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The critical-size supraalveolar peri-implant defect model: reproducibility in histometric data acquisition of alveolar bone formation and osseointegration

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Abstract

Objective: The objective of this report is to present the reproducibility of outcomes assessments in the Critical-Size Supraalveolar Peri-Implant Defect Model.

Materials and Methods: Two examiners without specific experience in histological analysis and one experienced examiner performed the histometric evaluation. A comprehensive training program in data acquisition and histological analysis was established, the inexperienced examiners underwent approximately 12 h of training over multiple sessions. A custom-designed image analysis software macro and a computer-based image system were used to analyse digital images generated by a microscope camera system. Nine parameters for newly formed and resident bone were evaluated. Examiners performed histometric analysis using 36 histologic sections selected from critical-size supraalveolar peri-implant defects in 12 male Hound Labrador Mongrel dogs. Buccal and lingual measurements were performed in 72 sites. Intra- and inter-examiner reproducibility were evaluated using the concordance correlation coefficient (CCC) and means ± SD of the differences. Systematic errors were evaluated using an *F*-test for equality of means and variances.

Results: Intra-examiner reproducibility was high for all parameters evaluated, the lowest CCC observed being 0.87. Inter-examiner reproducibility was also high, most CCCs exceeding 0.90. Minor systematic errors for intra- and inter-examiner comparisons were occasionally observed. The results imply a high temporal stability because recordings were performed 3 months apart. Measurement errors were stable throughout the range of observations for all parameters.

Conclusions: High examiner reproducibility and temporal stability can be achieved for histometric data acquisition using the Critical-Size Supraalveolar Peri-Implant Defect Model. Examiner reproducibility should be routinely assessed, reported, and accounted for to assure the quality of evidence generated by preclinical studies

Key words: alveolar ridge augmentation; critical-size defects; dental implants; experimental animal models; measurement error; reliability; reproducibility

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Conflict of interest and source of funding statement

The text is not intended to promote products of any kind. The authors declare that they have no conflict of interests.
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Critical-size defect models have been developed and used extensively to assess biologic potential, efficacy and safety of candidate bone biomaterials, devices, and of growth factor-based technologies intended for indications in the axial and appendicular skeleton before clinical evaluation and public release (Einhorn 1999, Buma et al. 2004, Liebschner 2004). In context, craniofacial critical-size defects have included mainly calvarial and mandibular defects using murine, porcine, and canine platforms (Schmitz & Hollinger 1986, Wikesjö & Nilveus 1991, Wikesjö et al. 1994, 2006, Bosch et al. 1998, Gosain et al. 2000, Huh et al.

2005, Schlegel et al. 2006). These experimentally created defects do not regenerate spontaneously within the experimental lifetime of the animals and allow the evaluation of implanted biologics, biomaterials, and devices that may induce/enhance tissue regeneration as well as associated adverse reactions (Schmitz & Hollinger 1986, Wikesjö & Nilveus 1991, Wikesjö et al. 1994, 2006). Our laboratories have developed and characterized the Critical-Size Supraalveolar Periodontal Defect Model (Wikesjö & Nilveus 1991, Wikesjö et al. 1994) and subsequently the Critical-Size Supraalveolar Peri-Implant Defect Model (Wikesjö et al. 2006) for the assessment of periodontal and alveolar bone regenerative technologies. These are well-characterized canine models that provide a discriminating evaluation of candidate therapies that have been successfully screened in laboratory bench evaluations and small animal model systems. These defect models have proven to be a ''litmus test'' for candidate therapies for periodontal wound healing/regeneration and alveolar bone augmentation/osseointegration, respectively (Wikesjö et al. 1990, 1999, 2008a, Haney et al. 1993, Sigurdsson et al. 1994, 1995, 1997, Caplanis et al. 1997).

