PROJECT TITLE:

Local and Systemic Inflammatory Bone Alterations Associated with the Survival of Dental Implants

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STRUCTURED ABSTRACT

Introduction: Dental implants are a durable functional and aesthetic option for tooth replacement. However, they are not exempt from failure. Current literature has highlighted the importance of systemic factors, such as vitamin D deficiency and osteoporosis, as well as local factors, including the presence of nearby periapical infections or implants placed in implant sites where previous endodontic failure with bone involvement had occurred. Moreover, we do not have to forget the paper of the prosthesis.

Hypothesis: Bone alterations, whether general or local, represent a risk factor for implant failure and peri-implantitis.

Objectives: To analyze implant failure and marginal bone loss among patients with local and/or systemic bone alterations compared with patients without these alterations.

Methods: Implant failures occurring in patients treated in the Master's Degree in Oral Medicine, Surgery and Implantology at the University of Barcelona (MCIO-UB) over the last 10 years will be analyzed and correlated with bone-related factors, both local and systemic, recorded in the clinical history. Cases without radiographic and clinical data allowing the study to be performed will be excluded.

Population: A total of 3,500 implants have been placed, with a recorded failure rate between 4% and 8%, depending on the different techniques performed; therefore, the study sample will include 192 implants. Cohorts of non-failed implants will be established by matching patients of the same sex and within ±5 years of age in whom no implant failure occurred.

INTRODUCTION

Dental implants have become a cornerstone in the field of restorative dentistry, offering a durable functional and aesthetic option for tooth replacement. (1)

Osseointegration, defined as the formation of a direct interface between the implant and the bone, is key to the survival of dental implants. It is important that the implant becomes integrated into the bone during the initial healing phase, resulting in asymptomatic fixation under functional loading, and that this osseointegration is maintained over time. (2)

Although implant therapy has a high survival rate, close to 95%, failures due to lack of osseointegration remain a major challenge. (1,3) These failures can be divided into early and late failures based on chronological criteria. Early failure is caused by lack of osseointegration and indicates inadequate bone healing; late failure, on the other hand, is caused by loss of osseointegration over time. (3)

Furthermore, marginal bone stability is important for long-term survival. Several surgical, prosthodontic and patient-dependent factors are related to marginal bone loss. Therefore, systemic factors, such as vitamin D deficiency or osteoporosis, and local factors, such as the presence of teeth with nearby periapical infections or implants placed in sites where endodontic failure had previously occurred, may be involved. (2,4)

Vitamin D is a fat-soluble steroid hormone mostly synthesized in the skin, stimulated by exposure to ultraviolet light. Nutritional intake is only a small source of vitamin D. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D, the main circulating metabolite of vitamin D, which is used to determine vitamin D levels. Renal and extra-renal hydroxylation of this metabolite results in its transformation into 1,25-dihydroxyvitamin D, which exerts endocrine, autocrine and paracrine functions as a steroid hormone. (5)

Calcium is absorbed by the small intestine in the presence of vitamin D. Calcium and phosphorus form hydroxyapatite crystals, which mineralize and strengthen bone tissue. Vitamin D also has functions beyond this classic role. Indeed, vitamin D receptors have been identified in helper T lymphocytes, macrophages, the prostate, the brain and other tissues. Through activation of osteoclasts and osteoblasts, this vitamin regulates mineral

homeostasis, including calcium and phosphates, as well as bone metabolism and mineralisation. It improves intestinal calcium absorption, decreases parathyroid hormone release and reduces bone resorption by inhibiting osteoclastogenesis. (6–8)

Vitamin D deficiency has been shown to increase the risk of early implant failure by 300%. In addition, it induces hypophosphatemia, hypocalcemia and secondary hyperparathyroidism resulting from hypocalcemia. (6) With regard to other analytical alterations, patients with renal insufficiency have been observed to present a broad spectrum of alterations of varying severity. The risk of bone alterations and implant-related risk should be considered. In this regard, lower mineral content and reduced bone thickness have been reported. (9,10)

On the other hand, osteoporosis is a systemic skeletal disorder that mainly affects elderly women. It is estimated to affect approximately 200 million individuals worldwide. Osteoporosis causes a decrease in bone density, degradation of bone microarchitecture and an increase in trabecular spaces within bone, resulting in greater fragility and an increased possibility of fractures. (11,12)

