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Peri-implant marginal bone loss rate pre- and post-loading: an exploratory analysis of associated factors.

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Abstract:

Objectives: To examine factors influencing rates of peri-implant marginal bone loss (RBL) calculated over different time-frames, at implants unaffected by peri-implantitis. **Material and Methods:** 154 implants from 86 patients were reviewed at 1.6-6.8 years after placement. Marginal bone levels (MBL) were assessed on intraoral-radiographs at 3 time-points: immediately post-placement, time of loading, and least 1-year post-loading. RBLs (mm/year) were computed using these 3 time-frames and corresponding MBL changes as: RBL-placement-loading, RBL-loading-review, RBL-placement-review. Exploratory ordination of 3 RBLs, corresponding time-durations, and 17 background factors was used for visualization. Hierarchical linear mixed effects models (MEM) with predictor selection were applied to RBL outcomes. The correlation of actual MBL with MBLs predicted by RBL placement-loading and RBL loading-review was tested. **Results:** Median RBL placement-loading was 0.9 mm/year (IQR=2.02), loading-review was 0.06 mm/year (IQR=0.16) and overall RBL placement-review was 0.21 mm/year (IQR=0.33). Among patient variance was highest for RBL placement-loading (sd=0.66). Longer time predicted lower RBL in all time-frames. Shorter time of loading significantly predicted lower RBL placement-review. Augmentation predicted lower RBL placement-loading, while anterior location and older age predicted lower RBLs placement-loading placement-review. Only MBL projected using RBL-placement-loading significantly correlated with actual MBL. **Conclusions:** RBL varied with the time-duration used for calculation in pre-, post-loading, and overall periods. In each period, RBL declined with increasing time. Earlier loading predicted lower overall RBL. Higher pre-loading RBL predicted worse actual bone level.

Introduction:

Maintenance of peri-implant marginal bone level is a key criterion for implant success. Surgical placement is usually followed by remodelling and peri-implant marginal bone loss Many thresholds of acceptable marginal bone loss are reported. Widely adopted thresholds are; 0.1-0.2 mm of bone loss per year (Albrektsson, Zarb, Worthington, & Eriksson, 1986) or loss of 2 mm (Misch et al., 2008) after the first year of loading. Other reported thresholds include; 2.5 mm bone loss after 5 years (Berglundh, Persson, & Klinge, 2002) and, 1-1.5mm (Derks & Tomasi, 2015) or 0.4mm (Koldsland, Scheie, & Aass, 2010) from the time-point of loading. Although these bone loss thresholds provide easy clinical 'cut-offs', they do not predict future bone loss. A common reference point for measuring bone loss is prosthetic loading. With advances in implant dentistry, earlier loading is more common than before. On the other hand, large augmentation/GBR procedures are also increasing. In such cases, implants are more likely to be loaded later than usual. Taken together these suggest a wide range of loading times exist in current clinical scenarios. If bone loss is measured from the loading event but the time of loading is ignored, such differences could be confounding. Marginal bone remodeling is a dynamic process. Thus, its rate changes over time. This is evident in the poor correlation of total marginal bone loss with time in function (Hasegawa, Hotta, Hoshino, Ito, Komatsu, & Saito, 2015). Therefore, the rate of bone loss (RBL) has been proposed as a better index of implant success than bone loss or bone level values (Galindo-Moreno, León-Cano, Ortega-Oller, Monje, O′Valle & Catena, 2015). RBL may have predictive use. High early RBL correlated to worse marginal bone levels, and a 'bone loser' phenotype could be identified (Galindo-Moreno, et al., 2015). However, in practice, the reported bone loss may be based on annual measurements or calculated from change in bone levels measured over varying time intervals. A previous study used four time-intervals and found different RBL values for each, leading to different implant success rates (Geraets, Zhang, Liu & Wismeijer, 2014).