Various diagnostic technologies have been used to evaluate new regenerative therapies in preclinical and clinical research related to implant dentistry (Toriumi et al. 1999, Fritz et al. 2000, Mol 2004, Mengel et al. 2005, Park et al. 2007, Plachokova et al. 2007, Patel et al. 2008). Nevertheless, histological and histometric analysis remains the standard allowing not only the quantitative assessment of bone regeneration, but also an in depth understanding of the biological events occurring at the various stages of wound healing (Li & Jee 2005, Wikesjö et al. 2006). In perspective, the use of reliable measuring tools appears fundamental to compare the outcomes of candidate therapies. Examiner reproducibility has not received appropriate attention in preclinical studies investigating periodontal and alveolar bone regeneration with only few studies formally measuring and reporting intra- and inter-examiner reproducibility (Koo et al. 2004b). The objective of this report is to present the reproducibility achieved using the Critical-Size Supraalveolar Peri-Implant Defect Model. Our hypothesis was that well-trained examiners without specific experience on histological analysis would reproducibly measure alveolar bone formation and implant osseointegration under the experimental conditions of this defect model.

Materials and Methods

Examiner training and data acquisition

Two examiners (Q. T. and G. S.) without specific experience in histological analysis and one experienced examiner (J. L.) performed the histometric evaluation. The inexperienced examiners underwent comprehensive training in data acquisition and histological analysis for approximately 12 h over multiple sessions. Detailed information about the animal model, anatomical structures and histological findings were provided by the model proposer (U. M. E. W.). Written material illustrating the animal model and its uses was provided. The examiners were trained to use an incandescent light microscope (BX 51, Olympus America Inc., Melville, NY, USA), a microscope digital camera system (Retiga 4000R QImaging, Burnaby, BC, Canada), and a computer-based image-analysis software (Image-Pro Plus™, Media Cybernetic, Silver Spring, MD, USA) with a custom-designed macro for quantitative evaluation of the Critical-Size Supraalveolar Peri-Implant Defect Model. Histometric tools and parameters were explained and presented *in loco* using a subset of the specimens. Written definitions of the parameters clearly identifying histological landmarks, reference points, and biological findings were provided and any questions clarified. The examiners independently performed training measurements with a 1-week interval. Measurements were then compared and inconsistencies were discussed and corrected. Examiners underwent a second training session after 1 month to assure that proper measuring techniques. After the completion of the training, the inexperienced examiners performed data acquisition twice with a 3-month interval between the first and second data collection. Following the same protocol, the experienced examiner collected data twice with a 1-week interval between measurements. All measurements were performed independently and all examiners were masked.

Histological samples

Specimens for the analysis originated from a study that evaluated local bone formation and osseointegration at oral implants coated with recombinant human growth/differentiation factor-5 (Polimeni et al. 2009). In brief, Critical-Size Supraalveolar Peri-Implant Defects were created in 12 male Hound Labrador Mongrel dogs. Endosseous oral implants with a titanium porous oxide surface (TiUnite™, ø4.0 × 10 mm; Nobel Biocare AB, Göteborg, Sweden) with or without an rhGDF-5 coating (Scil Technology GmbH, Martinsried, Germany) were placed into contralateral mandibular jaw quadrants (3 implants/jaw quadrant). Implants were placed 5 mm into the osteotomy site leaving 5 mm above the alveolar crest. Tension-free flaps were advanced, adapted, and sutured for primary intention healing. The animals were euthanized following an 8-week healing interval and the implant sites prepared for light microscopy histology using standard methods (Donath & Breuner 1982, Rohrer & Schubert 1992). Only specimens including implants coated with rhGDF-5 were used for this analysis. The examiners performed histometric analysis of 36 histologic slides depicting the most central section of the threaded titanium oral implants. Buccal and lingual measurements were performed in 72 sites available for analysis.

Histometric analysis

A computer-based image-analysis system custom-designed macro was used to analyze the digital images of the implant sites captured by the light microscope digital camera system. Figure 1 illustrates the nine parameters that were measured for the buccal and lingual surfaces of each implant. Implants were custom-made with a reference notch 5 mm apical to the implant platform, the landmark assisting in the precise placement of the implants but also serving as landmark differentiating between newly formed and resident bone in the histometric analysis.

