RESEARCH PROTOCOL

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Research Line: Diagnosis, prevention and treatment of periodontal and peri-implant diseases.
Research Title: Distance between dental implants as a risk indicator for peri-implant disease. A multicentric cross-sectional study

In the last decades, replacement of teeth with dental implants became a very frequent procedure, and it is associated with high rates of implant survival (Albrektsson and Donos, 2012). However, the incidence of technical and biological complications seems to be frequent (Scwartz et al., 2018). Since the number of subjects receiving dental implants is growing continuously (Schimmel et al., 2017), preventing and effectively resolving peri-implant diseases on the long-term without compromising esthetic results have become one of the major endeavors of this field.

In 2017, the World Workshop, jointly held by the European Federation of Periodontology and the American Academy of Periodontology on the classification of Periodontal and Peri-Implant Diseases, defined peri-implant disease as a pathological condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant connective tissue [i.e., peri-implant mucositis (PM)], and progressive loss of supporting bone [i.e., peri-implantitis (PI)] (Schwarz et al., 2018). The onset of peri-implant diseases is characterized by the presence of etiological factors similar to those involved in the etiology of periodontal diseases and it might occur within the first three years of function in a non-linear and accelerating pattern (Derks et al., 2016).

A systematic review and meta-analysis, performed by Jan Derks and colleagues in 2015, found a prevalence of 43% for PM and 22% of PI. Later on, in Spain, Rodrigo et al. (2018) observed a similar prevalence with 27% of subjects presenting PM and 24% of the subjects presenting bleeding on probing and radiographic bone loss ≥ 2mm after at least 5 years of function (PI).

In order to prevent such diseases, addressing active periodontal diseases previous to implant surgery is mandatory; however, several factors associated with less prevalence of such diseases have been investigated pre-clinically and clinically. In this sense, a minimum of 1.5mm of bone surrounding the dental implant (Monje et al., 2019), a hygienic prosthesis (Serino et al., 2009, Katafuchi et al, 2018), a correct 3D prosthetically driven implant position (Herman et al., 2000, Buser et al., 2004) and enroll the patient in a tailored SPT program (Schwarz et al., 2018) are crucial in order to obtain long-term success and peri-implant health.

Several of these factors focus on improving oral hygiene access and motivate the patient to be more effective. Thus, a relevant surgical aspect that clinicians must consider at the time of implant placement, in order to allow a correct prosthetic design, is the distance between adjacent tooth-implant and inter-implant distances. For the horizontal space between adjacent tooth-implant, a distance of at least 1.5–2 mm from the adjacent teeth has been advocated especially for the anterior teeth (Van Oosterwyck et al., 1998). In addition, to prevent esthetic complications, it is advised to leave 3–4 mm of space between dental implants (Tarnow at al., 2000, Esposito et al., 1993). In this study, however, platform-matched implants were used.

In this sense, preclinical and clinical studies investigated the influence of inter-implant distance on marginal bone loss around platform-switched implants. In 2006, a preclinical study demonstrated that distances of 1, 2, and 3mm between implants did not result in statistically significant differences on marginal bone level around implants with a platform switch (Novaes et al., 2006). Likewise, Rodriguez-Ciurana et al. (2009) observed a minimal bone resorption (i.e., 0.62 mm) around platform-switched implants placed less than 3 mm apart.

Recently, a long-term retrospective study evaluated the biological complication rate of three types of implant-supported fixed dental prosthesis (non-splinted crowns, three splinted crowns and a 3-unit implant supported bridge) over two or three bone-level implants. The results of the investigation indicated that the prevalence of peri-implantitis was higher (16.7%) when three splinted crowns with three implants were used when compared with a 3-unit implant supported bridge over two implants (2.8%) (Ravidà et al., 2019).

Nonetheless, to our knowledge, no study has yet evaluated the association between the inter-implant distance of contiguous dental implants and peri-implant diseases.

Therefore, the aim of this study is to analyze contiguous dental implants and its peri-implant status depending on different inter-implant distances.

1.BACKGROUND

Implants have become a popular and widely used treatment option for treating partial and total edentulism. As the number of implants placed increases, so does the incidence of peri-implant mucositis and peri-implantitis. Several factors, such as a 3D correctly placed implant has been associated with better esthetic and overall outcomes on the long-term. Nevertheless, understanding a minimal threshold for inter-implant distance depending on type of implant might be critical to prevent such diseases.

2. OBJECTIVES

2.1 General objective

To evaluate the association between the inter-implant distance of contiguous dental implants and the prevalence of peri-implant diseases.

2.2 Specific objective

To evaluate the association between implant type (bone/tissue-level) and the prevalence of peri-implant diseases according to the inter-implant distance of contiguous dental implants.

3. HYPOTHESIS

3.1 General Hypothesis

A reduced inter-implant distance (i.e., < 3mm) of contiguous dental implants will result in a higher prevalence of peri-implant diseases.

