontal dental clinic were approached. After obtaining informed consent, the medical history and demographic information were collected. Subjects were asked to complete a contact information sheet in order that they might be reached to schedule appointments or reschedule appointments as necessary. Exclusion/Inclusion criteria were evaluated at visit 1. After the eligibility had been determined by the inclusion and exclusion criteria, a subject identification code was assigned to each subject. The identification code did not consist information regarding to which group (test or control) the subject below to.

Customized radiographic stent

A customized radiographic stent was made at visit 1. (Figure I.) Vinyl polysiloxane (VPS) bite record material (Genie VPS © Putty, Rapid set , Sultan Healthcare, Inc.) was used on the radiographic bite block (AimRight Adhesive Holder System - Adhesive Bitewing Holders, Schick By Sirona, Charlotte, NC). Both the VPS material and bite block are standard materials used in the TUSDM periodontology clinic. Bite record material and bite block were placed intraorally and subject was asked to bite on bite record material to fabricate customized radiographic stent. (Figure II.) Stent was removed from subject's oral cavity once the bite record material was set. Stent was labeled with deidentified subject code. The customized radiographic stent was used to reposition digital film sensor at each time of radiographic exposure to obtain standardized radiography.

Visit 2

During the subject's normally scheduled implant placement procedure, investigator Dr. Hsiang-yun Huang (HH) used periodontal probe (Hu-Friedy, Chicago, IL, USA) with an endodontic stopper to record the distance from implant platform to the level of bone crest along the the long axis of implant fixture mesially (cMBL) and distally (cDBL) respectively after the implant was placed in bone (Figure III). Boley gauge caliper (Hu-Friedy, Chicago, IL, USA) was used to measure the distance on the periodontal probe into 0.1 millimeter increments(Figure IV). While implant platform was positioned subcrestally, cMBL and cDBL were then marked as negative value.

All implants included in this study were oxidized TiUnite rough surface taper implants with smooth machine collar (Nobel Biocare Replace® Select Tapered ™) were placed by residents of department of periodontology of TUSDM according to

manufacture's protocol and with faculty's supervision. The investigator was not the clinician for the dental implant procedure ; however, the investigator observed the procedure.

Standardized radiography

After the implant was placed, standard of care post-operative radiographs were obtained by using customized radiographic stent combined with a metal grid attached digital radiographic sensor. The metal mesh grid gauge (Dae Kwang DMS, Jung-Ku, Seoul) which is a similar size as the digital radiographic sensor (Schick Elite, size 2, Schick By Sirona, Charlotte, NC) was attached to digital radiographic sensor to superimpose the calibrator (Figure V). The sensor and metal mesh grid gauge were covered by plastic cover to which the customized radiographic stent was adhered. Subjects were asked to bite on the stent and allowed the sensor to be placed intraorally at the time of radiographic exposure by using parallel technique (Planmeca intra; 70Kv, 8ma, 0.080 sec; Cone to sensor distance: 9cm).

Visit 3: 2 or more Months after Visit 2

During subjects' normally scheduled stage II implant surgery (uncovering of implant), Standardized radiographs by utilizing customized radiographic stent and metal grid were obtained by investigator (HH) prior to the surgery.

The classification of early implant exposure (eIE) proposed by Tal *et al*.[46] from class 0 to class IV was recorded by investigator (HH).(Table I.) The width of keratinized mucosa over implant site (wKM) was measured by periodontal probe (Hu-Friedy, Chicago, IL, USA) with endodontic stopper. Same periodontal probe and endodontic

stopper were used to measure the soft tissue thickness (ST) on top of implant after implant uncovering. (Figure VI.) Boley gauge caliper (Hu-Friedy, Chicago, IL, USA) was used to read the distance on the periodontal probe into 0.1 millimeter increments and recorded it.

The investigator(HH) was not the clinician for the stage II surgery, but observed the procedure and took the measurements(eIE, wKM, ST) during the surgery. Standard of care radiograph was obtained by using customized radiographic stent and metal grid following the surgery.

Measurements from standardized radiograph

Image J 1.43r Software (National Institute of Health, Bethesda, MD, USA) was used to measure the peri-implant crestal bone level on digital standardized radiographs calibrated to 0.01 millimeter. Mesial and distal peri-implant crestal bone level (MBL, DBL) were measured by following the long axis of the implant from reference points which were mesial and distal point of implant platform respectively to the top of alveolar bone crest. (Figure VII.) While the crest of alveolar bone was coronal to implant platform, MBL and DBL were recorded as negative value.

Measurements were performed on radiographs obtained at the time of implant placement (visit 2) and radiographs obtained prior to Stage II surgery (visit 3). The fixed length of implant smooth collar, which is 1.50 mm, was used to calibrate the real value of the investigated measurement. The real value (X) in mm for the investigated measurement was recorded using the following method: X= A*1.50 / B where

A= distance in pixels obtained from the software for the investigated measurement.

B= distance in pixels obtained from the software for the length of the implant smooth collar.

The calculated measurements were rounded to the nearest 0.01mm reducing the measurement bias to 0.5%: Each radiograph was coded by subject's identification number with no information regarding to which study group the subject belonged to. Measurements were done twice by a single observer (HH) in a randomly selected order at 1-week intervals.

The mesial and distal peri-implant crestal bone level measured from the standardized digital radiographs obtained at the time of implant placement were marked as $MBL_{(Baseline)}$ and $DBL_{(Baseline)}$ respectively. While the mesial and distal peri-implant crestal bone level measured from the standardized digital radiograph obtained prior to stage II procedure were marked as $MBL_{(stage\ II)}$ and $DBL_{(stage\ II)}$ respectively.

