Tufts UNIVERSITY | School of Dental Medicine

Cone-beam Computed Tomography Analysis of Peri-implant Buccal Bone in Grafted and Native Bone: 1-year Results from a Prospective Controlled Cohort Study

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ABSTRACT

Aim & Hypothesis: The aim of this prospective clinical study is to compare the stability of peri-implant buccal bone and soft tissue between native bone (Group1) and grafted bone (Group 2: ridge preservation, Group 3: augmented ridge) after 1-year of implant loading.

Materials and Methods: Horizontal and vertical changes in peri-implant buccal bone on cone-beam computed tomography images from implant placement to 1 year of loading were compared between the groups. Horizontal thickness of the buccal bone was measured at implant shoulder level (L0), and 2 mm (L2), 4 mm (L4), 6 mm (L6) apical to the shoulder. Vertical distance was measured from the implant shoulder to the most coronal buccal bone level. Additionally, the patient-reported outcome measures were compared between the groups at 1-year follow-up.

Results: Among 30 enrolled subjects, 14 subjects completed 1-year follow-up. A total of 12 patients (6 patients in Group 1 and 6 patients in Group 2) were included in the statistical analysis. In Group 1, horizontal changes were +0.054 ± 0.394 mm at L0, -0.152 ± 0.563 mm at L2, -0.330 ± 1.076 mm at L4, and -0.313 ± 0.947 mm at L6. In Group 2, there was more horizontal resorption observed with-0.297 ± 0.571 mm at L0, -0.528 ± 0.787mm at L2, -0.613 ± 0.787 mm at L4, and -0.147 ± 0.616 mm at L6. However, there were no statistically significant differences between groups in horizontal and vertical changes of peri-implant buccal bone, peri-implant mucosal recession, and patient reported outcomes.

Conclusion: Within the limitation of the current study, there were no statistically significant differences among groups regarding horizontal and vertical changes of peri-implant buccal bone, peri-implant mucosal recession, and patient reported outcomes. Future well-controlled studies with larger sample size and long-term follow-up are needed.

DEDICATION

I dedicate this thesis to my beloved mother Tina Yang for the unconditional love, endless spiritual support, and the partnership for success in my life.

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LIST OF ABBREVIATIONS

CBCT: Cone-beam computed tomography

FOV: Field of view

RCT: Randomized controlled trial

PROMs: Patient-reported outcome measures

OHRQoL: Oral health-related quality of life

OHIP-14: Oral Health Impact Profile-14 patient questionnaire

VAS: Visual analog scale

GBR: Guided bone regeneration

FDBA: Freeze-dried bone allograft

HA: Hydroxyapatite

CTG: Connective tissue graft

3D: Three-dimensional

2D: Two-dimensional

AAID: American Academy of Implant Dentistry

AAOMR: American Academy of Oral and Maxillofacial Radiology

AAP: American Academy of Periodontology

TUSDM: Tufts University School of Dental Medicine

HIV: Human immunodeficiency virus

BIC: Bone-to-implant contact

Rec: Recession

LIST OF SYMBOLS

mm: Millimeter

kVp: kilovoltage peak

mAs: Milliampere-seconds

μSv: microsievert

V2: Visit 2

V4: Visit 4

L0: Implant shoulder level

L2: 2 mm apical to implant shoulder level

L4: 4 mm apical to implant shoulder level

L6: 6 mm apical to implant shoulder level

Cone-beam Computed Tomography Analysis of Peri-implant Buccal Bone in Grafted and Native Bone: 1-year Results from a Prospective Controlled Cohort Study

Rationale and background

Implant therapy has become a well-established and highly successful treatment in the rehabilitation of partially and fully edentulous patients. With spontaneous healing after tooth extraction, alveolar ridge alteration occurs, including loss of width and height, which may eventually prevent or compromise the future implant placement with the ideal three-dimensional position. Several human studies reported that the alveolar ridge underwent a mean horizontal reduction in width of 2.46–4.56 mm and a mean vertical reduction in height of 0.9~1.24 mm within six months after tooth extraction [34-36]. Furthermore, there was more loss of buccal plate than lingual plate after extraction [37].

Thus, alveolar ridge preservation technique has been developed utilizing bone grafting in extraction socket in order to minimize the ridge alteration after tooth extraction. Iasella et al. investigated the ridge alterations after tooth extraction and reported significantly less changes in ridge height and width s after ridge preservation e compared with extraction alone. The mean horizontal ridge resorption was 1.2 mm in the ridge preservation and 2.6mm in extraction alone. The vertical gain of 1.3mm was reported in ridge preservation, whereas the mean loss of 0.9mm was shown with extraction alone) [38]. However, in deficient edentulous ridges where extraction sockets underwent natural healing with ridge resorption, ridge augmentation may be required to rebuild the sufficient height and width of the alveolar ridge for dental implant placement for optimal functional and aesthetic outcomes.

After high survival rates of dental implants have been achieved [45], the focus of implant success has been shifted to improved esthetic outcomes and the long-term stability of the peri-implant tissues [1, 2]. Peri-implant tissues are divided into soft and hard tissue compartments around osseointegrated implant. The stability of peri-implant tissues is essential for the long-term success of dental implants because peri-implant buccal bone resorption can lead to peri-implant mucosal recession, thread exposure, and affect esthetic outcomes [1, 2]. To predict the stability of peri-implant hard and soft tissue, it is important to understand the extent of horizontal bone and vertical dimensional changes in the buccal bone after implant placement and loading. It is also critical to know the thickness of buccal bone required around implant to prevent its further bone resorption and soft tissue recession [3].

The stability of peri-implant buccal bone can be examined only by three-dimensional (3D) analysis. Currently, a cone-beam computed tomography (CBCT) scan offers adequate 3D image quality with reduced radiation exposure compared to conventional CT and renders more information which cannot be achieved by 2D periapical or panoramic radiographs.

Diagnostic accuracy of CBCT

The goal of radiographic selection criteria is to identify appropriate imaging modalities that complement the goals at each stage of implant therapy. Currently, CBCT is best method for the evaluation of volumetric and topographic changes of the alveolar ridge and should be considered for evaluation of site before and/or after implant placement.

As per the position statement by the American Academy of Oral and Maxillofacial Radiology (AAOMR), cross-sectional imaging is recommended for the assessment of all dental implants [4]. Currently, CBCT is the method of choice for cross-sectional imaging of dental implant and surgical sites in that it provides the greatest diagnostic yield at a lower radiation dose compared to other forms of 3D imaging such as conventional CT. Selection of this scanning protocol ensures reduction in radiation dose compared to the standard mode. CBCT which facilitates postsurgical assessments of implant sites can help clinicians evaluate the surgical outcome as a follow up modality.

There are two systematic reviews regarding the diagnostic accuracy of CBCT in assessing peri-implant bone [5, 6]. Pelekos et al. reviewed 18 studies, including 13 in vitro and 5 animal studies, and a qualitative synthesis reported that CBCT diagnostic accuracy showed higher sensitivity and specificity values for circumferential-intrabony and fenestration-type defects around implants, while showed lower values for dehiscence-type defects [5]. Another systematic review by Jacobs et al. included 60 studies for the qualitative analysis and reported that CBCT performed similar to intraoral radiographs, which are considered the gold standard techniques in mesiodistal detection and measurement of defects. Furthermore, buccolingual visualization of the defects is the main added value in the diagnosis of peri-implant bone defects with CBCT [6].

In a human study by González-Martín et al., they reported that 0.1 to 2.75mm of buccal bone thickness was not visible in 68% of cases when using CBCT. The accuracy was significantly influenced by buccal bone thickness, especially when buccal bone thickness was less than 1mm, and peri-implant marginal defects are present[7]. However, in an animal study with defleshed cadaver models, Dave et al. compared CBCT with conventional periapical radiography to detect peri-implant bone defects. The study showed that CBCT has excellent diagnostic precision for detection of peri-implant intrabony defects when the diameters were 0.35–0.675mm [8].

Artifacts around dental implants are common in CBCT images and include streaking, beam hardening or scatter from high-density metal [9, 10]. Thus, metal artifact from implant fixtures and metal crowns of implants or adjacent teeth make it more challenging to measure the peri-implant buccal bone precisely. Some studies compared the buccal marginal alveolar peri-implant and periodontal defects using a CBCT system with and without the application of metal artifact reduction mode [11, 12]. The results showed that even with metal artifact reduction modes, it did not improve diagnostic accuracy and failed to show any significant effects on dehiscence or fenestration detection. Nevertheless, CBCT remains to be an ideal and comparably harmless 3-dimensional imaging modality to access peri-implant buccal bone both horizontally and vertically [4, 13].

One recent cohort study by Meijer et al. used an innovative method to minimize the effects of scattering for the measurements of buccal bone thickness of immediate implant after 1-year follow-up [14]. Bone thickness measurements were performed using there-dimensional image diagnostic and treatment planning software (NobelClinician). First, the exact position of the implant was aligned with a planning implant as determined in an image computing program (Maxilim) with the concept of multimodality image registration. The exact position of the implant can be recognized, determined, and implemented in the patients DICOM files. Second, the buccal bone measurements were performed from the radius of the interior contour of the implant to the outer surface of the bone using the implant planning software. In this way, measuring at the interface between implant and bone, often disturbed by scattering, was avoided. The second part of the method was introduced into our current study [14].