Many patient, site, and implant-related factors have are associated with peri-implant bone loss. These include the duration of healing (Naert, Koutsikakis, Duyck, Quirynen, Van Steenberghe & Jacobs, 2002; Rouck, Collys, & Cosyn, 2008), the depth of implant placement (Valles, Rodríguez-Ciurana, Clementini, Baglivo, Paniagua, & Nart, 2018), location and type of implant-abutment interface (Atieh, Ibrahim, & Atieh, 2010; van Eekeren, Tahmaseb, & Wismeijer, 2015), abutment height (Nóvoa, Batalla, Caneiro, Pico, Liñares & Blanco, 2017; Blanco, J., Pico, A., Caneiro, L., Nóvoa, L., Batalla, P., & Martín-Lancharro, 2018), implant geometry and surface characteristics (Zechner et al., 2004; Şener-Yamaner, Yamaner, Sertgöz, Çanakçi, & Özcan, 2017), type and timing of occlusal load (Schincaglia, et al., 2016), bruxism and occlusal overload (Kozlovsky, et al., 2007; Zhou, Gao, Luo, & Wang, 2015), soft-tissue at implant site (Linkevicius, Puisys, Linkeviciene, Peciuliene, & Schlee, 2013; Suárez-López del Amo, Lin, Monje, Galindo-Moreno & Wang 2016), bone density (Chow, Chow, Chai, & Mattheos, 2016), augmentation procedures (Huang, Ogata, Hanley, Finkelman, & Hur, 2014). Inflammatory peri-implant disease and its risk factors; periodontal disease susceptibility (Corcuera-Flores, Alonso-Domínguez, Serrera-Figallo, Torres-Lagares, Castellanos-Cosano & Machuca-Portillo, 2016), smoking (Peñarrocha, Palomar, Sanchis, Guarinos & Balaguer, 2004; Levin, Hertzberg, Har-Nes, & Schwartz-Arad, 2008) and diabetes (Alrabiah et al., 2018) also influence marginal bone loss. Factors that influence how the rate of bone loss can change with time are not well understood.

Determining the best predictors is a challenge in exploratory studies. There are many potential explanatory variables, some of which may be correlated. Data-mining and multivariate exploratory statistics attempt to resolve this complexity. They are increasingly used to gain insights from clinical data. Ordination is an exploratory method which can visually depict the relationship of multiple variables, by reducing data-complexity. In implant dentistry, this technique has been used to select classifiers of peri-implantitis affected and resistant clusters (Papantonopoulos, Gogos, Housos, Bountis, & Loos, 2016). As peri-implant bone levels are also affected by patient-level factors, when many implants per patient are analysed such data is hierarchical. With appropriate analytics and mixed models, one can model such complex data and select the most relevant predictors.

The aims of the current study were: i) to explore how multiple background features were related to rates of peri-implant bone loss (RBLs) computed over different time-frames in reference to loading, ii) to identify amongst these background features, the most robust predictors of these RBLs iii) to analyse the impact of patient-level variation on these RBLs, and, iv) to analyse correlation, if any, between projected marginal bone levels using different RBLs in reference to loading, and the actual marginal bone levels measured at review.

Materials and Methods:

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong and the Ethics Committee of the Faculty of Dentistry, University of Hong Kong (reference number: UW 15-609). Retrospective data were sourced from patients treated by postgraduate students in the Implant Dentistry clinic, The University of Hong Kong (Ng, Fan, Leung, Fokas, & Mattheos, 2018).

Subject Recruitment: In brief, patients who had received implant treatment from 2009 to 2014 in the Centre of Advanced Dental Care, Prince Philip Dental Hospital, The University of Hong Kong had been invited to participate in the study and attend a recall visit. Prior to screening and clinical examination, patients had been informed about the research, and written informed consent was obtained. All procedures were aligned with the ICH-GCP guidelines.

