Factors Influencing Dental Implant Survival & Success:

A Retrospective Study

by

Guo-Hao Lin

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Master of Science
(Periodontics)
in the University of Michigan
2016

Master's Committee:
Professor Hom-Lay Wang, Chair
Professor Tae-Ju Oh
Assistant Professor Hsun-Liang Chan
Assistant Professor Furat George

DEDICATION

I dedicate this thesis to my parents who have supported me throughout all my years of education.

ACKNOWLEDGMENTS

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICIES

CHAPTER

<u>I. Introduction</u>

Dental implants have been widely used in partial or full edentulism for oral rehabilitation. Long-term prospective studies and systematic reviews have demonstrated that more than 95% survival rate could be expected after 5-year of loading.[1, 2] However, several etiologies might still contribute to early or late failure of dental implants such as biological, mechanical or iatrogenic factors.[2-4]

Criteria to determine survival and success of dental implants have been reported in several studies.[5-8] Based on the International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference report,[7] survival represents that the implant is still kept in the mouth instead of being removed, and should not present any mobility, pain on function or bone loss more than 1/2 of implant length. Albrektsson et al.[5] defined that a successful implant must present no mobility, no peri-implant radiolucency, bone loss less than 0.2 mm per year after the first year of loading, and no persistent pain, discomfort or infection. Failure of a dental implant is determined when an implant is with mobility, pain on function, uncontrolled exudates, or severe bone loss.[7] In this case, the implant should be removed.

The concept of "osseointegration," defined as "a direct functional and structural connection between living bone and the surface of a load carrying implant," was originally introduced by Dr. Branemark.[9] This finding has further influenced the evolution of implant dentistry on implant surface modifications, grafting procedures, bone substitutes, and surgical techniques. However, even with advancement of implant dentistry, early implant failure

still occurs and mostly involves in failure of achieving osseointegration during initial healing process after implant placement. This failure might result from poor bone quality or quantity, patient's medical condition, smoking status, infection, overheating of the bone, compression bone necrosis, lack of primary stability as well as poor experience and skills of surgeons.[10, 11]

On the contrary, late implant failure is related to unfavorable loading or occlusion, peri-implant diseases and non-ideal prosthetic designs.[11] Fu et al.[12] elaborated occlusal considerations and management of complications when restoring a dental implant. In this article, the authors summarized that implant stability, radiographic bone loss (RBL), loss of attachment, and loosening and fractures of implant fixtures and prosthetic components, could be attributed to occlusal overloading. Although most of the mechanical/prosthetic complications are reversible by means of replacement or adjustment of restorative counterparts, currently there is still a lack of effective treatment modalities for managing biological complications such as peri-implantitis.[13, 14]

Several local and systemic factors have been proposed and associated with an increased risk of peri-implantitis, for examples, smoking,[15, 16] diabetes,[17] previous history of periodontal diseases,[15, 16, 18] poor plaque control[19] and occlusal overload.[12] Other predisposing local factor related to peri-implantitis is retained excess cement, which leads to potential biological complications and marginal bone loss.[20, 21] It has been reported that a trend of bone loss exceeding 2 mm was found more in cement-retained restorations compared to screw-retained restorations,[21] which may compromise the future survival of the implants and restorations. In a previously published cross-sectional study, Schwarz et

al.[22] introduced binary logistic regression to assess the correlation with systemic factors. The results of the study showed that plaque (odds ratio, OR= 8.415) and gender "male" (OR= 2.003) were significantly correlated with the event peri-implant mucositis. In addition, plaque (OR= 9.250) and smoking (OR= 2.679) were significantly correlated with peri-implantitis. However, this study reviewed periodontal parameters and patients' systemic conditions, but not restorative- and implant-related factors. Another recently published study by Renvert et al.[23] also facilitated bivariate logistic regression model to analyze contributing factors related to peri-implantitis. Results of this study showed that OR of having peri-implantitis and a history of cardiovascular disease was 8.7, and OR of having a history of periodontitis was 4.5. Interestingly, smoking was not identified as a significant factor contributing to the outcome. Though these studies have examined the systemic factors and their association with peri-implant diseases, however, a comprehensive statistical modeling of patients' systemic, surgical as well as restorative risks has not been conducted in the literature. Therefore, the primary aim was to establish the ORs of various risks related to implant success. The secondary aim was to analyze the prevalence of peri-implant diseases in a single center.

II. Study Aim

The aim of this retrospective study was to study the ORs of various risks related to implant success. The secondary aim was to analyze the prevalence of peri-implant diseases in a single center.

III. Hypothesis

Implants placed in patients with systemic/local contributing factors, such as smoking, diabetes, previous history of periodontal diseases, poor plaque control, bone augmented sites, less experienced surgeons, and cement-retained multi-unit restorations, are more susceptible to have bone loss and implant failure.

IV. Materials and Methods

1. Data Retrieval

In this retrospective study, the clinical charts and radiographs of patients who underwent dental implant placement at the University of Michigan School of Dentistry (UMSOD) since year 2000 were reviewed. Records with periapical or bitewing radiographs taken at the time of prosthesis placement and at least one year after implant restoration were included. Two hundreds cases were planned to be included in this retrospective radiographic study. The charts were reviewed in a chronological order starting from March 2000 by a single examiner (GL) until 200 cases were selected based on the inclusion criteria (Figure I). Data regarding patients' demographic data, including study number, implant location, age, gender, faculty/resident provider and provider department, were recorded. Information of patients' systemic condition, including history of smoking status, diabetes mellitus, alcohol consumption, osteoporosis, depression, obesity, hypertension, and past history of periodontal diseases, were also retrieved during the chart review process. In addition, implant related factors, including year of service, implant system, length, diameter, surface texture, connection type, restoration type (crown/bridge/overdenture), cement/screw retained restorations, cantilever design and use of splinted/non-splinted crowns were also recorded. Furthermore, surgical related factors, including guided bone regeneration procedure, sinus lift procedure, types of bone graft used, types of membrane used, and one-stage or two-stage surgical approach, were also reported. Adverse events (restorative complications, biological complications), peri-implant parameters (deepest peri-implant probing depth, bleeding on probing, BOP, and RBL after physiologic bone

remodeling) and implant survival/success/failure were collected and entered into a database. Patient information was protected according to the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). The study protocol (Appendix I) was reviewed and approved by the Institutional Review Board of the University of Michigan (ID number: HUM00102699, Appendix II).

From the database, the implant success, survival and failure rates and implant and patient information were analyzed. Implant failure was defined as any implant removed for any reasons during the observation period. Implant survival was defined as any implant still functions in patient's mouth. Criteria used to define implant success (Table I) were modified from American Academy of Periodontology Position Paper published in 2000: (1) no records of persistent signs/symptoms such as pain, infection, neuropathies, parathesias, and violation of vital structures; (2) no record of implant mobility; (3) no continuous peri-implant radiolucency; (4) negligible progressive bone loss (less than 0.2 mm annually) after physiologic remodeling during the first year of function.[22] Due to the retrospective nature of the current study, patient-centered outcome measurements could not be used as one of the parameters to determine implant success.

The prevalence of peri-implant mucositis and peri-implantitis was also analyzed. The definition used to determine the disease identity was based on Koldsland et al. 2010 and Renvert et al. 2014.[23, 24] However, due to the heterogeneity of the disease definitions, the prevalence of the disease based on other criteria[5, 25] was also reported and discussed.

2. Radiographic measurement

Periapical or bitewing radiographs taken at the time of prosthesis placement and at least one year after implant restoration were used to determine RBL. The radiographs taken at prosthesis placement were set as baseline of bone level. The bone level of follow-up radiographs was compared to the baseline radiographs. RBL was determined as the bone level differences between the baseline and follow-up radiographs. However, if the bone level of baseline radiographs was above the junction of rough and smooth surface, the junction of rough and smooth surface was used as reference of baseline bone level. All measurements were performed by one independent examiner using a computerized software (ImageJ 1.48a; Wayne Rasband, National Institutes of Health, Bethesda, MD). Intra-examiner reproducibility was analyzed with correlation test for independent samples.

3. Statistical Analysis

Outcome analyses will be the overall implant success rate, in association with those recorded systemic and local contributing factors of the patients. The associations between implant success and the recorded variables were estimated by generalized linear mixed model. ORs and estimated RBL were calculated. A p value of 0.05 was used as the level of significance. All the statistical analyses were calculated using a computer program (SAS Institute Inc. 2011. Base SAS® 9.3 Procedures Guide. Cary, NC: SAS Institute Inc.).

V. Results

Among 685 charts reviewed, 200 charts were included in the study. The 200 charts included 550 dental implants placed between 2000 and 2014 UMSOD with a mean follow-up period of 6.25 years. The study population's average age was 62.8 ± 9.95 years old (ranged 22 to 91), with 101 males and 99 females. The demographic data of the study patients were listed as Table II. The characteristics and features of the included implants, restorative techniques, and surgical approach, were reported in Table III. Pertaining to measurement of RBL, the intra-examiner reproducibility revealed an exact intra-examiner correlation of 99%, with a p value of 0.43 for t-test for independent samples, indicating a high reproducibility and intra-examiner agreement of the radiographic measurements.

Success, Survival and Failure Rates of Implant Treatment

At the patient level, 93.5% (187 patients) was determined as survival and 6.5% (13 patients) of participants had at least one implant failed. Out of the 187 patients with implant survival, 151 patients (75.5%) were determined as treatment success, 36 patients (18.0%) had at least one implant with progressive peri-implant bone loss (Figure II).

