RESEARCH ARTICLE

Correlation among alveolar bone assessments provided by CBCT, micro-CT, and 14 T MRI


Objectives: The aim of this study was to evaluate bone mineral adipose tissue (BMAT) volume in 21 alveolar bone specimens, as determined by 14 T MRI, and correlate them to the radiodensity values obtained pre-operatively of regions of interest (ROIs) by cone beam computed tomography (CBCT), and to the bone-volume-to-tissue-volume ratio values obtained by micro-CT, the gold-standard for morphometric data collection.

Methods: Partially edentulous patients were submitted to a CBCT scan, and the radiographic bone densities in each ROI were automatically calculated using coDiagnostiX software. Based on the CBCT surgical planning, a CAD/CAM stereolithographic surgical guide was fabricated to retrieve a bone biopsy from the same ROIs scanned preoperatively, and then to orientate the subsequent implant placement. The alveolar bone biopsies were then collected and scanned using the micro-CT and 14 T MRI techniques. Pearson’s correlation test was performed to correlate the results obtained using the three different techniques.

Results: In the 21 eligible bone specimens (6 females, 15 males), age (mean age 52.9 years), micro-CT, and 14 T MRI variables were found to be normally distributed ($p > 0.05$). The strongest—and only statistically significant ($p < 0.05$)—correlation was found between micro-CT and 14 T MRI values ($r = 0.943$), and the weakest, between 14 T MRI and CBCT values ($r = -0.068$).

Conclusions: The findings suggest that 14 T MRI can be used to evaluate BMAT as an indirect marker for bone volume, and that CBCT is not a reliable technique to provide accurate bone density values.

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Keywords: Bone Marrow; Cone-Beam Computed Tomography; Dental Implants; Magnetic Resonance Imaging; X-Ray Microtomography
Introduction

A thorough examination of dental supportive structures must be performed before any type of maxillofacial surgical treatment can be carried out. The alveolar bone is one such structure and consists of two cortical plates and trabecular bone filled with bone marrow. This structure has been studied for many years using different tomographic techniques to assess mineral morphology and bone density, with the ultimate goal of achieving improved esthetic and functional results. Multislice computed tomography (MSCT) is considered the gold-standard for assessing bone mineral density (BMD) in Hounsfield units (HUs), whereas micro-computed tomography (micro-CT) is the gold-standard for assessing micro-architecture information, such as bone volume (BV) and bone fraction, i.e., the bone-volume-to-tissue-volume ratio (BV/TV) in ex-vivo specimens.

Cone-beam computed tomography (CBCT) is the technique most widely used by dental clinicians, and has several advantages over MSCT, such as producing less radiation, and being a cheaper and less time-consuming method. Although CBCT does not provide calibrated HU values, some studies have shown that the radiographic bone density (RBD) values provided by CBCT systems are strongly correlated to the HU values provided by MSCT, and to the BV/TV values provided by micro-CT; this suggests that CBCT can be relied on to assess bone density accurately.

The number of studies attempting to evaluate bone marrow adipose tissue (BMAT) as an indirect marker for bone density or volume has increased markedly with the development of MRI. It is well known that, as people grow older, the amount of bone density decreases and of marrow fat increases, suggesting a close association between these two biological variables. It is also recognized that some conditions, such as alcoholism, starvation, and high levels of glucocorticoids, are associated with higher levels of bone marrow fat, but also that the amount of bone marrow fat is not related to one's total body fat or body size.

The skeletal conversion from red (hematopoietic to yellow bone marrow starts in the phalanges of hands and feet before birth. By adult age, red bone marrow is stored in a few sites of the vertebrae, sternum, ribs, and pelvis. Regarding facial bones, the maxilla only contains yellow bone marrow during adulthood, whereas the mandible converts its marrow from red to yellow throughout childhood, and only the condyles might present some hematopoietic tissue by the adult age of 25.

Bone marrow tissue is known to comprise approximately 85% of the medullary bone, with bone trabecular comprising the remaining 15%. In addition, yellow bone marrow is known to consist of approximately 80% fat, 15% water, and 5% blood vessels. These features suggest that MR images could provide an indirect assessment of bone density/volume, especially considering that the BMAT signal is particularly intense in $T_1$ weighted MR images. Furthermore, as mentioned before, the amount of marrow fat is known to increase with age, a finding that may be taken into account when estimating bone density indirectly with MRI, by incorporating the patient’s age into the estimation.