The mesial and distal peri-implant bone loss from the time of implant placement to the time of stage II procedure (ΔMBL, ΔDBL) were calculated from $MBL_{(stage\ II)}$ - $MBL_{(Baseline)}$ and $DBL_{(stage\ II)}$ - $DBL_{(Baseline)}$ respectively. The average of ΔMBL and ΔDBL was marked as ΔBL.

Statistical Analysis

SAS (Version 9.0) and SPSS (Version 22) software were used for the statistical analysis of the data.

Descriptive statistics were presented as mean ± SD in years for the variables of age, in mm for the variables of wKM, ST, ΔMBL, ΔDBL and ΔBL. To adjust for the fact that some subjects had multiple implants, a mixed model was used to evaluate if there was a significant difference in ΔMBL, ΔDBL and ΔBL between test and control group. The mixed model was run with and without adjusting for potential confounders (eIE, ST and wKM). A mixed model was also used to evaluate whether there were statistically significant differences in wKM, ST and the rate of early implant exposure between the two groups.

V. RESULTS

Demographics

Thirty subjects, 12 females and 18 males, were enrolled in this study (Table II). Eleven subjects, 4 females and 7 males were in the test group while 19 subjects, 8 females and 11 males were in the control group. The mean age of the subjects in the test group was 57.63 years with standard deviation 14.65 years. The mean age of subjects in the control group was 57.63 years with standard deviation 11.37 years. There was no statistically significant difference in age between the two groups (P= 0.999).

Four subjects of the test group had two implants that were eligible to the inclusion criteria, the other subjects of the test group only had one eligible implant each. One implant from a subject who had two enrolled implants was removed after implant was placed due to infection. Two subjects from the test group were lost to follow-up . Data of stage II procedures could not be obtained due to the loss of follow-up.

Among those two subjects, one of them had two implants enrolled in the study; the other had one implant enrolled in study instead. In total, two subjects and four implants in the test group were not included in the data analysis.

In the control group, each subject contributed one implant only except two subjects contributed two implants respectively. One implant from one of the two subjects was intentionally replaced owing to the mal-placed long axis of implant fixture. Considering the explanted socket may have had an effect on bone remodeling, the implant was excluded from the data analysis. Two extra implants from the control group were also excluded. One was excluded because the subject was lost to follow-up for the stage II procedure. Another one had continuous discomfort and swelling of soft tissue post implant placement. The stage II procedure of that implant was performed only one month post implant placement to drain inflammation exudate which did not follow the study protocol. Overall, two subjects and three implants were not included in the final data analysis.

Due to the limited patient pool, strict inclusion/exclusion criteria, time constraints and few subjects loss to follow-up, the power of this study was 69% with data from 11 implants from the test group and 18 implants from the control group.

Number of implants had early implant exposure (eIE)

For eIE, eight and ten implants were classified as Class 0; which means the mucosa covering the implant were intact with no exposure noted, in the test and control group respectively. Three and eight implants had implant exposure which classified as Class

I, II, III and IV in test and control group respectively (Table III). More specifically, there were one implant classified to eIE class I, none implant classified to class II, two classified to class III and none classified to class IV in test group. There were two implants classified to eIE class I, one classified to class II, four classified to class III and one classified to class IV. There was no statistically significant difference regarding to the rate of early implant exposure between test and Control group (p=0.371).

Width of keratinized mucosa (wKM)

wKM was 2.51 ± 1.92 (mean ± SD) in mm for the test group and 2.65 ± 0.95 mm for the control group. There was no statistically significant difference in wKM between the groups (P=0.7211). (Table IV)

Soft tissue thickness (ST)

ST was 1.34 ± 0.41 (mean ± SD) in mm for the test group and 2.12 ± 0.67 mm for the control group (Table IV). Control group had statistically significant thicker soft tissue over the implant site (P=0.0050).

Mesial peri-implant bone loss (ΔMBL)

ΔMBL was 0.81 ± 0.85 (mean ± SD) in mm for the test group and 0.30 ± 0.72 mm for the control group (Table IV). When only utilized the test and control group as the factor and ΔMBL as the outcome, there was no significant difference in ΔMBL between the test and control group (p= 0.0562). After adjusting for the confounder

eIE, wKM and ST, there was a significant difference for ΔMBL between the GBR and control group (P =0.0092).

Distal peri-implant bone loss (ΔDBL)

ΔDBL was 0.67 ± 0.77 (mean ± SD) in mm for the test group and 0.20 ± 0.49 mm for the control group (Table IV). When only utilized the test and control group as the factor and ΔDBL as the outcome, there was a significant difference in ΔDBL between the test and control group (p= 0.0347). After adjusting for the confounder eIE, wKM and ST, there was a significant difference for ΔDBL between the GBR and control group (P =0.0038).

Peri-implant bone loss (ΔBL)

ΔBL was 0.74 ± 0.74 (mean ± SD) in mm for the test group and 0.25 ± 0.55 mm for the control group(table IV). When only utilized GBR and control group as factor and ΔBL as outcome, there was a statistically significant difference in ΔBL between the GBR and control group(p= 0.0280). After adjusting for the factors of eIE, wKM and ST, there was a statistically significant difference between the GBR and control group (P =0.0007).