Inclusion and exclusion criteria: The main inclusion criteria were: subjects aged 21 and above, in good general health (absence of uncontrolled systemic disease and conditions), having received an implant-supported fixed dental prosthesis on an implant of length ≥ 8mm, with at least one year post-loading at the time of review examination, no missing clinical or demographic data, and availability of intra-oral periapical radiograph of implants taken at the following 3 time-points: i) at date of fixture installation, ii) at the date of loading with the final prosthesis, iii) at review at least one year after loading. Implants with diagnosis of or having received treatment for peri-implantitis based on the current case-definition, (Berghlundh, et al., 2018; Renvert, Persson, Pirih & Camargo; 2018) were excluded. In brief, peri-implantitis was diagnosed where radiographic measurement of bone level of ≥3 mm and/or probing depth ≥6 mm was found concomitant with bleeding on probing.

Study Procedures: Demographic, dental and medical history; history of diabetes mellitus, other controlled systemic disease, medication status, smoking, parafunctional habits and past history of periodontal disease and details relevant to implant treatment were sourced from patient records. Clinical examination data included full-mouth periodontal examination including Probing Pocket Depth (PPD), full mouth plaque score (FMPS), and bleeding on probing (BoP). One Periapical radiograph with parallel technique had been taken for each of the implants.

Radiographic Measurement of marginal bone levels (MBL) and computation of rates of bone loss (RBL): Periapical Radiographs from each implant at the 3 time points were scanned at a resolution of 400 dpi and digitized by Epson Perfection V700™ Photo Dual lenses scanner. After digitalization, Image J™ (Wayne Rasband National Institutes of Health, USA) was used for obtaining precise measurements on the radiographs. Dimensions of the digitized radiographs were calibrated to account for distortion by using known distance between implant threads and implant diameter. Two examiners were calibrated with 6 random sets of radiographs with an intraclass correlation coefficients documented as 0.99 and then conducted all measurements (Ng et al., 2018).

MBLs were assessed by defining 2 specific landmarks on the 3 radiographs of each patient : The implant platform of tissue level (or shoulder of bone level implant) (PL) and the most coronal point of crestal bone (CB) in contact with the implant. A line parallel to the axis of the implant was drawn between CB and PL (CB-PL). Measures on mesial and distal aspects were obtained. To determine the RBLs in the placement-loading, loading-review, and overall (placement-review) period, the change in corresponding mesial CB-PL(ΔmCB-PL) and distal CB-PL (ΔdCB-PL) were computed, averaged to determine change in MBL per implant (ΔMBL), and divided by the duration of the corresponding time-frame in years, to obtain the 3 RBL values (in mm/year) per implant: A) RBL placement-loading, B) RBL loading-review, C) Overall RBL placement-review.

Statistical Analysis: All statistical analyses were performed in the R statistical environment (https://www.r-project.org/) using R version 3.1.3. 17 background (implant-, site-, and subject- related) variables were documented and categorised as described in Table S1 (supplementary file). These included continuous (Age, Time at loading, Time since placement, Time since loading, PPD, Full mouth plaque score), ordinal (BOP, Diabetes, Smoking, Periodontal Disease, Bruxism) and categorical (Gender, Soft tissue Biotype, Implant abutment interface, Type of Implant surface, Placement Type, Augmentation at implant site, Arch location; Antero-posterior location; Prosthesis Type; Retention Type, Antagonist Type). The 3 RBLs and background variables were used for ordination analysis using the 'Multiple Factor Analysis' (MFA) function in the R package '*FactoMineR*' (Husson, Josse, Le & Mazet, 2016). MFA is a dimensionality reduction method. It reduces complexity of multivariate data and allows visual interpretation of major patterns. It is suited to data that contains both continuous and categorical variables. MFA also allows grouping of variables where each group is normalized individually, in order to balance their influence. An MFA correlation circle plot depicts the continuous variables and factors plot depicts the categorical variables. These were drawn to visualize the inter-relationships of background variables and RBLs. To determine the best predictors of each RBL, a 'best subset' approach was applied to all possible predictors. The 'regsubsets' function in the '*leaps*' package (Lumley, 2009) was applied. A combination of 'model adjusted R squared' (indicating model-fit) and 'Bayesian Information Criteria' (BIC) (based on both model complexity and fit) were used. The predictor set that gave the best combination of highest adjusted R squared and lowest BIC values was selected. Linear-mixed effects regression models (MEM) were made with these selected predictors for each RBL as outcome (Pinheiro, Bates, DebRoy, Sarkar & R Core team, 2018). MEM is suitable for hierarchical or nested data. The patient was incorporated as a grouping factor (as random intercept) considering there were multiple implants in several patients. This accounted for among-patient variation in RBLs. Lack of multicollinearity of MEM predictors was confirmed by variable inflation factors

