2016

Trabecular Bone Microarchitecture in Association with Systemic and Local Factors as Potential Predictors of Implant Failure

Diego A. Camacho DMD
Virginia Commonwealth University, camachoda@vcu.edu

Trabecular Bone Microarchitecture in Association with Systemic and Local Factors as Potential Predictors of Implant Failure

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Dentistry at Virginia Commonwealth University

by

Diego A. Camacho DMD
DMD, Tufts University School of Dental Medicine, May 2013
BS in Psychology, University of Miami, December 2008

Director: Thomas C. Waldrop DDS, MS, Professor and Director, Graduate Periodontics

Virginia Commonwealth University

Richmond, Virginia

May 2016

Acknowledgement

It is difficult to know where to begin as several individuals in my lifetime have really guided and helped shape the person I am today. First off, I would like to thank my Mom and Dad. They have made many sacrifices for me and have truly been the definition of role models. I am especially thankful for their guidance, encouragement, and instilling a work ethic that has always driven me to achieve more.

To my fiancé, Katie, you have been the embodiment of patience and your intelligence is overwhelming. I cannot thank you enough for your love and support. Everyday we are together; is another day I realize how lucky I am to have you in my life.

Next, I would like to acknowledge my mentors who have played a big part in my educational and professional development. Dr. Paul Levi, you have touched many people in our field, and I am glad to say that I have been able to thrive since day one at Tufts under your tutelage. Dr. Deeb, thank you for your countless hours of discussion and passion for education, as you have been instrumental to my growth as a periodontist over the past few years. Dr. Carrico, thank you for being able to process and analyze my incredibly large data set in such a short time. Your impressive statistical mind has lead me to appreciate biostatistics and what it means in periodontics. Dr. Waldrop and Dr. Schenkein, thank you for giving me a chance to purse my dream in periodontics. VCU is one of the strongest programs in the country and I feel that I have been given the tools necessary to make an impact in private practice, patient's lives, and in the field as a whole. I hope to continue this legacy throughout my entire career.

Lastly, I would like to thank my research partners Nicholas and Michelle. You two really helped me accomplish a large task of data collection and your ideas were very valuable to the project.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

NF	Non-failed
F	Failed
TBS	Trabecular bone score
RFA	Resonance frequency analysis
ISQ	Implant stability quotient
BMD	Bone mineral density
HU	Hounsfield units
CT	Computed tomography
CBCT	Cone-beam computed tomography
NHP	Non-human primate
BMP	Bone morphogenic proteins
VCU	Virginia Commonwealth University
DXA	Dual-energy X-ray absorptiometry
μCT	Micro-CT
kVp	Kilovolt peak
mAs	Milliamp seconds

Abstract

TRABECULAR BONE MICROARTCHITECTURE IN ASSOCIATION WITH SYSTEMIC AND LOCAL FACTORS AS POTENTIAL PREDICTORS OF IMPLANT FAILURE

By Diego A. Camacho DMD

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Dentistry at Virginia Commonwealth University

Virginia Commonwealth University, 2016

Major Director: Thomas C. Waldrop DDS, MS, Professor and Director, Graduate Periodontics

Clinicians have described the success rates of dental implants. The use of implants is projected to increase in the future. With a 5-10% failure rate, it is unclear the exact factors that are associated with implant failures. To improve upon these success rates, it is critical to understand parameters associated with implant failure including: periodontitis, peri-implantitis, systemic diseases, site preparation, dental history of the implant site, bone quality, materials, occlusion, and treatment timelines. While bone quality is associated with failure, objective measures to assess bone quality and characteristics are scarce. Therefore, the aim of this study is

to determine whether possible comorbidities, associated dental parameters, and measurable bone quality are possible predictors of implant failure.

In this study, we utilized the electronic health record system axiUm® to retrospectively investigate non-failed (NF) and failed (F) dental implants from a patient cohort with 149 implants placed between 2012-2015 at Virginia Commonwealth University School of Dentistry. A chart review was conducted extracting information on age, gender, systemic diseases, smoking, occlusal trauma, parafunction, bone grafting history, treatment timelines, implant site/type/placement protocol, infection, torque at placement, bone quality and microarchitecture assessed by the novel, innovative technology: trabecular bone score (TBS).

A total of 149 implants, 46 failures and 105 non-failed controls, were selected based on similar implant sites. Preliminary data obtained from analysis suggests that average time from implant placement to failure was 6.6 months (0.55 years). Parafunction habit ($p=0.0202$) and increased number of implants ($p=0.0478$) were found to be associated with increased implant failure.

Introduction

Over the past three decades the use of dental implants has become an integral part of dental practice and has revolutionized dentistry. A study conducted in 2005 by the Millennium Research group found that the United States market accounted for $370 million in implant sales, which represented approximately 800,000 implants placed each year.[1] In addition, according to the American Academy of Implant Dentistry, the U.S. dental implant and prosthetic market is further projected to reach $6.4 billion by 2018.

Therefore, clinicians are relying heavily on implants when creating innovative treatment plans to aid compromised or non-treatable natural dentitions. With time of treatment being of essence, conservative approaches to therapy are changing in favor of shorter timelines that could lead to more implant failure. Traditionally, implant failure describes a terminal situation where the implant must be removed following its placement due to various factors causing it to fall below its acceptable level of performance. In clinical reports, authors have described failure rates of 1-2%; however, this may not be the complete story. When large-scale studies have been investigated, systematic reviews have reported failure rates as high as 2% to 8.6% with a 5 year follow up.[2] Surprisingly, a systematic review on 10-year longevity of teeth and implants reported an incidence of implant loss ranging from 1% to 18%.[3] Prior to failure implants may also develop peri-implantitis; which can be defined as the bacteriologic and/or traumatogenic occlusion-mediated loss of tissue integrity accompanied by alveolar bone loss.[4] While it is often

regarded as difficult to pinpoint the reasons for implant failure, it is necessary to comprehensively study the factors that could be related to implant failure in order to continue to improve success rates.

Contributing factors associated with failure can be categorized into host-related, operative-related, and implant-related considerations.[5, 6] Different host-related elements have thought to contribute to implant failure. Host-related elements associated with implant failure can be further broken down into systemic and local influences. Systemically, age and gender are two characteristics that the patient can not control. Studies have shown women are more prone to implant failure than men[7, 8] and older patients (>60 years old) have been associated with lower implant success rates.[9] Various medical conditions including uncontrolled diabetes mellitus,[10] osteoporosis and bisphosphonate therapy,[11-14] hormone disturbances and chronic steroid use,[15-20] high level usage of anti-depressants,[21] Vitamin D deficiency,[22, 23] as well as patients with cancer history treated with irradiation[24] have been shown to contribute to implant failure. These conditions have been suggested in both animal and human studies as contributing factors to implant failure, however are not deemed absolute contraindications for implant placement. Thus, further research is needed to delineate their contributing roles in failure.

Patients' habits have also been implicated in higher implant failure rates. These habits include smoking and parafunction (bruxism/clenching). Studies have shown three times more annual bone loss around implants as well as higher failure rates[25, 26] in patients who smoke compared to non-smokers. Additionally, the majority of the literature concludes that bruxism and occlusal overload is thought to be associated with bone loss or implant fail.[27-29]

While the aforementioned systemic factors are important contributing factors to implant failures, it is also necessary to consider local factors that are associated with implant failures

such as chronic and acute infections. Much like chronic periodontitis and the natural tooth, peri-implantitis is a chronic inflammatory process that can also affect the soft and hard tissues around implants by inducing color changes in the tissue, increasing bleeding and/or suppuration, stimulating hyperplastic tissue, and propagating a nidus for harmful periodontal pathogens all of which have been associated with gradual loss of bone support.[30, 31] Acute infections with the presence of purulent drainage, increased pain, and swelling in the operated area occur in 4-10% of implant patients. Majority of applied treatments are usually ineffective with two-thirds of the infected implants failing, most before prosthetic loading.[32]

While biology is regularly attributed to be the driving force behind implant success; clinician centered characteristics including operator experience, skill, technique, and judgment in treatment planning are also contributing factors. Additionally, surgical trauma and over heating the bone (of the osteotomy) have been suggested to lead to bone necrosis and irreversible tissue damage.[33, 34] These intra and post-operative complications have been associated with an increased risk (3.4-4.8 times as assessed by 1554 implants over 6.2 years) of implant failure.[35] Interestingly, increasing the number of implants placed per patient and improper ergonomics by clinicians have also been associated with the potential increased risk of failure.[36, 37] Judgment on implant placement can also be a contributing factor. Placing implants in sites adjacent to and with periapical pathology and/or infections have been shown to be at higher risks for implant failure.[38, 39] Likewise, studies on placing implants immediately into fresh extraction sockets have emerged with mixed reviews. Higher implant failure rates have been associated with immediate placement due to technique sensitivity and possibly jeopardized anatomic remodeling.[40-45] In contrast, many studies have observed immediate implant placement as an effective treatment with similar failure rates as healed sites.[26, 46, 47]

Studies suggest implant considerations such as length, diameter, and surface can have a contributing factor to success. Survival rates for shorter implants (<10mm) are significantly lower than longer implants (>10mm) with studies showing a direct increase in the failure rate as length decreases.[48] For example, Naert et al.[49] determined the hazard rate (i.e. implant failure) increased by 16% for every 1mm decrease in length. Interestingly, compared to narrow implants, wider implants have exhibited better implant survival results.[50] Lastly, roughened surface implants have shown significantly higher osseointegration and success rates when compared to smooth machine surfaces.[51, 52] However, roughened implants may provide surfaces capable of more microbial retention leading to an increased frequency of peri-implantitis.[53] Collectively, clinicians must understand the materials they are using and how to properly maintain the implants in order to ensure implant success.