Horizontal and vertical changes in peri-implant buccal bone following implant placement in CBCT studies

The peri-implant buccal bone dimensional change is a key determinant of the stability of peri-implant mucosal tissue. Peri-implant mucosal recession have critical influences not only on the esthetics and long-term success of implant but also patient satisfaction [1, 2]. Different clinical scenarios and bone conditions, including native bone, grafted bone with ridge preservation in post-extraction sockets, ridge augmentation prior to or simultaneously with implant placement, may affect the stability of the peri-implant buccal bone.

In the current literature, there are several studies reporting horizontal and vertical changes in peri-implant buccal bone using CBCT [15, 16, 17]. For implant placement in native bone, in a 1-year prospective clinical study [15], Kaminaka et al. found that horizontal ridge reduction after 1 year of loading was 0.08 mm at the platform level for conical connection implant, which was less than external connection (0.18 mm) and internal connection (0.14 mm) designs. They also found that the bone height changes between loading and 1 year after loading was 0.21 mm with conical connection implant, which was the greatest among three implant designs (external connection: 1.85 mm, internal connection 1.00 mm) [15].

There are only two CBCT studies reporting long-term stability of buccal bone around implants placed simultaneously with bone grafting [16, 17]. Jung, et al. reported on the dimensional changes of peri-implant buccal bone between two time-points—pre-grafting (baseline) and post-healing 5 years [16]. Single implants in the posterior maxilla or mandible were placed with simultaneous guided bone regeneration (GBR), using xenograft and membranes. The buccal vertical bone gain between implant placement and 5-year follow-up were 4.3~4.8 mm. The thickness of the buccal regenerated bone was only accessed at 5-year follow-up. At 1 mm, 3 mm, 5 mm below implant shoulder level, they revealed 2.0 mm, 2.7 mm, 3.1 mm respectively for using porcine collagen membranes, and 1.5 mm, 2.4 mm, 3.0 mm respectively for using polyethylene glycol membranes. Neither the bone height nor the thickness reached statistical significant differences between the two groups. In the other study by Buser et al., CBCT scan was obtained only once at 5 to 9 years post-loading follow-up for early implant placement with simultaneous GBR[17]. Their results showed 1.58 mm, 2.22 mm, 2.33 mm of peri-implant buccal thickness at 2 mm, 4 mm, 6 mm below implant shoulder levels respectively at the follow-up visit. In these studies [16, 17], the remaining grafted bone after healing was considered as a long-term bone gain. However, the dimensional changes following bone grafting were not evaluated due to the lack of baseline measurements after grafting procedures. Therefore, in the current literature, it is still unknown how stable the augmented bone is [18].

Regarding alveolar ridge preservation in post-extraction sockets, several controlled human studies reported less ridge alterations in grafted sockets compared to non-grafted sockets during the healing period [19, 34-38]. However, all these studies measured clinical alterations of the ridges from extraction to implant placement. Therefore, no studies have reported the radiographic changes in peri-implant buccal bone following implant placement in ridge preservation sites using CBCT images. In a recent retrospective study [32], Alexopoulou et al. used CBCT to evaluate hard tissue changes following immediate implant placement in molar sites combined with bone grafting and sealing socket abutment with 1 to 5 years follow-up, horizontal bone remodeling was not significant in any of the measured areas except in the most cervical level, where a mean bone remodeling of 0.73 mm was found and the proximal and buccal vertical bone changes were not significant. [32]

Horizontal and vertical changes in peri-implant buccal bone following implant placement in clinical and histologic studies

Dimensional changes of peri-implant buccal bone have also been reported in clinical studies [3, 21, 22]. In a prospective clinical study by Spray et al., the mean buccal bone horizontal resorption was 0.7 mm for integrated implants in native bone condition during submerged healing period of three to four months in the mandible and six to eight months in the maxilla. Bone quality type 4 had the least buccal bone resorption of 0.5 mm. While bone resorption was similar for both Hydroxyapatite (HA)-coated and non–HA-coated implants [21].

Also, in a 1-year prospective study by Takuma et al. showed buccal bone horizontal resorption around single-stage screw-type implants placed in the posterior native bone condition from implant placement to 6 months and 1 year after surgery [3]. The lateral contour of the buccal bone and mucosa was horizontally measured at five vertical heights at 1 mm intervals (+1 to –3 mm from the implant platform) using custom-designed instruments. Bone resorption on the proximal sides was assessed on periapical radiographs using the paralleling technique. The results showed that thicker bone (> 2 mm thick) tended to exhibit horizontal resorption during the first 6 months after surgery. Overall buccal horizontal bone resorption in the first year after implant placement was slightly greater in implants placed in the maxilla (mean: 0.69 mm) than in the mandible (mean: 0.49 mm). Mucosal recession was also measured on plaster casts of the dentition. The result indicated that there was no obvious correlation between buccal bone resorption and mucosal recession [3]. In a 12-month post-loading follow-up study with 47 implants, Merheb et al. clinically measured buccal bone thickness with implant placed in native bone condition with a specifically designed device, which allows buccal bone thickness measurements without the elevation of a muco-periosteal flap. The results reported that mean reduction in buccal bone thickness was 0.26, 0.36, 0.35 and 0.27 mm at the shoulder and 2, 4 and 6 mm apical to the implant platform at 12-month follow-up [22].

In a histologic study in 12 dogs by Qahash et al., bilateral, critical-size, supraalveolar, peri-implant defects were created with 10 mm titanium implants placed 5 mm deep into extraction sites, leaving 5 mm in a supra-alveolar position to investigate healing dynamics at buccal peri- implant sites in relation to the dimensions of the alveolar ridge. Vertical bone resorption was measured as the distance between the created implant reference notch and the residual buccal bone along the implant. Overall, vertical buccal bone resorption was frequently observed following implant placement (88.2% in SG-stained and 63.9% in fluorochrome-labeled specimens). The mean vertical buccal bone resorption was 0.55 mm in SG-stained and 1.26 mm in fluorochrome-labeled specimens. The results also showed that mean buccal resorption was significantly greater when the initial width was less than 2 mm [23].

Volumetric analysis of overall peri-implant tissue contour

With the advance of technology, there are new and non-invasive methods being developed for volumetric measurement of the overall peri-implant tissue contour including alveolar bone and soft tissue after implant placement. A 1-year prospective cohort study by Schneider et al. investigated the stability of anterior maxillary peri-implant tissue at different time points. Conventional impression was taken before (t1), after implant placement with simultaneous GBR with non-resorbable membrane (t2), after membrane removal and soft tissue augmentation (t3), immediately after crown placement (t4) and at 1-year post-loading (t5). The cast models were digitally scanned and superimposed allowing qualitative and quantitative analysis of alterations of the buccal peri-implant tissue. The results showed augmented tissue volume remained stable to a high degree within 1 year after crown insertion with a mild mean horizontal resorption of 0.04 mm. A mean gingival recession of 0.22 mm was recorded over the observation period. Interestingly, the pattern of gain or loss was not homogenous within the area. A decrease in volume was observed close to the peri-implant mucosal margin and an increase in volume in the more apical part of the area measured [24].

Another recent 1-year prospective study by Tian et al. used intraoral scanning system to measure the buccal soft tissue contour dynamics following maxillary anterior single immediate implants and immediate provisionalization. The per-implant tissue was assessed pre-op, post-op 3, 6, 12 months and the precise 3D configuration of the altered volume was calculated and reconstructed for visual analysis. The results showed a mean change in thickness of 0.62 mm that occurred mainly in the first 3 months and tended to be relatively stable after 6 months. The mid-facial recession at 3, 6, and 12 months was 0.05 mm, 0.03 mm, and 0.24 mm respectively [25].

The limitation of these volumetric analysis studies [24, 25] of overall peri-implant tissue contour was that they didn't differentiate bone and soft tissue. Therefore, the changes and relationship of bone and soft tissue cannot be compared separately. And there is no current study using volumetric analysis to compare the stability of alveolar ridge and soft tissue after implant placement in different bone conditions (native bone, after ridge preservation, or after staged approached GBR).

Influence of peri-implant buccal bone on peri-implant mucosal recession

Dimensional changes in peri-implant buccal bone following implant placement appear to induce mucosal recession, which can compromise esthetic outcomes [19]. Therefore, understanding the biological process of dimensional changes of peri-implant buccal bone and soft tissue following implant placement is a key for achieving a long-term esthetic success. Several authors [17, 20, 21] suggested a minimal thickness of 1.5 to 2 mm of buccal bone around implants based on biological concepts of bone remodeling in their clinical guidelines to prevent excessive marginal resorption. Spray et al. suggested that with the facial bone thickness less than 1.7 mm, crestal bone resorption around implant was more likely to occur [21]. However, the critical thickness is not supported by scientific evidence and the influence of the dimensions of peri-implant buccal bone on esthetic outcomes is still unknown [29]. Therefore, when implants are placed without thread exposure in either grafted or native bone, the clinical decision of whether or not to perform bone grafting to obtain a certain thickness is based on the surgeon's personal judgement.