All these data suggests that systemic bone metabolism may be a risk factor affecting osseointegration and its maintenance. However, the literature is not clear, at least regarding osteoporosis. In the meta-analysis by Lemos et al. (11), the implant survival rate showed no significant differences between patients with and without osteoporosis, and marginal bone loss ranged from 0.15 to 1.20 mm in patients with osteoporosis and from 0.06 to 0.87 mm in healthy patients, with a mean follow-up of 3.5 years. In addition, another systematic review reported implant survival of up to 98.7%, with no significant differences in osseointegration compared with healthy patients. (13) Conversely, it has been demonstrated that postmenopausal women with hyperparathyroidism have a protective effect against osteoporosis. (14)

In other recent studies, a significant association has been observed between LDL (low-density lipoprotein) cholesterol levels and periodontal bone loss (15).

Moreover, placing an implant near a tooth with inflammation in the form of a persistent apical lesion, or in a previous site where persistent periapical infection had existed, that is, with local bone involvement, may interfere with osseointegration. (16)

Peri-implantitis is an inflammatory disease, mediated by bacteria, that affects the hard and soft tissues surrounding dental implants. Dental implants are more prone to bacterial invasion than natural teeth, as they have a lower blood supply and the connective tissue fibers surrounding the implant are limited to the soft tissues and are arranged parallel to one another. (17) In addition, in the retrospective observational study by López-Martínez et al. (18), which examined implants adjacent to an endodontically treated tooth or implants subsequently placed in an area where a tooth with previous endodontic treatment had been extracted, peri-implantitis was observed in 31.5% of implants, compared with 2.84% of implants not related to endodontically treated teeth. In another retrospective study (19), which evaluated the prevalence of peri-implantitis in sites where teeth had previously undergone failed periapical surgery, apical peri-implantitis occurred in 35.7% of these implants. The sample included 14 implants.

For all the above reasons, we propose to study, among failed implants in our group, factors related to bone metabolism, primarily osteoporosis and vitamin D deficiency, and secondarily creatinine, glomerular filtration rate, blood urea nitrogen (BUN), urea, calcium, phosphorus, vitamin D, PTH, C-reactive protein and erythrocyte sedimentation rate (ESR). Also, total cholesterol, HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglycerides will be analyzed. Other variables analysed are local bone factors, including adjacency to a tooth with periapical pathology or implant placement in a site with previous periapical pathology.

HYPOTHESIS AND OBJECTIVES

Bone involvement, whether local or systemic, regardless of the existing bone volume, increases implant failure and peri-implantitis.

Null hypothesis: Bone involvement, whether local or systemic, regardless of the existing bone volume, does NOT increase implant failure and does NOT increase peri-implantitis.

The main objective is to assess the difference in the prevalence of implant failure and peri-implantitis between patients with local and/or systemic alterations involving bone involvement.

The specific objectives are:

- Osteoporosis and implant failure and/or peri-implantitis.
- Vitamin D levels and implant failure and/or peri-implantitis.
- Implant placement in a site of previous failed endodontic treatment and implant failure and/or peri-implantitis.
- Failed implant and/or peri-implantitis adjacent to a tooth with a periapical lesion.
- Different prosthesis and their relationship with peri-implantitis

METHODOLOGICAL DESIGN

This is a retrospective cohort study design.

PATIENTS AND SAMPLE

The sample will be selected from patients who have received dental implants at the Dental Hospital of the University of Barcelona (HOUB).

Inclusion criteria:

- Patients over 18 years of age.
- Patients with implants placed within the last 10 years.
- Patients with access to a complete medical and dental record.
- Patients whose implant follow-up has been documented through periapical radiographs and/or panoramic radiographs (OPG).
- Patients whose pre-implant tooth status has been recorded.
- Patients with blood test results performed within 6 months before or after implant placement.
- Implants lost due to peri-implant disease causing bone resorption.

Exclusion criteria for the study group:

- Failure to meet the inclusion criteria.

Sample size calculation:

Considering a total of 3,500 implants placed over a 10-year period and an expected proportion of 0.05, the calculated sample size is 192 implants. Although this is a retrospective study, we will aim to obtain the largest possible number of cases, with a minimum of 50. Considering that peri-implantitis in implants adjacent to a tooth with periapical pathology may be as high as 31%, compared with 2.8% in those without such

pathology (18), the minimum sample size for implants with and without peri-implantitis would be 36, with a confidence interval of 0.05.