(VIF). VIF<2 was indicated the predictors were not correlated. MEM parameters were bias- corrected by simulation (bootstrapping, n=1000) (Loy and Steele, 2016). Simulation-based correction of bias and model validation is particularly relevant to models with small sample sizes (Van der Leeden, Meijer, & Busing, 2008). The full MEMs were compared to null models with patient-level random intercept only models (parametric bootstrapped test, n=1000) (Halekoh & Højsgaard, 2014).

Lastly, 2 projected MBLs (p-MBLs) (using RBL placement-loading and RBL loading-review each), were determined by multiplying each RBL with the overall time in function and adding the obtained values to MBL measured at placement. Correlations of the 2 p-MBL with the actual MBL at review were assessed using Spearman's correlation test.

Results:

A total of 243 Straumann implants from 119 patient records were screened and 154 implants from 86 patients were included. Table 1 presents the descriptive statistics for all the background parameters and computed RBL values. The time from placement to loading ranged 1 month-2 years & 3 months (median=5 months, IQR=4 months), time from loading to review ranged 1 year-6 years & 1 month (median=3 years IQR=1 year & 1 month) and the total time from placement to review was 1 year & 7 months -6 years & 11 months (median=3 years & 10 months, IQR=10 months) (Figure 1, Table 1). Bone loss averaged per implant (ΔMBL) from placement to loading ranged from -1.56 to 3.16 mm (median=0.53, IQR=0.85), from loading-review ranged from -0.77 to 1.77 mm (median=0.22, IQR=0.46), and total bone loss from placement to review ranged from -1.08 to 3.98 mm (median=0.78, IQR=1.09).

Figure 2 depicts the ordination of variables along the first two MFA components. Together these components explained 18.92% of the total variance in the data, suggesting much variation remained unexplained. However several inter-relationships among the measured variables were evident. RBL values and their corresponding time-frames had high projections in opposing directions (Figure 2). Thus, they were inversely related to each other. History of periodontitis was closely grouped with implant-level PPD and risk factors of periodontitis, smoking and diabetes. BOP, age, and full-mouth plaque scores were similarly related and aligned with RBLs suggesting these are positively related. The qualitative variable levels projection showed posterior and mandibular location, transmucosal placement, no augmentation at implant site, tissue-level implant-abutment interface, single crown type prosthesis, cement retained type retention and SLA type surface as correlated. On the opposing aspect, anterior and maxillary location, submerged placement, bone level, augmentation at implant site, bone-level implant-abutment interface, SLActive type surface and cantilever type prosthesis were clustered

(Figure 2). From among these, 'best subset' based predictor selection gave 4 predictors for RBL placement-loading (Time: placement to loading, Augmentation, Age and Anteroposterior location), 3 predictors for RBL loading-review (Time Loading-Review, Anteroposterior location, Placement type) and 5 predictors for RBL placement-review (Time Placement-Loading, Time Placement-Review, Augmentation, Age and Anteroposterior location) (Figure S1).