In addition to the influence of peri-implant buccal bone thickness on the soft-tissue contour, a few studies [40, 41, 42] showed the impact of the soft tissue thickness on the crestal bone loss associated with establishment of biologic width naturally occurred after implant placement. Berglundh and Lindhe reported the length of the junctional epithelium was 2.0~2.1 mm around implant and the height of the suprabony connective tissue was 1.3 to 1.8 mm [40]. And when the soft tissue thickness was thin (≤2 mm), crestal bone resorption was observed consistently, which implies that a certain minimum width of the peri-implant mucosa may be required, and that bone resorption may take place to allow a stable soft tissue attachment to form.

Peri-implant soft tissue contour can be improved with connective tissue graft (CTG) procedures, there are CBCT studies investigating the effect of CTG in conjunction with single immediate implant in the aesthetic zone on the change of buccal bone thickness [33]. In a 1-year randomized controlled trial by Zuiderveld et al., the average change in buccal bone thickness was significantly larger in the test group treated immediately placed and provisionalized implants with CTG (-0.84 ± 0.61 mm) than in the control group without CTG (-0.46 ± 0.54 mm) and average loss of marginal bone was 0.05 ± 0.33 mm and 0.01 ± 0.38 mm, respectively. The application of CTG is accompanied with more loss of buccal bone thickness, but at the same time better maintains the mid-buccal mucosal level. [33]

To date, no published studies have compared the stability of peri-implant buccal bone between grafted and non-grafted native bone after loading. Therefore, the aim of the present study is to evaluate the dimensional changes in peri-implant buccal bone and soft tissue in grafted and native bone 1-year after implant placement. The primary objective of this study is to compare the stability of peri-implant buccal bone and soft tissue between grafted and native bone between implant placement and 1-year follow-up period. For grafted bone, two common conditions—sites previously treated with 1) ridge preservation and 2) ridge augmentation—will be included. The secondary objective of this study is to assess the influence of peri-implant buccal bone thickness on the stability of peri-implant buccal bone and soft tissue.

Aim and Hypothesis

The primary objective of this prospective clinical study was to compare the stability of peri-implant buccal bone (Aim 1) and soft tissue (Aim 2) between grafted and native bone (also known as pristine bone) in patients who require dental implants in an edentulous space. The dimensional changes of peri-implant bone and soft tissue were evaluated one year after implant placement. We analyzed dimensional changes in three different healing conditions—1) native bone, 2) previously grafted sockets, and 3) previously augmented alveolar ridges. The stability of peri-implant buccal bone in the primary objective is defined as dimensional stability. Secondarily, the influence of buccal bone thickness on the stability of peri-implant buccal bone and soft tissue were assessed (Aim 3).

In Aim 1 and 3, the changes during 1-year follow-up period following implant placement were evaluated by radiographic measurement in millimeters using cone-beam computed tomography (CBCT) scan. In Aim 2, the peri-implant buccal mucosal recession was measured with periodontal probe clinically at the 1-year follow-up visit.

Aim 1: Compare vertical and horizontal dimensional changes of peri-implant buccal bone following implant placement in three groups after a 1-year follow-up period by radiographic measurements. We hypothesized that the relative magnitude of vertical and horizontal bone resorption would be augmented ridges > grafted sockets > native bone.

Aim 2: Compare the extent of peri-implant buccal mucosal recession in three groups at 1-year follow-up. The gingival recession depth (facial mucosal recession) was measured in millimeters at 1-year follow-up. We hypothesized that the relative extent of peri-implant facial mucosal recession would be augmented ridges > grafted sockets > native bone.

Aim 3: Investigate the influence of buccal bone thickness on peri-implant vertical bone resorption and buccal mucosal recession in three groups at 1-year follow-up. We hypothesized that the buccal bone thickness would be inversely associated with both vertical bone loss and buccal mucosal recession.

Exploratory variables:

Additionally, as exploratory variables, this study assessed the patient-reported outcome measures (PROMs) including the oral health-related quality of life (OHRQoL) and patient assessment of esthetics in three groups at 1-year follow-up. The Oral Health Impact Profile-14 (OHIP-14) patient questionnaire was used to assess the OHRQoL using a Likert-like scale (from 1 to 5) before implant surgery and at 1-year follow-up. Patient assessment of esthetics was evaluated by the visual analog scale (VAS: 0-10) at 1-year follow-up [26, 28].

- We hypothesized that the scores of the OHIP-14 and the VAS would be augmented ridges < grafted sockets < native bone.
- We hypothesized that the scores of OHIP-14 would be higher at 1-year follow-up than pre-implant stage.

Research Design

The proposed study design is a single-center, prospective clinical and radiographic study to compare the stability of peri-implant buccal bone and soft tissue between grafted bone and non-grafted native bone following dental implant placement. The three different healing conditions—1) native bone, 2) previously grafted sockets, and 3) previously augmented alveolar ridges —were compared. (***Figure. a)***

Materials and Methods

This study was a single-blinded study where examiners were blinded upon data collection. A clinical examiner was blinded by not being informed of the treatment allocation; i.e. will not be informed what procedure was previously performed in order to minimize the risk of bias. All treatment procedures were completed prior to this study and are as follows: 1) native bone (>4 months of healing), 2) grafted sockets by ridge preservation technique (>4 months of healing), and 3) augmented ridge by GBR technique (>6 months of healing). (***Figure. a)***

Subject Characteristics

Subjects referred to the postgraduate clinic in the Department of Periodontology at Tufts University School of Dental Medicine (TUSDM), who need of one or two implants replacing teeth in a partially edentulous space in the maxilla or mandible were included in the study.

1) Inclusion Criteria

All subjects were required to meet the following inclusion criteria.

a. Healthy subjects without uncontrolled systemic disease or conditions that might interfere with hard and soft tissue healing such as bone metabolic disease (e.g., Paget's disease, osteoporosis, osteomalacia), uncontrolled diabetes, subject currently taking steroid medication, history of oral bisphosphonate intake greater than 3 years or any IV administration, and radiation therapy and/or chemotherapy.

b. Non-smokers or former smokers who quit smoking for at least 1 year before visit 1.

c. If the subject had a partial edentulous space planned for multiple implants, one implant site adjacent to natural tooth was included in the study for study measurements. If there were two sites adjacent to natural teeth in a partial edentulous space, the site to be included in the study was randomly selected using a computerized randomization scheme generated in R (version 3.1.2).

2) Exclusion Criteria

The subjects were not admitted in the study if any of the following exclusion criteria was met:

a. Subjects who had an infectious disease (self-reported - HIV, tuberculosis, hepatitis B or hepatitis C)

b. Known allergies to metal (due to the metal measuring device)

c. Subjects who had compromised healing potential:

- Bone metabolic disease (e.g. Paget's disease, osteoporosis, osteomalacia)

- Uncontrolled diabetes: HbA1c >=7, values measured within six months

- Subject currently taking steroid medication (not including inhaled steroids)

- History of oral bisphosphonate intake greater than 3 years or any IV administration

- Radiation therapy and/or chemotherapy for head and neck cancer

d. Pregnant or lactating subjects (self-reported)

e. Sites of previously failed implants or presence of surgical scar tissue from previous surgical procedure
f. Sites that required additional bone grafting at implant placement
g. Pathology presented within the alveolar ridge, in which study procedure considered in the current study, determined clinically or radiographically
h. Current smokers and former smoker who quit less than 1 year ago
i. Presence of pre-existing crowns that had a metal component (e.g. all-metal and porcelain-fused-to-metal crowns) adjacent to the partial edentulous alveolar ridge, in which study procedure is considered in the current study

Study timeline (*Table 1*)

Visit 1: Screening

Informed consent, demographic information and medical history were obtained. The pre-operative anatomy of the alveolar ridge was evaluated on the pre-existing radiographs. Eligibility and subject withdrawal criteria were reviewed to ensure the subject was qualified for the study.

Visit 2: Implant Placement Surgery

1) Patient questionnaire (Oral Health Impact Profile-14: OHIP-14)

   OHIP-14 questionnaire [17] was used to assess the oral health-related quality of life (OHRQoL) before implant surgery (***Table 2***). The questionnaire comprises 14 items divided into seven different domains: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. The questions will be answered using the Likert scale with a range of 1 (very often) to 5 (never).

2) Clinical parameter measurement

The following clinical parameters were recorded before implant placement

a. Width of the keratinized mucosa (wKM) at the mid-buccal aspect of the implant site was measured with a UNC15 periodontal probe (Hu-Friedy®, Chicago, IL, USA).
b. Soft tissue thickness (ST) over the implant site was measured using a UNC15 periodontal probe and an endodontic stopper (Hu-Friedy, Chicago, IL, USA). The distance (mm) between the endodontic stopper and the tip of the periodontal probe will be measured with an electronic digital caliper (Salvin® Dental Specialties, Charlotte, NC, USA).

3) Surgical procedures

Prior to surgery, the subjects were asked to rinse with a 0.12% chlorhexidine gluconate solution for 1 minute. Following administration of local anesthesia, incisions were made and mucoperiosteal flaps were elevated. A bone-level tapered moderately rough anodized titanium implant with an internal conical connection with built-in platform shifting (NobelReplace® Conical Conection, Nobel Biocare®, Gothenburg, Sweden) was placed. During implant placement surgery, radiographs of the implant were obtained to confirm implant angulation and safe distance to adjacent anatomical structures. Buccal and palatal/lingual flaps were repositioned and sutured.