To the best of our knowledge, only one pilot study has been performed to assess alveolar bone morphometry using a 15 T (Tesla) MRI scanner and a custom-built radiofrequency (RF) coil. In that study, seven bone specimens were retrieved at implant placement, using a 3 mm trephine burr, and then scanned with both a micro-CT scanner and a high-field MRI scanner, using a gradient-echo $T_1$ weighted pulse sequence. A strong and inverse correlation was found between BMAT and BV/TV, supporting the findings of previous medical studies evaluating the relationship between BMD and BMAT in other bones of the body. No other scanners were used to address the question of the feasibility of evaluating alveolar BV indirectly, without ionizing radiation.

It is important to note that the 14 T MRI scanner used in this study is a high-field instrument and is not a clinical tool, but rather a research tool. Common clinical MRI field strengths are 1.5 and 3.0 T. The very high field strength of 14 T affords a vastly improved signal-to-noise ratio (SNR), which enables very high 3D spatial resolution with voxel dimensions approaching 20 µm or less but permits scanning of only small, mm-sized ex-vivo specimens. However, under very limited circumstances and using specialized equipment (e.g., special RF coils, pulse sequences and image post-processing) it is possible to resolve individual trabeculae with clinical MRI scanners.

The aim of the present study was to evaluate the BMAT volume values (in mm$^3$ found in 21 alveolar bone specimens, as determined by 14 T MRI, and correlate them with the radiodensity values (given in “HU”) obtained pre-operatively from regions of interest (ROIs) by CBCT, and with the BV/TV ratio values (in %) obtained by micro-CT (the gold-standard for morphometric data collection). The main goal is to evaluate if BMAT images from alveolar bone specimens can be used as an indirect marker for bone volume and to assess the use of a research 14 T MRI scanner as a prelude to eventual translation of MRI methodology to the dental clinic.

A thoroughly rigorous comparison between in-vivo CBCT (CBCT exams of patients) and ex-vivo micro-CT (bone samples) measurements to estimate BMD is not strictly possible. For example, the small specimens available for micro-CT would not be embedded in the tissue of the head when scanned by CBCT, making beam hardening, scattering and other effects different between the two modalities. The presence of X-ray dense restorations or appliances in the patient’s dentition has
particular influence on image quality and pixel values which cannot be accounted for in micro-CT. The effects of patient motion would be present in one case and not the other. Parameters such as beam current and voltage might not be replicable between the two instruments. The measurement time and spatial resolution, and therefore the counting statistics and image intensity accuracy and noise, are likely to be vastly different as well.

Because it is essential to assess both alveolar bone quality and the anatomy prior to maxillofacial surgical treatment, it is reasonable to attempt at least a first-order assessment of the ability of CBCT to provide BMD information, imperfect though that assessment may be. Several studies attempting this have been reported.\textsuperscript{17,18} In the present report, and with the caveats stated above, we uniquely compare CBCT estimates of BMD with two established methods that differ widely in their underlying physical mechanisms. By comparing in-vivo CBCT scans with micro-CT and high field MRI scans of the biopsy specimens, we believed this is the best comparison that can be made given the current state of these technologies.

Methods and materials

CBCT and implant surgeries

This study was approved by the University Research Ethics Committee (CAAE: 84549818.0.0000.0075) and followed the ethical guidelines of the World Medical Association Declaration of Helsinki. An informed consent form was signed by all the patients who participated in this study.

The inclusion criteria were patients referred for implant placement between 2018 and 2019, aged 18 years or older. Pregnant females, smokers, patients who had metabolic disorders or insufficient alveolar BV, and patients previously submitted to ridge grafting at the Military Hospital, which has a partnership with the School of Dentistry (Figure 1). In total, 18 patients (13 males and 5 females) and 21 bone specimens were considered eligible for this study. All of the specimens had similar dimensions (3 mm diameter and 8- to-10 mm length) and were preserved in 10% buffered formalin. SLActive implants (Straumann AG, Basel, Switzerland) measuring 4.8 mm in diameter x 8.0 mm or 10.0 mm in length were placed, restored, and followed-up for more than 1 year. No complications or implant losses were observed during this period.