Newly formed bone:

- Defect height: distance from reference thread to the implant platform.
- Bone height: distance between the reference thread and the coronal extension of newly formed bone along the implant.
- Bone area: area of newly formed bone coronal to the reference thread along the implant.
- Bone–implant contact (BIC): percent BIC within newly formed bone from the reference thread to

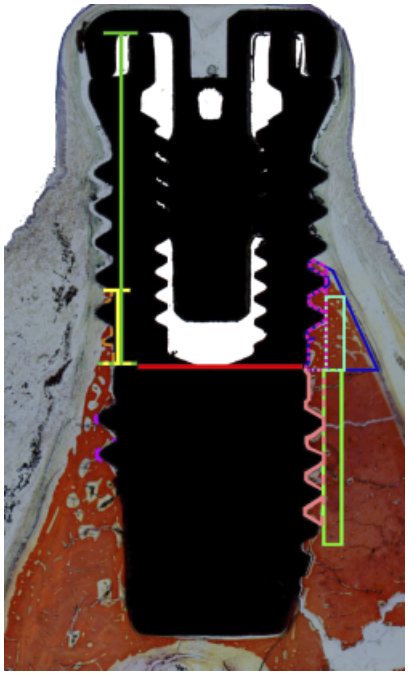

Fig. 1. Schematic representation of the histometric analysis. Reference thread (red line). Implant left side: defect height (green line), bone height (yellow line), new bone–implant contact (BIC) (dashed orange line) and resident BIC (dashed pink line). Implant right side: bone area (blue enclosure), new bone density outside the implant threads (light blue box), new bone density within the implant threads (pink enclosure), resident bone density within the implant threads (pale pink enclosure), and resident bone density outside the implant threads (green box).

the most coronal extent of bone along the implant.

- Bone density within the implant threads (BD_{WT}): ratio bone/marrow spaces in newly formed bone between the implant threads (thread root area) from the reference thread to the most coronal extent of newly formed bone along the implant.
- Bone density outside the implant threads (BD_{OT}): ratio bone/marrow spaces in newly formed bone immediately outside the implant threads within a rectangular template with a width equal to the height of the threads and length equal to the distance from the reference thread to the most coronal extent of newly formed bone along the implant.

Resident bone:

- Bone–implant contact (BIC): percent BIC within the resident alveolar bone from the reference thread to the most apical thread of the implant.
- Bone density within the implant threads (BD_{WT}): ratio bone/marrow spaces in the resident alveolar bone between the implant threads (thread root area) from the reference thread to the most apical thread of the implant.
- Bone density outside the implant threads (BD_{OT}): ratio bone/marrow spaces in the resident alveolar bone immediately outside the implant threads within a rectangular template with a width equal to the height of the threads and length equal to the distance from the reference to the most apical thread of the implant.

Statistical analysis

Intra-examiner reproducibility and measurements stability were evaluated by comparing the first and second measurements of each examiner. Inter-examiner agreement was assessed by comparing the two inexperienced examiners against each other and against the reference examiner. Intra-examiner and inter-examiner reproducibility were assessed calculating pair-wise concordance correlation coefficients (CCC; Lin 2000, Barnhart et al. 2007). Within the scope of the present analysis, CCC ranges between 0 and 1 with estimates closer to 1 indicating highly degree of agreement and small measurement error. Means ± SD of the differences between measurements were calculated and systematic differences were tested using an *F*-test for equality of means and variances (Bradley & Blackwood 1989). All analyses were performed using Stata's command concord (Stata 9.2 for Windows, Stata Corporation, College Station, TX, USA).

Scatterplots were constructed to compare the two inexperienced examiners using the experienced examiner as a reference. The two measurements performed by the experienced examiner were averaged and the average was used to establish a 45° reference line for each site. The inexperienced examiners measurements were plotted against this line. Observations that were located far from the reference line represent greater error than observations located close to the reference line.

Results

Intra-examiner reproducibility was very high for all parameters evaluated (Table 1). The lowest CCCs were 0.87 for BIC and BD_{WT} in resident bone indicating a high degree of agreement independent of previous experience. The magnitude of the measurement error was generally small with only few parameters reaching statistical significance. The reference examiner consistently showed higher reproducibility than the inexperienced examiners.

