INTRODUCTION

X-ray computed micro computed tomography (µCT) (Bonse & Busch, 1996) combined with synchrotron radiation X-ray sources enables a spatial resolution in the micrometer regime in three-dimensional (3D) imaging of bone microarchitecture combined with a high level of image sensitivity. In combination with X-ray optical elements the resolution can be further increased up to the nanometer scale (Withers, 2007). A synchrotron source is a large-scale facility: the common design comprises an electrun gun, a linear accelerator or microtron, where free electrons are accelerated to a medium energy, a circular accelerator, the actual synchrotron, in which the electrons are raised to their final energy in the GeV regime, and a storage ring where they are maintained at a constant energy. The actual radiation used for the experiments is generated in the storage ring: synchrotron radiation refers to the electromagnetic radiation produced when relativistic electrons circulating in the storage ring are deviated by strong magnetic fields (Wiedemann, 2002) with subsequent synchrotron light being emitted in a narrow beam, tangent to the curved trajectory of the electrons in the storage ring (Wiedemann, 2002). Beamlines where experiments can be carried out, surround the storage ring. Commonly their design is highly adapted to the experimental techniques used, such as X-ray diffraction, X-ray fluorescence or X-ray imaging.

In order to achieve high-spatial resolution for synchrotron radiation µCT (SRµCT) indirect detectors are commonly used; the luminescence image of a scintillator screen is captured by magnifying visible light optics and charge-coupled device (CCD) or complementary metal-oxide-semiconductor (CMOS)-based cameras. The effective pixel size of the detector needs to be adapted to the desired spatial resolution according to Shannon's theorem (Bonse and Busch, 1996). Such detectors operated at high spatial resolution commonly offer limited detection efficiency due to the thin scintillators required which make them less attractive for laboratory-based µCT. SRµCT enables efficient used of high-resolution indirect detectors and consequently offers several advantages in contrast to µCT. The high photon flux density allows not only for reaching high spatial resolution with SRµCT but at the same time the narrow-bandwidth

radiation for illumination also increases the contrast. SRμCT is considered as a gold standard of imaging the microstructure of bone (Peyrin et al., 2010) and is nowadays accessible as standard tool on many synchrotron light sources located around the globe (Rack et al., 2011). Due to the quasi-parallel beam geometry at a synchrotron light source the tomographic reconstruction can be done on a slice-by-slice basis, without the need of interpolation steps, which are frequently required when working in cone-beam geometry. It is the combination of high resolution, high signal-to-noise ratio, and the different contrast modalities that renders SRμCT an excellent suited analytical tool for studies in the biomedical field (Bernhardt et al., 2004;Feldkamp et al., 1989;Rack et al., 2011;Ritman, 2004;Ruegsegger et al., 1996;Ruhli et al., 2007;Stiller et al., 2009).

The application of SRμCT in the bio-medical field has recently been evaluated in a review by Neldam and Pinholt (Neldam and Pinholt, 2014). The review depicted that SRμCT has been used to evaluate osseointegration of titanium implants (Bernhardt et al., 2004), visualization of the vascular canals in cortical bone, microarchitecture of osteoporotic bone, and osseous microcracks (Bousson et al., 2004;Cooper et al., 2011;Larrue et al., 2011;Voide et al., 2009).

Studies have depicted osseointegration with a bone-to-implant contact of 60-80% when using light microcopy (Albrektsson 2008, Shah et al. 2014). Thus leaving parts of the implant surface not in direct contact with bone, hence, making it relevant to measure the implant-bone distance. Volume images obtained with SRμCT make it possible to distinguish between different material phases within a sample i.e. bone, titanium implant and cavities containing either air, blood vessels or fibrous tissue, by their different densities (Rack et al., 2006;Rack et al., 2011;Stiller et al., 2009) due to the high contrast given by the intense photon flux density. Classic histomorphometry enables evaluation of different levels of mineralization while μCT/SRμCT visualizes bone with a certain threshold of mineralization. At the 5-10 μm scale, SRμCT makes it possible to assess bone mineralization simultaneously with bone microstructure in both trabecular and cortical bone in 3D (Bonse et al. 1994, Peyrin, 2009).

The peri-implant bone volume fraction is defined as the bone surrounding an implant. Peri-implant bone volume contact fraction is the area in close proximity to the implant surface including the contact area, which is another important measure of osseointegration of dental implants. The peri-implant bone volume contact fraction is often evaluated within a threshold of 50 µm radial distances from the implant surface (Davies 1996). Visual inspection within this distance may define the maximum width of the artificial absorption coefficient lowering at the edge of the implant, originating from a refraction-based artefact.