Micro-CT

Each bone specimen collected was placed in a 5 mm nuclear magnetic resonance (NMR) glass tube, still containing the 10% formalin solution, and scanned with a high-resolution micro-CT scanner (Bruker SkyScan 1173, Kontich, Belgium) using the following parameters: 45 kV, 555 µA, 8.34 µm voxel size, 0.2 mm aluminum filter, and 48 min total scanning time. The images were reconstructed using Nrecon software (Bruker SkyScan), and a manual segmentation technique was applied to identify the volume of each alveolar specimen using CTAn software, v. 1.18 (Bruker SkyScan). External edges damaged by the cutting of the trephine burr were excluded from the ROI (Figure 2). The BV of each specimen was reconstructed, and automatically analyzed to determine its BV/TV ratio.

14 T MRI

A 14 T high-field multinuclear NMR spectrometer/imager was used to scan the bone specimens. It consisted of a Magnex (Oxford, UK) 14 T (600 MHz), 89 mm vertical bore magnet interfaced to a Bruker BioSpin (Billerica, MA) Avance III HD console. The computer operating system was Linux, and the Bruker
software program used was Paravision v. 6.0.1. Prior to performing the scans, the surfaces of all the specimens were patted dry and transferred to another 5 mm glass NMR tube containing fluorocarbon liquid (Fomblin perfluoropolyether, Ausimont, Thorofare, NJ). This fluid does not contain hydrogen atoms; it eliminates the intense proton signal from the fixation medium, and mitigates artifacts related to magnetic susceptibility differences at tissue–air interfaces. Using this so-called susceptibility matching fluid medium for the specimen provides sharp external boundaries in the MR image to delineate the specimen, and by eliminating the signal from the medium also reduces the possibility that the receiver runs out of dynamic range. A vacuum pump was used to pull out the air possibly trapped within the specimens, since air bubbles would also introduce susceptibility artifacts. An acrylic adapter was constructed to fit the 5 mm glass NMR tube inside the Bruker RF coil, with a 10 mm inner diameter and a 40 mm outer diameter (Figure 3).

First, a long duration scan was performed of the specimens, using the following pulse sequence: 3-D gradient-echo, 48.6 ms time of repetition (TR), 2.6 ms time of echo (TE) and matrix of 256 × 256 x 256, resulting in a total acquisition time of approximately 14 h. However, image blurring occurred that may be due to the instability of the spectrometer or to motion of the specimen because of gradient vibration during long duration scans. The 14-h scan was therefore divided into six shorter scans with the same parameters, but fewer signal averages, resulting in the total scan time being the same. This afforded the option to discard one or more of the shorter scans if image degradation occurred without having to discard the entire 14-h run. The reduction in SNR from rejecting one of six scans is only $1 - \sqrt{\frac{5}{6}} \approx 8.7$ percent. To reduce the possibility of specimen motion, cotton wool was placed immediately above and below the specimen to prevent it from rotating during the scan. The Fortran programming language (GNU Fortran 8.1.0) was used to develop a software program that could add multiple Bruker image files of the same specimen to produce the combined image file to achieve the full SNR, and another one was developed to convert Bruker image data format to VFF 3D image file format. Once in VFF format, the data were imported into MicroView software (MicroView 2.5.0–4196, Parallax Innovations, Canada) to be converted to DICOM files, and analyzed using open-source OsiriX software (OsiriX v. 6.0; Pixmeo, Geneva, Switzerland).
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OsiriX analysis
A rectangular hyperintense area corresponding to the specimen’s cylindrical shape was identified with the OsiriX program. Several 2D ROIs were drawn following the outline of each specimen in the sagittal plane, after which the program completed the missing ROIs in the remaining slices, in a semi-automatic fashion, to calculate the total volume of each specimen in 3D.

A circular ROI boundary was drawn outside the specimen perimeter to determine the signal/noise threshold for each scan. A custom threshold higher than the noise threshold was used to select all the hyperintense areas corresponding to the BMAT with the “3D growing region” segmentation tool (Figure 4). The percentages of BMAT and BV were then calculated based on the total volume and the volume corresponding to the hyperintense regions of each specimen.

Statistical analysis
The Shapiro–Wilk’s test was used to assess the normality of the data distribution. Pearson’s non-parametric test was used to assess the correlation among the three imaging techniques tested in the study. All of the statistical analyses were performed at a significance level of 5% (p < 0.05), using IBM SPSS Statistics software v. 24 (SPSS, Chicago, IL).

