UNIVERSIDADE FEDERAL DE JUIZ DE FORA

FACULDADE DE ODONTOLOGIA

PPG EM CLÍNICA ODONTOLÓGICA

CRISTINA DE PAULA NOVAES

IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES

JUIZ DE FORA

2016

CRISTINA DE PAULA NOVAES

IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES

Dissertação apresentada ao Programa de Pós - graduação em Clínica Odontológica, da Faculdade de Odontologia da Universidade Federal de Juiz de Fora, como requisito parcial para obtenção do título de Mestre. Área de concentração em Clínica Odontológica.

Orientadora: Profª. Drª. Maria das Graças Afonso Miranda Chaves

Coorientadora: Profª. Drª. Gisele Maria Campos Fabri

JUIZ DE FORA

2016

CRISTINA DE PAULA NOVAES

IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES

Exame de Qualificação apresentado ao Programa de Pós - graduação em Clínica Odontológica, da Faculdade de Odontologia da Universidade Federal de Juiz de Fora, como requisito parcial para obtenção do título de Mestre. Área de concentração em Clínica Odontológica.

Aprovada em ___ de _____ de 20__.

BANCA EXAMINADORA

Profª. Drª. Maria das Graças Afonso Miranda Chaves (Orientadora)

Universidade Federal de Juiz de Fora

_____

Profª. Drª. Sumatra Melo da Costa Pereira Jales

Universidade de São Paulo

_____

Prof. Dr. Abrahão Elias Hallack Neto

Universidade Federal de Juiz de Fora

DEDICATÓRIA

Ao meu pai, ***Clovis,*** *meu maior exemplo de humanidade, amor e perseverança. Minha determinação, persistência e paixão pelos estudos vieram de você, e é com você no meu coração que tenho força para seguir em frente.*

À minha mãe, ***Fátima****, pela sua dedicação e carinho perfeitos. Sua imensa força, coragem e imprescindível calma iluminam meu caminho.*

Obrigada pelo amor e compreensão nas horas de ausência.

Aos meus irmãos, ***Gustavo e Léo****, agradeço a segurança e certeza de que nunca estou sozinha nessa caminhada.*

Aos meus queridos sobrinhos, ***Luka e Laís****, que enchem de esperança meu coração e pensamentos. Vale à pena buscar um mundo melhor por vocês!*

Amo muito vocês!

AGRADECIMENTOS

*Agradeço a **Deus** por ter me dado força para superar as dificuldades.*

*À minha orientadora, **Profª. Drª. Graça Chaves**, pelo carinho, confiança e apoio na elaboração deste trabalho. Obrigada por me proporcionar esta oportunidade em alcançar mais essa conquista para o meu crescimento profissional!*

*À minha coorientadora, **Profª. Drª. Gisele Fabri** minha eterna gratidão por toda sua dedicação, carinho e incentivo. Agradeço nossas horas de convívio e aprendizado. Seu amor pelo que faz é admirável e me faz acreditar que tudo é possível!*

***Aos amigos** do Mestrado pelas gargalhadas e incertezas compartilhadas. Aos **alunos da graduação**, os quais ensinando, pude aprender. Lembrarei-me de todos com carinho.*

*Ao **Marcos Diego** pela força, e principalmente pelo amor. Obrigada por me trazer paz e coragem na correria de cada dia. Sua maneira de ver a vida torna tudo mais leve.*

*Desejo apresentar meu carinhoso agradecimento ao **Dr. Narciso Pazinatto, à Drª. Tereza Cristina Esteves, e à toda Equipe do Hospital 9 de Julho de Juiz de Fora** por confiar em meu trabalho, em especial à querida **Adkely**.*

*Ao **Dr. Abrahão Elias Hallack Neto** pela confiança e aprendizado. Sua humanidade e dedicação nos impulsionam a buscar sempre fazer o melhor pelos pacientes.*

*Ao amigo **Dr. Victor Quinet de Andrade Bastos**, à **Drª. Ângela Maria Gollner**, ao **Dr. Abrahão Elias Hallack Neto e à toda Equipe do Serviço de Hematologia e Transplante do Hospital Universitário/UFJF**, com quem aprendi a prática e a verdade do dia a dia do trabalho multiprofissional com dedicação e amor.*

***Aos pacientes**, que mesmo nos momentos de dificuldade, aceitaram em participar da pesquisa. Agradeço a paciência e carinho.*

*À **Profª. Drª. Ana Carolina Apolônio** e ao laboratório de Fisiologia e Genética Molecular Bacteriana do Departamento de Parasitologia, Microbiologia e Imunologia do ICB/UFJF, obrigada pelo apoio e parceria.*

*À **Profª. Drª. Ângela Coelho**, do Departamento de Estatística do ICE/UFJF, agradeço sua atenção e ensinamentos.*

*À **Profª. Drª. Sumatra Jales, Prof. Dr. Abrahão** e ao **Prof. Dr. Siqueira** por aceitarem o convite para participação da banca examinadora. É uma honra ter meu*

trabalho lido por profissionais que tanto admiro! Suas considerações serão de grande importância para minha formação. Guardarei este momento com carinho e levarei todo o aprendizado recebido. Obrigada.

Aos ***professores do Programa de Pós-graduação em Clínica Odontológica*** *pelas oportunidades de aprendizagem e troca de experiências.*

À ***secretaria de Pós-Graduação*** *por toda a disponibilidade e assistência.*

A todos, o meu muito obrigada!

“Conheça todas as teorias, domine todas as técnicas, mas ao tocar uma alma humana, seja apenas outra alma humana.”

Carl Jung

RESUMO

Introdução: A doença periodontal (DP) e mucosite oral (MO) são condições imunoinflamatórias que podem ser caracterizadas pela presença constante de inflamação sistêmica e bacteremia. **Objetivo:** Avaliar o impacto da terapia periodontal na MO e investigar a ocorrência de patógenos periodontais em pacientes submetidos à quimioterapia para tumores sólidos e prévia ao transplante de medula óssea (TMO) **Métodos:** Avaliação dos dados sócio demográficos, dados da quimioterapia e comorbidades, além de avaliação sistemática orofacial. Estas ocorreram previamente e entre 7 a 14 dias após início da quimioterapia no grupo saúde periodontal (GSP). No grupo doença periodontal (GDP) somente após início da quimioterapia, 7 a 14 dias. A mucosa oral foi examinada para avaliar a presença e grau da MO induzida por quimioterapia. Ainda, testes clínicos para diagnóstico de disfagia, avaliação de xerostomia e qualidade de vida relacionada à saúde bucal (OHIP-14); e classe socioeconômica dos pacientes. Foram coletadas em ambos grupos, amostras subgengivais através da inserção de cones de papel estéreis, nos períodos descritos acima. Análise e quantificação da densidade bacteriana para cada espécie e número total de patógenos periodontais do "complexo vermelho" determinadas através do ensaio biomolecular de FISH (*hibridação in situ fluorescente*). **Resultados**: 51 pacientes com idade média de 51.1, sendo 38(74.5%) do sexo feminino e classe socioeconómico C 22(43.1%) predominante. Mama foi o local do tumor primário mais acometido 21(41.1%) e a doxorrubicina agente quimioterápico 22(43.1%) prevalente. A morbidade mais associada a hipertensão 20(39.2%). GSP incluiu 33 pacientes e GDP 18 pacientes. Análises estatísticas revelaram que as distribuições dos pacientes em relação à incidência de MO não diferiu entre estes grupos. Grau 1 de MO foi o mais incidente. Dezesseis(31%) pacientes desenvolveram MO, 9(56.2%) submetidos ao regime de condicionamento quimioterápico prévio ao transplante, 7(43.7%) em quimioterapia comum para tumores sólidos. Na qualidade de vida relacionada à saúde bucal, pacientes com complicações bucais mostraram média OHIP-14 de 1.36, enquanto aqueles sem complicações bucais média de 0.56, após quimioterapia para tumores sólidos. **Conclusão**: A saúde periodontal, pode afetar a incidência e grau da MO induzida por quimioterapia. Observando-se apenas pacientes com saúde periodontal submetidos ao regime de condicionamento quimioterápico e quimioterapia convencional, encontrou-se menor incidência de MO, comparado a evidências científicas. A necessidade de inclusão de pacientes com periodontite grave para avaliar essa relação dificultou tal julgamento.

Palavras-chave: Doença Periodontal. Mucosite Oral. Periodontopatógenos. Quimioterapia.

ABSTRACT

Background: *Periodontal disease (PD) and oral mucositis (OM) are immunoinflammatory conditions that can be characterized by the constant presence of systemic inflammation and bacteremia.* ***Objective:*** *Evaluate the impact of periodontal therapy in oral mucositis and investigate the occurrence of putative periodontal pathogens in patients undergoing chemotherapy for solid tumors and scheduled for hematopoietic stem cell transplantation (HSCT).* ***Methods:*** *This study included an evaluation of demographic data, data chemotherapy and comorbidities, and global systematic dental assessment. These were obtained prior and between 7-14 days after initiated chemotherapy in periodontal health group (PH group). The Periodontal disease Group (PD Group) was evaluated during 7 to 14 days after of chemotherapy. The oral mucosa also was examined for scoring of chemotherapy-induced oral mucositis. Furthermore clinical tests for dysphagia diagnosis and evaluation of xerostomia and quality of life related to oral health; socio-economic class of patients was determined. Subgengival samples were collected by inserting sterile paper points for both groups, for same periods described above. Total number of bacterial cells and cells from each species determined by FISH (fluorescence in situ hybridization).* ***Results:*** *Fifty-one patients with solid tumors and scheduled for HSCT were assessed to evaluate the impact of periodontitis in OM. Mean age was 51.12, 38(74.5%) were female and socio-economic Class C 22(43.1%) was prevalent. The primary tumor site was most commonly breast cancer 21(41.1%) and prevalent chemotherapeutic agent was doxorubicin 22(43.1%). The prevalent morbidity associated was hypertension 20(39.2%). PH Group included 33 patients and PD Group enrolled 18 patients. Statistical analyses revealed that the distributions of patients with incidence of OM did not differ between both groups. The majority incidence of grade 1 chemotherapy-induced OM was observed. Sixteen(31%) patients developed oral mucositis, 9(56.2%) in patients undergoing conditioning regimen prior HSCT, and 7(43.7%) in patients undergoing common chemotherapy for solid tumors. Patients with oral complications showed a mean OHIP-14 index of 1.36, while those who did not develop oral complications had a mean OHIP-14 of 0.56, after chemotherapy for solid tumors.* ***Conclusion:*** *This study demonstrated that oral health, could affect experience and incidence of chemo-induced OM. When only patients periodontally healthy undergoing conditioning regimen of therapy and conventional chemotherapy were observed, was noted a lower incidence of oral mucositis, when compared with scientific evidences. The need of inclusion of patients with severe periodontitis to evaluate this relationship hampers such trial.*

Keywords: *Periodontal diseases. Oral mucositis. Periodontopathogens. Chemotherapy.*

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

DP	Doença Periodontal
MO	Mucosite Oral
TMO	Transplante de medula óssea
GSP	Grupo saúde periodontal
GDP	Grupo doença periodontal
OHIP-14	*Oral Health Impact Profile*
FISH	*Hibridação in situ fluorescente*
IL-1	Interleucina-1
IL-6	Interleucina-6
PGE2	Prostaglandina E2
TNF	Fator de necrose tumoral
IP	Índice de placa
SS	Índice de sangramento à sondagem
PCS	Profundidade clínica de sondagem
PCI	Profundidade clínica de inserção
IG	Índice gengival
LEC-MG	Limite esmalte cemento – margem gengival
=	Igual a
%	Porcentagem
nm	Nanômetro
mW	Miliwatt
J/cm^2	Joule por centímetro quadrado
>	Maior que
-	Menos
℃	Grau Celsius
/	Barra

SUMÁRIO

1 INTRODUÇÃO

O termo doença periodontal (DP) compreende um grupo de doenças inflamatórias que afetam os tecidos periodontais de proteção e de suporte do dente (osso alveolar, ligamento periodontal, cemento e gengiva). É caracterizada como uma doença imunoinflamatória crônica de etiologia multifatorial, sujeito e sitio específica que evolui continuamente com períodos de exacerbação e de remissão, resultando de uma resposta inflamatória e imune do hospedeiro à presença de bactérias específicas e seus produtos (LÖE, *et al*., 1978; HUGSON e JORDAN, 1982; BAELUM; MANJI; FEJERKOV,1988; BROWN; OLIVER; LÖE, 1990; GRAVES e COCHRAN, 2003; ALMEIDA et al., 2006; DI BENEDETTO *et al*., 2013). Esta resposta inflamatória está associada a elevados níveis locais e séricos de citocinas, tais como interleucina-1 (IL-1), interleucina-6 (IL-6), prostaglandina E2 (PGE2) e fator de necrose tumoral (TNF) que desencadeiam a libertação de proteína-C reativa a partir do fígado, contribuindo assim para inflamações sistêmicas (BURT, 2005; OLRICH; CULLINAN; SEYMOUR, 2009; BARTOLD; CANTLEY; HAYNES, 2010; CHAPPLE e GENCO, 2013; LIMA e LARA, 2013). Além desta importante resposta inflamatória insidiosa, a DP, muitas vezes constitui um foco infeccioso importante, podendo levar à bacteremia e ter inúmeras outras repercussões sistêmicas, inclusive, tornando o paciente com doenças crônicas e graves, refratário ao tratamento (SIQUEIRA e TEIXEIRA, 2001; HOLMSTRUP e GLICK, 2002; RABER-DURLACHER *et al*., 2002; TUNKEL e SEPKOWITZ, 2002; FABRI *et al*., 2014).

Como qualquer doença insidiosa, instala-se lentamente, sem apresentar sintomas específicos; geralmente, é negligenciada por pacientes e por profissionais de saúde, o que possibilita sua progressão e agravamento. Seus principais sinais e sintomas são sangramento gengival espontâneo ou provocado, mobilidade dental, sensação de dente crescido, halitose e, em estágios avançados, dor (LINDHE *et al*., 1999). Porém, pacientes com neutropenia grave, condição comum em pacientes submetidos à terapia para o câncer, os sinais e sintomas clínicos tradicionais de inflamação e edema não estão presentes (PETERSON *et al*., 1987); o que muitas vezes pode dificultar

seu diagnóstico (HEDEN; WENNSTRÖM; LINDHE, 1999; SIQUEIRA e TEIXEIRA, 2001).

Especialmente nestes pacientes, outra importante doença que acomete a boca é a mucosite oral (MO). Esta inflamação da mucosa constitui uma das mais importantes complicações bucais dos doentes em tratamento para o câncer e está associada a maior frequência e maior tempo de internação, uso de medicações narcóticas prolongadas e maior incidência de infecções oportunistas (RUESCHER *et al*., 1998; SONIS *et al*., 2001; LAMBERTZ *et al.*, 2010; GUSSGARD *et al*., 2014; CHAVELI-LÓPEZ e BAGÁN-SEBASTIÁN, 2016). A primeira manifestação na mucosa é o desenvolvimento de uma coloração esbranquiçada por insuficiência de queratina. Subsequentemente, a mucosa torna-se atrófica, edematosa, eritematosa e friável (VIEIRA e LOPES, 2006). Áreas de ulceração desenvolvem-se com a formação de uma membrana superficial fibrino-purulenta amarelada e removível, com regiões centrais necrosadas (VIEIRA e LOPES, 2006). Os sinais e sintomas da MO incluem eritema, edema, ulceração e dor, podendo interferir nas atividades diárias como fala, alimentação e deglutição, resultando em desidratação, má nutrição e infecções oportunistas (RUESCHER *et al*., 1998; SONIS *et al*., 2001; CORACIN *et al*., 2013; GUSSGARD *et al*., 2014; CHAVELI-LÓPEZ e BAGÁN-SEBASTIÁN, 2016). A ocorrência da mucosite oral, frequentemente, ocasiona modificações na terapia contra o câncer e interfere no prognóstico do doente (ROSENTHAL, 2007; RUSSO *et al*., 2008; LAMBERTZ *et al*.; 2010; CAMPOS *et al*, 2014). Adicionalmente, durante o tratamento do câncer, a contagem de neutrófilos pode estar diminuída e a função linfocitária pode ser alterada, colocando os doentes em risco para infecções bacterianas. A presença de mucosite pode atuar como uma porta de entrada para as bactérias bucais na corrente sanguínea, o que pode levar à bacteremia e sepse, com uma elevada morbidade e mortalidade (RABER-DURLACHER *et al*., 2002; TUNKEL e SEPKOWITZ, 2002; VAN DER VELDEN *et al*., 2014; CHAUDHRY *et al*., 2016). Acredita-se também que a gravidade da doença periodontal e inflamação podem estar relacionadas com maior risco de bacteremia nestes pacientes (HOLMSTRUP e GLICK, 2002).

Estudos demonstram que elevados índices de placa bacteriana e inflamação gengival estão correlacionados com a incidência de mucosite oral,

reforçando a ideia de que a inflamação é um fator preditivo de incidência de mucosite e retardo na cicatrização (SANTOS *et al*., 2011; CORACIN *et al*., 2013; KHAW *et al*., 2014). Este dado é especialmente importante nos pacientes em tratamento contra o câncer, que podem apresentar graus variados de imunossupressão, aumentando consideravelmente o risco para infecções bacterianas (em particular, infecções odontogênicas) (RABER-DURLACHER *et al*., 2002; TUNKEL e SEPKOWITZ, 2002; VAN DER VELDEN *et al*., 2014).

Diante da escassez de evidências científicas, torna-se oportuno a realização de estudos voltados para investigações que permitam elucidar a associação de doenças bucais infecciosas, como a doença periodontal e a mucosite oral nos pacientes submetidos à terapia para o câncer e a participação de tipos microbianos envolvidos nestas enfermidades. Desta maneira, o tratamento da periodontite e a consequente melhora da saúde bucal poderão contribuir para a redução da gravidade e da incidência de MO melhorando a sobrevida e a qualidade de vida nestes pacientes, já que poderá melhorar a tolerabilidade e permitir maior eficácia da terapia para o câncer.

Portanto, o objetivo desta pesquisa é avaliar o impacto da terapia periodontal na mucosite oral, caracterizar as principais complicações bucais da quimioterapia, relacionar ao nível sócio econômico, à qualidade de vida e pesquisar a ocorrência de periodontopatógenos putativos no paciente submetido à quimioterapia para tratamento de tumores sólidos e indicação de transplante de medula óssea (TMO). Com base neste conhecimento, poderemos contribuir para um melhor prognóstico e sobrevida, além de reduzir os custos por internações e medicamentos impactando, positivamente, na oncologia clínica.

2 PROPOSIÇÃO

Esta pesquisa teve como principal objetivo avaliar o impacto da terapia periodontal na mucosite oral no paciente submetido à quimioterapia para tratamento de tumores sólidos e indicação de transplante de medula óssea (TMO).

Os objetivos específicos foram:

- Caracterizar as principais complicações bucais da quimioterapia relacionando-as ao nível sócio econômico e à qualidade de vida;

- Pesquisar a ocorrência de periodontopatógenos putativos do complexo vermelho.

3 MATERIAL E MÉTODOS

3.1 Procedimentos Éticos

O estudo foi realizado entre o período de janeiro de 2015 a maio de 2016 em pacientes diagnosticados com tumores sólidos e em pacientes com indicação de transplante de medula óssea (TMO); indicados à tratamento quimioterápico. Estes pacientes foram tratados, respectivamente, no Instituto Oncológico do Hospital 9 de Julho de Juiz de Fora (ANEXO A), e no Serviço de Hematologia e Transplante de Medula Óssea do Hospital Universitário da Universidade Federal de Juiz de Fora (ANEXO B). Este estudo foi aprovado pelo Comitê de Ética em Pesquisa CEP/UFJF, parecer 1.684.653 (ANEXO C) de acordo com as atribuições definidas na Res. CNS 466/12 e com a Norma Operacional Nº001/2013 CNS. Todos os pacientes inseridos na pesquisa foram esclarecidos em relação ao estudo e forneceram livremente consentimento informado (ANEXO D).

3.2 Delineamento do estudo

Trata-se de um estudo intervencionista, longitudinal prospectivo, coorte, no qual 51 pacientes consecutivos com indicação e em tratamento quimioterápico foram incluídos em dois grupos. O Grupo saúde periodontal (GSP) composto de 33 pacientes com saúde periodontal; e o Grupo Doença Periodontal (GDP) constituído de 18 pacientes com diagnóstico de periodontite de acordo com os critérios da Academia Americana de Periodontologia (*Parameters on chronic periodontitis, 2000*) (Figura1).

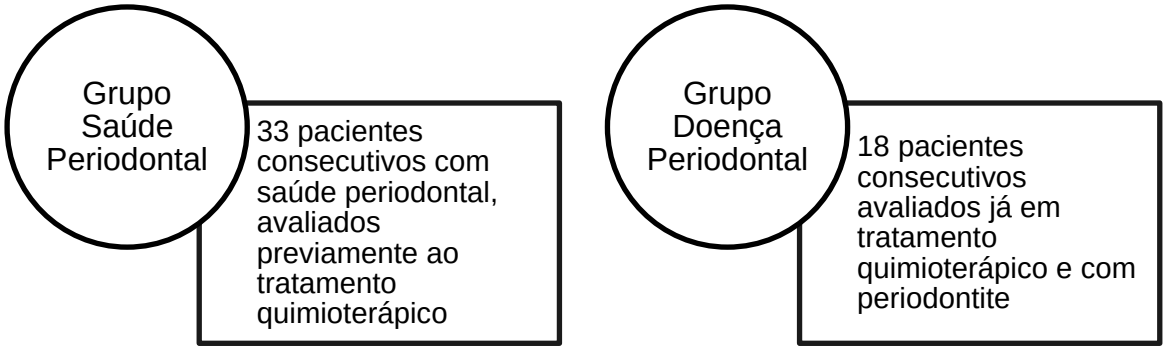


Figura 1 - Esquema do delineamento do estudo.

3.3 Fluxograma do delineamento do estudo

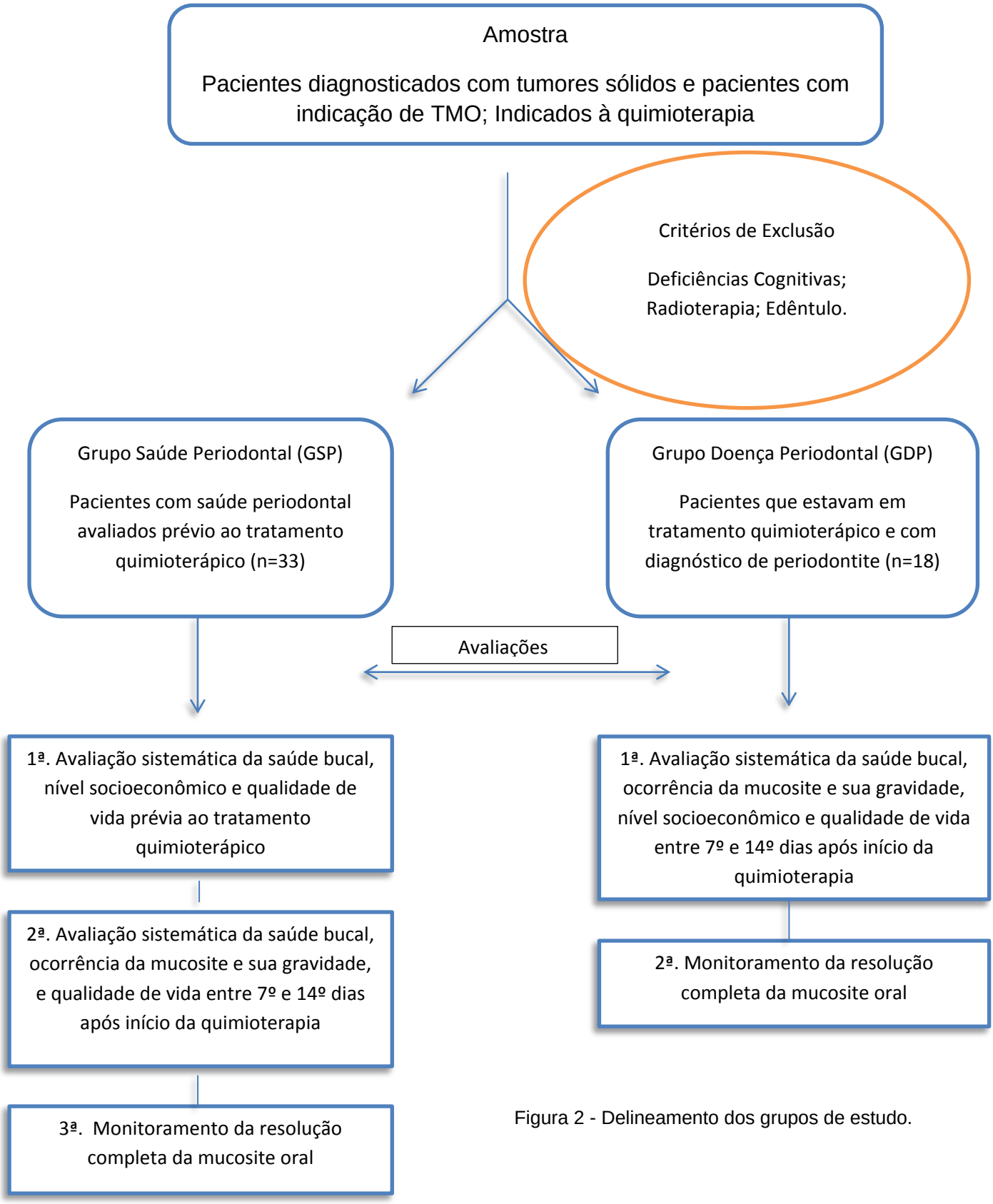


Figura 2 - Delineamento dos grupos de estudo.