The MEM outcomes are summarized in Table 3. Overall similar patterns were seen for RBL placement-loading and RBL placement-review models. The length of each corresponding time-frame had a significantly negative impact on all 3 RBL outcomes (Table 2). Per unit time, RBL declined the fastest during placement-loading but this effect was not significant (bias corrected β= -0.63, p=0.13) (Figure 3). It was the lowest for RBL-Loading-Review (bias corrected β= -0.05, p=0.04*). For RBL placement-review, an opposite effect of the time from placement to loading was seen. Here, greater time from placement to loading predicted greater RBL (bias corrected β=0.1, p=0.03*). Thus, earlier loading was independently associated with lower overall RBL at review. Age and anterior location significantly predicted lower RBLs placement-loading and placement-review. Scatter plots showed the relationship between Age and RBL values showed a bimodal relationship peaking at 50-60 years, followed by a decline (Figure S2). Similarly, Augmentation and anterior location significantly predicted lower RBL placement-loading but did not reach significance for RBL placement-review (Table 2). The variation in the patient-level intercept reflects the among-patient RBL variation. The highest value was noted for RBL placement-loading (bias corrected sd=0.66). Model R-squared value is a measure of model-fit or its explanatory value. It was highest for the RBL placement-review (R squared=0.48) and lowest for RBL loading-review (R squared=0.08). Thus, the best explained was RBL placement-review and the least explained was RBL loading-review. When the full MEM and patient-level random-intercept only models were compared, significant differences were noted for all 3 models. All patient-level intercept-only models had relatively lower R-squared values. However, for RBL placement-review, the patient-level intercept-only model (R squared=0.40) also performed relatively well compared to the full-model (R squared=0.48), showing inter-patient variation notably explained this RBL outcome.

Correlation tests showed p-MBL using RBL placement-loading was significantly and strongly correlated to actual MBL at review (Spearman's rho=0.79, p<0.001). No significant correlation was noted between p-MBL using RBL loading-review and actual MBL at review (Spearman's rho=-0.09, p=0.27) (Figure 4).

Discussion:

The present study used the rate of bone loss as an outcome. This was computed over 3 different time-frames. We found the actual bone level at review was poorly predicted using the post-loading rate of bone loss but closely predicted using the pre-loading rate. Overall, these findings support the annual rate of bone loss as an index for implant success as suggested earlier (Galindo-Moreno, et al., 2015), as it can have value in predicting the future bone loss. These findings also confirm that the rate of bone loss varies with the time over which it is calculated (Gearaets, et al. 2014). Together, they strongly support the need to standardize how annual rate of peri-implant bone loss is measured, reported, and interpreted.

A primary finding was that the rate of bone loss was not a stable linear trait but de-accelerated with time. Ordination showed RBLs and time-durations projected in opposing directions (Figure 2). The MEM validated this inverse relationship in both pre-, post- loading and overall measurement periods, after accounting for other predictors, time-frame, and inter-subject variation. These findings have important implications for future research. Data which summarise annual peri-implant bone loss reported in cross-sectional studies and meta analyses should be pooled only when it is calculated over similar times since placement. Alternatively, they must account for differences in total time in function, time-point of loading, and other influencing factors. This message is also relevant to future retrospective studies. As implants increase in both numbers and time in function, more retrospective assessments can be anticipated. These should define the annual rate of bone loss as a function of the total time over which it was calculated. In addition, if only the loading event is used as reference but its time-point is variable or ignored, simple comparisons may be erroneous.

The second main finding is that inter-patient variability contributed to much variation in the early or pre-loading rate of bone loss. Moreover, this pre-loading rate of bone loss was strongly predictive of later bone levels and the models for RBL placement-loading and RBL placement-review were very similar. Together these indicate an 'early bone loser type' who is more predisposed to worse marginal bone levels (Galindo-Moreno, et. al, 2015). As there were multiple implants per subject in many cases, a hierarchical model was used to predict RBL. The role of inter-patient variability was quantified and accounted for. A number of factors could explain such individual variation. These include host-bone tissue characteristics (Merheb, et. al, 2015) and local or systemic influences.

The third key finding is that earlier loading predicted a lower rate of bone loss in the long-term. Mechanical loading can modulate bone turnover so some authors have hypothesized that earlier loading may slow marginal bone loss (Bilhan, Mumcu & Arat, 2010; Schincaglia, et al., 2016). A tendency to lower bone loss at early versus conventionally loaded implants is reported (Helmy, Alqutaibi & Shawky, 2018). Biologically, certain extend of loading results in mechanical stimulation of osteocytes leading to increased bone mass (Klein-Nulend, Bakker, Bacabac, Vatsa, & Weinbaum, 2013). Notably, no immediate implants were included in the present analysis, which precludes any conclusions regarding these. Others have found immediate loading did not show any positive influence on bone levels (Elsyad, Al-Mahdy & Fouad, 2012; Elsyad, Elsaih & Khairallah, 2014).

