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Ultrasound-based Jawbone Surface Quality Evaluation after Alveolar Ridge Preservation

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An Original Article

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Summary: Ultrasound could classify jawbone surface quality that correlates with bone mineral density and bone volume fraction, potentially allowing for non-invasive and real-time evaluation of readiness of implant surgery after alveolar ridge preservation.

Abstract

Background: Bone readiness for implant placement is typically evaluated by bone quality/density on 2-dimensional radiographs and cone beam computed tomography at an arbitrary time between 4-6 months after tooth extraction and alveolar ridge preservation (ARP). The aim of this study is to investigate if high-frequency ultrasound (US) can classify bone readiness in humans, using micro-CT as a reference standard to obtain bone mineral density (BMD) and bone volume fraction (BVTV) of

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healed sockets receiving ARP in humans. **Methods:** A total of 27 bone cores were harvested during the implant surgery from 24 patients who received prior extraction with ARP. Ultrasound images were taken immediately before the implant surgery at the site co-registered with the tissue biopsy collection location, made possible with a specially designed guide then classified into 3 tiers using B-mode image criteria (1) favorable, (2) questionable, and (3) unfavorable. Bone mineral density (hydroxyapatite) and BVTV was obtained from micro-CT as the gold standard. **Results:** Hydroxyapatite and BVTV were evaluated within the projected US slice plane and thresholded to favorable (>2,200 mg/cm^3; >0.45 mm^3/mm^3), questionable (1,500 mg/cm^3 to 2,200 mg/cm^3; 0.4 to 0.45 mm^3/mm^3) and unfavorable (<1,500 mg/cm^3; <0.4 mm^3/mm^3). The present ultrasound B-mode classification inversely scales with bone mineral density. Regression analysis showed a significant relation between ultrasound classification and BMD as well as BVTV. T-test analysis demonstrated a significant correlation between ultrasound reader scores and the gold standard. When comparing Tier 1 with the combination of Tier 2 and 3, ultrasound achieved a significant group differentiation relative to mean BMD (p=0.004, true positive 66.7%, false positive 0%, true negative 100%, false negative 33.3%, specificity 100%, sensitivity 66.7%, ROC area under the curve 0.86). Similar results were found between ultrasound-derived Tiers and BVTV. **Conclusion:** Preliminary data suggest ultrasound could classify jawbone surface quality that correlates with BMD/BVTV and serve as the basis for future development of ultrasound-based socket healing evaluation after ARP.

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1. Introduction

After tooth extraction, a cascade of cellular healing events results in vertical and horizontal bone resorption [1-4]. The extent and magnitude of dimensional changes is dependent on systemic factors [4, 5], such as smoking, and local site characteristics, such as facial wall thickness and the remaining alveolar walls [6, 7]. Alveolar ridge preservation (ARP) is a surgical procedure, commonly using bone substitutes to fill the extraction socket in order to reduce bone dimensional alterations [6-8]. Current non-invasive imaging modalities evaluating ridge width and height include two-dimensional x-ray, and cone beam computed tomography (CBCT). Invasive methods are ridge mapping and surgical verification [9-12]. Although ARP is widely indicated in dental practice for its effectiveness in preserving ridge dimensions [3, 5-8, 13-16], evidence also shows it changes bone density [1, 4-8, 11, 13-20]. Bone density is another important parameter for implant function and longevity [1, 2, 5, 6, 8, 11, 13-15, 17, 19-28]. Additionally, a standard healing time of 3-6 months has been recommended [5, 7, 8, 16, 29]. Post-surgical complications may arise from persistent inflammation, infection, loss of bone grafts, and negative soft and hard-tissue changes [2, 3, 7, 14-16]. It is not uncommon, that failed ARP may only be found at the time of implant placement, requiring an additional bone grafting procedure or a surgical modification, and having a higher risk for implant complications [30]. Early diagnosis of unfavorable socket healing could potentially allow for early intervention and a reduction in treatment time. A customized time schedule tailored to each surgical site is desirable and yet to be established.

Medical CT can provide Hounsfield Units that correlate with absolute bone density but are not used currently for implant planning due to radiation concerns. Two-D x-rays as a projection image can provide pixel values as a subjective means to evaluate bone density [11, 18, 20, 23, 25, 31]. CBCT offers valuable insight into bone morphology and dimensions due to its cross-sectional nature; however, its relative voxel values, radiation exposure, low soft tissue contrast, and image artifacts from proximal radio-dense (metallic) objects are among the disadvantages [24, 32-34]. In a research setting, quantitative analysis with micro-CT is currently the gold standard to evaluate Bone Mineral

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Density (BMD) in units of hydroxyapatite in mg to cubic cm [6, 21-23, 35], and bone volume fraction (BVTV) in units of mm^3/mm^3 [36-38]. BMD has a highly significant correlation with implant insertion torque [18, 19, 25, 27, 39]. BVTV is the volume of mineralized bone per unit volume of the sample and has been shown to serve as an objective indicator for Bone Mineral Density (BMD) in the implant site and correlated with implant's initial stability [40].