Another implant factor believed to be imperative to integration and eventual long term survivability of the implant is implant stability. Non-invasive methods of detecting implant stability can be measured with insertion torque,[54] resonance frequency analysis (RFA), or implant stability quotient value (ISQ). RFA and ISQ values are calculated from external oscillations exerted onto implant/bone systems.[55, 56] These diagnostic tools can provide information about the local bone quality, implant stability, and degree of osseointegration. Low insertion torque, especially on early or immediately loaded implants, may increase the implant failure rate.[57, 58] Evidence for altered implant stability and increased failure rate has been suggested by studies with failing implants displaying a significantly lower ISQ values at one month follow-up.[56, 59] Therefore, the clinician's ability to achieve osseointegration relies heavily on primary stability and implant anchorage. Consequently, the lack of primary stability can result in soft tissue encapsulation and possible implant failure.

It is well documented that bone characteristics such as bone quality, quantity, and anatomical locations of the implant site can have significant influences on failure rates.[60, 61] Lekholm and Zarb[62] developed 4 categories classifying bone characteristics based on radiographic appearance and the surgeon's resistance to drilling: Type I bone, homogenous cortical/compact bone; Type II bone, in which a thick layer of cortical bone surrounds a core of dense trabecular bone; Type III bone, in which a thin layer of cortical bone surrounds a core of dense trabecular bone of favorable strength; and Type IV bone, characterized by a thin layer of cortical bone surrounding a core of low density trabecular bone of poor strength. Based on these categories, mandibles have thicker cortical plates and denser trabeculae than the maxilla. Posterior regions have a thinner cortex with a more porous trabeculae compared to anterior regions of the jaw.[63-66] Additionally, posterior regions tend to have less bone volume due to significant resorption in height and width that occurs in edentulous sites over extended periods of time. Greater implant failure rates are observed in maxilla and posterior regions of both jaws.[63, 67] Furthermore, studies have shown an increased implant failure rate with type III and IV bone qualities.[63, 67] Bone grafted sites and reconstructive procedures have also been linked to higher prevalence of failed implants.[2, 68]

While the bone classification methods described above are routine assessments for describing bone type, they are subjective and do not objectively assess bone quality, bone density, or bone mineral density (BMD). The quality of the bone also incorporates elements/features such as skeletal size, architecture, 3-dimensional orientation of the trabeculae, and matrix properties.[61] Certain diagnostic tools have been developed in dentistry to assess bone quality. For example, Hounsfield units (HU) can quantitatively differentiate tissues (-1000 (air) to +3000 (enamel)) in a particular region on computed tomography (CT) or cone-beam computed

tomography (CBCT). For more invasive measurements, surgically obtained bone cores can be collected for analysis. While bone quality is associated with failure, easily accessible and less-invasive technologies which also objectively, reliably, and consistently assess bone characteristics are scarce.

Trabecular Bone Score (TBS) is a current, innovative technology that has been fully validated within osteoporosis patients as a diagnostic predictor for spinal fracture risk.[69-74] TBS is a gray-level textural metric that can be extracted from a 2-dimensional (or 3-dimensional) radiographic image and can be applied to further investigate bone type and microarchitecture. Based on experimental variograms of the projected image, TBS has the potential to discern differences between scans that show similar bone mineral density (BMD) measurements thus providing valuable skeletal information.

An elevated TBS value reflects better skeletal microstructure while a low TBS value reflects a weaker skeletal microstructure.[75-79] Dental implants cross cortical bone and are fixed in the trabecular/cancellous/microarchitectural area of the maxillary or mandibular jaw bone. This is the region where osseointegration takes place. Thus, bone texture/microarchitecture analysis by TBS pre-operatively, intra-operatively, or after surgery may be beneficial for future dental implant success.

Summary statement. Due to the lack of understanding and knowledge of factors associated with implant failure, we examined a large-scale, retrospective study and developed a TBS pilot study to determine whether possible co-morbidities, local dental factors, implant parameters, and bone microarchitecture can help predict implant failure.

Materials and Methods

Type of Study

Data were collected via a retrospective study reviewing the electronic health record system axiUm® (Exam Academic, Vancouver, Canada) from patients with dental implants placed from 2012 to 2015 at Virginia Commonwealth University School of Dentistry. Records involving non-failed (NF) and failed (F) implants were examined. Implant failure was defined as implants lost due to spontaneous or surgical explanation. The ethical approval of this study was granted by the Institutional Review Board, and was assigned an exempt review status.

Subjects

To obtain the cohort, search was initiated using the the American Dental Association code D6010. This code identifies surgical placement of implant body as well as an endosteal implant at the time of second stage surgery and placement of healing cap. Search was additionally cross referenced with the implant removal procedural code D6100. Subjects with both codes were included in the F cohort while subjects with only the D6010 code were included in the NF cohort. Further evidence of implant failure was noted by diagnostic radiographs and review of clinical notes indicative of a definite status of failure. Key words in clinical notes included: implant failure, implant removal and/or re-do, no osseointegration, mobility of implant, and explanation. Successful implant placement was confirmed in the NF cohort via assessment of the following parameters: radiographic evaluations at follow-up visits, final implant restoration, successful reverse torque test, and continual appointments of ≥ 6 months after

implant placement. In the present study, patients were excluded regardless of cohort in cases with incomplete information regarding the implant placement, the follow-up radiographs or clinic notes. The charts of 111 patients were reviewed in detail.

Variables

Information extracted from the charts included patient demographics such as age at the time of implant placement, gender, medical history and smoking status. The recorded medical history included systemic diseases such as osteoporosis, diabetes mellitus I/II, cancer history, autoimmune disease, depression/anxiety, and vitamin D deficiency. Additionally, drug allergies and systemic medications including chronic steroid use were noted. Comprehensive dental history including: occlusal trauma and parafunction were obtained.

In order to understand the characteristics of the implant site, dental history and clinical parameters of the prior tooth (previous root canal treatment, presence of periapical pathology) and implant site development were investigated. Implant site description was organized into two categories: native/non-grafted and developed. A site was considered developed if it had received one or a combination of the following: extraction and site preservation, ridge augmentation, or sinus lift procedures. The various types of bone grafting materials and barrier membranes were recorded for all developed sites. Additional information about the implant site itself and surgical procedures performed was obtained from patient records. These data included location, tooth number, bone type, insertion torque, implant stability quotient (ISQ), grafting at time of placement, immediate or delayed implant placement, and one or two stage placement. Information about the implant manufacturer, model, platform size, diameter, length and surface characteristics was also obtained.

Timeline data was also considered in the study. The following time points were recorded: the time between site development to implant placement, the time between implant placement and failure, the time between implant placement and implant exposure or restoration, and the time between implant removal and replacement of the failed implant.

For implants in the F cohort, additional parameters were recorded to study their possible contribution to failure. These parameters included: the total number of implants per patient that failed or did not fail, repeated failures at specific implant site along with recorded timelines, grafting and barrier materials used for implant sites, presence of acute infection at the time of implant failure, peri-implantitis as defined by the radiographic progressive loss of bone around implant threads, and absence of primary osseointegration noted at the time of failure.

Quantification of Bone Microarchitecture by TBS

The bone microarchitecture was quantified by trabecular bone score (TBS) for 18 F and 18 NF patients by Medimaps (France) as previously described.[77-79] Briefly, periapical (acquisition/device/sensor), radiographs were collected from both cohorts prior to (with tooth or edentulous site) and at the time of implant placement. For the NF cohort, the final radiograph collected was at the time of implant exposure or restoration whereas the final radiograph for the F cohort was collected at the time of implant failure. The TBS analysis was performed on regions of interest compatible to the interdental space on all radiographs.

Statistical Analysis

Univariate tests were used to determine the association of the various parameters of interest with the dichotomous outcome (failure, control). Of particular interest, however, was the overall survival (in time) as a function of all the parameters of interest. A frailty survival model was used to estimate the survival time as a function of the variables of interest, while accounting

for the fact that implants were clustered within patients. Additionally, TBS scores were analyzed using a repeated measures ANOVA model with a two-way interaction (failure*time) to determine if the trend in TBS scores across time was different between failures and controls. All analyses were performed in SAS EG v 6.3 with a significance level of 0.05.

Results

Systemic and Local Factors. A total of 149 implants were included in the study from a total of 111 patients. Of these, 46 implants were failures and 103 were non-failed controls. Controls were selected based on age and implant position of the failures. They were loosely matched for these variables on a 2-1 basis. The follow-up time was significantly different for the failures and controls (p-value<0.0001) such that controls were followed for, on average, one year longer than controls. This eliminates the potential bias that controls have not been followed long enough to fail. Table 1 details all the parameters of interest for each group and a comparison between the two groups. From these univariate analyses, the parameter most associated with an implant failing was parafunction habit (p-value=0.0001), but total number of implants placed showed marginal significance (p-value=0.0919). A Kaplan-Meier survival curve is presented in Figure 1. This figure shows that a majority of the failures are happening within the first year of placement.