3.4 Amostra

Foram incluídos no estudo, pacientes diagnosticados com tumores sólidos e pacientes com indicação de transplante de medula óssea (TMO); indicados ao tratamento quimioterápico. Os pacientes foram então abordados e avaliados por única examinadora, sendo diagnosticados com saúde ou doença periodontal através dos critérios da Academia Americana de Periodontologia,

Grupo Saúde Periodontal (GSP): 33 pacientes consecutivos abordados previamente ao tratamento quimioterápico (quimioterapia para tumores sólidos, e quimioterapia prévia ao transplante de medula óssea), que receberam tratamento periodontal realizado na Faculdade de Odontologia da Universidade Federal de Juiz de Fora ou em outro serviço de escolha do próprio paciente. Foram então incluídos neste grupo, aqueles pacientes com saúde periodontal definido de acordo com os parâmetros da Academia Americana de Periodontologia (*Parameters on Chronic Periodontitis, 2000*), ou seja: Índice Gengival = 0-1; Profundidade Clínica de Sondagem inferior a 3 mm; Índice de Sangramento inferior a 20%. Durante a quimioterapia estes pacientes foram acompanhados para verificar a ocorrência e grau da mucosite oral.

Grupo Doença Periodontal (GDP): 18 pacientes consecutivos com tratamento quimioterápico já iniciado e diagnosticados com periodontite (*Parameters on chronic periodontitis, 2000)*. Estes pacientes foram avaliados para verificar e caracterizar a presença da MO e/ou DP. Pacientes diagnosticados com DP ou qualquer outra doença odontológica já em quimioterapia foram encaminhados para tratamento odontológico. O momento deste tratamento foi definido juntamente com o médico responsável.

Os pacientes diagnosticados com doença periodontal foram tratados na Clínica de Periodontia na Faculdade de Odontologia da Universidade Federal de Juiz de Fora.

A MO foi tratada tanto no grupo saúde periodontal, quanto no grupo doença periodontal.

Todos os pacientes que concordaram em participar do estudo assinaram o termo de consentimento livre e esclarecido.

3.4.1 Tratamento Periodontal

O tratamento periodontal consistiu de: A-Raspagem e alisamento coronário e radicular com o uso do aparelho ultrassônico sob anestesia local com prilocaína a 3% com 1:100.000 de felipressina. B-Orientação das medidas de higiene bucal através de identificação da placa dental com solução evidenciadora de fucsina e uso da escova dental segundo a técnica de Bass modificada, de fio dental e de escova interdental. C- O pós-operatório consistiu de cuidados locais (bochechos leves com clorexidina a 0,12%) e analgésico/anti-inflamatório não hormonal por 72 horas. D- Profilaxia antibiótica nos casos indicados de acordo com os critérios descritos pela *American Heart Association* de 1997.

Durante o tratamento periodontal o tecido inflamatório que geralmente é descartado foi fixado em formaldeído 4% e enviado para análise histomorfológica a fim de confirmar a presença de inflamação crônica no laboratório de Anatomia Patológica Bucal da mesma faculdade.

3.4.2 Tratamento da Mucosite Oral

Todos os pacientes receberam tratamento para MO, de acordo com o protocolo do Grupo de Estudos da Associação Multinacional de cuidados de suporte no câncer (MASCC/ ISOO) (LALLA *et al.,* 2014). O tratamento da MO consistiu em: utilização de laser de baixa potência He-Ne (632,8nm, 60mW) com aplicação pontual sobre a lesão da MO (4J/cm^2) e em varredura (2J/cm^2) sobre toda a mucosa bucal, em dias alternados.

3.4.3 Determinação do tamanho da amostra

Considerando os critérios de inclusão e exclusão estabelecidos, o tamanho da amostra proposto levou em consideração o cronograma do estudo com o tempo disponível para a pesquisa e a capacidade do observador em obter esses pacientes. Determinando assim um maior tamanho possível, dentro dos limites, para um resultado confiável dentro dessa amostra.

3.5 Critérios de Inclusão

Para serem elegíveis nesse estudo, foi necessário que os pacientes apresentassem:

- Diagnóstico histopatológico de tumores sólidos.

- Diagnóstico de patologia hematológica com indicação de Transplante de Medula Óssea (TMO).

- Indicação de tratamento quimioterápico, sendo os agentes quimioterápicos de escolha cisplatina; doxorubicina; fluorouracil/leucovorin/oxaliplatina; melfalano; fludarabina/bussulfan; fludarabina/melfalano; leucovorin/etoposide/ara-C/melfalano. Estes quimioterápicos foram selecionados por serem os de maior escolha para o tratamento das patologias nos hospitais incluídos na pesquisa.

- Autorização para realização da pesquisa assinando o termo de consentimento livre e esclarecido.

3.6 Critérios de Exclusão

Os pacientes excluídos apresentaram:

- Deficiências cognitivas.

- Tratamento Radioterápico concomitante.

- Edêntulos

.- Pacientes que não completaram o ciclo da quimioterapia devido a óbito ou abandono do tratamento e/ou estudo.

3.7 Avaliações

Todas as avaliações foram realizadas por uma única examinadora.

3.7.1 Grupo Saúde Periodontal (GSP)

33 pacientes consecutivos com saúde periodontal avaliados prévio ao tratamento quimioterápico.

- 1ª. Avaliação: Avaliação sistemática da saúde bucal, nível socioeconômico e qualidade de vida prévia ao tratamento quimioterápico.

- 2ª. Avaliação: Avaliação sistemática da saúde bucal, ocorrência da mucosite e sua gravidade, e qualidade de vida entre 7º e 14º dias após início da quimioterapia.
- 3ª. Avaliação: Monitoramento da resolução completa da mucosite oral.

3.7.2 Grupo Doença Periodontal (GDP)

Dezoito pacientes consecutivos em tratamento quimioterápico já iniciado e diagnosticados com periodontite.

- 1ª. Avaliação: Avaliação sistemática da saúde bucal, ocorrência da mucosite e sua gravidade, nível socioeconômico e qualidade de vida entre 7º e 14º dias após início da quimioterapia.
- 2ª. Avaliação: Monitoramento da resolução completa da mucosite oral.

3.8 Instrumentos de coleta de dados

Foram utilizados os seguintes instrumentos de avaliação:

3.8.1 Fichas clínicas e Questionários

Ficha clínica (ANEXO E) da Equipe de Dor Orofacial/ATM do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (SIQUEIRA e TEIXEIRA, 2001) para a obtenção de informações relativas aos dados demográficos do paciente, história médica, tipo de patologia apresentado por cada paciente e o tratamento ao qual foi submetido (informações obtidas nos prontuários). A ficha também avaliou o sistema estomatognático, a partir dos dados da história odontológica e exame físico orofacial sistemático. Esses dados foram utilizados para avaliar fatores de risco e agravantes das complicações bucais do tratamento quimioterápico. Foram avaliadas as seguintes complicações: Mucosite oral, para obtenção de dados sobre a presença e gravidade da mesma de acordo com a classificação da gravidade da mucosite oral segundo a Organização Mundial da Saúde – OMS; Candidíase; Trismo; e caracterização da dor orofacial quando presente. Testes clínicos para diagnóstico de disfagia (ANEXO F) (WU *et al.*, 2004). Avaliação periodontal através dos seguintes índices: Índice de Placa (IP) (SILNESS e

LÖE, 1964.); Índice de Sangramento à Sondagem (SS) (AINAMO e BAY, 1975); Profundida Clinica de Sondagem (PCS) (O'LEARY e RUDD, 1963) e Profundidade Clínica de Inserção (PCI) (AMERICAN ACADEMY OF PERIODONTOLOGY, 1999) para avaliar, através destes parâmetros clínicos o grau de comprometimento periodontal e atividade de doença. O índice gengival (IG) registra alterações da forma e contorno dos tecidos periodontais. O IP foi utilizado para avaliar a condição de higiene bucal, calculado pelo número de superfícies dentárias coradas por pastilhas evidenciadoras de placa, multiplicadas por 100 e dividido pelo número total de superfícies. Inflamação gengival foi avaliada pelo índice de sangramento gengival, determinado pelo número de superfícies sangrantes após sondagem com sonda periodontal, multiplicado por 100 e dividido pelo número total de superfícies. A PCS foi realizada introduzindo-se a sonda periodontal no sulco gengival, obtendo-se uma medida da margem gengival até o fundo do sulco. Também foi realizada a medida da distância entre a margem gengival e o limite esmalte-cemento (LEC-MG), que fornece dados com relação à presença ou ausência de recessão ou hiperplasia gengival. Com estas duas medidas (PCS e LEC-MG) foram obtidas a PCI, ou seja, a quantidade clínica de inserção de cada dente. Estas medidas foram realizadas nas seis faces de cada elemento (mesiovestibular, cervical, distovestibular, mesiolingual, lingual e distolingual) (Figura 3).

Figura 3 - Avaliação periodontal. Introdução da sonda periodontal no sulco gengival na região mesiovestibular do elemento 41 (incisivo central inferior esquerdo).

Questionário de Xerostomia (ANEXO G), que consta de oito perguntas validadas na literatura científica para avaliar a sensação de secura na boca do paciente (FOX; BUSCH; BAUM,1987; PAI; GHEZZI; SHIP, 2001) através da escala visual analógica (EVA). A xerostomia foi considerada para médias com valor > 2 (GOMES *et al*., 2014).

Questionário do perfil de impacto de saúde bucal (Oral Health Impact Profile - OHIP), (ANEXO H) criado por Slade e Spencer (SLADE e SPENCER, 1994) amplamente utilizado em diferentes culturas e perfis sociodemográficos. O OHIP foi desenvolvido para fornecer uma mensuração abrangente de disfunção, desconforto e incapacidade atribuída à condição bucal. Tais informações visam à complementação dos indicadores tradicionais de epidemiologia bucal de doenças clínicas e, desse modo, fornecem um perfil do "impacto da doença" em populações e a eficácia dos serviços de saúde em reduzir esses impactos. A versão original do OHIP apresenta sete dimensões, contendo 49 itens em um questionário respondido com uma escala do tipo Lickert, com cinco opções que variam de "nunca" até "sempre".

Questionário Classe socioeconômica (ALMEIDA e WICKERHAUSER, 1991) (ANEXO I), para caracterizar o perfil socioeconômico da população estudada.

3.8.2 Avaliação Microbiológica

A) Obtenção do espécime clínico

Para a obtenção do espécime clínico (coletas), foram coletadas amostras de placa subgengival de cada paciente.

Para a obtenção das amostras de placa subgengival, foram utilizados cones de papel absorvente para coleta de microrganismos dos sítios periodontais (Figura 4). Após um minuto em contato com o sítio eleito para coleta os cones foram introduzidos em tubos de micro centrífuga estéreis previamente pesados.

As coletas foram realizadas no Grupo Saúde Periodontal nos seguintes momentos: previamente ao tratamento quimioterápico, entre o 7º e 14º dias após início do tratamento quimioterápico. E no Grupo Doença Periodontal, as coletas foram realizadas entre o 7º e 14º dias após início da quimioterapia.

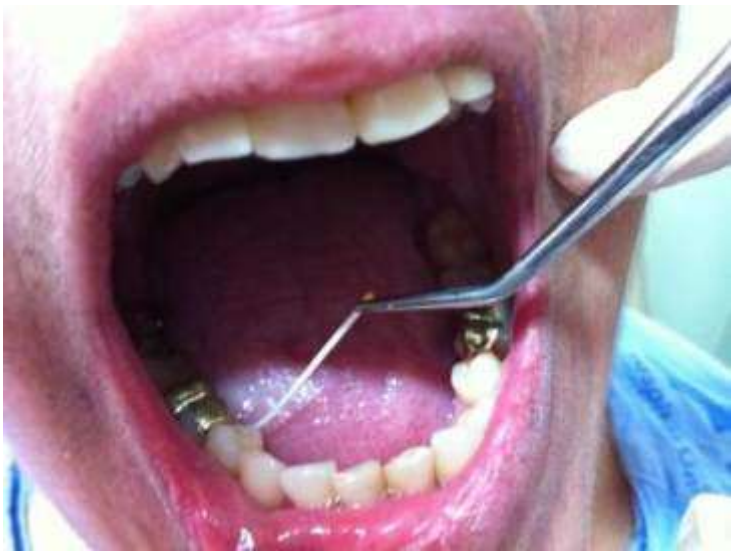


Figura 4 - Coleta com cone de papel absorvente na região de doença periodontal (sulco mesiolingual do dente pré-molar inferior direito).

B) Processamento do espécime

O material foi identificado (ANEXO J) e transportado para o laboratório de Fisiologia e Genética Molecular Bacteriana, Departamento de Parasitologia, Microbiologia e Imunologia do Instituto de Ciências Biológicas da Universidade Federal de Juiz de Fora, em contato com gelo reciclável, em caixa de isopor e processados em um intervalo máximo de 2 horas após a coleta.

No laboratório, cada amostra foi pesada e acrescentada um mililitro de salina estéril e homogeneizada. Esta foi armazenada a -20°C até o momento dos ensaios para FISH (*fluorescence in situ hybridization*) para quantificação da densidade das bactérias do complexo vermelho.

3.9 Análise Estatística

A análise dos dados foi conduzida de maneira a respeitar a natureza dos mesmos. Foram utilizados o teste de Mc Nemar (variáveis qualitativas) e teste do sinal para dados pareados (variáveis quantitativas), quando a intenção foi comparar observações, de um mesmo grupo, feita em tempos distintos (grupo saúde periodontal antes e depois da quimioterapia). Quando a intenção foi

comparar dois grupos distintos (grupo saúde periodontal e grupo doença periodontal) foram utilizados o teste exato de Fisher (variáveis qualitativas) e o teste de Wilcoxon (variáveis quantitativas). Por fim, quando a intenção foi comparar grupos independentes (grupos saúde periodontal com e sem complicação, como mucosite, por exemplo, e grupo doença periodontal com e sem complicação) foi utilizado o teste de Kruskall-Wallis. Em todos os testes estatísticos foi considerado um nível de 5% de significância.

4. ARTIGOS

4.1 Artigo 1

Review Article

CANCERTHERAPY-INDUCED ORAL MUCOSITIS AND PERIODONTITIS: EVIDENCES OF RELATIONSHIP

Aline Moreira, Cristina de Paula Novaes, Aneliese Holetz De Toledo Lourenço, Maria das Graças Afonso Miranda Chaves, Fábio Daumas Nunes, Gisele Maria Campos Fabri

*Correspondence:

Gisele Maria Campos Fabri

Faculdade de Odontologia da Universidade Federal de Juiz de Fora

Rua José Lourenço Kelmer s/n- São Pedro, Juiz de Fora – MG

CEP 36036-900 - Brazil

Tel: 55-(32) 3025-3065

gisele.fabri@ufjf.edu.br

Running title: ORAL MUCOSITIS AND PERIODONTITIS

Abstract

This narrative review aims to update the reader about the current issues surrounding central aspects implicated in the relationship between oral mucositis and periodontitis. We searched Medline/PubMed database. English-language publications were included. Paired reviewers selected articles for inclusion and extracted data. Forty three studies met our inclusion criteria. The majority of the studies were review (62,8%) and clinical studies (37,2%). There is a lack of studies regarding the association of periodontal disease and oral mucositis. However, there are pathogenic similarities between them. Look for scientific evidence to confirm the relationship of periodontal disease and oral mucositis is imperative. Hence, will be possible developing specific interventions to reduce efficiently, periodontal disease, a treatable condition that might interfere with the incidence and severity of oral mucositis, a particular adverse effect of cancer treatment.

Key Words: Periodontitis, oral mucositis, cancer therapy

STATEMENT OF CLINICAL RELEVANCE

This article aims to update the reader as to the current issues surrounding central aspects implicated in relationship between oral mucositis and periodontitis. The scientific evidence included helps clinicians understand the pathophysiology mechanism of this association, highlighting a proposition of a new look for the patients under cancer therapy.

Conflicts of interest: None.

ACKNOWLEDGEMENT

We are also grateful to Cynthia Savioli who moderated this paper and in that line improved the manuscript significantly**.**

This study did not receive any financial support.

The authors declare no conflicts of interest.

INTRODUCTION:

Oral mucositis (OM), a side effect of cytotoxic cancer therapy, is a pain full condition with negative impact in daily activities and also leads economic consequences. Despite of research efforts to better understand its pathogenesis and discover effective interventions, OM is still, an unmet need with a high priority for the development of an effective treatment.[1]

Periodontal inflammation is a prevalent condition on population, with known contribution to systemic inflammation, producing elevated levels circulating of cytokines [interleukin-1 (IL-1), interleukin-6 (IL-6)], prostaglandin E2 (PGE2), tumor necrosis factor (TNF) and C-reactive protein.[2-5]

Both conditions are characterized by an exuberant inflammatory reaction, regulated by an infiltration of immune cells, enzymes and proinflammatory cytokines such as TNF and interleukins, which outcome in both, soft and hard tissue, destruction. Further, OM and periodontal disease (PD) are two most common chronic inflammatory diseases in adults patients receiving cancer therapy,[4-6] and despite of the clear pathogenic similarities between them, its relationship is few studied.

Thus, we propose a new look for the patients under cancer therapy and that have periodontitis diagnose. The evidences indicate that these patients could suffer of a higher severity of oral mucositis. Therefore, the aim of this study is to review the physiopathological mechanisms that could explain this biological plausibility.

REVIEW METHODS:

PubMed/Medline databases were searched for articles in English language focused in pathogenic mechanisms of periodontal disease and oral mucositis.

The search strategy has involved a combination of titles and relevant keywords in the medical area.

The search terms that we used were "periodontal disease", “periodontitis pathogeneses”, “oral mucositis”, oral mucositis pathogeneses”, “systemic disease and periodontal disease”, “cytokines”, “inflammation”, “infection”.

The search included the period between 1997 and 2014, which considered clinical trials, systematic reviews and experimental animal studies.

All articles identified were full texts.

KNOWLEDGE ABOUT PERIODONTAL DISEASE

Periodontal disease (PD) is a complex disease in which the structures of tooth protection (classified as gingivitis) and tooth supporting (classified as periodontitis) are affected. Periodontitis are the main cause of oral infections and tooth loss. The etiology is multifactorial, with local and systemic factors enrolled. Opportunistic infections stand out among the risk factors for outset and development of PD, with a potential risk factor for bacteremia and focal infection. The clinical appearance of periodontal diseases is determined by host response against bacterial stimulus. Although, specific bacteria are the major etiologic agents of PD, the host response has an important role in damage of the periodontal tissues.[7,8]

PD show high prevalence, with about 90% of the adult population suffering from gingivitis, 60% having chronic periodontitis and 5–15% with aggressive periodontitis.[2,3,9]

The disease is initiated by certain species of sub gingival gram-negative anaerobic bacteria that co-exist within dynamic communities of highly organized architecture biofilm.[10] In periodontal health, the ordered structure of the dental plaque biofilm consists, predominately, of gram-positive, facultative anaerobic bacteria, although the onset of the disease is associated with a shift to gram-negative anaerobic bacteria, which begin to colonize the sub gingival pocket.[11] The high numbers of red complex members such as *Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia* correlates, strongly, with periodontal tissue destruction. *Prevotella intermedia and Fusobacterium nucleatum*, both members of the orange complex, are also associated with diverse forms of periodontal disease.[12]

Numerous evidences strongly suggest that host inflammatory response drives tissue destruction, and that the variability of host responses determines the variability in the clinical manifestation of periodontitis. Hence, although bacteria are necessary for disease initiation, they are not sufficient to cause disease progression. The inflammatory response in a susceptible host is crucial.[3,13]

The destruction of soft and hard tissues, seen in periodontitis, is the result of not only a large number of cytokines, but also, the sustained presence of other effector molecules released by resident and migrating cells. Together, these inflammatory mediators of inflammation are able to induce the cascade of molecular events associated with extracellular matrix degradation and resultant tissue damage.[3, 14]

The regulation of the immune response depends of inflammatory cytokine production by different subpopulations of helper T lymphocytes (Th), which act enhancing or attenuating the inflammatory response in periodontal tissues and, thus, determining the activity or the latency of periodontal lesions[4,6]. These cytokines include prostaglandin E2 (PGE2), tumor necrosis factor-alpha (TNF-α), IL-1 alpha (IL-1α), IL-1 beta (IL-1β), and others.[2]

A biologic system model has been explored with bacterial components, environmental factors and host-genetic variations associated with disease. In this model the products of microbial complexes active the immune inflammatory mechanisms that, subsequently, influence the behavior of bone and connective tissue metabolism. For each individual there are combinations of genetic variations and environmental factors. These genetic and environment factors act on biologic mechanisms to modify the expression of genes activated by the bacterial products. Within this framework, discrete modules of genetic, environment and other modifying factors would define a specific expression pattern that represents the shift from health to disease.[15]

PERIODONTAL DISEASE AND SYSTEMIC DISEASE: BRIEF UP-TO-DATE

Several systemic conditions are associated with a higher prevalence of periodontal disease like diabetes mellitus (DM). Chronic hyperglycemia due to structural changes occur (such as a reduction in vascularization and leucodiapedesis, and increased collagenase has been the reduction of scarring) which end accelerating periodontal destruction.[16,17] Thus, people with diabetes are at increased risk for periodontal disease.