Results
21 bone specimens were eligible to be included in this study. 15 specimens were collected from males, and the other 6, from females (mean age of 52.9 years). A normal distribution was found for the age, micro-CT, and 14 T MRI variables (p > 0.05). The BV percentages obtained from 14 T MRI images were compared to pre-surgical radiographic density values obtained by CBCT and to BV/TV values obtained by micro-CT (Tables 1 and 2).

The strongest and only statistically significant correlation observed (p < 0.01) was between micro-CT and 14 T MRI (r = 0.943) (Figures 5 and 6).

Discussion
Micro-CT has a high accuracy in micrometers for trabecular parameters and is considered the “gold-standard” for bone morphology and micro-structure in the ex-vivo bone model; whereas CBCT device has been widely applied in the clinical setting with a lower resolution.3,22 The reliability to evaluate bone density using CBCT remains controversial in the literature, so a correlation test was performed between the values of RBD and those of BV/TV ratios obtained by micro-CT, in order to ascertain if CBCT is a reliable technique for assessing bone density.

No correlation was found between these two variables (r = –0.133), contradicting the findings of previous studies.2,3,23 Considering that these studies used the same methodology to retrieve bone specimens, and the same micro-CT scanner, the lack of correlation found in the present study may be attributed to the lack of standardization among the different CBCT scanners and planning software, and different scanning parameters used across different studies.

In another recent study with 62 bone specimens, no correlation was found between the gray values measured by CBCT and the bone volume/density variables (BV/TV, BMD and porosity) measured by micro-CT and histomorphometry.24 This finding further stresses the lack of consistency among the results reported, and the difficulties involved in comparing and interpreting CBCT values.2 It is important to mention that values

Table 1 Mean and standard deviation values for the three imaging techniques performed to assess the bone volume of dental implant sites (two biopsy scans and one pre-surgical implant planning scan)

<table>
<thead>
<tr>
<th>Imaging techniques</th>
<th>Standard deviation</th>
<th>Min – Max</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-CT (BV/TV, biopsy)</td>
<td>±21.10%</td>
<td>13.20–82.30%</td>
<td>48.69%</td>
</tr>
<tr>
<td>CBCT (radiographic density, pre-surgical planning)</td>
<td>±121.50 HU</td>
<td>263–783 HU</td>
<td>412.81 HU</td>
</tr>
<tr>
<td>14 T MRI (% BV, biopsy)</td>
<td>±19.05%</td>
<td>8–76%</td>
<td>49.05%</td>
</tr>
</tbody>
</table>

BV, Bone volume; CBCT, cone-beam computed tomography; HU, Hounsfield units; Micro-CT, microcomputed tomography; TV, tissue volume.

Table 2 Pearson correlation among the three imaging techniques performed to assess the bone volume of dental implant sites (two biopsy scans and one pre-surgical implant planning scan)

<table>
<thead>
<tr>
<th>Imaging techniques</th>
<th>Correlation coefficient (r)</th>
<th>p-value</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-CT x CBCT</td>
<td>–0.133</td>
<td>&gt;0.05</td>
<td>Negative / no correlation</td>
</tr>
<tr>
<td>Micro-CT x 14 T MRI</td>
<td>0.943</td>
<td>&lt;0.01</td>
<td>Excellent</td>
</tr>
<tr>
<td>CBCT x 14 T MRI</td>
<td>–0.068</td>
<td>&gt;0.05</td>
<td>Negative / No correlation</td>
</tr>
</tbody>
</table>

Micro-CT: microcomputed tomography; CBCT: cone-beam computed tomography; BV: Bone volume; TV: tissue volume; HU: Hounsfield units; MRI: Magnetic resonance imaging.; *Pearson's nonparametric test.
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from the coDiagnostiX (DICOM viewer software) were given in “HU” values, however CBCT manufacturers do not calibrate gray values along the HU scale as originally designed for spiral CT; and proof found on one CBCT model and software cannot be interpreted as general truth.25

In the present study, no correlation was found between the RBD values and the percentages of BV obtained by the 14 T MRI scanner \((r = -0.068, p = 0.45)\). Very similarly, an excellent correlation was found in 21 bone specimens of the present study between BV percentage (14 T MRI) and BV/TV (micro-CT). Although different methodologies were used to assess and quantify BMAT in alveolar bone specimens, both studies used high-frequency MRI scanners (15 T MRI and 14 T MRI, respectively), which guaranteed images with high resolution and good SNR.