Ultrasound (US) as a non-ionizing, non-invasive, real-time, and chairside modality can image soft and hard tissue surfaces on a cross-sectional view plane and would be a desirable tool to evaluate healing longitudinally [9, 32, 33, 41-47]. Thanks to recent improvements in probe miniaturization and higher spatial resolution, US has been successfully used to assess crestal bone surface quality, soft-tissue dimensions, and tissue quality in the oral cavity [45, 46, 48, 49]. US has shown a 91% agreement with CBCT when comparing the cortical bone thickness of edentulous ridges [24]. Furthermore, previous studies validated the feasibility of high-resolution US to estimate edentulous crestal ridge width [43, 45, 46]. In light of the limitations of the current clinically available radiographic imaging modalities, this preliminary study aims to investigate if high-frequency, point-of-care US can differentiate micro-CT-derived bone density of healed sockets receiving ARP in humans.

2. Materials and Methods

2.1. Study design and subject recruitment

The present study was approved by the University of Michigan Medical School Institutional Review Board (IRB) (HUM00203875), in accordance with the Helsinki Declaration of 1975, as revised in 2013. Informed consent was obtained from all individuals who participated in the study. The design is a single-blinded, dual comparative study of US with micro-CT in one study group.

2.2. Setting and participants

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Subjects who had already received extraction with ARP and had been scheduled for dental implant surgery were recruited between January 2022, and December 2022. The inclusion criteria were: 1. Age of 18 years or older at enrollment, 2. Any edentulous site that received ARP as a standard clinical procedure for at least 4 months, 3. Already scheduled for dental implant surgery according to standard-of-care treatment. Exclusion criteria included: 1. No baseline or incomplete clinical data. 2. Tissue core biopsy could not be performed or analyzed. The patient recruitment process, clinical assessment, ultrasonographic examination, and tissue core biopsy were performed by two calibrated study members (H.L.C and A.R.B). Calibration was performed using a prototype, full-sized, 3D, periodontal ultrasound phantom created by our group in collaboration with CIRS Inc. (PIRATE, Model 134200, CIRS Inc., Virginia, USA). Seven data pairs compared guided and freehand images for the phantom's edentulous ridge. The data was analyzed for repeatability by computing the mean (μ) and standard deviation (σ) of the guided and non-guided (freehand) values. Soft and hard tissue distances from the reference standard were computed for repeatability, with guided scans having 2.2 times less standard deviation for soft tissue and 1.6 times less for bone. The coefficient of variation remained similar at 22.3% and 26.8% for soft tissue and 50.7% and 42.4% for bone in guided and non-guided scans, respectively.

2.3. Ultrasonographic image acquisition

The grafted sites were US imaged immediately before the implant surgery, using a commercially available linear array (64-μm axial image resolution) and miniature-sized (≈30-mm long × 18-mm wide × 12-mm thick) probe*. Second harmonic imaging (12-24 MHz) and spatial compounding (3 angles) were used for achieving optimal delineation of the soft- and hard tissues in the virtual convex field of view (~14 mm wide, 15 mm deep). Brightness mode (B-mode) images were obtained by placing the transducer into a 3-dimensionally registered reference guide based on the intra-oral optical and CBCT scan previously taken (A.R.B.) (Figure 1). Anatomical data from CBCT and intra-oral

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optical scans of the edentulous sites were saved in “Digital Imaging and Communication in Medicine” (DICOM) format and the “Standard Tessellation Language” (STL) format, respectively. The ultrasound guide creation followed a digital workflow: image acquisition, computer-aided design (CAD), and computer-aided manufacturing (CAM). Implant planning was determined based on available soft- and hard-tissue surfaces and clinical criteria. The ultrasound guide was designed using the CAD file of the transducer housing in three planes: axial, coronal, and sagittal. The ultrasound housing was oriented in 3D space (translational and rotational) for imaging the site of implant placement. In other words, the virtual implant abutment was centered within the aperture. In the axial plane, the probe was angled to ensure the image ran parallel to the implant. A "platform part" was added around the housing for US probe support, and a “splint part” was designed for stability with adjacent teeth (Figure 1 A and C). Additionally, the planned implant and respective abutment served as references for the bone core biopsy guide design (Figure 1 B and D). Therefore, the ultrasound images were taken at the same location where the bone core biopsy was harvested during the implant surgery.

2.4. Tissue biopsy collection and sample preparation

A 3D-printed guide with the desired implant position that was co-registered with the image location was used to obtain the bone core. A 2.8 mm internal diameter trephine drill was used to collect approximately 4 mm (length) bone core and placed in 10% formalin for 24 hours and then moved to 70% ethyl alcohol. To maintain tissue orientation a radiopaque gutta-percha cone was placed in the mesial aspect of the core, in a coronal orientation. Special care was taken to use a small size cone at a relative distance from the sample to avoid an artifact image on the sample.