Other diseases may also predispose to PD like autoimmune diseases. Patients with rheumatoid arthritis, dermatomyositis, lupus erythematosus and ankylosing spondylitis have more prevalent and more severe PD than patients without these conditions.[18-20] In addition, patients with chronic orofacial pain, and Alzheimer's disease also have worse gingival indexes.[21,22]

On the other hand, systemic exposure to periodontal pathogens, their toxins and periodontal inflammatory mediators may have deleterious effects on different organs or systems. It was reported three mechanisms by which periodontal infection can influence systemic health: metastatic infection (caused by the translocation of Gram-negative bacteria of periodontal pocket into the blood flow), metastatic lesions (e.g., vascular injury caused by the effects of toxins microbial and circulating pro-inflammatory mediators) and metastatic inflammation (due to the immune response to periodontal pathogens and their toxins).[10,23]

There is increasing evidence that systemic inflammation results from the entry of oral microbial agents and their virulence factors into the circulation. Elevated serum levels of C-reactive protein and other acute-phase reactants and raised biomarkers of oxidative stress evidence this. It is, therefore, biologically plausible that non-resolving chronic inflammation derived from periodontal disease impacts on systemic health.[5] (Figure 1)

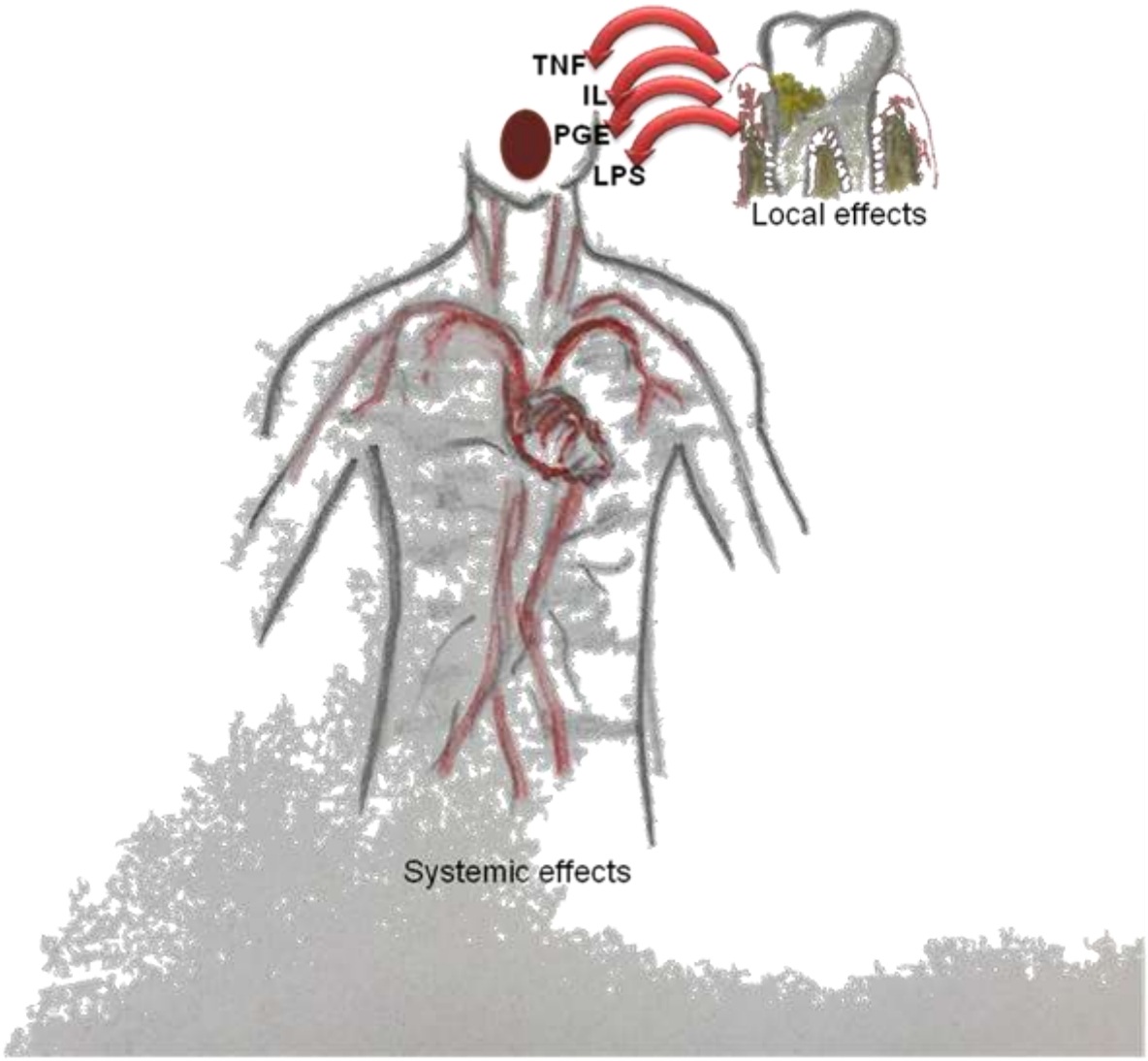


Figure 01- The destruction of soft and hard tissues in periodontitis is the result of a large number of cytokines and effector molecules released by resident and migrating cells. These signals and the oral microbial agents and their virulence factors entry into the circulation and impacts on systemic health (TNF- Tumour necrosis factor alpha, IL- Interleukin, PGE-prostaglandin, LPS-Lipopolysaccharide).
table

Furthermore, periodontitis shares many common risk factors with chronic systemic diseases. These factors include smoking, diabetes, obesity, nutritional dysfunction, stress, ageing and race／ethnicity, among others. The oral cavity can act as a reservoir and a potential source for dissemination of pathogens to distant body sites. Access to non-oral sites is facilitated by bacteremia, which occurs following even minor oral routines, such as daily tooth brushing, as well as by dental procedures.[17]

Indeed, gingivitis and periodontitis can also induce a series of immune changes in circulating immune complexes, due to the failure of autoimmune

regulation and tolerance, contributing to the emergence and progression of autoimmune diseases.[24]

Accordingly, dental and medical care should be more carefully integrated. Then, health education program should encourage the improved oral health beside the current healthy lifestyle guidelines, alongside smoking cessation, satisfactory diet and exercise. These current evidence is such that prevention and treatment of periodontal disease may reduce chronic systemic disease risk and the onset of others immune inflammatory diseases.[24]

ABOUT ORAL MUCOSITIS

Oral mucositis is an acute reaction associated with radiotherapy, chemotherapy or a combination of both treatments.[25] It is one of the most common complications of oral anticancer treatment, being found in about 40 - 46% of patients receiving chemotherapy.[26,27]

Among patients with head and neck tumors treated with radiotherapy, 90–97% presents some degree of mucositis and generally 50% develop grade III or grade IV mucositis.[28]

The clinical manifestations of OM include signs and symptoms of inflammation, varying from mild erythema, edema, and soreness to extreme pain and ulceration that require analgesic medication. Severe OM interferes with daily activities, such as speaking, eating, and swallowing, resulting in dehydration, malnutrition, and opportunistic infections, with a negative impact on the quality of life.[29-31] When severe oral mucositis develops, cancer treatment may be modified or even halted which can limit the efficacy of treatment, and this is estimated to occur in about 10–25% of all patients, although interruption rates as high as 47% have been reported.[31]

The progression of OM has been described in five stages.[1,32] The initiation phase is characterized by two events: injure DNA and strand breaks resulting in clonogenic death of basal epithelial cells directly by radiation and chemotherapy. Even more significant from the standpoint of ultimate tissue damage, is the generation of reactive oxygen species (ROS), which decreases the cell turnover, attacking epithelial cells and connective tissue and affecting, in

particular, epithelium, and blood vessels. The second stage is characterized by primary damage response to chemotherapy, radiation, and ROS initiating a series of interacting biological events. Transduction pathways triggered by DNA strand breaks and lipid peroxidation prompt the activation of a number of transcription factors, such as nuclear factor- *κ*B (NF-*κ*B), wintless pathway (Wnt), p53. Chemotherapy and radiation can directly activate NF-*κ*B. Indirectly, it can be activated by ROS. Among the 200 genes whose expression is governed by NF-*κ*B are those associated with the production of molecules, which have demonstrated activity in the pathogenesis of mucositis including cytokines and cytokine modulators, stress responders (i.e. COX-2, inducible Nitric Oxide -synthase, superoxide dismutase), and cell adhesion molecules. Importantly, apoptosis is an important consequence of the effects of NF-*κ*B in normal cells.[1]

Therefore, there is a production of various inflammatory mediators such as TNF-α, Interleukin-1β (IL-1β) and interleukin-6 (IL-6) that stimulate pro-apoptotic enzymes, blocking the growth and differentiation mechanisms and initiate the tissue damage.[32] This stage is recognized by signal amplification.

Ulceration is the most symptomatic and probably the most complex stage. The bacteria on the ulcer surface are active contributors to the mucositis process. Cell wall products (i.e. lipopolysaccharides, lipoteichoic acid, cell wall antigens, and a-glucans) penetrate into the submucosa, now rich in macrophages, stimulate those cells to further secrete pro-inflammatory cytokines. In granulocytopenic patients, there is a risk that intact bacteria may invade submucosal vessels to produce bacteremia or sepsis.[32]

The majority of cases of OM heal spontaneously. Ulcer resolution is the result of an active biological process in which signaling from the submucosa's extracellular matrix (ECM) guides the proliferation, migration and differentiation of the epithelium bordering the ulcer. This is the healing stage.[1]

The severity of mucositis depends of a number of factors including the administered dose, the dose fraction, the volume of tissue treated and the type of radiation given. The patient factors include the type of malignancy, patient age and oral health.[33]

BIOLOGICAL LINKS BETWEEN ORAL MUCOSITIS AND PERIODONTITIS

The debilitating effects of mucositis can result in unplanned treatment interruptions or even premature cessation of treatment. The risk of systemic infections and even death is increased in patients with mucositis, since the lesions act as a gate way of oral bacteria into bloodstream, which can lead to bacteremia and sepsis, with a high morbidity and mortalityin susceptible individuals.[34-36]

The role of the periodontal disease in some systemic conditions has been demonstrated. Some studies have shown that it plays an important role in cardiovascular, metabolic, autoimmune diseases and neurovascular conditions.[17, 20, 21, 23, 37] Periodontal disease can be related to refractory craniofacial pain and also to worsening of Alzheimer disease.[21, 22] In these studies, the main pathophysiological mechanisms involved are related to the constant release of cytokines that generates systemic inflammation as well as aspects related to bacteremia.[38]

Thus, both oral mucositis and periodontal disease are immunoinflammatory condition characterized with the continuing presence of systemic inflammation and bacteremia.[5, 17, 30] These conditions are prevalent in patients receiving cancer therapy and could put them at risk of systemic complications.[25] Considering these data, it is plausible to explore the possibility of link between OM and PD. However, clinical and/or laboratory studies involving oral mucositis and periodontal disease inter-relationships are scarce in the scientific literature available.

Recently, it was suggested a ´two-hit´model to justify the association between radiation-induced oral mucositis and periodontitis.[39] This model suggests that inflammation at the periodontium level which is periodontitis (first 'hit') followed by radiation (second 'hit') can lead to an exacerbated response in the form of oral mucositis. The converse may also hold true in that radiation-induced oral mucositis (first 'hit') exacerbates the inflammatory response of developing periodontitis (second 'hit').[39]

Really, many factors can directly affect the change of mucosal exposure to radiation, the protection of mucosal cells and the local inflammatory response.[40] It was reported that reducing dental plaque and gingival inflammation by oral care was positively correlated with OM, corroborating the idea that oral inflammation is predictive of OM incidence and healing time.[30, 41] Also, preliminary findings showed that there was a trend towards a greater proportion of periodontitis patients in the mucositis groups than in the non-mucositis group.[39]

Another relevant feature in this association is that the cytokines involved in the pathogenesis of OM are common to those involved in the pathogenesis of PD. The progression of both, PD and OM, occurs due to a combination of factors, including increased levels of pro-inflammatory cytokines (such as IL-1, IL-6, TNF-α), metalloproteinases (MMPs), prostaglandin E2 (PGE2) , low levels of anti-inflammatory cytokines (such as IL-10) and transforming growth factor (TGF-β).[2, 4, 6, 32]

As indicated previously, nuclear factor-*κ*B (NF-*κ*B) is thought to play an important role in the pathobiology of mucositis, particularly with respect to the upregulation and subsequent expression of the pro-inflammatory cytokines TNF, IL-1b and IL-6. The activation of NF-*κ*B can be facilitated by various factors including both radiation and chemotherapy as well as infectious agents and inflammatory cytokines[42] such as PD.

On the order hand, the inflammatory response altered by radio/chemotherapy put patient at risk for progression of PD[25, 36] triggering a new cycle of up regulation of cytokines (Figure 2).

Despite these findings, the role of microorganisms in the development and course of mucositis are not clear. The increase in gram negative organisms were seen during ulceration, and the reestablishment of normal bacterial proportions was a requirement for spontaneous ulcer resolution, irrespective of bacterial numbers.[1] Clinical trial results suggest that anti-bacterial strategies have been ineffective as OM interventions [43]. However, the interventions analyzed were systemic antimicrobial therapy, and, to affect periodontal biofilm, is crucial the mechanic removal of dental biofilm (root planning).

Further, clinical and laboratorial systematic investigations are required about PD and OM patients. The clinical success of prevention and therapy of

OM depends on several biological factors. Moreover, it is important to achieve more insight into the pathobiology of mucositis as well as into periodontitis, both with individual discrepancies and genetic variances that support susceptibility.

CONCLUSION

Investigate the association of PD and OM is particularly important. PD is a treatable condition and, if it really can interfere with the incidence and severity of OM, the establishment of specific interventions to reduce efficiently PD, could better control the OM, a serious adverse effect of cancer treatment. Despite advances in medical care to improve survival in cancer patients, infectious diseases are responsible for significant morbidity and mortality in these patients. Prompt diagnosis, appropriate management of oral infections, and preventive procedures are crucial to optimal assistance.

REFERENCES

1. Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol 2009;45:1015–1020.

2. Burt B. Research, Science and Therapy Committee. American Academy of Periodontology Position paper: epidemiology of periodontal diseases. J Periodontal 2005;76:1406–1419.

3. Bartold PM, Cantley MD, Haynes DR. Mechanisms and control of pathologic bone loss in periodontitis. Periodontol 2000 2010;53:55-69.

4. Lima HG, Lara VS. Immunological Aspects of Inflammatory Periodontal Disease: Involvement of Mast Cells (in Portuguese). UNOPAR Científica Ciências Biológicas e da Saúde 2013;15(3):225-9.

5. Chapple ILC, Genco R and on behalf of working group 2 of the joint EFP/AAP workshop* Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases J Periodontol 2013;84(4 Suppl.):S106-S112.

6. Ohlrich EJ, Cullinan MP, Seymour GJ. The immunopathogenesis of periodontal disease. Australian dental jornal 2009;54(1):2-10.

7. Armitage GC. Development of a Classification System for Periodontal Diseases and Conditions. Ann Periodontol 1999;4(1):1-6.

8. Lindhe J, Lang, NP, Karring, T. Tratado de Periodontologia Clínica e Implantologia Oral. 5ª. Ed. Rio de Janeiro: Editora Guanabara Koogan. 2010.

9. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. Periodontol 2000 1997;14:216-48.

10. Krauss JL, Potempa J, Lambris JD, Hajishengallis G. Complementary Tolls in the periodontium: how periodontal bacteria modify complement and Toll-like receptor responses to prevail in the host. Periodontol 2000 2010;52:141-162.

11. Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol 2000 2005;38:135-187.

12. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol 1998;25:134-144.

13. Page RC. The pathobiology of periodontal diseases may affect systemic diseases: inversion of a paradigm. Ann Periodontol 1998;3(1):108-20.

14. Reynolds JJ, Meikle MC. Mechanisms of connective tissue matrix destruction on periodontitis. Periodontol 2000. 1997;14:144-57.

15. Kornman KS. Mapping the Pathogenesis of Periodontitis: A New Look. J Periodontol 2008 Aug;79(8 Suppl):1560-8.

16. Kinane DF, Peterson M, Stathopoulou PG. Envieronmental and other modifyng factors of the periodontol disease. Periodontol 2000 2006;40:107-19.

17. Enwonwu CO, Salako N. The periodontal disease– systemic health–infectious disease axis in developing countries. Periodontol 2000 2012;60(1):64-77.

18. Fernandes EG, Savioli C, Siqueira JT, Silva CA. Oral health and the masticatory system in juvenile systemic lupus erythematosus. Lupus 2007;16(9):713-9.

19. Savioli C, Silva CA, Fabri GM, Kozu K, Campos LM, Bonfá E, Sallum AM, de Siqueira JT. Gingival capillary changes and oral motor weakness in juvenile dermatomyositis. Rheumatology (Oxford) 2010;49(10):1962-70.

20. Savioli C, Ribeiro AC, Fabri GM, Calich AL, Carvalho J, Silva CA, Viana VS, Bonfá E, Siqueira JT. Persistent Periodontal Disease Hampers Anti-Tumor Necrosis Factor Treatment Response in Rheumatoid Arthritis. J Clin Rheumatol 2012;18(4):180-4.

21. Fabri GM, Siqueira SR, Simione C, Nasri C, Teixeira MJ, Siqueira JT. Refractory craniofacial pain: is there a role of periodontal disease as a comorbidity? Arq Neuropsiquiatr 2009;67(2B):474-9.

22. Rolim ST, Fabri GM, Nitrini R, Anghinah R, Teixeira MJ, de Siqueira JT, Cestari JA, de Siqueira SR. Oral Infections and Orofacial Pain in Alzheimer's Disease: A Case-Control Study. J Alzheimers Dis 2014;38(4):823-9.

23. Teng YT, Taylor GW, Scannapieco F, Kinane DF, Curtis M, Beck JD, Kogon S. Periodontal Health and Systemic Disorders. J Can Dent Assoc 2002;68(3):188-92.

24. Takakubo Y1, Konttinen YT. Immune-regulatory mechanisms in systemic autoimmune and rheumatic diseases. Clin Dev Immunol 2012;2012:941346.

25. Turner L, Mupparapu M, Akintoye SO. Review of the Complications Associated with Treatment of Oropharyngeal Cancer: A Guide to the Dental

Practitioner. Quintessence international (Berlin, Germany: 1985) 2013;44(3):267-79.

26. Fadda G, Campus G, Luglie P. Risk factors for oral mucositis in paediatric oncology patients receiving alkylant chemotherapy. BMC Oral Health 2006;18(6):13.

27. Pinto MTF, Soares LG, da Silva DG, Tinoco EMB, Falabella MEV. Prevalência de Manifestações Orais em Pacientes Infanto-Juvenis Submetidos à Quimioterapia. Revista Pesquisa em Saúde 2013;14(1):45-8.

28. Carvalho PA, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA. Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: A double-blind randomized study in head and neck cancer patients. Oral Oncology Oral Oncol 2011;47(12):1176-81.

29. Hespanhol FL, Tinoco EMB, Teixeira HGC, Falabella MEV, Assis NMSP. Manifestações bucais em pacientes submetidos à quimioterapia. Ciência & Saúde Coletiva 2010;15(1):1085-1094.

30. Coracin FL, Santos PS, Gallottini MH, Saboya R, Musqueira PT, Barban A, Chamone Dde A, Dulley FL, Nunes FD. Oral health as a predictive factor for oral mucositis. Clinics (Sao Paulo) 2013;68(6):792-6.

31. Gussgard AM, Hope AJ, Jokstad A, Tenenbaum H, Wood R. Assessment of Cancer Therapy-Induced Oral Mucositis Using a Patient-Reported Oral Mucositis Experience Questionnaire. PLOS One. 2014 Mar 10;9(3):e91733.

32. SONIS ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, Bekele BN, Raber-Durlacher J, Donnelly JP, Rubenstein EB; Mucositis Study Section of the Multinational Association for Supportive Care in Cancer; International Society for Oral Oncology.. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. International Society for Oral Oncology. Cancer 2004;100(9 suppl):1995-2025.

33. Parulekar W, Mackenzie R, Bjarnason G, Jordan RC.. Scoring oral mucositis. Oral Oncology 1998;34(1):63-71.

34. Raber-Durlacher JE, Epstein JB, Raber J, van Dissel JT, van Winkelhoff AJ, Guiot HF, van der Velden U. Periodontal infection in cancer patients treated with high-dose chemotherapy. Support Care Cancer 2002 Sep;10(6):466-73.

35. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis 2002 Jun 1;34(11):1524-9.

36. Logan RM, Stringer AM, Bowen JM, Yeoh ASJ, Gibson RJ, Sonis ST, Keefe DM. The role of pro-inflammatory cytokines in cancer treatment-induced alimentary tract mucositis: pathobiology, animal models and cytotoxic drugs. Cancer Treat Rev. 2007;33(5):448-60.

37. Janket S, Baird AE, Chuang SK, Jones JA. Meta- analysis of periodontal disease and risk of coronary heart disease and stroke (Original research article). Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 2003;95(5):559-569.

38. Cullinan MP, Ford PJ, Seymour GJ. Periodontal disease and systemic health: current status. Aust Dent J. 2009;54(suppl 1):S62-9.

39. Khaw A, Logan R, Keefe D, Bartold M. Radiation-induced oral mucositis and periodontitis – proposal for an inter-relationship. Oral Diseases 2014; 20(3):e7–e18.

40. Albuquerque ILS, Camargo TC. Prevenção e tratamento da mucosite oral induzida por radioterapia: revisão de literatura. Rev Bras Cancerol 2007;53(2):195-209.

41. Santos PS, Coracin FL, Barros JC, Dulley FL, Nunes FD, Magalhães MG. Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis. Clin Transplant. 2011;25(2):325-8.

42. Sonis ST. A biological approach to mucostis. J Support Oncol. 2004;2(1):21-32; discussion 35-6.

43. Donnelly JP, Bellm LA, Epstein JB, Sonis ST, Symonds RP. Antimicrobial therapy to prevent or treat oral mucositis. Lancet Infect Dis 2003; (7):405–12.

4.2 Artigo 2

Understanding the orofacial complaints and complications burden in patients undergoing chemotherapy

Cristina de Paula Novaes[1], Rafaela Tristão e Silva[1], Ângela Mello Coelho[2], Fabio Daumas Nunes[4], Gisele Maria Campos Fabri[1], Maria das Graças Afonso Miranda Chaves[1]

[1]Dentistry School, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[2]Institute of Exact Sciences, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[3] School of Medicine, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[4] Dentistry School, Universidade de São Paulo, São Paulo, Brazil

AUTHORS' CONTRIBUTIONS

Study concept and design: MGAMC, GMCF

Assist in subject recruitment: CPN, MGAMC, GMCF

Acquisition of data: CPN, RTS

Analysis and interpretation of data: CPN, AMC, FDN, GMCP

Preparation of manuscript: CPN, RTS, AMC, FDN, GMCF

*Correspondence:

Gisele Maria Campos Fabri

Faculdade de Odontologia da Universidade Federal de Juiz de Fora

Rua José Lourenço Kelmer s/n- São Pedro, Juiz de Fora – MG

CEP 36036-900 - Brazil

Tel: 55-(32) 3025-3065

gisele.fabri@ufjf.edu.br

Running title: oral complications in chemotherapy

Abstract

Patients undergoing cancer therapy usually experience the oral complications. These manifestations are often unnoticed and not treated, then may be responsible for worsening of the general state of the patient's health. The aim of this study was to assess and characterize orofacial complaints and oral complications in patients undergoing cancer therapy. We evaluated 28 patients with solid tumors undergoing chemotherapy, through a systematic orofacial evaluation. The average age was 54.5 (± 12.46) years, with predominance of women n = 23 (82.14%). Socioeconomic classes B and C were the most prevalent in the study n = 13 (46.43%) each. Most of the patients had one n = 11 (39.29%) or two n = 9 (32.14%) comorbidities, most of them presented arterial hypertensive and were in use of antihypertensive drugs n = 13 (46.43%). The most frequent tumor was breast cancer n = 19 (67.86%) and the most patients had their diagnosis performed within 3 months n = 15 (53.57%). Eighteen (64.29%) patients developed oral complications during chemotherapy and xerostomia scored the highest incidence n = 14 (50%). The OHIP-14 mean index was 2.59 ranging from 0 to 7.29. These data reinforce the crucial role of the dentist in the multidisciplinary team, helping in the oral diagnose and provide a specific relieve of patients complaints impacting positively on their quality of life.

KEYWORDS: Cancer, Chemotherapy, Oral Manifestations, Quality of life

Introduction

The side effects and adverse reactions related to cancer therapies can trigger complications in the oral cavity. These effects cause acute and late toxicities that may be underreported, under recognized, and undertreated[1]. Numerous studies have identified, and report a wide range of incidence and severity for different oral complications from cancer therapies. These include: oral mucositis, xerostomia, bleeding, dysphagia, dysgeusia, caries, periodontal disease, infection (bacterial, viral, and fungal), pain, trismus, osteoradionecrosis, growth and developmental disturbances, and salivary gland dysfunction[2,3,4].

These oral complications can compromise patients' health and quality of life, and, worst of all, affect their ability to complete cancer treatment[5]. Furthermore, may lead to discomfort and even severe pain in the injured part of the body, patient's nutritional deficiency, delay in the administration of oncologic drugs or dose limitation, increase of hospitalization time and the related expenses, as well as septicemia and life threatening diseases in some cases [5,6,7].

Among oral complications, oral mucositis stands out. Oral mucositis refers to erythematous and ulcerative lesions of the oral mucosa observed in patients with cancer being treated with chemotherapy, and/or with radiation therapy to fields involving the oral cavity[8,9]. It has been consistently reported to occur in at least 75% of patients treated with irradiation for head and neck cancers, individuals receiving conditioning regimens for stem cell transplant and protocols for acute leukaemia. This adverse reaction occurs in 20–40 % of patients receiving conventional chemotherapy[10].

Mucositis and dry mouth were the most frequent concomitant oral manifestations associated with cancer therapies (16.33%)[6]. So, xerostomia is a subjective symptom of a dry mouth deriving from a lack of saliva[11]. It is important to note that a dry oral mucosa is friable and susceptible to trauma, inflammation, and irritation[12,13]. Considering these aspects, a decrease in salivary production or changes in its qualitative properties may cause a health-related poor quality of life[14] and oral lesions[12,13].