Compared with the reference examiner, both inexperienced examiners showed high CCCs for their measurements (Table 2). The lowest CCCs were 0.80 for newly formed bone area, 0.84

Table 1. Intra-examiner reproducibility for the Critical-Size Supraalveolar Peri-Implant Defect Model

	Reference examiner (measurement 1 *versus* 2)		Examiner 1 (measurement 1 *versus* 2)		Examiner 2 (measurement 1 *versus* 2)	
	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD
Newly formed bone						
Defect height (mm)	0.88	0.001 ± 0.09**	0.97	0.001 ± 0.05	0.91	0.01 ± 0.08
Bone height (mm)	0.99	0.02 ± 0.13	0.97	0.06 ± 0.26	0.99	0.03 ± 0.10*
Bone area (mm^2)	0.99	0.04 ± 0.19*	0.98	0.05 ± 0.23	0.96	0.11 ± 0.43**
BIC (%)	0.95	0.46 ± 7.71	0.87	2.52 ± 11.93	0.93	1.33 ± 9.12
BD_{WT} (%)	0.97	1.15 ± 6.21	0.90	1.35 ± 11.10	0.94	0.32 ± 9.10
BD_{OT} (%)	0.99	0.48 ± 4.19	0.98	0.55 ± 7.25	0.98	0.23 ± 7.26
Resident bone						
BIC (%)	0.97	0.13 ± 5.05	0.92	2.27 ± 7.80**	0.87	0.15 ± 10.39
BD_{WT} (%)	0.97	0.17 ± 5.22	0.92	0.69 ± 7.73	0.87	0.25 ± 10.43
BD_{OT} (%)	0.99	0.34 ± 4.50	0.97	0.36 ± 6.64	0.94	0.73 ± 9.63

BD_{OT}, Bone density outside the implant threads; BD_{WT}, bone density within the implant threads; BIC, bone–implant contact; CCC, concordance correlation coefficient.
*$p<0.05$; **$p<0.01$.

Table 2. Examiner reproducibility compared to the reference examiner for the Critical-Size Supraalveolar Peri-Implant Defect Model

	Examiner 1 measurement 1 *versus* reference examiner		Examiner 1 measurement 2 *versus* reference examiner		Examiner 2 measurement 1 *versus* reference examiner		Examiner 2 measurement 2 *versus* reference examiner	
	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD	CCC	MeanΔ ± SD
Newly formed bone								
Defect height (mm)	0.92	0.01 ± 0.07	0.87	0.001 ± 0.09	0.95	0.001 ± 0.06	0.93	0.001 ± 0.07
Bone height (mm)	0.86	0.10 ± 0.59	0.88	0.07 ± 0.56	0.92	0.04 ± 0.43	0.96	0.02 ± 0.31
Bone area (mm^2)	0.80	0.15 ± 0.86**	0.88	0.05 ± 0.61*	0.95	0.08 ± 0.36	0.97	0.03 ± 0.29
BIC (%)	0.93	1.58 ± 8.69	0.95	0.25 ± 7.74	0.96	1.75 ± 6.33	0.90	0.77 ± 10.60
BD_{WT} (%)	0.87	2.70 ± 12.38	0.90	2.39 ± 11.03	0.90	3.04 ± 10.96*	0.96	1.69 ± 6.54
BD_{OT} (%)	0.97	1.71 ± 9.53	0.98	1.48 ± 7.98	0.97	2.07 ± 9.54	0.99	1.52 ± 6.56
Resident bone								
BIC (%)	0.84	0.58 ± 11.21	0.89	0.72 ± 9.12	0.91	1.12 ± 8.16	0.93	1.15 ± 7.52
BD_{WT} (%)	0.85	0.66 ± 11.20	0.92	0.91 ± 8.22	0.94	2.16 ± 6.50**	0.92	2.85 ± 7.69*
BD_{OT} (%)	0.95	1.47 ± 9.18	0.97	0.74 ± 6.54	0.98	0.61 ± 6.16	0.98	0.97 ± 5.03

BD_{OT}, Bone density outside the implant threads; BD_{WT}, bone density within the implant threads; BIC, bone–implant contact; CCC, concordance correlation coefficient.
*$p < 0.05$; **$p < 0.01$.