Evaluation the consistency of the clinical and radiographic measurement method of peri-implant crestal bone level at the time of implant placement.

Bland-Alman plot (FigureVIII and Figure IX) was constructed to compare the peri-implant crestal bone level value obtained from clinical measurement (cMBL and

cDBL) to the value obtained from radiographic measurement (MBL and DBL). The absolute mean value of MBL minus cMBL was 0.49 mm with a standard deviation 0.40 mm. The absolute mean value of DBL minus cDBL was 0.43 mm with a standard deviation 0.41 mm.

Distribution of the amount of peri-implant bone loss (ΔBL)

Distribution of the percentage of the amount of peri-implant bone loss was showed (Table V). The mean bone level change in both groups were within 0.5 mm.The control group had more percentage of peri-implant bone gain (44.4%) while the test group had less percentage of bone gain (9.1%).

Implant survival rate:

One implant from the test group was determined failed which contributed to 93.3% implant survival rate. No implant was determined as failed in the control group, which contributed to 100% survival rate. However it should be noticed that three and one implants were lost of follow up in test and control group respectively. The status of those implants could not be determined.

VI. Discussion

The implant used in this study protocol has been limited to implants placed in the mandibular posterior alveolar ridge. In order to avoid possible sinus augmentation, maxillary posterior arch was not included in the study. Sinus augmentation will need additional augmentation at apical bone site which will interfere with the study. The

inclined angulaion of maxillary and mandibular anterior alvoelar ridge created difficulty to obtain radiographs parallal to the long axis of implants. Thus, implants placed in anterior alveolar ridges were also not included in the present study.

Early implant exposure

The effect of early implant exposure(eIE) was viewed as a co-variable in the present study.Block and Kent found spontaneous early implant exposure of the submerged implant during healing appeared to be associated with a higher incidence of peri-implant crestal bone loss[47]. The degree of early implant exposure was classified into Class 0 (no exposure)to Class IV(fully exposed) .[46]

In a prospective clinical trial conducted by Tal *et al.* , there was a statistically significant difference of peri-implant bone loss associated with the class of early implant exposure. The peri-implant bone loss of ClassI early implant exposure during the submerged healing period was significant from the class II and class III early implant exposure classification.

In the present study, the significant difference of peri-implant bone loss between the different classification of eIE was not evaluated due to the limited number of samples in each classification. However, it was calculated that there was no statistically significant difference for the early implant exposure rate comparing implants placed in augmented bone versus implants placed in the pristine bone.

Width of keratinized mucosa (wKM) and Soft tissue thickness (ST)

There was no statistically significant difference for the wKM between the test group and the control group. However, there was a statistically significant difference for the soft tissue thickness(ST) between the two groups. The control group had greater mean soft tissue thickness of 0.78 mm than the test group. A prospective clinical trial found thicker mucosa implant site had statistically significant less peri-implant bone loss from the time of implant placement to one-year post prosthesis delivery[48]. This might indicate that the less peri-implant bone loss in the control group was probably due to the thickness of soft tissue on the top of implants instead of the difference between augmented and pristine bone.

Peri-implant bone loss between the test and control group

Mixed effect model was applied to evaluate the difference of peri-implant bone loss between test and control group. The results of this study revealed that there were more peri-implant crestal bone loss both mesially and distally. The difference between test and control group was statistically significant for the distal peri-implant bone loss but not for the mesial peri-implant bone loss. The was more mean peri-implant crestal bone loss for implants placed in previously augmented alveolar bone (test group) than implants placed in pristine alveolar bone (control group) from the time of implant placement to the stage II procedure.

The possible confounders : early implant exposure (eIE), soft tissue thickness (ST) and the width of keratinized mucosa (wKM) were adjusted to the result. After adjusting the above confounders, there was still statistically significant more peri-

implant bone loss for implants placed in augmented bone than implants placed in pristine bone either mesially or distally.

Zitzmann *et al*. [26] conducted a 5-year prospective longitudinal study to compare the differences between implants placed in pristine bone, resorbable membrane augmented bone, and non-resorbable membrane augmented bone. The mean peri-implant bone loss at 5 years was 2.02 mm around implants placed in non-resorbable membrane augmented bone, 1.73 mm for pristine bone and 1.83 mm for resorbable membrane augmented bone. There was significant difference for bone loss between non-resorbable membrane augmented bone group and the other two groups. Unlike the present study, the bone augmentation procedure in the study of Zitzmann *et al.* was performed simutaneously with implant placement instead of staged approached. The premature membrane and cover screw exposure were not discussed in their study, which the present study adjusted the effect of confounders on peri-implant bone loss.

A cross-sectional study conducted by Benić *et al.* measured the peri-implant bone level on machine surface implant via periapical radiography post mean 57 months after implant placement. [36] The mean peri-implant bone level at the time of follow up radiograph exposed was 1.33 mm for the bone augmented group and 1.60 mm for native bone group. According to Benić *et al.* the difference was not statistically significant. However, the limitation of this cross-sectional study was that it can only measure the current peri-implant bone level but not the change of peri-implant bone loss over time.

A randomized 3 year prospective clinical trial done by Barone *et al.*[40] compared the peri-implant bone level changes over three years post implants placement. Implants in the test group were placed in previously bone graft preserved extraction socket. Implants in the control group were placed in naturally healed extraction socket. There was no statistically significant difference for the bone level changes between the two groups which is different from our findings. The difference of results might be caused by the procedure differences between ridge/socket preservation and GBR. The ridge/ socket preservation did not augmented bone but just preserve the volume of pre-existing ridge. Residual bone graft were limited in the extraction socket of tooth. It could not be secured that the peri-implant bone in ridge post socket/ ridge preservation were augmented bone.