2.5. Micro-CT samples

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The tissue biopsies were placed in a 14 mm diameter specimen holder and scanned using a micro-CT system†. Scan settings were voxel size 5 µm, 70 kVp, 114 µA, 0.5 mm AL filter, 1000 projections around 180°, and integration time 500 ms. Micro-CT analysis was calibrated in units of absolute hydroxyapatite (HA) mg per cm^3, and bone volume fraction (BVTV) in units of mm^3/mm^3. BMD and BVTV values were calculated using a 'bone texture' plugin with commercially available software (3D Slicer). Bone cores were analyzed individually to create crestal bone surface and intraalveolar segments. A segmentation of tissue biopsies (cuboid) was created to obtain an absolute bone mineral density in the cortical slice, seen by ultrasound. Segmentations were matched to the ultrasound slice thickness (500 µm). Hydroxyapatite was evaluated within the projected US slice plane (Figure 2).

2.6. US reader score classification

The interface quality between the soft and hard tissues was classified by 3 experienced and masked readers (H.L.C., A.R.B., J.W.). A total of 27 ultrasound images were scored 3 times in 3 different time points to allow for memory washout, and the mean scores were used for analysis. Ultrasound images were classified into one of three classes: favorable (1), questionable (2), and unfavorable (3). This classification was modified from Sinjab et al. 2022 [45] (Figure 3).

- Hard tissue evaluation:
  - Tier 1: A clear, bright/hyperechoic, continuous, and thin interface, indicating the formation of an intact crestal bone surface.
  - Tier 2: Interrupted, less bright/less hyperechoic, irregular, and thicker interface, indicating partial formation of the crestal bone surface.

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- Tier 3: Unclear, interrupted dark/least hyperechoic, irregular, and thick interface, indicating disruption of the crestal bone formation and soft tissue invagination.

- Soft tissue evaluation:

  - Tier 1: Smooth epithelial surface with bright/hyperechoic line and an underneath hypoechoic layer. The submucosal layer is homo-echogenic. No hyperechoic structures, e.g., gas bubbles or bone particle present within the tissues.

  - Tier 2: Depressed epithelial surface with bright/hyperechoic line and an underneath hypoechoic layer. Presence of hyperechoic structures, e.g., gas bubbles or bone particles present within the tissues.

  - Tier 3: Marked surface depression without clear bright/hyperechoic line and an underneath hypoechoic layer. Presence of hyperechoic structures, e.g., gas bubbles or bone particles penetrating the full thickness of the tissue layer.

2.7. Statistical analysis

The micro-CT-derived BMD was compared among the 3 tiers with ANOVA. The significance level was set at 0.05. All statistical analyses and processing were performed using custom Matlab scripts including its statistics toolbox and commercially available software‡. Inter- and intrareader calibration for US reader scores was performed using intraclass correlation coefficient (ICC). A Receiver Operating Characteristics (ROC) curve was utilized based on the sensitivity and specificity to determine the accuracy of this diagnostic test in identifying favorable and unfavorable healing defined by BMD.

3. **Results**

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A total of 27 bone cores were harvested from 24 patients (aged 18 to 90 y/o, median 61, 13 males and 11 females). A total of 11, 7, 4, 4, and 1 sample were from maxillary incisors, maxillary premolars, mandibular incisors, mandibular premolars, and a mandibular molar, respectively. The biomaterials used were mineralized cancellous bone allograft from 2 brands [§,**] in 15 and 2 sites, respectively, and cortical cancellous mix 50/50 bone allograft[††] in 10 sites. In addition, absorbable collagen wound dressing [‡‡] in 13 sites, and absorbable collagen membranes from brands [§§, ***] in 1 and 13 sites, respectively were used. The median healing period between the extraction surgery plus ARP and the implant surgery when the bone core was collected was 4.4 months ± 12 months (standard deviation) ranging between 3.4 months to 5 years. The reader score classification grouped 10 sites as Tier 1 (favorable), 7 sites as Tier 2 (questionable), and 10 sites as Tier 3 (unfavorable) sites (Figure 4A). The mean ICC intra reader performance for the 3 time points was 0.923, 0.976, and 0.956 for readers 1, 2, and 3, respectively. Whereas the mean ICC inter reader performance was 0.877, 0.859, and 0.838, for time points 1, 2, and 3, respectively. The average intra reader and inter reader performance was 0.9501 and 0.8315, showing a good to excellent agreement in both cases [50, 51]. The median crestal BMD values for Tier 1 were 2,948 mg/cm^3, Tier 2 was 1,741 mg/cm^3, and Tier 3 with 1,703 mg/cm^3 (Figure 5). The mean BVTV values for Tier 1 were 0.623 mm^3/mm^3, Tier 2 was 0.383 mm^3/mm^3, and Tier 3 with 0.319 mm^3/mm^3. T-test analysis demonstrated a significant correlation between ultrasound reader scores and the gold standard. For BMD there was significant difference between Tier 1 versus Tier 2 ($p = 0.020$), between Tier 1 versus Tier 3 ($p = 0.009$ (Figure 4B). The median BMD was significantly higher in Tier 1 versus Tier 2+3 ($p = 0.001$). Similar results were found BVTV values with significant differences between Tier 1 versus Tier 3 ($p = 0.018$), and in Tier 1 versus Tier 2+3 ($p = 0.003$) (Figure 4C).