An overall frailty survival model was used to estimate the survival time for implants based on the parameters of interest, while adjusting for clustered data (multiple implants within same patient) The results of this model are given in Table 2. The results indicate that an implant in a patient without a parafunction habit is 0.219 times less likely to fail than a patient with a parafunction habit (Table 3). Conversely, a patient with parafunction is 4.6 times more likely to have an implant failure. Figure 2 displays the Kaplan-Meier curve by parafunction. For total implants, since the hazard ratio indicates for every additional implant placed, the risk of failing increases by 1.2 times (Table 3)

Table 1: Summary of Parameters for Failures and Controls

	Controls	Failures	P-value
Number of Patients	72	39	
Number of Implants	103	46	
Average Number of Implants Per Person	2.5	3.1	0.0919
Demographics/Patient Health History			
Age (mean, SD)	60.9, 13.9	58.9, 13.8	0.4670
Gender (n, %) Male	27, 0.37	19, 0.49	0.2292
Systemic Disease (n, %)	50, 0.68	26, 0.67	0.7637
DM D2	8, 0.11	6, 0.15	0.5174
Osteoporosis (n, %)	2, 0.03	1, 0.03	0.9472
Cancer History (n, %)	5, 0.07	5, 0.13	0.3020
Chemo/Radiation (n, %)	0, 0.00	0, 0.00	
Autoimmune Disease (n, %)	0, 0.00	1, 0.03	0.1723
Chronic Steroid Use (n, %)	1, 0.01	0, 0.00	0.4597
Depression/Anxiety: Taking antidepressants (n, %)	12, 0.17	7, 0.18	0.8641
Vitamin D Deficiency (n, %)	6, 0.08	4, 0.1	0.7355
Smoking History	17, 0.24	7, 0.18	0.4890
Parafunction Habit*	0, 0.00	6, 0.13	0.0001
History of the Implant Site			
Site Preparation (Bone Graft)	73, 0.70	29, 0.63	0.3868
Site Preparation Type			0.6696
Extraction+Site Preservation (EXT+SP)	46, 0.63	17, 0.59	
Ridge Augmentation (RA)	9, 0.12	3, 0.1	
Sinus Lift (SL)	5, 0.07	4, 0.14	
EXT SP+RA	7, 0.1	4, 0.14	
EXT SP+SL	1, 0.01	1, 0.03	
SL+RA	4, 0.05	0, 0.00	
Other	1, 0.01	0, 0.00	
Previous RCT/ENDO/PARL/PAP	42, 0.40	24, 0.52	0.1798
Implant Specific Parameters			
Implant Manufacturer			0.3224
BioHorizons	50, 0.48	17, 0.40	
Biomet 3i	0, 0.00	1, 0.02	
Keystone	9, 0.09	3, 0.07	
Nobel	25, 0.24	16, 0.35	
Zimmer	20, 0.19	9, 0.20	
Implant Diameter (mm) mean, SD	4.47, 0.64	4.34, 0.62	0.2829
Implant Length (mm) mean, SD	11.88, 1.14	11.84, 1.49	0.3712

Location				
Location				0.6762
	MDA	13, 0.13	8, 0.17	
	MDP	32, 0.31	12, 0.26	
	MXA	21, 0.2	12, 0.26	
	MXP	38, 0.37	14, 0.3	
Associated Bone Quality (LIMITED SUBSET)				
Bone Quality at Initial Placement				
	Class 1	3, 0.11	1, 0.08	
	Class 2	19, 0.68	2, 0.15	
	Class 3	6, 0.21	8, 0.62	
	Class 4	0, 0.00	2, 0.15	
Timeline				
Follow-up Time*		1.7, 1.11	0.55, 0.61	<0.0001
Time between Bone Graft and Implant Placement		0.61, 0.69	0.59, 0.41	0.911

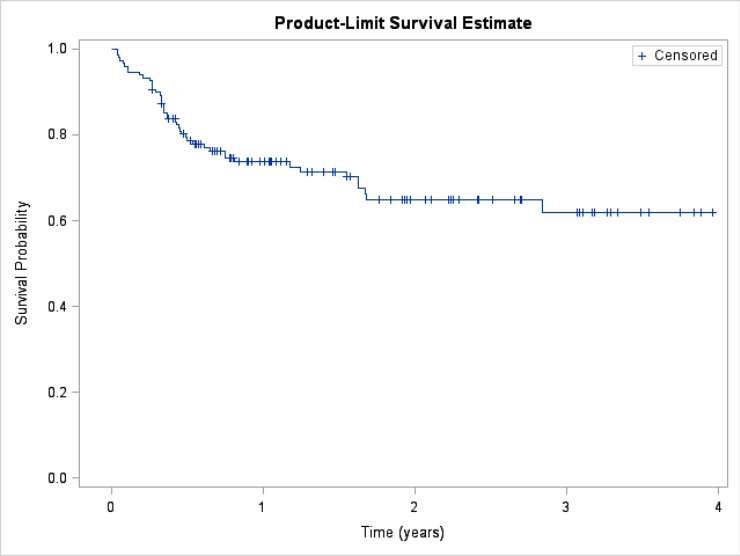

Figure 1: Overall Implant Survival

Table 2: Frailty Survival Model Results

Effect	Chi-Square	Adjusted DF	Adjusted P-value
Total Number of Implants for Patient	2.128	0.4022	0.0478
Parafunction Habit	2.5554	0.2509	0.0202
Patient Study ID (Random Effect)	92.4585	49.5895	0.0002

Table 3: Hazard Ratio for Final Model Factors

Effect	Estimate	SE	Hazard Ratio
Total Number of Implants	0.19	0.128	1.205
Parafunction Habit (No vs Yes)	-1.52	0.951	0.219

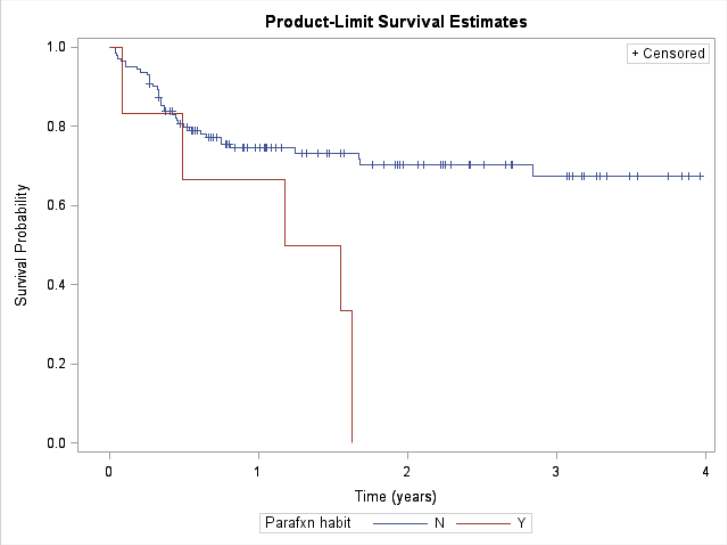

Figure 2: Survival Curves by Parafunction Habit

TBS Scores. TBS Scores were available on 13 failures and 13 controls at a minimum of 2 time points (pre-operative, intra-operative, post-operative). Using repeated measures ANOVA, with a time by failure interaction term, there was not sufficient evidence of a significant difference in the trend of bone quality (p-value=0.8976) (Table 4). Figure 3 presents the mean TBS score for the failures and controls at each time point. Although there are no statistically significant differences, there is a trend in the data towards marginal significance when comparing overall TBS scores of the failure group versus the non-failure group (p-value=0.0775) (Table 4).

Table 4: Repeated Measures ANOVA Model Results

Effect	Num DF	Den DF	F Value	Pr > F
Failure (Yes vs No)	1	22	3.43	0.0775
Time	2	36	0.94	0.4015
Failure*Time	2	36	0.11	0.8976

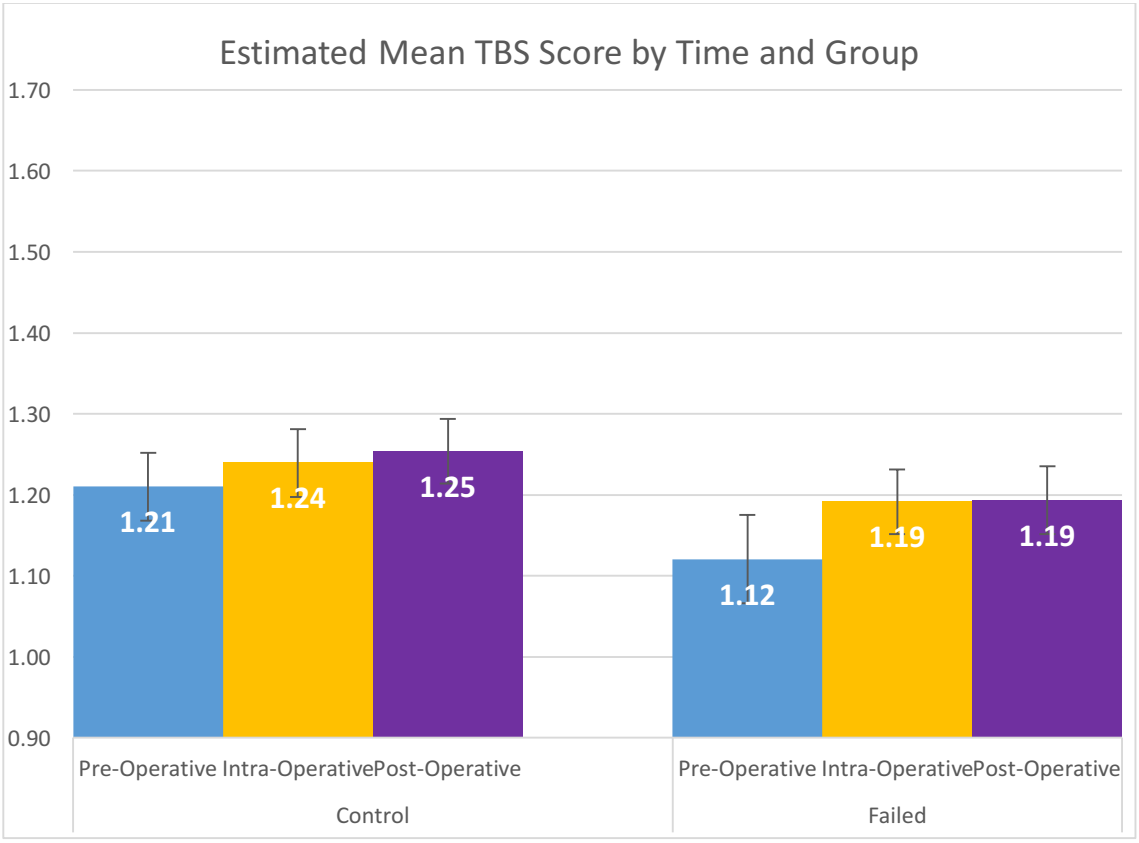

Figure 3: TBS Bone Quality by Time Point and Implant Outcome

Discussion

The goal of this 4-year university based retrospective study was to examine a large-scale database to determine whether possible co-morbidities, local dental factors and implant parameters, as well as measured bone quality can help predict implant failure. Additionally, this is the first reported study in the dental field to evaluate trabecular bone microarchitecture longitudinally, as assessed by TBS, to investigate alterations in bone patterns associated with implant failure. Our study has shown significant correlation between implant failure and parafunction (bruxism/clenching/occlusal overload) as well as increased number of implants per patient. Furthermore, our novel findings from our TBS pilot study demonstrated differences in bone quality assessed by longitudinal TBS scores when comparing pre-operative time points and total scores between the controls (non-failures) and failure cases. Taken together, these results provide insight and valuable implications in the design of treatment planning, assessment of bone characteristics, and surgical protocols for successful dental implant placement.