4) Dental cone-beam computed tomography (CBCT) and radiographic evaluation

Imaging of the surgical sites was performed with iCAT FLX (Classic Imaging Sciences International, Hatfield, PA, USA) CBCT device which is a 3-dimensonal imaging technique utilizing x-rays. Small volume feature (voxel size: 0.30 mm, kVp: 120, mAs: 5, 61μSv, field of view [FOV]: 16 × 6 mm [1 jaw]) was used to minimize radiation. CBCT images were acquired with iCAT® (Classic Imaging Sciences International, Hatfield, PA, USA) immediately after implant surgery or within 2 weeks post-operatively. To improve the visualization of the peri-implant soft tissues within the CBCT, a plastic self-retractor (PhotoMed®, Van Nuys, CA, USA) was applied on the subject to separate the cheek from the gum for research.[22]

For the radiographic measurements, Invivo™ 6 3D imaging software (Anatomage, San Jose, California, USA) was used. Bucco-oral cross-sectional images were used for the following measurements at the mid-buccal aspect of each implant. All radiographic measurements were performed by one single blinded and calibrated examiner. The following radiographic parameters were recorded.

a) Thickness of peri-implant buccal bone: The horizontal thickness (mm) of the buccal bone was measured at 4 apicocoronal levels corresponding to the implant shoulder (L0) and 2 mm (L2), 4 mm (L4) and 6 mm (L6) apical to the shoulder ***(Figure. f)***
b) Vertical distance (mm) from the implant shoulder to the most coronal

peri-implant buccal bone level ***(Figure. g)***

Visit 3 (Stage II Implant Surgery): 3-4 months ± 14 days after Visit 2

All implants underwent implant uncovering procedures 3-4 months after implant placement. After adequate soft tissue healing (>2weeks), the prosthetic procedures were performed for the implant restorations.

Visit 4 (1 year post implant surgery follow-up): 1 year ± 3 months after Visit 3

1) Patient questionnaires (OHIP-14) and esthetic satisfactory scores

   For the Oral Health Impact Profile-14 (OHIP-14) ***(Table 2)***, 14 questions [17] will be answered using the Likert scale (1-5) as described at Visit 2. Patient satisfaction concerning soft tissue esthetics will be evaluated using the visual analog scale (VAS) ***(Figure. d).*** The following question was asked "Are you satisfied with the esthetic appearance of the soft tissue around your implant-supported crown restoration?" [23]. The subject was asked to rate their level of satisfaction with a range of 0 (not at all satisfied) to 10 (very satisfied).

2) Peri-implant soft tissues were clinically evaluated, and the following parameter were assessed.

   a. Probing depths and presence of bleeding on probing were accessed using a periodontal probe at implant and adjacent sites (6 sites: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual-disto-lingual)
   b. Peri-implant buccal mucosal recession depth: The distance (mm) from the

mucosal margin to the implant crown margin at the mid-buccal aspect of the implant was measured using a periodontal probe.

c. Width of peri-implant keratinized mucosa was measured using a periodontal probe over mid-buccal side of the implant

3) The second dental cone-beam computed tomography (CBCT) and radiographic evaluation was obtained after one year of implant loading with the same methods as described as in Visit 2. ***(Figure. f, g)***

CBCT measurement and analysis

Invivo™ 6 3D imaging software was used to measure the peri-implant buccal bone thickness and vertical changes from CBCT images acquired with iCAT® from Visit 2 (immediately after implant placement or within 2 weeks post-operatively) and Visit 4 (1 year after implant loading) ***(Figure. c, f).*** To minimize metal artifacts, implant planning feature on Invivo™ 6 3D imaging software was used to superimpose the NobelReplace® Conical Connection implant outline with the corresponding diameter and length onto the CBCT images where implants actually presented. After determining the implant shoulder and long axis , the distance from the most buccal surface of peri-implant bone to the implant long axis was measured. The horizontal peri-implant buccal bone thickness was then calculated after subtracting the value of the diameters of the tapered implant at implant shoulder level (L0), and 2 mm (L2), 4 mm (L4), 6 mm (L6) apical to the implant shoulder levels. The diameter of implant at each apico-coronal level was measured from ImageJ® Java-based image processing program (National Institutes of Health, Madison, WI, USA) ***(Table 3).*** Each radiographic parameter from each CBCT image was measured 3 times for average and intrapersonal calibration. The horizonal and vertical changes between Visit 2 and Visit 4 were measured to compare among different treatment groups.

Statistical Analysis

A sample size calculation was performed using nQuery Advisor (version 7.0) with the following assumptions: a type I error of 0.017; a type II error of 20%; a mean bone height of 2.18 (SD = 0.72) for the GBR group; a mean bone height of 0.21 (SD = 0.28) for the pristine bone group [19]; an estimated mean height of 1.2 (SD = 0.5) for the ridge preservation group. A minimum sample size was determined to be 11 subjects per group for a total of 33 subjects. To accommodate 20% dropout rate, the sample size was increased to 14 subjects per group for 42 subjects.

Descriptive statistics (means and standard deviations for continuous items, counts and percentages for categorical variables) were calculated. Independent-t test was used to compare differences in vertical and horizontal dimension changes, peri-implant mucosal recession, and patient-reported outcomes between the two groups; if the assumption of normality was unmet, the Mann-Whitney U test would be used instead. Normality of the data were assessed graphically with histograms. The relationship between initial buccal bone thickness and vertical dimension and peri-implant mucosal recession were investigated with Pearson correlation. The assumptions of absence of outliers and linearity were checked graphically with scatterplot, and if the assumption was unmet, the Spearman correlation would be used instead. All p-values less than 0.05 were considered statistically significant. The IBM SPSS Statistics software was used in the analysis (version 27.0). Intrapersonal calibration was assessed with intraclass correlation coefficient calculated by the statistical software Stata (version 13.1).

Results

Subject characteristics

Of 35 screened subjects, 30 patients were enrolled in the study. 14 subjects completed 1-year CBCT follow-up by April, 2021. One patient (TL024) dropped out after Visit 2 due to infection and early implant failure. Another patient (XH027) was excluded due to late implant failure with biological and biomechanical complication with hyperocclusion. Flow chart of subjects for the study procedures, enrollment, follow-up and analysis was demonstrated in ***Figure. b.*** Among 14 subjects, 6 were male and 8 were female, with age ranged from 26 to 82 years old (mean: 55.57, SD: 15.35) (Table 4).

There was only one subject completed 1-year follow-up in Group 3 (GBR). Due to the insufficient number of patients. it was not possible to conduct statistical analysis including Group 3.

Therefore, Mann-Whitney U test was used to compare differences in vertical and horizontal dimension changes between Group 1 and Group 2. Total 12 subjects were included in the statistical analysis, with 6 subjects in Group 1 (native bone group) and 6 subjects in Group 2 (ridge preservation group). Subject characteristics were reported in ***Table. 4***.

Intrapersonal calibration and implant diameters measurement

In the CBCT images acquired from Visit 2 (V2) and Visit 4 (V4), each radiographic measurement, including horizontal measurement (L0, L2, L4, L6) and vertical distance from implant shoulder to the most coronal peri-implant buccal bone (V) were measured 3 times for mean and intrapersonal calibration to access horizontal and vertical changes in peri-implant buccal bone between two visits by single examiner. Intrapersonal calibration showed excellent reliability at each horizontal level (***Table 5-1)*** and with an overall 0.997 intraclass correlation coefficient which indicated excellent reliability. For the vertical measurement, intraclass correlation coefficients also presented 0.999 and 0.988 respectively at Visit 2 and Visit 4, with an overall value of 0.990, which indicated excellent reliability (***Table 5-2).***

As for the tapered designed nature of NobelReplace® Conical Conection implant, the implant diameter at each corono-apical level was different. Thus, ImageJ® Java-based image processing program was used to measure for those implant fixtures included in the current study (***Table 3).*** The intrapersonal calibration at each corono-apical level (L0, L2, L4, L6) from implants with different diameter and length also showed overall values of 0.999 intraclass correlation coefficients indicating excellent reliability (***Table 5-3).***

Horizontal changes in peri-implant buccal bone from CBCT measurement

The changes in CBCT measurements of peri-implant buccal bone thickness between Visit 2 and Visit 4 were reported in ***Table 6-1***. The majority of the subjects had less than 2 mm initial peri-implant buccal bone thickness at implant shoulder level (L0) at Visit 2. Overall, the mean horizontal change after 1 year of implant loading presented was -0.122 ± 0.502 mm at implant shoulder (L0), -0.340 ± 0.681mm at 2 mm apical to implant shoulder (L2), -0.476 ± 0.847 mm at 4 mm apical to implant shoulder (L4), and -0.230 ± 0.766 mm at

6 mm apical to implant shoulder (L6).