In the placement-loading period, augmentation had a significant protective effect on RBL. As all augmentations were grouped in this analysis, including different defect size and type, materials, GBR, and sinus floor augmentation, it is difficult to draw clear conclusions. GBR has been associated with lower marginal bone loss after loading (Jung, Herzog, Wolleb, Ramel, Thoma & Hämmerle, 2016). No difference or less bone loss was found by some (Bazrafshan & Darby, 2018; Zumstein; Billström & Sennerby, 2010). Others found augmented sites had greater bone loss in the pre-loading (Huang et al., 2014) and long-term durations (Zitzmann, Schärer & Marinello, 2001). Sinus floor augmentation has also shown greater marginal bone loss in the first year (Galindo-Moreno, Fernández-Jiménez, Avila-Ortiz, Silvestre, Hernández-Cortés & Wang, 2013). The type of augmentation material and protocols can differently influence bone loss (Benic, Bernasconi, Jung & Hämmerle, 2017; Schwarz, Schmucker & Becker, 2016). Bone loss was lower in bone substitute grafted or untreated sites but increased in sites treated with membranes (Zambon, Mardas, Horvath, Petrie, Dard & Donos, 2011). How augmentation parameters impact bone turnover before and after loading needs greater study. Implant-abutment connection type, abutment height, and patient factors also have interaction effects (Galindo-Moreno, et al., 2013). Augmentation was also clustered with implant submergence, anterior and maxillary location, bone level type implant in the ordination plot (Figure 2). These reflect that a need to augment was linked to clinical choices of submergence and bone level interface. Among these, the factor which drives the clinical decision may be the more important predictor in reality. Future studies should assess the driving factors of clinical decisions. A tendency of submerged implants for lower RBL loading-review was noted. This conflicted with past reports (Sanz et al., 2013; Paul, Petsch, & Held, 2017;) but was similar to Flores-Guillen et al. (Flores-Guillen, Álvarez-Novoa, Barbieri, Martín & Sanz, 2018). Bone turnover is slower before abutment connection in the case of submerged implants (Hermann, Cochran, Nummikoski & Buser, 1997). However, this is not consistent with the observation that an effect was observable after loading. Older age weakly predicted slower rates of bone loss. Aging negatively affects bone density and cancellous bone mass, increases cell apoptosis, but also reduces osteoblast activity

(Boskey & Coleman, 2010). Others found aging was associated with greater marginal bone loss at implants which peaked at 50-60 years (Negri, et al., 2014). These contradictions may be explained by the large spread of age in the present cohort. A bimodal relationship, with the rate of bone loss peaking at the age of 50-60, but slow in more advanced age was seen (Supplementary File, Figure S2). A limitation is that the 18-21 age group was not included, as potential active jaw-growth was considered a contraindication (Björk, 1963).

Implants diagnosed with or having been treated for peri-implantitis (Berghlundh et. al., 2018; Renvert et al., 2018) were not included in the study, which prevents any extrapolation of findings to implants with substantial disease. A number of case-definitions for peri-implantitis are reported (Renvert et. al., 2018). The consensus case-definition adopted here considers bleeding on probing and/or deep ≥6 mm probing depth concomitant to bone levels of ≥3 mm as diagnostic of peri-implantitis. Implants that lost ≥3 mm peri-implant bone but were free from bleeding on probing were thus included. Patients in the present study were enrolled in a maintenance program, which implies that past professional care had been delivered as necessary. The ordination (Figure 2) depicted bleeding on probing and RBLs projected in similar directions. This indicated a positive relationship existed.