Moreover, other oral complication associated with cancer therapy, is dysphagia. It is a symptom of swallowing dysfunction that not only deprives people of the pleasure from eating but also endangers patient health by creating a risk of aspiration pneumonia and malnutrition[15,16]. It is related to a number of factors such as direct impact of the tumor, cancer resection, chemotherapy, and radiotherapy and to newer therapies such as epidermal growth factor receptor inhibitors[17]. Concomitant oral complications such as xerostomia may exacerbate subjective dysphagia[17].

Oral candidiasis is one of the most common opportunistic infection of the oral cavity[18,19]. Oral candidiasis manifested as acute or chronic disease and either superficial or disseminated systemic mycosis. It has been associated with multiple host risk factors and it is common in patients with head and neck cancers, especially during chemotherapy and radiotherapy. It usually manifest as acute erythematous candidiasis, but the diagnosis may often be missed, as it may be mistaken for radiation mucositis[20].

Last but not least, another important complication is orofacial pain. It may be caused by cancers or cancer-related therapy. The incidence of pain varies widely based on the patient population and the type of treatment. The most common etiology of cancer pain is local tumor invasion (primary or metastatic), involving inflammatory and neuropathic mechanisms. As malignant disease advances, pain usually becomes more frequent and more intense. Additional expressions of orofacial cancer pain include distant tumor effects, involving paraneoplastic mechanisms. Pain secondary to cancer therapy varies with the treatment modalities used: chemo-radiotherapy protocols are typically associated with painful mucositis and neurotoxicity. Surgical therapies often result in nerve and tissue damage, leading, in the long term, to myofascial and neuropathic pain syndromes[21,22].

Considering our limited understanding of the burden of illness in the oral cavity from various cancer therapies and how it impacts the quality of life of the patient undergoing cancer therapy, we performed the systematic orofacial assessment of patients undergoing chemotherapy. It is essential knowing the patient and act promptly, through the identification and treatment of oral complications, thus allowing better comfort and results of therapy in patients undergoing cancer treatment.

Methods

Patients

This study was conducted from January 2015 to April 2016, at a local hospital. Were evaluated 28 patients with cancer diagnosis. All subjects were informed about purposes of the study and provided written informed consent. The study was approved by the Ethics Committee (n. 1.684.653). Inclusion criteria were patients with solid tumors undergoing chemotherapy treatment. Exclusion criteria for this study were cognitive impairment, patients undergoing radiotherapy concomitant chemotherapy, patients who received treatment for oral complications previously, and patients with cognitive deficit.

Assesments

The study involved a retrospective analysis of data on the demographic characteristics of the study population, clinical diagnosis of cancer as well as treatment used, which were obtained from medical records. Cross-sectional study was also performed to evaluate the stomatognatic system from dental history data, orofacial physical examination, clinical tests for dysphagia diagnostics[23], questionnaires for the evaluation of xerostomia[24,25] and quality of life related to oral health[26]. The socio-economic class[27] of all patients was determined. All the evaluations were performed between 7-14 days after the first day of chemotherapy[28]. They were applied to all patients equally by an experienced and trained dentist.

Instruments of evaluation:

1. Standardized clinical form to obtain information on patient demographics, their medical history and presence of chronic diseases as covariates, type of cancer presented by each patient and treatment which was submitted (information obtained from medical records). Further, were assessed the stomatognathic system, from the data of dental history and orofacial physical examination[22]. This data was

assessed to assess the presence of the signs and symptoms of oral changes and/or oral complications of cancer treatment.

2. Oral mucositis (OM) and its severity were assessed according to the classification of the World Health Organization – WHO[29].

3. Clinical diagnostic tests for dysphagia[23], and characterization of orofacial pain, when presented.

4. Xerostomia Questionnaire which consists of eight questions. To evaluate the feeling of dryness in the patient's mouth[24,25.] Based on the severity of the symptoms, the patients were classified as xerostomic or not. Xerostomia was considered for averages values > 2[30], according to the visual analogue scale (VAS).

5. Questionnaire of oral health impact profile[26] (Oral Health Impact Profile - OHIP). The OHIP was developed to provide a comprehensive measurement of dysfunction, discomfort and disability attributed to oral health. The OHIP-14, wich was used in this study, contains 14 items that are grouped into seven dimensions of impact: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. The participants respond to each item according to the frequency of the impact on a 5-point Likert scale (ranging from 0 to 4): never, hardly ever, occasionally, fairly often, and very often.

6. Questionnaire socioeconomic ABA-ABIPEME[27] to evaluation the socioeconomic class of the population studied.

Statistical analysis

A descriptive study was made for the demographic, oncologic and associated comorbities and oral complaints data. In order to relate oral complications with the patients values of gingival index (GI) the Fisher's exact test was used and to study possible relations between oral complication and plaque index (PI), CPOD index and OHIP evaluations, the Wilcoxon test was applied.

Results

Demographic data

Twenty eight patients with solid tumors with chemotherapy indication were assessed, 05 (17.86%) men and 23 (82.14%) women, with a mean of 54.5±12.46 years (ranging from 31 to 77 years). The general characteristics are presented in Table 1.

Table 1. Socio-demographic and clinical data variables description of cancer patients (n=28)

Demographic data	**Study Group n=28**
Sex n(%)	F=23 (82.14) M=5 (17.86)
Age (mean ± SD) **(minimum-maximum)**	54.5 ±12.46 (31-77)
Socioeconomic class n(%)	
A	0 (0)
B	13 (46.43)
C	13 (46.43)
D	2 (7.14)
E	0 (0)

n = number of patients; %= relative frequency in percentage; F=Female; M=Male; SD=standard deviation.

Oncologic disease characteristics

Breast cancer was the most frequent site of tumor n=19 (67.8%), followed by gastrointestinal n=3(10.7%) and sarcoma n=2(7.1%). The prevalent diagnostic time was until 3 months n=15(53.5%) at the moment of dental assessment. There was predominance of adjuvant treatment n=17(60.7%). And the most prevalent chemotherapeutic agent was doxorubicin n=20(71.4%).

Twenty-two (78.5%) patients have some comorbidity. Eleven (39.2%) of them had only 1 and eleven (39.2%) had 2 or more comorbidities. The most prevalent morbidity associated was hypertension n=13(46.4%) and gastritis n=7(25%). In consequence, there was predominance of current use of

antihypertensive drugs n=14(50%) and antacid n=7(25%). The oncologic disease characteristics and comorbidities of all patients are detailed in Table 2.

Table 2. Oncologic diseases characteristics and associated comorbidities

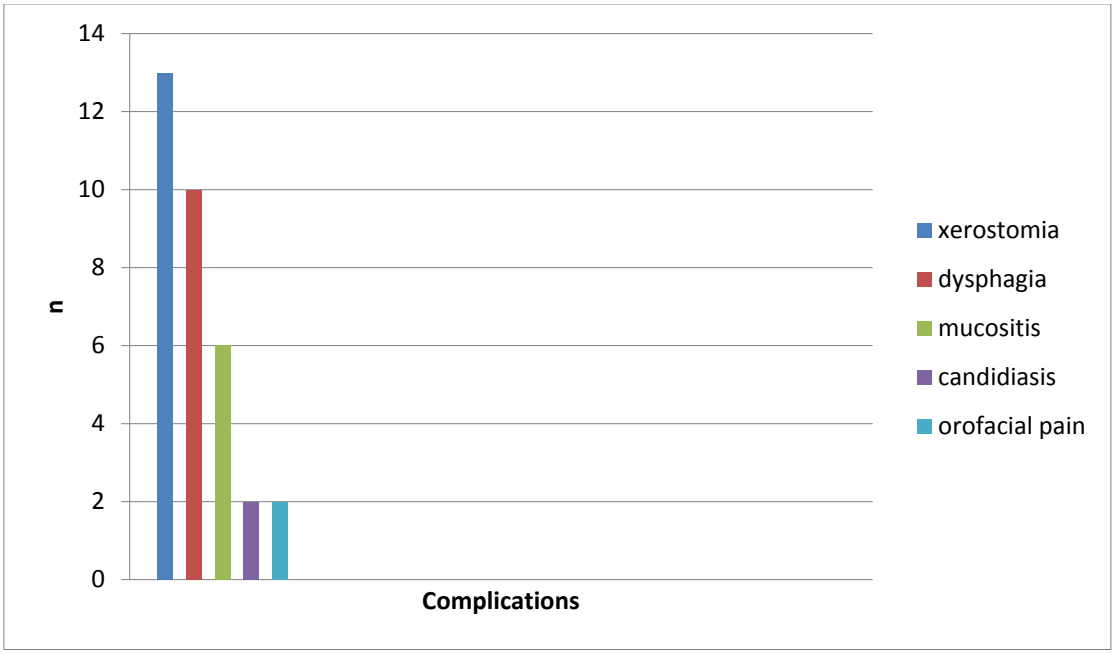
Variables	**n (%)**
Tumor site	
Breast	19 (67.86)
Gastrointestinal	3 (10.71)
Sarcoma	2 (7.14)
Colo Uterino	1 (3.57)
Lung	1 (3.57)
Gall Bladder	1 (3.57)
Mediastinal neuroendocrine	1 (3.57)
Diagnostic time	
<3 months	15 (53.57)
3-6 months	9 (32.14)
6-12 months	1 (3.57)
>12 months	3 (10.71)
Treatment	
Adjuvant	17 (60.71)
Curative	4 (14.29)
Neoadjuvant	2 (7.14)
Palliative	5 (17.86)
Chemotherapeutic agent	
Doxorubicin	20 (71.43)
Cisplatin	5 (17.86)
Fluorouracil/leucovorin/oxaliplatin	3 (10.71)
Presence of associated disease	
No one	6 (21.43)
1	11 (39.29)
2 or more	11 (39.29)
Drugs	
Antihypertensive	14 (50)
Analgesic	3 (10.71)
Anticonvulsant	2 (7.14)
Antibiotic	1 (3.57)
Non-steroidal anti-inflammatory	1 (3.57)
Antacid	7 (25)
Thyroid	2 (7.14)
Antidepressant	1 (3.57)
Hypoglycemic	1 (3.57)
D vitamin	1 (3.57)
Antiviral	1 (3.57)
None	5 (17.86)

n= number of patients; %=relative frequency in percentage

Oral complaints and complications evaluation

In this study, 18 participants (64.2%) had, at least, one oral complaint and/or complication resulting from chemotherapy, while 10 (36.8%) had never noticed no change in the oral cavity. The most prevalent oral complication was xerostomia n=14 (50%), followed by dysphagia n=10 (35.7%), mucositis n=6 (21.4%), candidiasis n=2 (7.1%) and orofacial pain n=2 (7.1%). The oral complications are shown in figure 1.

Figure 1: Presence of oral complications



Oral Health Data

About the oral health data, the gingival index 1 was the most prevalent, n=15(52.7%) patients. The mean plaque index was 25.6% (range from 1.78 to 100%) and the mean CPOD index was 15.48 (range from 2 to 26). Observing the patients in relation to the development of oral complication, the statistical analyses indicated that the group with oral complication (n=18) and without oral complication (n=10) were different related to CPOD index ($P<0.05$). In relation to gingival index (GI) and plaque index (PI) no statistically significant association could be determined ($p>0.05$). The oral health characteristics divided into these two groups, with or without oral complications, are shown in Table 4.

Table 4. Oral Health Characteristics

Variable	With Oral Complication (n=18)	Without Oral Complication (n=10)	P-value
Gingival Index			
0	0 (0)	1 (10)	
1	10 (55.56)	5 (50)	0.6300
2	8 (44.44)	4 (40)	
Plaque index			
Mean	25.85	25.43	0.0717
Standard Deviation	18.83	29.82	
Maximum	69.04	100	
Minimum	3	1.78	
CPO-d			
Mean	15.06	15.9	
Standard Deviation	4.90	7.42	0.0006
Maximum	24	26	
Minimum	5	2	

n= number of patients; If the p-value is inferior to 0.05 the equality between groups is rejected, if not, the equality is not rejected.

Oral health-related quality of life (OHIP-14)

In the OHIP-14 questionnaire, the patients with oral complications scored worse compared with the patients without oral complications. The questions 2 and 4 that refer change in taste and feeding discomfort had the highest mean values noticed in both groups, with and without oral complications. Change in taste (0.6 versus 0.33) and feeding discomfort (0.77 versus 0.4), respectively. However, with regard to the functional disability (question 12) and difficulty in performing daily tasks (question 14) were not reported by any patient. Evaluation of oral health-related quality of life (OHIP-14) with the values of all questions for cancer patients (n=28) with oral complications and without oral complications are shown in Table 5.

About all domains of the OHIP-14 questionnaire (Table 6), patients with oral complications showed a mean OHIP-14 index of 0.44, while those who did not develop oral complications had a mean OHIP-14 of 0.23. The domains functional limitation (0.66 versus 0.45) and physical pain (0.9 versus 0.43)

showed significant differences in relation to the patients with oral complications and patients without oral complications.

Table 5. Evaluation of oral health-related quality of life (OHIP-14) in cancer patients (n=28)

Questions	With Oral Complication (n=18) M(SD)	Without Oral Complication (n=10) M(SD)	p-value
1. Had trouble pronouncing words	0.06 (0.24)	0.15 (0.25)	NA
2. Felt that sense of taste had worsened	0.6 (0.6)	0.33 (0.55)	0.2525
3. Had painful aching in mouth	0.13 (0.24)	0.03 (0.11)	NA
4. Was uncomfortable when eating foods	0.77 (0.52)	0.4 (0.56)	0.3085
5. Has been feeling self-conscious	0,3 (0,51)	0.14 (0.3)	NA
6. Has felt tense	0.18 (0.38)	0 (0)	NA
7. Diet has been unsatisfactory	0.26 (0.41)	0.1 (0.22)	NA
8. Has had to interrupt meals	0.13 (0.28)	0.1 (0.2)	NA
9. Finds it difficult to relax	0.23 (0.55)	0 (0)	NA
10. Has been a bit embarrassed	0.22 (0.42)	0.28 (0.54)	NA
11. Has been irritable with other people	0.17 (0.41)	0 (0)	NA
12. Has had difficulty during usual jobs	0 (0)	0 (0)	NA
13. Has found life less satisfying	0.07 (0.19)	0.12 (0.37)	NA

14. Has been totally unable to function	0 (0)	0(0)	NA

n= number of patients; M=mean; SD=Standard Deviation; If the p-value is inferior to 0.05 the equality between groups is rejected, if not, the equality is not rejected. NA= not applicable due to the fact that the numbers of zeros on the sample was greater them 50%.

Table 6. Oral health-related quality of life (OHIP-14) in cancer patients (n=28)

Domains	With Oral Complication (n=18) M(SD)	Without Oral Complication (n=10) M(SD)	p-vaue
Functional limitation	0.66 (0.58)	0.45 (0.68)	0.0889
Physical pain	0.9 (0.54)	0.43 (0.54)	0.2525
Psychological discomfort	0.48 (0.64)	0.14 (0.3)	NA
Physical disability	0.39 (0.48)	0.2 (0.35)	NA
Mental disability	0.46 (0.61)	0.28 (0.53)	NA
Social disability	0.17 (0.41)	0 (0)	NA
Handicap Overall	0.07 (0.19)	0.12 (0.37)	NA

n= number of patients; M=mean; SD=Standard Deviation; If the p-value is inferior to 0.05 the equality between groups is rejected, if not, the equality is not rejected. NA= not applicable due to the fact that the numbers of zeros on the sample was greater them 50%.

Discussion

The orofacial systematic clinical evaluation in patients undergoing chemotherapy is crucial to the knowledge of the disease process determinants and definition of therapeutic strategies in these patients. One advantage of the present study was the global systematic dental assessment performed between 7-14 days after the beginning of cancer therapy. This is the highest period of incidence of oral complications[28]. The evaluations included a systematic assessment from dental history data, orofacial physical examination, clinical tests for dysphagia diagnostics[23] and questionnaires for the evaluation of xerostomia[24,25] and quality of life related to oral health[26.] Moreover, the socio-economic class of all patients was determined[27].

Of note, the most prevalent oral complication was xerostomia. Their prevalence and negative effects on the patient's quality of life require the physician to confront the issue[15]. This oral complication was found in 43,3% of our patients, contrasting with previous study[6] when dry mouth was found in 10.58% of the cases and it was the second most prevalent oral complication. In agreement with the level of scientific evidence which evaluates the various substances employed in the treatment or clinical management of patients with hypersalivation/xerostomia, more clinical studies are needed to evaluate the drugs, substances, and techniques which are presented as useful therapies for these pathologies[15].

In our trial, we found that most of patients were female (80%) similarly of others studies[6,24]. In relation to age group, our research corroborates the literature, which reports a higher incidence of cancer from the 5th decade on[6]. We found a mean of 54,83 ±11,92 years old (range from 31 to 77).

We found a significant association between quality of life (OHIP-14) and oral complications. Patients with oral complications showed an average in OHIP-14 of 1.36, while those who did not develop oral complications had a mean of 0.56. This find is in line with previous studies that showed correlations between oral complications and poor index of quality of life[2,5] .

Based on the results of this study, we can conclude that several different oral complications were observed in the population analyzed, and xerostomia was the most frequent manifestation. Patients who developed oral complications had worse quality of life and belong to class B or C.

In conclusion, this study reinforces the importance of the dentist in the multidisciplinary team for cancer treatment, either in the diagnostic phase or during treatment in order to provide the patient a complete and effective treatment.

References

1. Epstein JB, Thariat J, Bensadoun RJ, Barasch A, Murphy BA, Kolnick L, Popplewell L, Maghami E.Oral Complications of Cancer and Cancer Therapy: From Cancer Treatment to Survivorship. Ca Cancer J Clin. 2012;62(6):400–22.

2. Brennan MT, Elting LS , Spijkervet LK. Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: methodology and quality of the literature. Support Care Cancer. 2010;18:979–84.

3. Cooperstein E, Gilbert J, Epstein JB, Dietrich MS, Bond SM, Ridner SH, Wells N, Cmelak A, Murphy BA. Vanderbilt Head and Neck Symptom Survey version 2.0: report of the development and initial testing of a subscale for assessment of oral health. Head Neck. 2012;34(6):797-804.

4. Moslemi D, Nokhandani AM, Otaghsaraei MT, Moghadamnia Y, Kazemi S, Moghadamnia AA. Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature. Radiother Oncol. 2016;120(1):13-20.

5. Kapoor V, Basur S, Pandey A. Chemotherapy and Oral Complications - The Most Neglected Side of Cancer. J Adv Med Dent Scie Res. 2015;3(1):71-80.

6. Magnabosco Neto AE, Westphalen FH**.** Analysis of oral complications related to cancer therapy. Arch Oral Res. 2013;9(2):159-64.

7. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. Clin Infect Dis. 2002;34(11):1524–29.

8. Bousaadani AE , Eljahd L , Abada R , Rouadi S , Roubal M , Mahtar M. Prevention and treatment of mucositis in children with oral cancers: Practical recommendations . Cancer Radiother. 2016,20(3):226-30.

9. Scully C, Sonis S, Diz PD. Oral mucositis. Oral Diseases. 2006;12:229–41.

10. Hayashi H, Kobayashi R, Suzuki A, Yamada Y, Ishida M, Shakui T, Kitagawa J, Hayashi H, Sugiyama T, Takeuchi H, Tsurumi H, Itoh Y. Preparation and clinical evaluation of a novel lozenge containing polaprezinc, a zinc-L-carnosine, for prevention of oral mucositis in patients with hematological cancer who received high-dose chemotherapy. Med Oncol. 2016;33(8):91.

11. Pinna R, Campus G, Cumbo E, Mura I, Milia E. Xerostomia induced by

radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage. Ther Clin Risk Manag. 2015;4(11):171-88.

12. Eveson, JW. Xerostomia. Periodontology 2000. 2008;48:85–91.

13. Turner L, Mupparapu M, Akintoye SO. Review of the complications associated with treatment of oropharyngeal cancer: a guide for the dental practitioner. Quintessence Int. 2013;44(3):267-79.

14*. Mortazavi S, Imanimoghaddam M, Davachi B, Pakfetrat A, Alimohammadi M.* Evaluation of Magnetic Resonance sialography and Ultrasonography findings in Salivary Glands of patients with xerostomia. Cumhuriyet Dent J. 2016;19(1):23-34.

15. Miranda-Rius J, Brunet-Llobet L, Lahor-Soler E, Farré M. Salivary Secretory Disorders, Inducing Drugs, and Clinical Management. Int. J. Med. Sci. 2015;12(10):811-24.

16. Noll SF, Bender CE, Nelson MC. Rehabilitation of patients with swallowing disorders. In: Braddom RL (ed.): Physical Medicine and Rehabilitation, 1st ed. Philadelphia: W.B. Saunders. 1996, 533–54p.

17. Raber-Durlacher JE, Brennan MT, Leeuw IMVD, Gibson RJ, Eilers JGE, Waltimo T, Casper P. Bots CP, Michelet M, Sollecito TP, Rouleau TS, Sewnaik A, Bensadoun RJ, Fliedner MC, Silverman Jr S, Spijkervet FKL. Swallowing dysfunction in cancer patients. Support Care Cancer. 2012;20:433–43.

18. Coronado-Castellote L, Jimenez-Soriano Y. Clinical and microbiological diagnosis of oral candidiasis. J Clin Exp Dent. 2013;5(5):279–86.

19. Melkoumov A, Goupil M, Louhichi F, Raymond M, de Repentigny L, Leclair G. Nystatin nanosizing enhances in vitro and in vivo antifungal activity against *Candida albicans*. J Antimicrob Chemother. 2013;68(9):2099–2105.

20. Epstein JB, Polsky B. Oropharyngeal candidiasis: a review of its clinical spectrum and current therapies. Clin Ther. 1998;20(1):40–57.

21 Epstein JB, Elad S, Eliav E, Jurevic R, Benoliel R. Orofacial Pain in Cancer: Part II—Clinical Perspectives and Management. JDR. 2007;86(6):506-18.

22. Siqueira, JTT de; Jales, S, Vilarim R. de CB. [Dor orofacial e cuidados paliativos orais em pacientes com câncer]. Onco&. 2013;25-28. Portuguese.

23. Meng-Chun WU, Yeun-Chung C, Tyng-Guey W, Li-Chan LIN. Evaluating Swallowing Dysfunction Using a 100-ml Water Swallowing

Test.Dysphagia.2004;19:43–47.

24. Fox PC, Busch KA, Baum BJ. Subjective reports of Xerostomia and objective measure of salivary gland performance. J Dent Association. 1987;115:581-84.

25. Pai S, Ghezz EM, Ship JA. Development of a visual analogue scale questionnaire for subjectiove assessment of salivery dysfuncton. Oral surg Oral Med Oral Pathol Oral Radiol Endod. 2001;3:311-16.

26. Slade GD, Spencer AJ. Development and evaluation of the Oral Health Impact Profile. Community Dent Health. 1994;11:3-11.

27. Almeida PM, Wickerhauser H. [Critério ABA (Associação Brasileira de Anunciantes) e ABIPEME (Associação Brasileira dos Institutos de Pesquisa de mercado)]. 1991;1-29p. Portuguese.

28. Wong HM. Oral Complications and Management Strategies for Patients Undergoing Cancer Therapy. The Scientific World Journal. 2014;7:1-14.

29. World Health, Organization. Handbook for reporting results of cancer treatment. Geneve:. World Health Organization. 1979;15–22p.

30. Gomes AO, Torres SR, Maiolino A, Dos Santos CW, Silva Junior A, Correa ME,Moreira MC, Gonçalves Lde S. Early and late oral features of chronic graft-versus-host disease. Rev Bras Hematol Hemoter. 2014;36(1):43-9.

4.3 Artigo 3

Does periodontal inflammation impact oral mucositis?

CP Novaes[1], MGAM Chaves[1], AM Coelho[2], AE Hallack Neto[3], JTT Siqueira[4], GM Fabri[1]

[1] Dentistry School, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[2] Institute of Exact Sciences, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[3] School of Medicine, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[4] Oral Facial Team, Clinica Hospital, School of Medicine, Universidade de São Paulo, São Paulo, Brazil

*Correspondence:

Gisele Maria Campos Fabri

Faculdade de Odontologia da Universidade Federal de Juiz de Fora

Rua José Lourenço Kelmer s/n- São Pedro, Juiz de Fora – MG

CEP 36036-900 - Brazil

Tel: 55-(32) 3025-3065

gisele.fabri@ufjf.edu.br

Running title: Periodontal inflammation and oral mucositis

Background: Periodontal disease and oral mucositis are immunoinflammatory conditions characterized by constant presence of systemic inflammation and bacteremia. **Objectives:** Evaluate the impact of periodontitis in oral mucositis (OM) in patients undergoing chemotherapy for solid tumors and scheduled for hematopoietic stem cell transplantation (HSCT). **Methods:** Evaluation of demographic data, data chemotherapy and comorbidities, and global systematic dental assessment, were assessed. The assessments were obtained prior and between 7-14 days after initiated chemotherapy in periodontal health group (PH group). Periodontal disease Group (PD Group) was evaluated only between 7-14 days of chemotherapy. Oral mucosa was examined for scoring of chemotherapy-induced OM. **Results:** PH Group included 33 patients and PD Group enrolled 18 patients. The distributions of patients with incidence of OM did not differ between both groups. Sixteen(31%) patients developed OM, 9(56.2%) underwent conditioning regimen prior HSCT, 7(43.7%) in common chemotherapy for solid tumors. **Conclusion:** This study demonstrated that oral health, apparently, could affect experience and incidence of chemo-induced OM. When only patients periodontally healthy undergone conditioning regimen of therapy and conventional chemotherapy were observed, was noted a lower incidence of OM, when compared with scientific evidences. The need of inclusion of patients with severe periodontitis to evaluate this relationship hampers such trial.