Table 3. Inter-examiner reproducibility for the Critical-Size Supraalveolar Peri-Implant Defect Model

	Examiner 1 measurement 1 *versus* examiner 2 measurement 1		Examiner 1 measurement 1 *versus* examiner 2 measurement 2		Examiner 1 measurement 2 *versus* examiner 2 measurement 1		Examiner 1 measurement 2 *versus* examiner 2 measurement 2	
	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD	CCC	Mean Δ ± SD
Newly formed bone								
Defect height (mm)	0.97	0.01 ± 0.04	0.92	0.01 ± 0.07	0.94	0.01 ± 0.06	0.92	0.01 ± 0.08
Bone height (mm)	0.93	0.06 ± 0.41	0.94	0.03 ± 0.40	0.90	0.12 ± 0.48	0.92	0.09 ± 0.43
Bone area (mm^2)	0.83	0.23 ± 0.78**	0.91	0.13 ± 0.51**	0.82	0.19 ± 0.82**	0.90	0.08 ± 0.57*
BIC (%)	0.97	0.17 ± 5.53	0.95	1.50 ± 7.20	0.85	2.35 ± 13.27	0.94	1.02 ± 8.33
BD_{WT} (%)	0.97	0.34 ± 6.48	0.96	0.65 ± 7.09	0.86	1.01 ± 13.24	0.92	0.70 ± 10.09
BD_{OT} (%)	0.99	0.35 ± 5.17	0.99	0.59 ± 5.65	0.98	0.20 ± 8.42	0.99	0.04 ± 4.73
Resident bone								
BIC (%)	0.93	1.70 ± 7.06*	0.93	1.85 ± 6.78*	0.85	0.57 ± 11.13	0.94	0.42 ± 7.02
BD_{WT} (%)	0.89	1.50 ± 9.19	0.95	1.26 ± 6.29*	0.82	2.19 ± 12.00	0.93	1.94 ± 7.25
BD_{OT} (%)	0.96	0.86 ± 7.82	0.98	0.13 ± 6.12	0.94	0.50 ± 9.61	0.97	0.24 ± 6.79

BD_{OT}, Bone density outside the implant threads; BD_{WT}, bone density within the implant threads; BIC, bone–implant contact; CCC, concordance correlation coefficient.
*$p < 0.05$; **$p < 0.01$.

for resident bone BIC, and 0.85 for resident bone BD_{WT}. These CCCs pertained to the first measurements of examiner 1 and they all improved during the second measurements. All CCCs for the second examiner were above 0.90 indicating very high agreement with the reference examiner.

Inter-examiner reproducibility for the inexperienced examiners was very high with most CCCs exceeding 0.90 (Table 3). The lowest CCC for inter-examiner reproducibility was 0.82 for new bone area and resident bone BD_{WT}. Inter-examiner error (Table 3) was higher than intra-examiner error (Table 1), but inter-examiner error only reached consistent statistical significance for newly formed bone area. Punctual significant differences were also observed for some inter-examiner comparisons for newly formed bone BIC and resident bone BD_{WT}. In both cases the mean difference between examiners was smaller than 2% (Table 3).

Figures 1–5 show individual measurements of the inexperienced examiners plotted against the reference examiner's average measurements. Most observations for newly formed bone height and area, and BD_{OT} were close to the 45° line, indicating good overall agreement (Figs 2 and 3). No increase in error could be observed throughout the range of these variables indicating that measurement error was constant and not associated with increasing values. Similarly, observations were spread above and below the reference line indicating that systematic error was not prevalent. Greater measurement errors for newly formed bone BIC (Fig. 4) and BD_{WT} (Fig. 5) were observed as seen by the spread of observations around the 45° line. The measurement error was relatively constant throughout the range of the variables and no systematic error could be observed.