3.2 Specific Hypothesis

Tissue level implants (i.e., one-piece implants) placed with an inter-implant distance < 3mm will result in a higher prevalence of peri-implant diseases than bone level implants.

4. MATERIAL AND METHODS

4.1 Study Design

The present research project has been designed as a multicentric cross-sectional study. The STROBE guidelines have been followed in the design of this observational study.

4.2 Ethical issues

The study will be performed after the approval of the Ethics Committee of the Universitat Internacional de Catalunya (UIC) and Faculdade de Medicina Dentária da Universidade de Lisboa (FMDUL) and will be intended to be registered in clinicaltrials.gov. Also, this research will be conducted according to the principles outlined in the Declaration of Helsinki (revised, amended, and clarified in 2013). In addition, all study participants will provide written informed consent before participating in the study.

4.3 Study population

Subjects will be selected from an electronic database collected at the CUO (UIC) / CU (FMDUL) and composed of patients treated with at least two contiguous dental implants before 2021. This investigation will use a stratified random sampling based on year of implant placement to select a representative sample of subjects with implant-supported restorations conducted during the period 2001–2020 at the CUO and CU. Then, two examiners (I.T. / F.F.) will contact patients by telephone

once every 2 days (with a maximum of 3 attempts) for an evaluation by the same investigators (I.T / F.F).

Criteria for subject selection will be as follows:

- The patient must be ≥18 years of age and systemically healthy;
- Partially edentulous patients, rehabilitated until 2020 (i.e., a minimum of 3 years of function time) with at least two contiguous implant-supported restorations in the maxilla or mandible;
- Screw or cemented-retained prosthesis;
- Fixed dental prosthesis (i.e., single crowns and partial prosthesis);
- No implant mobility.

Moreover, the exclusion criteria will be the following:

- Pregnant and lactating women;
- Patients who have taken systemic antibiotics during the 3 months prior to the examination;
- Patients being treated with drugs that may induce a gingival overgrowth;
- Patients undergoing orthodontic treatment (since it can influence periodontal diagnosis);
- Patients who have received mechanical debridement during the 3 months prior to the exam;
- Patients who have received surgical treatment for peri-implantitis;
- Psychophysical inability to carry out study procedures.

4.4 Study Groups

Patients who meet the selection criteria will be included in the study and will be classified based on the inter-implant distance:

Group 1: Inter-implant distance ≤ 3mm

Group 2: Inter-implant distance > 3 mm

4.5 Sample Size Calculation

Sample size calculation has been based on the primary outcome variable (prevalence of peri-implant diseases). Previous studies have observed a patient-level prevalence of peri-implant diseases of 24%. Our hypothesis is that the prevalence of peri-implant diseases is higher when the inter-implant distance is reduced, around 44%. Accepting an alpha risk of 5% and a beta risk of 20% in a two-sided test, a total of 180 patients with adjacent dental implants (90 patients in each group) are required. Therefore, 90 patients will be recruited at each center. A loss rate of 12% has been

estimated.

4.6 Researchers training

All participating researchers will attend two training and calibration online meetings. The main aims of these meetings will be to review the objectives of the study and the protocol, standardize case selection, and data collection process.

4.7 Data collection

Two calibrated investigators will consecutively call patients for an appointment and will be responsible of enrolling the patients.

The study variables will be recorded in a case report form (CRF) specially designed for the study. Each study patient will be assigned a numerical code comprising a 3-digit patient code (assigned correlatively as they are included in the study). Only the study investigators will be able to identify the patient by their code.

Medical history of the patients will be reviewed. Patients will also be advised of their role in this study and asked to sign an informed consent. After giving consent, patients will undergo a full-mouth manual probing using a periodontal probe PCP-UNC 15 (HuFriedy®, Rockwell St, Chicago, IL) to determine their periodontal and peri-implant status and, if necessary, a full-mouth periapical radiographic examination will be performed.

4.11 Statistical analysis

The Shapiro-Wilk test will be used to determine if the data follow a Gaussian distribution. Descriptive statistics will be expressed as mean ± standard deviations (SD), median or percentage for parametric, non-parametric and categorical data, respectively.
Comparisons between study groups will be performed using Chi-square test (Fisher's exact test with observed frequencies <5) for categorical variables while continuous variables will be tested using Student's T test (Mann Whitney U test in variables that are not normally distributed). For ordinal variables, the linear relationship will be calculated using Kendall's tau coefficient.
A final logistic regression model will be performed including the prevalence of peri-implant diseases as a dependent variable. The study group and other potential cofactors will be included as independent variables.
Intra- and inter-examiner reproducibility will be calculated with the intraclass correlation coefficient.

A p-value <0.05 will be considered statistically significant. R Studio software will be used for all analyses.