Samples with a BMD and BVTV value exceeding a threshold of >2,200 mg/cm^3 and >0.45 mm^3/mm^3, respectively, were deemed clinically acceptable bone density for implant insertion

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surgery [18, 21, 22, 25, 52]. Furthermore, BMD and BVTV values 1,500 mg/cm^3 to 2,200 mg/cm^3; 0.4 to 0.45 mm^3/mm^3 were deemed questionable and <1,500 mg/cm^3; <0.4 mm^3/mm^3 unfavorable, respectively. Tier 1 did not show any grafts with a mean BMD less than 2,200, thus reflecting a specificity of 100% (Figure 6A and B). Yet, the combination of Tiers 2 and 3 led to a sensitivity of 66.7%. When comparing Tier 1 to Tier 3, i.e., removing Tier 2, the specificity remains at 100%, however, sensitivity increased to 72.7 %. The resulting p-value increased to 0.009 (Figure 6C and D). In neither scenario are any false positives observed. The area under the curve (AUC) of 0. 86 was obtained when Tier 1 was plotted with Tiers 2+3 (Figure 6A and B), and 0.83 when Tier 1 was plotted with Tier 3 (Figure 6C and D) [53, 54]. Similar results were found between ultrasound-derived Tiers and BVTV. When comparing Tier 1 with the combination of Tier 2 and 3, ultrasound achieved a significant group differentiation relative to mean BVTV (p=0.003, true positive 72.7.7%, false positive 0%, true negative 100%, false negative 27.3%, specificity 100%, sensitivity 72.7%, ROC area under the curve 0.90 (Figure 6E to H). Regression analysis showed a significant relation between ultrasound classification and BMD as well as BVTV (See Supplemental Figure A in online Journal of Periodontology).

4. Discussion

In the present study, the results show that jawbone surface quality classified based on ultrasound correlates with median BMD and BVTV (p-value <0.05). The AUC values of ~0.9 suggest ultrasound could be able to differentiate cases between BMD >2,200 HA mg per cm^3, BVTV >0.45 mm^3/mm^3 and those below that threshold. The high specificity (100%) suggested that all cases that did not have BMD or BVTV below the threshold were not classified as Tier 1. In this regard, ultrasound gives the clinician the ability to recognize adequately matured grafts, and potentially reduce waiting time from the standard 3-6 months. On the other hand, the presence of a sensitivity of 72.7% for Tier 1 when compared to Tier 3, and 66.7% for Tier 1 when compared to Tier 2 + 3, may

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be related to the cases that had BMD higher than the threshold but were classified as unfavorable healing on ultrasound. These findings were also confirmed when comparing BVTV values with US reader scores. This might be associated with the ultrasound scan angles due to the tight space of the edentulous ridge, which precluded a perpendicular image of the bone surface. In these cases, the operator should try to re-direct the transducer to obtain a relatively perpendicular orientation to the bone to avoid false negative interpretations. In other words, the operator should exhaust the effort to rule out the absence of a sharp bone-soft tissue interface by "looking at" the bone surface at different angles to reduce the false negatives.

Two-dimensional X-rays, cone-beam computed tomography (CBCT), tactile sensation during osteotomy, and implant insertion torque resistance are among the common methods to assess bone density [20-22, 27, 28, 52]. The tactile sensation and torque resistance test are considered late indicators because they are performed during implant surgery. Radiographs can infer bone density prior to the implant surgery; unfortunately, inherent limitations in image forming mechanisms render them not reliable for providing objective bone density assessment [20, 27]. Specifically, 2-D radiographs could overestimate the bone density with the presence of thick facial and/or lingual plates because of the superimposition of the 3-D anatomy [4, 10, 23, 31, 53]. CBCT provides relative bone density values that may not be clinically relevant. The bone density evaluation is particularly unreliable with the presence of heterogeneous structures, such as bone particulates and adjacent metallic structures due to the averaging effect from the computer algorithm estimation. The clinical gold standard for understanding bone density before implant placement is the analysis of BMD and trabecular microstructure on medical CT [18, 19, 23, 25, 27, 39]. Its equivalence in the research setting is the micro-CT. Implant stability strongly depends on the quality and quantity of the surrounding bone [20, 55, 56]. Thus, BMD and BVTV values have been used to assess implant stability preoperatively and have a highly significant correlation with the insertion torque [18, 20, 25, 27, 40]. Misch and Judy 1987 [28] classified bone density into four types (D1-D4), from dense cortical bone to fine trabecular bone based on medical

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CT. Medical CT incurs high radiation dose and are not recommended to be applied repeatedly on the same patients. Consequently, the correlation of BMD with B-mode ultrasonography could potentially bridge this diagnostic gap by serving as a non-invasive qualitative imaging technique for evaluating bone maturation and implant readiness.