Aim of the study

The aim of this study was to present application of high-resolution 3D SRµCT images at a 5 µm voxel size in evaluating peri-implant bone volume contact fraction, bone-to-implant contact (BIC), and peri-implant bone volume fraction, in an experimental goat mandible model, representing recipient and grafted bone after vertical augmentation.

MATERIALS AND METHODS

Bone sample

One bone sample comprising a titanium dental implant (AstraTech OsseoSpeed, ST Molndal, Sweden) 8 mm long, 3.5 mm in diameter, comprising lower 5.5 mm macro threads and upper 2.5 mm micro threads was used for evaluation. The implant was installed ad modum AstraTech in a critical size defect of the base at the mandible of goats (Fig. 1). Immediate vertical bone augmentation was performed with bone chips of 0.5x3x1 mm^3 - 0.5x5x1 mm^3 in size processed in bone mills (Liebinger, Freiburg, Germany; Quentin, Leimen, Germany), and the defect was covered by a titanium membrane (Riemser Artzen mittle AG, Greifswald, Insel Riems, Germany). The bone sample including the dental implant was, after 20 weeks of healing, fixated in 10% formaldehyde (Rigshospitalets Apotek, Rigshospitalet, Denmark), dehydrated in graded alcohol solutions and finally embedded in Technovit in an acrylic cylinder, 12 mm in diameter and 2 cm in height (Donath, 1993). The sample was left uncut for scanning purposes.

The region of interest (ROI) for this study was defined as the part of the sample, which included bone and micro threads of the implant representing *de novo* formed bone of the original defect (Fig. 2). For comparison the macro thread area surrounded by the recipient bone was used. The peripheral limitation of the ROI was bounded by a circle band placed 2000 µm away from the implant surface (Fig. 3).

Synchrotron radiation facility

The SRµCT scans were carried out at the ID19 beamline, at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France. ID19 is ideally suited for such an experiment, as it offers a sufficient high photon flux density and sufficient coherence properties at higher energies. Furthermore, the flexible layout of the experimental setup allows one to exploit propagation-based phase contrast with sample-detector distances of up to several meters. Due to the necessity of X-ray imaging through a dental implant made from titanium, a comparable high photon energy of approximately 67 keV, pink, i.e. the emitted radiation of a wiggler insertion device (a magnetic device) was filtered to reach a rather narrow bandwidth, was chosen. An indirect detector (lens-coupling of a scintillator to a CCD camera with 2048x2048 pixel), with a pixel size of 5 µm acquired tomographic scans of the region of interest (ROI), which was slightly smaller (10 mm wide) than the sample (~20 mm wide). The sample was continuously rotated over 360 degrees, as 1999 equiangularly dispersed radiographic images were taken.

The tomograms were reconstructed at the ID19 beamline. Standard filtered projection algorithm was applied via the ESRF inhouse-developed software PyHST (Mirone et al., 2014). The size of the reconstructed tomogram was 2048x2048x1024 voxels. Voxel values present the common Gaussian spread i.e. noise, overlapped with refraction phenomena, which were present at interfaces such as implant-bone interfaces, an effect known as edge-enhancement (Cloetens et al., 1996). The segmentation was performed using VG Studio Max 2.1 (Volume Graphics GHBM, Heidelberg, Germany) also at the European Synchrotron Radiation Facility in Grenoble, France.

The tomogram height was 1024 pixels since only half of the detector height was necessary to obtain data from the ROI (Fig. 2). The vertical height of the tomograms was reduced to 500 voxels i.e. 2.5 mm, which was done by inclusion of the part of the tomogram containing the ROI of the implant (Fig. 2).

RESULTS AND DATA ANALYSIS

Data analysis

Analysis of a given slice consisted of three steps:

1. Segmentation followed by
2. Circle-band construction and
3. Bone fraction determination

1) *Segmentation:* The sample consisted of three major components; the titanium dental implant, the surrounding bone and the cavities, which were distinguished by, and segmented by different absorption coefficients. Due to the implant's low-noise high-intensity in the image volume it was easily segmented by thresholding.

2) *Circle-band construction:* This data analysis evaluated the bone distribution of 1999 radial lines (Fig. 3) radiating from the implant surface one-dimensional, representing the bone distribution along the radial dimension at the 1999 places on the implant surface. The segmentation of the tomographic data was done on 2D horizontal sections.

   Two lines were defined representing the outer perimeter and the implant surface. A circle band of 2000 μm in width was defined around the dental implant, representing the area between the implant surface (blue circle) and the outer periphery at one mm radial distance (red circle). Due to the presence of implant threads the image of the implant was not strictly circular (Fig. 3).

