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A associação entre doença periodontal e infeções de prótese articular: desenho de um estudo

The association between periodontal disease and prosthetic joint infections: study design

Master's Degree in Dental Medicine

Faculty of Dental Medicine of Porto, University of Porto

Review Article

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The association between periodontal disease and prosthetic joint infections: study design

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Scientific Area: Periodontology

Abstract

Objective: design an observational study that could assess if there is an association between periodontal disease, namely periodontitis and prosthetic joint infections.

Introduction: Late prosthetic joint infections tend to occur 1 or 2 years after joint implant placement by hematogenous spread of bacteria. These microorganisms may originate from the oral cavity, which is a significant source of bacteria. Studies published so far have failed to provide concrete guidance regarding the performance of antibiotic prophylaxis prior to invasive dental treatments. Although periodontitis has a substantial impact on oral bacteraemia, the relationship between this pathology and prosthetic joint infection is unclear. Whether prophylactic antibiotics are needed prior to invasive dental treatment in patients with prosthetic joints is a question that remains unanswered.

Materials and Methods: The literature research was conducted up to March 2022, using the databases: Google Academic, Scientific Electronic Library Online (SciELO), PUBMED (Medline), SCOPUS (Elsevier) and Web of Science (Clarivate Analytics).

Results: A case-control study was found to be the most suitable type of study to be conducted at this point. As so, we designed a case control-study where cases were patients with late prosthetic joint infections and controls were matched prosthetic patients without any infection history, to minimize confounders.

Conclusion: The design of this observational clinical study is a starting point to execute an investigation that may clarify the relationship between periodontitis and prosthetic joint infections. With a thorough compliance with the protocol presented and a reliable and rigorous data collection and management, this study may bring relevant results, regarding this long discussed subject.

Keywords: periodontal disease, oral infections, clinical trials, medical research, critical appraisal, prosthetic joint infection (PJI), antibiotic prophylaxis, observational studies, case-control studies, study design.

Resumo

Objetivo: desenhar um estudo observacional que permita avaliar se existe uma associação entre a doença periodontal, nomeadamente periodontite, e infeções de prótese articular.

Introdução: As infeções de prótese articular tardias tendem a ocorrer 1 ou 2 anos após a colocação da prótese articular, por disseminação hematogénica de bactérias. Estes microrganismos podem ter origem na cavidade oral, que é uma fonte significativa de bactérias. Estudos publicados até à data não forneceram orientações concretas sobre o desempenho da profilaxia antibiótica previamente a tratamentos dentários invasivos. Embora a periodontite tenha um impacto substancial na bacteremia oral, a relação entre esta patologia e as infeções de prótese articular não é clara. A necessidade de profilaxia antibiótica previamente a tratamentos dentários invasivos em pacientes com próteses articulares é uma questão que permanece por responder.

Materiais e Métodos: A investigação bibliográfica foi realizada até março de 2022, utilizando as bases de dados: Google Academic, Scientific Electronic Library Online (SciELO), PUBMED (Medline), SCOPUS (Elsevier) e Web of Science (Clarivate Analytics).

Resultados: Um estudo caso-controlo foi considerado como o tipo de estudo mais adequado para ser realizado neste momento. Como tal, desenhámos um estudo caso-controlo no qual os casos eram pacientes com infeções de prótese articular tardias e os controlos correspondentes eram pacientes protéticos sem qualquer histórico de infeção, por forma a minimizar os fatores confundidores.

Conclusão: O desenho deste estudo clínico observacional constitui um ponto de partida para executar uma investigação que pode clarificar a relação entre a periodontite e as infeções de prótese articular. Com um cumprimento minucioso do protocolo apresentado e uma recolha e tratamento de dados fiáveis e rigorosos, este estudo pode trazer resultados relevantes relativamente a esta questão há muito discutida.

Palavras-chave: doença periodontal, infeções orais, ensaios clínicos, investigação médica, avaliação crítica, infeção de prótese articular, profilaxia antibiótica, estudos observacionais, estudos de caso-controlo, desenho de estudo.

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Abbreviations

STROBE – STrengthening the Reporting of OBservational studies in Epidemiology

ADA – American Dental Association

AAOS – American Academy of Orthopaedic Surgeons

PJI – “Prosthetic joint infection”

W.A.I.O.T. – World Association Against Infection in Orthopaedics and Traumatology

PPD – “Probing pocket depth”

BOP – “Bleeding on probing”

AAP – American Association of Periodontology

EFP – European Federation of Periodontology

CAL – “Clinical attachment loss”

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Introduction

According to the literature, prosthetic joint infections (PJI) may occur due to contamination during the surgical procedure or may be late infections. In the first case, infection occurs up to 3 months after surgery. Conversely, late infections tend to occur 1 or 2 years after joint implant placement and are caused by hematogenous spread of bacteria. These microorganisms may originate from several sites, namely the oral cavity, which is a significant source of bacteria. (1, 2) It is thought that oral biofilm may cause bacteremia in procedures such as dental extractions and periodontal treatment, although there is no demonstrated link between invasive dental treatments and prosthetic infections, so far. (3) Nevertheless, several physicians choose to perform antibiotic prophylaxis, adopting a defensive practice. (1, 2)

Due to the constant uncertainty and debate on this issue, several guidelines have been published since the 1990's to guide dentists and orthopaedic surgeons on this matter. (3)

In 1997, the American Dental Association (ADA) and the American Academy of Orthopaedic Surgeons (AAOS) stated, in a joint publication, that antibacterial prophylaxis was not recommended for healthy patients with joint replacements prior to dental treatment. This vague recommendation was updated in 2003 to fully clarify the clinicians when and when not perform antibacterial prophylaxis. It was stated that only particular groups of patients should undergo prophylaxis, namely patients with a joint replacement for less than 2 years, patients with a history of joint replacement infection and patients with a joint replacement for more than 2 years, but with systemic conditions causing a higher risk of infection, such as immunosuppression.