Major limitations of this study include its exploratory nature, retrospective design, single time-point assessment, modest sample size, short observation periods and a limited number of potential predictors addressed. For example, implants of less than 8mm are common alternatives to augmentation and so these may affect bone loss of in clinical populations (Tabrizi; Arabion; Aliabadi & Hasanzadeh, 2016; Nielsen, Schou, Isidor, Christensen & Starch-Jensen, 2018). The current cohort did not include these. All the implants analyzed were placed by postgraduate students, thus were cases that were deemed suitable for training. Operator experience and competency are variables that can impact surgical accuracy. The lack of cases treated by experts in this population is another possible source of bias

(Cushen & Turkyilmaz, 2013). Many implant-related variables such as abutment height and implant surface (Spinato, Bernardello, Sassatelli & Zaffe, 2017; Blanco, et al., 2018) or soft-tissue thickness (Suárez-López del Amo et al., 2016), which have been related to bone loss were not evaluated. While many known patient and implant level factors were explored, only a small set of the most influential variables were evaluated as explanatory variables. Considering the modest size of this cohort, the inclusion of large numbers of predictors would weaken statistical robustness. For the same reason, interactions between predictors were not examined. The model for RBL loading-review was notably weak. Another limitation is that we determined the correlates of bone loss rates using a single time-point clinical observation. Annually obtained clinical and radiographic assessments are needed to accurately understand how bone loss changes over time and other factors.

The main strength of this study is the analytical strategy which showed an integrated view of multiple variables' relation to RBL. The insights from this exploratory study caution against simplistic conclusions based on retrospectively determined bone loss rates. Prospective studies with very well-characterized cohorts are essential to confirm the true risk factors of RBL. These findings are indicative and best viewed as a basis for hypothesis development. They do, however, demonstrate the value of clinical data mining in implant dentistry. Larger data repositories from clinical populations of multi-center origin can be collected and similarly analyzed.

Conclusion: i) For each period (pre-, post- loading, and overall time since placement) the average rate of bone loss declined with increasing time. Shorter loading time predicted a lower overall rate of bone loss. Anterior location and older age predicted lower rate of bone loss in pre-loading and overall periods, while augmentation predicted a lower pre-loading rate. ii) Between-patient variability was highest for the early/pre-loading rate of bone loss and iii) marginal bone levels predicted using this pre-loading/early rate strongly correlated to the actual marginal bone levels at review.

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Table 1: Descriptive statistics for RBL values and background variables

Variable	**Descriptive Statistics**
Age (years)*	57 (15), 26-79
Gender	Male=53 (34.41%), Female=101 (65.58 %)
Time at loading (years since placement)*	0.42 (0.34), 0.08-2.25
Time since placement (years)*	3.75 (0.83), 1.58-6.75
Time since loading (years)*	3.04 (2), 1.00-6.08
PPD (average of mesial and distal measures/implant) (mm)*	3.00 (1.38), 1.00-5.00
BOP (implant level)	0/Absent=84 (54.54%), 1/Present=70 (45.45%)
Full mouth plaque score (%)*	34.25 (32.1), 6.00-37.5
Diabetes#	0/Absent=144 (93.51%), 1/Present=10 (6.49%)
Smoking#	0/Absent= 144 (93.51%), 1/Present=10 (6.49%)
History of Periodontitis#	0/Absent=71 (46.10%), 1/Present=83 (53.90%)
Bruxism#	0/Absent=125 (81.17%), 1/Present=29 (18.83%)
Implant abutment interface#	Bone Level (BL) =31 (20.13%), Tissue Level (TL) =123 (79.87%)
Implant Surface#	SLA=150 (97.40%), SLActive=4 (2.60%)
Placement Type#	Submerged= 13 (8.44%), Transmucosal= 141 (91.56%)