3) *Bone fraction determination:* The bone fraction was determined by the bone segmentation within the circle band and presented as a function of radial distance. Data analysis for the two areas were performed in 2D and reconstructed in 3D. After segmentation and reconstruction of the bone sample, cavities along the implant surface were visualized.

Sample data

This section gives the full volume results for the one sample comprising the two areas. The tomographic 3D voxel size was 5 μm. For each of the 1999 different angles in the ROI the peri-implant bone volume fraction and BIC was evaluated.

Grafted bone area

The peri-implant bone volume contact fraction was 62.2% (Table 1). The BIC was approximately 4% (Table 1), (Fig. 4 and 5a), and within the first 65 μm the peri-implant bone volume fraction increased to approximately 50% (Fig. 5a). At a distance of 285 μm from the implant surface—the peak of the curve—the peri-implant bone volume fraction was approximately 82%. The peri-implant bone volume fraction levelled out at a 400 μm distance to approximately 78% (Fig. 5a). The mean peri-implant bone volume fraction was 75.6%, and the maximum peri-implant bone volume fraction was 82%. The total peri-implant bone volume fraction was 75.9%.

Recipient bone

The peri-implant bone volume contact fraction was 63.3% (Table 1). The BIC was approximately 3.5% (Table 1), (Fig. 5b), and within the first 50 μm the peri-implant bone volume fraction was approximately 50% (Fig. 5b). At a distance of 285 μm from the implant surface—the peak of the curve—the peri-implant bone volume fraction was approximately 76%. The peri-implant bone volume fraction levelled out at a 400 μm distance to approximately 80-85% (Fig. 5b). The mean peri-implant bone volume fraction was 79.3%, and the maximum peri-implant bone volume fraction was 85%. The total peri-implant bone volume fraction was 80.7%.

DISCUSSION

The present study introduces a 3D high-resolution method for evaluating the bone volume fraction at the surface and at different levels around a titanium dental implant based on SRμCT. A circle band analysis is presented which makes the different obtainable areas of interest for evaluation in 3D valuable. The experimental model implied a dental titanium implant in an augmented vertical

critical size defect at the mandibular base of goats simulating an atrophic mandibular alveolar process mainly comprising cortical bone. The aim was to present SRμCT images as a high-resolution 3D method at a 5 μm voxel size for evaluating peri-implant bone volume fraction and BIC in recipient and *de novo* formed bone.

The peri-implant bone volume contact fraction was 62.2% and 63.3%, the BIC was approximately 4% and 3.5%, the mean peri-implant bone volume fraction was 75.6% and 79.3%, and the maximum peri-implant bone volume fraction was 82% and 85% for the grafted and the recipient regions, respectively.

The BIC in the present study was approximately 3-4%. The value of BIC has been discussed in many studies representing different evaluation modalities. Sarve et al. found a BIC of 54-69%, at pixel size of 4.40 μm on two samples in human bone, 29 years post-surgery (Sarve et al. 2013) and scanned at the HASYLAB, DESY in Hamburg. Bernhardt et al. (Bernhardt et al., 2004), found a BIC of approximately 30% 4 weeks after implant installation, at voxel size 6.4 μm on a single sample in a Beagle dog scanned at the HASYLAB, DESY in Hamburg. In rats, Sarve et al. (Sarve et al. 2011) found a BIC of 45.8-70.1% 4 weeks after implant installation, at a pixel size of 4.40 μm scanned at the HASYLAB, DESY in Hamburg. In goats, Bernhardt (Bernhardt et al., 2005) found a BIC ranging between 44-70% 12 weeks after implant installation, at voxel size 10 μm, of 16 bone samples evaluated at the HASYLAB, DESY in Hamburg.

Discussing BIC is a matter of quality assessment of the surface of the titanium dental implant represented by the presence or lack of artefacts. The BIC is most often evaluated in a two-three-pixel size zone, which in the present study comprised 10-15 μm. Using SRμCT with a pink photon flux density at an X-ray photon energy sufficient to transmit the dental implants volume images free of artefacts and with a high contrast and signal-to-noise ratio. In order to acquire those tomographic images at high photon energies, the ID19 beamline of the ESRF was chosen. ID19 presents parallel beam geometry and a high number photons accessible for hard X-ray imaging using a wiggler insertion device. The acquired images allow for an estimate and precise bone detection.

BIC evaluation is also dependent of segmentation of the resin used for preparation of the specimens, which gives image noise, and difficulty in the segmentation procedure of new bone formation represented by osteoid. However, the formation of mineralized tissue in the present study was secured by an observation time of 20 weeks.