Six years later, the AAOS issued a unilateral statement advising prophylaxis in all patients with joint replacements before invasive dental treatment, but did not specify which treatments should be included in this group, nor the most appropriate antibacterial regimens. (1)

Following the AAOS publication in 2009, this organization rejoined with the ADA in 2012, issuing a publication highlighting three recommendations: the dentist should consider stopping prophylaxis routinely prior to dental treatments

in patients with joint replacements; the panel found no scientific evidence to recommend or advise against topical oral antibacterials; the dental practitioner should promote efficient oral hygiene in these patients. (3, 4)

In 2015, the ADA went further and released a new guideline stating, with some certainty, that there is no association between dental procedures and PJI, advising against antibiotic prophylaxis for most patients. (5, 6)

Finally in 2017, the AAOS and the ADA re-joined and adopted the Appropriate Use Criteria for Management of Patients with Orthopaedic Implants Undergoing Dental Procedures, to determine in which cases the antibiotic prophylaxis was recommended. The panel concluded that antibiotic prophylaxis was relevant only in very few cases and built a digital platform to help clinicians to decide. However, these sets of guidelines ignore the patients' periodontal status.

In 2019, our group re-assessed the scientific literature to attempt to understand whether there was scientific evidence to support antibiotic prophylaxis in patients with periodontitis to decrease the risk of PJI. This study re-analysed the existing literature and found a major knowledge gap. Periodontal status of the included patients cannot be ascertained because of methodological flaws, such as self-assessment and self-report of the patient's periodontal status (telephonic interview), incomplete clinical data (periodontal charts) and the absence of match criteria in relation to confounding factors. (5)

As can be seen from the above, guidelines published by the ADA and AAOS have so far failed to provide concrete guidance regarding the performance of antibiotic prophylaxis prior to invasive dental treatments, namely periodontal treatments. (1) These happens probably because of the difficulty in carrying out such research. However, periodontal disease has a substantial impact on oral bacteraemia (7), and it would be important to study its role as a possibly significant risk factor for PJI.

On the other hand, PJI bring consequences not only for the patient, who besides having greater morbidity due to infection, will need another joint replacement surgery, but also represents a significant burden for the global health care industry. (8)

Thus, the limitations identified so far allow us to understand what is the best way to design a clinical study that overcomes these limitations and answers the research question. (9)

Therefore, the aim of this work is to design an observational study that can help to clarify the association between periodontitis and PJI. To do so, we intend to explore which type of study best suits this research question and analyse each item that should be included in the study design, based on the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist (10) for observational studies.

Materials and Methods

The purpose of this narrative review is to design a study that can clarify the association between periodontitis and PJI, as well as discuss the issues and limitations of previous studies and how to overcome those limitations.

The literature research was conducted up to March 2022, using the databases: Google Academic, Scientific Electronic Library Online (SciELO), PUBMED (Medline), SCOPUS (Elsevier) and Web of Science (Clarivate Analytics).

The following terms were used in the search: "periodontal disease", “periodontitis”, "oral infections", "oral disease", "clinical trials", "cohort studies", "medical research", "critical appraisal", "antibiotic prophylaxis", "prosthetic joint infection (PJI)", "observational studies", "case-control studies" and "study design". The Boolean operators "or" and "and" were also used and combined with these terms whenever appropriate.

The articles were selected based on the reading of the title and abstract, which had to be related to the theme of the monograph. The inclusion criteria defined for this research were articles published in the last 10 years in Portuguese, English and Spanish. The exclusion criteria were articles not related to the purpose of this review, studies in which the information collected had been obtained by unreliable means or the sample selection had not followed the guidelines established.

1. Study Design

1.1. General Design

We intend to design an observational study to clarify the association between periodontitis and PJI.

In this observational study, the target population will be patients with prosthetic joint monitored by the Orthopaedics specialty of one of the nearest city hospitals, with whom it would be necessary to establish a protocol. By assessing the periodontal clinical status of the patients, it will be possible to determine which patients have periodontitis as well as its stage, grade and extension. Subsequently, by calculating the odds ratio, which consists of the ratio between the odds of exposure in cases and the odds of exposure in controls, we will try to understand if there is a higher probability of developing PJI in patients who also suffer from periodontitis.

To design such clinical study is essential to have a proper research question and the adequate resources available to carry out the study. It is also mandatory to be aware of ethical issues in clinical studies. In interventional studies, patients are usually submitted to certain treatments or may even be exposed to potential risk factors for the disease under study. This type of study allows the researcher to manipulate an independent variable to understand its impact on a dependent variable. (11) On the other hand, this type of study allows randomisation of the participants included in the study, ensuring greater representativeness of the population. However, in this case, this type of study would not be ethically feasible since it is not intended to test any treatment for the disease in study, nor periodontitis can be induced in the participants, which in this case is the potential risk factor for PJI. Observational studies may have fewer ethical issues and are easy to conduct, however there is no random selection of participants for experimental groups, nor any manipulation of variables, as participants are only observed and data are collected to answer the research question. (11) As a result, in observational studies it is not so easy to achieve representativeness of the population, and some bias may be generated, but ultimately, they become appropriate and the best option to answer certain research questions.