Only at the implant shoulder level (L0) in Group 1 (native bone), there was mild horizontal bone gain of 0.054 ± 0.394 mm (mean ± SD). Otherwise, horizontal resorption was observed with -0.152 ± 0.563 mm at L2, -0.330 ± 1.076 mm at L4, and -0.313 ± 0.947 mm at L6. In Group 2 (ridge preservation), there was more horizontal resorption at all apicocoronal levels: -0.297 ± 0.571 mm at L0, -0.528 ± 0.787mm at L2, -0.613 ± 0.787 mm at L4, and -0.147 ± 0.616 mm at L6 **(*Table 6-2*).** At L2, the horizontal resorption was about 3.47 times more in Group 2 (ridge preservation) compared to Group 1 (native bone) and 1.85 times more at 4 mm below implant shoulder level (L4). But at L6, horizontal resorption was greater in Group 1.

Mann-Whitney U Test was used to compare the medians of buccal bone thickness changes at each level between Group 1 and Group 2. There was a trend that Group 2 had more bone resorption at L0, L2, L4 levels than Group 1, but there were no statistically significant differences. (p-value=0.522 (L0), 0.631 (L2), 0.262 (L4) $\geq$ 0.05) **(*Table 6-2*)**

Vertical changes in peri-implant buccal bone from CBCT measurement

The vertical peri-implant buccal bone changes ***(Figure. g)*** after 1 year of implant loading ranged from -1.34 mm (resorption) to 0.7 mm (gain) **(*Table 7-1*)**, with overall resorption of -0.472 ± 0.609 mm. Interestingly, in Group 1 (native bone), -0.663 ± 0.221 mm was observed which was greater than -0.280 ± 0.660mm in Group 2 (ridge preservation). The results were opposite from our initial hypothesis. The data were not normally distributed and therefore, Mann-Whitney U test were used to compare between the two groups instead of independent-t test. Although there was more vertical loss observed in Group 1, the difference was not statistically significant (p-value=0.378>0.05) (***Table 7-2***)

Clinical measurements and peri-implant mucosal recession

Among 14 subjects who completed 1-year follow-up, 13 patients showed no buccal peri-implant mucosal recession. Only one subject (JY017) ***(Figure. e-1)*** presented with 0.3 mm buccal peri-implant mucosal recession. Two subjects (LP003, CM025) showed 0.5 mm lingual peri-implant mucosal recession with no buccal recession. Regarding the width of keratinized mucosa, 11 subjects showed enough KT (≧2 mm) around implant and only 1 subject (JY017) showed 1.5 mm keratinized peri-implant mucosa which was the same patient who developed peri-implant mucosal recession. Two subjects presented without keratinized peri-implant mucosa while peri-implant mucosal tissue was healthy without bleeding on probing and patients presented with good oral hygiene. All 14 subjects showed ≦3 mm probing depth at mid-buccal site of the implants ***(Figure. e).*** As the data were not normally distributed, Mann-Whitney U test was used to compare buccal peri-implant mucosal recession between groups instead of independent-t test. The results showed no statistically significant difference among groups (p-value=0.317>0.05).

Patient-reported outcome measures (PROMs)

The oral health-related quality of life (OHRQoL) and patient assessment of esthetics was evaluated in three groups at 1-year follow-up. The Oral Health Impact Profile-14 (OHIP-14) patient questionnaires were distributed at Visit 2 before implant placement and at Visit 4 after 1-year implant loading. Most of the subjects showed similar or improved OHIP-14 scores after 1-year (Visit 4), except 1 subject (XH027) showed lower OHIP-14 scores whose implant failed and was removed and it was not included in the statistical analysis. Patient assessment of esthetics was evaluated by the visual analog scale (VAS: 0-10) at 1-year follow-up and all of them were very satisfied with the crown restoration and soft tissue profile around the implant with VAS ≧8 ***(Table. 8-1).*** The data were not normally distributed, and Mann-Whitney U test was used instead of independent-t test. There were no statistically significances between groups for either OHIP-14 score change (p-value= 0.810>0.05) nor esthetic VAS scores (p-value=0.789>0.05). ***(Table 8-2)***

Influence of buccal bone thickness on peri-implant vertical bone resorption and buccal mucosal recession

Spearman correlation was used to investigate the influence of baseline peri-implant buccal bone thickness at each level at Visit 2 (V2-L0, V2-L4, V2-L4, V2-L6) on peri-implant vertical bone resorption (V-change) and on buccal mucosal recession (Rec) after 1-year follow-up.-The initial buccal bone thickness was not associated with peri-implant vertical bone resorption (p-value=0.073(V2-L0), 0.390(V2-L2), 0.194(V2-L4), 0.341(V2-L6)) nor buccal mucosal recession (p-value=0.893(V2-L0), 0.334 (V2-L2), 0.893(V2-L4), 0.893(V2-L6)) with all the correlation coefficient p-values > 0.05 (***Table 9).***

Discussion

To date, no published studies have compared the stability of peri-implant buccal bone between grafted and non-grafted native bone after implant loading. Therefore, this is the first study comparing the horizontal and vertical l changes of peri-implant buccal bone between different clinical conditions of implant sites, including 1) native bone and grafted bone where 2) ridge preservation or 3) ridge augmentation by GBR was previously performed before implant placement. We hypothesized that grafted bone would have more buccal bone resorption compared to native bone condition over time. Initially, a 3-arm study was planned. However, due to the difficulties in recruiting subjects in GBR group during the COVID-19 pandemic, the analysis was only performed between Group 1(native bone) and Group 2 (ridge preservation) for horizontal and vertical dimensional changes of peri-implant buccal bone in CBCT. Although the results didn’t reach statistical significance between the two groups, there was a trend observed after 1-year of implant loading that ridge preservation group had more bone resorption at implant shoulder level, and 2 mm, 4 mm apical to implant shoulder levels than the native bone group.

The results of the current study showed that, the mean gain of peri-implant buccal bone thickness in the native bone group was 0.054 mm after 1 year of loading. The result can be compared with a CBCT study by Kaminaka et al., in which they found 0.08 mm horizontal ridge resorption for conical connection implants at the platform level after 1 year of loading [15]. At 2 mm apical to implant platform level, our study showed 0.152 mm resorption which is similar to their observation with 0.11mm resorption. They did not assess the buccal bone thickness changes more apically, while we found greater amount of resorption at 4mm (0.330mm) and 6mm (0.312mm) apical to implant shoulder levels.

However, it might be more reasonable to focus on the thickness changes at 2mm apical to implant shoulder level (L0) to access the long-term stability of the peri-implant buccal bone considering that a certain amount of bone resorption occurs at bone crest around implants as soon as the implant is in contact with the oral environment to establish biologic width [20]. The first bone-to-implant contact (BIC) is mostly observed at 1.5 to 2.0 mm below the implant shoulder according to Adell et al. [41]. This bone resorption occurs not only in a vertical but also in a horizontal direction, as pointed out by Tarnow et al, that the mean horizontal bone loss is 1.3 to 1.4 mm after implant exposure procedure [42]. Spray et al. also observed that there was clinical measurement of 0.7mm horizontal resorption at bone crest between implant placement and uncovering and an initial peri-implant buccal bone thickness of 1.8mm or more was related with less resorption or stable peri-implant buccal bone with no changes [21].

In the grafted bone condition, no other CBCT studies have accessed the peri-implant buccal bone thickness after loading of implants placed in ridge preservation sites. In our study, the results showed 0.297mm, 0.528mm, 0.613mm, 0.147mm of horizontal resorption at implant shoulder, and 2mm, 4mm, 6mm apical to implant shoulder levels in the ridge preservation group.

There are two CBCT studies with long-term follow-up investigating the amount of buccal bone thickness around implants placed with simultaneous ridge augmentation using GBR technique [16, 17]. Buser et al. showed that the mean peri-implant buccal bone thickness of augmented ridge after 5 to 9 years of loading was 1.58mm, 2.22mm, 2.33mm at 2mm, 4mm, 6mm below implant shoulder levels respectively. However, this study did not investigate the horizontal changes due to the lack of baseline peri-implant buccal thickness data at implant placement. Jung's study also presented similar results with Buser's study in which they evaluated the thickness of peri-implant augmented buccal bone after 5 years of loading, and the simultaneous GBR was performed with implant placement and the buccal defects were augmented with xenograft and covered with a porcine collagen membrane (control) or with a PEG membrane (test). The thickness of the buccal regenerated bone at 1mm below implant shoulder level after 5 years of loading revealed 2.0mm (control) and 1.5mm (test). At 3 mm apical to implant shoulder, the thickness amounted 2.7mm (control) and 2.4mm (test). At 5 mm below the implant shoulder, it demonstrated values of 3.1mm (control) and 3.0mm (test). And based on their results, no statistically significant differences were observed between the two groups, which indicated sufficient and stable peri-implant augmented buccal bone after long-term loading regardless of different types of membrane were used. In the current study our aim was to compare horizontal and vertical peri-implant bone changes in different bone conditions from the time of implant placement (baseline). For the grafted bone condition, previously augmented ridge with GBR (staged approach) were included (Group 3: GBR group), Therefore, our results cannot be compared with previous studies with simultaneous GBR approach [16, 17]. Additionally, only one subject completed 1-year follow-up after implant placement in GBR group [16].