Implications of Systemic, Local, Operative, and Implant Factors as Predictors of Implant Failure.

Parafunction

Strong evidence already exists in literature that bruxism and occlusal overload are associated with bone loss and implant failure. This conclusion is based on extensive literature reviews,[27-29] histologic animal studies using non-human primate model systems,[80, 81] clinical case reports,[82] and retrospective studies.[83] One of the initial non-human primate (NHP) studies[80],

demonstrated six out of eight implants placed with occlusal overload became loose and exhibited varying amounts of bone loss ranging from 1.8-1.9 mm, substantial loss to the apical portion of the implant, to no osseointegration. Furthermore, Miyata et al.[81] showed that implants with supraoccluding prostheses with varying heights may be susceptible to bone resorption whether in the presence or absence of peri-implant inflammation in a NHP model. In line with the animal models, Fugazzotto et al.[83] demonstrated in a 15+ year follow-up retrospective study analyzing 1472 molar implants that detectable parafunction was the culprit for implant loss in 8 out of 11 failures which were in function from 0-3 years. In an analysis of 589 consecutive implants, Naert et al.[84] also suggested parafunctional habits and overload may be the most likely trigger of marginal bone loss and implant failure. This outcome may be even more pertinent to immediately loading of implants, as Glauser et al.[85] noted that patients with parafunctional habits (bruxer) tended to lose implants at a more frequent rate of 41% versus 12% (non-bruxer). These classic studies are in agreement with our findings of parafunction (bruxism/clenching/occlusal trauma) being significantly related (p-value=0.0001) to implant failure and bone loss. We demonstrated hazards ratios for implant failure suggesting that implants in patients without parafunction are 0.2 times as likely to fail (i.e. less likely); conversely, patients with parafunction are 4.6 times likely to fail (more likely). In contrast to our data and others, canine studies[86, 87] reported no evidence of an association with occlusal overload and bone loss in the absence of plaque (potentially even demonstrating an increase in bone density/apposition). However, when introducing plaque and inflammation, Kozlovsky et al.[87] demonstrated that peri-implant breakdown and bone loss was significantly accelerated by the occlusal overload in canines.

What are the mechanisms by which parafunction leads to failure? Biomechanically, once the physiologic threshold of bone adaptation is exceeded, micro-fractures can occur at the bone

to implant interface.[88] If the micro-fractures amass faster than they could be repaired, as seen with uncontrolled and unpredictable (occlusal) forces associated with bruxism, fibrous encapsulation of the implants instead of osseointegration is often detected, thus potentially presenting an explanation for the contribution to the failure[85, 88] With the addition of peri-implantitis (inflammation) to occlusal overload, a combined hypothesis may exist for failure.[89] For instance, a bidirectional relationship could exist: overload that caused a loss of osseointegration could be more prone to bacterial infection and epithelial downgrowth. On the other hand, bacterial invasion could initiate bone loss to a point that the supporting bone may no longer be able to withstand habitual loading. These hypotheses could explain some of our findings. We demonstrated in our failure cohort that 61% of failures were noted to have had peri-implantitis, defined in our study by progressive longitudinal radiographic bone loss. At the time of implant removal, 60% of the cohort were also found to have lacked primary osseointegration. Due to ethical limitations in inducing occlusal trauma for implant failure, literature is scarce in unbiased prospective and randomized controlled clinical trials in human subjects. Moreover, due to vast heterogeneity in study designs and high risk of bias, meta-analyses are also proven difficult to conduct in order discover causation between occlusal trauma and implant failure. Therefore, as a recommendation to clinicians, it is imperative to fabricate proper restorations, perform occlusal equilibrations, provide occlusal/night-guards, and institute proper oral/implant hygiene in order to decrease the likelihood of failure.

Increased number of implants and operator experience

Increasing the number of implants placed per patient has also been associated with the potential increased risk of failure in implant literature. Smith et al.[90] demonstrated that surgical complications arose when patients had one more implant placed when compared to patients

without surgical complications. Furthermore, the study also identified that patients with implant failures had an average of twice as many implants placed (4.1) compared to patients without implant failures (2.2). Naert et al.[49] also confirmed that increasing the number of implants per patient increased the the hazard rate by 0.14 times with every additional implant placed. These studies coincide with our results as our calculated hazards ratio was 1.205, indicating that for every additional implant placed, the risk of failure increased by 1.2 times. This could be possibly due to extended operating times, wound contamination, increased tissue trauma and desiccation, compromised blood supply and longer healing times.[90]

What are other possible contributing factors to failure? Improper ergonomics of the clinician may hamper vision, access to the site, and consequently result in complications during placement leading to accidents or failure.[36, 37] Additionally, operator experience and skill have been shown to have correlations to implant failure.[91, 92] Prior studies have categorized placing 50 implants or more as "experienced" implantologists and noted that less experienced clinicians had twice the amount of failures.[91] Similarly, Zoghbi et al.[92] determined that less experienced clinicians achieved an 84% implant osseointegration rate compared to 94.4% in the more experienced clinicians. Although we did not record the level of clinician experience in our study, it may account for some of our failures since implants were placed at a teaching university setting with surgeons having different levels of experience. This discrepancy in skill may have led to an operator error affecting the quality of the site. Thus, with proper technique, careful attention to detail, and overall more experience, any future potential failures could be limited.

Bone and Implant Failure

Bone characteristics such as bone quality, quantity, and anatomical locations of the implant site have been shown to significantly influence implant failure rates.[60, 61] Bone grafted and developed sites have also been linked to higher prevalence of failed implants. For example,

Han et al.[68] determined that a portion of early (.78%, p =.0237) and late failures (7.4%, p = <.0001: occlusal overload + unknown) were related to reconstructive procedures. Additionally, Naert et al.[49] demonstrated a hazard rate of 4.2 times higher when a membrane and/or a graft was used in conjunction with implant placement. A systematic review of 73 articles by Esposito et al.[2] determined that 14.9% of failed implants (Branemark) was reported in bone grafting procedures. When sorting out sinus grafts and onlay grafts, the failure rates were reported as high as 9.1% and 20.6%, respectively. These aforementioned studies are of interest because we observed similar trends in our grafting procedures although not statically significant. Our work revealed 63-70% of the 149 placed implants were placed in sites that underwent some form of site development including ridge preservation, ridge augmentation, and/or sinus lifts. Surprisingly, double the amount of failures were seen for implants that had previously received sinus augmentation procedures (7% non-failed vs 14% failed). We hypothesize that this may be due to potential graft contamination, location of implant placement, poor quality bone of the posterior maxilla, or the possibility that the graft was not allowed to fully mature before implant placement. Unfortunately, our study cannot yet precisely determine if these are the reasons for failure. While all our patients were matched for implant site placement, precise healing periods were not stratified from the overall healing times for all the combined procedures. Additionally, implant stability at implant placement could not be referred to for valuable information as it was often not measured. Therefore, insertion torque values, implant stability quotient/resonance frequency analysis, and bone quality measurements (Type I-IV; Lekholm and Zarb) were not found to be significantly related to implant failure, when in fact they could have played a role in the outcome (or in evaluation of the failure).

Periapical pathology

Existing periapical pathology at the implant placement site or present at adjacent sites has shown to contribute to a higher risk of implant failure.[38, 39] Sussman[93-95] reported that during early osseointegration stages, implants may be vulnerable because they may not be able to endure the bacterial challenge from the adjacent pathosis. In contrast, recent large scale reviews/studies have shown that if precautions are taken (i.e. removal of infection, thorough debridement, and use of antibiotics) that the placement of implants into periapically infected sites may be a safe and viable option.[96-99] Although our study demonstrated that 52% of the failed sites had a previous history of root canal therapy or prior periapical pathology compared to 40% in non-failed controls, this was not statistically significant. While our results did not prove otherwise, it is possible that in a percentage of these implants, the periapical pathology may have had a contribution to the failure. Thus, we highly recommend that precautions be taken as mentioned above and sites are rid of any infection (prior to placement) in the best possible manner.

Systemic Related Factors

As one ages, overall healing including healing associated with bone fractures is delayed.[100] Furthermore, fluctuations are also detected in collagen, amount of available bone morphogenic proteins (BMP), mineral composition, as well as content and conformation of the with aging.[101] Altered healing capacity of host bone may account for diminished osseointegration and subsequent implant failure. While the role of gender in implant failure has yet to be fully elucidated, studies have correlated implant failure in women to hormone and bone changes (i.e. osteoporosis) associated with menopause. For men, implant failure is often correlated with smoking and poor oral hygiene habits. In contrast, several studies have found no direct evidence linking sex to implant survival.[102-104] Additionally, various studies as described previously have

shown that systemic medical conditions and the proposed treatment options can contribute to implant failure including but not limited to diabetes, hormone imbalances, cancer, vitamin deficiencies, and osteoporosis. Interestingly, we did not observe any significant findings relating aging, gender, systemic diseases, or smoking history to implant failure. We attribute the lack of significance to our small and limited sample size. Therefore, additional studies are warranted in order to determine how the gender, age, and associated medical conditions of VCU's patient population contributes to implant failure.

Poor oral hygiene and Peri-implantitis

Poor oral hygiene, untreated periodontal disease, and infections have been suggested to play a role in implant survival. A recent study by Kourtis et al.[26] evaluated 1692 patients and demonstrated that patients with insufficient oral hygiene had a 13.8% implant failure rate compared to 2.5% implant failure rate in patients with good oral hygiene. This result is consistent with meta analyses by Wen et al.[105] and Safii et al.[106] documenting that a history of chronic periodontitis was a statistically significant risk factor for the long-term survival of dental implants.