The peri-implant bone volume fraction in the present study in the grafted and in the recipient bone was 50% at a distance of 50-65 μm, and 76-82% at a distance of 285 μm away from the implant surface, respectively. This is comparable to other studies (Rebaudi et al., 2004; Sarve et al., 2013). This implies that our experimental study model is representative. Bernhardt et al., 2005 found a bone volume ranging between 40-67% after 12 weeks of healing of implants in a goat defect model at a distance of 0-700 μm.

Histomorphometry comprises a 2D fraction of a 3D structure and only represents a number of 10 μm thick sections in a process of cutting and grinding with subsequent loss of tissue in the preparation procedure. By performing 3D evaluation by the SRμCT method, it is possible to obtain data from the entire surface in a bone cylinder. When using SRμCT the resolution can be reduced due to refraction artefacts at the interfaces between materials of different electron densities (Rack et al., 2006;Rack et al., 2011;Stiller et al., 2009). It can be challenging to compare bone volume results evaluated by classical histomorphometry (2D) and results obtained from μCT and SRμCT. In the study by Rebaudi et al. (Rebaudi et al., 2004) bone volume differences evaluated by histology and by μCT ranged between 9-16%. In the study by Bernhardt et al. (Bernhardt et al., 2004) the difference in bone quantification was non-significant and less than 1% using SRμCT, however, when looking at the BIC the difference was about 10% (Bernhardt et al., 2004). Bernhardt et al. (Bernhardt et al., 2012) found a difference in BIC of 4.9%, and bone-implant-volume difference of 1.2% for histomorphometry—with 3-4 histological sections—compared to SRμCT. The number of histological sections, which they were able to compare directly to SRμCT, could explain the small differences. They conclude that 3-4 histological sections could be sufficient to evaluate bone-implant-volume with only minor discrepancy to 3D measurements.

Evaluation of BIC with SRμCT can cause some challenges due to the partial volume effect (PVE) which forces BIC measurements to be performed as a minimum of 1-2 pixels away from the implant surface. The PVE appears when structures are at the same size or smaller than the pixel size and therefore is not correctly detected. Consequently, the PVE can be reduced by higher resolution i.e. lower pixel size. SRμCT requires high contrast for detecting bone in proximity to a titanium surface; the bone need to be fully mineralized to be detected correctly (Bernhardt et al., 2012). When the implant surface is covered by a thin layer of mineralized tissue the PVE may arise because the absorption coefficients will be a mixture of bone and implant. Subsequently, PVE will always be found near interfaces and result in an underestimation of the bone, however this has not been found to be significant (Bernhardt et al., 2012; Mangano et al., 2013; Sarve et al., 2013). Bernhardt et al. (Bernhardt et al., 2012) defined a distance of 18 μm, 5 pixels, from the implant surface to be the position to obtain BIC values in SRμCT slices. Mangano et al. performed their BIC evaluations 2 pixels, 15 μm, from the implant surface. Sarve et al. (Sarve et al., 2013) performed BIC measurements 11 μm from the surface i.e. 1 pixel from the surface. This present study has a resolution of 5 μm, hence, it is possible to evaluate the BIC even closer to the implant surface compared to previous studies.

Our data represented by peri-implant bone volume fractions are in accordance with the leading studies within the field of 3D evaluations. Therefore the BIC difference in the present paper is assumed to be due to the higher performance of SRμCT with subsequent higher resolution, larger numbers of images and consequently expected higher precision.

CONCLUSION

A semi-automatic computer algorithm in order to determine the peri-implant bone volume fraction of the ROI in three dimensions was presented. The BIC was 3-4% in proximity to the implant surface, and 400 μm away from the dental implant the peri-implant bone volume fraction showed a steady level of nearly 80%. This kind of study, with immediate vertical bone augmentation around a dental implant, has not been performed before and evaluated at a spatial

resolution of 5 µm. As shown in this study, there is a tremendous difference of the peri-implant bone volume fraction comprising 50% when looking at a distance from the implant surface of 50-65 µm, compared to a bone fraction of 4% at a distance of 5 µm from the implant surface.

The method has been successful in depicting the bone and cavities in three dimensions thereby enabling us to give a much more precise answer to the fraction of the BIC compared to previous methods. The next step will be to further develop our method into an even more accurate image of the bone fraction in the very near proximity (0-50 µm) of the dental implant.

Whether the peri-implant bone volume fraction of 3-4% is an actual image of BIC or is due to the surgical design are unknown and not the aim of this study but will be evaluated in a future publication, which is in progress.

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