The results showed that the mean augmented buccal bone thickness in ridge preservation group after 1 year of loading were 0.663mm (V4-L0), 2.354mm (V4-L2), 3.511mm (V4-L4), 4.555mm (V4-L6) at implant shoulder, and 2mm, 4mm, 6mm apical to implant shoulder levels, with 0.297mm, 0.528mm, 0.613mm, 0.147mm horizontal resorption at each level between implant placement and 1-year follow-up. In comparison with these two studies (Buser [17] and Jung [16]), more horizontal resorption is expected in our study after 1 year of loading based on the mean buccal bone thickness we observed from previous studies with longer follow-up period. Since the peri-implant buccal bone thickness after 5 or more years of loading in their results was thinner than those we had in our 1-year results.

The wound healing pattern and biology of grafted bone conditions may be different between ridges treated with ridge preservation and ridge augmentation with GBR. We should take into consideration that the most buccal bone characteristic differences between these different scenarios. In ridge preservation condition, after extraction, there was still certain amount of pristine bone wall at the most buccal surface and the allograft bone materials were mainly in the extraction socket, and with the 4 to 6 months of healing time allowed bone to be mature for implant placement. While in simultaneous GBR or staged-approached GBR conditions, the most buccal surfaces are augmented and composed with mainly allograft or xenograft bone materials. Thus, the amount of new bone formation, the percentage of remaining bone graft materials, and buccal peri-implant dimensional stability after implant loading is still concerned over time compared to native bone. Although our current statistical analysis didn’t show statistically significant differences between native bone and ridge preservation group, there was a trend of more resorption in ridge preservation group. Thus, clinicians might still consider extra buccal contour grafting when baseline peri-implant buccal bone was thin, due to more horizontal resorption might be expected along the way after implant loading and long-term follow-up.

In our study, there was no statistically significant evidence that the vertical changes of peri-implant buccal bone were different between grafted or non-grafted sites, nor associated with the initial peri-implant buccal bone thickness. The vertical change of peri-implant buccal bone can only be measured through three-dimensional CBCT images as discussed in our study methods. However, it was rarely reported or discussed in the literatures and most of the other studies investigated the peri-implant crestal bone changes at mesial or distal aspects of implant using periapical films.

In native bone condition, only Kaminaka et al. used CBCT to investigate the vertical change measured to the most coronal level of peri-implant buccal bone and reported -1.85mm for implant with external connection, -1.00mm with internal connection and -0.21mm for conical connection at 1-year follow-up [15]. In our study, the same reference points were used and -0.663mm was observed in native bone condition with conical connection implants, which was greater than their result. In grafted bone condition, two CBCT studies [15, 16] measured peri-implant buccal bone vertical loss, but the measurement was based on the distance from the implant shoulder to the first bone-to-implant contact (BIC), which was the inner surface of the peri-implant buccal bone. Jung et al reported 0.44~0.95mm vertical change in implant placement with simultaneous GBR after 5 years of loading [16]. Benic et al. reported 2.9mm vertical loss in immediate implant placement with simultaneous GBR after 7 years of loading [43].

Regarding the peri-implant mucosal recession, 13 out of 14 subjects in the current study showed no buccal peri-implant mucosal recession. Only one subject (JY017) ***(Figure. e-1)*** presented with 0.3mm peri-implant mucosal recession. Interestingly, this subject presented with limited amount of keratinized mucosa (1.5mm) around implant, which was less than the rest of patients with ≧2mm. According to the consensus of 2017 AAP workshop [44], the need for a minimum amount of keratinized mucosa to maintain peri-implant tissue health is still a controversial issue. Several studies [44] failed to associate the lack of a minimum amount of keratinized mucosa with mucosal inflammation, while other studies suggested that plaque build-up and marginal inflammation were more frequent at implant sites with <2mm of keratinized mucosa. In our study population, all patients presented healthy peri-implant tissue with ≦3mm PD at mid-buccal site of implants without bleeding on probing. Although we expected thin initial peri-implant buccal thickness or the vertical bone loss would have more impact on peri-implant mucosal recession, this subject (JY017) did not have these features, but was the only one with recession presented the greatest horizontal loss at L4 and L6 among all the subjects instead of L0 and L2.

For the patient reported outcome measures, we hypothesized that the scores of the OHIP-14 and the esthetic VAS obtained from the questionnaires would be greater in native bone compared to grafted bone but they were not significantly different between groups. Although the increased number of visits are required with ridge preservation or GBR patients and longer overall treatment time, most of the subjects were satisfied with the implant function and prostheses and soft tissue profiles regardless which treatment modality was performed.

There are several limitations of this study. Firstly, the small sample size that completed the follow-up visit in each group prevented us from thorough statistical analysis as initially planned and the 3-arm comparison could not be performed. Secondly, with the nature of the clinical study design, the original tooth extraction site and the socket defect shape, bone grafting and membrane materials used could not be standardized in each subject among groups. Third, there are many confounding factors, such as soft tissue thickness and the corono-apical position of implant placement (supra-crestal, flush, or subcrestal), may affect the peri-implant marginal bone loss and also have influence the stability of peri-implant buccal dimensional change. Furthermore, when comparing our results with other CBCT studies, depending on CBCT machines/manufactures and image processing programs, the measurements can be different.

Future well-controlled clinical and radiographic studies with larger sample size and long-term follow-up are needed to access the peri-implant buccal bone stability and the differences between native bone and augmented bone conditions including the sites with ridge preservation, simultaneous GBR and stage-approached GBR.

Conclusion

Within the limitation of the current study, there were no statistically significant differences among groups regarding horizontal and vertical changes of peri-implant buccal bone, peri-implant mucosal recession, and patient reported outcomes. Future well-controlled studies with larger sample size and long-term follow-up are needed.

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APPENDICES

Appendix A: Tables

***Table 1**. Study Timeline*

	Visit 1 Screening	Visit 2 Implant surgery	Visit 3 2nd stage surgery	Visit 4 1-year follow-up
Informed Consent Form	X			
Demographics	X			
Medical History	X	X	X	X
Evaluate eligibility and withdrawal criteria	X	X	X	X
Oral Mucosal Tissue Examination	X	X	X	X
Clinical measurement		X	X	X
Surgery		X	X	
CBCT		X		X
Questionnaire for OHIP-14		X		X
VAS Questionnaire				X
Adverse Event Assessment		X	X	X

***Table.* 2**. *A list of q*uestions in OHIP-14 [17] divided into the 7 domains

Domain	**Questions (answers: 1= very often, 2= fairly often, 3= occasionally, 4= hardly ever, and 5= never)**
(1) Functional limitation	1. Have you had trouble pronouncing any words because of problems with your teeth, mouth or dentures? 2. Have you felt that your sense of taste has worsened because of problems with your teeth, mouth or dentures?
(2) Physical pain	3. Have you had a painful aching in your mouth? 4. Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth or dentures?
(3) Psychological discomfort	5. Have you been self-conscious of your teeth, mouth or dentures? 6. Have you felt tense because of problems with your teeth, mouth or dentures?
(4) Physical disability	7. Has your diet been unsatisfactory because of problems with your teeth, mouth or dentures? 8. Have you had to interrupt meals because of problems with your teeth, mouth or dentures?
(5) Psychological disability	9. Have you found it difficult to relax because of problems with your teeth, mouth or dentures? 10. Have you been a bit embarrassed because of problems with your teeth, mouth or dentures?
(6) Social disability	11. Have you been a bit irritable with other people because of problems with your teeth, mouth or dentures? 12. Have you had difficulty doing your usual jobs because of problems with your teeth, mouth or dentures?
(7) Handicap	13. Have you felt that life in general was less satisfying because of problems with your teeth, mouth or dentures? 14. Have you been totally unable to function because of problems with your teeth, mouth or dentures?

Table 3. *Implant diameters at implant shoulder level, and 2mm, 4mm, 6mm apical to the implant shoulder level*

Implant Diameters	3.5 x 10mm	4.3 x 10mm	5 x 8mm	5 x 10mm	5 x 11.5mm
Implant shoulder level (L0)	3.5mm	4.3mm	5mm	5mm	5mm
2mm apical to implant shoulder level (L2)	3.332mm	4.078mm	4.53mm	4.532mm	4.532mm
4mm apical to implant shoulder level (L4)	2.979mm	3.656mm	4.054mm	4.207mm	4.192mm
6mm apical to implant shoulder level (L6)	2.773mm	3.561	3.169mm	4.085mm	4.135mm

Table 4. *Subject characteristics*

Subject	***Gender***	***Age***	***Race***	***Implant (diameter x length)***	***Group***
CL001	F	44	African American	4.3 x 10mm	2
SC002	F	40	Asian	4.3 x 10mm	1
LP003	F	56	Caucasian	4.3 x 10mm	1
AD005	M	57	Hispanic	4.3 x 10mm	1
FP006	F	69	Caucasian	5 x 10mm	2
PK008	M	82	Caucasian	5 x 11.5mm	1
JS009	M	56	Caucasian	4.3 x 10mm	3
TL011	M	68	Asian	5 x 11.5mm	2
RH012	M	53	Caucasian	5 x 10mm	2
SK015	F	71	Asian	4.3 x 10mm	2
JY017	F	26	Asian	4.3 x 10mm	1
SS018	F	35	Asian	4.3 x 10mm	2
CM025	M	66	Caucasian	5 x 10mm	1
XH027	F	55	Asian	4.3 x 10mm	2