METHODS, TECHNIQUES, TESTS, AND INTERVENTIONS

- Initially, a list of failed implants placed over the last 10 years will be obtained. The patients' clinical records will then be reviewed to determine whether they presented with osteoporosis or vitamin D deficiency. Regarding vitamin D deficiency, the diagnosis will be considered valid if supported by laboratory test results. In cases of osteoporosis, the condition will be confirmed if the patient reports a history of osteoporosis and/or if there is a medical report and/or bone densitometry confirming the diagnosis.
- Additionally, laboratory analyses will be reviewed for the presence of abnormalities in calcium-phosphate metabolism. The number of failed implants per patient will be recorded, with patients being included if they have at least one failed implant.
- In cases of systemic disorders, any medication taken for the condition under investigation will also be recorded.
- Patient-related data, including sex and age, will be collected.
- Data related to the day of surgery will also be collected, including whether regenerative procedures were performed and whether any complications occurred.
- For patients who experienced implant failure, it will be assessed whether the failed implants were adjacent to an endodontically treated tooth or located in a site where a previous endodontic failure had occurred. The patient's radiographic records will be reviewed to determine whether mesial and distal bone loss has occurred around the remaining implants. Bone loss will be quantified in millimeters on both the mesial and distal aspects, based on the radiograph taken on the day of implant placement and the implant length.
- In cases of systemic conditions affecting bone metabolism, results will be reported both per implant and per patient in order to minimize bias.

- Implants adjacent to a tooth with pathology, or implants placed in a previously affected site, will be considered positive if less than 3 months have elapsed since tooth extraction (20).
- Endodontic failure will be analyzed according to the presence of signs and symptoms, including pain and the development or persistence of inflammation and fistulas. Radiographically, endodontic failure is defined as the enlargement of a periapical radiolucent lesion over a period of 6 to 24 months. Histologically, it is characterized by the absence of healing or by destruction of the periapical structures in the presence of inflammatory cells (21,22).

Teeth will be evaluated using the **Periapical Index (PAI)** (23), which categorizes periapical status as follows:

1. Periapical bone destruction almost certainly absent.
2. Periapical bone destruction probably absent.
3. Uncertain.
4. Periapical bone destruction probably present.
5. Periapical bone destruction definitely present.

Likewise, the size of the periapical lesion will be measured on periapical radiographs (mesiodistal × coronoapical dimensions).

Peri-implantitis will be categorized according to the degree of mesial and distal bone loss around implants using the classification proposed by **Monje et al.** (24):

- **Mild:** 3 to 4 mm of bone loss or < 25% of the implant length.
- **Moderate:** 4 to 5 mm of bone loss or ≥ 25% to 50% of the implant length.
- **Advanced:** > 6 mm of bone loss or > 50% of the implant length.

The following primary variables will be analysed:

Items	Variables
Sex	Categorical (dichotomous)

Age	Numerical (continuous)

The implantology-related variables to be studied will be as follows:

Measurement	Variable Type
Implant analysed	Categorical (polychotomous)
Time from insertion to failure/last radiographic revision	Numerical (continuous)
Type of regeneration (if present)	Categorical (polychotomous)
Dimensions of the achieved regeneration (mm)	Numerical (continuous)
Type of material used for regeneration	Categorical (polychotomous)
Implant platform-to-bone crest relationship measurements (mm)	Numerical (continuous)
Mesial-distal bone loss measurement (mm)	Numerical (continuous)
Time from implant placement to radiographic assessment of bone loss (months)	Numerical (continuous)
Implant failure	Categorical (dichotomous)
Time from implant placement to implant failure (months)	Numerical (continuous)
Type of implant (brand and internal/external connection)	Categorical (polychotomous)
Type of prosthesis	Categorical (polychotomous)

The following variables will be studied to determine the relationship of the implants to an adjacent tooth with a radiographic periapical lesion:

Measurement	Variable Type
Tooth or teeth adjacent to implans	Categorical (polychotomous)
Implant analyzed	Categorical (polychotomous)
Distance to the tooth (mm)	Numerical (continuous)
Periapical Index (PAI)	Categorical (polychotomous)
Implant site in relation to a previous endodontic failure	Categorical (dichotomous)
Dimensions of the periapical lesion (mm)	Numerical (continuous)
Signs and symptoms of endodontic failure	Categorical (polychotomous)
Time since tooth extraction	Numerical (continuous)

The variables used to determine the presence of attachment bone loss of teeth next to implants will be:

Measurement	Variable Type
Teeth analysed (adjacent to studied implant)	Categorical (polychotomous)
Distance from cemento-enamel junction to most coronal point of the bone cortical, measured in buccal and palatine/lingual areas	Numerical (continuous)