The diagnostic value of ultrasound in evaluating surface bone density relies on the appearance of the soft tissue and the hard-soft tissue interface. At a histological level, "a hard tissue bridge-cortical bone-formed, which closed the socket" during normal healing [2, 4, 6, 8, 13-15, 48]. Progenitor cells originating from the surrounding bone walls migrate centrally to form woven bone that later matures and finishes lastly at the coronal aspect of the socket. Therefore, evaluating surface bone quality could indicate the overall socket healing. A high-intensity (hyperechoic) line in a US image indicates a strong likelihood of the presence of a boundary between the hard and soft tissue [57, 58]. This high-intensity interface is followed by a low-intensity (hypoechoic) region. This 'shadow region' denotes that interior bone surfaces cannot be imaged with US [26, 57-59]. In cases of suboptimal healing, various degrees of soft tissue invagination result in the irregularity of this interface and reduced intensity [45]. Sound can penetrate deeper into the healed socket before it bounces back, giving a thicker interface appearance. In totally failed sockets, due to complete soft tissue invagination, the sound can penetrate into the entire socket. In orthopedics, musculoskeletal ultrasound has demonstrated clinical values in diagnosing bone fractures and evaluating osteoporosis with a variety of quantitative parameters [26, 57, 59-61]. These parameters could be applied for evaluating jawbone quality in the future.

Limitations of this study include the small sample size being a proof-of-principle study, reader-dependent evaluation of the ultrasound images, inability of micro-CT and ultrasound to differentiate bone particulates from new bone, and the angle-dependent imaging acquisition that tends to underestimate the surface bone quality. Future research should focus on the development of a standard scanning protocol, refine the ultrasound classification system, and the algorithm-based

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quantitative bone maturation analysis, including artificial intelligence to reduce reader biases with a larger subject pool.

5. Conclusions

Preliminary encouraging data suggested the potential value of ultrasound as a non-invasive tool to evaluate bone surface and soft tissue characteristics that correlated with bone mineral density and bone volume fraction.

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No conflict of Interest to declare.

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Footnotes

* L30-8, Mindray/Zonare of North America, San Jose, CA, USA

† µCT100 Scanco Medical, Bassersdorf, Switzerland

‡ Prism GraphPad, San Diego, CA, USA

§ Puros, Zimvie, Palm Beach Gardens, FL, USA

** OraGraft, LifeNet Health, Virginia Beach, VA, USA

†† Straumann, Andover, MA, USA

‡‡ CollaPlug and CollaTape, Zimvie, Palm Beach Gardens, CA, USA

§§ BioMend Extend, Zimmer, Palm Beach Gardens, FL, USA

*** OraMEM, Salvin Dental, Charlotte, NC, USA

Figure legends:

Figure 1. A. 3D depiction of digitally designed and tooth-supported ultrasound guide (orange). An intraoral scan of soft and hard tissues is shown in blue. The ultrasound transducer (green) is placed, buccal-lingual, to coincide with the location of the tissue biopsy. B. 3D depiction of a traditional digitally designed surgical guide to obtaining the tissue biopsy and placing the implant. C. Intraoral photo of a digitally designed and tooth-supported ultrasound guide and the ultrasound transducer with the probe cover for infection control. D. Intraoral photo of a digitally designed surgical guide.

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Figure 2. An example of a bone core with micro-CT. Segmentation of tissue biopsies (cuboid) to obtain absolute bone mineral density in the cortical slice, seen by ultrasound. Segmentations were matched to the ultrasound slice thickness (500 μm).

Figure 3. Cross-sectional ultrasound image examples of the edentulous ridge for three distinct cases (*top row*). A: Tier 1, favorable healing shows a smooth and homo-echogenic soft tissue layer. The bone crest is clearly delineated continuous, homogeneous bone surface, and thin interface thus suggesting the formation of an intact crestal bone surface. B: Tier 2, questionable healing shows soft tissue depression, irregularity, and the presence of hyperechoic structures in the inner submucosal layer. The bone surface is mostly continuous but heterogeneous, indicating the partial formation of crestal bone surface. C: Tier 3, unfavorable healing shows soft tissue invagination with irregular layers and the presence of hyperechoic structures embedded in the soft tissue. Bone crest has a discontinuous, heterogeneous, irregular, depressed, and thicker interface with the presence of soft tissue invaginations suggesting subpar crestal bone formation. Illustration of the anatomical landmarks in an Ultrasound B-mode image of an edentulous ridge occlusal view (*bottom row*). Annotations across the illustrations indicate buccal (B), palatal/lingual (P/L), occlusal (O), soft tissue (ST), bone crest (BC), hypoechoic alveolar bone (Hypo-AB) image below the bone crest, soft tissue depression (STd), hyperechoic structures (Hyper-st), soft tissue invagination (STi). A. Tier 1. B. Tier 2. C. Tier 3.