There are several types of observational studies. In retrospective studies, the information needed to conduct the research is collected from pre-existing records or even interviews with participants. In the case of the study that is intended to be designed, this would be the most appropriate option, considering that to assess the relationship between periodontitis and PJI, it is necessary to find out which patients have suffered from a PJI. By determining the periodontal status of patients, we will be able to observe if there is an association between the two pathologies. (12)

All observational studies have important roles in providing clinical evidence. Therefore, it is important to know which study best serves the needs of the research question.

Case-control studies select participants based on their health outcome, and only later will the exposure of both cases and controls be studied. Therefore, this type of study is the most suitable for our research question, which starts from a previous knowledge of the individuals' state of disease (infection of a prosthetic joint). (11) Only later it will be obtained data regarding previous exposure (periodontitis), since this is a retrospective clinical design. As such, this type of study makes it possible to assess whether there is a significant difference in exposure between cases and controls, which may suggest that exposure is related to the disease in question. (13)

In addition to being appropriate to the research question, a case-control study allows the use of smaller samples than other types of observational studies, which facilitates the development of the research, and also requires a short time period and reduced investment. (14). On the other hand, the use of smaller samples reduces the representativeness of the population, which is a limitation of the study. Case-control studies are also a good option for low prevalence diseases since prospectively following a large cohort of patients over time would be too laborious and expensive. However, the strength of association between exposure and disease is inferior then what could be achieved in a large cohort study. (11)

1.2. Study Groups

The study sample will be composed of patients with at least one prosthetic joint monitored by the Orthopaedics specialty of the selected hospital, who agree to participate. The definition of cases and controls will depend on a clear diagnosis of PJI, without regard to exposure.

Therefore, the group of cases will consist of patients with PJI, the outcome of interest. From these cases, a control group will be created consisting of patients without PJI. Cases and controls originate from the same population and have equal probability to be exposed to the exposure of interest.

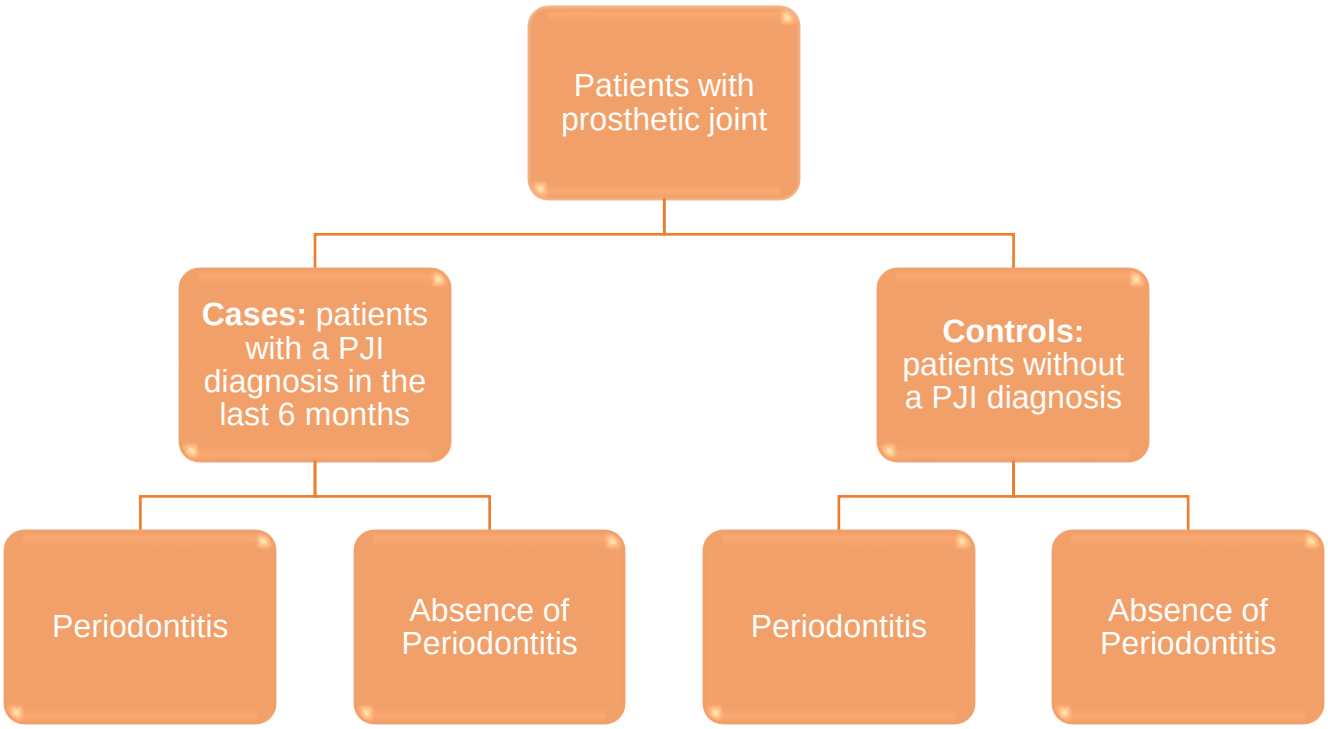

Figure 1 – Definition of study groups.

1.3. Bias

In observational studies it is important to assess whether the observed association is the result of systematic bias, confounding bias, whether it is a chance finding, whether the association is real and also, when it is concluded on an association, if there is causality. Only after assessing these issues can concrete conclusions be reached. (15) It is also important to distinguish bias,

which can result in an incorrect interpretation of the results, from random error. (16)

1.3.1. Random Error

The random error cannot be eliminated, representing the probability that the observed association is a chance finding. Through significance tests and confidence intervals, this error can be determined. (15)

1.3.2. Systematic Bias

Systematic bias include selection bias, as well as information bias. (15) There is selection bias when there are significant differences between individuals who participate in the study and those who, despite also being eligible to participate, are not part of the study.