At the implant level, 95.45% (525 implants) of the implants was determined as survival and 4.55% (25 implants) of the implants was removed. Out of the 525 survival implants, 395 implants (71.82%) met success criteria and 130 implants (22.63%) presented with progressive bone loss (Figure III).

For the survival implants, the average probing depth was 5.16 ± 1.48 mm, and average RBL was 0.66 ± 3.45 mm. Linear regression analysis revealed an estimated annual RBL of 0.08 mm for the survival implants (Figure IV). For the implants met success criteria, the average probing depth was 3.63 ± 0.93 mm, and average RBL was minimal.

Prevalence and Severity of Peri-implant Diseases

Based on the criteria published by Koldsland et al. 2010[24] and Renvert et al. 2014,[23] the prevalence of peri-implant mucositis in our study was 57.5% and 61.64% at the patient level and the implant level, respectively. Besides, the prevalence of peri-implantitis was 61.64% and 16.00% at the patient level and the implant level, respectively (Table IV).

Based on the criteria of the most recently published study by Derks et al.,[25] the prevalence of peri-implant mucositis in our study was 29.5% at the patient level and 35.8% at the implant level; the prevalence of peri-implantitis was 40.0% and 41.8% at the patient and implant level, respectively. If the disease severity is considered, the prevalence of moderate to severe peri-implantitis (≥2.0mm RBL with BOP or suppuration) in our study was 12.0% at the patient level and 16.0% at the implant level. Mean RBL of implants with peri-implantitis was 1.99 ± 1.52 mm. For implants with moderate to severe peri-implantitis, mean RBL of the implants with peri-implantitis was 3.29 ± 1.74 mm (Table V).

Factors Associated with Implant Success at Patient Level

Significantly higher ORs associated with implant success at the patient level were found for patients who were not smokers at the time of implant placement (OR= 3.68), patients

without diabetes (OR= 5.85), patients without psychological disorder (OR= 4.93), patients with no previous history of periodontal disease (OR= 7.13), and patients who only received single implant placement (OR= 3.58).

After the adjustment of the potential inter-variable influence using regression analysis, all aforementioned parameters were still presented statistical significance except for psychological disorder (p= 0.17). The complete data of ORs and estimated RBL were presented in Table VI.

Factors Associated with Implant Success at Implant Level

Significantly higher ORs associated with implant success at implant level were found for implants placed by faculty instead of residents (OR= 4.40), certain implant system (OR= 2.26), and rough implant surface (OR= 3.03). In terms of restorative factors, implant-supported single crowns were found to have higher success rate compared to bridge restoration (OR= 3.62). Restorations without the use of cantilever (OR= 6.94) and non-splinted crowns (OR= 1.93) were also found to significantly contribute to higher success rate. Deeper probing depth (OR= 3.51) was also found to be negatively associated with implant success. It is worth mentioning that BOP did not find to be significantly associated with implant success (OR= 1.52).

After the adjustment of the potential inter-variable influence using regression analysis, provider level (p= 0.0013), restoration type (single crown vs. bridge, p= 0.0468) and absence of cantilever (p<0.0001) still presented statistical significance. Also, deeper

probing depth (p< 0.0001) was still presented negative association with implant success. The data of ORs and estimated RBL were presented in Table VI.

Complication Types and Rates

The current study recorded 27.5% (151 implants) of restorative complication rate and 18.0% (99 implants) of biological complication rate among 550 analyzed implants. Overdenture attachment loosening presented as the most frequent restorative complication (25%). Porcelain and ceramic fracture presented as the second most commonly restorative complication followed by loosening of abutment screw. Suppuration and bleeding associated complications were the most frequently recorded biological complication (Table VII).

VI. Discussion

According to American Academy of Periodontology Academy Statement, peri-implant mucositis was defined as a disease in which the presence of inflammation is confined to the soft tissues surrounding a dental implant with no signs of loss of supporting bone following initial bone remodeling during healing. Peri-implantitis has been characterized by an inflammatory process around an implant, which includes both soft tissue inflammation and progressive loss of supporting bone beyond biological bone remodeling.[26] Consensus Report of the Sixth European Workshop on Periodontology also defined peri-implant mucositis as an inflammatory lesion that resides in the mucosa, while peri-implantitis affects the supporting bone.[27] Although these definitions reflect the true identify of peri-implant diseases as infectious diseases, it is difficult for clinicians to make a clinical diagnosis accurately if a clear classification is not readily available partly due to biologic bone remodeling which occurs immediately following implant placement. The degree of biologic bone remodeling depends on several factors, including level of implant placement, tissue thickness, implant design and implant surface topography.[28-31]

A clearer definition for peri-implant diseases is imperative to aid clinicians to diagnose peri-implant mucositis and peri-implantitis. Since this definition has not been listed in the developed classification system,[32] the prevalence of peri-implant diseases is difficult to be evaluated. Several clinical trials have introduced different bone level change as threshold to define peri-implantitis. In 1986, Albrektsson and co-workers[5] described that gradual bone loss of 0.2 mm after the first year of function could be considered successful treatment. In

2006, Roos-Jansaker et al. [33] introduced three threads of radiographic bone loss as the definition of peri-implantitis. Later on, Koldsland et al.[24] in an epidemiologic study described peri-implantitis as more than 2 mm radiographic bone loss with the presence of BOP/suppuration. In this study, the prevalence of peri-implant diseases was reported ranging from 11.3% to 47.1%, based on different analyzed population. In 2012, Froum and Rosen[34] used percentage of bone loss of total implant length as a cut-off point to determine severity of peri-implantitis. In this particular study, early peri-implantitis was defined as probing depth ≥4 mm with BOP/suppuration and bone loss <25% of the implant length. Moderate peri-implantitis was defined as probing depth ≥6 mm with BOP/suppuration and bone loss ≥25% but ≤50% of the implant length. Advanced peri-implantitis was defined as probing depth ≥8 mm with BOP/suppuration and bone loss >50% of the implant length. In 2014, a retrospective study by Renvert et al.[23] defined peri-implantitis as loss of bone ≥2.0 mm from the implant platform level to the most coronal level of bone to implant contact radiographically, and this study reported a prevalence of peri-implantitis of 39.3% and 47.8% at implant level and patient level, respectively. Most recently, Derks et al.[25] reported that 45% of the patients presented with peri-implantitis (BOP/suppuration and bone loss >0.5 mm). The study further analyzed moderate/severe peri-implantitis (BOP/suppuration and bone loss >2 mm) was seen in 14.5% of patients. These variances of disease prevalence highly present a large heterogeneity of the different definitions introduced. Therefore, to facilitate a more predictable treatment guideline and accurate diagnosis, a widely accepted and clear classification system should be updated.

Based on the definition of Koldsland et al.,[22] the current study retrospectively analyzed 550 dental implants placed in 200 subjects and found that prevalence of peri-implant diseases was approximately 69.5% of the patients and 77.6% of the implants. Factors such as provider level, restoration type and cantilever design had significant impact on implant success. This result was in accordance with recent studies published by Derks et al.[25, 35] In their studies, history of periodontitis (OR= 3.3), smokers (OR= 2.3), implant length less than 10 mm (OR= 3.8), certain implant brands, number of implants placed ≥4 (OR= 15.09), prosthetic therapy delivered by general practitioners (OR= 4.27), exhibited higher ORs for implant loss or moderate/severe peri-implantitis. Interestingly, our study did not find statistical significance on association between implant success and implant length. Recent systematic reviews and meta-analysis[36, 37] also failed to warrant the influence of implant length on implant survival. This result might have been explained by the limited number of short implants (<10 mm) included in our study (N=16), various demographic data and systemic conditions of participants as well as different study designs.

History of periodontal disease has been widely accepted as a major risk factor for peri-implant diseases.[26] Based on the result of the current study, it represents the highest risk (OR= 7.13) among all the identified factors. Several systematic reviews[16, 18, 38-40] have also addressed the relationship between the history of periodontal disease and peri-implantitis. Karoussis et al.[39] in 2003 firstly described this finding in a prospective study. The authors conjectured that periodontal pathogens recognized in residual periodontal pockets of the remaining dentition might be sources of infection for the subsequent bacterial colonization of newly installed sterile implants. Also, individual host susceptibility might be different

when pathogenic bacteria are present. However, although a history of periodontal disease might play a role in development of peri-implantitis, limited clinical trials were conducted to evaluate the difference in bone loss and implant success between populations with or without history of periodontitis.[38] Therefore, future well-designed clinical trials are needed to further warrant this linkage.

Smoking has also been identified as another risk factor of peri-implant disease.[15, 16, 41] An OR ranging from 3.6 to 4.6 has been reported.[26] On the cellular level, tobacco smoke can exert its effects on the periodontium and peri-implant tissues through local and systemic mechanisms. Smoking causes a decrease in polymorphonuclear neutrophils (PMN) chemotaxis and phagocytosis,[42, 43] as well as activation of pro-inflammatory mediators such as IL-6, TNF-α and IL-1β.[44] Smoking also causes peripheral vasoconstriction, leading to local ischemia and decreased nutrient flow. This characteristic has an effect on the make-up of the pathogenic subgingival bacterial profile, which was shown to have increased levels of periodontal pathogens in smokers compared to non-smokers.[45] In a systematic review published by Klokkevold and Han,[16] the implant success rates reported for smokers ranged from 52% to 100% with a pooled estimate of 77% for smokers compared to a pooled estimate of 91% for nonsmokers. The authors further discussed the potential relationship between smoking and bone quality as well as implant surface topography. Similarly, a ten year follow-up study published by Rasperini et al.[46] found that cigarette smoking negatively influences the long-term implant outcomes and marginal bone levels in periodontally healthy or compromised patients. Although a few studies have stated that the use of rough-surface implants might minimize the effect of smoking on implant success,[47] this theory

still needs more clinical trials to prove. Also, the potential benefit of smoking cessation to implant survival/success is rarely evaluated in the currently available literature. A proposed protocol by Bain[48] involved complete cessation of smoking for 1 week before and 8 weeks after initial implant placement. However, this protocol is lack of evidence support and might merely represent a personal opinion. Therefore a solid influence of smoking cessation on implant treatment outcome still cannot be drawn at this point.