Figure 4. Ultrasound reader score distribution (A), Ultrasound tier classification versus BMD micro-CT values (B), and Ultrasound tier classification versus BVTV micro-CT values (C).

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Figure 5. Example tissue biopsies with median crestal bone mineral density (BMD) values and bone volume fraction (BVTV) above, at, and below the threshold were considered favorable, i.e., BMD 2,200 mg/cm^3 and BVTV 0.45 mm^3/mm^3. The obtained values were compared to the reader score of the ultrasound base ridge classification.

Figure 6. *(Left panel)* Sensitivity and specificity of the ultrasound versus BMD test of Tier 1 compared to Tier 2 + 3. A. Area Under the Curve (AUC) showed 0.86 and B. Positive and negative predictive values between Tier 1 and Tier 2+3 showed specificity (100%), sensitivity (66.7%), and false positive (0%). Sensitivity and specificity of the ultrasound test of Tier 1 compared to Tier 3. C. Area Under the Curve (AUC) analysis showed 0.83 and D. Positive and negative predictive values between Tier 1 and Tier 3 showed specificity (100%), sensitivity (72.7%), and false positives (0%). *(Right panel)* Sensitivity and specificity of the ultrasound versus BVTV test of Tier 1 compared to Tier 2 + 3. E. Area Under the Curve (AUC) showed 0.90 and F. Positive and negative predictive values between Tier 1 and Tier 2+3 showed specificity (100%), sensitivity (72.7%), and false positive (0%). Sensitivity and specificity of the ultrasound test of Tier 1 compared to Tier 3. G. Area Under the Curve (AUC) analysis showed 085. H. Positive and negative predictive values between Tier 1 and Tier 3 showed specificity (100%), sensitivity (72.7%), and false positives (0%).

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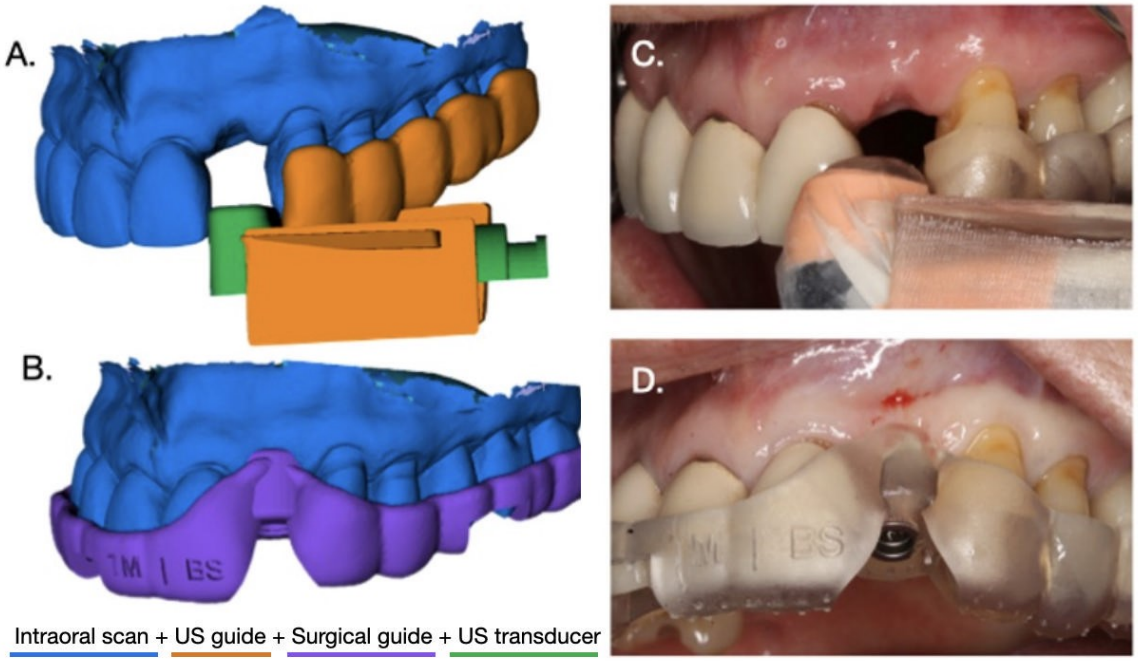