Kim17 reviewed the factors limiting the use of CBCT for estimating BMD, and for applying corrections that might enable its routine use. An extensive review by Campos et al,18 concludes that CBCT is not the method of choice for measuring BMD.

There were some limitations in the present study, including the relatively small sample size of 21 specimens, and the small size of the alveolar bone specimens (3.0 mm diameter x 8.0 mm length). SNR in the present study could be improved with use of a 5 mm transverse solenoid RF coil to improve the filling factor (fraction of the coil volume that is occupied by the specimen), rather than the 10 mm birdcage coil that was available; the increased SNR could be traded off to reduce the overall scan time. Studies are warranted using a larger number of alveolar bone specimens and, if possible, larger specimens of maxillomandibular bone, to confirm the findings of this investigation. In addition, the pulse sequences and parameters used in the present study to assess BMAT could be adapted for clinical studies, with intraoral coils made specifically for the evaluation of the maxilla and mandibles of patients. Intraoral coils35 can reduce the distance from the coil conductors to the alveolar bone to increase the filling factor, thus providing higher sensitivity and enhanced SNR and image quality, or reduced scan time.

The authors of the latter study found a strong and inverse correlation between BMAT (assessed using 15 T MRI) and BV/TV (assessed using micro-CT) in seven 3 mm alveolar bone biopsies \((r = -0.68, p = 0.45)\).11 Very similarly, an excellent correlation was found in 21 bone specimens of the present study between BV percentage (14 T MRI) and BV/TV (micro-CT). Although different methodologies were used to assess and quantify BMAT in alveolar bone specimens, both studies used high-frequency MRI scanners (15 T MRI and 14 T MRI, respectively), which guaranteed images with high resolution and good SNR.

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Figure 5 Correlation between micro-CT and 14 T MRI images in the frontal plane. Micro-CT displays dense bone as bright and marrow or fixation medium as dark, whereas the contrast is reversed for MRI; the aprotic susceptibility matching fluid medium appears dark on MRI. (A): micro-CT reconstruction of an alveolar specimen showing areas with absence of bone tissue (red arrow). (B): 14 T MRI reconstruction of the same specimen showing the same area (red arrow) with a hyper-intense signal related to the presence of BMAT. Note that it is not possible to find exactly coincident image planes in the corresponding CT and MR images. BMAT, bone mineral adipose tissue.

Figure 6 Correlation between micro-CT and 14 T MR images, axial view. (A): micro-CT reconstruction of a specimen showing areas with absence of bone tissue (red arrow). (B): 14 T MRI reconstruction of the same specimen showing the same area (red arrow) with a hyper-intense signal related to the presence of BMAT. BMAT, bone mineral adipose tissue.
The MRI technique has some disadvantages, such as poor accessibility, high cost, patient claustrophobia, patient motion artifacts, and dental restoration artifacts, and is also contraindicated for patients with cardiac pacemakers. Nevertheless, it has the important advantages of not emitting ionizing radiation and allowing the identification and differentiation of pathological processes taking place in soft tissues, such as periodontitis—a condition usually only seen as bone loss in radiographs and tomographs. The results of the present study, along with those of previous medical studies, may contribute to ascertaining whether BMAT is distributed homogeneously in all parts of the body, whether the formation of adipose tissue is merely a passive compensation for bone loss, or whether both adipose and bone tissues have the same precursor that favors the occurrence of different processes (adipogenesis or osteogenesis) at different stages of life, thus ultimately contributing to clarifying the phenomena of bone deterioration and fragility.

The use of 14 T vertical bone MRI scanning is impractical as a clinical tool because of the great expense and general lack of availability of the equipment. However, lower field MRI “microscopes” are considerably less expensive, and might someday be considered practical clinical tools for trabecular bone assessment in ex-vivo specimens. Progress is being made in high performance MRI coils that could enable clinical MRI with spatial resolution approaching that achieved in the current study.55

Conclusions

Based on the comparison between biopsy specimens scanned by micro-CT (the gold-standard for BMD measurement) and radiodensity values from CBCT of the locations from which the specimens were subsequently harvested, we find that CBCT BMD values are not at all representative of true BMD. For biopsy specimens, micro-CT BMD values are highly correlated with 14 T 3D MRI BMD values. Although neither micro-CT nor 14 T MRI are practical clinical tools, these results suggest that MRI may, in some other form, have the potential for assessing BMD in dental applications.

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