The role of diabetes in development of peri-implantitis is controversial. The hyperglycemic environment leads to capillary basement membrane thickening, impaired oxygen diffusion and waste elimination. PMN migration is also diminished, which impairs the host defense mechanism and an overall altered immune function against infection.[49] In addition, hyperglycemia also leads to production and accumulation of advanced glycation end products (AGEs). AGEs bind to monocytes and macrophages, causing them to release more pro-inflammatory cytokines such as IL-1β, TNF-α and PGE2, which result in tissue destruction.[50] However, most systematic reviews refuted diabetes as a risk factor of peri-implantitis and implant failure[15, 16, 41, 51] and it might result from the fact that most participants in these selected studies were patients with well-controlled diabetes. In the current study, an OR of 5.85 was identified and indicated a significant association between diabetes and implant failure. From the study result, it can be speculated that diabetes in our study population was not well controlled during the study period.

Another interesting finding of the current study is increased number of implant placed in a single patient is associated with lower implant success rate. This finding was consistent

with the result published by Derks et al.[25] In their study, patients who received 4 or more than 4 implants presented with a higher incidence of moderate to severe peri-implantitis. A more strenuous maintenance protocol might be beneficial for patients who have received multiple implants.

Two prosthetic factors were identified as risk indicators for implant failure: the use of cantilever (OR= 6.94) and the design of bridge (OR= 3.62). When cantilever design is used, the highest stresses were located at the ridge crest on the distal surface of the distal implant,[52, 53] which might trigger more peri-implant bone loss. A recent systematic review[54] concluded that the use of cantilevers into implant-borne prostheses may be associated with a higher incidence of minor technical complications (9.7% without cantilevers vs. 20.3% with cantilevers). In this study, lower 5-year implant survival rate for fixed prostheses with cantilevers (91.9%) was also noted compared to the ones without cantilevers (95.8%). Pertaining to the design of implant-supported restorations, studies investigating the difference between bridge design and single crown restorations are limited. Although current study reported a significant negative impact of bridge restorations on implant success, Pjetursson et al. [4] reported 89.4% and 86.7% estimated survival rate after ten years of service for implant-supported single crowns and fixed partial dentures, respectively. Their study revealed a long-term comparable implant outcomes could be expected between single crowns and bridge restorations. The different result between current study and Pjetursson et al. might result from the primary outcome measurement. It is worth noting that in the current study, we aimed to identify the factors related to implant success, instead of implant survival, since implant success is more clinically relevant and important to

clinicians. This finding might shed a light to restorative clinicians in the future to understand the importance of prosthetic design related to implant success. Therefore, future prospective clinical trials are needed to further investigate the association between prosthetic design and implant success.

Providers' level of experience is another significant factor for implant success. Current study revealed more experienced surgeons (faculty members) demonstrated higher implant success rate compared to less experienced surgeons (residents). This result is consistent with previous study published by Derks et al.,[25] which reported a less experienced provider population (general practitioners) exhibited higher OR for moderate/severe peri-implantitis compared to a more experienced provider population (specialists).

Recently, a few studies reported certain implant systems might contribute to higher late implant loss.[25, 35] The authors speculated that reasons such as progressive marginal bone loss, damages on the interface between the implant and the bone tissue, or harm to the implant, might be the causes of this phenomenon. However, the present study failed to warrant the influence of implant system or surface on implant outcomes. This might result from the lack of sample size for certain implant surface/system in the current study. Also, comparing the outcomes of various implant brand might not be meaningful and representative since each implant brand has been evolving the macro- and micro- implant design as well as surface topography of its products. Therefore, future studies should focus on comparing various methods of implant macro- and micro- designs and surface treatment and the effects of these modifications on implant outcomes.

Since most currently available implant-related studies introduced probing depth and BOP as important parameters to evaluate implant outcomes, the current study also examined the association between these two parameters and implant success. Interestingly, the result showed that deepest probing depth (OR= 3.51, p value < 0.0001) was significantly negatively associated with implant success and mean probing depth for success implant was 3.63 ± 0.93 mm, for survival implant was 5.16 ± 1.48 mm. Therefore, probing depth less than 4 mm should be considered as one of the guidelines to warrant peri-implant tissue health.

On the contrary, BOP failed to show the significant association related to implant success (OR= 1.52, p value= 0.0833). This finding indicated that clinicians should cautiously determine the peri-implant tissue health in the future when introducing BOP as one of the criteria. Since peri-implant tissue is more fragile to probing force and the attachment is not as firm as periodontium,[55] presence of BOP might not accurately represent the inflammatory status of the peri-implant tissues. Previous studies have reported that BOP around dental implants were shown to be greater despite lower plaque scores and fewer signs of inflammation.[56, 57] Also, absence of BOP has been reported as a good indicator of healthy peri-implant mucosa but presence of BOP might have limit diagnostic value.[58] Therefore, presence of BOP, based on the result of the present study, has been noted as a poor indicator to determine peri-implant health and might not be of great diagnostic value.

Based on American Academy of Periodontology Academy Statement,[26] absence of BOP is not an indicator to warrant implant success. However, most published articles still introduced BOP around peri-implant tissues as one of the criteria to determine peri-implant diseases. Since several studies[59-61] have shown that peri-implant mucositits is a reversible inflammatory process if treated appropriately, therefore implants with peri-implant mucositis should not be considered as unsuccessful. In other words, implant success is not a term to describe implants free of peri-implant disease, it represents implants without progressive RBL and suppuration. These successful implants might present healthy or inflamed peri-implant soft tissues, however this inflammation could be resolved by providing non-surgical/surgical treatment.

In the present study, most implant failures occur within the first five years (84.6%) after final restoration placement. It represents that using 1-year follow-up after final restoration placement to determine implant outcomes might be insufficient. A longer follow-up (>1 year) after placement of definite restoration is recommended to identify the pattern of RBL and further determine the outcome of implant treatment. In addition, negligible RBL after the first year of implant loading, probing depth of peri-implant soft tissue less than 4mm, and free of implant related complications should be considered as a new definition of implant success.

Several limitations exist in the present study: (1) due to the retrospective nature, no patient centered outcomes, such as treatment satisfaction or esthetics, could be retrieved; (2) many crucial clinical parameters related to peri-implant tissue health, such as oral hygiene

status,[26] the amount of keratinized tissue,[62, 63] peri-implant tissue thickness[29, 30] and occlusion,[26, 55] could not be evaluated; (3) the reported prosthetic and biological complication rates might be lower than the previously published data[64, 65] since the complication rates were calculated based on the report of treatment notes and chart review retrospectively; (4) impact of maintenance protocol after implant placement / definite restoration on implant outcomes could not be analyzed; (5) the outcomes of various implant surface/brand could not be comprehensively evaluated due to limited sample size for certain implant surface/system.

The current study also shed light on several aspects of future study directions. First, a widely accepted classification/diagnosis system for peri-implant diseases should be facilitated as soon as possible since the disease prevalence is difficult to be determined owing to heterogeneity of currently available definitions of the diseases. Second, the relationship between smoking cessation and implant success needs to be identified. Third, the influence of smoking on peri-implant bone loss should be investigated. Fourth, more clinical trials investigating the influence of implant-supported bridges and single crowns restorations on implant outcomes are needed. Fifth, the effect of cantilever design on peri-implant bone level change should be warranted. Sixth, there is a lack of large multi-center clinical trials to evaluate implant outcomes among various implant surface topography and implant brands.

VII. Conclusion

The data of the present study suggest that smoking, diabetes, previous history of periodontal disease and multiple implant placement are negative indicators for implant success. Furthermore, provider level, restoration type and cantilever design also have significant impact on implant success. Deep probing depth could be used as an indicator of peri-implant inflammation but not BOP.

In addition, negligible RBL after the first year of implant loading, probing depth of peri-implant soft tissue less than 4mm, and free of implant related complications should be considered as a new definition of implant success. A longer follow-up (>1 year) after placement of definite restoration is recommended to identify the pattern of RBL and further determine the outcome of implant treatment.

VIII. Conflict of Interest Statement

The authors report no conflicts of interest related to this study.