Time frame

The present study measured the peri-implant bone level changes from the time of implant placement to the time of stage II procedure. Many retrospective studies monitor the bone level by using the time of prosthesis delivery as a baseline. However, the bone remodeling process might have been initiated right after implant placement.By set the time of implant placement as a baseline, this would reveal more information regarding to the difference of the amount of peri-implant bone loss between augmented and pristine bone. The present study monitored the peri-implant bone level starting at the time of implant placement and found the difference of peri-implant bone loss between pristine and augmented bone.

Peri-implant alveolar bone gain

At the time of stage II procedure, it was noticeable that the control group had more percentage of alveolar bone level gain when compared to the test group. It may due to that pristine bone had more percentage of vital bone tissue which can stimulate alveolar bone tissue deposition, On the other hand, augmented bone had more percentage of soft tissue and residual bone graft instead. [24]

Consistence of clinical and radiographic measurement for peri-implant bone level:

The peri-implant bone level between the radiographic and clinical measurement were not consistent . It may be explained by the fact that a flat alveolar ridge was not always available at the implantation site. Thus, adjacent slope next to the implant site may blocked the periodontal probe from being positioned to the accurate point.

Previous literature indicated the reliability of using standardized radiography compared to histological findings. [44] In addition, radiographic measurement was a relatively non-invasive method to monitor peri-implant bone level for further long-term follow-up study. Thus, standardized radiograph was chosen to obtained the peri-implant bone level.

Although the present study tried to randomize sample by covering the identity of the group of each radiograph, the examiner can still have a chance to distinguish augmented and pristine bone on radiograph itself only. For further research,

computer-based digital subtraction radiography may be considered to compute peri-implant crestal bone changes to reduce potential bias.

Limitation

The authors understand that the present research project has specific limitations. The implants included in this study were rough surface taper implant with a smooth surface implant collar and the time frame was limited to time from implant placement to stage II procedure.The results and conclusions should not be extrapolated to different type of implant surface design and long-term basis conclusion.

Furthermore, there was no calibration exercised done for examiner HH and surgical procedure were done by different surgeons. The variations of surgical experiences and techniques may contribute to the bias.

Moreover, despite the fact that radiographic measurements were evaluated with a photographic assessment software and was measured in a randomly order, examiner bias may still exist.

Due to the limited patient pool and strict inclusion/exclusion criteria, limited number of subjects for the test group were enrolled. The power of the current study was 69% despite the small number of p value.

Further research

All subjects of this research were enrolled in a research protocol that will analyze the peri-implant bone level via standardized radiograph at implant placement, stage II procedure, prosthesis delivery and one year post prosthesis delivery. This thesis project analyzes the results at implant placement and stage II procedure; which was the time frame that the author hypothesised that peri-implant bone level difference between the test and the control group was most pronounced.

Further study may investigate on the peri-implant bone level difference on the long – term follow up basis. And may investigate on if different implant surface design had different effects on the peri-implant bone level between augmented bone and pristine bone.

VII. Conclusion:

Within the limits of the present study, the authors conclude that there is significant more peri-implant crestal bone loss in augmented bone than pristine bone during the submerged pre-prosthetic healing. Further studies with large sample size are recommended to confirm the findings.

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IX. Figures and Tables

Figure I.

Customized radiographic stent

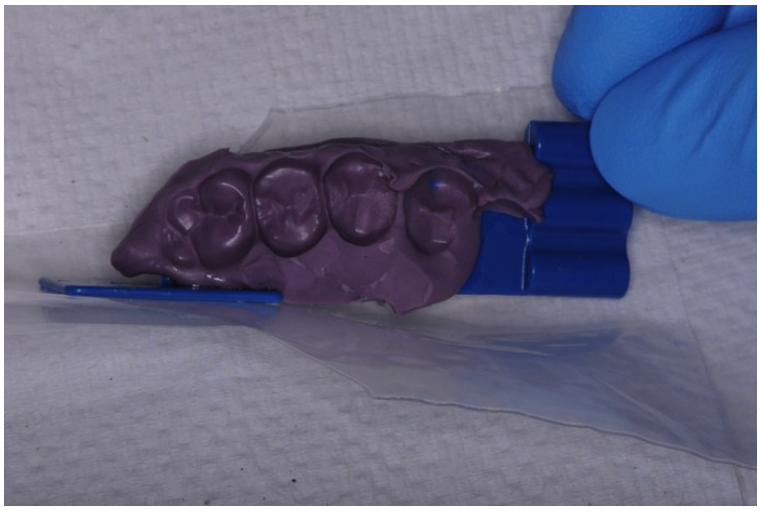


Figure II.