Keywords: oral mucositis; chemotherapy; oral health; periodontitis; inflammation

Introduction

The term periodontal disease (PD) comprises a group of inflammatory diseases that affects the structures of tooth protection (classified as gingivitis) and tooth supporting (classified as periodontitis) (Di Benedetto *et al*, 2013). It is characterized as a chronic immunoinflammatory disease of multifactorial etiology, with local and systemic factors enrolled. The clinical appearance of periodontal diseases are caused by bacterially derived factors and antigens that stimulate a local inflammatory reaction and activation of the innate immune system (Graves and Cochran, 2003), with periods of exacerbation and remission, resulting in an inflammatory and immune response of the host to the presence of specific bacteria and their products (Loe *et al*, 1978; Hugson and Jordan 1982; Bælum *et al*, 1988; Brown *et al*, 1990; Almeida *et al*, 2006 Ceppi *et al*, 2006). The regulation of the immunoinflammatory response depends of high local and serum levels of cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), prostaglandin E2 (PGE2) and tumor necrosis factor (TNF) that trigger release of C-reactive protein from the liver, thus contributing to systemic inflammation (Burt, 2005; Bartold *et al*, 2010; Lima and Lara, 2013; Chapple and Genco, 2013). These cytokines mediate periodontal tissue destruction by stimulating bone resorption. The enhancing or attenuating the inflammatory response in periodontal tissues, determining the activity or the latency of periodontal lesions (Ohlrich *et al*, 2009). In addition to this important insidious inflammatory response, PD often constitutes an important source of infection, can lead to bacteremia and have numerous other systemic effects, including making patients with chronic and serious diseases refractory to treatment (Siqueira and Teixeira, 2001; Holmstrup and Glick, 2002; Raber-Durlacher *et al*, 2002; Tunkel and Sepkowitz, 2002; Fabri *et al*, 2009; Fabri *et al*, 2014).

Periodontitis and oral mucositis are immunoinflammatory conditions that can be characterized by the constant presence of systemic inflammation and bacteremia (Enwonwu and Salako, 2012; Coracin *et al*, 2013; Chapple and Genco, 2013; Al-Ansari *et al*, 2015). These conditions are prevalent in patients receiving cancer therapy, which could lead them to a greater risk of systemic complications (Turner *et al*, 2013).

The term “mucositis” was created in 1980 to describe inflammation of the oral mucosa in patients undergoing radiotherapy or chemotherapy (Sonis, 2004). Actuallly, oral mucositis is considered to be the most severe non-hematological complication of anticancer treatment (Curado *et al*, 2014; Chaveli-López and Bagán-Sebastián, 2016; Hayashi *et al*, 2016; Chaudhry *et al*, 2016). Severe oral mucositis may serve as a dose-limiting factor , can thus necessitate modification or even an interruption in the course of radiotherapy or chemotherapy (Sonis *et al*, 2001; Ruescher *et al*, 1998; Scully *et al,* 2003; Lambertz *et al,* 2010; Gussgard *et al*, 2014; Gerecke *et al*, 2016). The clinical manifestations of OM include signs and symptoms of inflammation, varying from mild erythema, edema or ulceration. The symptoms ranging from mild burning sensation to large and painful ulcers that limit basic oral functions such as speech, the swallowing of saliva or eating, resulting in dehydration, malnutrition and opportunistic infections (Sonis *et al*, 2001; Ruescher *et al*, 1998; Parulekar *et al*, 2012; Coracin *et al*, 2013; Gussgard *et al*, 2014; Chaveli-López and Bagán-Sebastián, 2016). The pathogenesis of oral mucositis involves the production of various inflammatory mediators and proteins such as such as tumor necrosis factor TNF-α, Interleukin-1β (IL-1β) and interleukin-6 (IL-6), that lead to apoptosis and the cascade of events tissue damage (Sonis *et al*, 2004). This pathophysiological process of OM shows similarities with the setup mechanism of PD. It is proposed that both conditions are characterized by an exuberant inflammatory reaction, regulated by an infiltration of immune cells, enzymes and proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukins, which result in both soft and hard tissue destruction (Ohlrich *et al*, 2009; Savioli *et al*, 2012; Lima and Lara, 2013).

Indeed, studies have shown that elevated plaque levels and gingival inflammation are correlated with the incidence of oral mucositis, reinforcing the idea that inflammation as a predictor of incidence of mucositis and delayed wound healing (Santos *et al*, 2011; Coracin *et al*, 2013; Khaw *et al*, 2014). This fact is especially important in patients undergoing cancer treatment, which may have varying degrees of immunosuppression, greatly increasing the risk for bacterial infections (particularly dental infections) (Raber-Durlacher *et al*, 2002; Tunkel and Sepkowitz, 2002; Van Der Velden *et al*, 2014).

However, the scientific evidence is not completely established on this interrelationship. Therefore, the objective of this research was to evaluate the impact of periodontal disease in oral mucositis in patients undergoing chemotherapy for solid tumors and scheduled for hematopoietic stem cell transplantation (HSCT). Based on this knowledge, we can contribute to a better prognosis and survival and reduce the costs of hospitalization and drugs impacting positively in clinical oncology.

Materials and Methods

Fifty-one consecutive patients with solid tumors (n=35) and scheduled for hematopoietic stem cell transplantation (HSCT) (n=16) were referred from regional hospitals for regularly followed up at the Dentistry School. These patients had undergone chemotherapy with the following drugs: cisplatin; doxorubicin; fluorouracil/leucovorin/oxaliplatin; melphalan; fludarabine/busulfan; fludarabine/melphalan; leucovorin/etoposide/ara-C/melphalan. Exclusion criteria were edentulous patients, chemo-radiotherapy, radiotherapy, chemotherapeutic agents that differs from those defined in the inclusion criteria, patients who do not complete the cycle of chemotherapy due to death or abandonment of treatment and / or study, and cognitive disorders. Moreover, patients diagnosed with severe periodontitis, when chemotherapy regime had been discontinued. The local ethical committee approved this study number 1.684.653, and an informed consent was obtained.

This study included an evaluation of demographic data (age, sex, socio-economic class (Almeida and Wickrhauser, 1991), clinical and histopathological diagnosis of diseases, data chemotherapy and comorbidities, that were obtained from medical records, and a global systematic dental assessment.

The global systematic dental assessment included: orofacial clinical features, general dental condition (Siqueira and Teixeira, 2001) and periodontal assessment (American Academy of Periodontology, 1999). Periodontal evaluation was performed by an expert dentist. Evaluation included 3 standardized epidemiological indices: dental plaque index (PI) (Aynamo and Bay, 1975), gingival bleeding index (GBI) (O'leary, 1967), and clinical attachment level (CAL) (American Academy of Periodontology, 1999). Clinical

attachment level included 2 measures: probing pocket depth (PPD) and cementoenamel junction (CEJ) at 6 sites per tooth (American Academy of Periodontology, 1999). Dental plaque index was used to evaluate the level of oral hygiene, which was calculated according to the number of dental surfaces stained by a dental plaque disclosing agent, multiplied by 100 and divided by the total number of surfaces. Gingival bleeding index was used to evaluate gingival inflammation and was expressed as the number of bleeding surfaces after probing with a periodontal probe, which was then multiplied by 100 and divided by the total number of surfaces. Probing pocket depth was determined as the distance from the bottom of the pocket to the gingival margin. Cementoenamel junction was measured as the distance from the gingival margin to the CEJ, identifying hyperplasia (negative values) or recession (positive values). Clinical attachment level was calculated as the sum of PPD and CEJ. Gingival index (GI) was used to record changes in the shape and contour of the periodontal tissues, classified into values of 0 to 4, in which 0-1 are considered to gingival health (Silness and Loe, 1964).

Periodontal disease was defined by clinical features according to the presence of concomitant edema, erythema, gingival bleeding and/or suppuration on probing, and periodontal probing depths, according to the American Academy of Periodontology (Armitage, 1999). Using this classification, the severity of PD was categorized based on the amount of CAL: mild, 1 to 2 mm; moderate, 3 to 4 mm; and severe, 5 mm or greater.

The assessments were obtained prior and between 7-14 days after initiated chemotherapy in periodontal health group (PH group). The Periodontal disease Group (PD Group) was evaluated also between 7 to 14 days after the first day of chemotherapy.

The oral mucosa also was examined by a single examiner for scoring of chemotherapy-induced oral mucositis. The examination was performed 7-14 after the start of chemotherapy. In case of a clinical diagnosis, these were established for each patient according to the World Health Organization (WHO) system (Sonis and Fey, 2002). This study was limited to “acute mucositis” which occurs during active therapy with no intention of capturing potential mucositis that can occur in other period or delayed consequences of mucositis (Khaw *et al*, 2014).

Statistical Analysis

The data were analyzed accordingly to its nature: the quantitative demographic data (age) and the periodontal attachment data (PPD, CAL and CEJ) were analyzed using the Wilcoxon Test; while the qualitative demographic data (gender and socio economic class), the data on diseases characteristics, comorbidities and drugs, were all analyzes by the Fisher's Exact Test. The Periodontal inflammatory parameters (PI and GBI) were studied in 2 parts, first the groups with periodontal health before and after chemotherapy were compared using the Sign Test for paired samples, than the groups with periodontal health (each one) and the group with periodontal disease were compared using the Wilcoxon Test.

The information between groups with periodontal health before and after chemotherapy was analyzes using the Sign Test for paired data. For the information between groups with periodontal health with oral mucositis, periodontal health without oral mucositis, periodontal disease with oral mucositis and periodontal disease without oral mucositis the Krushal-Wallis Test was performed, along with its multiple comparison test, when necessary.

Results

1. General Features and Disease Profile

Fifty-one consecutive patients with solid tumors and scheduled for hematopoietic stem cell transplantation were assessed. The mean $\pm$ standard deviation age, in years, was 51.12 $\pm$ 14.86 (range 14-77 y) and 38(74.5%) were female. Socio-economic Class C 22(43.1%) was prevalent.

The primary tumor site was most commonly breast cancer 21(41.1%). Followed by multiple myeloma 6(11.7%) and gastrointestinal cancer 5(9.8%). About the diseases and therapy, the most frequent diagnostic periods were longer than 12 months 19(37.2%) and less than 3 months 18(35.2%); curative treatment 22(43.1%) and adjuvant 19(37.2%); and the most prevalent chemotherapeutic agent was doxorubicin 22(43.1%), followed by cisplatin and melphalan 6(11.7%), each one. In relation to co-morbidities the study showed

32(62.7%) patients that had one or more co-morbidities, 17(33.3%) had 1 type and 15(29.4%) 2 or more associated morbidities. The most prevalent morbidity associated and drugs were hypertension 20(39.2%) and antihypertensive drugs 22(43.1%), respectively.

2. Global Evaluation of Patients in Chemotherapy According to the Presence or Absence of Periodontal Health

2.1. Demographic data

The periodontal health group (*PH Group*), included 33 patients with mean age of 49.24±16.18 years (14-73 y) composed by 9 (27.2%) men and 24(72.7%) women. The periodontal disease group (*PD Group*) enrolled 18 patients, 4 (22.2%) men and 14 (77.8%) women with mean age of 54.55±11.71 years (35-77 y). The statistical analysis led to the conclusion that the groups were similar as to the gender and social economic class, but differed in age, the Wilcoxon test indicates that the periodontal disease group presented older patients than the periodontal health group.

2.2. General characteristics of diseases, comorbidities and drugs

In relation to co-morbidities the PH Group showed 20(60.6%) patients that had one or more co-morbidities, and the PD Group showed 12(66.6%) patients with these findings. Eleven (33.3%) have 1 type and 9(27.2%) 2 or more associated morbidities in the first group; and 6(33.3%) for one, 2 or more comorbidities in PD Group. The most prevalent morbidity associated and drugs were similar for patients with health or periodontal disease. Hypertension [11(33.3%) versus 9(50%)] and gastritis [5(15.1%) versus 3(16.6%)], antihypertensive drugs [13(39.3%) versus 9(50%)] and antacid [6(18.1%) versus 4(22.2%)], respectively.

The statistical analyses led to the conclusion that both groups are similar when it comes to its characteristics of diseases, comorbidities and drugs; but the two groups differed as to the distribution of patients accordingly to diagnostic period. In this case, PH group distribution favored periods less than 6 months and greater than 12 months and PD group favored only period less than 3 months. In relation to chemotherapy agents, 15(45.5%) patients with

periodontal health were in induction and conditioning regimens of therapy primarily in HSCT (Melphalan, Fludarabine/busulfan, Fludarabine/melphalan, Leucovorin/etoposide/ara-C/melphalan). In contrast, in periodontal disease group, only 2(11.1%) of patients used this course of chemotherapy.

The general characteristics and the frequencies of categorical variables related to general characteristics of oncological diseases, for 33 patients of PH Group and for 18 patients of PD group are found detailed in Table 1.

Table I. Demographic characteristics and frequency of categorical variables for all 51 patients according to the presence (*PH Group*) or absence (*PD Group*) of periodontal health

Variables	**Periodontal Health Group (n=33)**	**Periodontal Disease Group (n=18)**	***P*-value**
Gender, n(%)			
Female	23 (69.6)	14(77.8)	0.7444
Male	10 (30.4)	4 (22.2)	
Age (mean)±SD (Minimum-Maximum)	49.24±16.18 (14-73)	54.55±11.71 (35-77)	0.000004
Socio-economic Class, n (%)			
A	0	0	
B	14(42.2)	6(33.3)	0.801
C	13(39.3)	9(50.0)	
D	6 (18.1)	3(16.6)	
E	0	0	
Categorical variables			
Tumor site (%)			
Breast	13(39.4)	8(44.4)	
Uterine cervical	0	1(5.6)	
Gastrointestinal	1(3.0)	4(22.2)	
Lung	0	2(11.1)	
Sarcoma	2(6.1)	0	
Gall Bladder	1(3.0)	0	
Mediastinal neuroendocrine	1(3.0)	0	0.1438
Multiple Myeloma	4(12.1)	2(11.1)	
Non- hodgkin lymphoma	2(6.1)	1(5.6)	
Bone marrow aplasia	2(6.1)	0	
Plasma cell leukemia	1(3.0)	0	
Hodgkin lymphoma	4(12.1)	0	
Acute myeloid leukemia	2(6.1)	0	
Diagnostic Period (%)			

<3months	9(27.3)	9(50.0)	0.01286
3-6 months	8(24.2)	3(16.7)	
6-12 months	0	3(16.7)	
>12months	16(48.5)	3(16.7)	
Treatment (%)			
Curative	18(54.6)	4(22.2)	0.1167
Neoadjuvant	1(3.0)	2(11.1)	
Adjuvant	10(30.3)	9(50.0)	
Palliative	4(12.1)	3(16.7)	
Chemotherapeutic agents (%)			
Cisplatin	3(9.1)	3(16.7)	0.3142
Doxorubicin	14(42.4)	8(44.4)	
Fluorouracil/leucovorin/ oxaliplatin	1(3.0)	4(22.2)	
Melphalan	5(15.2)	1(5.6)	
Fludarabine/busulfan	2(6.1)	0	
Fludarabine/melphalan	4(12.1)	1(5.6)	
Leucovorin/etoposide/ara-C/melphalan	4(12.1)	1(5.6)	

n: number of patients; SD= standard deviation; (%) relative frequency in percentage. If P-value is lower than 0.05 the null hypothesis (equality between groups) is rejected, if not the null hypothesis is not rejected.

2.3. Periodontal assessment for Periodontal Health versus Periodontal Disease

2.3.1. Periodontal attachment parameters (CAL, PPD, CEJ) for PH Group versus PD Group

The statistical analyses led to the conclusion that the mean CAL, PPD and CEJ values were higher for the periodontal disease group.

2.3.2. Periodontal inflammatory parameters (PI, GBI, GI) for PH Group versus PD Group

The statistical analysis indicated that the PI and GBI values were different between periodontal heath groups, both, at baseline and at 7 to 14 days of chemotherapy, and periodontal disease group, relating periodontal disease group with a higher value for both periodontal inflammatory parameters.

The GI periodontal inflammatory parameter behaved the same way as the other two periodontal inflammatory parameters (PI and GBI), by the Fisher's Exact Test. The periodontal attachment parameters (CAL, PPD, CEJ) and the periodontal inflammatory parameters (PI, GBI GI) for PH Group versus PD Group are presented on table 2.

Table 2. Periodontal attachment CAL, PPD and CEJ according to the presence (PH Group) or absence (PD Group) of periodontal health and Periodontal inflammatory parameters PI, GBI and absolute and relative frequencies (in percentage) of GI according to the presence (*PH Group*) or absence (*PD Group*) of periodontal health at baseline and 7-14 of chemotherapy.

Periodontal attachment, (mm)	**PH Group (n=33) at baseline (mean ± SD)**	**PD Group (n=18) 7-14 chemotherapy (mean ± SD)**	***P*-value**
CAL	1.6703±0.2629	2.0922±0.2926	< 0,001
PPD	1.7648±0.3007	2.2372±0.4378	< 0,001
CEJ	0.1088±0.2881	0.1778±0.3045	< 0,001
Periodontal inflammatory parameter, (mm)	**PH Group (n=33) at baseline (mean ± SD)**	**PD Group 7-14 chemotherapy (n=18) (mean ± SD)**	***P*-value**
PI	10.53 ± 10.86	37.41 ± 19.75	> 0.0001
GBI	3.786± 3.03	19.14 ± 7.22	> 0.0001
Periodontal inflammatory parameter, (mm)	**PH Group (n=33) 7-14 chemotherapy (mean ± SD)**	**PD Group 7-14 chemotherapy (n=18) (mean ± SD)**	***P*-value**
PI	14.60 ± 15.19	37.41 ± 19.75	> 0.0001
GBI	5.37 ± 4.93	19.14 ± 7.22	> 0.0001
GI	**PH Group (n=33) at baseline n(%)**	**PD Group (n=18) 7-14 chemotherapy n(%)**	***P*-value**
0	14 (42.42%)	0	< 0.0001
1	18 (54.55%)	4 (22.22%)	
2	1 (3.03%)	14 (77.78%)	
3	0	0	

GI	**PH Group (n=33) 7-14 chemotherapy n(%)**	**PD Group (n=18) 7-14 chemotherapy n(%)**	***P*-value**
0	6 (18.18%)	0	< 0.0001
1	22 (66.67%)	4 (22.22%)	
2	5 (15.15%)	14 (77.78%)	
3	0	0	

CAL: clinical attachment level; PPD: probing pocket depth; CEJ: cementoenamel junction; mm: millimeters; mean: sample mean; SD: sample standard deviation; n: number of patients; Severity of PD: mild: CAL = 1 to 2 mm; moderate: CAL= 3 to 4 mm; and severe: 5 mm or greater. PI: dental plaque index; GBI: gingival bleeding index; GI: gingival index; (%) relative frequency in percentage; If P-value is lower than 0.05 the null hypothesis (equality between groups) is rejected, if not the null hypothesis is not rejected.

2.4. Periodontal assessment follow-up for Periodontal Health Group

2.4.1. Periodontal inflammatory parameters at Baseline and 7-14 days of chemotherapy evaluation for PH Group

The statistical analysis indicated that the PI and GBI values were different between periodontal heath groups at baseline and at 7 to 14 days of chemotherapy. The analysis also showed that the values at 7 to 14 days of chemotherapy were higher than at baseline.

The periodontal inflammatory GI of periodontal health group at base line and at 7 to 14 days of chemotherapy in this table represents the amount of patients that changed GI categories between 7-14 days of chemotherapy. Unfortunately the amount of zeros on the table did not allow the use of Mc Nemar or Stuart-Maxwell test to analyze the whole table at once, so the data was divided into three different sets and then de Mc Nemar test was applied. The test indicated that the patients in the GI category 0 had a higher probability of changing the category than those in categories 1 or 2 had of changing to category 0 ($p = 0.0133$); and those patients in category 1 or 2 had similar probabilities of moving to another category or stay in the same one (p-value > 0.1336).

The analysis of periodontal inflammatory parameters PI and GBI and the GI of periodontal health group at base line and at 7 to 14 days of chemotherapy are displayed on table 3.

Table 3. Periodontal inflammatory parameters PI and GBI and Absolute and relative frequencies (in percentage) of periodontal inflammatory parameter GI of Periodontal Health Group (PH Group) at baseline and undergoing chemotherapy (7-14 days)

Periodontal inflammatory parameters, (mm)	PH Group at baseline (n=33) (mean ± SD)	PH Group 7-14 chemotherapy (n=33) (mean ± SD)	*P*-value
PI	10.53 ± 10.86	14.60 ± 15.19	0.0003
GBI	3.78 ± 3.03	5.37 ± 4.93	0.0046

PH Group at Baseline	**PH Group undergoing chemotherapy (7 – 14 days)**			
GI	**GI 0**	**GI 1**	**GI 2**	**Total**
0	6 (18.18%)	8 (24.24%)	0	14 (42.42%)
1	0	14 (42.42%)	4 (12.12%)	18 (54.55%)
2	0	0	1 (3.03%)	1 (3.03%)
3	0	0	0	0
Total	6 (18.18%)	22 (66.67%)	5 (15.15%)	33 (100%)

PI: dental plaque index; GBI: gingival bleeding index; mm: millimeters; mean: sample mean; SD: sample standard deviation; n: number of patients; GI; gingival index; n: number of patients; (%) relative frequency in percentage. If P-value is lower than 0.05 the null hypothesis (equality between groups) is rejected, if not the null hypothesis is not rejected.

3. Incidence and Grade of Oral Mucositis of Patients in Chemotherapy According to the Presence or Absence of Periodontal Health

3.1. PH Group versus PD Group According to Oral Mucositis Incidence

Fisher's exact test was applied to determine whether the distribution of patients regarding the incidence of oral mucositis differs among periodontal health group and periodontal disease group during 7-14 days of chemotherapy. The test resulted in a P-value equal to 0.7605 ($p>0.05$), that is, the distributions of patients with incidence of oral mucositis did not differ between both groups (Table 4).

About these total 16 (31%) oral mucositis, 9 (56.2%) developed in patients undergoing conditioning regimen prior HSCT, and 7 (43.7%) in patients undergoing common chemotherapy for solid tumors.

3.1.2. PH Group versus PD Group According to Oral Mucositis Grade

To further assess whether the presence or absence of periodontal health could be associated with oral mucositis, Fisher's exact test was performed to verify if the five (0-4) oral mucositis scores differed according to periodontal health group and periodontal disease group during 7-14 days of chemotherapy. No statistically significant association could be determined ($p>0.05$). The majority incidence of grade 1 chemotherapy-induced oral mucositis was observed. The results of Fisher´s exact text with a possible association with the severity of oral mucositis with presence or absence of periodontal health are shown in Table 4.

Table 4: Distribution of patients with Periodontal Health (PH Group) and Periodontal Disease (PD Group) undergoing chemotherapy (7-14 days) according to Oral Mucositis Incidence and according to Oral Mucositis Grade

Oral Mucositis (OM) Incidence	**PH Group (n=33) 7-14 chemotherapy n (%)**	**PD Group (n=18) 7-14 chemotherapy n (%)**		***P*-value**
Absence	22(66.67%)	13 (72.22%)		
Presence	11(33.33%)	5 (27.78%)		0.7605
OM Grade	**PH Group (n=33) 7-14 chemotherapy**	**PD Group (n=18) 7-14 chemotherapy**	**Total n(%)**	***P*-value**
OM grade 0	22(66.67%)	13(72.22%)	35(68.63%)	
OM grade 1	7(21.21%)	4(22.22%)	11(21.57%)	
OM grade 2	3(9.09%)	1(5.56%)	4(7.84%)	
OM grade 3	1(3%)	0(0%)	1(1.96%)	1
OM grade 4	0	0	0	
Total number of subjects	33	18	51	

OM: oral mucositis; n: number of patients; (%) relative frequency in percentage; If P-value is lower than 0.05 the null hypothesis (equality between groups) is rejected, if not the null hypothesis is not rejected.