Table I: Criteria used to determine implant success, survival and failure

Survival			Failure
Success	**Peri-implant mucositits**	**Peri-implantitis**	Implant mobility; Implant has to be removed due to failure of osseointergration
No progressive RBL after physiologic bone remodeling; No exudate/suppuration	No progressive RBL after physiologic bone remodeling; With exudate/suppuration	Progressive RBL after physiologic bone remodeling	

Table II: Demographic data of the selected participants

Total: 200 patients (100%)		
Gender	Male: 101 (50.5%)	Female: 99 (49.5%)
Age	62.8 ± 9.95 years old, ranging 22 to 91	
Smoking status	Yes: 72 (36.0%)	No: 128 (64.0%)
Diabetes	Yes: 46 (23.0%)	No: 154 (77.0%)
Obesity (BMI>30)	Yes: 53 (26.5%)	No: 147 (73.5%)
Alcohol abuse history	Yes: 8 (4.0%)	No: 192 (96.0%)
Osteoporosis	Yes: 21 (10.5%)	No: 179 (89.5%)
History of psychological disorder	Yes: 16 (7.8%)	No: 184 (92.2%)
HTN (medication control or >140/90)	Yes: 70 (35.0%)	No: 130 (65.0%)
History of periodontal disease	Yes: 104 (52.0%)	No: 96 (48.0%)
Number	Average 2.73 ± 1.44 implants/subject, ranging 1 to 9	

Table III: Characteristics and features of the included implants, restorative techniques, and surgical approach

Total implants: 550			
Follow-up year(s)	Average 6.25 ± 3.61 years, ranging 1 to 14		
Location	Maxillary anteriors: 21, Maxillary posteriors: 196, Mandibular anteriors: 6, Mandibular posteriors: 327		
Implant length	Average 11.40 ± 1.48 mm, ranging 7.0 to 15.0		
Implant diameter	Average 4.32 ± 0.51 mm, ranging 3.3 to 6.0		
Department placed	Perio: 518, Prostho: 24, Endo: 8		
Provider level	Faculty: 69	Resident: 481	
System	Nobel Biocare: 301, Zimmer: 101, Straumann: 104 BioHorizons: 21, Dentatus: 6, 3i: 13, Astra: 4		
Surface	Rough: 466	Smooth: 84	
Radiographic bone loss	Average 0.84 ± 1.38 mm, ranging 0 to 9.5		
Deepest probing depth	Average 4.60 ± 1.73 mm, ranging 3 to 12		
Bleeding on probing	Yes: 345 (62.73%)	No: 205 (37.27%)	
Abutment connection	Flat: 509	Platform switching: 41	
Restoration type	Crown: 456	Bridge: 86	Overdenture: 8
Prosthesis connection type	Cement-retained: 459	Screw-retained: 91	
Cantilever attached	Yes: 26	No: 524	
Splinted restoration	Yes: 298	No: 252	
Ridge augmentation performed (GBR)	Yes: 156	No: 394	
Sinus lift performed	Yes: 60	No: 490	
Staged approach	1-stage: 243	2-stage: 307	
Restorative complications	Yes: 152	No: 398	
Biological complications	Yes: 99	No: 451	

Table IV: Treatment outcomes at patient level and implant level based on Koldsland et al. 2010. The prevalence of peri-implant diseases was also analyzed and presented.

	Survival			Failure
	Healthy	**Peri-implant mucositits**	**Peri-implantitis**	
Patient level	30.50% (61/200)	57.50% (115/200)	≥2.0mm RBL: 5.5% (11/200)	6.50% (13/200)
Implant level	22.36% (123/550)	61.64% (339/550)	≥2.0mm RBL: 11.45% (63/550)	4.55% (25/550)

Table V: The prevalence of peri-implant diseases based on the criteria published by Derks et al. 2016

	Healthy	Peri-implant mucositits	Peri-implantitis	
Patient level	30.50% (61/200)	29.50% (59/200)	≥0.5mm RBL: 33.50% (67/200) ≥2.0mm RBL: 5.50% (11/200)	6.50% (13/200) All with ≥2.0mm RBL
Implant level	22.36% (123/550)	35.82% (197/550)	≥0.5mm RBL: 37.28% (205/550) ≥2.0mm RBL: 11.45% (63/550)	4.54% (25/550) All with ≥2.0mm RBL

Table VI: Odds ratios and estimated RBL related to implant success; factors presented statistically significant difference after regression adjustment were marked in bold.

	Odds Ratio	P value	Estimated RBL (mm)
Systemic Factors			
Age	1.83	0.7280	0.0006
Gender	1.37	0.0605	0.1327
Smoking status	**3.68**	**<0.0001**	0.7157
Diabetes	**5.85**	**<0.0001**	0.5315
Obesity (BMI>30)	2.37	0.0824	0.1972
Alcohol abuse history	1.01	0.9927	0.7613
Osteoporosis	1.31	0.1377	0.0545
History of psychological disorder	4.93	0.0109*	1.3480
Hypertension	1.03	0.0608	0.0368
History of periodontal disease	**7.13**	**<0.0001**	0.7106
Implant/Clinical Factors			
Number of implants	**3.58**	**0.0010**	0.6693
Follow-up year(s)	1.05	0.6542	0.2516
Location	1.13	0.9849	0.2516
Implant length	1.00	0.9912	0.0004
Implant diameter	1.45	0.1229	0.0962
Department placed	1.16	0.1544	0.0037
Provider level	**4.40**	**0.0021**	0.5925
System	2.26	<0.0001*	0.8145
Surface	3.03	0.0122*	0.5645
Deepest probing depth	**3.51**	**<0.0001**	0.4336
Bleeding on probing	1.52	0.0833	0.4570
Restorative Factors			
Abutment connection	1.38	0.2739	0.4374
Restoration type (single crown vs. bridge)	**3.62**	**0.0312**	0.9160
Prosthesis connection type	1.08	0.6932	0.2055
Cantilever attached	**6.94**	**0.0019**	2.0297
Splinted restoration	1.93	0.0178*	0.5652
Staged approach	1.35	0.3253	0.2664
Surgical Factors			
Ridge augmentation performed	1.30	0.4100	0.2738
Sinus augmentation performed	1.88	0.0585	0.8474
Various bone grafting materials	1.32	0.8938	0.1450
Various barrier materials	1.14	0.9695	0.4634

*: No statistically significant difference was detected after regression analysis.

Table VII: Incidence of restorative and biological complications

Restorative Complications	Incidence
Overdenture attachment loosening	25.00% (2/8)
Porcelain/ceramic fracture	14.18% (78/550)
Abutment screw loosening	7.27% (40/550)
Prosthesis screw loosening	2.73% (15/550)
Open contact	2.00% (11/550)
Abutment screw fracture	0.91% (5/550)
Biological Complications	**Incidence**
Suppuration	9.82% (54/550)
Bleeding related complications	6.55% (36/550)
Fistula	1.63% (9/550)

Figure I: Flowchart elaborating the study process
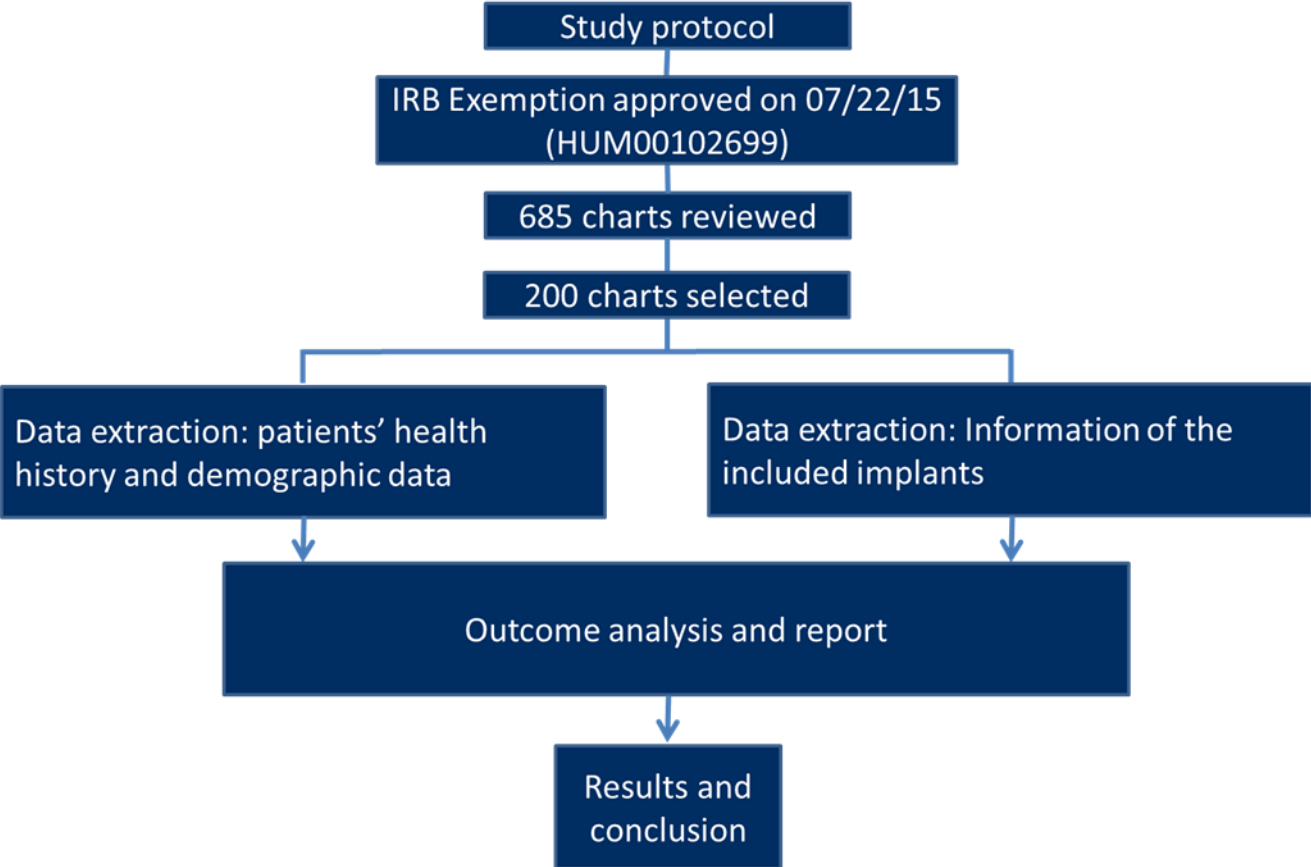
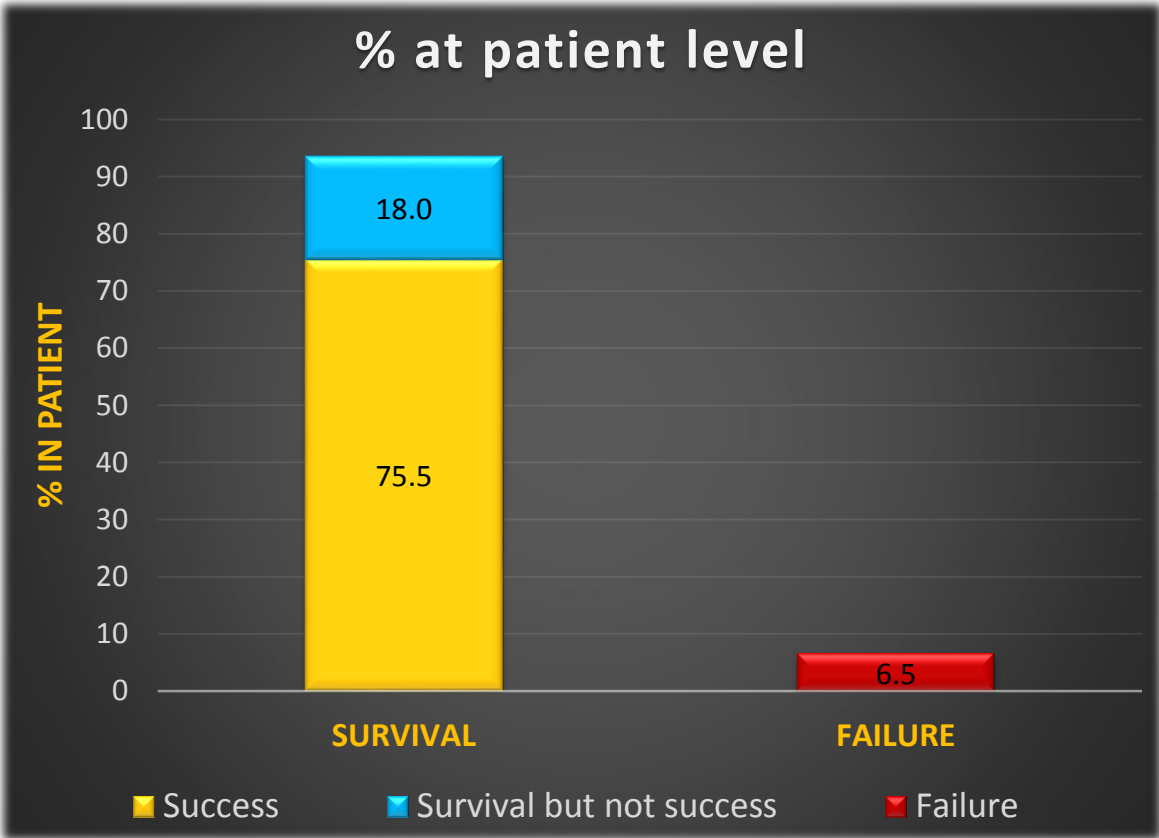**Figure II:** Implant outcome at patient level