Information bias occur when errors are made in the measurement of either exposure or outcome. In our study, this type of bias may occur with the assessment of exposure through periodontal diagnosis. (16)

A complete and precise periodontal diagnosis will allow the same accuracy in assessing exposure in cases and controls. Some previous studies have defined the periodontal status of patients based on telephonic questionnaires, which may lead to an incorrect interpretation of the results. (5) When information is collected through self-reporting by participants, they may tend to transmit biased information. It is frequent that cases transmit more reliable information than controls, as they often present the pathology under study and, for this reason, are more observant.

Furthermore, if the researchers know who the cases and controls are while performing periodontal diagnosis, this may influence their perception of the information and lead to potential errors. Therefore, blinding is an important feature, as it prevents the researcher from knowing in advance the outcome of the participant.

1.3.3. Control for Confounding

In observational studies randomization is not possible, which may lead to confounding. (15) Confounding factors may influence the association that is observed between exposure and outcome. (11)

The age of patients is a characteristic that is associated with both, with older patients having a higher prevalence of periodontitis and PJI. In addition to age, smoking and diabetes are also confounders, as they are associated with an increased risk of developing PJI (17, 18) and also harm periodontal health as they increase the onset and also disease progression. (19, 20)

Thus, in order to attempt that cases and controls have a similar distribution of ages (plus or minus 5 years), as well as smoking habits and diabetes, it is intended to perform a matched case-control study, so that each individual in the control group matches a respective case, regarding these variables. (14) This will prevent the age factor, different smoking habits and presence of diabetes from compromising the study.

1.4. Study Duration

The entire development of the study is expected to require approximately 2 years. The cases to be included will be patients with a PJI (regardless the type of joint) diagnosed in the past 6 months and with a prosthetic joint for a minimum of 1 year.

For each subject, the duration of participation in the study will not exceed 6 months, between the collection of the patient's clinical records and the periodontology consultation.

1.5. Setting

The participants will be patients attending the Orthopaedics unit of one of the nearest city hospitals. The patients' area of residence may be variable, so the study population will not cover the community of only one geographical area,

although it is expected that only participants of the northern Portugal will be included.

Dental visits will be carried out for about one year and a half, at the clinic of the Faculty of Dental Medicine of the University of Porto, and the necessary material for periodontal diagnosis is a full dental equipment with a diagnostic tray (mirror and periodontal probe) and disposable material such as: medical coat, hair cap, face masks, gloves, shoe covers, paper dental bibs, plastic cup and napkins.

1.6. Study Population

1.6.1. Eligibility Criteria

The participants to join the case group must be patients at the hospital's Orthopaedics consultation. A diagnosis of infection within the last 6 months was defined for cases.

The World Association Against Infection in Orthopaedics and Traumatology (W.A.I.O.T.) defines PJI according to the ability of some available tests to confirm or exclude the infection. These tests include clinical examination, namely signs of a draining sinus or an exposed prosthetic joint, serum (interleukin-6, procalcitonin and D-Dimer) and synovial fluid markers (cultural examination, white blood cell count, leukocyte esterase strip and alpha-defensin immunoassay or lateral flow test), imaging tests (combined leukocyte and bone marrow scintigraphy), as well as histological (frozen section) and microbiological analyses. (21) Therefore, for each patient, it will be necessary to assess which criteria have been used to define infection.

The participants selected to the control group must be patients with prosthetic joint yet without a diagnosis of infection in the last 6 months.

Both case participants and controls should be autonomous adults capable of deciding for themselves.

1.6.2. Exclusion Criteria

Pregnancy and breastfeeding result in exclusion from the study for both cases and controls.

Furthermore, patients who have undergone periodontal treatment between the diagnosis of the PJI and the assessment of periodontal status will also be excluded from the study.