Augmentation at implant site#	Augmentation=80 (51.95%), No Augmentation=74 (48.05%)
Soft tissue Biotype#	Thick/Medium =126 (81.82%), Thin=28 (18.18%)
Anteroposterior Location	Anterior= 20 (12.99%), Posterior= 134 (87.01%)
Arch Location	Maxillary= 63 (40.91%), Mandibular=91(59.09%)
Prosthesis Type	Cantilever=04 (2.60%), Fixed Dental Prosthesis=18 (11.69%), Single Crown=132 (85.71%)
Retention Type	Cement Retained= 91 (59.09%), Screw Retained=63 (40.91%)
Antagonist Type	Antagonist Tooth= 128 (83.12%), Antagonist tooth supported (dental) Fixed Dental Prosthesis= 15 (9.74%), Antagonist Implant supported Fixed Dental Prosthesis=11 (7.14%)
RBL placement-loading (mm/year)	0.90 (2.02), -4.68-9.19
RBL loading-review (mm/year)	0.06 (0.16), -1.64-1.67
RBL placement-review (mm/year)	0.21 (0.33), -0.29-1.28

* Median (Inter-quartile range), Range; # Counts for variable response levels

Table 2: Bootstrapped Linear Mixed-Effects Regression Models for RBL outcomes

Predictors	**RBL Placement- Loading[1]**		**RBL Loading-Review[2]**		**RBL Placement-Review[3]**	
Fixed Effects (Bias corrected, Bootstrap, n=1000)						
	Estimate (95% ci)	***p value***	***Estimate (95% ci)***	***p value***	***Estimate (95% ci)***	***p value***
(Intercept)	3.62 (2.79,5.55)	**<0.001**	0.26 (0.04,0.42)	**0.02**	0.65 (0.40,1.02))	**<0.001**
Time Placement-Loading	-0.63 (-1.37,0.19)	0.13	---	---	0.10 (0.01,0.30)	**0.03**
Time Loading-Review	---	---	-0.05 (-0.08, -0.01)	**0.04**	---	---
Time Placement-Review	---	---	---	---	-0.07 (-0.12, -0.03)	**<0.001**
Age	-0.03 (-0.06,-0.02)	**<0.001**	---	---	-0.003 (-0.008, -0.0005)	**0.02**
Anteroposterior Location (Reference:Posterior)	-0.78 (-0.50,-1.75)	**<0.001**	0.10 (-0.30,0.00)	0.18	-0.06 (-0.02,-0.21)	**0.02**
Augmentation (Reference level: No)	-0.57 (-0.03,-1.22)	**0.04**	---	---	-0.006(-0.1,0.09)	0.86
Placement Type (Reference level: Transmucosal)	---	---	-0.10 (-0.03,0.34)	0.21	---	--
Random Effects (Bias corrected, Bootstrap n=1000)						
	sd (95% ci)		***sd (95% ci)***		***sd (95% ci)***	
Patient (Intercept)	0.66 (0.0,1.07)		0.02 (0.0,374.8)		0.21 (0.11,0.22)	
Residual	1.64 (1.36,1.84)		0.28 (0.23,0.32)		0.21 (0.17,0.24)	
Model Comparison* (Bootstrap, n=1000)	*MEM vs Random effect only model*		*MEM vs Random effect only model*		*MEM vs Random effect only model*	
	Model AIC/R squared	***LRT, p-value***	***Model AIC/R squared***	***LRT, p-value***	***Model AIC/R squared***	***LRT, p-value***
	622.8/23.0 vs 626.8/14.4	17.6, **<0.001**	63.9/0.08 vs 60.0/0.04	10.8**, 0.01**	59.2/0.48 vs 38.5/0.40	19.8, **0.003**

Significant p-values (<0.05) in bold font. *Model comparisons: likelihood ratio and parametric bootstrap tests, MEM against Model with random patient level intercept only.
Variable inflation factors:

1. Model RBL-placement- loading: Time placement to loading =1.07, Age=1.03, Antero-Posterior location=1.07, Augmentation=1.02
2. Model RBL-loading-review=Time.loading.to.review=1.01, Antero-Posterior location=1.34, Placement Type=1.35
3. Model RBL-placement-review=Time placement.to.loading=1.07, Time placement to review=1.06, Age=1.04, Antero-Posterior location=1.07, Augmentation=1.08