Fabrication of customized radiographic stent

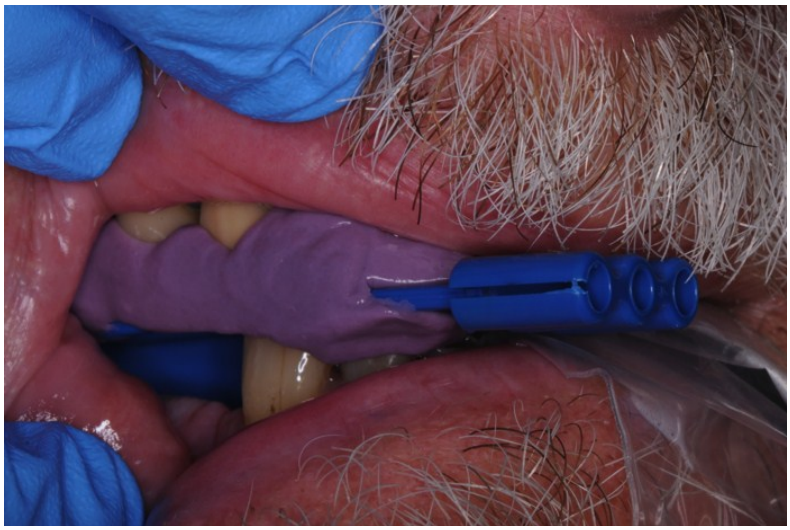


Figure III.

Measured the distal peri-implant bone level clinically (cDBL) with a periodontal probe and an endodontic stopper.

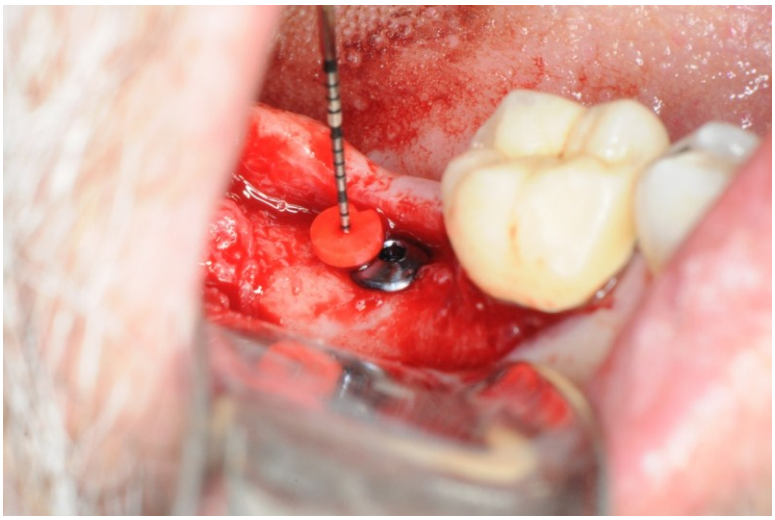


Figure IV.

Boley gauge caliper was used to measure the distance on the periodontal probe.

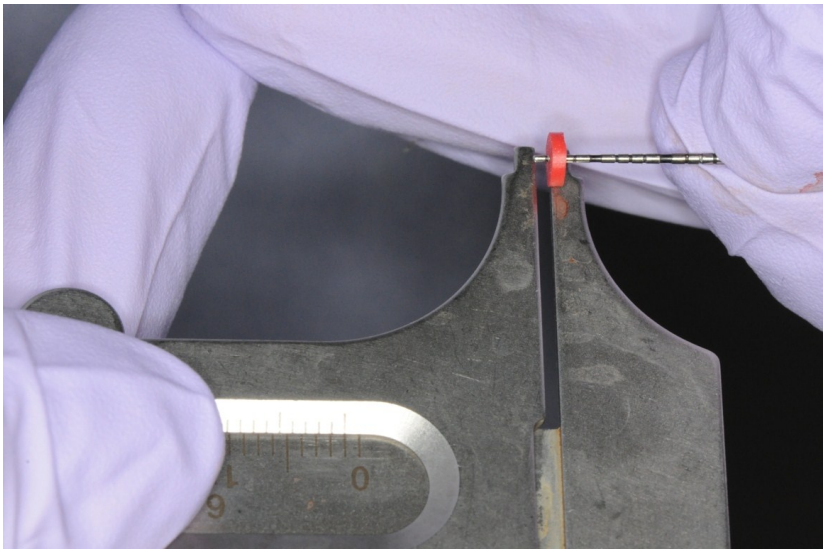


Figure V.

Standardized radiograph

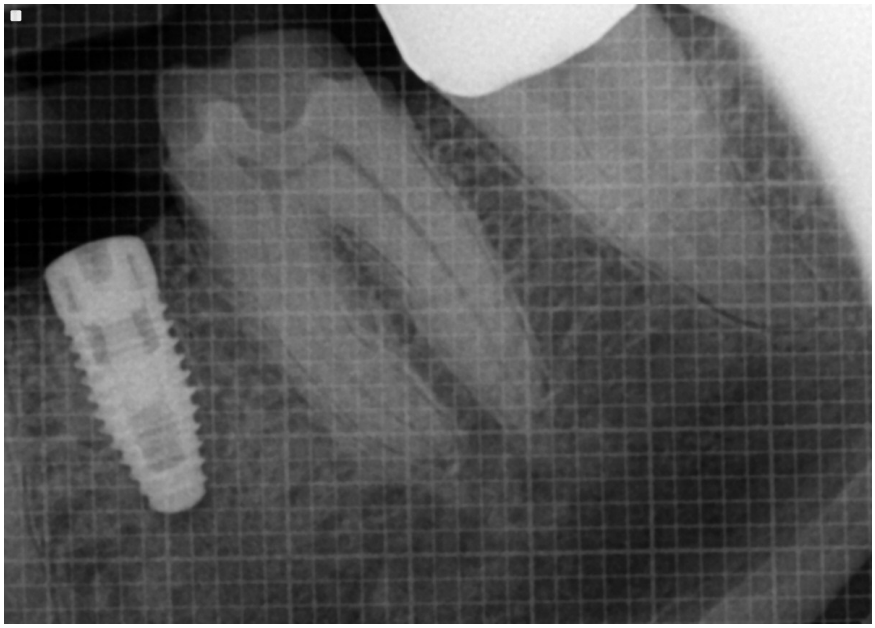


Figure VI.