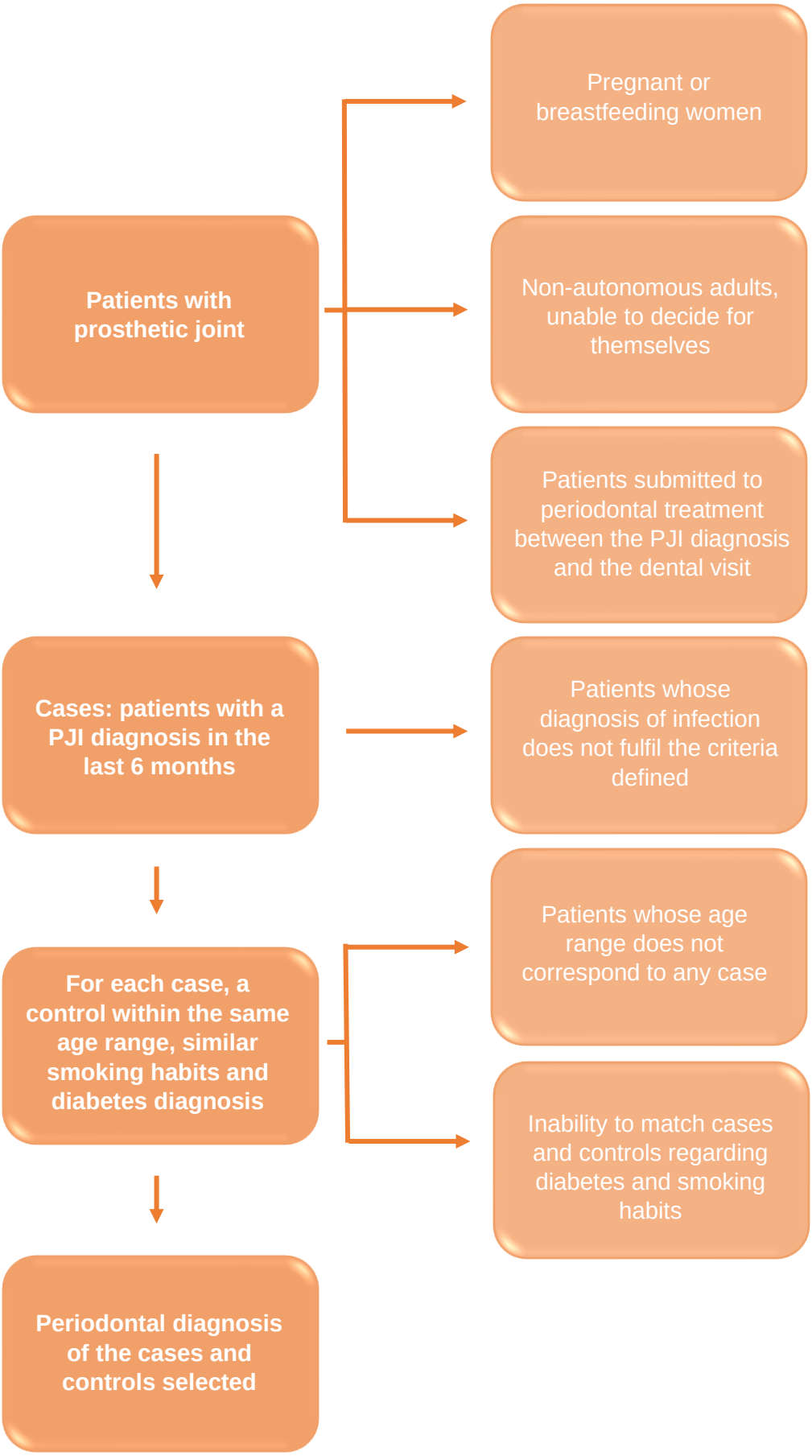

Figure 2 – Flow chart of the selection of participants throughout the study.

2. Study Procedures

2.1. Screening Visit

At the first consultation, which will be held at the selected hospital, each participant will receive an informed consent form which they must read and sign.

In addition, the researcher will also complete the data collection sheet (supplemental data 1), based on the patient's clinical records.

2.2. Allocation Concealment

One of the main information bias occurs when examiners are aware of the disease status of the participants. In other words, they know who the cases and controls are. The fact that examiners know whether a participant is a case or a control during the periodontal assessment may influence their perception of the information and lead to errors in diagnosis. Thus, blinding is very important to avoid this type of bias.

After the screening visit, each participant will have a code assigned, which will prevent the examiner, at the time of the dental consultation, from knowing whether the patient is a case or a control. After the periodontal diagnosis, the code assigned will allow pairing this same diagnosis with the information previously collected in the patient's data collection sheet.

On the other hand, although the whole study will be explained to each individual at the beginning of their participation, they should not be aware of the relevance of the existence of a relationship between periodontitis and PJI. Patients, depending on whether they are cases or controls, may in some way mislead the examiner because they know that a higher prevalence of periodontitis may be expected in cases.

2.3. Dental Visit

During this observational period, the periodontal status of each participant will be assessed by performing a periodontology consultation at the Faculty of Dental Medicine of the University of Porto.

The probing depth will be measured with a periodontal probe in 6 sites *per* tooth and the bleeding points will be recorded (also 6 sites *per* tooth). Gingival recessions will also be measured and other relevant aspects such as tooth mobility, plaque index, suppuration sites and also oral infections that may be present.

Radiographic evaluation is also an essential component in determining the periodontal diagnosis. Thus, an orthopantomography will be performed on each patient in order to proceed to the radiographic evaluation of the patient.

2.4. Participant Withdrawal

Participants are free to withdraw from the study at any time, without any repercussions. They may also be withdrawn from the study if they compromise the investigation or do not attend the consultations necessary for the research to proceed.

2.5. Schedule of Study Procedures

Study Phase	Screening Visit	Dental Visit
Informed Consent	X	
Data Collection Sheet	X	
Review Inclusion and Exclusion Criteria	X	
Periodontal Diagnosis		X

Table 1 - Schedule of study procedures.

3. Data Collection

For data collection, the researcher will fill all the crucial data for the research, in a data sheet, as previously mentioned. This will be done based on the clinical records of each patient, which will be made available by the hospital after obtaining the appropriate authorisation. The following information will be collected from each patient's clinical records:

- Sociodemographic data, such as the patient's age and gender.
- Smoking habits.
- Antibiotic therapy treatment in the last 6 months.
- Health history, namely diseases of the heart, asthma, kidneys, blood, diabetes or other disease the patient may have; surgeries or other relevant medical episodes; family medical history of periodontal disease.
- Dental history of the last 6 months – periodontal treatments, prosthetic treatments that may influence periodontal health, dental pain, gingival health, namely bleeding when brushing and frequent swelling of the gums.
- Date of last dental appointment and treatment performed.
- Date of last tartarectomy.
- Oral hygiene habits – how many times a day the patient brushes their teeth, brushing technique and type of brush.
- In patients with a history of infection of prosthetic joint (cases), it must also include the date of the diagnosis and the date of the treatment.
- Periodontal diagnosis, which should include data such as probing pocket depth (PPD) and bleeding on probing (BOP).

Regarding the periodontal diagnosis, a Periodontology appointment will be carried out at the Faculty of Dental Medicine of the University of Porto.

According to the new classification of periodontal diseases, directed by the American Association of Periodontology (AAP) and the European Federation of Periodontology (EFP), a patient is defined as a case of periodontitis if interdental clinical attachment loss (CAL) is present at ≥ 2 non-adjacent teeth or if there is buccal or oral CAL ≥ 3mm with pocketing > 3mm at ≥ 2 teeth.