3.2. Periodontal assessment and follow-up According to the Presence or Absence of Periodontal Health considering Oral Mucositis of Patients in Chemotherapy

3.2.1. Periodontal inflammatory parameters (PI, GBI) for PH Group versus PD Group considering Oral Mucositis

The Kruskal-Wallis test showed that at least two amongst the four groups tested were different for both periodontal inflammatory parameters PI and GBI. The multiple comparison test applied afterwards indicated that the periodontal health group without oral mucositis presented mean PI lower than the periodontal disease groups (without and with oral mucositis). The periodontal health group and periodontal disease groups did not differ amongst themselves.

The results were somewhat different for the GBI parameter, in this case the periodontal health group without and with oral mucositis had the same GBI mean which was lower than the mean GIB found for the periodontal disease group without and with oral mucositis (both with means that did not differ amongst themselves). The values are shown in table 5.

Table 5. Periodontal inflammatory parameters PI and PGI according to the absence or presence of Oral Mucositis in Periodontal Health (PH Group) and Periodontal Disease (PD Group) Groups

Periodontal inflammatory parameter (mm)	**PH Group (n=22) without OM (mean ± SD)**	**PH Group (n=11) With OM (mean ± SD)**	**PD Group (n=13) Without OM (mean ± SD)**	**PD Group (n=5) With OM (mean ± SD)**	***P*-value**
PI	10.79 ± 9.72	22.23 ± 21.08	38.52 ± 22.67	34.53 ± 10.13	< 0.0001
Letter	A	a b	b	b	
GBI	4.75 ± 3.78	6.61 ± 6.73	18.43 ± 7.03	21.01 ± 8.21	< 0.0001
Letter	a	a	b	b	

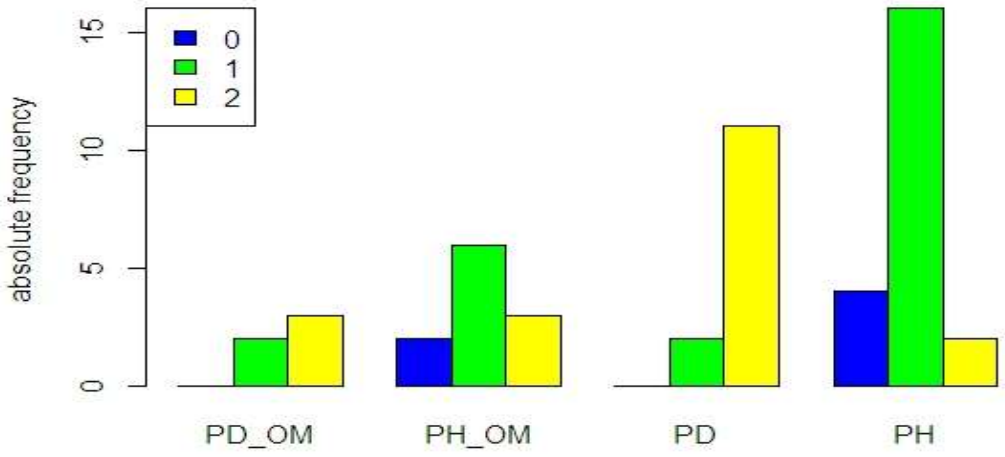
OM: oral mucositis; PI: dental plaque index; GBI: gingival bleeding index; mm: millimeters; mean: sample mean; SD: sample standard deviation; n: number of patients; If P-value is lower than 0.05 the null hypothesis (equality between groups) is rejected, if not the null hypothesis is not rejected; groups followed by different letters differed amongst themselves and groups followed by the same letters did not differ amongst them.

3.2.2. Periodontal inflammatory parameters (GI) for PH Group versus PD Group considering Oral Mucositis

The periodontal inflammatory parameter IG did not present similar distribution for all four groups observed accordingly to the Fisher's Exact Test performed. It was possible to verify that the periodontal disease group without oral mucositis (PD) differed from groups periodontal health without oral mucositis (PH) and periodontal health with oral mucositis (PH_OM) ($p = 0.0003$).

The GI distributions presented on figure 1 indicated that both periodontal disease groups (periodontal disease group without oral mucositis and periodontal disease group with oral mucositis) had more patients on the higher levels of IG and both periodontal health groups (periodontal health group without oral mucositis and periodontal health group with oral mucositis) had more patients on lower levels.

Figure 1: GI inflammatory parameter distribution for the four groups studied: Periodontal health groups without oral mucositis (PH) and with oral mucositis (PH_OM) and periodontal disease groups without oral mucositis (PD) and with oral mucositis (PD_OM)



GI: gingival index used to record changes in the shape and contour of the periodontal tissues, classified into values of 0 to 4, in which 0-1 are considered to gingival health; PH: Periodontal health group without oral mucositis; PH_OM: periodontal health group with oral mucositis; PD: periodontal disease group without oral mucositis; PD_OM: periodontal disease group with oral mucositis; n: number of patients; (%) relative frequency in percentage.

Discussion

This original research assesses the association of periodontal disease and chemotherapy-induced oral mucositis for the first time. Estimates indicate an increase of 72% in the incidence and 78% in mortality (917,300 new cases and 557,800 deaths in 2030) from cancer in Latin America. The cancer incidence patterns observed in Latin American and Caribbean countries are directly related to social and economic inequalities, whereas mortality standards reflect the structure and organization of the health system of each country (Curado *et al*, 2014). Data from this study reinforce these findings; once that the prevalent socio-economic class observed was class C (above US$ 700, monthly) (Almeida and Wickerhauser, 1991). The widespread tumor site for solid tumors in this study was the breast cancer, followed by multiple myeloma scheduled for hematopoietic stem cell transplantation (HSCT). Breast cancer incidence has risen 50% in two decades where there is national or more commonly, regional registry (Bray and Piñeros, 2016). It is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 25% of all cancer cases and 15% of all cancer deaths worldwide (Torre *at al*, 2015). Multiple myeloma accounts for around 1% of all cancers worldwide and 10–15% of all hematological neoplasms (Gerecke *et al*, 2016).

The global evaluation of oncological patients according to the presence or absence of periodontal health (PH) demonstrated that patients are similar according gender, socioeconomic class, prevalence of comorbidity, drugs intake and sort of chemotherapeutic agents. However, patients with PH were younger than patients with periodontal disease (PD). Moreover, the dental evaluation occurred after a delayed diagnosis in PH Group compared to the PD Group. Furthermore, 15 (45%) patients with periodontal health were in conditioning regimen of therapy primarily in HSCT. In contrast, in periodontal disease group, only 2(11.1%) of patients used this course of chemotherapy. This fact may indicate a regime of chemotherapy more aggressive in patients of PH group.

The present research carefully monitored patients through a systematic periodontal evaluation, including criteria of clinical attachment level and inflammatory parameters. The periodontal assessment of all patients revealed that periodontal parameters regarding attachment level were significantly

different between PH Group and PD Group, showing higher PPD and CAL values for the periodontitis patients, as expected. Nevertheless, patients of PD group present mild to moderate periodontitis, since in patients diagnosed with severe periodontitis the chemotherapy regime had been discontinued. The CEJ measures are similar in both groups. The CEJ represents the anatomic limit between the crown and root surface area, identifying gingival hyperplasia or recession of (Ceppi *et al*, 2006). Although, in periodontal research, attachment loss (PPD, CAL) is considered to be a more informative method of assessment of periodontal disease for both cross-sectional and longitudinal studies (American Academy of Periodontology, 2001).

The crucial purpose of this investigation was to evaluate the role of periodontal disease in the incidence of OM. The highlight of the present study was the baseline assessment of Health Group before chemotherapy, which allowed a more precise causal effect relationship of the influence of oral health in OM. The periodontal inflammatory parameters (PI, GPI, GI) of patients with oral health at baseline showed a significant difference in follow-up 7-14 days. Monitoring clinically the patients was noted that, some of then failed with oral hygiene by different reasons (sickness, depression, fatigue, nausea) resulting from chemotherapy. A few days later the OM was installed in these patients. Probably, the worse in periodontal inflammatory condition could be predisposing to OM. Previous studies showed that reduction of periodontal inflammation was associated with a lower prevalence of OM in HSCT (Al-Ansari *et al*, 2015).

Sixteen (31%) patients developed oral mucositis after chemotherapy. At least 40%, and up to 70%, of individuals treated with standard chemotherapy regimens or upper-body radiation develop oral mucositis (Scully *et al,* 2003). This adverse reaction occurs in 20–40 % of patients receiving conventional chemotherapy (Hayashi *et al,* 2016), similar rates were found in present study, which included only patients in this therapy (43.7%). Observing scientific evidences about oral mucositis incidence only in patients undergoing hematopoietic stem cell transplantation (HSCT) were noted rates between in approximately 75% to 100 % (Al-Ansari *et al,* 2015) and ulcerative mucositis scores of grades III and IV (Chaudhry *et al*, 2016). Interestingly, this study showed lower incidence and lower grade of oral mucositis (56.2% incidence; score of grade I) for this regimen. Probably, the patients scheduled to HSCT

evaluated in present research were in majority composed with periodontal health.

When observed patients of PH group the data showed an unexpected incidence of chemo-induced oral mucositis. Then, the incidence of OM between PH group and PD group was unexpectedly similar and, regarding the distribution of patients with respect to the degree of oral mucositis, no differences were verified between two groups. Probably, the lack of severe periodontitis in patients with PD group may have influenced these data.

The only previous pilot study evaluated associations between radiation-induced oral mucositis and periodontitis in patients under radiotherapy (Khaw *et al*, 2014). There was a trend towards a greater proportion of periodontitis patients in the mucositis groups (grades = 1–4) than in the non-mucositis group (grade = 0). However, the authors argue that, due to the small sample size of this pilot study, these trends were not statistically significant, similar to that observed in the present study.

The presence of inflammation, with constant release of cytokines, is the central pathophysiological mechanisms involved in the role of periodontal disease in some systemic conditions, including oral mucositis (Savioli *et al*, 2012; Coracin *et al*, 2013, Fabri *et al,* 2014). Despite of the higher inflammatory parameters in PD group, the incidence of OM in this group was similar to PH group. The data demonstrated that even if the presence of periodontitis had an effect on the incidence of oral mucositis, this association would have been hidden by the aggressiveness of cancer therapy, similar previously described by radio-induced OM (Khaw *et al*, 2014). When observed PH group patients with oral mucositis, almost all of them were in conditioning therapy. Other aspect to be considered is the age of the patients in PH group. Younger individuals are more susceptible to oral mucositis than older individuals and this may be related to the higher proliferative index of basal epithelial cells in the former group (Parulekar *et al*, 2012).

In conclusion, this study demonstrated that oral health, apparently, could affect experience and incidence of chemo-induced oral mucositis. When only patients periodontally healthy undergoing conditioning regimen of therapy and conventional chemotherapy were observed, was noted a lower incidence of oral mucositis, when compared with scientific evidences (Coracin *et al*, 2013; Al-

Ansari *et al,* 2015). However, did not demonstrate a positive statistical correlation between periodontitis and incidence of OM. The need of inclusion of patients with severe periodontitis to evaluate this relationship hampers such trial.

References

Ainamo J, Bay I (1975). Problems and proposals for recording gingivitis and plaque. *International Dental Journal* **25**: 229-235.

Al-Ansari S, Zecha JA, Barasch A *et al* (2015). Oral Mucositis Induced By Anticancer Therapies. *Curr Oral Health Rep.* **2**: 202-211.

Almeida RF, Pinho MM, Lima C *et al* (2006). Associação entre doença periodontal e patologias sistêmicas. *Rev Port Clin Geral* **22**: 379-90.

Almeida PM, Wickerhauser H (1991). "O Critério ABA/ABIPEME – Em Busca de uma Atualização" *Associação Brasileira dos Institutos de Pesquisa de Mercado***.**

American Academy of Periodontology (2000). Parameter on Chronic Periodontitis With Slight to Moderate Loss of Periodontal Support. *J Periodontol 2000* **71**: 853-855.

Armitage GC (1999). Development of a Classification System for Periodontal Diseases and Conditions. *Annals of Periodontology,* São Francisco **4**: 1-6.

Baelum V, Manji F, Fejerkov O (1988). Profiles of destructive periodontal disease in different populations. *J. Periodontol* **15**: 445-452.

Bartold PM, Cantley MD, Haynes DR (2010). Mechanisms and control of pathologic bone loss in periodontitis. *Periodontology 2000* **53**: 55-69.

Bellm LA, Epstein JB, Rose-Ped A *et al* (2000). Patient reports of complications of bone marrow transplantation. *Support Care Cancer* **8**: 33–39.

Bray F, Piñeros M (2016). Patrones, tendencias y proyecciones del câncer en América Latina y el Caribe: un contexto global. *Salud Publica Mex* **58**:104-117.

Brown L, Oliver R, Löe H (1990). Evaluating periodontal status of U.S. employed adults. *Journal of the American Dental Association* **121**: 226-232.

Burt B (2005). Reasearch, Science and therapy committee of the American Academy of Periodontology. Position Paper: Epidemiology of Periodontal Diseases. *Journal of Periodontology* **76**: 1406-1419.

Chaudhry HM, Bruce AJ, Wolf RC *et* al (2016). The Incidence and Severity of Oral Mucositis among Allogeneic Hematopoietic Stem Cell Transplantation Patients: A Systematic Review. *Biol Blood Marrow Transplant* **22**: 605-616.

Chapple ILC, Genco R (2013). And on behalf of working group 2 of the joint EFP/AAP workshop* Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. *J Periodontol* **84**: 106-112.

Ceppi E, Dall'Oca S, Rimondini L *et al* (2006). Cementoenamel junction of deciduous teeth: SEM-morphology. *Eur J Paediatr Dent* **7**:131-134.

Chaveli-López B, Bagán-Sebastián, JV (2016). Treatment of oral mucositis due to chemotherapy. *J Clin Exp Dent* **8**: 201-209.

Coracin FL, Santos PS, Gallottini MH *et al* (2013). Oral health as a predictive factor for oral mucositis. *Clinics* **68**: 792-796.

Curado MP, de Souza DL (2014). Cancer burden in Latin America and the Caribbean. *Ann Glob Health* **5**: 370-377.

Di Benedetto, A, Gigante, I, Colucci, S *et al* (2013). Periodontal disease: linking the primary inflammation to bone loss. *Clin Dev Immunol* **50:** 37-54.

Enwonwu CO, Salako N (2012). The periodontal disease– systemic health–infectious disease axis in developing countries. *Periodontol 2000* **60**: 64-77.

Fabri GM, Siqueira SR, Simione C *et al* (2009). Refractory craniofacial pain: is there a role of periodontal disease as a comorbidity?. *Arquivos de neuro-psiquiatria* **67**: 474-479.

Fabri GM, Savioli C, Siqueira JT *et al* (2014). Doença periodontal em doenças reumáticas pediátricas. *Rev Bras Reumatol* **54**: 311-317.

Graves DT, Cochran D (2003). The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. *J Periodontol* **74**: 391-401.

Gerecke C, Fuhrmann S, Strifler S *et al* (2016). The Diagnosis and Treatment of Multiple Myeloma. *Dtsch Arztebl Int* **11**: 470-476.

Gussgard AM, Hope AJ, Jokstad A *et al* (2014). Assessment of Cancer Therapy-Induced Oral Mucositis Using a Patient-Reported Oral Mucositis Experience Questionnaire. *Plos one* **9**: 917-933.

Hayashi H, Kobayashi R, Suzuki A *et al* (2016). Preparation and clinical evaluation of a novel lozenge containing polaprezinc, a zinc-L-carnosine, for prevention of oral mucositis in patients with hematological cancer who received high-dose chemotherapy. *Med Oncol* **33**: 91.

Holmstrup P, Glick, M (2001). Treatment of periodontal disease in the immunodeficient patient. *Periodontology 2000* **28**: 190-205.

Hu K, Lou L, Tian W *et al* (2016). The Outcome of Breast Cancer Is Associated with National Human Development Index and Health System Attainment. *PLoS One* **8**:7.

Hugson A, Jordan T (1982). Frequency distribution of individuals aged 20-70 years according to severity of periodontal disease. *Community dentistry and oral epidemiology* **10:** 187-192.

Khaw A, Logan R, Keefe D *et al* (2014). Radiation-induced oral mucositis and periodontitis – proposal for an inter-relationship. *Oral Diseases* **20**: 7-18.

Lambertz CK, Gruell J, Robenstein V *et al* (2010). No Stops: Reducing treatment breaks during chemoradiation for head and neck cancer. *Clinical Journal Oncology Nursing* **v. 14**: 585-593.

Lima HG, Lara VS (2013). Aspectos Imunológicos da Doença Periodontal Inflamatória: Participação dos Mastócitos/ Immunological Aspects of Inflammatory Periodontal Disease: Involvement of Mast Cells. *UNOPAR Científica Ciências Biológicas e da Saúde* **15**: 225-229.

Löe H, Theilade E, Jensen SB (1965). Experimental gingivitis in mam. *Journal of Periodontology* **36**: 177-187.

Ohlrich EJ, Cullinan MP, Seymour, GJ (2009). The immunopathogenesis of periodontal disease. *Australian dental journal* **54**: 2-10.

O'leary TJ, Rudd KD (1963). An instrument for measuring horizontal mobility. *Peridontics* **1**: 249.

Parkin DM, Fernandez LMG (2006). Use of statistics to assess the global burden of breast cancer. *Breast J* **12**:70. Parulekar W, Mackenzie R, Bjarnason G *et al* (1998). Scoring oral mucositis. *Oral Oncology* **34**: 63-71.

Raber-Durlacher JE, Epstein JB, Raber J *et al* (2002). Periodontal infection in cancer patients treated with high-dose chemotherapy. *Supportive care in cancer* **10**: 466-473.

Ruescher TJ, Sodeifi A, Scrivani SJ *et al* (1998). The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. *Cancer* **82**: 2275-2281.

Silness J, Löe H (1964). Periodontal disease in pregnancy II. Correlation between oral higyene and periodontal condition. *Acta Odontol. Scand* **22**: 121-135.

Santos PS, Coracin FL, Barros JC *et al* (2011). Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis. *Clinical Transplantation* **25**: 325-328.

Savioli C, Ribeiro AC, Fabri GM *et al* (2012). Persistent Periodontal Disease Hampers Anti-Tumor Necrosis Factor Treatment Response in Rheumatoid Arthritis. *J Clin Rheumatol* **18**: 180-184.

Scully C, Epstein J, Sonis S (2003). Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1, pathogenesis and prophylaxis of mucositis. *Head Neck* **25**:1057-1070.

Siqueira JTT, Teixeira MJ (2001). "Dor Orofacial. Diagnóstico, Terapêutica e Qualidade de Vida", *Editora Maio* - **656**.

Sonis ST (2004). A biological approach to mucostis. *J Support Oncol* **2**: 21-32.

Sonis ST (2010). Efficacy of palifermin (keratinocyte growth factor-1) in the amelioration of oral mucositis. *Core Evid* **4**:199–205.

Sonis ST, Elting LS, Keefe D *et al* (2004). Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *International Society for Oral Oncology Cancer* **100**: 1995-2025.

Sonis ST, Fey EG (2002). Oral complications of cancer therapy. *Oncology* **16**: 680-688.

Sonis ST, Oster G, Fuchs H *et al* (2001). Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *Journal of clinical oncology* **19**: 2201-2205.

Tunkel AR, Sepkowitz KA (2002). Infections caused by viridans streptococci in patients with neutropenia. *Clinical infectious diseases* **34**: 1524-1529.

Turner L, Mupparapu M (2013). Akintoye, S. O. Review of the Complications Associated with Treatment of Oropharyngeal Cancer: A Guide to the Dental Practitioner. *Quintessence international* **44**: 267–279.

van der Velden WJ, Herbers AH, Netea MG *et a*l (2014). Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. *British Journal of Haematology* **167**: 441-452.

4.4 Artigo 4

Bacterial density in chemotherapy patients: red complex as protagonist

CP Novaes[1], GM Fabri[1], AM Coelho[2], ACM Apolônio[3], DE Cesar[4], MGAM Chaves[1]

[1] Dentistry School, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[2] Institute of Exact Sciences, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[3] Department of Parasitology, Microbiology and Immunology, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

[4] Biological Sciences Institute, Department of Ecology, Universidade Federal de Juiz de Fora, Juiz de Fora, Brazil

*Correspondence:
Maria das Graças Afonso Miranda Chaves
Faculdade de Odontologia da Universidade Federal de Juiz de Fora
Rua José Lourenço Kelmer s/n- São Pedro, Juiz de Fora – MG
CEP 36036-900 - Brazil
Tel: 55-(32) 3025-3065
duque05@gmail.com

Running title: chemotherapy and red complex

Background: Nowadays, there is hypothesis that chemotherapy may inhibit the commensal bacteria within the oral cavity and induce an ecological shift of oral microbiota toward a community predominated by Gram-negative. **Objective:** Investigate the relationship between red complex bacterial density and oral complications in patients undergoing chemotherapy. **Methods:** This study included fourty-four patients. Fifteen were diagnosed with periodontitis (PD Group) and 29 periodontally healthy (PH Group). The assessments were obtained prior and between 7-14 days after initiated chemotherapy in periodontal health group (PH group). The Periodontal disease Group (PD Group) was evaluated during 7 to 14 days after of chemotherapy. These included: periodontal assessment; oral mucosa was examined for scoring of chemotherapy-induced oral mucositis (OM); clinical tests for dysphagia and evaluation of xerostomia. Subgengival samples were collected by inserting sterile endodontic paper points for both groups. Total number of bacterial cells and cells from each species were determined by FISH(*fluorescence in situ hybridizati*on). **Results:** Twenty-nine(65.9%) patients were treated for solid tumors, 15(34.1%) scheduled for hematopoietic stem cell transplantation (HSCT). Mean age was 50.5 years, 32(72.7%) were female. Twenty-nine(65.9%) were considered in PH Group, while 15(34.1%) patients in PD Group. OM was found in 16(36.3%) patients, xerostomia 24(54.5%) and dyspaghia 21(47.7%).

Keywords: periodontal pathogens; red complex; chemotherapy; oral complications

Introduction

Oral bacterial biofilms were the first human-associated biofilms to have been studied extensively. Recent statistics show that oral diseases affect 3.9 billion people globally (1). Between these, periodontitis is the most common conditions affecting humans (2,3). Periodontal disease is a host-driven inflammatory response to a pathogenic bacterial biofilm in the subgingival environment that leads to the destruction of the supporting structures of the teeth (4,1). The microbial species constituting these biofilms are part of the endogenous oral microbiota. In classical studies, the increase in numbers and proportions of the tree “red complex” species (*Porphyromonas gingivalis, Treponema denticola and Tannerella forsythia*) in subgingival biofilms has been highly associated with the presence of periodontitis (5). The cell wall of “red complex contains the endotoxin lipopolysaccharide (LPS). LPS activates macrophages to produce inflammatory mediators (6,7).

Then, despite of the most bacterial species cause no harm under healthy conditions, in patients with malignancies, the delicate homeostasis between host defense and commensal bacteria could be disturbed. The cancer itself causes these deregulation or cancer-related secondary immunodeficiency, the anti-cancer treatment, or yet the supportive therapies that all may contribute to a shift in the oral microbiota of the oral cavity from mainly Gram-positive to Gram-negative bacteria (8,9,10,11,12). In addition, the chemotherapeutics can be bacteriostatic or bactericidal, thus affecting the oral bacterial community (13,14,15).

Preliminary data obtained from culture-based methodologies have shown that antineoplastic agents can affect oral microbial composition. Cytotoxic antineoplastic agents can therefore compromise oral mucosal immunity, which can lead to decreased Secretory Immunoglobulin A (SIgA) secretion, salivary dysfunction, decreased salivary antimicrobial properties, and damage of the mucosal barrier lining the oral mucosa, further disrupting eubiosis of oral microbiota (16,17,18). Numerous studies have identified and reported a wide of incidence and severity for different oral complications from cancer therapies. These include: oral mucositis (19,20,21,22), xerostomia, (23,24,25) bleeding, dysphagia (26,27), disgeusia (20), caries, periodontal

disease, infection (bacterial, viral, and fungal) (28), pain, trismus (23), osteoradionecrosis, growth and developmental disturbances, and salivary gland dysfunction (20).