Figure III: Implant outcome at implant level
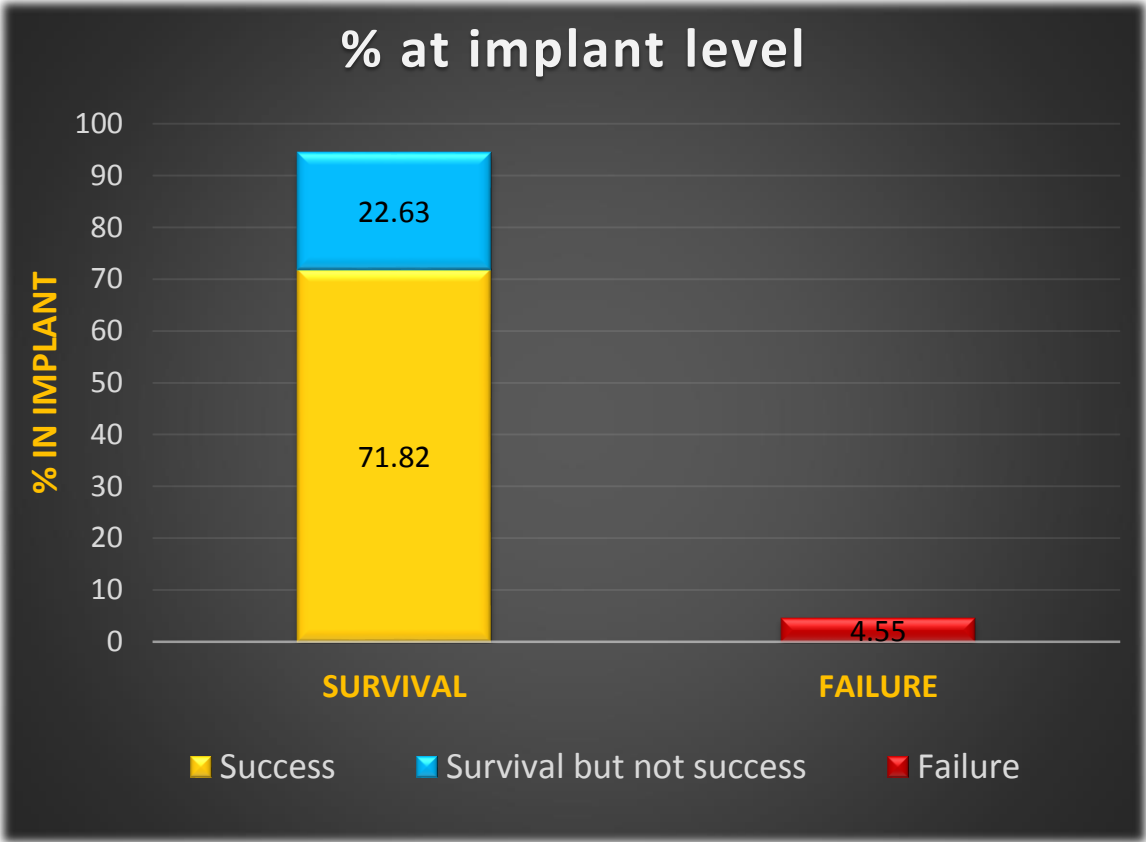
Figure IV: Result of linear regression analysis showed an estimated annual RBL of 0.08 mm for the survival implants
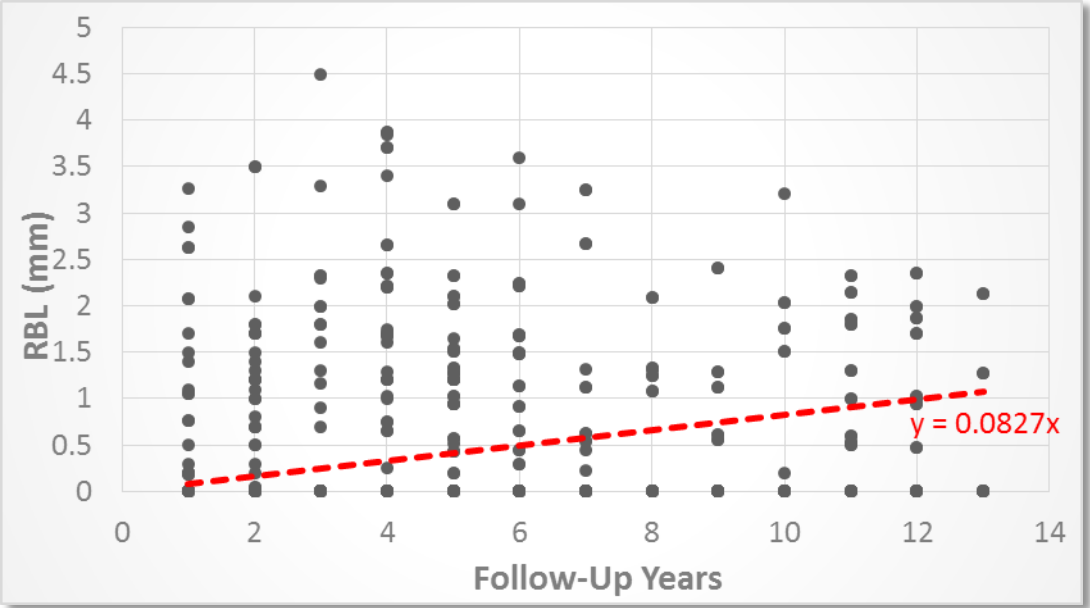
The scatter plot shows RBL (mm) on the y-axis ranging from 0 to 5, and Follow-Up Years on the x-axis ranging from 0 to 14. A red dashed trend line is shown with the equation $y = 0.0827x$.

Risk Factors of Dental Implant Survival & Success:

A Retrospective Study

Principal Investigator:

Hom-Lay Wang, D.D.S., PhD

Co-Investigators:

Guo-Hao Lin, D.D.S.

Furat George, B.D.S., M.S.

Hsun-Liang Chan, D.D.S., M.S.