Furthermore, CAL cannot be related to other non-periodontal causes, namely:

- Gingival recession due to trauma.
- Caries extending to the cervical region of the tooth.
- CAL on the distal aspect of a second molar caused by malposition or extraction of a third molar.
- Endodontic lesion that causes drainage through the marginal periodontium.
- Vertical root fracture.

Therefore, in this consultation the periodontogram will be filled in and the periodontal diagnosis of the patient will be determined according to the criteria of the new classification of periodontal diseases. (22)

4. Statistical Considerations

4.1. Variables

The variables under study are patients' age, gender, disease status in relation to PJI, periodontal diagnosis, PPD, BOP, smoking habits, diabetes and antibiotherapy.

The variables gender, disease status in relation to PJI, periodontal diagnosis, BOP, smoking habits, diabetes and antibiotherapy are nominal variables, while the variables age and PPD are quantitative variables.

The variables age, gender, disease status in relation to PJI, PPD, BOP, smoking habits, diabetes and antibiotherapy are independent variables. Conversely, the variable periodontal diagnosis is a dependent variable.

4.2. Statistical Methods

Data will be analysed using the statistical program IBM SPSS Statistics 27®.

The main outcome is prosthetic joint infection and the exposure is periodontal disease, both dichotomous variables. The chi-square test will be used to examine the differences between the variables and the OR will also be calculated. In case-control studies, we can only estimate the odds ratio. As the prevalence of the outcome is unknown, the relative risk cannot be measured. We

then calculate the odds ratio by comparing the distribution of the exposure factor, which will allow us to measure the association between exposure and outcome. However, if the outcome is a rare disease, then the relative risk and the odds ratio will have similar values. (14)

4.3. Sample Size and Power

The number of individuals participating in the study is related to the infection rate of PJI, as well as the infection rate of periodontal disease, and also depends on the number of patients monitored at the Orthopaedics unit of the hospital who have a prosthetic joint. In Europe, the PJI rate is 1,4% (23), which represents a significantly low infection rate. However, periodontitis affects about 50% of the population. (24)

To determine a sample size estimate, the GPower tool was used. The statistical test "Proportions: Inequality, two independent groups (Fisher's exact test)" and the type of power analysis "A priori: Compute required sample size - given α, power, and effect size" were selected.

Regarding the input parameters, we considered 1 tail and both p1 and p2 0,014. Considering that the PJI rate is 0,014 (1,4%), if periodontitis has a prevalence of approximately 50%, then both in periodontitis patients and in those without periodontitis, the PJI rate is 0,014. Furthermore, a significance level (α) of 0,05, a power (1-β) of 0,80 and allocation ratio N2/N1 of 1 were considered.

Based on these values, the GPower tool predicts a total sample size of 100 participants, with 50 participants in the cases and 50 in the control group.

5. Confidentiality

All patient records will be anonymized and kept confidential and will not be used for any purpose other than the study in question.

6. Ethical Considerations

6.1. Risk Assessment

The risks associated with the present investigation are not greater than minimal, as it is only intended to assess the periodontal health of the participants.

Therefore, both at a physical and psychological level, no risks are foreseen for the participants.

6.2. Benefits of Study Participation

Participation in the present study may have direct benefits for the participant, who may enjoy a free periodontology consultation, with a complete periodontal diagnosis and a cost-free teeth scaling.

In addition, there are also indirect benefits for the participant, who will be able to profit, as a member of society, from the scientific progress arising from the research.

6.3. Risk-Benefit Assessment

Given that there are no anticipated risks associated with the research, but some benefits to the participant are listed, both directly and indirectly, it can be concluded that participation in the study is rewarding for the subjects.

7. Informed Consent

All participants will receive an informed consent at the screening visit. In this consent there will be a detailed explanation of the study, listing all the data that will be collected from each subject.

In addition, the voluntary nature of the study will also be clarified, as well as the right to withdraw at any time and the risk-benefit assessment for the participants.

8. Risk Mitigation Plan

Risks and Mitigation Strategies				
Risk Cause	**Risk Effect**	**Risk Ranking**	**Action**	**Mitigation Strategies**
Selection bias.	Significant differences between individuals who participate in the study and those who do not.	Moderate	Avoid	Particular attention regarding the eligibility criteria for the selection of participants.
Errors in the assessment of exposure through the periodontal diagnosis.	Biased information collected by the researcher.	Low	Avoid	The investigator must ensure maximum precision in the assessment of the patient's periodontal status.
The investigator may have knowledge of the disease state of a patient (case or control).	Misperception of information.	Low	Avoid	Ensure that the researcher only has access to the patient code and not the clinical record prior to periodontal assessment.
Inability to match cases and controls, regarding smoking habits and diagnosis of diabetes.	Errors in the association observed between exposure and outcome.	Moderate	Mitigate	Exclusion of diabetics and smokers from the study as these conditions are important risk factors for both pathologies.
Participant withdrawal from the study.	Smaller sample.	Low	Avoid	Ensure that all patients understand the entire study and its conditions before agreeing to participate.

Insufficient number of cases.	Smaller sample.	High	Mitigate	Consider the surrogate endpoints, which would be the indicators of infection, in order to increase the number of cases.
Reduced time to achieve a reasonable sample according to the calculated estimate.	Smaller sample.	High	Mitigate	Conduct a multicenter study, establishing protocols with more than one hospital in order to increase the number of cases.
Difficulty of the participants to go to the Faculty for the dental visits.	Difficulty in scheduling appointments and complying with the stipulated calendar.	Moderate	Mitigate	Perform the dental visits in the respective hospital, as only a light source, reclining chair and disposable material are needed.