Nowadays, there is hypothesis that chemotherapy may inhibit the commensal bacteria within the oral cavity and induce an ecological shift of oral microbiota toward a community predominated by Gram-negative anaerobes exhibiting high virulence phenotype, thus initiating a cascade of inflammatory processes (29,15,18). However, until now, it is unclear whether there is an association between the shift of oral microbiota and oral complications caused by the effect of chemotherapy.

The aim of this prospective study was to investigate the relationship between red complex bacterial density and oral complications in patients undergoing chemotherapy.

Patients and Methods

Patients

This study included fifty-one consecutive patients undergoing chemotherapy referred from regional hospitals for regular followed up at the Dentistry School. Patients were treated for solid tumors (n=35) and scheduled for hematopoietic stem cell transplantation (HSCT) (n=16). The local ethical committee approved this study (1.684.653) and written informed consent was obtained from participants. Exclusion criteria were edentulous patients, presence of concurrent radiotherapy, patients who did not complete the cycle of chemotherapy due to death or abandonment of treatment and / or study, and cognitive disorders.

From the total of 51 patients recruited, 18 were diagnosed with periodontitis (PD Group) and 33 periodontally healthy (PH Group). One experienced calibrated dentist performed all periodontal diagnosis. Periodontal disease was defined by clinical features according to the presence of concomitant edema, erythema, gingival bleeding and/or suppuration on probing, and periodontal probing depths, according to the American Academy of Periodontology (30). Using this classification, the severity of PD was

categorized based on the amount of CAL: mild, 1 to 2 mm; moderate, 3 to 4 mm; and severe, 5 mm or greater.

Information regarding demographic data (age, sex), clinical and histopathological diagnosis of diseases and chemotherapy prescription, were obtained from medical records.

Oral Assessment and Sampling

All the assessments were obtained prior and between 7-14 days after initiated chemotherapy in PH group (n=33). The PD group (n=18) was evaluated also between 7 to 14 days after the first day of chemotherapy.

The assessments included: periodontal assessment included 3 standardized epidemiological indices: dental plaque index (PI) (31), gingival bleeding index (GBI) (32), and clinical attachment level (CAL). Clinical attachment level included 2 measures: probing pocket depth (PPD) and cementoenamel junction (CEJ) at 6 sites per tooth (33).

Furthermore, the oral mucosa also was examined by a single examiner for scoring of chemotherapy-induced oral mucositis according to the WHO system (34); clinical tests for dysphagia diagnostics (35); and evaluation of xerostomia (36).

Subgengival Sample Collection

Subgengival samples were collected by inserting steril endodontic paper points (size 30) from at least three paper points per site per patient by a single examiner. For periodontally healthy patients (PH Group), the steril paper points were inserted into the gingival sulci, while for periodontitis patients (PD Group), the deepest site was selected. They were inserted into the most convenient sites until mild resistance was felt, for 60 seconds, following isolation and supragingival plaque removal. The paper points were transferred into sterile microtubes. The microtubes were weighed before and immediately after sampling to allow quantitative analysis. The samples were fixed and stored in paraformaldehyde solution, 2% final concentration. The materials were stored at −20°C until further microbiological analysis by FISH (*fluorescence in situ hybridization*).

Results and Discussion

A redação final do artigo dentro do prazo estabelecido foi impossibilitada devido a erro decorrente das análises das amostras microbiológicas. Estas estão sendo refeitas e serão posteriormente submetidas à análise estatística. O artigo final será submetido em periódico internacional.

References

1. Aruni AW, Dou Y, Mishra A, Fletcher HM. The Biofilm Community-Rebels with a Cause. Curr *Oral Health Rep* 2015;2:48-56.

2. Dentino A, Lee S, Mailhot J, Hefti AF. Principles of periodontology. *Periodontol 2000* 2013;6:16-53.

3. Camelo-Castillo AJ, Mira A, Pico A, et al. Subgingival microbiota in health compared to periodontitis and the influence of smoking. *Front Microbiol* 2015;24:119.

4. Fujinaka H, Takeshita T, Sato H, et al. Relationship of periodontal clinical parameters with bacterialcomposition in human dental plaque. *Arch Microbiol* 2013;195:371-83.

5. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. *J Clin Periodontol* 1998;25:134-44.

6. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. *Periodontol 2000* 1997;14:216-48.

7. Fukamachi H, Matsumoto C, Omiya Y, et al. Effects of Hangeshashinto on Growth of Oral Microorganisms. Evid Based Complement Alternat Med 2015;51:29-47.

.8. Jenkinson HF, Lamont RJ. Oral microbial communities in sickness and in health. *Trends Microbiol* 2005;13:589-95.

9. Dewhirst FE, Chen T, Izard J, et al. The human oral microbiome. *J Bacteriol* 2010;192:5002-17.

10. Ahn J, Chen CY, Hayes RB. Oral microbiome and oral and gastrointestinal cancer risk. *Cancer Causes Control* 2002;23:399–404.

11. Ye Y, Carlsson G, Agholme MB, et al. Oral bacterial community dynamics in paediatric patients with malignancies in relation to chemotherapy-related oral mucositis: a prospective study*. Clin Microbiol Infect* 2013;19:559-67.

12. Vozza I, Cavallè E, Corridore D, et al. Preventive strategies in oral health for special needs patients. *Ann Stomatol (Roma)* 2016;6:96-9.

13. Woo SB, Sonis ST, Monopoli MM, Sonis AL. A longitudinal study of oral ulcerative mucositis in bone marrow transplant recipients. *Cancer* 1993;72:1612-7.

14. Napenas JJ, Shetty KV, Streckfus CF. Oral mucositis: review of pathogenesis, diagnosis, prevention, and management. *Gen Dent* 2007;55:335-44.

15. Laheij AM, de Soet JJ, von dem Borne PA, et al. Oral bacteria and yeasts in relationship to oral ulcerations in hematopoietic stem cell transplant recipients. *Supp Care Cancer* 2012;20:3231-40.

16. Krisanaprakornkit S, Kimball JR, Weinberg A, Darveau RP, Bainbridge BW, Dale BA. Inducible expression of human beta-defensin 2 by Fusobacterium nucleatum in oral epithelial cells: multiple signaling pathways and role of commensal bacteria in innate immunity and the epithelial barrier. *Infect Immun* 2000;68:2907-15.

17. Barrach RH, Souza MP, Silva DP, Lopez PS, Montovani JC. Oral changes in individuals undergoing hematopoietic stem cell transplantation. *Braz J Otorhinolaryngol* 2015;81:141-7.

18. Wang Y, Zhou X, Xu X. Oral microbiota: an overlooked etiology for chemotherapy-induced oral mucositis? *J Formos Med Assoc* 2015;114:297-9.

19. Scully C, Epstein J, Sonis S. Oral mucositis: a challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: part 1, pathogenesis and prophylaxis of mucositis. *Head Neck* 2003;25:1057-70.

20. Brennan S, Corry J, Kleid S, et al. Prospective trial to evaluate staged neck dissection or elective neck radiotherapy in patients with CT-staged T1-2 N0 squamous cell carcinoma of the oral tongue*. Head Neck* 2010;32:191-8.

21. Vanhoecke B, De Ryck T, Stringer A, Van de Wiele T, Keefe D. Microbiota and their role in the pathogenesis of oral mucositis. *Oral Dis.* 2015 ;21:17-30.

22. Kapoor V, Basur S, Pandey A. Chemotherapy and Oral Complications - The Most Neglected Side of Cancer*. J Adv Med Dent Scie Res* 2015;3:71- 80.

23. Eveson JW. Xerostomia. *Periodontol 2000* 2008;48:85-91.

24. Magnabosco Neto AE, Westphalen FH. Analysis of oral complications related to cancer therapy. *Arch Oral Res* 2013;9:159-164.

25. Vidal-Casariego A, Fernández-Natal I, Calleja-Fernández A, et al. Nutritional, microbiological, and therapeutic factors related to mucositis in head and neck cancer patients: a cohort study. *Nutr Hosp* 2015;32:1208-13.

26. Raber-Durlacher JE, von Bültzingslöwen I, Logan RM, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic

review of cytokines and growth factors for the management of oral mucositis in cancer patients. *Supp Care Cancer* 2013;21:343-55.

27. Majdaeen M, Kazemian A, Babaei M, Haddad P, Hashemi FA. Concomitant boost chemoradiotherapy in locally advanced head and neck cancer: treatment tolerance and acute side effects*. J Cancer Res Ther* 2015;11:24-8.

28. Aitken-Saavedra J, Rojas-Alcayaga G, Maturana-Ramírez A, et al. Salivary gland dysfunction markers in type 2 diabetes mellitus patients. *J Clin Exp Dent* 2015;7:501-5.

29. Al-Ansari S, Zecha JA, Barasch A, de Lange J, Rozema FR, Raber-Durlacher JE. Oral Mucositis Induced By Anticancer Therapies. *Curr Oral Health Rep* 2015;2:202-211.

30. Armitage GC. Development of a classification system for periodontal diseases and conditions. *Ann Periodontol* 1999;4:1-6.

31. Ainamo J, Bay I. Problems and proposals for recording gingivitis and plaque. *Int Dent J* 1975;25:229-235.

32. O'Leary TJ, Rudd KD. An instrument for measuring horizontal mobility. *Peridontics* 1963;1:249.

33. American Academy of Periodontology. Parameter on Chronic Periodontitis With Slight to Moderate Loss of Periodontal Support. *Periodontol 2000* 2000;71:853-855.

34. Sonis ST, Fey EG. Oral complications of cancer therapy. Oncology (Williston Park) 2002;16:680-6.

35. Wu MC, Chang YC, Wang TG, Lin LC. Evaluating swallowing dysfunction using a 100-ml water swallowing test. *Dysphagia* 2004;19:43-7.

36. Pai S, Ghezzi EM, Ship JA. Development of a Visual Analogue Scale questionnaire for subjective assessment of salivary dysfunction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;91:311-6.

5. CONSIDERAÇÕES FINAIS

Em conclusão, este estudo demonstrou que a saúde periodontal, pode, afetar a incidência e o grau de mucosite oral induzida por quimioterapia. Pacientes com saúde periodontal submetidos ao regime de condicionamento quimioterápico para transplante de medula óssea e quimioterapia convencional para tumores sólidos, desenvolveram menor incidência e menor gravidade de mucosite oral em comparação com evidências científicas. No entanto, não houve uma correlação estatística positiva entre a periodontite e a incidência da mucosite oral. Provavelmente, seja necessária a inclusão de pacientes com periodontite grave para avaliar melhor esta possível associação entre a doença periodontal e a mucosite oral induzida por quimioterapia.

Várias foram as complicações bucais experimentadas pelos pacientes em quimioterapia, sendo a xerostomia a mais prevalente, seguida de disfagia e mucosite oral. Mais estudos clínicos são necessários para avaliar a influência dos tipos de agentes quimioterápicos, uso de drogas e comorbidades em relação à queixa de boca seca prevalente neste estudo.

Houve uma associação significativa entre a qualidade de vida (OHIP-14), a classe socioeconômica e as complicações bucais. Os pacientes que desenvolveram mais complicações bucais apresentaram pior qualidade de vida, e pertenciam às classes socioeconômicas B ou C, em sua maioria.

REFERÊNCIAS

AINAMO, J.; BAY I. Problems and proposals for recording gingivitis and plaque. **International Dental Journal,** v. 25, n. 4, p. 229-235, 1975.

ALMEIDA, P. M.; WICKERHAUSER, H. O Critério ABA/ABIPEME – Em Busca de uma Atualização. **Associação Brasileira dos Institutos de Pesquisa de Mercado,** São Paulo, 1991.

ALMEIDA, R.F. et al. Associação entre doença periodontal e patologias sistémicas. **Revista Portuguesa de Clínica Geral***,* v. 22, p. 379-90, 2006.

AMERICAN ACADEMY OF PERIODONTOLOGY. Parameter on Chronic Periodontitis With Slight to Moderate Loss of Periodontal Support. **Periodontology 2000**, v. 71, p. 853-855; Mai. 2000.

BAELUM, V.; MANJI, F.; FEJERKOV, O. Profiles of destructive periodontal disease in different populations. **Journal of Periodontology,** v. 15, n. 7, p. 445-452, Ago. 1988.

BARTOLD, P. M.; CANTLEY, M. D.; HAYNES, D. R. Mechanisms and control of pathologic bone loss in periodontitis. **Periodontology 2000,** v. 53, n. 1, p. 55-69, Jun. 2010.

BROWN, L.; OLIVER, R.; LÖE, H. Evaluating periodontal status of U.S. employed adults. **Journal of the American Dental Association,** v. 121, n. 2, p. 226-232, Ago. 1990.

BURT, B. Research, science and therapy committee of the American Academy of Periodontology. Epidemiology of Periodontal Diseases. Position Paper. **Journal of Periodontology***,* v. 76, p. 1406-1419, Mai. 2005.

CAMPOS, M. I. et al. Oral mucositis in cancer treatment: Natural history, prevention and treatment (Review). **Molecular and Clinical Oncology,** v. 2, n. 3, p. 337-340, Mai. 2014.

CHAPPLE, I. L. C.; GENCO, R. And on behalf of working group 2 of the joint EFP/AAP workshop* Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases **Journal of Periodontology,** v. 84, n. 4, p. 106-112, 2013.

CHAUDHRY, H. M. et al. The Incidence and Severity of Oral Mucositis among Allogeneic Hematopoietic Stem Cell Transplantation Patients: A Systematic Review. Biology of Blood and Marrow Transplantation, v. 22, n. 4, p. 605-616, set. 2016.

CHAVELI-LÓPEZ, B.; BAGÁN-SEBASTIÁN, J. V. Treatment of oral mucositis due to chemotherapy. **Journal of Clinical and Experimental Dentistry,** v. 8, n. 2, p. 201-209, Abr. 2016.

CORACIN, F. L. et al. Oral health as a predictive factor for oral mucositis. **Clinics**, v. 68, n. 6, p. 792-796, Jun. 2013.

DI BENEDETTO, A. et al. Periodontal disease: linking the primary inflammation to bone loss. **Clinical and Developmental Immunology**, *v.* 50, p.37-54, 2013.

FABRI, G. M. C. et al. Doença periodontal em doenças reumáticas pediátricas. **Revista Brasileira de Reumatologia**, v. 54, n. 4, p. 311-317, 2014.

FOX, P. C.; BUSCH, K. A.; BAUM, B. J. Subjective reports of xerostomia and objetive measures of salivary gland performance. **The Journal of the American Dental Association,** v. 115, n. 4, p. 581-584, Out. 1987.

GOMES, A. O. et al. Early and late oral features of chronic graft-versus-host disease. **Revista Brasileira de Hematologia e Hemoterapia,** v. 36, n. 1, p. 43-49, 2014.

GRAVES, D. T.; COCHRAN, D. T. The contribution of interleukin-1 and tumor necrosis factor to periodontal tissue destruction. **Journal of Periodontology**, v. 74, n.3, p. 391-401, Mar. 2003.

GUSSGARD, A. M. et al. Assessment of Cancer Therapy-Induced Oral Mucositis Using a Patient-Reported Oral Mucositis Experience Questionnaire. **Plos one**, v. 9, n. 3, p. 917-933, Mar. 2014.

HEDEN, G.; WENNSTRÖM, J.; LINDHE, J. Periodontal tissue alterations following Emdogain treatment of periodontal sites with angular bone defects. A series of case reports. **Journal of Clinical Periodontology**, v. 26, n. 12, p. 855-860, Dez. 1999.

HOBBIE, J. E.; DALEY, R. J.; JASPER, S. Use of nucleopore filters for counting bacteria by fluorescence microscopy. **Applied and Environmental Microbiology**, v. 33, p. 1225 -1228, 1997.

HOLMSTRUP, P.; GLICK, M. Treatment of periodontal disease in the immunodeficient patient. **Periodontology 2000**, v. 28, n. 1, p. 190-205, 2002.

years according to severity of periodontal disease. **Community dentistry and oral epidemiology**, v. 10, n. 4, p. 187-192, Ago. 1982.

KHAW, A. et al. Radiation-induced oral mucositis and periodontitis – proposal for an inter-relationship. **Oral Diseases,** v. 20, n. 3, p. 7-18, 2014.

LALLA, R. V. et al. Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. **Cancer,** v. 120, n. 10, p. 1453-1461, Mai. 2014.

LAMBERTZ, C. K. et al. No Stops: Reducing treatment breaks during chemoradiation for head and neck cancer. **Clinical Journal Oncology Nursing**, v. 14, n. 5, p. 585-593, Abr. 2010.

LIMA, H. G.; LARA, V. S. Aspectos Imunológicos da Doença Periodontal Inflamatória: Participação dos Mastócitos/ Immunological Aspects of Inflammatory **Periodontal Disease: Involvement of Mast Cells,** UNOPAR Científica Ciências Biológicas e da Saúde, v. 15, n. 3, p. 225-9, 2013.

LINDHE, J. et al. **Tratado de Periodontia Clínica e Implantodontia Oral**. Ed. Guanabara Koogan, Rio de Janeiro, 1999.

LÖE, H. et al. The natural history of periodontal disease in man. The rate of periodontal destruction before 40 years of age. **Journal of Periodontology**, v.49, n.12, p. 607-620, 1978.

OHLRICH, E. J.; CULLINAN, M .P.; SEYMOUR, G. J. The immunopathogenesis of periodontal disease. **Australian dental journal,** v. 54, n. 1, p. 2-10, 2009.

O'LEARY, T. J.; RUDD, K. D. An instrument for measuring horizontal mobility. **Peridontics**, v. 1, p. 249, 1963.

PAI, S. et al. Development of a visual analogue scale questionnaire for subjective assessment of salivary dysfunction. **Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology,** v. 91, n. 3, p. 311-316, Mar. 2001.

PETERSON, D. E. et al. Microbiology of acute periodontal infection in myelosuppressed cancer patients. **Journal Clinical Oncology**, v. 5, n. 9, p. 1461-1468, Set. 1987.

RABER-DURLACHER, J. E. et al. Periodontal infection in cancer patients treated with high-dose chemotherapy. **Supportive care in cancer**, v. 10, n. 6, p. 466-473, Set. 2002.

ROSENTHAL, D. I. Consequences of mucositis-induced treatment breaks and dose reductions on head and neck cancer treatment outcomes. **Journal Supportive Oncology**, v.5, n. 4, p. 23–31, Out. 2007.

RUESCHER, T. J. et al. The impact of mucositis on alpha-hemolytic streptococcal infection in patients undergoing autologous bone marrow transplantation for hematologic malignancies. **Cancer**, v. 82, n. 11, p. 2275-2281, Jun. 1998.

RUSSO, G. et al. Radiation treatment breaks and ulcerative mucositis in head and neck cancer. **The Oncologist**, v. 13, n. 8, p. 886–898, Ago. 2008.

SANTOS, P. S. et al. Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis. **Clinical Transplantation**, v. 25, n. 2, p. 325-328, Mar./Abr. 2011.

SILNESS, J.; LÖE H. Periodontal disease in pregnancy II. Correlation between oral higyene and periodontal condition. **Acta Odontologica Scandinavica,** v. 22, p.121-135, 1964.

SIQUEIRA, J. T. T.; TEIXEIRA, M. J. **Dor Orofacial. Diagnóstico, Terapêutica e Qualidade de Vida,** Curitiba, Editora Maio, p. 656, 2001.

SLADE, G. D.; SPENCER, A. J. Development and evaluation of the Oral Health Impact Profile. **Community Dental Health,** v. 11, p. 3–11, 1994.

SONIS, S. T. et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. **Journal of clinical oncology**, v.19, n. 8, p. 2201-2205, Abr. 2001.

TUNKEL, A. R.; SEPKOWITZ, K. A. Infections caused by viridans streptococci in patients with neutropenia. **Clinical infectious diseases**, v. 34, n. 11, p. 1524-1529, 2002.

VAN DER VELDEN, W. J. F. M. et al. Mucosal barrier injury, fever and infection in neutropenic patients with cancer: introducing the paradigm febrile mucositis. **British Journal of Haematology,** v. 167, p. 441-452, 2014.

VIEIRA, A. C. F.; LOPES, F. F. Mucosite oral: efeito adverso da terapia antineoplásica. **Revista de Ciências Médicas e Biológicas**, v. 5, n. 3, p. 268-274, 2006.

WU, M. C. et al. Evaluating swallowing dysfunction using a 100-ml water swallowing test. **Dysphagia**, v. 19, n. 1, p. 43-47, 2004.// Wu MC, Chang YC, Wang TG, Lin LC.

ANEXOS

ANEXO A – Declaração de Infraestrutura do Instituto Oncológico do Hospital 9 de Julho de Juiz de Fora

DECLARAÇÃO DE INFRAESTRUTURA E CONCORDÂNCIA

Referente ao projeto de pesquisa de título **"Impacto da Terapia Periodontal na Mucosite Oral e Identificação de Microrganismos Orais Prevalentes"**, sob a responsabilidade dos pesquisadores Gisele Maria Campos Fabri, que tem por objetivo: avaliar o impacto da terapia periodontal na mucosite oral e identificar os microrganismos orais prevalentes, eu, **Narciso Pazinatto**, na qualidade de responsável pelo Instituto Oncológico, do Hospital 9 de Julho de Juiz de Fora, declaro:

Ter anuência para realização dos procedimentos da pesquisa, e

Existência da infraestrutura necessária a realização da mesma.

Juiz de Fora, 3 de junho de 2016

ANEXO B - Declaração de Infraestrutura do Serviço de Hematologia e Transplante de Medula Óssea do Hospital Universitário da Universidade Federal de Juiz de Fora.

DECLARAÇÃO

Eu, **ABRAHÃO ELIAS HALLACK NETO,** na qualidade de responsável pelo programa de **SERVIÇO DE HEMATOLOGIA E TRANSPLANTE DE MEDULA ÓSSEA (TMO) DO HOSPITAL UNIVERSITÁRIO/UNIVERSIDADE FEDERAL DE JUIZ DE FORA,** autorizo a realização da pesquisa intitulada **IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES** a ser conduzida sob a responsabilidade do pesquisador **PROF. GISELE MARIA CAMPOS FABRI/ EQUIPE CRISTINA DE PAULA NOVAES**; e DECLARO que esta instituição apresenta infraestrutura necessária à realização da referida pesquisa. Esta declaração é válida apenas no caso de haver parecer favorável do Comitê de Ética da UFJF para a referida pesquisa.

Juiz de Fora, 14 de JANEIRO de 2015

ASSINATURA_____

ANEXO C – Documento de Aprovação pelo Comitê de Ética em Pesquisa CEP/UFJF.

UNIVERSIDADE FEDERAL DE JUIZ DE FORA/MG

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES

Pesquisador: Gisele Maria Campos Fabri

Área Temática:

Versão: 5

CAAE: 30370114.5.0000.5147

Instituição Proponente: FACULDADE DE ODONTOLOGIA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.684.653

Apresentação do Projeto:

Apresentação do projeto esta clara, detalhada de forma objetiva, descreve as bases científicas que justificam o estudo, de acordo com as atribuições definidas na Resolução CNS 466/12 de 2012, item III.

Objetivo da Pesquisa:

O objetivo deste estudo é avaliar a influência do tratamento periodontal na melhora da mucosite oral e identificar os microrganismos orais prevalentes nos pacientes submetidos a terapia para o câncer. O Objetivo da pesquisa está bem delineado, apresenta clareza e compatibilidade com a proposta, tendo adequação da metodologia aos objetivos pretendido, de acordo com as atribuições definidas na Norma Operacional CNS 001 de 2013, item 3.4.1 - 4.

Avaliação dos Riscos e Benefícios:

Identificação dos riscos e as possibilidades de desconfortos e benefícios esperados, estão adequadamente descritos. A avaliação dos Riscos e Benefícios estão de acordo com as atribuições definidas na Resolução CNS 466/12 de 2012, itens III; III.2 e V.

Comentários e Considerações sobre a Pesquisa:

O projeto está bem estruturado, delineado e fundamentado, sustenta os objetivos do estudo em sua metodologia de forma clara e objetiva, e se apresenta em consonância com os princípios

Endereço: JOSE LOURENCO KELMER S/N
Bairro: SAO PEDRO **CEP:** 36.036-900
UF: MG **Município:** JUIZ DE FORA
Telefone: (32)2102-3788 **Fax:** (32)1102-3788 **E-mail:** cep.propesq@ufjf.edu.br

UNIVERSIDADE FEDERAL DE JUIZ DE FORA/MG

Continuação do Parecer: 1.604.653

éticos norteadores da ética na pesquisa científica envolvendo seres humanos elencados na resolução 466/12 do CNS e com a Norma Operacional Nº 001/2013 CNS.