Figure 1

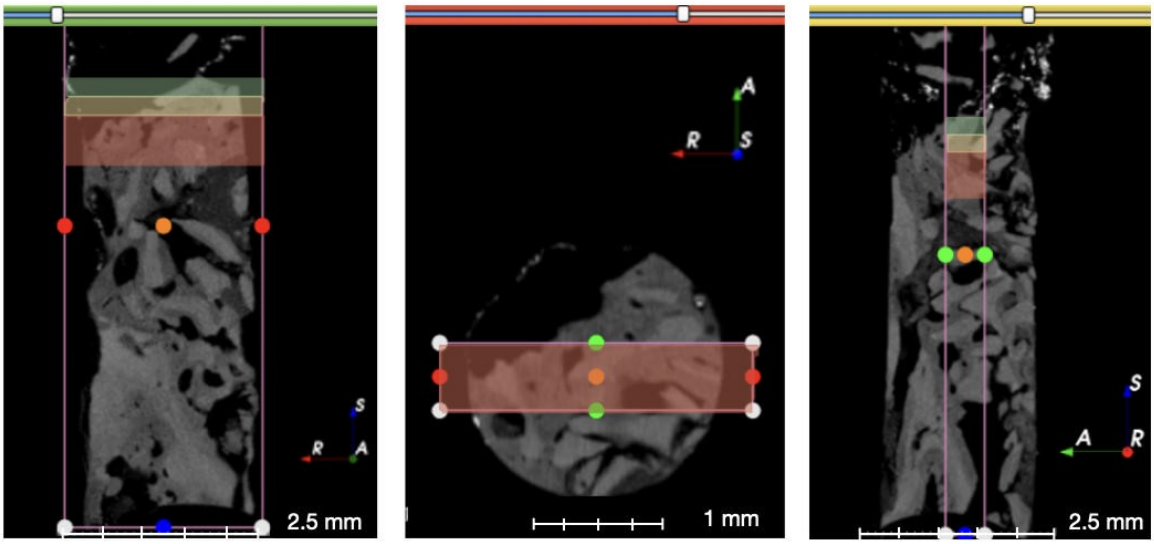


Figure 2

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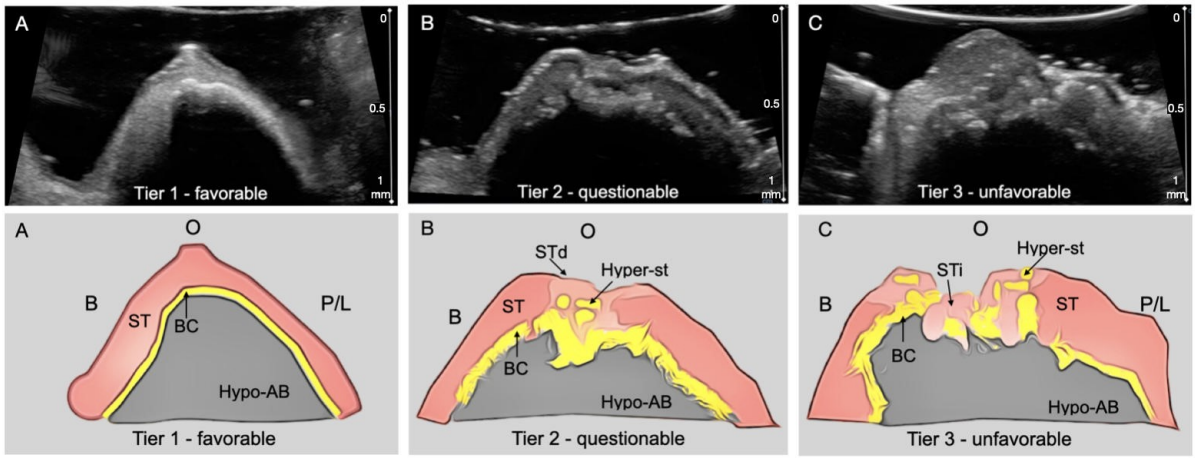