Parameters analysed in relation with implant-supported prosthesis are:

Measurement	Variable Type
Type of prothesis	Categorical (polychotomous)

Distance from cemento-enamel junction to most coronal point of the bone cortical, measured in buccal and palatine/lingual areas	Numerical (continuous)
Number of implants supporting the prosthesis	Numerical (discrete)
Number of crowns splinted	Numerical (discrete)
Presence of cantilever	Categorical (dichotomous)
Dimensions of the cantilever in mm (horizontal and vertical)	Numerical (continuous)
Distance of the cantilever to bone coronal surface in mm	Numerical (continuous)
Presence of a transepitelial abutment	Categorical (dichotomous)
Use of platform-switching method	Categorical (dichotomous)
Dimension of the abutment in mm (mesio-distal)	Numerical (continuous)
Dimension of the implant platform in mm	Numerical (continuous)
Angle of the implant platform with the abutment (mesial and distal)	Numerical (continuous)
Angle of the axial axis of the implant with the outermost point of the crown (mesial and distal) in single crowns	Numerical (continuous)
Distance from the implant platform to the beginning of the porcelain of the crown, measured in mesial, central and distal points	Numerical (continuous)
Gap between the implant platform and the abutment (if present) in mm, measured in mesial, central and distal points	Numerical (continuous)

The parameters analysed from the blood tests and medical history will be as follows:

Variable	Variable Type
Creatinine	Numerical (continuous)
Blood Urea Nitrogen (BUN)	Numerical (continuous)
Glomerular Filtration Rate (GFR)	Numerical (continuous)
Urea	Numerical (continuous)
Calcium	Numerical (continuous)
Phosphorus	Numerical (continuous)
25-Hydroxyvitamin D (25(OH)D)	Numerical (continuous)
Parathyroid Hormone (PTH)	Numerical (continuous)
C-Reactive Protein (CRP)	Numerical (continuous)
Erythrocyte Sedimentation Rate (ESR)	Numerical (continuous)
Osteoporosis	Categorical (dichotomous)
Total cholesterol level	Numerical (continuous)
LDL cholesterol level	Numerical (continuous)
HDL cholesterol level	Numerical (continuous)
Triglycerides	Numerical (continuous)

To summarize, the methodology used will be the following:

- Failed implants will constitute **Cohort 1**.
- For each failed implant, one non-failed implant will be selected from a patient with comparable characteristics, including sex, age, implant type, surgical data/complications, regenerative procedures, and type of prosthesis. This matching process will help standardize the results. However, as previously

mentioned, in cases involving systemic disorders, outcomes will be reported both per implant and per patient.

- Considering that the survival rate of dental implants is approximately 95% (with failure rates ranging from 4% to 8% depending on the techniques used) over a period of 1 to 10 years, non-failed implants placed in **April 2024 or earlier** will be selected (25).
- These non-failed implants may fall into one of two categories:
    1. **Mesial and/or distal bone loss present (Cohort 2).**
    2. **No bone loss (successful implant) (Cohort 3).**
- In each case, the systemic and local characteristics and antecedents described above will be recorded.

Data Interpretation and Statistical Methods

Data from all variables will be entered into **Microsoft Excel 2019** (Microsoft Corporation, Washington, USA, 2013) and analyzed using **SPSS version 26.0 for Windows** (SPSS, Illinois, USA, 2019).

Data management will include logical, range, and consistency checks. For categorical variables, descriptive analyses will be performed using tables of absolute and relative frequency measures (frequency and percentage), followed by bivariate analysis using the **chi-square test** when the assumptions for its application are met.

For continuous variables, normality will be assessed using the **Shapiro-Wilk test** ($p > 0.1$) and by visual inspection of **normal P-P plots** and **box plots**. If the assumptions for parametric testing are satisfied, descriptive analyses will be based on the **mean and standard deviation**, and bivariate comparisons will be performed using **one-way ANOVA for independent samples**.

If the assumptions for parametric testing are not met, descriptive analyses will be based on the **median and interquartile range (IQR)**, and bivariate analyses will be performed using non-parametric tests (**Kruskal-Wallis test**).

WORK PLAN
The Principal Investigator will collect patient information from the computerized database of the Dental Hospital of the University of Barcelona (HOUB). Likewise, the Principal Investigator will be responsible for data analysis and interpretation of the results. The Principal Investigator's intra-examiner agreement, assessed using **Cohen's Kappa coefficient**, is **0.82**.

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