Discussion

This report presents the reproducibility that can be achieved by trained examiners using the Critical-Size Supraalveolar Peri-Implant Defect Model. Intra- and inter-examiner reproducibility

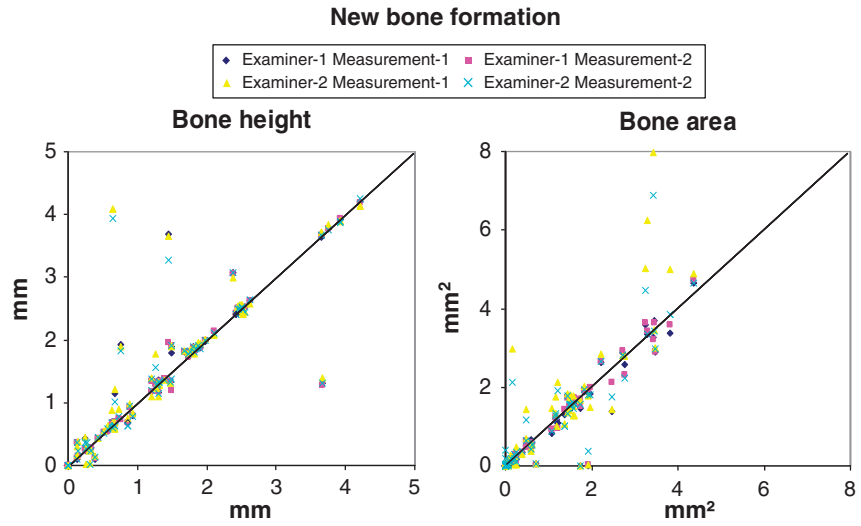

Fig. 2. Scatterplot for newly formed bone area and height for both examiners at the two time-points. Reference line represents the mean for the reference examiner measurements and provides a measure of the true value. Observations close to the reference line have lower measurement error.

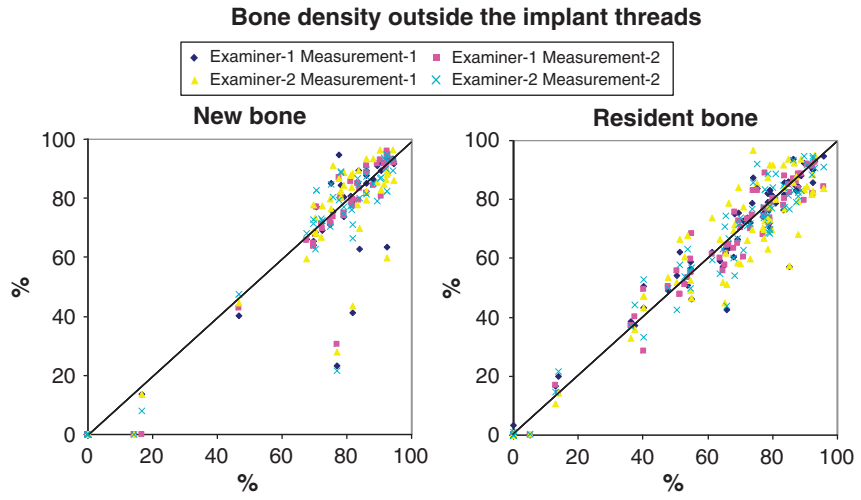

Fig. 3. Scatterplot for bone–implant contact in newly formed and resident bone for both examiners at the two time-points. Reference line represents the mean for the reference examiner measurements and provides a measure of the true value. Observations close to the reference line have lower measurement error.

were high for all parameters evaluated assuring the precision of the data gathered. The results also imply a high temporal stability because measurements were performed 3 months apart. Collectively these results demonstrate the high reproducibility that can be achieved when clearly defined clinically relevant parameters are measured by trained examiners using custom-designed data acquiring tools and a discriminative animal model. The present findings further support the suitability of this experimental model in the research and development of novel technologies for implant dentistry and alveolar bone regeneration.