**Group 1: native bone, Group 2: ridge preservation, Group 3: GBR*

Table 5-1. *Intraclass correlation coefficient (ICC) for CBCT horizontal measurements*

Visit 2	***V2-L0***	***V2-L2***	***V2-L4***	***V2-L6***	***Combined***
ICC	0.988	0.976	0.996	0.995	0.997
Reliability	Excellent	Excellent	Excellent	Excellent	Excellent
Visit 4	***V4-L0***	***V4-L2***	***V4-L4***	***V4-L6***	***Combined***
ICC	0.990	0.990	0.993	0.996	0.997
Reliability	Excellent	Excellent	Excellent	Excellent	Excellent
Overall combined					
ICC	0.997				
Reliability	Excellent				

Table 5-2. *Intraclass correlation coefficient (ICC) for CBCT vertical measurements (V)*

Visit 2	***V2-V***
ICC	0.999
Reliability	Excellent
Visit 4	***V4-V***
ICC	0.988
Reliability	Excellent
Overall combined	
ICC	0.990
Reliability	Excellent

Table 5-3. *Intraclass correlation coefficient (ICC) of implant diameters measurement*

Implant Diameters	**3.5 x 10mm**	**4.3 x 10mm**	**5 x 8mm**	**5 x 10mm**	**5 x 11.5mm**
ICC	0.999	0.999	0.999	0.999	0.999
Reliability	Excellent	Excellent	Excellent	Excellent	Excellent
Overall combined					
ICC	0.999				
Reliability	Excellent				

**ICC values < 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values > 0.90 indicate excellent reliability*

Table 6-1. *CBCT measurements of peri-implant buccal bone thickness and changes at each level between Visit 2 (implant placement) and Visit 4 (1-year post-loading)*

Subject	***Group***	***V2-L0 (mm)***	***V4-L0 (mm)***	***Thickness Change -L0 (mm)***	***V2-L2 (mm)***	***V4-L2 (mm)***	***Thickness Change -L2 (mm)***	***V2-L4 (mm)***	***V4-L4 (mm)***	***Thickness Change -L4 (mm)***	***V2-L6 (mm)***	***V4-L6 (mm)***	***Thickness Change -L6 (mm)***
CL001	2	1.193	0.157	-1.037	2.874	2.794	-0.080	3.422	2.585	-0.837	3.016	2.330	-0.687
SC002	1	0.150	0.853	0.703	2.558	3.441	0.883	4.919	5.582	0.663	6.786	6.820	0.033
LP003	1	0.793	0.830	0.037	1.081	1.008	-0.073	1.582	1.589	0.007	2.743	2.523	-0.220
AD005	1	0.350	0.067	-0.283	2.054	1.654	-0.400	4.085	3.532	-0.553	6.390	5.436	-0.953
FP006	2	0.690	0.723	0.033	3.217	2.267	-0.950	4.993	4.223	-0.770	6.374	5.981	-0.393
PK008	1	0.827	0.520	-0.307	2.197	1.861	-0.337	3.571	3.961	0.390	5.479	6.563	1.083
TL011	2	0.047	0.023	-0.023	1.591	1.781	0.190	2.801	3.037	0.237	3.743	3.919	0.177
RH012	2	0.257	0.407	0.150	2.687	2.224	-0.463	4.150	3.877	-0.273	4.171	4.951	0.780
SK015	2	1.507	0.483	-1.023	3.051	1.151	-1.900	3.489	1.915	-1.573	3.610	2.743	-0.867
JY017	1	0.407	0.260	-0.147	1.594	0.801	-0.793	3.519	1.169	-2.350	4.463	2.753	-1.710
SS018	2	2.067	2.183	0.117	3.874	3.907	0.033	5.890	5.427	-0.463	7.301	7.408	0.107
CM025	1	0.313	0.633	0.320	1.604	1.411	-0.193	2.539	2.402	-0.137	3.596	3.486	-0.110

**V2: Visit 2, V4: Visit 4, L0: implant shoulder level, L2: 2mm below implant shoulder level, L4: 4mm below implant shoulder level, L6: 2mm below implant shoulder level*

Table 6-2. *Comparison of peri-implant buccal bone thickness changes among groups at each level at 1-year follow-up*

Level	***Group***	***N***	***Mean (mm)***	***Standard Deviation (SD) (mm)***	***P-value***
L0	1	6	0.0538	0.39409	0.522
	2	6	-0.2972	0.57094	
	Overall	12	-0.12167	0.502358	
L2	1	6	-0.1522	0.56316	0.631
	2	6	-0.5283	0.78685	
	Overall		-0.34025	0.681302	
L4	1	6	-0.3300	1.07568	0.262
	2	6	-0.6132	0.60943	
	Overall	12	-0.47158	0.846542	
L6	1	6	-0.3128	0.94653	0.631
	2	6	-0.1472	0.61633	
	Overall	12	-0.23000	0.766413	

**P-value based on Mann-Whitney U Test*

***Table 7-1**. CBCT measurements of peri-implant buccal bone vertical changes between Visit 2 (implant placement) and Visit 4 (1-year post-loading)*

Subject	***Group***	***V2-V (mm)***	***V4-V (mm)***	***Vertical Change (mm)***
CL001	2	0.48	-0.86	-1.34
SC002	1	0.00	0.00	0.00
LP003	1	0.00	-1.19	-1.19
AD005	1	0.00	-0.67	-0.67
FP006	2	-0.73	-0.73	0.00
PK008	1	0.00	-0.68	-0.68
TL011	2	-1.23	-1.53	-0.30
RH012	2	-0.70	0.00	0.70
SK015	2	0.35	0.00	-0.35
JY017	1	-0.89	-2.22	-1.33
SS018	2	0.00	-0.39	-0.39
CM025	1	-0.59	-0.71	-0.11

** V: vertical measurement from implant shoulder to most coronal buccal bone level at Visit 2 (V2) and Visit 4 (V4)*

***Table 7-2**. Comparison of peri-implant buccal bone vertical changes among groups at 1-year follow-up*

<table>
<tr><th></th><th>Group</th><th>N</th><th>Mean (mm)</th><th>Standard Deviation (SD) (mm)</th><th>P-value</th></tr>
<tr><td rowspan="3">Vertical Change</td><td>1</td><td>6</td><td>-0.663</td><td>0.542</td><td rowspan="2">0.378</td></tr>
<tr><td>2</td><td>6</td><td>-0.280</td><td>0.660</td></tr>
<tr><td>Overall</td><td>12</td><td>-0.472</td><td>0.609</td><td></td></tr>
</table>

**P-value based on Mann-Whitney U Test*

Table 8-1. Patient-reported outcome measures (PROMs)

Subject	***Gender***	***Age***	***Group***	***V2-OHIP-14 (score 14~70)***	***V4-OHIP-14 (score 14~70)***	***Esthetic VAS (score 0~10)***
CL001	F	44	2	44	68	10
SC002	F	40	1	48	69	8
LP003	F	56	1	67	70	10
AD005	M	57	1	61	70	10
FP006	F	69	2	63	68	10
PK008	M	82	1	66	65	9
JS009	M	56	3	64	70	10
TL011	M	68	2	69	70	9
RH012	M	53	2	69	69	10
SK015	F	71	2	56	70	9
JY017	F	26	1	54	69	9
SS018	F	35	2	61	58	9
CM025	M	66	1	70	70	10
XH027	F	55	2	63	37	9

**V2: Visit 2, V4: Visit 4, OHIP-14: Oral Health Impact Profile-14 (OHIP-14), VAS: visual analog scale*

Table 8-2. *Comparison of OHIP-14 score change and Esthetic VAS among groups at 1-year follow-up*

	Group	***N***	***Mean (mm)***	***Standard Deviation (SD) (mm)***	***P-value***
OHIP-14 score change	1	6	7.83	8.819	0.810
	2	6	6.83	10.265	
	Overall	12	7.33	9.139	
Esthetic VAS	1	6	9.33	.816	0.789
	2	6	9.50	.548	
	Overall	12	9.42	.669	

**P-value based on Mann-Whitney U Test*

Table 9. Correlation coefficient between of peri-implant buccal bone thickness at each level with peri-implant vertical bone resorption and buccal mucosal recession at 1-year follow-up

		V2-L0	***V2-L2***	***V2-L4***	***V2-L6***
Vertical Change (V-change)	Correlation coefficient	-0.536	0.273	0.403	0.301
	P-Value	0.073	0.390	0.194	0.341
Mucosal Recession (Rec)	Correlation coefficient	-0.044	-0.306	-0.044	0.044
	P-Value	0.893	0.334	0.893	0893

**P-value based on Spearman's Correlation test; V2: Visit 2, L0: implant shoulder level, L2: 2mm below implant shoulder level, L4: 4mm below implant shoulder level, L6: 2mm below implant shoulder level*

Appendix B: Figures

Figure. a *Illustrations of three different bone condition and treatment modalities before implant placement*

Figure. b *Flow chart of subjects for the study procedures, enrollment, follow-up and analysis*