Measuring the soft tissue thickness (ST)

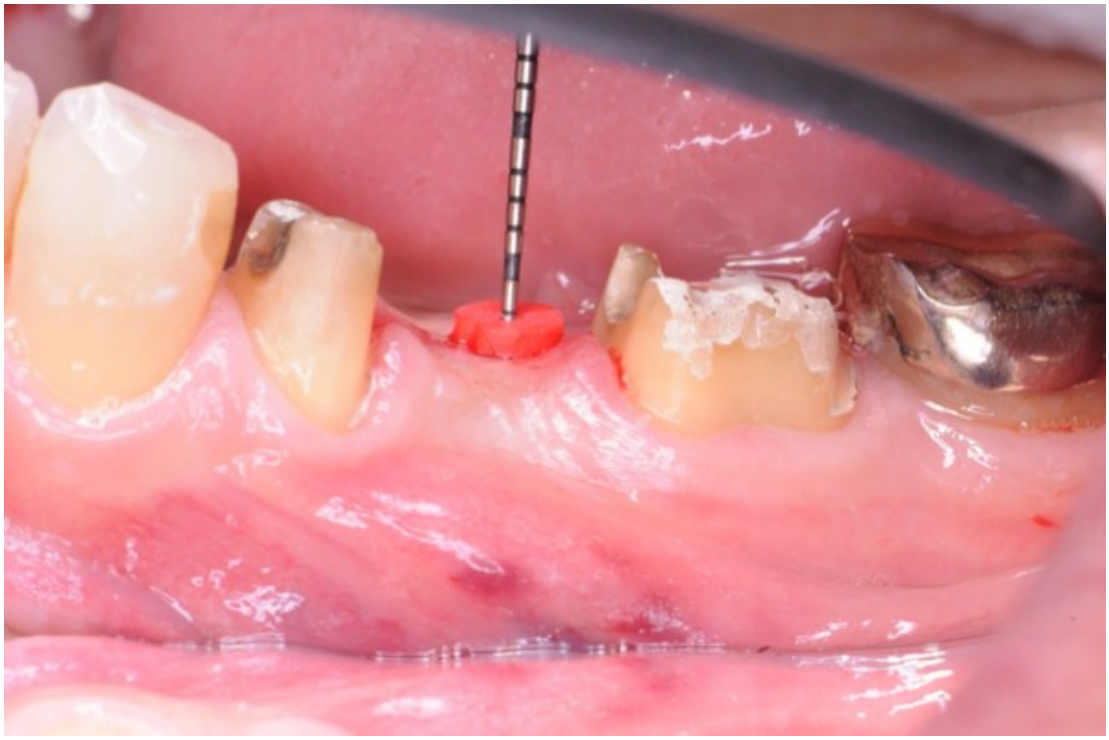


Figure VII.