Study Coordinator:

Andrea Cranston, RDH, BSDH

Study Site:

Graduate Periodontics

Department of Periodontics and Oral Medicine

University of Michigan School of Dentistry

1011 N. University Ave., Ann Arbor, MI 48109-1078

Table of Contents

Introductory Statement

General Investigational Plan

Study Protocol

Introductory Statement

Implant therapy is a widely adopted treatment option for replacing missing teeth; however, biological, mechanical or iatrogenic factors might trigger early or late failure of dental implants.[1-3] Early implant failure is mostly caused by not achieving implant osseointegration after its insertion while late implant failure is largely related to unfavorable loading or occlusion, peri-implant disease or non-ideal prosthetic design.[4] Several local and systemic factors have been identified to be associated with an increased risk of implant failure, such as smoking,[5, 6] diabetes,[7] previous history of periodontal diseases,[5, 6, 8] poor plaque control,[9] occlusal overload.[10]. However, limited evidence is present to demonstrate the rate and cause of implant failure. Therefore, the aim of this retrospective study is to investigate implant failure rate in a single center with multiple different training backgrounds; surgeons and prosthodontists and further identify the potential systemic/local risk factors associated with implant failure.

General Investigational Plan

A retrospective study is planned to investigate implant failure rate and to identify the potential systemic/local risk factors associated with implant failure. The clinical charts and radiographs of patients who underwent dental implant placement at the University of Michigan School of Dentistry (UMSOD) from March 2000 through March 2014 will be examined and analyzed. Data regarding the implant manufacturer, location in the mouth, implant diameter, implant length, implant placed with vertical/horizontal bone augmentation procedures, smoking status, history of diabetes, history of previous periodontal diseases, reasons of implant removal, implant survival time, as well as surgeons' and prosthodontists' experience, will be collected and entered into a database. Patient information will be protected according to the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Outcome analyses will be the cumulative implant survival and success rates, in association with those recorded systemic and local contributing factors of the patients. Statistical

analyses will be introduced to analyze cumulative implant survival rate as well as associations between implant survival and the recorded variables.

Study Protocol

I. Introduction

Dental implants have been widely used in partial or full edentulous arches for oral rehabilitation. Long-term prospective studies and systematic reviews have demonstrated that more than 95% survival rate could be expected after 5-year of loading.[2, 11] However, several reasons might still contribute to early or late failure of dental implants such as biological, mechanical or iatrogenic factors.[1-3]

Criteria to determine survival and success of dental implants have been reported in several studies.[12-15] Based on the International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference report,[14] survival represents that the implant is still kept in the mouth instead of being removed, and should not present mobility, pain on function or bone loss more than 1/2 of implant length. Albrektsson et al.[12] defined that a successful implant must present no mobility, no peri-implant radiolucency, bone loss less than 0.2 mm per year after the first year of loading, and no persistent pain, discomfort or infection. Failure of a dental implant is determined when an implant demonstrates mobility, pain on function, uncontrolled exudates, or severe bone loss.[14] In this case, the implant should be removed.

The concept of "osseointegration," defined as "a direct functional and structural connection between living bone and the surface of a load carrying implant," was originally introduced by Dr. Branemark.[16] This finding has further influenced the evolution of implant dentistry on implant surface modifications, grafting materials, and surgery techniques. However, early implant failure mostly involves the failure of achieving osseointegration during initial healing process after implant placement. It might result from poor bone quality or quantity, patient's medical condition, smoking, infection, overheating of the bone, compression bone necrosis, lack of primary stability as well as poor experience and skills of surgeons.[4, 17]

On the contrary, late implant failure is related to unfavorable loading or occlusion, peri-implant disease and non-ideal prosthetic design.[4] Fu et al.[10] elaborated the occlusal considerations and management of complications when restoring a dental implant. It was summarized that implant stability, radiographic bone levels, loss of attachment, and

loosening and fractures of implant fixtures and prosthetic components, could be used to assess the influence of occlusal overloading. However, although most of the mechanical/prosthetic complications are reversible by means of replacement or adjustment of restorative counterparts, currently there is still a lack of effective treatment modalities for managing peri-implantitis.[18, 19]

Several local and systemic factors have been proposed and associated with an increased risk of peri-implantitis, such as smoking,[5, 6] diabetes,[7] previous history of periodontal diseases,[5, 6, 8] poor plaque control,[9] and occlusal overload.[10] Other predisposing local factor related to peri-implantitis is retained excess cement, which leads to potential biological complications and marginal bone loss.[20, 21] It has been reported that a trend of bone loss exceeding 2 mm was found more in cement-retained restorations compared to screw-retained restorations,[21] which may compromise the future survival of the implants and restorations.

II. Study Aim

The aim of this retrospective study is to investigate the implant survival, success and failure rates in a single center with multiple surgeons and prosthodontists and to identify the potential systemic/local risk factors associated with implant failure.

III. Hypothesis

Implants placed in patients with systemic/local risk factors, such as smoking, diabetes, previous history of periodontal diseases, poor plaque control, symptoms/signs of occlusal overload, required bone augmentation, less experienced surgeon, and cement-retained multi-unit restorations, are more susceptible bone loss and failure.

IV. Materials and Methods

1. Data Retrieval

In this retrospective study, the clinical charts and radiographs of patients who underwent dental implant placement at the University of Michigan School of Dentistry (UMSOD)

from March 2000 through March 2014 will be reviewed. A minimal of 200 charts are planned to be included in this retrospective radiographic study. The charts will be reviewed in a random order and once 200 charts are reviewed that have the inclusion criteria, no more charts will be reviewed. Subjects who are at least 18 years old that have had at least one implant placed at UMSOD with at least a one-year follow-up periapical radiograph(s) of the implant(s) will be included. Data regarding patients' and implants' information (patients' study number, location of the tooth number, age, gender, faculty/resident provider level and provider department), year of implant placed, systemic conditions including past history of smoking status, diabetes mellitus, alcohol consumption, osteoporosis, depression, obesity, hypertension, and past history of periodontal diseases, restorative related factors (implant system, length, diameter, surface texture, connection type, restoration type such as crown/fixed dental prosthesis/overdenture, cement/screw retained prosthesis, cantilever, splinted/non-splinted crowns), surgical related factors (simultaneous guided bone regeneration procedure, sinus lift procedure, types of bone graft used, types of membrane used, staged surgical approach, insertion torque), adverse event (restorative complications, biological complications), peri-implant parameters (deepest peri-implant probing depth, bleeding on probing, first-year radiographic bone loss and annual radiographic bone loss after first year service of implant restoration, if available) and implant survival/success/failure will be collected and entered into a database.

From this database, the cumulative survival rate and implant and patient information will be analyzed. Implant failure is defined as any implant removed for any reason during the observation period. Early implant failure is defined as implant removed before final restoration completed, and late implant failure is defined as implant removed after final restoration completed. Implant survival is defined as an implant still in function in the patient's mouth. Implant success is defined based on American Academy of Periodontology Position Paper in 2000: (1) absence of persistent signs/symptoms such as pain, infection, neuropathies, parathesias, and violation of vital structures; (2) implant immobility; (3) no continuous peri-implant radiolucency; (4) negligible progressive bone loss (less than 0.2 mm annually) after physiologic remodeling during the first year of function; and (5)

patient/dentist satisfaction with the implant supported restoration.[22] The study protocol will be reviewed and approved by the University of Michigan Institutional Review Board.

2. Statistical Analysis

Outcome analyses will be the cumulative implant survival rate, in association with those recorded systemic and local contributing factors of the patients. Implant survival will be estimated. The associations between implant survival/success/failure rates and the recorded variables will be estimated by Pearson chi-square test and Fisher exact test ($P= 0.05$).

V. Timetable

3 months	3 months	3 months	2 months

Study initiation — Chart review — Data extraction — Data analyses — Completion of manuscript and submit for publication
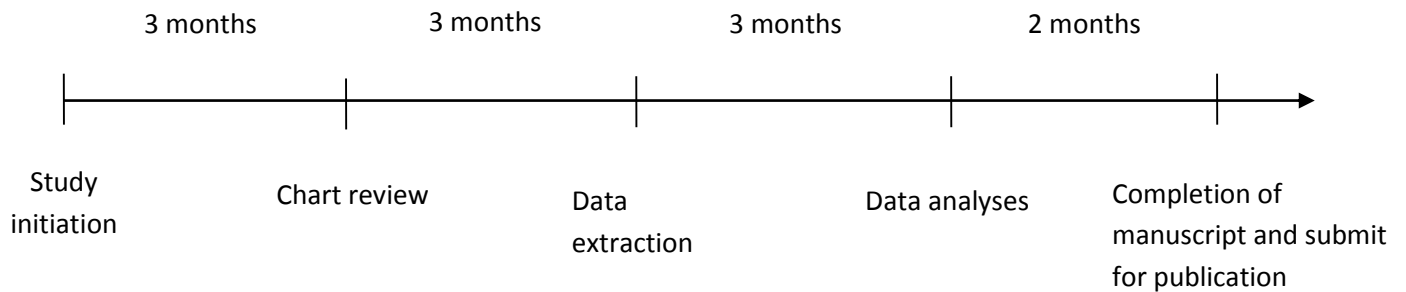
VI. References (of the study protocol)