Table 2 - Risks of the study and mitigation strategies.

9. Protocol Synopsis

Title	The association between periodontal disease and prosthetic joint infections: study design.
Objective	Design an observational study that allows the execution of an investigation to clarify the association between periodontal disease and PJI.
Study Design	It is intended to design an observational clinical study, namely a retrospective case-control study. The target population is patients with prosthetic joint monitored by the Orthopaedics specialty of one of the nearest city hospitals. By assessing the periodontal status of patients, it would be possible to perform a periodontal diagnosis and subsequently, understand if there is a higher probability of developing PJI in patients who also suffer from periodontitis.
Study Population	Eligibility Criteria: Cases: patients with a PJI diagnosed in the past 6 months and with a prosthetic joint for a minimum of 1 year. Controls: patients with prosthetic joint yet without a PJI diagnosed in the past 6 months. Both cases and controls must be autonomous adults capable of deciding for themselves. Exclusion Criteria: Pregnancy and breastfeeding women. Patients who have undergone periodontal treatment between the diagnosis of the PJI and the assessment of periodontal status.
Outcome	Prosthetic joint infection.

Exposure	Periodontal disease.
Confounding Factors	Age, smoking habits and diabetes, obtained from the data collection sheet.
Study Duration	The entire development of the study is expected to require approximately 2 years. For each subject, the duration of participation in the study will not exceed 6 months.
Study Phases	<u>Screening Visit:</u> Informed Consent; Data Collection Sheet; Review Inclusion and Exclusion Criteria. <u>Dental Visit:</u> Periodontal Diagnosis.

Table 3 - Protocol synopsis.

Discussion

About 50% of the world's population suffers from periodontitis. This is a silent disease, in the sense that the signs are not very noticeable and patients frequently visit their dentist when the disease has already progressed substantially. Furthermore, the Portuguese population has a low frequency of dental visits, and according to the Oral Health Barometer 2021, 41% of the Portuguese population has not visited the dentist for over a year. (25)

With the increasing ageing of the world's population, certain procedures that did not occur so frequently in the past are now becoming fairly common. This is the case of prosthetic joint replacement surgery, performed predominantly on elderly people. (26) Therefore, it is becoming increasingly important to understand the best way to manage and prevent certain pathologies, such as PJI.

In addition, the problem of antibiotic resistance also arises and antibiotic prophylaxis should be performed wisely. Looking at Europe, the European Surveillance of Antimicrobial Consumption Network found that there is a higher consumption of antibiotics in southern Europe. Furthermore, 25,000 patients die each year in the European Union from infections caused by multi-resistant bacteria. (27)

For dentists, the relationship between their area of expertise and possible consequences in other regions of the body is not always clear. After several years of uncertainty, it is now necessary to understand the relationship between periodontal disease and PJI, so that the dentists know how to proceed and even when to prescribe antibiotic prophylaxis.

Main Results

Through a review of the existing literature to date, it was concluded that there is still no concrete answer to the possible relationship between periodontal disease and PJI. (9)

An extensive and detailed scientific research was carried out to design the most suitable study to answer the research question.

The clinical study considered most appropriate to perform an investigation that could bring relevant results, despite its limitations, was the case-control study.

Study Design

Case-control studies are generally used to investigate rare pathologies, with a low prevalence, focusing also on variables that may constitute possible risk factors (14). This characteristic is present in PJI, which are known to have an infection rate of approximately 1.4% in Europe (23). Therefore, the design of a case-control study seems to be the best option to assess the possible relationship between the exposure factor and the outcome.

As it is intended to study the relationship between periodontal disease and PJI, it is important that the periodontal diagnosis performed at the time of the study represents the periodontal status at the time of infection. Thus, the cases were defined as patients who had been diagnosed with infection for a maximum of 6 months, because if the infection had been diagnosed for more than 6 months, there might not be compatibility between the periodontal status at the time of infection and at the time of the study.

Strengths and Limitations

By performing periodontology consultations to conduct a detailed periodontal diagnosis, this research allows the exposure assessment of each participant to be reliable, which may be a strength of this study, since in some investigations already conducted, the collection of information was carried through self-report by the participants (5). Since periodontal disease is a silent pathology, self-report is not the ideal strategy for exposure assessment.

A limitation of this study is the fact that there is no randomisation of participants in order to balance the characteristics of the population. In this type of study design, the association between exposure and outcome, if it occurs, may result from the existence of confounding factors, which are related to both exposure and outcome and may simulate a relationship when, sometimes, it does

not actually exist. In the case of this particular investigation, age, smoking habits and diabetes are confounding factors and, for this reason, it was designed a matched case-control study.

When matching cases and controls, it is possible to overcome the confounding. However, this alternative constitutes another limitation of the present study, as it may lead to more bias. Matching in demographic variables, such as age, makes the sample less representative of the population. (11)

Despite these limitations, we believe that conducting a matched case-control study is the best alternative for the research question that was raised.

Conclusion

The relationship between periodontal disease and PJI is still unclear. Until this research question is clarified, other subjects remain unanswered, in particular the need for antibiotic prophylaxis prior to invasive dental treatment in patients with prosthetic joints.

A prompt reply to these questions is necessary, so that clinicians and dentists can be aware, in their daily clinical practice, of the implications of certain treatments, and what preventive measures to adopt.

Therefore, the design of this observational clinical study is a starting point to execute a research that may clarify this subject. Despite the limitations that have already been mentioned, with a thorough compliance with the protocol presented and a reliable and rigorous data collection and management, this study may bring relevant results, regarding this long discussed subject.