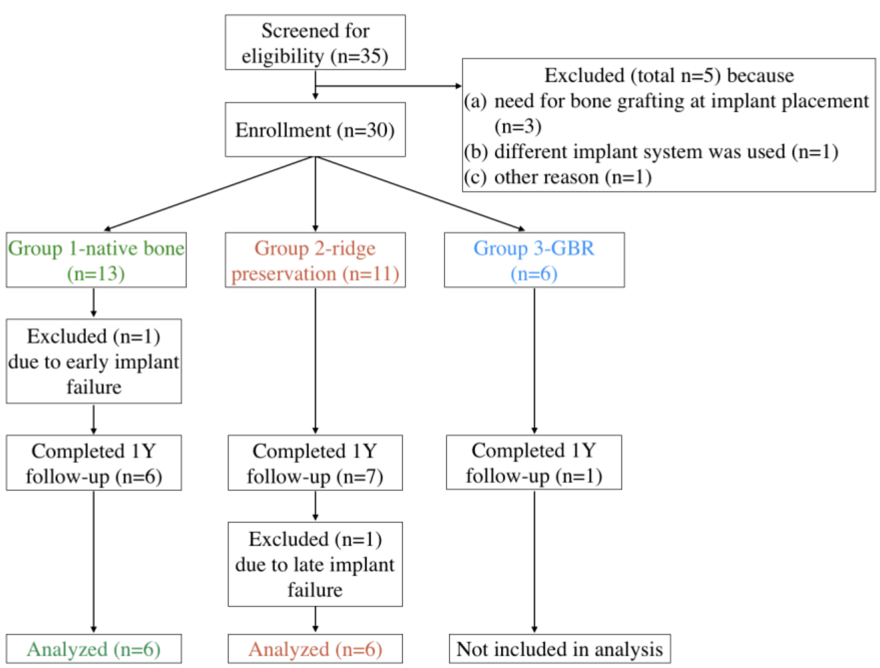
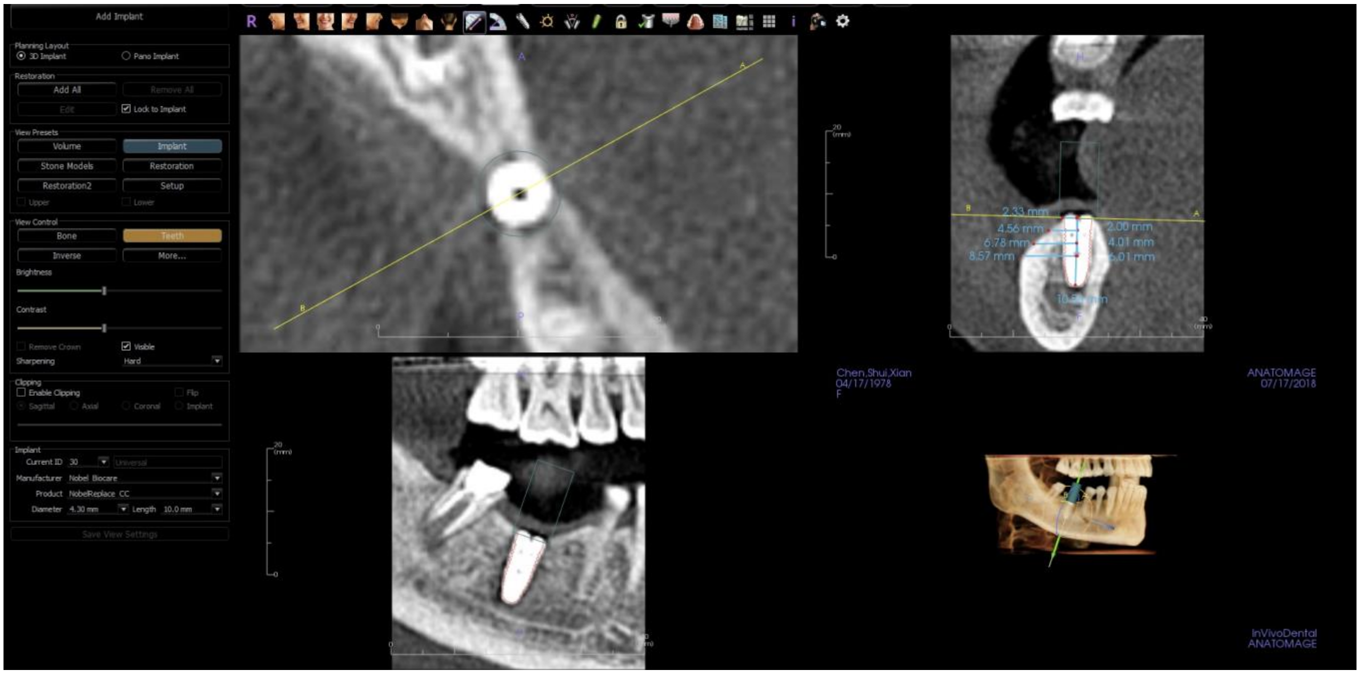


Figure. c *CBCT measurement with Invivo™ 6 3D imaging*



** Implant planning feature was used to superimpose to locate the NobelReplace® Conical Conection implant outline with the corresponding diameter and length onto the CBCT images.*

Figure. d *Visual Analogue Scale (VAS) for patient esthetic satisfaction [23]*

not at all satisfied **very satisfied**

0 1 2 3 4 5 6 7 8 9 10

Figure. e *Clinical esthetic profile and examination of peri-implant soft tissue condition at 1-year follow-up*

e-1 **Subject (JY017) showed 0.3mm buccal peri-implant mucosal recession with 0.3 mm limited keratinized peri-implant mucosa around implant #19 at 1-year follow-up*

e-2 **Subject (CM025) showed no buccal peri-implant mucosal recession with 3 mm adequate keratinized peri-implant mucosa around implant #20 at 1-year follow-up*

e-3 ** Subject (RH012) showed no buccal peri-implant mucosal recession with 2 mm adequate keratinized peri-implant mucosa around implant #30 at 1-year follow-up*

***Figure. f** Example of horizontal measurements on CBCT images;*

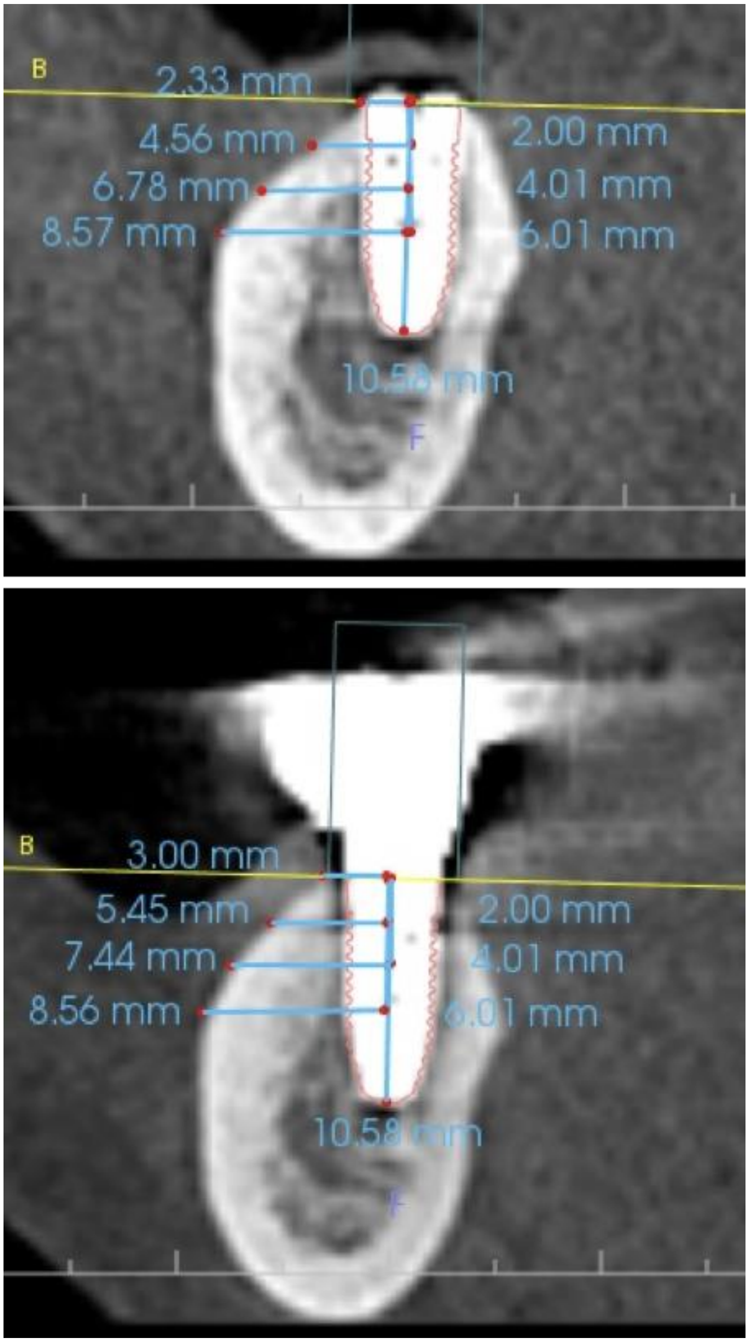


***Figure. g** Example of vertical measurements from Visit 2 and Visit 4 on CBCT images*