Furthermore, peri-implant disease such as peri-implantitis (inflammatory response affecting soft tissue accompanied with peri-implant bone loss) has exhibited variable recorded prevalence rates on both the patient and implant level in meta-analyses and systematic reviews. One study suggested a prevalence rate of 28% - 56% in subjects and 12–40% in implant sites.[107] In contrast, a study by Mombelli et al.[108] suggested a rate of 20% in patients and 10% in implants with similar numbers reported by Atiech et al.[109] (18.8% of participants and 9.6% of implants). Furthermore, studies have reported individuals with peri-implantitis were twice as likely to report a problem with an implant as individuals with healthy implants[110]. This finding could

possibly be related to our study because the failure cohort presented with 61% peri-implantitis. Due to the nature of our retrospective analysis and the lack of proper documentation with consistent periodontal charting, critical information such as probing depths, plaque scores, and bleeding on probing was lacking. Therefore, our current ability to address and detect peri-implantitis was limited to defining the disease as progressive bone loss surrounding the implant from available radiographs for varying time points of each patient. Reviewed radiographs included the date of placement until last deemed successful follow up visit of a non-failed implant or date of failure from failed implants. Nevertheless, the following factors associated with peri-implantitis would need to be addressed and controlled: definition of the disease, the differential diagnoses, the selected thresholds for probing depths and bone loss, differences in therapy, oral hygiene and maintenance of patients, as well as taking into account differences in study populations.[108] Thus, these certain factors and rigorous documentation need to be taken into account in future studies to properly discover correlations of peri-implantitis with implant failure.

Implant-related factors (length, diameter, surface)

Do implant dimensions and surface characteristics play a role in failure? As mentioned previously, most studies would suggest that longer, wider, roughened surface implants are more related with implant success and survival. Failure rates for shorter implants (<10mm) have been shown to be significantly higher than for longer implants (>10mm).[48] Wider diameter implants have exhibited better implant survival results.[50] Lastly, roughened surface implants have shown significantly higher osseointegration and success rates when compared to smooth machine surfaces.[51, 52] Interestingly, we were not able to discern any statistical significant differences in the specific implant characteristics between the non-failed and failed cohorts. This could be

largely due to the similarity in implant diameter (mean 4.47 mm NF vs. 4.34 mm F), length (11.8 mm NF and F), and surface (rough) between both groups. In order to see true differences in these factors, a larger population and number of implants with varying dimensions would need to be studied.

Implications for TBS and Predicting Implant Failure. What is the importance of assessing bone quality? Researchers and clinicians have been searching for ways to use densitometry techniques and morphologic analysis in order to correlate skeletal bone characteristics of the maxilla and mandible to the lumbar spine as a diagnostic tool in hopes of early detection of osteoporosis from routine dental assessments. On the other hand, attempts have also been made to quantify trabecular bone changes in hopes of providing insight to bone apposition or deterioration to aid in implant success. Together, understanding the bone in these distinct areas in the body can help both the osteoporosis and dental implantology field. In fact, it has been proposed that hip and spine densities could indicate jaw bone density and aid in assessing bone quality prior to implant therapy.[111] Do correlations exist between the bone in the jaw and the spine? Studies[112, 113] using digitized intraoral radiographs (periapicals) correlated trabecular patterns of the maxilla and mandible to BMD readings of lumbar spine, femur, and hip from dual-energy X-ray absorptiometry (DXA) for both normal and osteoporosis patients. Additional studies[61, 114] have also identified correlations between interdental bone density of the maxilla and the lumbar spin. Therefore, an innovative technology which detects bone quality is of interest to both the osteoporosis and dental fields.

The trabecular bone network is important in the evaluation of overall bone tissue quality and characteristics. Many factors influence bone quality and strength such as bone microarchitecture, mineralization, turnover, microfracture accumulation, and disordered bone

remodeling. Unlike BMD which measures total bone mass, understanding bone microarchitecture provides a better evaluation of bone strength and arrangement of skeletal size, 3-D architecture, and matrix properties. When examining bone architecture alone, its deterioration is a result of a decrease in the number of trabeculae of cancellous bone, an increase inter-trabecular distances, and a loss of trabecular connectivity.[115] Furthermore, trabecular bone loss is also accompanied with reduction in the thickness of cortical bone and an increase in its porosity.[115] One novel technology detecting bone microarchitecture is TBS which is a textural index/parameter that quantifies gray level variations in pixel intensities. Interestingly, TBS was originally explored in DXA images of the lumbar spin, providing an indirect index of trabecular microarchitecture.[76, 78, 116] Based on these studies, an elevated TBS value reflects better skeletal microstructure with dense and well-connected trabeculae with little spaces between spans, while a low TBS value reflects a weaker skeletal microstructure with a porous nature.[75-79]

Why use TBS in dentistry and implantology? In dentistry, diagnostic measurements to assess bone quality such as Hounsfield units (HU) can be used to examine different tissue (soft/hard). This technology is only utilized with CT or CBCT. Therefore, constraints to using this technology include limited availability in dental offices due to purchasing cost of CT/CBCT equipment plus higher dosage radiation exposure to patients, especially if to be used in repeated examination. For more invasive measurements, surgically obtained bone cores can be collected for analysis. However, bone core sampling prior to implant placement is rare in routine clinical practice. Unlike its rarity in private practice, bone core analysis may be used in research settings. However, the substantial cost to acquire the cores and use of expensive micro-CT (μCT) limits its practicality and possible transition to clinics. TBS, on the other hand, is not a direct physical measurement of bone microarchitecture, but computes the overall score of a 3D structure on a

2D plane/image (Silva 46). Therefore, this capability of TBS is of great value as it can quantify the quality of the bone from standard dental intra-oral radiographs and other 3D imaging modalities, when available to clinicians. While TBS was not used in the study, Taguchi et al.[117] did determine positive correlations exist between mandibular trabecular patterns of panoramic radiographs and same density regions as measured on CT scans. Taken together, TBS is a unique technology because it can be used on various types of 2D and 3D images that clinicians routinely use without affecting the value of the score generated.

Although, the TBS clinical value has been fully validated within the osteoporosis diagnosis (as a diagnostic predictor for spinal fracture risk), [69-74] its value for the dental implantologists has yet to be fully elucidated. Only two studies[118, 119] relating TBS to dental implants and the dental field have been presented to date. Le Nost et al.[118] evaluated *ex-vivo* mandibles (12 mandibles, 48 implants) and Lelong et al. [119] evaluated *in-vivo* mandibles and maxillae (13 implants) with the addition of intra-oral radiographs prior to surgery and implant placement. TBS was found to highly correlate with implant stability assessed by using ISQ (implant stability quotient), immediately after implantation. Despite these data, very little is known about the potential use of this technology for diagnostic treatment options in the dental field. While these studies[118, 119] have yet to be published in peer-reviewed journals, we have extended upon their cross-sectional study approach and performed a retrospective analysis that includes longitudinal data with various time points. We were particularly interested in how the quality of the bone could affect or predict implant failure. In this regard, we analyzed patients' pre-operative, intra-operative, and post-operative radiographs which was often the last known successful date or implant failure date. We quantified the TBS scores from the region of interest drawn in

to ensure interdental space and to account for the region where the implant was placed. Using this design, we would be able to observe either the osseointegration phase, bone turnover, or possible bone quality deterioration. Figure 5 demonstrates TBS readouts of the trabeculae. Locations of red and yellow represent more degraded bone compared to green areas which signifies better quality and microarchitecture.

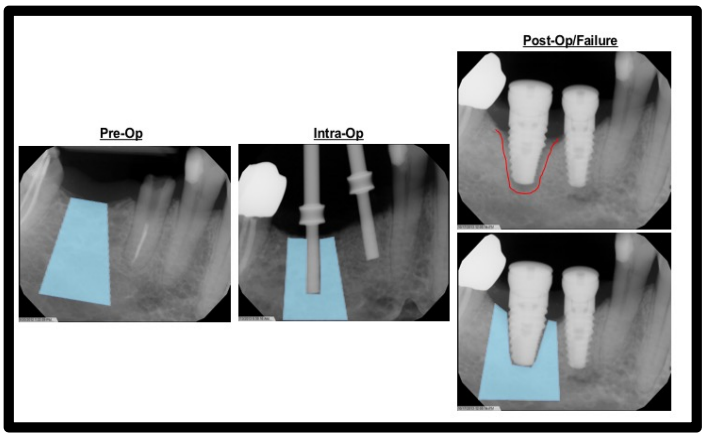

Figure 4: Drawing Method for Region of Interest

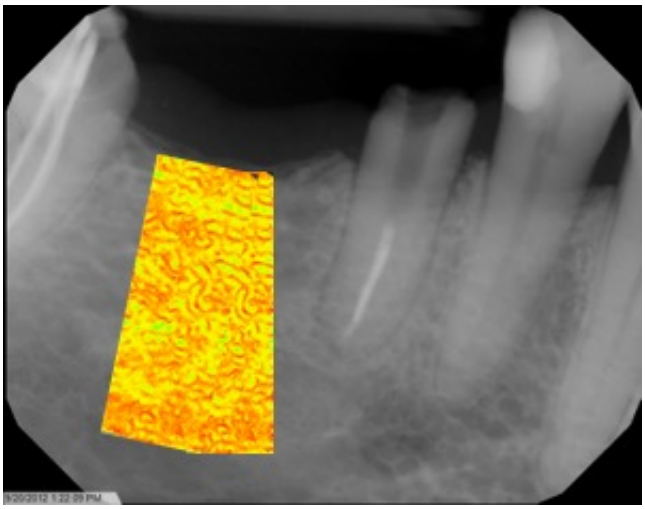

Figure 5: Bone Quality Readout from TBS

In order to evaluate the potential of TBS in the dental field and to optimize our desired regions of interest, we initiated a pilot study of 26 patients (13 NF, 13F) and 69 overall scans. Although there are no statistically significant differences in our graphs, there is a trend in the data towards marginal significance when comparing overall TBS scores of the failure group versus the non-failure group (p-value=0.0775) (Table 4). For the control non-failed group, as time progressed, we demonstrated the bone microarchitecture scores improved suggesting that osseointegration had properly occurred or the bone quality improved due to stimulation from stable occlusal forces. In contrast, TBS scores in the failure cohort initially increased but then plateaued. Surprisingly, the post-operative time point did not decrease as we hypothesized based on the fact that many of the failure radiographs presented with an increase in radiolucency around implants (indicating bone loss or decrease in density/microarchitecture). What is of great interest is the overall combined scores which revealed that the non-failure group had higher TBS scores than the failure cohort. Even more promising and striking was the difference of the pre-operative time periods from both groups suggesting that the failed group had something inherently wrong with the implant site initially or a systemic issue that could have influenced the outcome. Although we did not find a statistically significant difference from the pre-operative time periods because of our sample size, the TBS scores are still clinically relevant. This conclusion is based on the osteoporosis model where the range of bone qualities assessed by TBS have a small degree of difference ranging from degraded bone (≤1.2) to partially degraded (1.2-1.35) to normal (≥1.35). Therefore, these TBS changes could mirror that of the osteoporosis model where small scale changes could translate to drastic differences in bone quality (Figure 6).