Measure the MBL and DBL on radiography

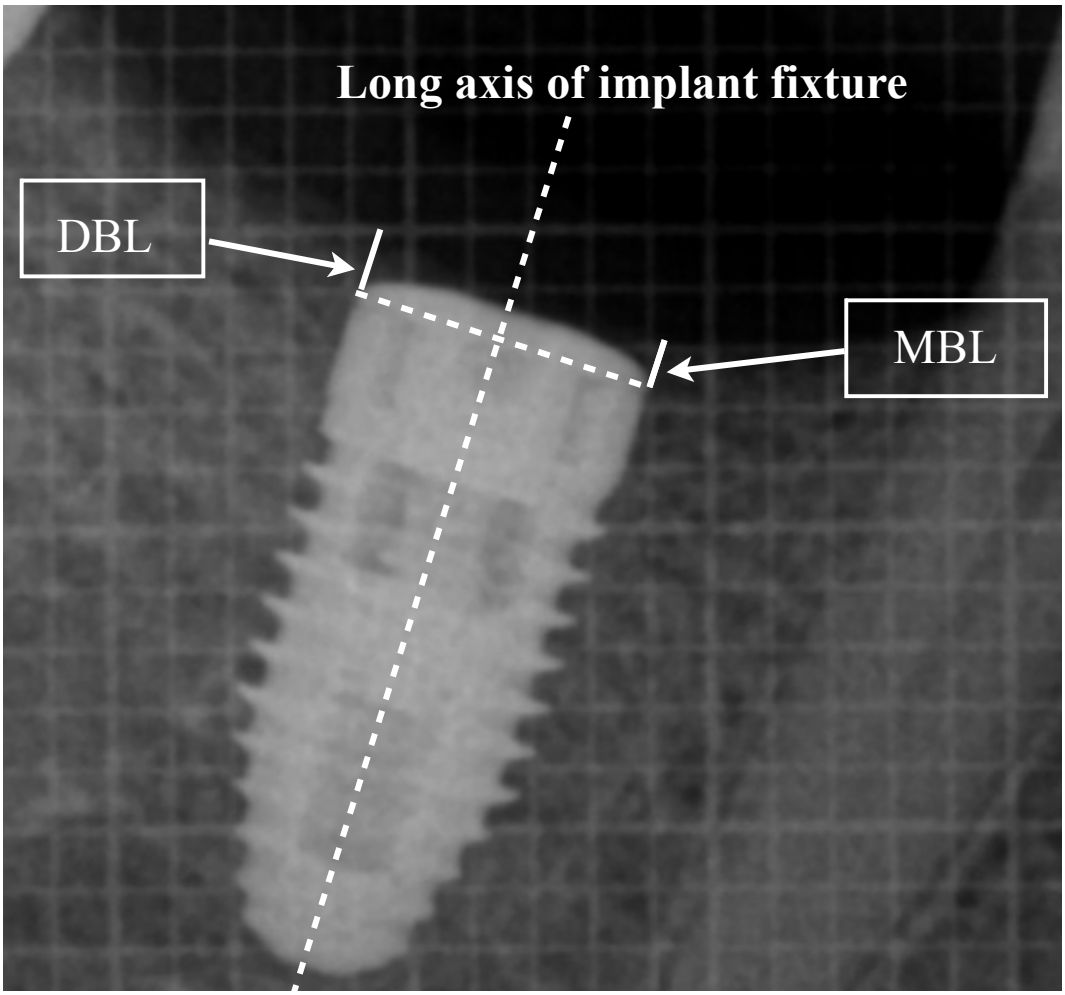


Figure VIII.

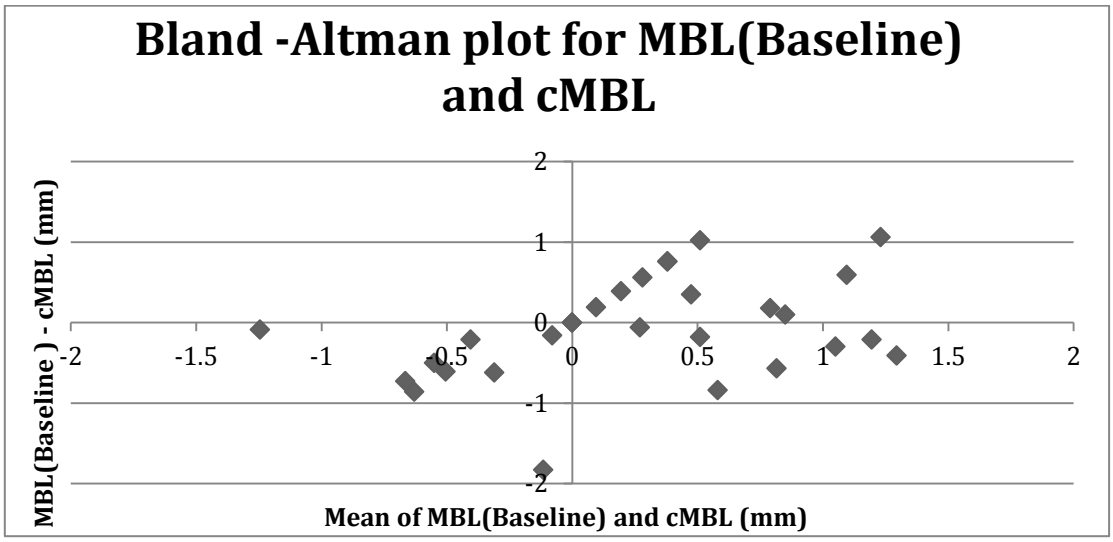


Figure IX.

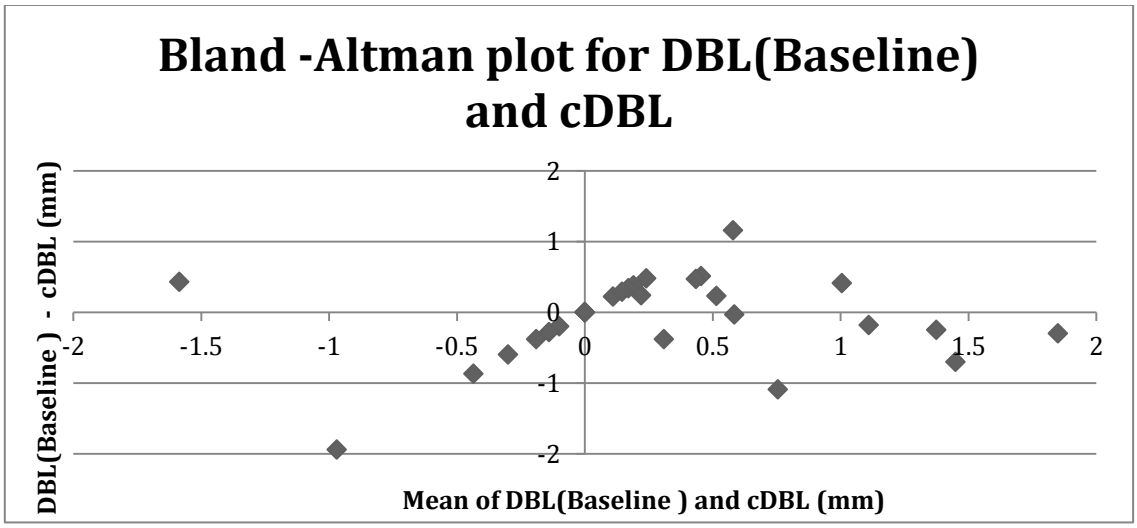


Table I.