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Supplemental Data

Data Collection Sheet

Name:	Assigned Code:
Occupation:	
Birthplace:	Date of Birth: ___/___/_____
Age: ___ years	Gender: M ☐ F ☐
Telephone Contact:	
Address:	
Smoking Habits: Yes ☐ No ☐	
Antibiotic therapy treatment in the last 6 months:	
Health History: Heart Diseases: Yes ☐ No ☐ If so, please indicate: Asthma: Yes ☐ No ☐ Kidneys Diseases: Yes ☐ No ☐ If so, please indicate: Blood Diseases: Yes ☐ No ☐ If so, please indicate: Diabetes: Yes ☐ No ☐ If so, please indicate type: Other Diseases: Yes ☐ No ☐ If so, please indicate: Surgeries: Yes ☐ No ☐ If so, please indicate: Relevant Medical Episodes: Yes ☐ No ☐ If so, please indicate: Family History of Periodontal Disease: Yes ☐ No ☐	

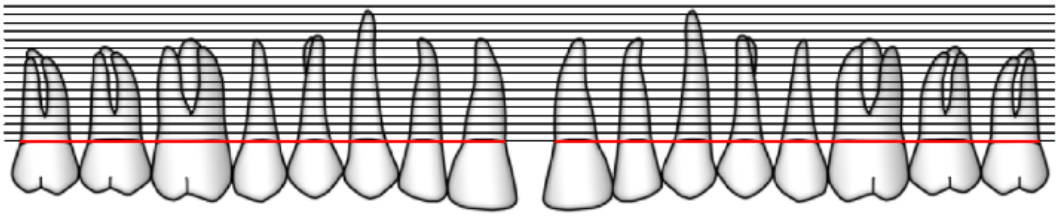
Dental History of the Last 6 Months: Periodontal Treatments: Yes ☐ No ☐ If so, please indicate: Prosthetic Treatments: Yes ☐ No ☐ If so, please indicate: Dental Pain: Yes ☐ No ☐ Gingival Health: Bleeding when brushing: Yes ☐ No ☐ Frequent swelling of the gums: Yes ☐ No ☐
Date of last dental appointment: ___/___/_____ Treatment performed:
Date of last tartarectomy: ___/___/_____
Oral Hygiene Habits: How many times a day brushes: ___ times a day Brushing technique (explain): Type of brush: Soft ☐ Medium ☐ Hard ☐ Doesn´t know ☐
In case of prosthetic joint infection in the last 6 months: Date of the diagnosis: ___/___/_____ Date of the treatment: ___/___/_____
Date of Dental Visit: ___/___/_____
Periodontal Diagnosis:

Periodontogram

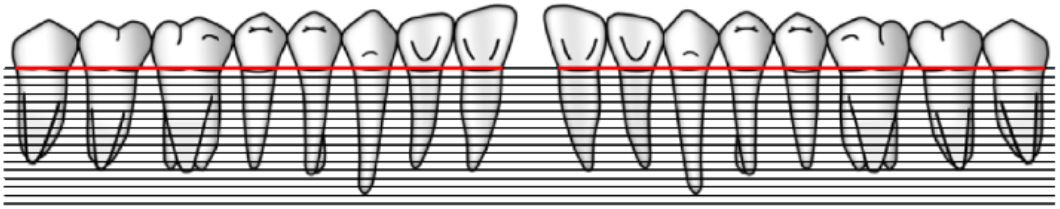
Patient Assigned Code: _____

	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Mobility	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Implant																
Furcation																
Bleeding on Probing																
Plaque																
Gingival Margin	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Probing Depth	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0

Buccal



Lingual



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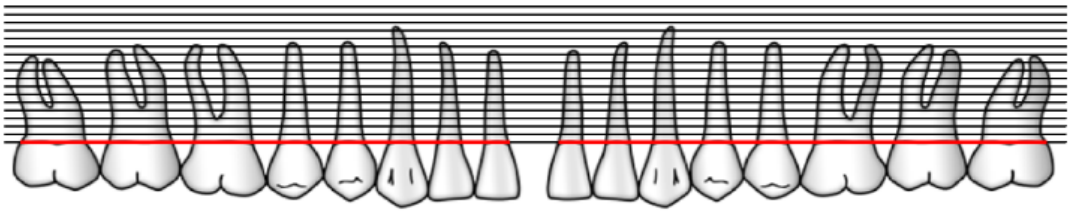
Probing Depth	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Plaque																
Bleeding on Probing																
Furcation	|	|	|		|						|		|	|
Note																

Mean Probing Depth = 0 mm Mean Attachment Level = 0 mm 0 % Plaque 0 % Bleeding on Probing

Note																
Furcation																
Bleeding on Probing																
Plaque																
Gingival Margin	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Probing Depth	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0

Lingual



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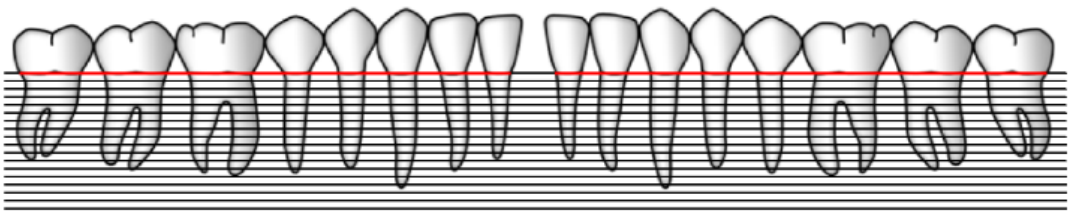

Gingival Margin	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Probing Depth	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0	0 0 0
Plaque																
Bleeding on Probing																
Furcation																
Implant																
Mobility	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38

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