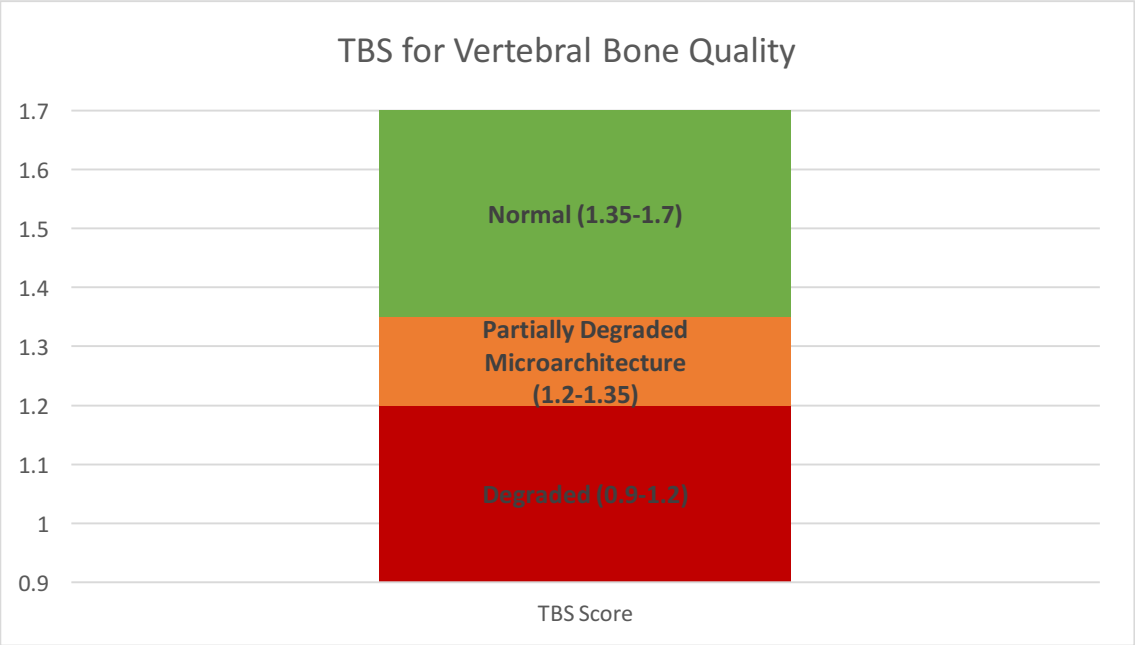

Figure 6: TBS for Vertebral Bone Quality

While our TBS data is promising, there are various limitation in our study. As noted previously, we only reported trends in the data because we had a limited data set in our pilot study. Additionally, a few technical aspects of data acquisition are also limiting factors. TBS software could be affected by effects of resolution, distance, geometry of acquisition, and image quality (contrast, luminosity, and noise.[79] Dental/medical x-ray tubes and different x-ray sensors may have inherent differences or settings applied such as different kilovolt peak (kVp) and milliamp seconds (mAs) which could both affect the quality and quantity of the x-ray beam produced, respectively; therefore, altering data. Additionally, 2D imaging may present with overlaps, distortion, and magnification of bone defects and can also affect data acquisition.[120] To the best of our knowledge, the TBS software in our dental pilot study was not notably affected by potential differences in hardware. However, prospective studies would be best if radiographic

stents were used, as well as image calibration with similar settings, and near identical image acquisition protocols. To further validate the TBS dental software, bone cores could be taken at surgical appointments and cross-analyzed with radiographs.

Future Directions and Value. What is the potential diagnostic value of TBS? With the implementation of TBS technology in the dental field, we have developed an overall model where TBS has the potential to be an additional diagnostic tool in treatment planning and surgical protocols for individualized patient therapy. As seen in Figure 7, correlations between TBS and clinical/health parameters, may provide a comprehensive assessment focused on: choice of implant design/manufacturer, timing of placement (immediate vs. delayed approach; one stage vs. two stage, timing of whether and when to use preventative bone treatment (site preservation, ridge augmentation, sinus augmentation, bone grafting at time of placement), evaluation of bone treatment healing and osseointegration, evaluation of bone and implant for restorative purposes, or even recommendations for medical status changes such as vitamin supplementation or need for potential medical intervention. TBS technology could also be used to monitor lesion resolution in endodontics, tooth movement in orthodontics, and discrimination of trabecular changes in periodontitis patients.[120]

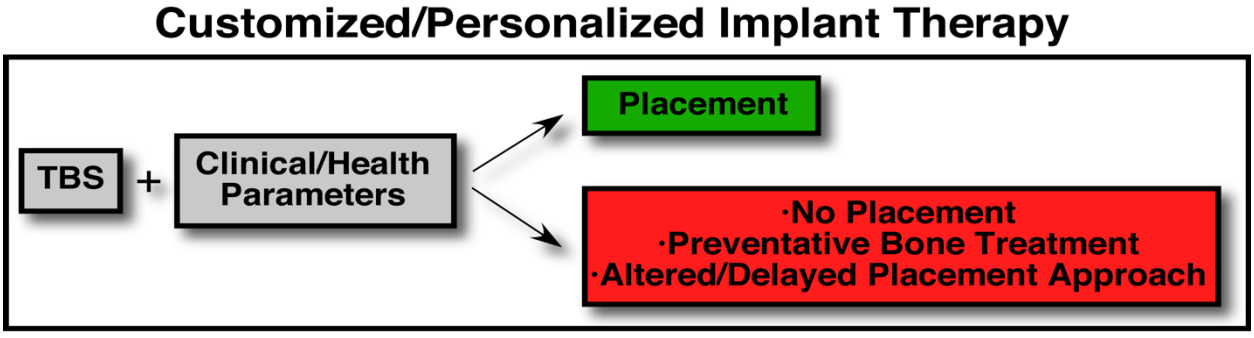

Figure 7: Proposed Model for the Future Application of TBS

References

1. Sonick M. The Economic Future of Implant Dentistry is so Bright You Have to Wear Shades. *Contemporary Esthetics* 2006:2-3.
2. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (I). Success criteria and epidemiology. *Eur J Oral Sci* 1998;106:527-551.
3. Tomasi C, Wennstrom JL, Berglundh T. Longevity of teeth and implants - a systematic review. *J Oral Rehabil* 2008;35 Suppl 1:23-32.
4. Richardson CE. Peri-Implant Disease: Current Considerations and Parameters for Care. *Inside Dentistry (Suppl)* [serial online]. 2014(September 2014).
5. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (II). Etiopathogenesis. *Eur J Oral Sci* 1998;106:721-764.
6. Al-Sabbagh M, Bhavsar I. Key local and surgical factors related to implant failure. *Dent Clin North Am* 2015;59:1-23.
7. Manor Y, Oubaid S, Mardinger O, Chaushu G, Nissan J. Characteristics of early versus late implant failure: a retrospective study. *J Oral Maxillofac Surg* 2009;67:2649-2652.
8. Babbush CA, Shimura M. Five-year statistical and clinical observations with the IMZ two-stage osteointegrated implant system. *Int J Oral Maxillofac Implants* 1993;8:245-253.
9. Brocard D, Barthet P, Baysse E, et al. A multicenter report on 1,022 consecutively placed ITI implants: a 7-year longitudinal study. *Int J Oral Maxillofac Implants* 2000;15:691-700.
10. Bornstein MM, Cionca N, Mombelli A. Systemic conditions and treatments as risks for implant therapy. *Int J Oral Maxillofac Implants* 2009;24 Suppl:12-27.
11. Gaetti-Jardim EC, Santiago-Junior JF, Goiato MC, Pellizer EP, Magro-Filho O, Jardim Junior EG. Dental implants in patients with osteoporosis: a clinical reality? *J Craniofac Surg* 2011;22:1111-1113.
12. Osteoporosis prevention, diagnosis, and therapy. *Jama* 2001;285:785-795.
13. Mohammad AR, Hooper DA, Vermilyea SG, Mariotti A, Preshaw PM. An investigation of the relationship between systemic bone density and clinical periodontal status in post-menopausal Asian-American women. *Int Dent J* 2003;53:121-125.
14. Moedano DE, Irigoyen ME, Borges-Yanez A, Flores-Sanchez I, Rotter RC. Osteoporosis, the risk of vertebral fracture, and periodontal disease in an elderly group in Mexico City. *Gerodontology* 2011;28:19-27.
15. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. *J Bone Miner Res* 2000;15:993-1000.
16. Van Staa TP, Abenhaim L, Cooper C, Zhang B, Leufkens HG. The use of a large pharmacoepidemiological database to study exposure to oral corticosteroids and risk of