Examiner reproducibility has not received particular attention in preclinical research on dental implants. An exploratory search of the indexed literature published the last 5 years using PubMed database and pertinent keywords (''dental implants'' AND ''bone regeneration'' AND dogs) resulted in 44 publications. Of these only one article explicitly reported examiner reproducibility (Schwarz et al. 2007) besides those from our laboratory. Obviously, studies that did not report measurement errors are not necessarily unreliable. However, without reproducibility estimates readers cannot objectively assess data acquisition quality. Unreliable examiners may introduce bias to the measurements affecting the results and ultimately the validity of the findings (Barnhart et al. 2007). Large measurement errors also increase results variability decreasing the power to detect differences between interventions (Tosteson et al. 2003). Examiner agreement was evaluated by calculating the CCC (Lin 2000, Barnhart et al. 2007) and the means ± SD of the difference between measurements. CCC was first introduced in 1989 and readily become one of the most used indexes for assessing agreement. It provides an estimate of the agreement between two variables and estimates close to one indicate excellent agreement. Historically, the Intraclass Correlation Coefficient (ICC) has also been used to estimate reproducibility of continuous measurements. However, as ICC is based on analysis of variance models it has stricter statistical assumptions than CCC (Barnhart et al. 2007). Nevertheless, in the present study CCC and ICC estimates were similar. Reproducibility was further assessed plotting each observation against the overall mean estimate for each site. This approach allows the evaluation of the magnitude, direction, and range of the measurement error. An important requirement to be able to assess the reproducibility of continuous variables is the amplitude of the values. The Critical-Size Supraalveolar Peri-Implant Defect Model exhibits a very limited native osteogenic potential (Wikesjö et al. 2006), therefore the control group of the original study was not included in the analysis to provide a wide range of values for all parameters.

Previous studies from our laboratory have shown a high degree of reliability for the examiner with CCCs values usually ranging between 0.95 and 0.99 (Wikesjö et al. 2006, 2008a–c). However, these estimates were always based on evaluations performed by highly trained and experienced examiners within our research group. The question that remained unanswered was if the critical-size model and its evaluation tools were well suited for inexperienced examiners following a short-term adequate training. The present findings showed that a high degree of reliability can be achieved, nevertheless it is also clear

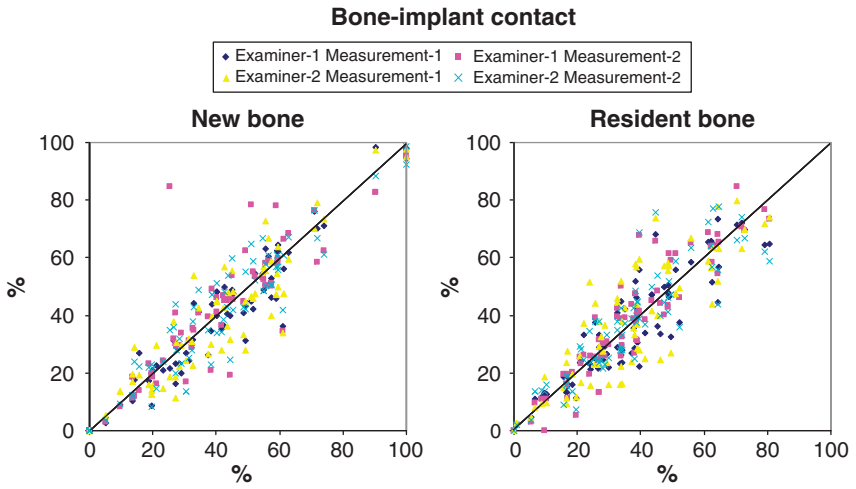

Fig. 4. Scatterplot for bone density within the implant threads in newly formed and resident bone for both examiners at the two time-points. Reference line represents the mean for the reference examiner measurements and provides a measure of the true value. Observations close to the reference line have lower measurement error.