1.   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.
2.   Jung RE, Pjetursson BE, Glauser R, Zembic A, Zwahlen M, Lang NP. A systematic review of the 5-year survival and complication rates of implant-supported single crowns. *Clin Oral Implants Res* 2008;19:119-130.
3.   Pjetursson BE, Bragger U, Lang NP, Zwahlen M. Comparison of survival and complication rates of tooth-supported fixed dental prostheses (FDPs) and implant-supported FDPs and single crowns (SCs). *Clin Oral Implants Res* 2007;18 Suppl 3:97-113.
4.   Sakka S, Baroudi K, Nassani MZ. Factors associated with early and late failure of dental implants. *J Investig Clin Dent* 2012;3:258-261.
5.   Heitz-Mayfield LJ, Huynh-Ba G. History of treated periodontitis and smoking as risks for implant therapy. *Int J Oral Maxillofac Implants* 2009;24 Suppl:39-68.
6.   Klokkevold PR, Han TJ. How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? *Int J Oral Maxillofac Implants* 2007;22 Suppl:173-202.
7.   Salvi GE, Carollo-Bittel B, Lang NP. Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks. *J Clin Periodontol* 2008;35:398-409.
8.   Van der Weijden GA, van Bemmel KM, Renvert S. Implant therapy in partially edentulous, periodontally compromised patients: a review. *J Clin Periodontol* 2005;32:506-511.
9.   Ferreira SD, Silva GL, Cortelli JR, Costa JE, Costa FO. Prevalence and risk variables for peri-implant disease in Brazilian subjects. *J Clin Periodontol* 2006;33:929-935.
10.   Fu JH, Hsu YT, Wang HL. Identifying occlusal overload and how to deal with it to avoid marginal bone loss around implants. *Eur J Oral Implantol* 2012;5 Suppl:S91-103.
11.   Ferrigno N, Laureti M, Fanali S, Grippaudo G. A long-term follow-up study of non-submerged ITI implants in the treatment of totally edentulous jaws. Part I: Ten-year life table analysis of a prospective multicenter study with 1286 implants. *Clin Oral Implants Res* 2002;13:260-273.
12.   Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. *Int J Oral Maxillofac Implants* 1986;1:11-25.
13.   Buser D, Weber HP, Lang NP. Tissue integration of non-submerged implants. 1-year results of a prospective study with 100 ITI hollow-cylinder and hollow-screw implants. *Clin Oral Implants Res* 1990;1:33-40.
14.   Misch CE, Perel ML, Wang HL, et al. Implant success, survival, and failure: the International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference. *Implant Dent* 2008;17:5-15.

15. Schnitman PA, Shulman LB. Recommendations of the consensus development conference on dental implants. *J Am Dent Assoc* 1979;98:373-377.
16. Branemark PI. Osseointegration and its experimental background. *J Prosthet Dent* 1983;50:399-410.
17. Bashutski JD, D'Silva NJ, Wang HL. Implant compression necrosis: current understanding and case report. *J Periodontol* 2009;80:700-704.
18. Chan HL, Lin GH, Suarez F, MacEachern M, Wang HL. Surgical management of peri-implantitis: a systematic review and meta-analysis of treatment outcomes. *J Periodontol* 2014;85:1027-1041.
19. Khoshkam V, Chan HL, Lin GH, et al. Reconstructive procedures for treating peri-implantitis: a systematic review. *J Dent Res* 2013;92:131S-138S.
20. Korsch M, Walther W. Peri-Implantitis Associated with Type of Cement: A Retrospective Analysis of Different Types of Cement and Their Clinical Correlation to the Peri-Implant Tissue. *Clin Implant Dent Relat Res* 2014. (Epub ahead of print)
21. Sailer I, Muhlemann S, Zwahlen M, Hammerle CH, Schneider D. Cemented and screw-retained implant reconstructions: a systematic review of the survival and complication rates. *Clin Oral Implants Res* 2012;23 Suppl 6:163-201.
22. Iacono VJ; Committee on Research, Science and Therapy, the American Academy of Periodontology. Dental implants in periodontal therapy. *J Periodontol* 2000;71:1934-42.

APPENDIX II: IRB Exempt Determination Letter

UNIVERSITY OF MICHIGAN
eResearch.umich.edu

Medical School Institutional Review Board (IRBMED) • 2800 Plymouth Road, Building 520, Suite 3214, Ann Arbor, MI 48109-2800 • phone (734) 763 4768 • fax (734) 763 9603 • irbmed@umich.edu

To: Hom-Lay Wang

From:

Michael	Geisser
Alan	Sugar

Cc:

Hsun-Liang	Chan
Furat	George
Guo-Hao	Lin
Andrea	Cranston
Hom-Lay	Wang

Subject: Notice of Exemption for [HUM00102699]

SUBMISSION INFORMATION:
Title: Risk Factors of Dental Implant Survival & Success: A Retrospective Study
Full Study Title (if applicable): Risk Factors of Dental Implant Survival & Success: A Retrospective Study
Study eResearch ID: HUM00102699
Date of this Notification from IRB: 7/22/2015
Date of IRB Exempt Determination: 7/22/2015
UM Federalwide Assurance: FWA00004969 (For the current FWA expiration date, please visit the UM HRPP Webpage)

IRB EXEMPTION STATUS:
The IRBMED has reviewed the study referenced above and determined that, as currently described, it is exempt from ongoing IRB review, per the following federal exemption category:

EXEMPTION #4 of the 45 CFR 46.101.(b):
Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or

through identifiers linked to the subjects.

Note that the study is considered exempt as long as any changes to the use of human subjects (including their data) remain within the scope of the exemption category above. Any proposed changes that may exceed the scope of this category, or the approval conditions of any other non-IRB reviewing committees, must be submitted as an amendment through eResearch.

Although an exemption determination eliminates the need for ongoing IRB review and approval, you still have an obligation to understand and abide by generally accepted principles of responsible and ethical conduct of research. Examples of these principles can be found in the Belmont Report as well as in guidance from professional societies and scientific organizations.

PRIVACY BOARD REVIEW:
The Privacy Board has reviewed the project referenced above and has granted a Waiver of HIPAA Authorization. The Privacy Board has determined that the proposed project conforms with applicable regulations and policies. This project must be conducted in accordance with the description and information provided in the application and associated documents.

Note: This project is regulated under the HIPAA Privacy Rule, which requires you to account for certain disclosures of Protected Health Information (PHI).

SUBMITTING AMENDMENTS VIA eRESEARCH:
You can access the online forms for amendments in the eResearch workspace for this exempt study, referenced above.

ACCESSING EXEMPT STUDIES IN eRESEARCH:
Click the "Exempt and Not Regulated" tab in your eResearch home workspace to access this exempt study.

Michael Geisser
Co-chair, IRBMED

Alan Sugar
Co-chair, IRBMED

BIBLIOGRAPHY

1.   Ferrigno N, Laureti M, Fanali S, Grippaudo G. A long-term follow-up study of non-submerged ITI implants in the treatment of totally edentulous jaws. Part I: Ten-year life table analysis of a prospective multicenter study with 1286 implants. *Clin Oral Implants Res* 2002;13:260-273.

2.   Jung RE, Pjetursson BE, Glauser R, Zembic A, Zwahlen M, Lang NP. A systematic review of the 5-year survival and complication rates of implant-supported single crowns. *Clin Oral Implants Res* 2008;19:119-130.

3.   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.

4.   Pjetursson BE, Bragger U, Lang NP, Zwahlen M. Comparison of survival and complication rates of tooth-supported fixed dental prostheses (FDPs) and implant-supported FDPs and single crowns (SCs). *Clin Oral Implants Res* 2007;18 Suppl 3:97-113.

5.   Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. *Int J Oral Maxillofac Implants* 1986;1:11-25.

6.   Buser D, Weber HP, Lang NP. Tissue integration of non-submerged implants. 1-year results of a prospective study with 100 ITI hollow-cylinder and hollow-screw implants. *Clin Oral Implants Res* 1990;1:33-40.

7.   Misch CE, Perel ML, Wang HL, et al. Implant success, survival, and failure: the International Congress of Oral Implantologists (ICOI) Pisa Consensus Conference. *Implant Dent* 2008;17:5-15.

8.   Schnitman PA, Shulman LB. Recommendations of the consensus development conference on dental implants. *J Am Dent Assoc* 1979;98:373-377.

9.   Branemark PI. Osseointegration and its experimental background. *J Prosthet Dent* 1983;50:399-410.

10.   Bashutski JD, D'Silva NJ, Wang HL. Implant compression necrosis: current understanding and case report. *J Periodontol* 2009;80:700-704.

11.   Sakka S, Baroudi K, Nassani MZ. Factors associated with early and late failure of dental implants. *J Investig Clin Dent* 2012;3:258-261.

12.   Fu JH, Hsu YT, Wang HL. Identifying occlusal overload and how to deal with it to avoid marginal bone loss around implants. *Eur J Oral Implantol* 2012;5 Suppl:S91-103.

13.   Chan HL, Lin GH, Suarez F, MacEachern M, Wang HL. Surgical management of peri-implantitis: a systematic review and meta-analysis of treatment outcomes. *J Periodontol* 2014;85:1027-1041.

14.   Khoshkam V, Chan HL, Lin GH, et al. Reconstructive procedures for treating peri-implantitis: a systematic review. *J Dent Res* 2013;92:131S-138S.

15.   Heitz-Mayfield LJ, Huynh-Ba G. History of treated periodontitis and smoking as risks for implant therapy. *Int J Oral Maxillofac Implants* 2009;24 Suppl:39-68.

16. Klokkevold PR, Han TJ. How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? *Int J Oral Maxillofac Implants* 2007;22 Suppl:173-202.

17. Salvi GE, Carollo-Bittel B, Lang NP. Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks. *J Clin Periodontol* 2008;35:398-409.

18. Van der Weijden GA, van Bemmel KM, Renvert S. Implant therapy in partially edentulous, periodontally compromised patients: a review. *J Clin Periodontol* 2005;32:506-511.

19. Ferreira SD, Silva GL, Cortelli JR, Costa JE, Costa FO. Prevalence and risk variables for peri-implant disease in Brazilian subjects. *J Clin Periodontol* 2006;33:929-935.