fractures: validation of study population and results. *Pharmacoepidemiol Drug Saf* 2000;9:359-366.
17. Kanis JA, Johansson H, Oden A, et al. A meta-analysis of prior corticosteroid use and fracture risk. *J Bone Miner Res* 2004;19:893-899.
18. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest* 1998;102:274-282.
19. Nasu M, Amano Y, Kurita A, Yosue T. Osseointegration in implant-embedded mandible in rats fed calcium-deficient diet: a radiological study. *Oral Dis* 1998;4:84-89.
20. Fujimoto T, Niimi A, Sawai T, Ueda M. Effects of steroid-induced osteoporosis on osseointegration of titanium implants. *Int J Oral Maxillofac Implants* 1998;13:183-189.
21. Antidepressants linked to tooth implant failure, new study finds Available at: http://www.buffalo.edu/news/releases/2016/03/020.html. Accessed: 4-16-16.
22. Dvorak G, Fugl A, Watzek G, Tangl S, Pokorny P, Gruber R. Impact of dietary vitamin D on osseointegration in the ovariectomized rat. *Clin Oral Implants Res* 2012;23:1308-1313.
23. Kelly J, Lin A, Wang CJ, Park S, Nishimura I. Vitamin D and bone physiology: demonstration of vitamin D deficiency in an implant osseointegration rat model. *J Prosthodont* 2009;18:473-478.
24. Moy PK, Medina D, Shetty V, Aghaloo TL. Dental implant failure rates and associated risk factors. *Int J Oral Maxillofac Implants* 2005;20:569-577.
25. Chung DM, Oh TJ, Lee J, Misch CE, Wang HL. Factors affecting late implant bone loss: a retrospective analysis. *Int J Oral Maxillofac Implants* 2007;22:117-126.
26. Kourtis SG, Sotiriadou S, Voliotis S, Challas A. Private practice results of dental implants. Part I: survival and evaluation of risk factors--Part II: surgical and prosthetic complications. *Implant Dent* 2004;13:373-385.
27. Misch CE, Suzuki JB, Misch-Dietsh FM, Bidez MW. A positive correlation between occlusal trauma and peri-implant bone loss: literature support. *Implant Dent* 2005;14:108-116.
28. Isidor F. Influence of forces on peri-implant bone. *Clin Oral Implants Res* 2006;17 Suppl 2:8-18.
29. Chang M, Chronopoulos V, Mattheos N. Impact of excessive occlusal load on successfully-osseointegrated dental implants: a literature review. *J Investig Clin Dent* 2013;4:142-150.
30. Klinge B, Hultin M, Berglundh T. Peri-implantitis. *Dent Clin North Am* 2005;49:661-676, vii-viii.
31. Sanchez-Garces MA, Gay-Escoda C. Periimplantitis. *Med Oral Patol Oral Cir Bucal* 2004;9 Suppl:69-74; 63-69.
32. Camps-Font O, Figueiredo R, Valmaseda-Castellon E, Gay-Escoda C. Postoperative Infections After Dental Implant Placement: Prevalence, Clinical Features, and Treatment. *Implant Dent* 2015;24:713-719.
33. Eriksson AR, Albrektsson T. Temperature threshold levels for heat-induced bone tissue injury: a vital-microscopic study in the rabbit. *J Prosthet Dent* 1983;50:101-107.
34. Iyer S, Weiss C, Mehta A. Effects of drill speed on heat production and the rate and quality of bone formation in dental implant osteotomies. Part II: Relationship between drill speed and healing. *Int J Prosthodont* 1997;10:536-540.

35. Strietzel FP, Lange KP, Svegar M, Hartmann HJ, Kuchler I. Retrospective evaluation of the success of oral rehabilitation using the Frialit-2 implant system. Part 1: Influence of topographic and surgical parameters. *Int J Prosthodont* 2004;17:187-194.
36. Balshi TJ. Preventing and resolving complications with osseointegrated implants. *Dent Clin North Am* 1989;33:821-868.
37. Balshi TJ, Lee HY, Hernandez RE. The use of pterygomaxillary implants in the partially edentulous patient: a preliminary report. *Int J Oral Maxillofac Implants* 1995;10:89-98.
38. Lefever D, Van Assche N, Temmerman A, Teughels W, Quirynen M. Aetiology, microbiology and therapy of periapical lesions around oral implants: a retrospective analysis. *J Clin Periodontol* 2013;40:296-302.
39. Bell CL, Diehl D, Bell BM, Bell RE. The immediate placement of dental implants into extraction sites with periapical lesions: a retrospective chart review. *J Oral Maxillofac Surg* 2011;69:1623-1627.
40. Deng F, Zhang H, Shao H, He Q, Zhang P. A comparison of clinical outcomes for implants placed in fresh extraction sockets versus healed sites in periodontally compromised patients: a 1-year follow-up report. *Int J Oral Maxillofac Implants* 2010;25:1036-1040.
41. Malo P, Rangert B, Dvarsater L. Immediate function of Branemark implants in the esthetic zone: a retrospective clinical study with 6 months to 4 years of follow-up. *Clin Implant Dent Relat Res* 2000;2:138-146.
42. Chaushu G, Chaushu S, Tzohar A, Dayan D. Immediate loading of single-tooth implants: immediate versus non-immediate implantation. A clinical report. *Int J Oral Maxillofac Implants* 2001;16:267-272.
43. De Bruyn H, Collaert B. Early loading of machined-surface Branemark implants in completely edentulous mandibles: healed bone versus fresh extraction sites. *Clin Implant Dent Relat Res* 2002;4:136-142.
44. Horwitz J, Zuabi O, Peled M, Machtei EE. Immediate and delayed restoration of dental implants in periodontally susceptible patients: 1-year results. *Int J Oral Maxillofac Implants* 2007;22:423-429.
45. Zafiropoulos GG, Deli G, Bartee BK, Hoffmann O. Single-tooth implant placement and loading in fresh and regenerated extraction sockets. Five-year results: a case series using two different implant designs. *J Periodontol* 2010;81:604-615.
46. Barone A, Toti P, Quaranta A, Derchi G, Covani U. The Clinical Outcomes of Immediate Versus Delayed Restoration Procedures on Immediate Implants: A Comparative Cohort Study for Single-Tooth Replacement. *Clin Implant Dent Relat Res* 2015;17:1114-1126.
47. Evian CI, Emling R, Rosenberg ES, et al. Retrospective analysis of implant survival and the influence of periodontal disease and immediate placement on long-term results. *Int J Oral Maxillofac Implants* 2004;19:393-398.
48. Olate S, Lyrio MC, de Moraes M, Mazzonetto R, Moreira RW. Influence of diameter and length of implant on early dental implant failure. *J Oral Maxillofac Surg* 2010;68:414-419.
49. Naert I, Koutsikakis G, Duyck J, Quirynen M, Jacobs R, van Steenberghe D. Biologic outcome of implant-supported restorations in the treatment of partial edentulism. part I: a longitudinal clinical evaluation. *Clin Oral Implants Res* 2002;13:381-389.
50. Shin SW, Bryant SR, Zarb GA. A retrospective study on the treatment outcome of wide-bodied implants. *Int J Prosthodont* 2004;17:52-58.

51. Cochran DL. A comparison of endosseous dental implant surfaces. *J Periodontol* 1999;70:1523-1539.
52. Feller L, Jadwat Y, Khammissa RA, Meyerov R, Schechter I, Lemmer J. Cellular responses evoked by different surface characteristics of intraosseous titanium implants. *Biomed Res Int* 2015;171945:1-8.
53. Teughels W, Van Assche N, Sliepen I, Quirynen M. Effect of material characteristics and/or surface topography on biofilm development. *Clin Oral Implants Res* 2006;17 Suppl 2:68-81.
54. Johasson PaS, KG. Assessment of bone quality from placement resistance during implant surgery. *Int J Oral Maxillofac Implants* 1994;9:279-288.
55. Meredith N, Alleyne D, Cawley P. Quantitative determination of the stability of the implant-tissue interface using resonance frequency analysis. *Clin Oral Implants Res* 1996;7:261-267.
56. Sennerby L, Meredith N. Implant stability measurements using resonance frequency analysis: biological and biomechanical aspects and clinical implications. *Periodontol 2000* 2008;47:51-66.
57. Ottoni JM, Oliveira ZF, Mansini R, Cabral AM. Correlation between placement torque and survival of single-tooth implants. *Int J Oral Maxillofac Implants* 2005;20:769-776.
58. Cannizzaro G, Leone M, Ferri V, Viola P, Gelpi F, Esposito M. Immediate loading of single implants inserted flapless with medium or high insertion torque: a 6-month follow-up of a split-mouth randomised controlled trial. *Eur J Oral Implantol* 2012;5:333-342.
59. Glauser R, Sennerby L, Meredith N, et al. Resonance frequency analysis of implants subjected to immediate or early functional occlusal loading. Successful vs. failing implants. *Clin Oral Implants Res* 2004;15:428-434.
60. Drage NA, Palmer RM, Blake G, Wilson R, Crane F, Fogelman I. A comparison of bone mineral density in the spine, hip and jaws of edentulous subjects. *Clin Oral Implants Res* 2007;18:496-500.
61. Lindh C, Obrant K, Petersson A. Maxillary bone mineral density and its relationship to the bone mineral density of the lumbar spine and hip. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;98:102-109.
62. Lekholm UaZ, GA. *Tissue integrated prostheses: osseointegration in clinical dentistry*: Quintessence Publishing Company; 1985: 199-209.
63. Friberg B, Jemt T, Lekholm U. Early failures in 4,641 consecutively placed Branemark dental implants: a study from stage 1 surgery to the connection of completed prostheses. *Int J Oral Maxillofac Implants* 1991;6:142-146.
64. Truhlar RS, Farish SE, Scheitler LE, Morris HF, Ochi S. Bone quality and implant design-related outcomes through stage II surgical uncovering of Spectra-System root form implants. *J Oral Maxillofac Surg* 1997;55:46-54.
65. Von Wowern N. Variations in bone mass within the cortices of the mandible. *Scand J Dent Res* 1977;85:444-455.
66. Von Wowern N. Varations in structure within the trabecular bone of the mandible. *Scan J Dent Res* 1977;85:613-622.
67. Drago CJ. Rates of osseointegration of dental implants with regard to anatomical location. *J Prosthodont* 1992;1:29-31.
68. Han HJ, Kim S, Han DH. Multifactorial evaluation of implant failure: a 19-year retrospective study. *Int J Oral Maxillofac Implants* 2014;29:303-310.