Figure 3

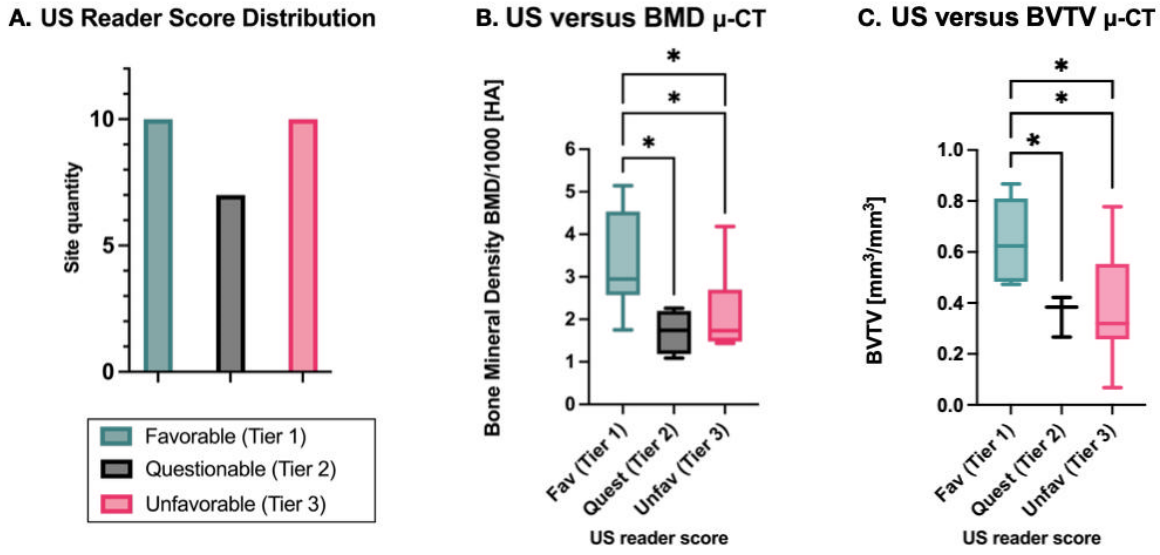


Figure 4

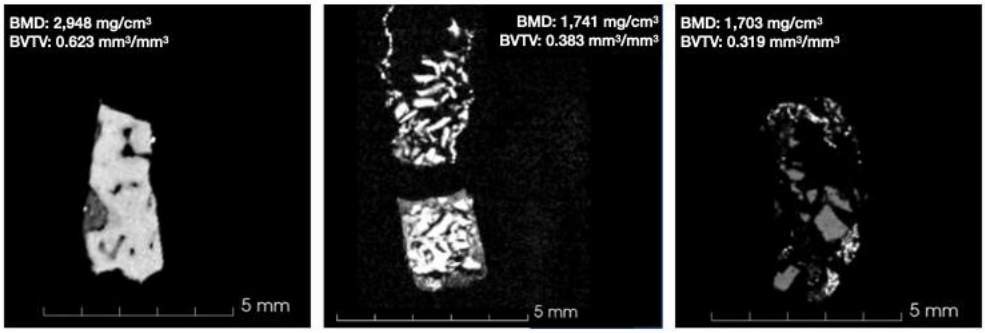
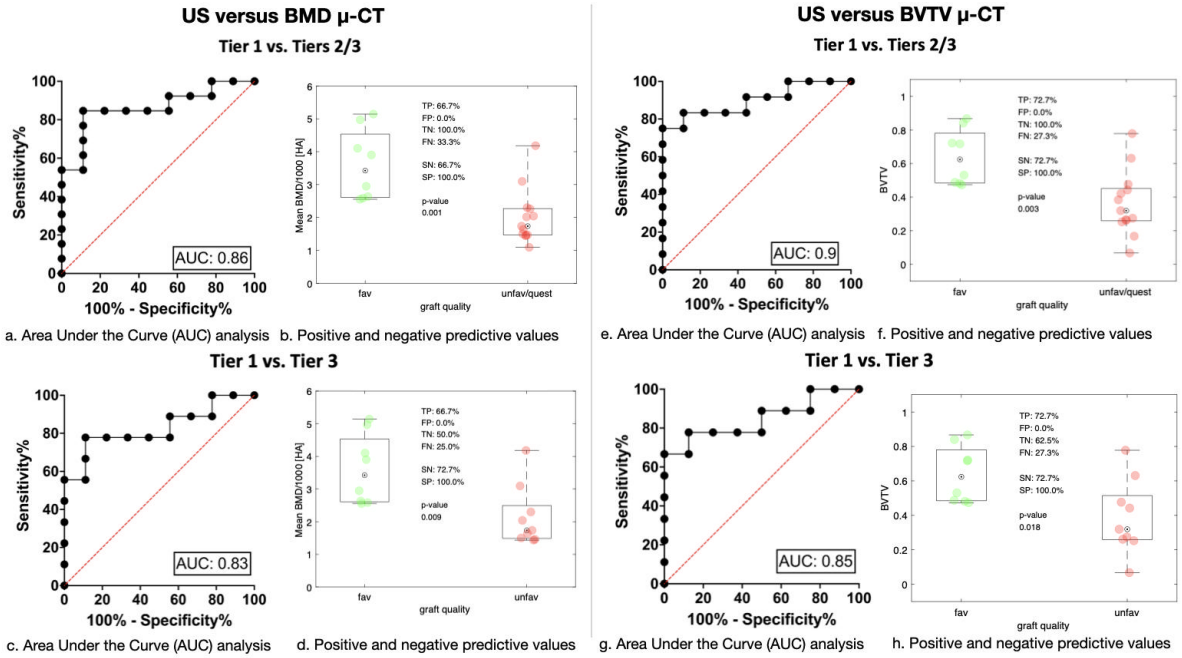


Figure 5

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a. Area Under the Curve (AUC) analysis b. Positive and negative predictive values

e. Area Under the Curve (AUC) analysis f. Positive and negative predictive values

c. Area Under the Curve (AUC) analysis d. Positive and negative predictive values

g. Area Under the Curve (AUC) analysis h. Positive and negative predictive values

Figure 6

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