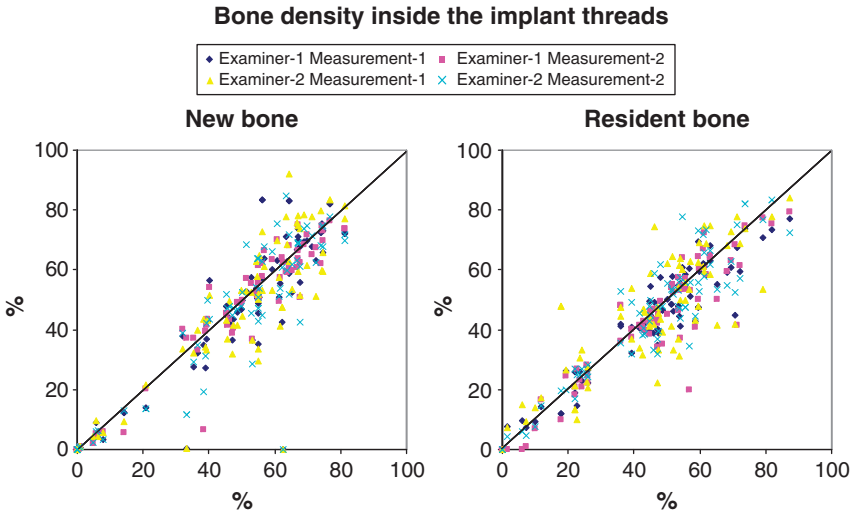

Fig. 5. Scatterplot for bone density outside the implant threads in newly formed and resident bone for both examiners at the two time-points. Reference line represents the mean for the reference examiner measurements and provides a measure of the true value. Observations close to the reference line have lower measurement error.

that experience can improve measurement reliability because experienced examiners consistently achieved CCC exceeding 0.95 for all parameters evaluated in the present and previous studies (Wikesjö et al. 2006, 2008a–c). It is also important to acknowledge that the present findings are constrained by the experimental conditions of the study and that generalizations of the results to other settings and observers should be made with caution.

Intra- and inter-examiner reproducibility of histometric parameters using the Critical-Size Supraalveolar Periodontal Defect Model has also been assessed (Koo et al. 2004b). Overall, intra- and inter-examiner reproducibility achieved in the peri-implant defect was higher than that obtained in the periodontal defect. This is probably related to the greater complexity of the periodontal tissues compared with the peri-implant tissues after tissue regeneration. Periodontal regeneration is composed of several tissues, i.e., cementum, periodontal ligament fibers, and alveolar bone, whereas only alveolar bone is evaluated following bone augmentation/regeneration. Linear and area measurements showed the highest reproducibility in both animal models, whereas bone density measurements appeared more difficult to evaluate. Experienced examiners have been able to achieve high reproducibility in bone density assessment (Koo et al. 2004b, Wikesjö et al. 2008a–c) underlining the importance of experience in more challenging parameters. As expected, intra-examiner reliability was slightly higher than inter-examiner reliability in both Critical-Size Defect Models.

The present study contributes to the characterization of the Critical-Size Supraalveolar Peri-Implant and Periodontal Defect Models. These animal models have been used in more than 50 reports and are among the most used models for preclinical evaluation of periodontal wound healing/regeneration and alveolar augmentation/osseointegration. Previous methodological studies from our group have shown the stability of both critical-size defects (Wikesjö et al. 1994, 2006), appropriate sample size (Wikesjö et al. 1994), and histometric assessment strategy (Koo et al. 2004a). This study provides important information regarding the overall measurement error that can be attained using these experimental methodologies. In conclusion, high examiner reproducibility can be achieved for the histometric data acquisition used to evaluate the Critical-Size Supraalveolar Peri-Implant Defect Model.

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Clinical Relevance

Scientific rationale for the study: Examiner reliability has not received particular attention in preclinical research with only few studies assessing and reporting measurement errors. Lack of examiner reliability may introduce bias affecting the validity of the results. Large measurement errors increase variability decreasing the power to detect differences between interventions when actually present.

Principal findings and Practical implications: The present study contributes to further characterize the Critical-Size Supraalveolar Peri-Implant Defect Model as a ''litmus test'' for candidate therapies for alveolar bone augmentation and osseointegration. This study shows that high examiner reproducibility can be achieved under the experimental conditions of this defect model.