69. Nassar K, Paternotte S, Kolta S, Fechtenbaum J, Roux C, Briot K. Added value of trabecular bone score over bone mineral density for identification of vertebral fractures in patients with areal bone mineral density in the non-osteoporotic range. *Osteoporos Int* 2014;25:243-249.
70. Dufour R, Winzenrieth R, Heraud A, Hans D, Mehsen N. Generation and validation of a normative, age-specific reference curve for lumbar spine trabecular bone score (TBS) in French women. *Osteoporos Int* 2013;24:2837-2846.
71. Roux JP, Wegrzyn J, Boutroy S, Bouxsein ML, Hans D, Chapurlat R. The predictive value of trabecular bone score (TBS) on whole lumbar vertebrae mechanics: an ex vivo study. *Osteoporos Int* 2013;24:2455-2460.
72. Lamy O, Metzger M, Krieg MA, Aubry-Rozier B, Stoll D, Hans D. [OsteoLaus: prediction of osteoporotic fractures by clinical risk factors and DXA, IVA and TBS]. *Rev Med Suisse* 2011;7:2130, 2132-2134, 2136.
73. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. *J Bone Miner Res* 2011;26:2762-2769.
74. Rabier B, Heraud A, Grand-Lenoir C, Winzenrieth R, Hans D. A multicentre, retrospective case-control study assessing the role of trabecular bone score (TBS) in menopausal Caucasian women with low areal bone mineral density (BMDa): Analysing the odds of vertebral fracture. *Bone* 2010;46:176-181.
75. Briot K. DXA parameters: beyond bone mineral density. *Joint Bone Spine* 2013;80:265-269.
76. Winzenrieth R, Michelet F, Hans D. Three-dimensional (3D) microarchitecture correlations with 2D projection image gray-level variations assessed by trabecular bone score using high-resolution computed tomographic acquisitions: effects of resolution and noise. *J Clin Densitom* 2013;16:287-296.
77. Bousson V, Bergot C, Sutter B, Levitz P, Cortet B. Trabecular bone score (TBS): available knowledge, clinical relevance, and future prospects. *Osteoporos Int* 2012;23:1489-1501.
78. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg MA. Correlations between trabecular bone score, measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. *J Clin Densitom* 2011;14:302-312.
79. Pothuaud L, Carceller P, Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. *Bone* 2008;42:775-787.
80. Isidor F. Histological evaluation of peri-implant bone at implants subjected to occlusal overload or plaque accumulation. *Clin Oral Implants Res* 1997;8:1-9.
81. Miyata T, Kobayashi Y, Araki H, Ohto T, Shin K. The influence of controlled occlusal overload on peri-implant tissue. Part 3: A histologic study in monkeys. *Int J Oral Maxillofac Implants* 2000;15:425-431.
82. Mattheos N, Schittek Janda M, Zampelis A, Chronopoulos V. Reversible, non-plaque-induced loss of osseointegration of successfully loaded dental implants. *Clin Oral Implants Res* 2013;24:347-354.

83. Fugazzotto PA. A comparison of the success of root resected molars and molar position implants in function in a private practice: results of up to 15-plus years. *J Periodontol* 2001;72:1113-1123.
84. Naert I, Quirynen M, van Steenberghe D, Darius P. A study of 589 consecutive implants supporting complete fixed prostheses. Part II: Prosthetic aspects. *J Prosthet Dent* 1992;68:949-956.
85. Glauser R, Ree A, Lundgren A, Gottlow J, Hammerle CH, Scharer P. Immediate occlusal loading of Branemark implants applied in various jawbone regions: a prospective, 1-year clinical study. *Clin Implant Dent Relat Res* 2001;3:204-213.
86. Heitz-Mayfield LJ, Schmid B, Weigel C, et al. Does excessive occlusal load affect osseointegration? An experimental study in the dog. *Clin Oral Implants Res* 2004;15:259-268.
87. Kozlovsky A, Tal H, Laufer BZ, et al. Impact of implant overloading on the peri-implant bone in inflamed and non-inflamed peri-implant mucosa. *Clin Oral Implants Res* 2007;18:601-610.
88. Frost HM. Wolff's Law and bone's structural adaptations to mechanical usage: an overview for clinicians. *Angle Orthod* 1994;64:175-188.
89. Carmichael R.P. AP, Zarb GA, McCullouch CAG Biological, microbiological, and clinical Aspects of the peri-implant mucosa. In: Albrektsson TaZG, ed. *The Branemark osseointegrated implant*: Quintessence Publishing Company, 1989:39-78.
90. Smith RA, Berger R, Dodson TB. Risk factors associated with dental implants in healthy and medically compromised patients. *Int J Oral Maxillofac Implants* 1992;7:367-372.
91. Lambert PM, Morris HF, Ochi S. Positive effect of surgical experience with implants on second-stage implant survival. *J Oral Maxillofac Surg* 1997;55:12-18.
92. Zoghbi SA, de Lima LA, Saraiva L, Romito GA. Surgical experience influences 2-stage implant osseointegration. *J Oral Maxillofac Surg* 2011;69:2771-2776.
93. Sussman HI, Moss SS. Localized osteomyelitis secondary to endodontic-implant pathosis. A case report. *J Periodontol* 1993;64:306-310.
94. Sussman HI. Cortical bone resorption secondary to endodontic-implant pathology. A case report. *N Y State Dent J* 1997;63:38-40.
95. Sussman HI. Endodontic pathology leading to implant failure--a case report. *J Oral Implantol* 1997;23:112-115; discussion 115-116.
96. Del Fabbro M, Boggian C, Taschieri S. Immediate implant placement into fresh extraction sites with chronic periapical pathologic features combined with plasma rich in growth factors: preliminary results of single-cohort study. *J Oral Maxillofac Surg* 2009;67:2476-2484.
97. Crespi R, Cappare P, Gherlone E. Fresh-socket implants in periapical infected sites in humans. *J Periodontol* 2010;81:378-383.
98. Waasdorp JA, Evian CI, Mandracchia M. Immediate placement of implants into infected sites: a systematic review of the literature. *J Periodontol* 2010;81:801-808.
99. Novaes AB, Jr., Novaes AB. Immediate implants placed into infected sites: a clinical report. *Int J Oral Maxillofac Implants* 1995;10:609-613.
100. Ekeland A, Engesoeter LB, Langeland N. Influence of age on mechanical properties of healing fractures and intact bones in rats. *Acta Orthop Scand* 1982;53:527-534.
101. Syftestad GT, Urist MR. Bone aging. *Clin Orthop Relat Res* 1982:288-297.

102. Penarrocha M, Guarinos J, Sanchis JM, Balaguer J. A retrospective study (1994-1999) of 441 ITI(r) implants in 114 patients followed-up during an average of 2.3 years. *Med Oral* 2002;7:144-155.
103. Balshi SF, Wolfinger GJ, Balshi TJ. A retrospective analysis of 44 implants with no rotational primary stability used for fixed prosthesis anchorage. *Int J Oral Maxillofac Implants* 2007;22:467-471.
104. Snauwaert K, Duyck J, van Steenberghe D, Quirynen M, Naert I. Time dependent failure rate and marginal bone loss of implant supported prostheses: a 15-year follow-up study. *Clin Oral Investig* 2000;4:13-20.
105. Wen X, Liu R, Li G, et al. History of periodontitis as a risk factor for long-term survival of dental implants: a meta-analysis. *Int J Oral Maxillofac Implants* 2014;29:1271-1280.
106. Safii SH, Palmer RM, Wilson RF. Risk of implant failure and marginal bone loss in subjects with a history of periodontitis: a systematic review and meta-analysis. *Clin Implant Dent Relat Res* 2010;12:165-174.
107. Zitzmann NU, Berglundh T. Definition and prevalence of peri-implant diseases. *J Clin Periodontol* 2008;35:286-291.
108. Mombelli A, Muller N, Cionca N. The epidemiology of peri-implantitis. *Clin Oral Implants Res* 2012;23 Suppl 6:67-76.
109. Atieh MA, Alsabeeha NH, Faggion CM, Jr., Duncan WJ. The frequency of peri-implant diseases: a systematic review and meta-analysis. *J Periodontol* 2013;84:1586-1598.
110. Daubert DM, Weinstein BF, Bordin S, Leroux BG, Flemming TF. Prevalence and predictive factors for peri-implant disease and implant failure: a cross-sectional analysis. *J Periodontol* 2015;86:337-347.
111. Jacobs R, Ghyselen J, Koninckx P, van Steenberghe D. Long-term bone mass evaluation of mandible and lumbar spine in a group of women receiving hormone replacement therapy. *Eur J Oral Sci* 1996;104:10-16.
112. White SC, Rudolph DJ. Alterations of the trabecular pattern of the jaws in patients with osteoporosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999;88:628-635.
113. Lee BD, White SC. Age and trabecular features of alveolar bone associated with osteoporosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;100:92-98.
114. Southard KA, Southard TE. Comparison of digitized radiographic alveolar features between 20- and 70-year-old women. A preliminary study. *Oral Surg Oral Med Oral Pathol* 1992;74:111-117.
115. Seeman E, Delmas PD. Bone quality--the material and structural basis of bone strength and fragility. *N Engl J Med* 2006;354:2250-2261.
116. Silva BC, Leslie WD, Resch H, et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res* 2014;29:518-530.
117. Taguchi A, Tanimoto K, Akagawa Y, Suei Y, Wada T, Rohlin M. Trabecular bone pattern of the mandible. Comparison of panoramic radiography with computed tomography. *Dentomaxillofac Radiol* 1997;26:85-89.
118. Le Nost P. VP, Michelet F., Winzenrieth R., Ella B., Lelong C. TBS Is A Major Key Factor Of Implant Primary Stabillity. In: *IADR/AADR/CADR General Session and Exhibition* Seattle, Washington, 2013.
119. Lelong C SD, Le Nost P., Orellana D., Audebert A., Porras Smith L. TBS assesses implant primary stability in daily clinical routine. *Clin Oral Implant Res* 2014;25.

120. Sener E, Cinarcik S, Baksi BG. Use of Fractal Analysis for the Discrimination of Trabecular Changes Between Individuals With Healthy Gingiva or Moderate Periodontitis. *J Periodontol* 2015;86:1364-1369.