Classification of early implant exposure (eIE) of submerged endosseous implant proposed by Tal (1999)

0	The mucosa covering the implant is intact
I	A breach in the mucosa covering the implant is observed. Oral implant communication can be detected with a periodontal probe but the implant surface cannot be observed without mechanically interfering with the mucosa
II	The mucosa above the cover screw is fenestrated; the cover screw is visible. The borders of the perforation's aperture do not reach or overlap the borders of the cover screw at any point
III	Cover screw is visible. In some parts, the borders of the perforation aperture overlap the borders of the cover screw
IV	Cover screw is completely exposed

Table II.
Study population-Demographics

	Test	Control	P value
Age			
Mean ± SD (years)	57.63 ±14.65	57.63 ± 11.37	.999#
Gender			
Female (number of subjects)	4	8	.534*
Male (number of subjects)	7	11	
Number of implants	15	21	
Number of subjects were not included in data analysis	2	2	
Number of implants were not included in data analysis	4	3	

Independent-samples test
* Fisher's exact test

Table III.

Numbers of implants of different classification of early implant exposure (eIE)

	Test[#] n= 11	Control N=19
No exposure (Class 0) (Number of implants)	8	10
Had exposure (Number of implants)	3	8
Distribution of eIE (Number of implants)		
Class I	1	2
Class II	0	1
Class III	2	4
Class IV	0	1

No significant difference in the early implant exposure rate between test and control group. P value = 0.371 (generalized estimating equations)

eIE: early implant exposure

Table IV

Clinical Measurements and Bone loss at Stage II procedure

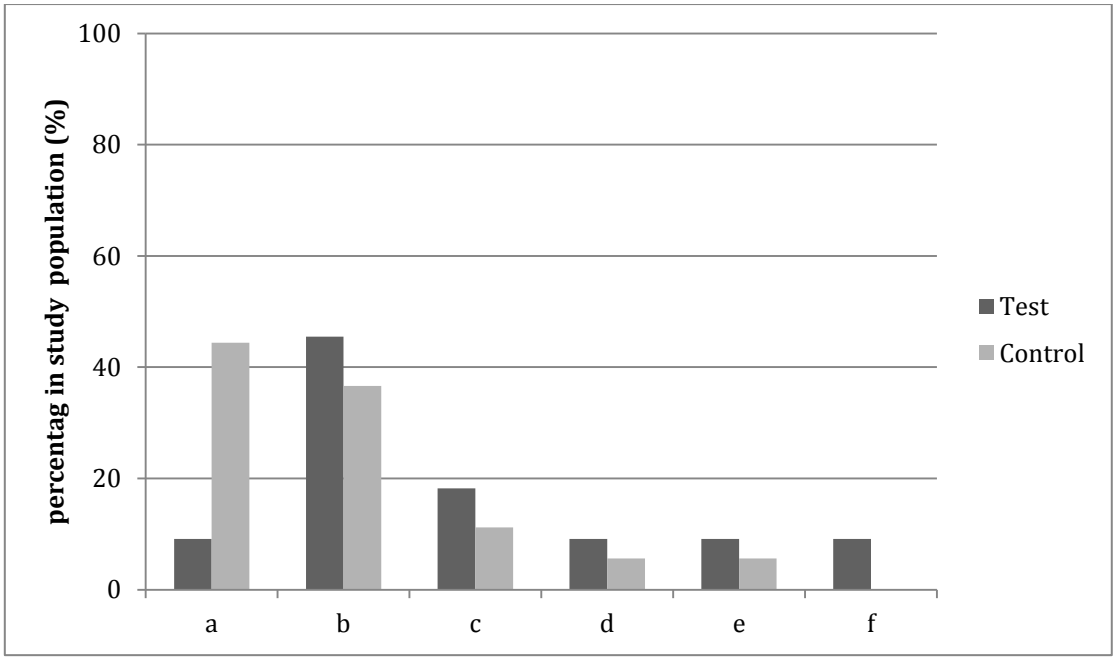
	Test	Control	P-value*	P-value*#
wKM ¶				
Mean ± SD (mm)	2.51 ± 1.92	2.65 ± 0.95	0.7211	
ST¶¶				
Mean ± SD (mm)	1.34 ± 0.41	2.12 ± 0.67	0.0050	
ΔMBL¶¶¶				
Mean ± SD (mm)	0.81 ± 0.85	0.30 ± 0.72	0.0562	0.0092#
ΔDBL¶¶¶¶				
Mean ± SD (mm)	0.67 ± 0.77	0.20 ± 0.49	0.0347	0.0038#
ΔBL§				
Mean ± SD (mm)	0.74 ± 0.74	0.25 ± 0.55	0.0280	0.0007#

¶ :Width of Keratinized mucosa
¶¶: Soft tissue thickness
¶¶¶ :$MBL_{(Stage\ II)} - MBL_{(Baseline)}$
¶¶¶¶: $DBL_{(Stage\ II)} - DBL_{(Baseline)}$
§ : Average of ΔMBL and ΔDBL

*: Mixed effects model
P-value adjusted for early implant exposure (eIE), soft tissue thickness (ST) , and width of keratinized mucosa (wKM)

Table V.

Distribution of ΔBL in test and Control group



a: -0.5 mm < ΔBL < 0 mm
b: 0 mm ≤ ΔBL < 0.5 mm
c: 0.5 mm ≤ ΔBL < 1.0 mm
d: 1.0 mm ≤ ΔBL < 1.5 mm
e: 1.5 mm ≤ ΔBL < 2.0 mm
f: 2.0 mm ≤ ΔBL < 2.5 mm

ΔBL: Average of ΔMBL and ΔDBL