20. Korsch M, Walther W. Peri-Implantitis Associated with Type of Cement: A Retrospective Analysis of Different Types of Cement and Their Clinical Correlation to the Peri-Implant Tissue. *Clin Implant Dent Relat Res* 2014;17 Suppl 2:e434-43.

21. Sailer I, Muhlemann S, Zwahlen M, Hammerle CH, Schneider D. Cemented and screw-retained implant reconstructions: a systematic review of the survival and complication rates. *Clin Oral Implants Res* 2012;23 Suppl 6:163-201.

22. Ahead of print. Schwarz F, Becker K, Sahm N, Horstkemper T, Rousi K, Becker J. The prevalence of peri-implant diseases for two-piece implants with an internal tube-in-tube connection: a cross-sectional analysis of 512 implants [published online ahead of print July 14, 2015]. *Clin Oral Implants Res*; doi: 10.1111/clr.12609.

23. Renvert S, Aghazadeh A, Hallstrom H, Persson GR. Factors related to peri-implantitis - a retrospective study. *Clin Oral Implants Res* 2014;25:522-529.

24. Koldsland OC, Scheie AA, Aass AM. Prevalence of peri-implantitis related to severity of the disease with different degrees of bone loss. *J Periodontol* 2010;81:231-238.

25. Derks J, Schaller D, Hakansson J, Wennstrom JL, Tomasi C, Berglundh T. Effectiveness of Implant Therapy Analyzed in a Swedish Population: Prevalence of Peri-implantitis. *J Dent Res* 2016;95:43-49.

26. American Academy of Periodontology Academy Statement. Peri-implant mucositis and peri-implantitis: a current understanding of their diagnoses and clinical implications. *J Periodontol* 2013;84:436-443.

27. Lindhe J, Meyle J, Group DoEWoP. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. *J Clin Periodontol* 2008;35:282-285.

28. Galindo-Moreno P, Leon-Cano A, Ortega-Oller I, Monje A, O'Valle F, Catena A. Marginal bone loss as success criterion in implant dentistry: beyond 2 mm. *Clin Oral Implants Res* 2015;26:e28-34.

29. Linkevicius T, Apse P, Grybauskas S, Puisys A. Reaction of crestal bone around implants depending on mucosal tissue thickness. A 1-year prospective clinical study. *Stomatologija* 2009;11:83-91.

30. Suarez-Lopez Del Amo F, Lin GH, Monje A, Galindo-Moreno P, Wang HL. Influence of soft tissue thickness upon peri-implant marginal bone loss: a systematic review and meta-analysis. *J Periodontol* 2016;87:690-699.

31.   Wennerberg A, Albrektsson T. Effects of titanium surface topography on bone integration: a systematic review. *Clin Oral Implants Res* 2009;20 Suppl 4:172-184.

32.   American Academy of Periodontology Task Force Report on the Update to the 1999 Classification of Periodontal Diseases and Conditions. *J Periodontol* 2015;86:835-838.

33.   Roos-Jansaker AM, Renvert H, Lindahl C, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. *J Clin Periodontol* 2006;33:296-301.

34.   Froum SJ, Rosen PS. A proposed classification for peri-implantitis. *Int J Periodontics Restorative Dent* 2012;32:533-540.

35.   Derks J, Hakansson J, Wennstrom JL, Tomasi C, Larsson M, Berglundh T. Effectiveness of implant therapy analyzed in a Swedish population: early and late implant loss. *J Dent Res* 2015;94:44S-51S.

36.   Monje A, Fu JH, Chan HL, et al. Do implant length and width matter for short dental implants (<10 mm)? A meta-analysis of prospective studies. *J Periodontol* 2013;84:1783-1791.

37.   Telleman G, Raghoebar GM, Vissink A, den Hartog L, Huddleston Slater JJ, Meijer HJ. A systematic review of the prognosis of short (<10 mm) dental implants placed in the partially edentulous patient. *J Clin Periodontol* 2011;38:667-676.

38.   Karoussis IK, Kotsovilis S, Fourmousis I. A comprehensive and critical review of dental implant prognosis in periodontally compromised partially edentulous patients. *Clin Oral Implants Res* 2007;18:669-679.

39.   Karoussis IK, Salvi GE, Heitz-Mayfield LJ, Bragger U, Hammerle CH, Lang NP. Long-term implant prognosis in patients with and without a history of chronic periodontitis: a 10-year prospective cohort study of the ITI Dental Implant System. *Clin Oral Implants Res* 2003;14:329-339.

40.   Schou S, Holmstrup P, Worthington HV, Esposito M. Outcome of implant therapy in patients with previous tooth loss due to periodontitis. *Clin Oral Implants Res* 2006;17 Suppl 2:104-123.

41.   Strietzel FP, Reichart PA, Kale A, Kulkarni M, Wegner B, Kuchler I. Smoking interferes with the prognosis of dental implant treatment: a systematic review and meta-analysis. *J Clin Periodontol* 2007;34:523-544.

42.   Numabe Y, Ogawa T, Kamoi H, et al. Phagocytic function of salivary PMN after smoking or secondary smoking. *Ann Periodontol* 1998;3:102-107.

43.   Kenney EB, Kraal JH, Saxe SR, Jones J. The effect of cigarette smoke on human oral polymorphonuclear leukocytes. *J Periodontal Res* 1977;12:227-234.

44.   Rawlinson A, Grummitt JM, Walsh TF, Ian Douglas CW. Interleukin 1 and receptor antagonist levels in gingival crevicular fluid in heavy smokers versus non-smokers. *J Clin Periodontol* 2003;30:42-48.

45.   Zambon JJ, Grossi SG, Machtei EE, Ho AW, Dunford R, Genco RJ. Cigarette smoking increases the risk for subgingival infection with periodontal pathogens. *J Periodontol* 1996;67:1050-1054.

46.   Rasperini G, Siciliano VI, Cafiero C, Salvi GE, Blasi A, Aglietta M. Crestal bone changes at teeth and implants in periodontally healthy and periodontally

compromised patients. A 10-year comparative case-series study. *J Periodontol* 2014;85:e152-159.

47. Grunder U, Gaberthuel T, Boitel N, et al. Evaluating the clinical performance of the Osseotite implant: defining prosthetic predictability. *Compend Contin Educ Dent* 1999;20:628-633, 636, 638-640.

48. Bain CA. Smoking and implant failure--benefits of a smoking cessation protocol. *Int J Oral Maxillofac Implants* 1996;11:756-759.

49. Mealey B. Diabetes and periodontal diseases. *J Periodontol* 1999;70:935-949.

50. Salvi GE, Yalda B, Collins JG, et al. Inflammatory mediator response as a potential risk marker for periodontal diseases in insulin-dependent diabetes mellitus patients. *J Periodontol* 1997;68:127-135.

51. Mombelli A, Cionca N. Systemic diseases affecting osseointegration therapy. *Clin Oral Implants Res* 2006;17 Suppl 2:97-103.

52. Rodriguez AM, Aquilino SA, Lund PS, Ryther JS, Southard TE. Evaluation of strain at the terminal abutment site of a fixed mandibular implant prosthesis during cantilever loading. *J Prosthodont* 1993;2:93-102.

53. White SN, Caputo AA, Anderkvist T. Effect of cantilever length on stress transfer by implant-supported prostheses. *J Prosthet Dent* 1994;71:493-499.

54. Zurdo J, Romao C, Wennstrom JL. Survival and complication rates of implant-supported fixed partial dentures with cantilevers: a systematic review. *Clin Oral Implants Res* 2009;20 Suppl 4:59-66.

55. Kim Y, Oh TJ, Misch CE, Wang HL. Occlusal considerations in implant therapy: clinical guidelines with biomechanical rationale. *Clin Oral Implants Res* 2005;16:26-35.

56. Bragger U, Burgin WB, Hammerle CH, Lang NP. Associations between clinical parameters assessed around implants and teeth. *Clin Oral Implants Res* 1997;8:412-421.

57. Karoussis IK, Muller S, Salvi GE, Heitz-Mayfield LJ, Bragger U, Lang NP. Association between periodontal and peri-implant conditions: a 10-year prospective study. *Clin Oral Implants Res* 2004;15:1-7.

58. Lang NP, Wilson TG, Corbet EF. Biological complications with dental implants: their prevention, diagnosis and treatment. *Clin Oral Implants Res* 2000;11 Suppl 1:146-155.

59. Graziani F, Figuero E, Herrera D. Systematic review of quality of reporting, outcome measurements and methods to study efficacy of preventive and therapeutic approaches to peri-implant diseases. *J Clin Periodontol* 2012;39 Suppl 12:224-244.

60. Renvert S, Polyzois IN. Clinical approaches to treat peri-implant mucositis and peri-implantitis. *Periodontol 2000* 2015;68:369-404.

61. Salvi GE, Aglietta M, Eick S, Sculean A, Lang NP, Ramseier CA. Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. *Clin Oral Implants Res* 2012;23:182-190.

62. Brito C, Tenenbaum HC, Wong BK, Schmitt C, Nogueira-Filho G. Is keratinized mucosa indispensable to maintain peri-implant health? A systematic review of the literature. *J Biomed Mater Res B Appl Biomater* 2014;102:643-650.

63. Lin GH, Chan HL, Wang HL. The significance of keratinized mucosa on implant health: a systematic review. *J Periodontol* 2013;84:1755-1767.

64. Goodacre CJ, Bernal G, Rungcharassaeng K, Kan JY. Clinical complications with implants and implant prostheses. *J Prosthet Dent* 2003;90:121-132.

65. Goodacre CJ, Kan JY, Rungcharassaeng K. Clinical complications of osseointegrated implants. *J Prosthet Dent* 1999;81:537-552.