Considerações sobre os Termos de apresentação obrigatória:

O protocolo de pesquisa está em configuração adequada, apresenta FOLHA DE ROSTO devidamente preenchida,com o título em português, identifica o patrocinador pela pesquisa, estando de acordo com as atribuições definidas na Norma Operacional CNS 001 de 2013 item 3.3 letra a; e 3.4.1 item 16. Apresenta o TERMO DE CONSENTIMENTO LIVRE ESCLARECIDO em linguagem clara para compreensão dos participantes, apresenta justificativa e objetivo, campo para identificação do participante, descreve de forma suficiente os procedimentos, informa que uma das vias do TCLE será entregue aos participantes,assegura a liberdade do participante recusar ou retirar o consentimento sem penalidades,garante sigilo e anonimato, explicita riscos e desconfortos esperados, ressarcimento com as despesas,indenização diante de eventuais danos decorrentes da pesquisa,contato do pesquisador e do CEP e informa que os dados da pesquisa ficarão arquivados com o pesquisador pelo período de cinco anos, de acordo com as atribuições definidas na Resolução CNS 466 de 2012, itens:IV letra b; IV.3 letras a,b,d,e,f,g e h; IV. 5 letra d e XI.2 letra f. O Pesquisador apresenta titulação e experiência compatível com o projeto de pesquisa, estando de acordo com as atribuições definidas no Manual Operacional para CPEs. Apresenta DECLARAÇÃO de infraestrutura e de concordância com a realização da pesquisa de acordo com as atribuições definidas na Norma Operacional CNS 001 de 2013 item 3.3 letra h.

Conclusões ou Pendências e Lista de Inadequações:

Diante do exposto, a emenda ao projeto está aprovada, pois está de acordo com os princípios éticos norteadores da ética em pesquisa estabelecido na Res. 466/12 CNS e com a Norma Operacional Nº 001/2013 CNS, segundo este relator, aguardando a análise do Colegiado. Data prevista para o término da pesquisa:Fevereiro de 2017.

Considerações Finais a critério do CEP:

Diante do exposto, o Comitê de Ética em Pesquisa CEP/UFJF, de acordo com as atribuições definidas na Res. CNS 466/12 e com a Norma Operacional Nº001/2013 CNS, manifesta-se pela APROVAÇÃO a emenda ao protocolo de pesquisa proposto, no qual destaca-se o objetivo de ampliar a pesquisa e viabilizar a adequada coleta dos dados, alteração do tamanho da amostra, sem mudança essencial nos objetivos e na metodologia do projeto original.

Endereço: JOSE LOURENCO KELMER S/N
Bairro: SAO PEDRO **CEP:** 36.036-900
UF: MG **Município:** JUIZ DE FORA
Telefone: (32)2102-3788 **Fax:** (32)1102-3788 **E-mail:** cep.propesq@ufjf.edu.br

UNIVERSIDADE FEDERAL DE JUIZ DE FORA/MG

Continuação do Parecer: 1.604.653

Incluímos na Equipe pesquisadores que contribuirão, cada um, em sua linha de pesquisa, com o processo de coleta de dados (Cristina de Paula Novaes), tratamento odontológico dos pacientes (Maria das Graças Afonso Miranda Chaves, Anellese Holetz de Toledo Lourenço e Cristina de Paula Novaes), análise dos dados(Ana Carolina Morais Apolônio, Ângela Mello Coelho) e elaboração do artigo científico. Foram incluídas instituições participantes que permitirão um acompanhamento mais eficaz dos pacientes em tratamento para o câncer (Hospital Universitário da Universidade Federal de Juiz de Fora-MG e Instituto Oncológico 9 de Julho também em Juiz de Fora). Vale lembrar ao pesquisador responsável pelo projeto, o compromisso de envio ao CEP de relatórios parciais e/ou total de sua pesquisa informando o andamento da mesma, comunicando também eventos adversos e eventuais modificações no protocolo.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_547042_E2.pdf	16/06/2016 17:19:12		Aceito
Orçamento	OrcamentoHU_folha3.jpg	16/06/2016 17:06:02	Cristina de Paula Novaes	Aceito
Orçamento	OrcamentoHU_folha2.jpg	16/06/2016 17:05:30	Cristina de Paula Novaes	Aceito
Orçamento	OrcamentoHU_folha1.jpg	16/06/2016 17:04:33	Cristina de Paula Novaes	Aceito
Projeto Detalhado / Brochura Investigador	ProjetoPlataformaBrasilJunho.doc	16/06/2016 17:03:20	Cristina de Paula Novaes	Aceito
Declaração de Instituição e Infraestrutura	declaracaoinfraestruturaoncologico.jpg	16/06/2016 17:02:31	Cristina de Paula Novaes	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TclePlataformaBrasilJunho.doc	16/06/2016 17:01:03	Cristina de Paula Novaes	Aceito
Declaração de Instituição e Infraestrutura	DeclaracaoinfraestruturaeconcordanciaHU.pdf	03/03/2016 16:54:31	Cristina de Paula Novaes	Aceito
Outros	ComprovanteregistroprojetoHU.jpg	03/03/2016 15:33:27	Cristina de Paula Novaes	Aceito
Declaração de	ComprovanteregistropesquisadorHU.	03/03/2016	Cristina de Paula	Aceito

Endereço: JOSE LOURENCO KELMER S/N
Bairro: SAO PEDRO **CEP:** 36.036-900
UF: MG **Município:** JUIZ DE FORA
Telefone: (32)2102-3788 **Fax:** (32)1102-3788 **E-mail:** cep.propesq@ufjf.edu.br

UNIVERSIDADE FEDERAL DE JUIZ DE FORA/MG

Continuação do Parecer: 1.684.653

Pesquisadores	jpg	15:30:40	Novaes	Aceito
Declaração de Instituição e Infraestrutura	infraestrutura_hu.jpg	06/01/2016 15:48:25	Cristina de Paula Novaes	Aceito
Outros	Plataformabrasil_anexos.docx	05/01/2016 19:37:56	Cristina de Paula Novaes	Aceito
Folha de Rosto	PGROSTOASS.pdf	14/04/2014 18:26:45		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

JUIZ DE FORA, 18 de Agosto de 2016

Assinado por:
Vânia Lúcia Silva
(Coordenador)

Endereço: JOSE LOURENCO KELMER S/N
Bairro: SAO PEDRO **CEP:** 36.036-900
UF: MG **Município:** JUIZ DE FORA
Telefone: (32)2102-3788 **Fax:** (32)1102-3788 **E-mail:** cep.propesq@ufjf.edu.br

ANEXO D – Termo de Consentimento Livre e Esclarecido.

UNIVERSIDADE FEDERAL DE JUIZ DE FORA

PRÓ-REITORIA DE PESQUISA

COMITÊ DE ÉTICA EM PESQUISA EM SERES HUMANOS - CEP/UFJF

36036-900 JUIZ DE FORA - MG – BRASIL

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O Sr. (a) está sendo convidado (a) como voluntário (a) a participar da pesquisa **IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES**

Nesta pesquisa pretendemos avaliar a presença de mucosite oral (MO) nos pacientes em tratamento para o câncer e a presença de doença periodontal (DP) nos pacientes diagnosticados com mucosite oral. Pesquisar a ocorrência de periodontopatógenos putativos, e correlacionar os microrganismos pesquisados com a mucosite oral (MO) e a doença periodontal (DP). Além de conhecer a presença e a gravidade da DP e MO, queremos incentivar e tornar possível a avaliação odontológica dos pacientes em tratamento para o câncer.

Para esta pesquisa adotaremos os seguintes procedimentos: Serão realizados os exames comuns em Odontologia, como o exame da mucosa da boca, da língua, assoalho da boca e tecido gengival. Além dos procedimentos odontológicos você responderá questionários sobre seu estado de saúde geral. Todos esses procedimentos não são testes novos ou desnecessários, são procedimentos de rotina, bem conhecidos e indispensáveis para conhecer os problemas odontológicos. Os riscos dos exames odontológicos são mínimos e são habituais desses procedimentos, ou seja: leve desconforto para afastar os lábios e bochechas, leve pressão e desconforto durante o exame das gengivas. Os exames radiográficos solicitados também são de baixo risco, havendo exposição segura à radiação por raios X. Faremos também uma limpeza profunda nos seus dentes e gengivas para tratar a infecção e inflamação. O risco também é mínimo e inclui leve dor nas gengivas após esta limpeza e amortecimento da boca e lábios pela anestesia odontológica necessária para este tratamento. Conhecer os fatores contribuintes para melhora ou piora da sua condição oral possibilita melhorar o tratamento reduzindo custos ambulatoriais e melhorando a sua qualidade de vida e de outros possíveis doentes.

Para participar deste estudo o Sr (a) não terá nenhum custo, nem receberá qualquer vantagem financeira. Apesar disso, caso seja identificado e comprovado danos provenientes desta pesquisa, o Sr.(a) tem assegurado o direito a indenização. Terá o esclarecimento sobre o estudo em qualquer aspecto que desejar e estará livre para participar ou recusar-se a participar. Poderá retirar seu consentimento ou interromper a participação a qualquer momento. A sua participação é voluntária e a recusa em participar não acarretará qualquer penalidade ou modificação na forma em que é atendido pelo pesquisador, que tratará a sua identidade com padrões profissionais de sigilo. Os resultados da pesquisa estarão à sua

disposição quando finalizada. Seu nome ou o material que indique sua participação não será liberado sem a sua permissão.

O (A) Sr (a) não será identificado em nenhuma publicação que possa resultar.

Este termo de consentimento encontra-se impresso em duas vias, sendo que uma cópia será arquivada pelo pesquisador responsável, na Faculdade de odontologia/departamento de Clínica odontológica da UFJF e a outra será fornecida ao senhor. Os dados e instrumentos utilizados na pesquisa ficarão arquivados com o pesquisador responsável por um período de 5 (cinco) anos, e após esse tempo serão destruídos. Os pesquisadores tratarão a sua identidade com padrões profissionais de sigilo, atendendo a legislação brasileira (Resolução Nº 466/12 do Conselho Nacional de Saúde), utilizando as informações somente para os fins acadêmicos e científicos.

Eu, _____, portador do documento de Identidade _____ fui informado (a) dos objetivos da pesquisa **IMPACTO DA TERAPIA PERIODONTAL NA MUCOSITE ORAL E IDENTIFICAÇÃO DE MICRORGANISMOS ORAIS PREVALENTES,** de maneira clara e detalhada e esclareci minhas dúvidas. Sei que a qualquer momento poderei solicitar novas informações e modificar minha decisão de participar se assim o desejar.

Declaro que concordo em participar. Recebi uma cópia deste termo de consentimento livre e esclarecido e me foi dada à oportunidade de ler e esclarecer as minhas dúvidas.

Juiz de Fora, _____ de _____ de 20 .

Nome	Assinatura participante	Data

Nome	Assinatura pesquisador	Data

Nome	Assinatura testemunha	Data

Em caso de dúvidas, com respeito aos aspectos éticos desta pesquisa, você poderá consultar:

CEP - Comitê de Ética em Pesquisa em Seres Humano-UFJF

Campus Universitário da UFJF

Pró-Reitoria de Pesquisa

CEP: 36036-900

Fone: (32) 2102- 3788 / E-mail: cep.propesq@ufjf.edu.br

Pesquisador Responsável: Gisele Maria Campos Fabri

Endereço: Campus Universitário da UFJF

Faculdade de Odontologia

CEP: 36036-900

Juiz de Fora – MG

Fone: (32) 2102-3857

E-mail: gisele.fabri@ufjf.edu.br

Cristina de Paula Novaes

ANEXO E – Ficha Clínica da Equipe de Dor Orofacial/ATM do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

FICHA CLÍNICA PARA AVALIAÇÃO DE COMPLICAÇÕES BUCAIS DA TERAPIA QUIMIOTERÁPICA

IDENTIFICAÇÃO DO PACIENTE:

Nome:

Idade:

Sexo: ( ) Feminino ( ) Masculino

Naturalidade: ( ) Juiz de Fora ( ) Outras:_____

Nacionalidade: ( ) Brasileiro ( ) Outros:_____

Dados Gerais da Terapia:

Agente Quimioterápico:

Local (is) acometido (os) pelo câncer/doença:

Tempo de diagnóstico: ( ) até 3 meses ( ) 3 a 6 meses
( ) 6 a 12 meses ( ) mais de 12 meses.

Tipo de tratamento:

( )QUIMIOTERAPIA : ( ) Curativa ( ) Adjuvante
( ) Neoadjuvante ( ) Paliativa

Medicamentos utilizados:_____

Tempo de tratamento: ( ) até 3 meses ( ) 3 a 6 meses
( ) 6 a 12 meses ( )mais de 12 meses.

Tratou-se de alguma dessas doenças:

( )Artrite reumatoide ( )Asma ( )Bronquite ( )Hepatite ( )Amigdalite

( )Derrame (AVC) ( )Fibromialgia ( )Sinusite ( )Pressão alta (HAS) ( )Diabete

( )Úlcera ( )Gastrite ( )Rinite ( )Coração ( )Depressão

( )Doença renal (rins) ( )Infecções ( )Enxaqueca ( )Herpes zoster (cobreiro)

( )Parkinson ( )Outra: _____

Medicamentos utilizados:

( ) Antibióticos	( ) AINES	( ) Hipoglicemiantes	( )Anti-hipertensivos
( ) Antivirais	( ) Ansiolíticos	( ) Analgésicos	( ) Imunossupressores
( ) Antifúngicos	( ) Anticoagulantes	( ) Antidepressivos	( ) Outros: _____

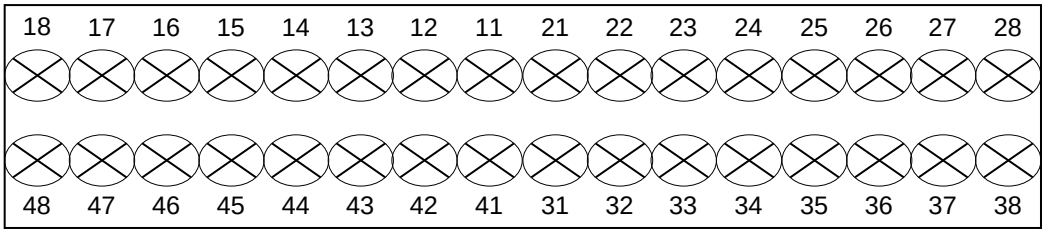
Descrição: _____

Índice gengival:

IG = 0	IG = 1	IG = 2	IG = 3
gengiva normal	gengiva com moderada inflamação, discreta mudança de cor, discreto edema, sem sangramento a sondagem	gengiva com moderada inflamação, vermelhidão, edema e com sangramento a sondagem	gengiva inflamação acentuada, vermelhidão, edema as ulcerações e com sangramento espontâneo

Índice de placa: n.º de superfícies coradas x 100 = ___%

n.º de dentes x 4



COMPLICAÇÕES BUCAIS PRESENTES:

( ) MUCOSITE: ( )Grau 0 ( )Grau 1 ( )Grau 2 ( )Grau 3 ( )Grau 4

GRAU	CRITÉRIOS PARA A CLASSIFICAÇÃO
0	Ausência de anormalidade detectada.
1	Presença de eritema sem tratamento necessário.
2	Quadro doloroso sem necessidade de analgésicos, com dificuldade na alimentação.
3	Presença de ulceração dolorosa exigindo o uso de analgésicos e impossibilitando a alimentação.
4	Presença de necrose com necessidade de nutrição parenteral.

Severidade da mucosite oral segundo a Organização Mundial da Saúde (OMS).

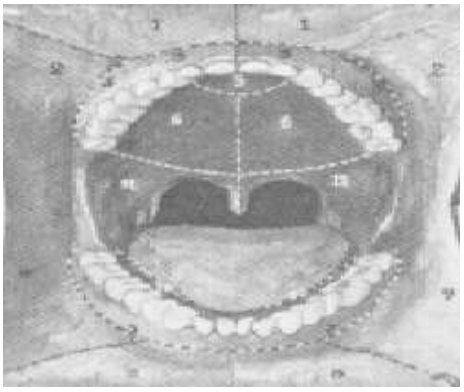
Locais: ( )1 ( )2 ( )3 ( )4 ( )5 ( )6 ( )7 ( )8 ( )9 ( )10

( )CANDIDÍASE

Locais: ( )1 ( )2 ( )3 ( )4 ( )5 ( )6 ( )7 ( )8 ( )9 ( )10

( )TRISMO

( )DOR OROFACIAL



CARACTERIZAÇÃO DA DOR OROFACIAL:

Você tem dor na face ou na boca? ( ) sim ( ) não

Há quanto tempo você tem essa dor? _____( )Dias ( )Meses ( )Anos

Região dolorida: _____

Periodicidade: ( )Diária ( )2-3 X sem ( )Sem ( )Quinz ( )Mensal.

Período do dia que tem dor: ( )M ( )T ( )N ( )Indiferente

Como ela aparece? ( )Espontânea: ( )N ( )S ( )Provocada: ( )N ( )S Como? _____

Quanto tempo dura a sua dor? ( )segs ( )mins ( )horas ( )dias ( )Outro _____

Tipo (característica) da dor: ( )Pontada ( )Peso ( )Queimor ( )Choque ( )Latejante ( )Contínua ( )Outro _____.

Intensidade da dor: ( ) fraca ( ) moderada ( ) forte Nota de 0 a 10: _____

Essa dor te acorda durante o sono? ( )N ( )S

Período do dia em que a dor é pior: ( )M ( )T ( )N ( )sono ( )indiferente ( )Outro:_____

Sabe o que iniciou a sua dor? ( )N: ( ) S Como?_____

O que piora a sua dor? _____

O que acalma a sua dor? _____

Dente		17		16		15		14		13		12		11	
face		V	L	V	L	V	L	V	L	V	L	V	L	V	L
PCS	D														
	C														
	M														
LEC-MG	D														
	C														
	M														
PCI	D														
	C														
	M														
SS	D														
	C														
	M														
G inserida															
A retenção															
Furca															
Mobilidade															
Diagnóstico															
Obs															

Dente		21		22		23		24		25		26		27	
face		V	L	V	L	V	L	V	L	V	L	V	L	V	L
PCS	D														
	C														
	M														
LEC-MG	D														
	C														
	M														
PCI	D														
	C														
	M														
SS	D														
	C														
	M														
G inserida															
A retenção															
Furca															
Mobilidade															
Diagnóstico															
Obs															

Dente		47		46		45		44		43		42		41	
face		V	L	V	L	V	L	V	L	V	L	V	L	V	L
PCS	D														
	C														
	M														
LEC-MG	D														
	C														
	M														
PCI	D														
	C														
	M														
SS	D														
	C														
	M														
G inserida															
A retenção															
Furca															
Mobilidade															
Diagnóstico															
Obs															

Dente		31		32		33		34		35		36		37	
face		V	L	V	L	V	L	V	L	V	L	V	L	V	L
PCS	D														
	C														
	M														
LEC-MG	D														
	C														
	M														
PCI	D														
	C														
	M														
SS	D														
	C														
	M														
G inserida															
A retenção															
Furca															
Mobilidade															
Diagnóstico															
Obs															

ANEXO F – Testes Clínicos para Diagnóstico de Disfagia.

Testes clínicos para diagnósticos de disfagia

Critérios:

Teste Engolir 100 ml de água

1- **Sentado na posição vertical colocar um copo de 100 ml de água destilada para seus lábios.**
2- **Ao receber um sinal beber a água o mais rapidamente possível.**
3- **Um cronômetro com uma capacidade de leitura de 1 s é usado para medir o tempo para tomar todo o conteúdo**
4- **Os sinais de dificuldade de deglutição, definida como tosse ou uma voz rouca após o teste, são registados.**
5- **Os participantes que engasgarem durante a deglutição são convidados a parar de beber imediatamente, independentemente de terem terminado a água. Nesses casos, o cronômetro deve ser pausado.**
6- **Marcar a quantidade de água ingerida em ml**
7- **Velocidade da deglutição (ml / s), definida como a quantidade de água bebida dividida pelo tempo decorrido no cronômetro, é calculada.**
8- **A velocidade de ingestão anormal é definida como velocidade da deglutição abaixo de 10 ml / s, de acordo com a definição utilizada na literatura.**

NOME:_____

DATA:_____

Quantidade de água ingerida: _____

Tempo:_____

Velocidade de Ingestão:_____

Classificação:

( ) Velocidade normal de ingestão ( ) Velocidade anormal de ingestão

ANEXO G – Escala Visual Analógica para avaliação da Xerostomia.

Faculdade de Odontologia – UFJF
Escala Visual Analógica para avaliação da Xerostomia

Nome: _____DATA:

- 0= ausência de sensação de ressecamento
- 10= sensação de ressecamento extremamente forte

1- O quanto você percebe dificuldade na fala pela sensação de secura na boca?

0 10

2- O quanto você percebe dificuldade na mastigação pela sensação de secura na boca?

0 10

3- Quantidade de saliva na sua boca

0 10

4- Grau de ressecamento na boca

0 10

5- Grau de ressecamento na garganta

0 10

6- Grau de ressecamento no lábio

0 10

7- Grau de ressecamento na língua

0 10

8- O quanto você sente sede

0 10

ANEXO H - Questionário OHIP.

Questionário OHIP - Faculdade de Odontologia – UFJF

NOME:_____DATA:_____

Responda cada questão marcando um "X" no espaço que melhor representa a sua resposta.

	nunca	poucas vezes	às vezes	quase sempre	sempre
01. Você já teve alguma dificuldade em pronunciar alguma palavra devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
02. Você já sentiu que o seu paladar piorou (algum alimento perdeu o sabor) devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
03. Você já teve dor na sua boca?	0 □	1 □	2 □	3 □	4 □
04. Você já sentiu desconforto ao comer algum alimento devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
05. Você já se sentiu constrangido(a) por causa dos seus dentes?	0 □	1 □	2 □	3 □	4 □
06. Você já ficou tenso(a) devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
07. Alguma vez você já deixou de saborear algum alimento devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
08. Você já teve que interromper alguma refeição devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
09. Você já sentiu alguma vez dificuldade em relaxar devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
10. Você já ficou envergonhado(a) devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
11. Você já ficou irritado(a) com outras pessoas devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
12. Você já sentiu alguma dificuldade em realizar alguma das suas atividades diárias (escola, passeios, festas, esportes, namorar) devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
13. Você já sentiu que a sua vida em geral não estava muito boa devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □
14. Você já se sentiu totalmente incapaz de realizar alguma atividade do seu dia-a-dia devido a problemas causados pelos seus dentes?	0 □	1 □	2 □	3 □	4 □

ANEXO I – Questionário Classe Socioeconômica.

Anexo F- CLASSE SÓCIO-ECONÔMICA ABA-ABIPEMI

A. Quem é o chefe da família na sua casa?
( ) o próprio entrevistado
( ) outro

B. Qual foi o último ano da escola que o chefe da família cursou?

Grau de instrução máximo	Pontos
Não estudou ou primário incompleto	0
Primário completo ou ginásio incompleto	5
Ginásio completo ou colegial incompleto	10
Ginásio incompleto ou universitário incompleto	15
Universitário completo	21

C. Na sua casa tem?

Aparelho de vídeo cassete	( ) não	( ) sim	(10 pontos)
Máquina de lavar roupa	( ) não	( ) sim	(8 pontos)
Geladeira	( ) não	( ) sim	(7 pontos)
Aspeirador de pó	( ) não	( ) sim	(6 pontos)

D. Quantos (cada ítem abaixo) existe em sua casa?

Ítem	nenhum (pontos)	1 (pontos)	2 (pontos)	3 (pontos)	4 (pontos)	5 (pontos)	6 ou + (pontos)
Carro	0	4	9	13	18	22	26
TV em cores	0	4	7	11	14	18	22
Banheiro	0	2	5	7	10	12	15
Empregada mensalista	0	5	11	16	21	26	32
Rádio	0	2	3	5	6	8	9

Classe sócio-economica ABA-ABIPEMI	Total de pontos
A	89 ou mais
B	59 A 88
C	35 A 58
D	20 A 34
E	0 A 19

ANEXO J - Ficha para identificação de coleta da Análise Microbiológica.

	Nome:			Coletas:	
	Prontuário:			Data	Momento
	Nascimento:		Idade:		Avaliação:
	Diagnóstico:				
	TMO:				
	História pregressa:				
					Elemento dentário: