UNIVERSIDADE FEDERAL DE ALFENAS

MILENA MORAES DE CARVALHO

FOTOBIOMODULAÇÃO DE LESÕES GENGIVAIS DECORRENTES DE DOENÇAS AUTOIMUNES: REVISÃO SISTEMÁTICA E META-ANÁLISE

Alfenas/MG
2022

MILENA MORAES DE CARVALHO

FOTOBIOMODULAÇÃO DE LESÕES GENGIVAIS DECORRENTES DE DOENÇAS AUTOIMUNES: REVISÃO SISTEMÁTICA E META-ANÁLISE

Dissertação apresentada como parte dos requisitos para obtenção do título de Mestre do Programa de Pós- Graduação em Ciências Odontológicas da Universidade Federal de Alfenas (UNIFAL-MG). Área de concentração: Odontologia.

Orientadora: Profª. Drª. Marina Lara de Carli Dias.
Coorientadora: Profª. Drª. Suzane Cristina Pigossi.

Alfenas/MG
2022

Dados Internacionais de Catalogação-na-Publicação (CIP)
Sistema de Bibliotecas da Universidade Federal de Alfenas
Biblioteca Central – Campus Sede

Carvalho, Milena Moraes de
C331f Fotobiomodulação de lesões gengivais decorrentes de doenças autoimunes: revisão sistemática e meta-análise / Milena Moraes de Carvalho – Alfenas, MG, 2022.
101 f.: il. –

Orientador: Marina Lara de Carli Dias..
Dissertação (Mestrado em Ciências Odontológica) – Universidade Federal de Alfenas, 2022.
Bibliografia.

1. Doenças autoimunes. 2. Gengivite. 3. Laserterapia. I. Dias, Marina Lara de Carli. II. Título.

CDD- 617.6

Ficha Catalográfica elaborada por Marlom Cesar da Silva
Bibliotecário-Documentalista CRB6/2735

MILENA MORAES DE CARVALHO

FOTOBIOMODULAÇÃO DE LESÕES GENGIVAIS DECORRENTES DE DOENÇAS AUTOIMUNES: REVISÃO SISTEMÁTICA E METAANÁLISE

A Banca examinadora abaixo-assinada aprova a Dissertação apresentada como parte dos requisitos para a obtenção do título de Mestre pela Universidade Federal de Alfenas. Área de concentração: Odontologia.

Aprovada em: 03 de fevereiro de 2022

Profa. Dra. Marina Lara de Carli Dias
Instituição: Universidade Federal de Alfenas-MG

Profa. Dra. Andréa Lusvarghi Witzel
Instituição: Universidade de São Paulo

Prof. Dr. João Adolfo Costa Hanemann
Instituição: Universidade Federal de Alfenas-MG

Documento assinado eletronicamente por **Marina Lara de Carli Dias, Professor do Magistério Superior**, em 03/02/2022, às 12:02, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

Documento assinado eletronicamente por **João Adolfo Costa Hanemann, Professor do Magistério Superior**, em 04/02/2022, às 10:08, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

Documento assinado eletronicamente por **Andrea Lusvarghi Witzel, Usuário Externo**, em 04/02/2022, às 14:24, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do Decreto nº 8.539, de 8 de outubro de 2015.

A autenticidade deste documento pode ser conferida no site https://sei.unifal-mg.edu.br/sei/controlador_externo.php?acao=documento_conferir&id_orgao_acesso_externo=0, **informando o código verificador 0649624 e o código CRC FF013DF5.**

Criado por rosana.oliveira, versão 7 por marina.carli em 03/02/2022 12:02:47.

Dedico esse trabalho a minha família: minha mãe Izabel, meu pai Claudio e minha irmã Bruna, pelo apoio incondicional e pelo incentivo diário paraque eu fosse atrás desse objetivo. Dedico também a minha orientadora e amiga, Profa. Marina, que não apenas confiou a mim esse trabalho, mas me guiou de forma impecável até aqui. Sem vocês esse trabalho não existiria.

AGRADECIMENTOS

Agradeço, em primeiro lugar a **Deus** que, em sua infinita bondade, não deixa de mostrar sua presença em minha vida e me dá forças para superar os obstáculos do caminho.

À **Universidade Federal de Alfenas,** minha segunda casa, por me oferecer a oportunidade da tão sonhada Pós-Graduação e por fornecer meios para tornar esse objetivo concretizável.

À **Professora Marina Lara de Carli**, minha orientadora, por todo o conhecimento transmitido, pela dedicação, paciência e prontidão em ensinar. Por todas as oportunidades fornecidas para que eu me desenvolvesse, pela disponibilidade em tirar todas as minhas dúvidas, por me tranquilizar quando a pandemia modificou todos os nossos planos e por criar novas possibilidades para que essa dissertação se tornasse possível. Meu agradecimento eterno!

À **Professora Suzane Cristina Pigossi**, minha co-orientadora, por toda paciência em me ensinar as metodologias de Pesquisa, pelo grande suporte na elaboração dos artigos, pelo imenso apoio até mesmo na busca pelo Doutorado e por estar sempre disposta e de prontidão para me ajudar! Agradeço imensamente a confiança e a amizade! A você, o meu muito obrigada!

Ao **Professor João Adolfo Costa Hanemann**, meu primeiro contato nesse retorno à Unifal e que tornou tudo muito mais fácil! Agradeço por gentilmente compartilhar comigo seus casos clínicos, por todo o apoio e incentivo na escrita de artigos e participação em congressos e jornadas acadêmicas e por me oferecer a oportunidade de acompanhá-lo durante o atendimento aos seus pacientes na Clínica de Estomatologia, onde tanto pude aprender! Sou muito grata por isso!

Aos demais **Professores do Programa de Pós-Graduação em Ciências Odontológicas**, por se desdobrarem e aprenderem, junto com os alunos, uma forma diferente de ensinar durante o distanciamento social e pela perfeita condução do curso em tempos tão difíceis de pandemia.

Agradeço a minhas queridas colegas do Programa, **Marcela, Elisângela e Larissa**, por serem um apoio ao longo dessa jornada. Agradeço a vocês pela amizade, pelos momentos compartilhados e por tornarem esse processo muito mais leve. É maravilhoso ter com quem contar! E **aos demais colegas do Programa**, por compartilharem experiências e conhecimentos, que muito agregaram ao meu aprendizado! O meu muito obrigada a todos vocês!

Agradeço também a todos os alunos da graduação que, direta ou indiretamente, fizeram parte desse meu período de formação. Em especial, a **Thaís, Roberta, Jovânia e Alexandra**, que tanto me ajudaram ao longo desses dois anos! Vocês fizeram a diferença!

E, sem dúvidas, agradeço imensamente **a minha família (minha mãe Izabel, meu pai Claudio e minha irmã Bruna)** pelo apoio incondicional, por me incentivarem diariamente a seguir meus objetivos, independentemente das inúmeras dificuldades. Obrigada por acreditarem em mim e não me permitirem pensar em desistir. Sem vocês esse trabalho não seria possível. Minha eterna gratidão!

O presente trabalho foi realizado com apoio da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) – Código de Financiamento 001.

Feliz aquele que transfere o que sabe e aprende o que ensina.

(CORALINA, 2007)

RESUMO

Diversas doenças autoimunes podem afetar a cavidade oral, com destaque para o líquen plano oral (LPO), penfigoide das membranas mucosas (PMM) e pênfigo vulgar (PV). Essas doenças podem se manifestar como lesões gengivais e são comumente tratadas com corticosteroides tópicos. Por conta de seus efeitos adversos e de lesões refratárias a essas terapias, outras alternativas de tratamento são propostas, como a fotobiomodulação (FBM). Assim, o objetivo deste estudo foi avaliar os efeitos da FBM nessas lesões, abordando a seguinte questão: "A FBM é eficaz para tratar lesões gengivais autoimunes?". Uma busca eletrônica foi realizada até julho de 2020 em quatro bases de dados: MEDLINE-PubMed, Embase, Scopus e Web of Science. Dezessete estudos foram incluídos, dos quais seis foram usados para a meta-análise. Mulheres com LPO foram as mais acometidas, apresentando envolvimento gengival concomitante a outras localizações, principalmente mucosa jugal e língua. Os resultados da meta-análise não mostraram diferenças significativas entre a FBM e o corticosteroide tópico na redução da dor no acompanhamento de 60 dias; no entanto, a escala visual analógica dedor (EVA) e a escala clínica Thongprasom mostraram redução significativa quando comparados antes e depois da FBM em 30 e 60 dias de acompanhamento. Portanto, conclui-seque a FBM se tornou uma importante ferramenta no manejo das lesões gengivais autoimunes, apresentando redução significativa da dor e melhora dos escores clínicos das lesões após a terapia, sem apresentar diferenças significativas quando comparadas a corticoterapia tópica. Até o momento, existem poucas evidências fortes para avaliar a eficácia da FBM em lesões gengivais autoimunes.

Palavras-chave: doenças autoimunes; gengivite; laserterapia.

ABSTRACT

Several autoimmune diseases can affect the oral cavity, especially oral lichen planus (OLP), mucous membrane pemphigoid (PMM) and pemphigus vulgaris (PV). These diseases can present as gingival lesions and are commonly treated with topical corticosteroids. Because of their adverse effects and injuries refractory to these therapies, other alternatives have been developed, such as photobiomodulation (PBM). Thus, the aim of this study was to evaluate the effects of PBM on these lesions, addressing the following question: "Is PBM effective to treat autoimmune gingival lesions?". An electronic search was performed until July 2020 in four databases: MEDLINE-PubMed, Embase, Scopus and Web of Science. Seventeen studies were included, of which six were used for the meta-analysis. Women with OLP were the most affected patients, presenting gingival involvement concomitant to other sites, mainly buccal mucosa and tongue. Meta-analysis results showed no significant differences between PBM and topical corticosteroid in pain reduction at baseline and 60-day follow-up; however, Visual Analogue Score (VAS) and Thongprasom clinical scale showed significant reduction when compared before and after PBM at 30 and 60-day follow-up. PBM has become an important tool in the management of autoimmune gingival lesions, showing significant pain reduction and improvement of clinical scores of the lesions after therapy, without showing significant differences when compared to topical corticosteroid. Up to now, there is little strong evidence to assess the efficacy of PBM in autoimmune gingival lesions.

Keywords: autoimmune diseases; gingivitis; laser therapy.

SUMÁRIO

1	**INTRODUÇÃO EXPANDIDA**.....	10
1.1	**Gengivite Descamativa**.....	11
1.1.1	LÍQUEN PLANO ORAL.....	13
1.1.2	PENFIGOIDE DAS MEMBRANAS MUCOSAS.....	17
1.1.3	PÊNFIGO VULGAR.....	18
1.1.4	TRATAMENTO.....	20
2	**OBJETIVOS**.....	24
3	**PHOTOBIOMODULATION OF GINGIVAL LESIONS RESULTING FROMAUTOIMMUNE DISEASES: SYSTEMATIC REVIEW AND META-ANALYSIS**…….	25
4	**REFERÊNCIAS**.....	54
	APÊNDICE A: Metodologia detalhada da pesquisa.....	58
4.1	Pergunta Principal.....	58
4.2	Estratégia de Busca.....	58
4.3	Critérios de Elegibilidade e Seleção dos Estudos.....	60
4.4	Extração de Dados.....	61
4.5	Avaliação de Qualidade.....	61
4.6	Medidas de Efeito do Tratamento.....	62
4.7	Síntese dos Dados.....	62
	ANEXO A: Normas da Revista *Clinical Oral Investigations*.....	64

1 INTRODUÇÃO EXPANDIDA

As doenças autoimunes são marcadas por uma resposta exagerada do organismo que leva a danos e disfunções de órgãos e tecidos (ORTONA *et al*., 2016). A partir de uma predisposição genética, e de fatores ambientais que desencadeiam as vias imunológicas, essas doenças levam à destruição de tecidos específicos ou múltiplos (TAKAHASHI *et al*., 2019). Além disso, a falha em distinguir o que é próprio do que não é próprio ao organismo é conhecida como violação da tolerância e é a base dessas condições (WANG *et al*., 2015). Uma ampla gama de doenças autoimunes pode afetar a cavidade oral, embora as mais comunssejam líquen plano oral (LPO), penfigoide das membranas mucosas (PMM), pênfigo vulgar (PV) e epidermólise bolhosa (EB) (ARDUINO, 2017). Ainda, as lesões orais podem ser a primeira e ocasionalmente a única manifestação de vários distúrbios imunológicos que afetama pele e a mucosa (MUSTAFA *et al*., 2015).

O LPO é uma doença inflamatória crônica de origem autoimune, mediada por linfócitos T que acomete o tecido epitelial, cuja etiologia e patogênese não são completamenteconhecidas (PAIVA *et al*., 2016). Seu aspecto clínico pode variar de ceratótico (reticular ou semelhante a placa) a eritematoso e ulcerativo, e os locais mais comumente afetados na cavidade oral são a mucosa jugal, a língua e a gengiva (ZAKRZEWSKA, 2001; SHIVHARE *et al*., 2016). Por sua vez, o PMM descreve um grupo de doenças inflamatórias crônicas subepiteliais imunomediadas, que manifestam um padrão heterogêneo de lesões orais, oculares, cutâneas, genitais, nasofaríngeas, esofágicas e laríngeas (CAFARO *et al*., 2012). A cavidade oral e, em particular o tecido gengival, são os locais mais comumente afetados, correspondendo de 83-100% de todos os casos (CHAN, 2001).

Outra doença autoimune com importante manifestação oral é o PV, que compreende um grupo de doenças autoimunes bolhosas raras que acomete a pele e as mucosas (PORRO *et al*., 2019). As lesões orais geralmente precedem as lesões cutâneas ou são a única manifestação da doença, acometendo áreas como lábios, gengiva, mucosa oral e palato (DAL PRÁ *et al*., 2020). As manifestações orais do PV podem ser muito dolorosas, prejudicando a ingestão oral e, consequentemente, afetando negativamente a qualidade de vida dos pacientes (ZAND; SHIRKAVAND, 2017).

Apesar de heterogêneos, todos os distúrbios citados acima compartilham duas características: uma patogênese imunomediada e, possivelmente, um quadro clínico comum,

representado por lesões orais, com atenção especial para aquelas na forma gengival (LO RUSSO *et al*., 2008). Em geral, as lesões gengivais causadas por distúrbios dermatológicos autoimunes são descritas como lesões eritematosas difusas, bolhas, erosões ou ulcerações, localizadas principalmente na gengiva inserida e no palato e são chamadas de gengivite descamativa (GD) (ARDUINO *et al*., 2017; GARCIA-POLA *et al*., 2019). Assim, sabe-se que a GD é um achado clínico com diversas etiologias potenciais e, embora existam outros diagnósticos diferenciais, LPO, PMM e PV são os mais comuns (MADERAL *et al*., 2018).

Atualmente, existem tratamentos específicos focados nas manifestações gerais da doença relacionadas à sua patogênese. Os corticosteroides tópicos têm sido indicados em diferentes formas e prescritos em diferentes dosagens, ou também administrados na forma sistêmica, além de outros fármacos como imunossupressores e antibióticos de amplo espectro (KARAGOZ *et al*., 2016; MADERAL *et al*., 2018). No entanto, o uso de esteroides sistêmicos apresenta um risco aumentado de efeitos colaterais adversos. Consequentemente, modalidades alternativas de tratamento surgiram. Dentre elas, destaca-se a terapia a laser de baixa potência, também chamada de fotobiomodulação (FBM) (SOBANKO; ALSTER, 2008; JAJARM *et al*., 2018). Diferentes tipos de laser (hélio-neônio e diodo) com dose, potência de saída e tempo de irradiação diversificados são aplicados no local da lesão e a irradiação é repetida por várias sessões (CAFARO *et al*., 2014). Sua utilização é vinculada aos efeitos anti-inflamatórios esperados, alívio da dor e regeneração acelerada dos tecidos danificados, sem demonstrar os efeitos adversos associados ao tratamento medicamentoso (SOBANKO; ALSTER, 2008; JAJARM *et al*., 2018). Portanto, o objetivo desta revisão sistemática foi avaliar os efeitos da FBM em lesões gengivais decorrentes de doenças autoimunes, incluindo LPO, PMM e PV.

1.1 Gengivite Descamativa

GD é um termo clínico que representa a expressão oral de diferentes doenças mucocutâneas (GARCIA-POLA *et al*., 2019). Primeiramente descrita por Prinz, em 1932, indica a presença de eritema, descamação, erosão e formação de bolhas em gengiva inserida e marginal (GARCIA-POLA *et al*., 2019; LO RUSSO *et al*., 2008;). GD é uma entidade

clinicamente relevante porque afeta a saúde oral e pode ser uma característica de doença sistêmica (LO RUSSO *et al*., 2008).

As lesões de GD envolvem principalmente a porção vestibular da gengiva dos dentes anteriores, especialmente em um padrão difuso. No entanto, as lesões podem ocorrer em áreas restritas em diferentes locais e, lesões gengivais limitadas podem, nas fases iniciais ou em recidivas da doença, preceder lesões gengivais mais extensas com envolvimento de outras mucosas (LO RUSSO *et al*., 2008). Clinicamente, apresenta dor moderada, em parte devido ao depósito de placa na margem gengival, sendo, em alguns casos, a primeira manifestação da doença (GARCIA-POLA *et al*., 2019).

Vale ressaltar que o termo Gengivite Descamativa não é um diagnóstico específico, mas descreve um quadro clínico frequentemente encontrado associado a vários distúrbios mucocutâneos e condições sistêmicas, como sugerido por Glickman e Smulow em 1964 (LO RUSSO *et al*., 2008). McCarthy e colaboradores em 1960 foram os primeiros a sugerir que GD não é uma entidade, mas uma resposta gengival para uma variedade de distúrbios sistêmicos de diferentes etiologias (TOFAN *et al*., 2018). Essa alteração está presente mais frequentemente em LPO, PMM e PV (MADERAL *et al*., 2018). Embora mais raro, também pode ser causada por outras patologias imunológicas, como lúpus eritematoso, eritema multiforme, doença enxerto *versus* hospedeiro, epidermólise bolhosa, gengivite plasmocitária e doenças do colágeno (GARCIA-POLA *et al*., 2019). Afeta predominantemente mulheres mais velhas e na menopausa, embora possa ocorrer em pessoas jovens e crianças (LO RUSSO*et al*., 2008).

PMM é responsável por 35% a 48% dos casos de GD; LPO e PV representam 24% a 45% e 3% a 15%, respectivamente (LO RUSSO *et al*., 2008). Além de afetarem a cavidade oral, essas desordens podem gerar alterações mucocutâneas extraorais, por exemplo em laringe, conjuntiva, esôfago, mucosa nasal e genital e na pele (LO RUSSO *et al*., 2009).

Por conta da diversidade de sua origem, GD representa um distúrbio de mucosa oral relevante. Devido ao fato de que nem sempre se torna possível relacionar GD a um diagnóstico prévio, é importante que os cirurgiões-dentistas conheçam o seu conceito e sejam capazes de distinguir entre gengivite inflamatória clássica e GD na presença de placa dental (GARCIA-POLA *et al*., 2019). Além disso, a importância dos clínicos reconhecerem e corretamente diagnosticarem GD se deve ao fato de que os distúrbios sistêmicos que a geram são raros, agressivos e precisam de tratamento imediato (TOFAN *et al*., 2018). Acuradas

investigações clínicas, histológicas e sorológicas são geralmente exigidas para diferenciar desordens associadas à GD, fornecer a terapia adequada e melhorar o prognóstico dos pacientes (LO RUSSO *et al*., 2008).

Segundo Lo Russo e colaboradores (2008), quando são reconhecidas lesões de GD, o primeiro passo consiste em obter um histórico médico cuidadoso. O início e progressão das lesões gengivais deve ser investigado com cuidado porque a maioria distúrbios associados à GD têm início subagudo e o paciente geralmente não tem conhecimento disso (especialmente em LPO e PMM). Portanto, se torna necessário um conhecimento prévio das doenças relacionadas a GD, principalmente LPO, PMM e PV.

1.1.1 LÍQUEN PLANO ORAL

O Líquen Plano (LP) é uma doença mucocutânea inflamatória crônica, mediada por células T, de causa desconhecida. Afeta a pele, a membrana mucosa (particularmente amucosa oral e genital e, muito raramente, também a mucosa anal, do nariz, da laringe, da conjuntiva e da uretra) as unhas e os cabelos, cuja aparência varia de ceratótica (reticular oude placa) a eritematosa e ulcerativa (NICO *et al*., 2011; SHIVHARE *et al*., 2016). Foi descritopela primeira vez pelo médico inglês Erasmus Wilson em 1869. Líquen é derivado da palavra grega - *Leichen* - "musgo da árvore" e palavra derivada do latim - *planus*, "plano" (SHIVHARE *et al*., 2016).

O LPO é uma doença mucocutânea mediada imunologicamente, apresentando forte correlação com o estado de estresse dos indivíduos (CHENG *et al*., 2016; DANIELLI *et al*., 2010; PAIVA *et al*., 2016; SOUSA *et al*., 2005). Embora a etiologia do LPO seja desconhecida, a patogênese é bem definida através da infiltração linfocítica e o envolvimento dos queratinócitos da camada basal, degeneração celular e apoptose por células T CD8+ autocitotóxicas, indução e liberação de citocinas pró-inflamatórias (LAVAEE; SHADMANPOUR, 2019).

Segundo Sugerman e colaboradores (2002) , podem estar relacionados mecanismos específicos e não específicos no desenvolvimento do LPO. No mecanismo específico, os queratinócitos da membrana basal apresentam antígenos e os linfócitos T citotóxicos causam a morte desses queratinócitos. No mecanismo não específico, há degranulação de mastócitos e

ativação de metaloproteinases de matriz. Juntos, esses dois mecanismos podem levar ao acúmulo de células T na lâmina própria, uma interrupção da membrana basal, migração de linfócitos T intra-epiteliais e a apoptose de queratinócitos (SUGERMAN *et al*., 2002).

Evidências atuais sugerem que a doença está relacionada a uma alteração da imunidade mediada por células, precipitada por fatores endógenos ou exógenos, resultandoem uma resposta alterada a autoantígenos. A maioria das células T ativadas no infiltrado inflamatório do LPO são CD8. As células T ativadas associadas ao aumento da produção de citocinas Th1 [Interleucinas (IL): IL-1, IL-8, IL-12; Fator de Necrose Tumoral Alfa (TNF-α)] aumentam a expressão de moléculas de adesão intercelulares (ICAM-1) nas células de Langerhans e macrófagos, levando à apresentação de antígenos do complexo maior de histocompatibilidade pelos queratinócitos. Esta resposta imune alterada resulta em apoptose dos queratinócitos da camada basal e pode determinar a atividade da doença. (NICO *et al*., 2011). A imunidade humoral também tem sido associada ao surgimento da doença, possivelmente como um fenômeno secundário à lesão iniciada antes da destruição dos queratinócitos basais via linfócitos T citotóxicos (VÉLEZ, 2012).

Em relação à epidemiologia, o LPO é mais comum em adultos de meia idade (quinta década de vida), sendo raro o acometimento em crianças. As mulheres são mais afetadas, normalmente em uma razão de 3:2 em relação aos homens (NEVILLE *et al*., 2009). A prevalência de LPO é de 1% a 2% da população (LAVAEE; SHADMANPOUR, 2019). Pacientes com LP cutâneo apresentam manifestação oral em mais de 60% dos casos. Entretanto, apenas a minoria dos portadores de LPO, aproximadamente 15%, desenvolvem lesões cutâneas. Além do acometimento da pele e da mucosa oral, pode-se encontrar lesões distribuídas em outros sítios anatômicos. LP nos genitais ocorre em aproximadamente 20% dos pacientes com LPO e pode também ser observado LPO e esofágico concomitantes. Ainda se encontram lesões em couro cabeludo e sinais em unhas, glande e conjuntiva (CHENG *et al*., 2016).

Na cavidade oral, a mucosa jugal, a língua e a gengiva são os locais mais comuns para ocorrência do LPO. Clinicamente, pode ser classificado dentro de diferentes variantes: reticular, erosivo, atrófico, bolhoso, tipo placa e papular. O tipo reticular é a variante mais comum de LPO e comumente se manifesta como linhas ceratóticas brancas (estrias de Wickham), cercadas por tecido eritematoso. LPO reticular geralmente não apresenta qualquer sintoma ou desconforto (JAJARM *et al*., 2018). Normalmente envolve a região posterior da

mucosa jugal bilateralmente. Outras áreas da mucosa oral também podem estar envolvidas concomitantemente, como a borda lateral e o dorso da língua, a gengiva, o palato, e o vermelhão labial. O líquen plano reticular é assim chamado por causa de seu padrão característico de linhas brancas entrelaçadas, no entanto, as lesões brancas podem, em alguns casos, apresentar-se como pápulas. Estas lesões são tipicamente não estáticas, e podem apresentar piora ou melhora em semanas ou meses. O padrão reticular pode não ser tão evidente em algumas localizações, como no dorso da língua, onde as lesões se apresentam como placas queratóticas com atrofia das papilas. Além disso, mucoceles superficiais podem se desenvolver no interior ou adjacente às áreas de mucosa que estão envolvidas pelo LPO (NEVILLE *et al*., 2009).

LPO erosivo ou ulcerativo é o segundo tipo mais comum e comumente causa dor, levando o paciente a procurar ajuda profissional; manifesta-se pela presença de áreas eritematosas, atróficas, com diferentes graus de ulceração, podendo apresentar estrias de Wickham na periferia das lesões. As lesões geralmente estão localizadas bilateralmente na mucosa oral, nas laterais e região posterior da língua, nas gengivas, no palato e na mucosa labial. As lesões geralmente são crônicas e a remissão espontânea é rara (GRANDO *et al*., 2013). Algumas vezes, a atrofia e ulceração estão confinadas à mucosa gengival produzindo, portanto, GD. Se o componente erosivo for grave, pode ocorrer separação entre o epitélio e o tecido conjuntivo subjacente, resultando na apresentação relativamente rara do LP bolhoso (NEVILLE *et al*., 2009). Lesões do tipo placa têm sido relatadas mais comumente em fumantes, com a persistência da lesão mesmo em caso de cessação do hábito. Em indivíduos de pele escura, pode ser visto um padrão reticular pigmentado (CHENG *et al*., 2016).

Aproximadamente dois terços dos pacientes com LPO apresentam desconforto. A intensidade dos sintomas é variável e se manifesta, em alguns casos, apenas se em contato com alimentos ácidos ou apimentados. Alguns estudos relatam sintomatologia dolorosa espontânea. Sensação de mucosa rígida, com redução de flexibilidade e limitação da abertura de boca são outros sinais e sintomas relatados. Dessa forma, o LP pode apresentar significativo impacto negativo na qualidade de vida do paciente (PARASHAR, 2011).

LPO raramente regride espontaneamente, é considerada uma lesão potencialmente maligna e tratamento e proservação a longo prazo são necessários (LAVAEE; SHADMANPOUR, 2019). A taxa de transformação maligna do LPO é de aproximadamente 1,09% e pode ser ainda maior em lesões atrófico-erosivas (FITZPATRICK; HIRSCH;

GORDON, 2014).

As lesões de pele do LP são classicamente descritas como pápulas poligonais, purpúreas e pruriginosas. Em geral, afetam as superfícies flexoras das extremidades. Asescoriações podem não ser visíveis, apesar do fato de que as lesões são pruriginosas, podendo ferir o paciente como resultado da coceira. Um exame cuidadoso da superfície das pápulas da pele revela linhas brancas finas semelhantes a um rendilhado (estrias de Wickham). Outros locais de envolvimento extrabucal incluem a glande do pênis, a mucosa vulvar e as unhas (NEVILLE *et al.*, 2009).

As características histopatológicas do LP são típicas, porém não específicas, porque outras condições, como a reação liquenoide a medicamentos, a reação liquenoide ao amálgama, a doença do enxerto *versus* hospedeiro (DEVH), o lúpus eritematoso (LE), a estomatite ulcerativa crônica e a reação da mucosa bucal à canela, também podem exibir um padrão histopatológico semelhante (NEVILLE *et al*., 2009).

Graus variáveis de ortoqueratose e paraqueratose podem estar presentes na superfície do epitélio, dependendo do local onde foi realizada a biópsia. A espessura da camada espinhosa também pode variar. As cristas epiteliais podem estar ausentes ou hiperplásicas,mas classicamente são pontiagudas ou têm forma de "dentes de serra" (NEVILLE *et al*.,2009).

A destruição da camada de células basais do epitélio (degeneração hidrópica) também é evidente, sendo acompanhada por um intenso infiltrado inflamatório semelhante a uma faixa, predominantemente de linfócitos T logo abaixo do epitélio subjacente. Queratinócitos em degeneração podem ser observados em áreas do epitélio e na interface do tecido conjuntivo e têm sido denominados de corpos coloides, citoides, hialinos ou de Civatte(NEVILLE *et al*., 2009; WERNECK *et al*., 2015).

Não é esperado um grau significativo de atipia epitelial no LPO, embora algumas lesões possam apresentar infecção por *Candida* sobreposta e ter uma aparência mais preocupante. Ocasionalmente, a resposta inflamatória crônica do hospedeiro a células atípicas da displasia epitelial pode ser quase indistinguível histopatologicamente do LP, particularmente nos casos mais leves de displasia epitelial. Essa ambiguidade pode contribuir para a controvérsia relacionada ao potencial de transformação maligna do LP. As características imunopatológicas do LP são inespecíficas. A maioria das lesões mostra adeposição de uma banda desalinhada de fibrinogênio na zona da membrana da basal

(NEVILLE *et al*., 2009).

Em comparação com a doença cutânea, as lesões orais exibem menos cristas epiteliais em “dentes de serra” e mais frequentemente exibem atrofia epitelial. Amostras de biópsia de LPO podem apresentar melanose e incontinência de melanina com melanófagos associados, particularmente em indivíduos de pele escura. A incontinência de melanina não é específica do LPO e é encontrada em uma ampla gama de desordens inflamatórias que compartilham um processo inflamatório liquenoide (CHENG *et al*., 2016).

1.1.2 PENFIGOIDE DAS MEMBRANAS MUCOSAS

PMM é uma rara doença bolhosa autoimune que envolve predominantemente as mucosas e, ocasionalmente, a pele. Embora as mucosas oral e ocular sejam os locais afetados mais comuns, a nasofaringe, esôfago, laringe e região anogenital também podem estar envolvidas (TAYLOR *et al*., 2015). A doença causa dano subepitelial e cicatrização dessas superfícies mucosas; portanto, seu nome anterior penfigoide cicatricial. Embora o PMM possa ser relativamente leve se a doença estiver limitada à mucosa nasal e oral, podem ocorrer complicações graves com risco de vida se a traqueia ou o esôfago estiverem envolvidos; caso haja acometimento ocular, pode provocar cegueira (THORNE *et al*., 2004).

Em relação a etiologia, fatores genéticos e ambientais têm um substancial efeito sobre a suscetibilidade ao PMM. Não existem predileções raciais ou geográficas, mas pode haver antecedentes imunogenéticos e associação com moléculas do complexo maior de histocompatibilidade. PMM é caracterizado pela deposição linear de Imunoglobulinas IgG (97%), IgA (27%) ou C3 (78%) ao longo da zona da membrana basal epitelial (ZMB). Autoanticorpos contra vários componentes epiteliais da ZMB provavelmente desempenham um papel na patogênese desse grupo de doenças (CHAN *et al*., 2002; TAYLOR *et al*., 2015). A resposta dos autoanticorpos pode ser direcionada contra diferentes autoantígenos da membrana basal (moléculas de adesão específicas localizadas nos hemi-desmossomos dos queratinócitos epidérmicos basais e na lâmina lúcida da ZMB, dos quais o colágeno tipo XVII e VII, juntamente com a laminina 332, são melhor caracterizados (JASCHOLT *et al*., 2017; TAYLOR *et al*., 2015). Acredita-se amplamente que as lesões de PMM sejam o resultadode uma perda subepitelial de adesão mediada por autoanticorpos, embora os mecanismos moleculares subjacentes sejam amplamente desconhecidos (TAYLOR *et al*., 2015).

PMM é uma doença rara, que afeta não mais que 5 a 7,5 de cada 10.000 indivíduos. A sua incidência foi estimada entre 1,3 e 2,0 por milhão por ano em estudos dermatológicos franceses e alemães. Entretanto, estudos de coorte oftalmológicos e orais sugerem uma incidência mais alta. As mulheres são mais frequentemente afetadas que os homens, sendo a proporção mulher/homem aproximadamente de 2:1. PMM ocorre principalmente napopulação idosa, comumente observado entre 50 e 80 anos de idade. As crianças raramente são afetadas. (TAYLOR *et al*., 2015)

Clinicamente, a cavidade oral apresenta a maior frequência aproximada de envolvimento, seguida da mucosa ocular, nasal, nasofaringe, anal, genital, pele, laringe e esôfago, em ordem decrescente de acometimento. Em mucosa oral, a doença se manifesta como manchas eritematosas, bolhas, erosões, úlceras recobertas por pseudomembrana, localizados mais comumente em gengiva inserida e mucosa palatina e, menos comumente, emmucosa labial, língua e mucosa jugal. (CHAN *et al*., 2002) Lesões orais são geralmente persistentes. As bolhas cheias de líquido se desenvolvem e depois se rompem, deixando úlceras dolorosas que cicatrizam lentamente por vários dias a semanas. A gravidade dadoença é extremamente variável, oscilando de bolhas ocasionais a bolhas e ulcerações graves persistentes. (TAYLOR *et al*., 2015) Embora qualquer área da mucosa oral possa estar envolvida, descamação gengival associada a eritema e lesões erosivas e/ou vesículo-bolhosas são comumente encontradas, denominadas como GD (JASCHOLT *et al*., 2017).

A manifestação ocular da doença se apresenta como inflamação conjuntival e erosões, adesão das pálpebras conjuntivas, fusão das pálpebras na pele, alteração da forma das pálpebras, triquíase, neovascularização córnea e cicatrizes. Vesículas são raramente observadas. Lesões anogenitais podem se manifestar como bolhas, erosões e cicatrizes, comou sem fusão dos tecidos. (CHAN *et al*., 2002)

Em relação às características histológicas, PMM geralmente demonstra uma divisão subepitelial (separando o epitélio do tecido conjuntivo subjacente na região da membrana basal) com um leve infiltrado inflamatório de eosinófilos, linfócitos e neutrófilos, semelhante às alterações observadas em outras formas de penfigoide (NEVILLE *et al*., 2009; XU *et al*., 2013).

1.1.3 PÊNFIGO VULGAR

O pênfigo é uma doença autoimune caracterizada pela formação de bolhasintraepiteliais. As lesões são vesículo-bolhosas e aparecem na pele e nas mucosas (TOFAN *et al*., 2018). Essa condição representa quatro doenças relacionadas: PV; pênfigo vegetante; pênfigo eritematoso e pênfigo foliáceo. PV é a mais comum dessas doenças (*vulgaris* significa *comum* em latim). Mesmo assim, ele não é observado com muita frequência. Estima-se que a incidência seja de um a cinco casos por milhão de pessoas diagnosticadas por ano na população geral. No entanto, o pênfigo vulgar é uma condição importante porque, se não tratada, muitas vezes resulta na morte do paciente. Além disso, as lesões bucais são muitas vezes o primeiro sinal da doença, sendo as mais difíceis de resolver com o tratamento. (NEVILLE *et al*., 2009)

Pacientes com PV desenvolvem uma produção anormal, por razões desconhecidas, de autoanticorpos que são dirigidos contra glicoproteínas de superfície da célula epidérmica, desmogleína 3 e desmogleína 1. Essas desmogleínas são componentes dos desmossomos (estruturas de adesão entre as células epiteliais) e os autoanticorpos atacam essescomponentes desmossomais, inibindo a interação molecular que é responsável pela aderência.Como resultado desse ataque imunológico aos desmossomos, uma fenda se desenvolve dentro do epitélio, causando a formação de uma bolha intraepitelial. (NEVILLE *et al*., 2009) A formação de autoanticorpos contra componentes dos desmossomos tem sido considerada o principal processo na patogênese do pênfigo. Além do importante papel da imunidade humoral, a imunidade celular também tem sido destacada (PORRO *et al*., 2019).

Da mesma forma que outras doenças autoimunes, o PV é mais prevalente entre as mulheres. A proporção homem/mulher varia de 1:1,5 em Israel e Irã, para 1:4 na Tunísia. PV pode ocorrer em qualquer idade e o início da doença geralmente ocorre entre 40 e 60 anos de idade. Uma frequência aumentada em idosos e crianças tem sido observada. Curiosamente, em alguns países do Oriente Médio e no Brasil o início da doença é precoce, estimando-se que 17,7% dos casos ocorram antes dos 30 anos. (PORRO *et al*., 2019)

Lesões orais são a primeira manifestação do PV em 50% a 70% dos casos e ocorrem em 90% dos pacientes durante o curso da doença (PORRO *et al*., 2019). O aspecto clínico das lesões orais varia de vesículas, bolhas (raramente vistas intactas) a úlceras e erosões generalizadas (TOFAN *et al*., 2018). As áreas mais afetadas são a mucosa jugal e palatina, lábios e gengivas. As erosões são múltiplas e presentes em diferentes tamanhos e formas irregulares; elas se estendem perifericamente e geralmente há um atraso na reepitelização. O

envolvimento gengival manifesta-se principalmente como GD (PORRO *et al*., 2019). A sintomatologia é grave, os pacientes mal conseguem beber ou comer. Em alguns casos, a hospitalização é recomendada. A higiene bucal é dificultada, levando a um risco aumentado de infecção bacteriana associada. (TOFAN *et al*., 2018)

Pacientes que sofrem de PV apresentam, posteriormente, envolvimento cutâneo. As erosões da mucosa geralmente precedem as manifestações cutâneas da doença e geralmente resultam em um curso prolongado de erros de diagnóstico, em condições, por exemplo, de ulceração aftosa. Em alguns casos, a ulceração oral pode ser a única manifestação da doença. As superfícies mucosas que podem estar envolvidas incluem a orofaringe, esôfago, conjuntiva, nasal, laringe, uretra, vulva e colo do útero (VENUGOPAL; MURRELL, 2011). O envolvimento cutâneo pode ser localizado ou generalizado. A maioria dos pacientes desenvolve bolhas flácidas com conteúdo claro na pele normal ou eritematosa. As bolhas se rompem facilmente, resultando em erosões dolorosas que sangram com facilidade. As lesões cutâneas podem ser observadas em qualquer local, mas há uma predileção pelo tronco, virilha,axilas, couro cabeludo e face; as palmas das mãos e as solas dos pés são geralmente poupadas.Essas erosões ficam cobertas por crostas, sem tendência a cicatrizar. (PORRO *et al*., 2019) O envolvimento ocular é observado com menos frequência, normalmente apresentando-se como uma conjuntivite bilateral (NEVILLE *et al*., 2009).

Em relação às características histopatológicas, os espécimes de biópsia do tecido perilesional mostram uma separação intraepitelial característica, que ocorre logo acima da camada de células basais do epitélio. Algumas vezes, toda a camada superficial do epitélio está descamada, deixando somente as células basais, que são descritas sendo semelhantes a "fileira de pedras de sepulturas". As células da camada espinhosa do epitélio de superfície apresentam acantólise e tendem a assumir uma forma arredondada (células de Tzanck). Um infiltrado leve a moderado de células inflamatórias crônicas normalmente é observado no tecido conjuntivo subjacente. (NEVILLE *et al*., 2009)

1.1.4 TRATAMENTO

Devido ao amplo espectro de manifestações potenciais e à complexidade dos métodos de diagnóstico, a colaboração multidisciplinar é frequentemente necessária para otimizar o manejo do paciente com GD (GARCIA-POLA *et al*., 2019). Portanto, é absolutamente

impetuoso que os clínicos a reconheçam e realizem o diagnóstico corretamente. Especialmente porque os distúrbios sistêmicos que a geram são raros, por vezes agressivos e precisam de tratamento imediato (TOFAN *et al*., 2018).

Atualmente, entre muitos tratamentos acessíveis, os corticosteroides tópicos de alta potência permanecem como a modalidade mais confiável e efetiva para o tratamento de lesões orais de LPO sintomático e PMM (CAFARO *et al*., 2014; XU *et al*., 2013). Os agentes tipicamente prescritos incluem betametasona, clobetasol, dexametasona e triamcinolona (JAJARM *et al*., 2018). O propionato de clobetasol parece ser um dos esteroides tópicos mais eficazes, pois em uma base adesiva levou à remissão completa em 56-75% dos pacientes. Infelizmente, alguns pacientes são refratários aos corticosteroides tópicos (CAFARO *et al*., 2014).

Lesões de GD podem ser tratadas com a aplicação de corticosteroides tópicos à base de gel na lesão. A aplicação pode ser facilitada pela colocação de uma tala oclusiva elástica formada a vácuo que cobre a gengiva envolvida (XU *et al*., 2013). Alguns pesquisadores recomendam o uso de pomadas compostas de corticosteroides com uma base adesiva de metilcelulose, mas a cooperação do paciente pode ser reduzida, pois este material é de difícil aplicação. O paciente deve ser avisado que, sem dúvida, a condição reaparecerá, e nestes casos os corticosteroides devem ser reaplicados (NEVILLE *et al*., 2009).

Nos casos de PMM que não respondem à terapia tópica com esteroides, deve-se considerar o uso de tacrolimus. O tacrolimus é comumente usado para profilaxia na prevenção da rejeição de órgãos transplantados. Existem muitos relatos de casos e ensaios clínicos do uso bem-sucedido do tacrolimus no tratamento do LPO, PV e doença crônica do enxerto *versus* hospedeiro. Embora os relatos de sucesso da terapia de PMM com tacrolimus tópico sejam limitados, demonstrou-se eficaz em alguns casos de PMM resistente envolvendo mucosa oral, pele e conjuntiva (XU *et al*., 2013).

Por ser uma doença sistêmica, no PV o tratamento usualmente consiste em corticoterapia sistêmica (NEVILLE *et al*., 2009; TOFAN *et al*., 2018). Muitas vezes há combinação com outros medicamentos imunossupressores (denominados agentes poupadores de esteroides), como a azatioprina. Embora alguns clínicos recomendem o uso de corticosteroides tópicos no tratamento das lesões bucais, a melhora observada é sem dúvida pela absorção sistêmica dos agentes tópicos, resultando em uma maior dose sistêmica (NEVILLE *et al*., 2009). O tratamento deve ser iniciado o mais cedo possível, com o objetivo

de alcançar e manter a remissão da doença. Para isso, o tratamento geralmente é bastante prolongado e pode durar muitos anos (média: 5 a 10 anos) (PORRO *et al*., 2019).

Por mais que os corticosteroides tópicos continuem sendo a base da terapia, seu uso a longo prazo pode causar alguns efeitos adversos, como candidíase, atrofia da mucosa oral e desconforto na aplicação (KAZANCIOGLU; ERISEN, 2015). Outras desvantagens incluem supressão adrenal, hipertensão, distúrbio gastrointestinal e hiperglicemia (EL SHENAWY; ELDIN, 2015). Gorsky *et al*. (1996) mostraram que lesões de candidíase foram encontradasem 32% dos pacientes com LPO que receberam corticoterapia. Além disso, alguns pacientes podem não responder efetivamente apenas à aplicação tópica de corticosteroide (KAZANCIOGLU; ERISEN, 2015). Deve-se considerar a absorção sistêmica ao usar esteroides tópicos (XU *et al*., 2013).

Entre as opções terapêuticas disponíveis para LPO, os corticosteroides são os mais amplamente aceitos, mas ainda não foi alcançada uma cura definitiva. Parece razoável a busca de métodos alternativos capazes de modular a resposta inflamatória relacionada à doença (DILLENBURG *et al*., 2014). Além disso, considerando a resistência aos esteroides tópicos em alguns pacientes e suas desvantagens, outro tratamento alternativo eficaz com efeitos colaterais mínimos parece ser vital (EL SHENAWY; ELDIN, 2015).

A FBM é outro método de tratamento que tem sido usado para tratar lesões de LPO com efeitos colaterais mínimos (JAJARM *et al*., 2018). É uma abordagem cada vez mais utilizada na medicina, que tem efeitos bioestimulantes em potencial e também se aplica aos tecidos orais, melhorando a cicatrização de feridas, a epitelização após cirurgia periodontal e prevenindo ou curando a mucosite oral induzida. A bioestimulação a laser pode obter diferentes reações biológicas intracelulares para estimular habilidades regenerativas, sem efeitos adversos indesejados, reduzindo também o suporte farmacológico e sua possível invasão (CAFARO *et al*., 2014). Os principais efeitos dessa terapia são analgesia, biomodulação e aceleração da cicatrização de feridas. A FBM tem vantagens sobre as terapiasatuais para LPO, como a não invasão, e a ausência de efeitos colaterais (DILLENBURG *et al*.,2014).

Na FBM, diferentes tipos de laser (hélio-neônio e diodo) com diferentes energias e durações são irradiados para o local da lesão e a irradiação é repetida por várias sessões (JAJARM *et al*., 2018). Ao contrário dos lasers de alta potência usados para decompor os tecidos termicamente, considera-se que a FBM funcione através da interação da luz com a

célula e o tecido. Essa interação pode ser afetada por alguns parâmetros, como comprimento de onda, potência, densidade de energia, duração do tratamento e tempo de intervenção, método de aplicação, estrutura e condição do tecido. A dose de laser aplicada é um importanteparâmetro do tratamento com FBM (KAZANCIOGLU; ERISEN, 2015).

A FBM inclui comprimentos de onda entre 500 e 1100 nm e normalmente envolve a intensificação de campos eletromagnéticos excitados por fontes externas de energia, emitindo um feixe de luz laser coerente, bem colimado e monocromático. Esse mecanismo implica em regulação redox, que explica os efeitos clínicos na resposta inflamatória crônica (LPO) caracterizada por acidose e hipóxia, com potencial de cicatrização e regeneração tecidual, sem distúrbios sistêmicos e efeitos indesejáveis no tecido saudável (AKRAM *et al*., 2018). Dessa forma, sugeriu-se que reduz a inflamação, diminuindo, de maneira dose-dependente, os níveis de prostaglandina E2, prostaglandina-endoperóxido-sintase 2, IL-1β, TNF-α, influxo celular de granulócitos (neutrófilos), estresse oxidativo, edema e sangramento. Outro mecanismopode estar relacionado à estimulação da mitocôndria para aumentar a produção de trifosfatode adenosina, resultando em um aumento nas espécies reativas de oxigênio, que influencia a sinalização redox, afetando a homeostase intracelular ou a proliferação de células. (CAFARO *et al*., 2014)

Dillenburg e colaboradores em 2014 compararam a eficácia da FBM com propionato de clobetasol tópico a 0,05% no tratamento de 42 pacientes com LPO atrófico e erosivo. O achado mais marcante foi a manutenção da melhora dos sinais e sintomas clínicos até dois meses após o término do tratamento com FBM, demonstrando maior controle do LPO em comparação ao alcançado com o clobetasol (DILLENBURG *et al*., 2014).

Esse tratamento é uma modalidade promissora que tem sido empregada em diferentes condições adversas de saúde (DILLENBURG *et al*., 2014). Além disso, pode ser considerada como um tratamento alternativo para o LPO sintomático e nos casos em que os esteroides tópicos são contra-indicados (ELSHENAWY *et al*., 2015).

2 OBJETIVOS

O presente estudo teve como objetivo realizar uma revisão sistemática com meta-análise para investigar os efeitos da fotobiomodulação quando utilizada em lesões gengivais decorrentes de doenças autoimunes, incluindo líquen plano oral, penfigoide das membranas mucosas e pênfigo vulgar.

3 PHOTOBIOMODULATION OF GINGIVAL LESIONS RESULTING FROM AUTOIMMUNE DISEASES: SYSTEMATIC REVIEW AND META-ANALYSIS

Milena Moraes de Carvalho, DDS[a], Marco Antonio Rimachi Hidalgo, DDS, MSc[b], Raquel Mantuaneli Scarel Caminaga, PhD[c], Noé Vital Ribeiro Junior DDS, PhD[d], Felipe Fornias Sperandio, DDS, PhD[e,f], Suzane Cristina Pigossi, DDS, PhD[d], Marina Lara de Carli, DDS, PhD[d]

[a]MSc student, School of Dentistry, Federal University of Alfenas, Alfenas, MG, Brazil

[b]PhD student, Department of Morphology, Genetics, Orthodontics and Pediatric Dentistry, School of Dentistry at Araraquara, UNESP- São Paulo State University (FOAr/UNESP), Araraquara, São Paulo, Brazil.

[c]Professor, Department of Morphology, Genetics, Orthodontics and Pediatric Dentistry, School of Dentistry at Araraquara, UNESP- São Paulo State University (FOAr/UNESP), Araraquara, São Paulo, Brazil.

[d]Professor, School of Dentistry, Federal University of Alfenas, Alfenas, MG, Brazil

[e]Professor, Department of Pathology and Parasitology, Institute of Biomedical Sciences, Federal University of Alfenas, Alfenas, MG, Brazil

[f]Oral Medicine Oral Pathology Resident, Faculty of Dentistry, University of British Columbia, Vancouver, BC, Canada

Corresponding author:

Marina Lara de Carli, DDS, PhD – marina.carli@unifal-mg.edu.br

School of Dentistry, Federal University of Alfenas

Rua Gabriel Monteiro da Silva, 700 – Centro – Alfenas – Minas Gerais – Brazil

Zip Code 37130 – 001

Abstract

Objectives: To evaluate the effects of photobiomodulation (PBM) in gingival lesions resulting from autoimmune diseases; to compare PBM and topical corticosteroid (CS) treatment and to assess PBM outcome over time of follow-up.

Material and Methods: A comprehensive electronic search was performed in four electronic databases. Treatment effects were measured through visual analogic scale of pain (VAS) and clinical evolution of lesion (Thongprasom scale for OLP). Meta-analysis was performed to compare PBM with topical corticosteroid treatment and to evaluate PBM effect over time of follow-up.

Results: Seventeen studies were included in this review, of which six were used for the meta-analysis. Meta-analysis results showed no significant differences between PBM and topical CS in pain reduction at baseline (MD = 0.20, 95% CI = -0.92, 1.32, $p = 0.72$) and 60-day follow-up (MD = 0.63, 95% CI = -3.93, 5.19, $p = 0.79$); however, VAS showed significant pain reduction when compared before and after PBM at 30-day (MD = -3.52, 95% CI = -5.40, -1.64, $p = 0.0002$) and 60-day (MD = -5.04, 95% CI = -5.86,-4.22, $p < 0.00001$) follow-up. Thongprasom clinical scale for OLP also showed significant improvement at 30-day follow-up (MD = -2.50, 95% CI = -2.92, -2.08, $p < 0.00001$) after PBM.

Conclusion: PBM led to significant pain and clinical scores reduction of the lesions, not having shown significant differences when compared to topical CS.

Clinical Relevance: PBM has been used in the treatment of autoimmune gingival lesions, but there is little strong evidence to support its use.

Key words: Lichen Planus, Oral; Pemphigoid, Benign Mucous Membrane; Pemphigus Vulgaris; Photobiomodulation Therapy.

1. Introduction

Autoimmune diseases relate to an exaggerated immune response that leads to damage and dysfunction of specific or multiple organs and tissues [1]. These diseases cause the destruction of tissues and happen on a background of genetic predisposition and environmental factors that trigger the immunological pathways. Furthermore, the failure to distinguish self from non-self tissues or cells is known as violation of tolerance and is thebasis for these illnesses [2]. A wide range of autoimmune diseases can affect the oral cavity, although the most common are oral lichen planus (OLP), mucous membrane pemphigoid (MMP), pemphigus vulgaris (PV) and epidermolysis bullosa (EB) [3]. In addition, oral lesions may be the first and occasionally the only clinical manifestation of several immunological disorders that affect the skin and mucosal surface [4].

OLP is a chronic inflammatory disease of autoimmune origin, mediated by T lymphocytes, which affects stratified squamous epithelial tissue; however, etiology and pathogenesis are not completely known [5]. Its clinical appearance can vary from keratotic (reticular or plaque like) with erythematous and ulcerative appearance and the most commonly affected sites in the oral cavity are the buccal and lingual mucosa, and the gingiva [6, 7]. In turn, MMP is a group of chronic, inflammatory, immune-mediated sub-epithelial bullous diseases, which manifest a heterogeneous pattern of oral, ocular, cutaneous, genital, nasopharyngeal, esophageal and laryngeal lesions [8]. The oral cavity and, in particular, the gingival tissue are the most common affected sites, accounting for 83-100% of all MMP patients [9]. Furthermore, patients diagnosed with this comorbidity have higher levels of gingival inflammation and periodontal parameters than healthy control patients, and comparable data were also seen in gingival OLP [10, 11].

Another autoimmune disease with an important oral manifestation is PV, comprising a group of rare autoimmune bullous diseases that affects the skin and mucous membranes [12]. Oral lesions usually precede skin lesions or are the only manifestation of the disease, affecting areas such as lips, gingiva, oral mucosa and palate [13]. Oral manifestations of PV can be very painful, disrupting oral intake and, consequently, negatively affecting patients' quality of life [14].

Despite their heterogeneous nature, all the disorders mentioned above share two characteristics: an immune-mediated pathogenesis and possibly a common clinical picture represented by oral lesions, with special attention to those in the gingival form [15]. In general, the gingival lesions caused by autoimmune dermatologic disorders are described with diffuse erythematous lesions, blisters, erosions, or ulcerations, mainly located on the attached gingiva and on the palate and are called desquamative gingivitis (DG), a term proposed by Prinz in 1932 [3, 16]. Thus, it is known that DG is a clinical finding with several potential etiologies, and although there are other differential diagnoses, OLP, MMP and PV are themost common [17]. According to different case series, MMP is responsible for 35% to 48%of cases of DG. OLP and PV account for 24% to 45% and 3% to 15% of cases, respectively [18-25].

Currently, there are specific treatments that focus on the general manifestations of the disease related to its pathogenesis. Topical CS have been indicated in different forms and prescribed with different dosages, or also their administration in systemic form, in addition to other drugs such as immunosuppressants and broad-spectrum antibiotics [17, 26]. However, the use of systemic steroids presents an increased risk of adverse side effects. Consequently, alternative treatment modalities have emerged. Among them, photobiomodulation (PBM), also called low-level laser therapy (LLLT), or laser therapy, stands out [13, 27, 28]. Different

types of laser (ultraviolet, helium-neon and diode) with distinct doses, output power and time of irradiation are applied to the injury site and the irradiation is repeated for several sessions [29]. They can be used due to their proposed anti-inflammatory effects, pain relief and accelerated regeneration of damaged tissues, without demonstrating the adverse effects associated with drug intake treatment [27, 28]. Therefore, the purpose of this systematic review is to access the effects of PBM when used in gingival lesions resulting from autoimmune diseases, including OLP, MMP and PV.

2. Materials and Methods

2.1. Protocol registration and focused question

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and a protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO - CRD42020200843). We established our research question according to the Participants, Interventions, Control and Outcomes (PICO) principle. The focused question of interest was “Is PBM effective to treat autoimmune gingival lesions?”.

Population: patients with gingival lesions due to autoimmune diseases, including OLP, oral MMP and oral PV

Intervention: gingival autoimmune lesions treated with PBM

Comparison: autoimmune gingival lesions treated with conventional drug therapy or other treatment modality (when comparative groups exist)

Outcome: to verify the efficacy of PBM in autoimmune gingival lesions.

2.2. Eligibility criteria

The eligibility criteria were as follows: all case reports, case series, longitudinal studies and randomized clinical trials, in which the patients presented gingival lesions due to autoimmune diseases, including OLP, oral MMP and oral PV, and that were treated with PBM. Children, pregnant women and patients with only cutaneous, ocular or genital lesions were not included in this review. Additionally, *in vitro* and *in vivo* studies, review papers, book chapters, conference proceedings, protocol articles, studies with insufficient data to perform qualitative analysis, studies that did not fulfill the diagnostic criteria and published studies in a language other than English were excluded from the study.

2.3. Literature search

Electronic searches were carried out in four databases for publications until July 2020:National Library of Medicine, Washington, D.C. (MEDLINE-PubMed); Embase®; Scopus, and ISI Web of Science. Key words were selected according to Medical Subject Headings [MeSH—National Center for Biotechnology Information (NCBI)] and considering the PICO criteria; the key words were combined as follows: “lichen planus, oral, or oral lichen planus” and “photobiomodulation therapy, or photobiomodulation therapies or low-level light therapy or low-level light therapies or light therapies, low-level or light therapy, low-level or therapies, low-level light or therapy, low-level light or therapies, photobiomodulation or therapy, photobiomodulation or LLLT or laser therapy, low-level or laser therapies, low-level or laser therapy, low level or low-level laser therapies or laser irradiation, low-power or irradiation, low-power laser or laser irradiation, low power or low-power laser therapy or low power laser therapy or laser therapy, low-power or laser therapies, low-power or laser therapy, low power or low-power laser therapies or low-level laser therapy or low level laser therapy or low-power laser irradiation or low power laser irradiation or laser biostimulation or

biostimulation, laser or laser phototherapy or phototherapy, laser". The same combinations were made between treatment and oral MMP ("mouth" or "oral" and "pemphigoid, benign mucous membrane" or "benign mucosal pemphigoid" or "benign mucosal pemphigoids" or "mucosal pemphigoid, benign" or "mucosal pemphigoids, benign" or "pemphigoid, benign mucosal" or "pemphigoids, benign mucosal" or "pemphigoid, cicatricial" or "cicatricial pemphigoid" or "benign mucous membrane pemphigoid" or "mucous membrane pemphigoid, benign" or "ocular cicatricial pemphigoid" or "cicatricial pemphigoids, ocular" or "ocular cicatricial pemphigoids" or "pemphigoids, ocular cicatricial" or "pemphigoid, ocular cicatricial" or "cicatricial pemphigoid, ocular") and between treatment and oral PV ("mouth or oral" and "pemphigus or pemphigus vulgaris").

2.4. Screening and selection

The studies were selected by two independent researchers (MMC and MLC). Titles and abstracts of retrieved articles were screened for eligibility, considering the inclusion/exclusion criteria described above, and irrelevant studies were excluded. Following this, full texts of the studies that met the eligibility criteria were selected and were accessed by both authors for inclusion. Disagreements between the investigators were resolved by consensus or werereferred to a third review author (SCP) for the final decision. Studies that met the selection criteria were processed for data extraction. Fig. 1 describes the screening process according toPRISMA guidelines.

2.5. Data extraction

Two reviewers (MMC and MLC) performed the data extraction independently. The general characteristics of the studies were collected and divided into two tables: Table 1 (articles

without a control group) and Table 2 (articles with a control group). The qualitative data from these studies was tabulated according to the study type, number, mean age and gender of the subjects, diagnosis, as well as the method used, follow-up period, evaluation methods and main outcomes (Table 1 and 2).

Furthermore, the laser parameters of the included studies were also collected. This information can be seen in Table 3. At this stage, we also accessed the quantitative data from studies for later realization to the meta-analysis.

2.6. Quality assessment

Two authors (SCP and MMC) assessed the quality of the included studies separately. Any disagreement was discussed with a third reviewer (MLC). The methodological quality of case reports and case series were evaluated using the framework for appraisal suggested by Murad *et al*. [30] based on the domains of selection, ascertainment, causality and reporting. Randomized clinical studies were evaluated using the Cochrane collaboration tool [31], and for non-randomized studies, the RoBANS scale (Risk of Bias Assessment Tool for Nonrandomized Studies) was used [32]. The judgment of case reports and case series was made based on the issues considered most critical. Six points were awarded for studies of the highest quality. A total score equal or below 2 it was determined as "low quality", a score of 3or 4 was determined as "moderate quality" and a score equal or above 5 was determined as "high quality". In turn, clinical studies were assessed for the risk of bias within six domains, which were judged to be uncertain, low or high risk.

2.7. Measures of treatment effect

Treatment effects were measured through visual analogic scale of pain (VAS) and clinical evolution of lesion (Thongprasom scale) [33].

2.8. Data synthesis

In the meta-analysis, the studies were separated into laser vs. control group and laser outcome (PBM outcome over follow-up periods). For the studies with no control, a comparison of the laser effect over time of follow-up was made. The number of individuals per group, the age of each group (mean and standard deviation), the numerical values of mean and standard deviation of evaluation criteria were assessed. Studies with no control were grouped considering VAS scores and Thongprasom clinical scores. The effect size was estimated and reported as the mean difference (MD). Statistical software (Review Manager [RevMan],Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to pool the data and to produce the forest plots. Additionally, narrative analysis to explore the relationship between studies was performed.

3. Results

3.1. Study selection

A total of 528 potentially relevant studies were initially identified. By removing the duplicate articles, 350 remained. After evaluation of titles and abstracts 214 were identified as *in vivo* or *in vitro* studies, reviews, articles that are not written in English, book chapters, conference papers and letters to the editor, and were thus deleted. The remaining 136 articles underwent a new evaluation and 89 studies were removed because they did not meet the inclusion criteria. Therefore, a total of 47 articles were selected for thorough full text reading. After full-text screening, 17 of the 47 studies were included in the current review [8, 13, 34-46] and 30 were

excluded. The reasons for excluding these articles can be seen in the study identification flowchart according to PRISMA (Fig. 1). Only 6 articles [8, 29, 36-38, 46] presented adequate quantitative data, making it possible to carry out the meta-analysis.

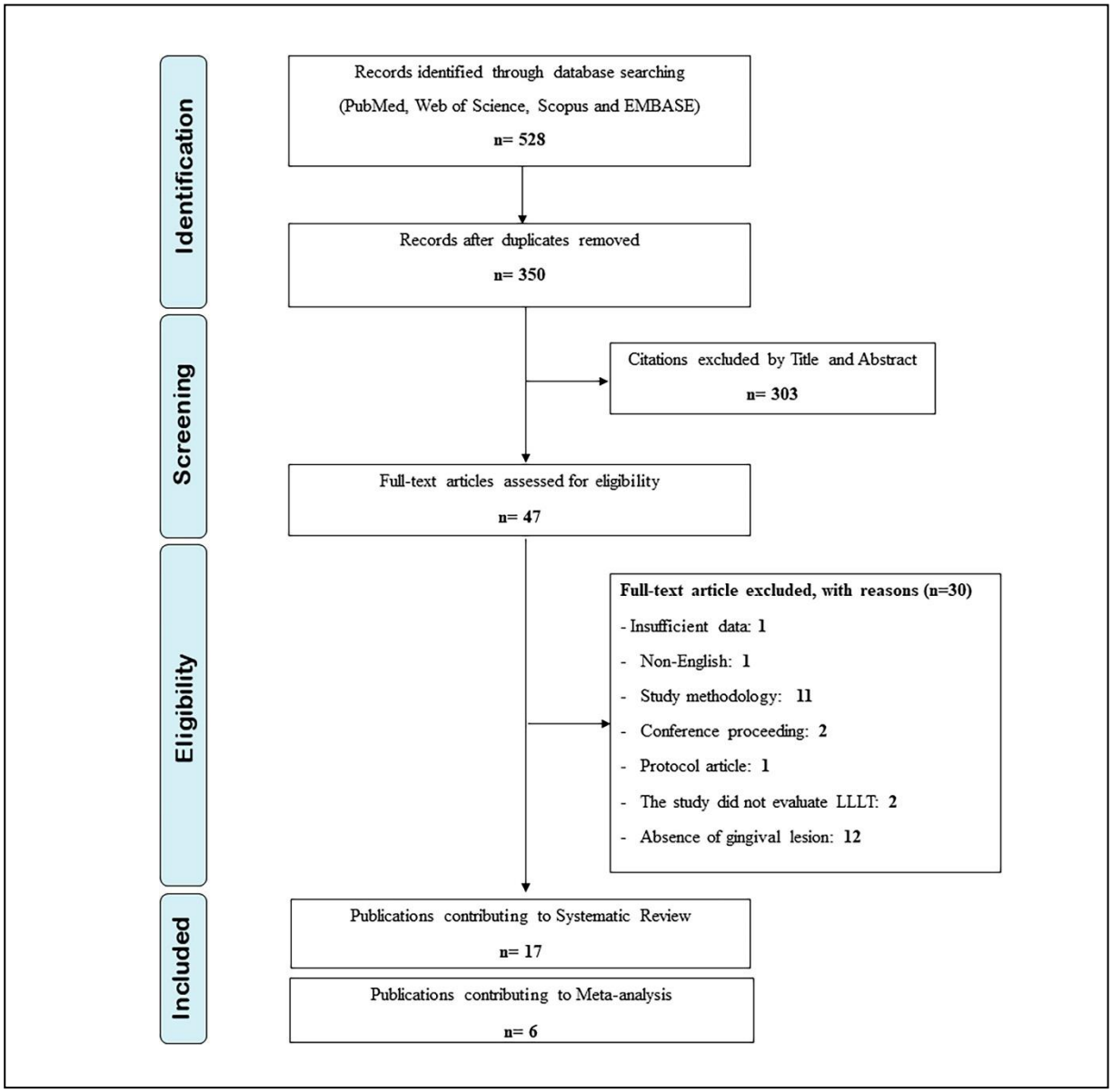

Fig. 1 Criteria for the selection of articles. Flow chart of methodology according to PRISMA guidelines

3.2. Qualitative evaluation

Seventeen published articles were included in the qualitative evaluation [8, 13, 29, 34-47], for a total 239 patients with oral lesions resulting from autoimmune diseases. Type of study, number, mean age and sex of the subjects, diagnosis, as well as the diagnostic method used, follow-up period, evaluation methods and main outcomes can be seen in tables 1 and 2.

Most of the studies included in this systematic review were case series (8 papers - 47%), followed by case reports (5 papers - 29.4%), randomized controlled trials (RCTs), and non-RCTs (2 papers – 11.8%, each). The number of subjects ranged between 1 to 42 individuals in the included studies. Two studies did not report gender of the subjects, while in the remaining fifteen studies majority of the subjects were females (75.35%).

Among the 239 cases included herein, 141 (11 articles) confirmed the presence of gingival lesions and 98 (6 articles) did not indicate the specific location of the oral lesions. Of the 141 informed cases, just 1 case (1 study) showed isolated desquamative gingivitis. The remaining 140 cases presented gingival involvement and other concomitant intraoral sites, in which the buccal mucosa and the tongue were affected in 136 of them (97.14%).

OLP was the most prevalent diagnosis, representing 91.21% of the cases (n=218); PV was found in sixteen cases (6.7%) and MMP in only five cases (2.09%). Histopathological analysis was the sole diagnostic method in 218 cases (91.6%); in other cases, a combination of methods was used for reaching the diagnosis, namely combining histology with direct immunofluorescence in 17 cases (7.14%), or even associating Enzyme-Linked Immunosorbent Assay (ELISA) to these two techniques (3 cases – 1.26%). Only 1 case (1 study) did not reveal the diagnostic method used.

Table 1: General characteristics of the included studies in the systematic review (PBM outcome).

Autor	Study type	Number of Subjects	Mean age (years)	Gender	Diagnosis Method	Final diagnosis	Follow-up (month)	Evaluation methods	Outcome
Trehan et al. (2004)	Case series	9	68 (37-87)	M: 6 F: 3	HP Analyses	OLP	NI	VAS	PBM was effective
Oliveira et al. (2009)	Case report	1	47	M: 1	NI	MMP	6	VAS Clinical assessment POMS	Concomitant use of systemic steroids and PBM was effective
Cafaro et al. (2010)	Case series	13	60.9 (±13.67)	M: 5 F: 8	HP Analyses	OLP	3	VAS Thongprasom	PBM was effective
Ylmaz et al. (2010)	Case report	1	55	F: 1	HP Analyses; Direct Immuno	MMP	12	Clinical assessment	PBM was effective
Cafaro et al. (2012)	Case report	3	79.4 (±6.71)	M: 1 F: 2	HP Analyses; Direct Immuno; ELISA	MMP	13.33 (± 9.45).	VAS	PBM was effective
Fornaini (2012)	Case series	19	59.47 (45-84)	F: 19	HP Analyses;	OLP	NI	NRS System Morphological aspects	PBM was effective
Cafaro et al., (2014)	Case series	30	64.5 (±11.27)	M: 11 F: 19	HP Analyses	OLP	26.6 (±6.38).	VAS Thongprasom	PBM was effective
El Shenawy *et al*. (2015) [b]	Case series	10	(45-60)	NI	HP Analyses	OLP	2	VAS Clinical assessment	PBM was effective
Derikvand *et al*. (2017)	Case report	1	46	F: 1	HP Analyses	OLP	1	VAS Clinical assessment	PBM was effective
Liu *et al*. (2017)	Case series	6	47.5 (±14.94)	M:2 F:4	HP Analyses	OLP	6	Clinical assessment	PBM was effective
Zand *et al*. (2017)	Case series	14	47.7 (± 14.7)	NI	HP Analyses; Direct Immuno	PV	4 days	VAS	PBM was effective
Mutafchieva *et al*. (2018)	Case series	12	54.4 (24-73)	M: 1 F: 11	HP Analyses	OLP	1	VAS Thongprasom EI	PBM was effective
Dal Prá et al. (2020)	Case report	2	41.5	F: 2	HP Analyses; Direct Immuno	PV	6	Clinical assessment	Concomitant use of systemic steroids and PBM was effective

Abbreviations: M = Male; F = Female; NI = not informed; HP = histopathological; OLP = Oral lichen planus; MMP = Mucous membrane pemphigoid; PV = Pemphigus Vulgaris; VAS = Visual Analog Scale; NRS = Numerical Rating Scale; Immuno = immunofluorescence; EI = Efficacy indices; POMS = Profile of Mood States; PBM = Photobiomodulation

Table 2: General characteristics of the included studies in the systematic review (PBM vs. control group).

Autor	Study type	Control	Number of Subjects	Mean age (years)	Gender	Diagnosis Method	Final diagnosis	Follow-up (month)	Evaluation methods	Outcome
Agha-Hosseini *et al*. (2012)	RCT	CO_2 laser surgery	C: 13 S: 15	50.7	M: 7 F: 21	HP Analyses	OLP	3	VAS Thongprasom	PBM displayed better results than CO2 laser surgery
Dillenburg et al. (2014)	RCT	Clobetasol 0.05%	C: 21 S: 21	58.2 (±14.23)	M: 7 F: 35	HP Analyses	OLP	3	VAS Thongprasom BAI FS	PBM was more effective than topical corticosteroid (P < 0.01)
El Shenawy et al. (2015)[a]	CT	Triamcinolone 0.1%	C: 12 S: 12	52.9	M: 6 F: 18	HP Analyses	OLP	NI	VAS	Corticosteroid was more effective than PBM (p = 0.02).
Othman *et al*. (2016)	CT	Triamcinolone	C: 12 S: 12	35-70	M: 6 F: 18	HP Analyses	OLP	NI	Thongprasom RAE score TNF-α	No statistically significant difference between the two groups

Abbreviations: M = Male; F = Female; NI = not informed; HP = histopathological; OLP = Oral lichen planus; MMP = Mucous membrane pemphigoid; PV = Pemphigus Vulgaris; VAS = Visual Analog Scale; Immuno = immunofluorescence; RCT = Randomized clinical trial; CT: clinical trial; C: Control group; S: Study group; RAE = Reticular score; PDT = photodynamic therapy; EI = Efficacy indices; BAI = Beck anxiety inventory; FS = Functional scores; PBM = Photobiomodulation

All included studies reported the effect of PBM on pain alleviation and clinical enhancement of the oral lesions. To assess pain levels before and after PBM, the most used method was the VAS, used in twelve articles (70.6%). Four articles (23.5%) did not perform this measurement and only one used another method of pain assessment, the NRS System. Regarding clinical evaluation of the lesions, the Thongprasom scale was used in six studies (35.3%); other seven articles performed only clinical assessments and observed the

morphological aspects of the lesions with no classification. In addition to VAS and Thongprasom sign scoring, one study verified treatment efficacy index (EI); one assessed levels of anxiety and functional scores (FS), and another article evaluated reticular score (RAE) and the serum pro-inflammatory mediators. Furthermore, an evaluation of the Profileof Mood States (POMS) was also found in one article. Follow-up period was reported in thirteen studies (76.5%), with an average of 6.4 months, ranging from 4 days to 26.6 months.

Thirteen included articles (76.5%) did not present comparative groups and only four (23.5%) resorted control groups. Three studies compared the efficacy of PBM with CS and one compared the efficacy of PBM to CO_2 laser surgery (table 2), being two articles (59.32%) [34, 36] showing PBM better than the control group [CO_2 laser surgery [34] and clobetasol 0.05% [36]].

Referring to studies with no comparative groups (13 papers), PBM was effective over time of follow-up on all of them [8, 13, 14, 29, 35, 38-41, 43, 45-47]. In 11 studies (84.6%) the laser was applied singly and in 2 studies (15.4%) it was used concurrently with steroid therapy (Table 1). Five articles reported the effect of the laser directly on the gingival tissues [13, 29, 43, 46, 47]. Three studies [13, 29, 43] showed that all gingival cases were successful treated with PBM, while two studies [46, 47] reported unsatisfactory response to the laser for some patients. The remaining twelve papers showed general results, without individualizing or differentiating the outcomes according to the lesion site.

3.3. Laser parameters of included studies

The laser parameters used in the included studies showed a great variation (Table 3). The laser source most used was diode laser, seen in twelve papers (178 cases). The second source found was excimer laser (used with low level in 2 studies – 15 cases), followed by

neodymium laser, CO_2 laser (low level) and pulsed diode laser (1 article, each). In all studies, laser was used with wavelengths ranging from 308 to 10600 nm and power output ranging from 0.007 W to 3W. The most of articles did not report power density values (14 – 82.3%). Twelve papers reported laser fluence/energy density that ranged from 0.1 up to 133.3 J/cm^2.

Concerning exposure time, a variation between the studies from 3.73 seconds to 8 minutes was observed. Only six studies reported the spot size of the laser, which ranged between 0.03 to 0.8 cm^2. The number of reported laser sessions ranged from one singlesession to 48 sessions.

Table 3: Laser parameters of the included studies.

Autor	Source	Wavelength (nm)	Energy density (fluence) (J/cm^2)	Power output (mW)	Power Density (mW/cm^2)	Time of Irradiation (seconds)	Laser schedule session/ week (total sessions)	Spot size (cm^2)
Trehan *et al*. (2004)	Excimer laser	308	0.1	NI	NI	Less than 60	Once a week/ (maximum 30 sessions)	NI
Oliveira *et al*. (2009)	Diode laser	660	60	30	NI	NI	Twice a week/ 6 months	0.3
Cafaro *et al*. (2010)	Pulsed diode laser	904	4	7	NI	60	Twice a week/ until the resolution of signs	0.8
Ylmaz *et al*. (2010)	Diode laser	810	5	NI	NI	40	Once a day/ 7 days	NI
Agha-Hosseini *et al*. (2012)	Diode laser	633; 890	0.3-0.5	NI	NI	5	Five sessions every other day	NI
Cafaro *et al*. (2012)	Diode laser	980	4	300	1500	3.73	Twice a week/ until the resolution of signs	0.28
Fornaini (2012)	Neodymium laser	532	4	NI	NI	60	Twice a week/ 6 sessions	NI
Cafaro *et al*. (2014)	Diode laser	980	4	300	1000	3.73	Once a week/ until the resolution of signs	0.28
Dillenburg *et al*. (2014)	Diode laser	660	6	40	1000	6	Three times a week/ 12 sessions	0.04
El Shenawy *et al*. (2015) [a]	Diode laser	970	NI	3000	NI	120	Twice a week (maximum 10 sessions)	NI
El Shenawy *et al*. (2015) [b]	Diode laser	970	NI	3000	NI	60	Twice a week/ (maximum 10 sessions)	NI
Othman *et al*. (2016)	Diode laser	970	NI	2000	NI	480	Twice a week/ (maximum 10 sessions)	NI
Derikvand *et al*. (2017)	Diode laser	980	4 or 6	200 or 300	200 or 300	20	Four initial sessions followed by 3 sessions per week (total of 10 sessions)	1
Liu *et al*. (2017)	Excimer laser	308	0.25-0.75	NI	NI	NI	Once a week/ Average treatment times was 13.5 (7–20)	NI
Zand *et al*. (2017)	CO_2 laser	10600	NI	1000	NI	5	Single session	NI
Mutafchieva *et al*. (2018)	Diode laser	810	1.2	500	NI	30	Three times a week/ 12 sessions	NI
Dal Prá *et al*. (2020)	Diode laser	660	66.66–133.33	100	NI	4	Daily for a week and with improvement in the condition, the sessions were interspersed until regression	0.03

Abbreviations: NI = not informed

3.4. Quality assessment

Regarding the case reports and case series, a total of seven studies were considered with high quality and six with moderate quality (Table 4). The quality assessment of nonrandomized clinical studies can be seen in Table 5. For details about the quality assessment of randomized clinical studies see Fig. 2.

Table 4: Methodologic quality assessment of cases series and case report.

First Author	Year	Case Report/ Case Series	Selection		Ascertainment				Causality				Reporting		Quality Assessment*
			Question 1		Question 2		Question 3		Question 4		Question 5		Question 6		
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	
Trehan	2004	Case Series	*		*			*	*			*	*		Moderate
Oliveira	2009	Case Report	*			*	*			*	*		*		Moderate
Ylmaz	2010	Case Report	*		*			*	*		*		*		High
Cafaro	2010	Case Series	*		*		*		*			*	*		High
Cafaro	2012	Case Report	*		*		*		*		*		*		High
Fornaini	2012	Case Series		*	*		*		*			*	*		Moderate
Cafaro	2014	Case Series	*		*		*		*		*		*		High
El Shenawy	2015	Case Series	*		*		*		*			*	*		High
Derikvand	2015	Case Report		*	*		*		*			*	*		Moderate
Liu	2017	Case Series		*	*			*	*		*		*		Moderate
Zand	2017	Case Series	*		*			*	*			*	*		Moderate
Mutafchieva	2018	Case Series	*		*		*		*			*	*		High
Dal Prá	2020	Case Report	*		*			*	*		*		*		High

Question 1: Did the patient(s) represent the whole case(s) of the medical center?; Question 2: Was the exposure adequately ascertained?; Question 3: Was the outcome adequately ascertained?; Question 4: Were other alternative causes that may explain the observation ruled out?; Question 5: Was follow-up long enough for outcomes to occur?; Question 6: Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

Table 5: Methodologic quality assessment of non-randomized clinical studies.

First Author	Year	Domain					
		1	2	3	4	5	6
El Shenawy	2015	Low	Low	Unclear	High	Low	Low
Othman	2016	High	High	High	High	Low	Unclear

Domain 1: Selection bias caused by inadequate selection of participants; Domain 2: Selection bias caused by inadequate confirmation and consideration of confounding variable; Domain 3: Performance bias caused by inadequatemeasurement of intervention (exposure); Domain 4: Detection bias caused by inadequate blinding of outcome assessment; Domain 5: Attrition bias caused by inadequate handling of incomplete outcome data; Domain 6: Reportingbias caused by selective outcome reporting.

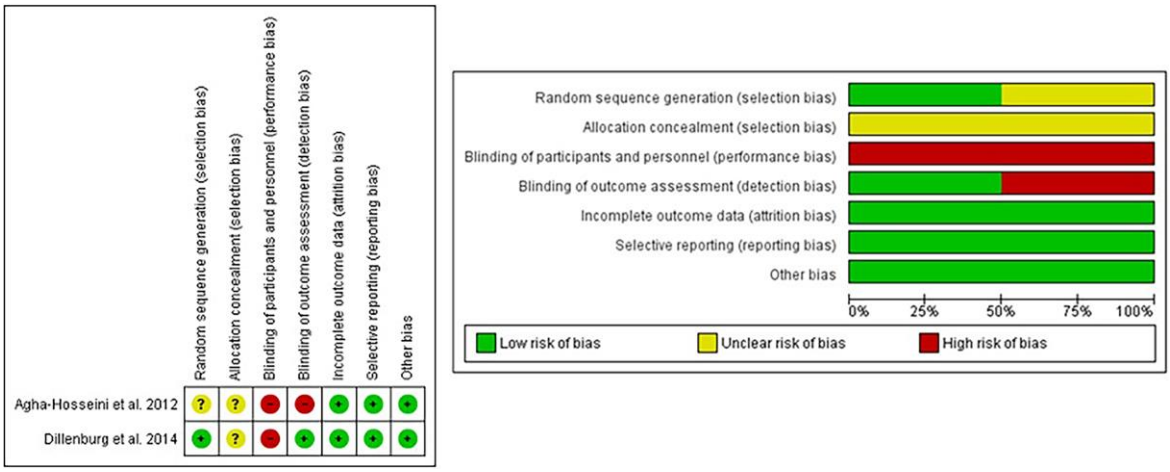

Fig. 2 Methodological quality assessment of randomized clinical trials. a. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

3.5. Quantitative evaluation (meta-analysis)

For assessing the VAS scores between PBM and control groups (CS), we extracted the data from two studies allowing for baseline and 60-day follow-up analyses. No statistically significant differences between the PBM and CS groups for pain at baseline (MD = 0.20, CI =

95% -0.92,1.32, $p = 0.72$) (Fig. 3a) and at 60-day follow-up (MD = 0.63, CI = 95% - 3.93,5.19, $p = 0.79$) (Fig. 3b) was found.

The effect of PBM over time of follow-up in studies with no control group was assessed through VAS scores and Thongprasom sign scoring. Firstly, the data from twostudies allowing for VAS baseline *versus* 30-day follow-up analysis, showing statistically significant differences between them (MD = -3.52, CI = 95% -5.40, -1.64, $p = 0.0002$) (Fig. 3c). VAS scores baseline *versus* 60-day follow-up analysis was made considering two studies,and the results presented statistically significant differences between them (MD = -5.04, CI = 95% -5.86, -4.22, $p < 0.00001$) (Fig. 3d). Thongprasom sign scores were evaluated at baselineand 30-day follow-up from two studies, showing statistically significant differences between them (MD = -2.50, CI = 95% -2.92, -2.08, $p < 0.00001$) (Fig. 3e). 30-day follow-up after PBM, VAS and Thongprasom scores were significantly reduced; VAS score decreased by 3.52 points while Thongprasom score was reduced by 2.50 points. High levels of heterogeneity were observed only for VAS scores baseline *versus* 30-day follow-up ($I^2 = 70\%$) nevertheless, considering the nature of this score, meta-analysis was still carried out.

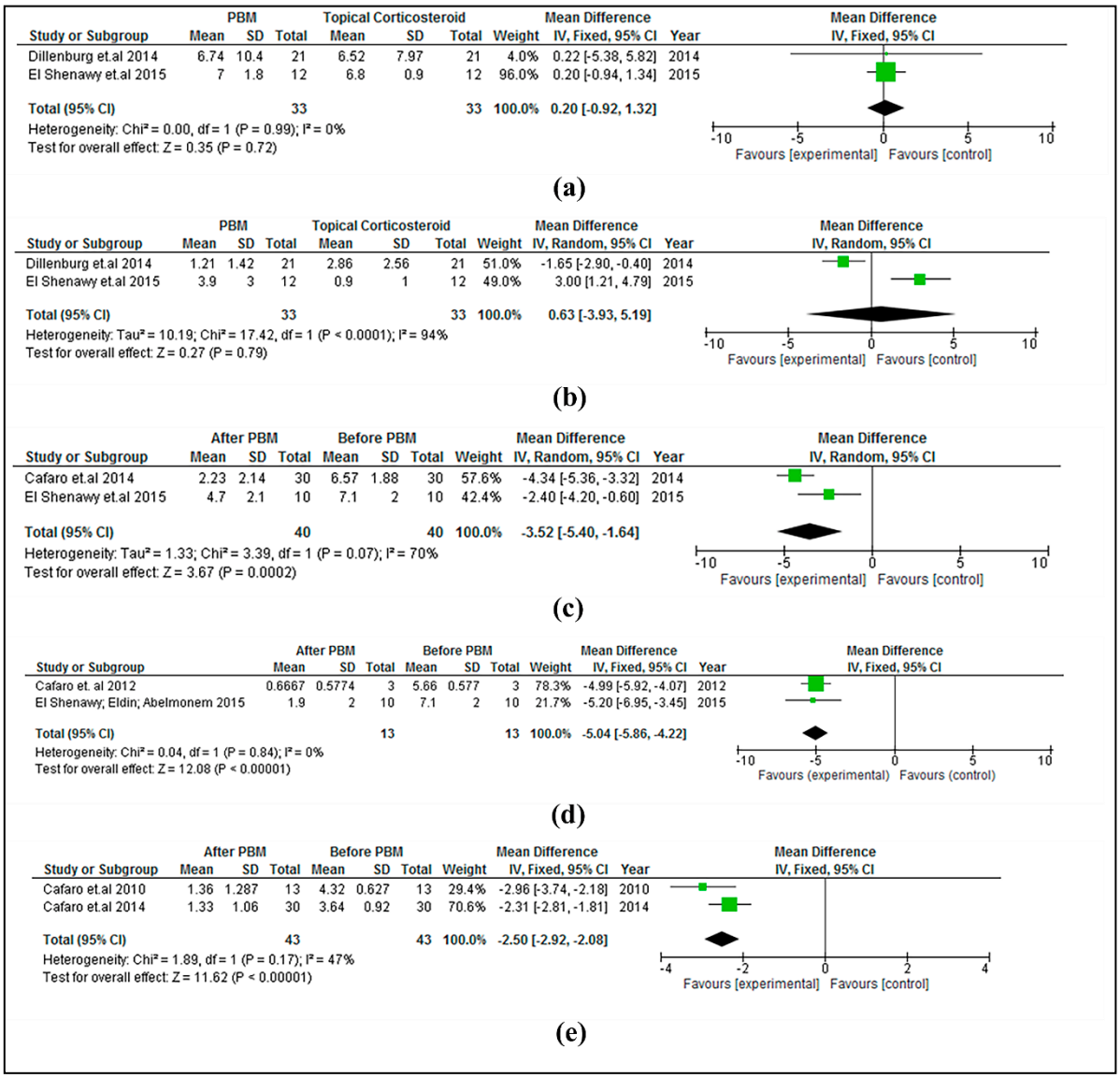

Fig. 3 Forests plots that graphically represents the meta-analysis of Visual Analogue Scale (VAS) and Thongprasom clinical scores. a. VAS scores for PBM and topical CS groups at baseline. b. VAS scores for PBM and topical CS groups at 60-day follow-up. c. VAS scores at baseline and at 30-day follow-up after PBM. d. VAS scores at baseline and at 60-day follow-up after PBM. e. Thongprasom clinical scores at baseline and at 30-day follow-up after PBM

4. Discussion

Women with OLP were the most affected patients with DG, which agrees with literature as most autoimmune diseases are more prevalent in females than males [1, 48]. Differences in

prevalence and severity between genders result from complex and still poorly understood interactions involving hormonal and environmental factors in genetically susceptible individuals [49]. Estrogens are potent stimulators of autoimmunity and androgens seem to play a protective role in the development of autoimmune diseases [50, 51]. However, the appearance of at least 50% of autoimmune disorders has been attributed to "unknown triggering factors" [52, 53]. Physical and psychological stress have been implicated in the development of these diseases, being one of the most commonly reported triggers for the progress of OLP, with greater predictability in females [54, 55]. In addition, the COVID-19 pandemic is a current factor that has seriously affected mental health worldwide [56]. As people deal with quarantine, isolation and travel restrictions, fear and chaos become evident and include fear of losing beloved ones, fear of losing sustenance, phobia of contracting the infection, all of which impact mental health and quality of life of the subjects [55, 57, 58]. Forpatients with autoimmune disorders, COVID-19-related anxiety can lead to exacerbations of the disease [59].

Gingival lesions in autoimmune diseases usually present as diffuse erythematousareas, blisters, erosions and ulcerations, located mainly in the attachment gingiva and / or palatal mucosa, which may be surrounded by keratosis with tiny reticulations or with interspersed keratotic plaques [3, 15]. However, due to the lack of data in the includedarticles, the most common gingival manifestation could not be established. Interesting data obtained in the current systematic review was that the gingival manifestation was concomitantly with lesions in another oral location in 99.3% of the reported cases. Only one case presented isolated gingival lesion. Gingival tissue is recognized for its sensitivity to inflammation, fibrotic response and propensity to drug-induced overgrowth [60, 61], differentiating it from the lining mucosa in the oral cavity. In this sense, gingival lesions

should be evaluated separately from other locations. Unfortunately, the revised papers did not perform such assessment, hindering the real response of the gingival tissue to treatment with PBM.

Topical CS remain the most widely used treatment for oral lesions of autoimmune origin [29, 62]. Nevertheless, the lack of adherence of the topical drug formulation to the affected sites for a longer duration has been considered as a factor in reducing the efficacy of this treatment [63]. Moreover, topical CS vasoconstrictor, anti-inflammatory and immunosuppressive properties are not enough to suppress the immune and inflammatory mechanism involved in the development of the gingival lesions for some patients [64]. Theuse of these drugs also may result in the development of secondary candidiasis, frequently requiring the concomitant prescription of antifungal agents [65]. Thereby, PBM appears as a therapeutic option for these injuries.

PBM is a treatment that uses a continuous laser or light emitting diode (LED) with a wavelength of 600 to 1000 nm applied for the purpose of analgesia, stimulation of tissue repair and/or reduction of inflammation, showing advantages over current OLP therapies such as noninvasiveness and the absence of side effects [36, 66]. The qualitative evaluation showed that all included studies reported the effect of PBM on pain alleviation and clinical enhancement of the oral lesions. Moreover, the meta-analysis revealed no statistically significant differences between PBM and topical CS groups in reducing pain. Therefore, considering that topical CS are first-line therapy for many autoimmune diseases, such as OLP [67], PBM has proved to be as effective as topical CS, and can be considered an option for patients with restrictions on the use of these medications. Furthermore, PBM does not demonstrate the side effects inherent to the medication, such as oral candidiasis. A

disadvantage of PBM is that it is restricted to the dental office, while CS is administered at home.

The low number of included RCT with the same evaluation criteria and few evaluated patients in each included study represents a limitation. Additionally, one study was responsible for 96% of the weight in the analysis, which could be improved if there were a greater number of included studies. Baseline analysis showed an absence of sample heterogeneity, demonstrating that the sample used in the studies had similar characteristics between the evaluated groups. However, at 60-day follow-up analysis, there was great heterogeneity in the sample (I^2=94%), with very divergent results, which contributed to the absence of significant differences between the evaluated studies; it is noteworthy that the weight distribution in the present analysis was more uniform compared to the baseline analysis. Again, the lack of randomized controlled trials with the same assessment tool leadsto an analysis with little strong evidence.

Concerning the analyses of laser outcome (effect over time) using pain and Thongprasom clinical scores, results are very favorable to the use of PBM in autoimmune gingival lesions, even with a heterogeneous sample in the VAS evaluation (baseline and 30-day comparison; I^2=70%). It was also observed that the improvement in pain extends up to 60 days of follow-up, showing a homogenous sample (I^2=0%). These results present some limitations; first, in the 60-day analysis, there was irregular distribution of weight, one study accounted for 78.3% of the weight in the analysis; second, both VAS analyses were performed with only 2 studies, with no other papers fulfilling the necessary criteria. Concerning Thongprasom analysis, more homogeneous sample is noted (I^2=47%), however, the irregular distribution of weight remains as a limitation, with one study representing 70.6% of weight in the analysis.

A variety of scoring systems have been proposed to evaluate disease severity and monitor the response to such treatments, testing the effectiveness of these drugs within and among patients [68]. VAS and Thongprasom sign scores are the most used methods in the analysis of pain and clinical evaluation of OLP, respectively [68, 69]. VAS was developed to obtain pain measurements with more variability using a continuous single line trace [70]. In addition to VAS, NRS system it is also considered to be highly feasible for clinical research and practice, providing very little burden to professionals and patients [69]. Despite the validated tools for pain assessment, measuring the subjective experience of pain is a continuing challenge in the medicine [71]. To analysis clinical improvement, Thongprasom's score is typically preferred by investigators because of its ease of application and it does not require any sophisticated calculations [68].

Some limitations were observed in the present study. The lack of well-conducted RCT's was a hamper factor to better assessing PBM effectiveness; most of the studiessystematically included in this review were case reports and case series, making a stronger meta-analysis unfeasible. Another limitation refers to the absence of clinical informationabout gingival injuries in several studies, as well as the lack of individual analysis, separating gingival lesions from others, which would allow a more reliable assessment of the effects of PBM on gingival tissue. Our results highlight the need for conducting more RCT-type studies that investigate the use of PBM in autoimmune gingival lesions, besides emphasizing the importance that the studies present their data in more detail about the response to treatment in each specific location, given the different responses presented by lesions in different intraoral sites.

In conclusion, PBM has become an important tool in the management of autoimmune gingival lesions and has shown significant pain reduction and improvement of clinical scores

of the intraoral lesions after therapy, without showing significant differences when compared to topical CS. Up to now, there is little strong evidence to assess the efficacy of PBM in autoimmune gingival lesions.

Acknowledgements

The authors wish to thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Grant/Award Number: MCTIC Universal no 408884/2018-5; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Grant/Award Number: Finance Code 001 and Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) for financially supporting the present study.

Conflict of interest

The authors state no conflict of interests. All authors have read and approved the final article.

Author contributions

Milena Moraes de Carvalho, Marina Lara de Carli and Suzane Cristina Pigossi contributed to study conception and design and data collection. Marco Antonio Rimachi Hidalgo, Raquel Mantuaneli Scarel Caminaga, Milena Moraes de Carvalho, Marina Lara de Carli and Suzane Cristina Pigossi contributed to statistical analysis and data interpretation. Noé Vital Ribeiro Junior and Felipe Fornias Sperandio contributed to data interpretation. All authors contributed to the manuscript draft and to critically revise the manuscript.

References

1. Ortona E, Pierdominici M, Maselli A, Veroni C, Aloisi F, Shoenfeld Y (2016) Sex-based differences in autoimmune diseases. Annali dell'Istituto superiore di sanita 52:205-212. doi:
2. Wang L, Wang FS, Gershwin MEJJoim (2015) Human autoimmune diseases: a comprehensive update. 278:369-395. doi:

3. Arduino PG, Romano F, Sasia D, Broccoletti R, Ricceri F, Barbui AM, Brossa S, Cipriani R, Cricenti L, Cabras M, Aimetti M (2017) Subgingival Microbiota in White Patients With Desquamative Gingivitis: A Cross-Sectional Study. J Periodontol 88:643-650. doi: 10.1902/jop.2017.160745
4. Mustafa MB, Porter SR, Smoller BR, Sitaru CJAr (2015) Oral mucosal manifestations of autoimmune skin diseases. 14:930-951. doi:
5. Paiva SN, Braga CC, Almeida-Coburn KL, Bautz WG, de Barros LAP, da Gama-de-Souza LN (2016) Oral Lichen Planus: Clinical Profile and Determination of Oral Epithelial Dysplasia. International journal of odontostomatology 10:99-106. doi: 10.4067/s0718-381x2016000100016
6. Zakrzewska JJTBjoo, surgery m (2001) Re: Mollaoglu N. Oral Lichen Planus: A Review. Br J Oral Maxillofac Surg 2000; 38: 370-377. 39:407. doi:
7. Shivhare P, Gupta A, Yadav M, Konidena A, Shankarnarayan L (2016) Evaluation of different diagnostic criteria of diseases manifesting the oral cavity - A review. Part-1. J Oral Biol Craniofac Res 6:135-141. doi: 10.1016/j.jobcr.2015.12.012
8. Cafaro A, Broccoletti R, Arduino PG (2012) Low-level laser therapy for oral mucous membrane pemphigoid. Lasers Med Sci 27:1247-1250. doi: 10.1007/s10103-012-1137-9
9. Chan LSJCid (2001) Mucous membrane pemphigoid. 19:703-711. doi:
10. Arduino PG, Farci V, D'Aiuto F, Carcieri P, Carbone M, Tanteri C, Gardino N, Gandolfo S, Carrozzo M, Broccoletti RJOD (2011) Periodontal status in oral mucous membrane pemphigoid: Initial results of a case-control study. 17:90-94. doi:
11. Lo Russo L, Gallo C, Pellegrino G, Lo Muzio L, Pizzo G, Campisi G, Di Fede O (2014) Periodontal clinical and microbiological data in desquamative gingivitis patients. Clin Oral Investig 18:917-925. doi: 10.1007/s00784-013-1038-8
12. Porro AM, Seque CA, Ferreira MCC, Enokihara M (2019) Pemphigus vulgaris. An Bras Dermatol 94:264-278. doi: 10.1590/abd1806-4841.20199011
13. Dal Prá KJ, de Assis Tristão S, Franco JB, Matias DT, Carrillo CM, de Melo Peres MPS, Ribas PF (2020) Oral management of pemphigus vulgaris in the intensive care unit. Spec Care Dentist 40:280-284. doi: 10.1111/scd.12454
14. Zand N, Mansouri P, Fateh M, Ataie-Fashtami L, Khiabanloo SR, Safar F, Chalangari R, Martits K, Shirkavand A (2017) Relieving pain in oral lesions of pemphigus vulgaris using the non-ablative, non-thermal, CO2 laser therapy (NTCLT): Preliminary results of a novel approach. Journal of Lasers in Medical Sciences 8:8-12. doi: 10.15171/jlms.2017.02
15. Lo Russo L, Fedele S, Guiglia R, Ciavarella D, Lo Muzio L, Gallo P, Di Liberto C, Campisi G (2008) Diagnostic pathways and clinical significance of desquamative gingivitis. J Periodontol 79:4-24. doi: 10.1902/jop.2008.070231
16. Garcia-Pola MJ, Rodriguez-Lopez S, Fernanz-Vigil A, Bagan L, Garcia-Martin JM (2019) Oral hygiene instructions and professional control as part of the treatment of desquamative gingivitis. Systematic review. Med Oral Patol Oral Cir Bucal 24:e136-e144. doi: 10.4317/medoral.22782
17. Maderal AD, Lee Salisbury P, 3rd, Jorizzo JL (2018) Desquamative gingivitis: Clinical findings and diseases. J Am Acad Dermatol 78:839-848. doi: 10.1016/j.jaad.2017.05.056
18. Scully C, Carrozzo M, Gandolfo S, Puiatti P, Monteil RJOS, Oral Medicine, Oral Pathology, Oral Radiology,, Endodontology (1999) Update on mucous membrane

pemphigoidA heterogeneous immune-mediated subepithelial blistering entity. 88:56-68. doi:
19. Nisengard R, Rogers III RJJop (1987) The treatment of desquamative gingival lesions. 58:167-172. doi:
20. Nisengard RJ, Neiders MJJop (1981) Desquamative lesions of the gingiva. 52:500-510. doi:
21. Markopoulos A, Antoniades D, Papanayotou P, Trigonidis GJQI (1996) Desquamative gingivitis: A clinical, histopathologic, and immunologic study. 27. doi:
22. Rogers III RS, Sheridan PJ, Nightingale SHJJotAAoD (1982) Desquamative gingivitis: clinical, histopathologic, immunopathologic, and therapeutic observations. 7:729-735. doi:
23. Yin WY, Maier T, Kratochvil FJ, Zieper MBJJop (1998) Analysis of desquamative gingivitis using direct immunofluorescence in conjunction with histology. 69:678-685. doi:
24. Vaillant L, Chauchaix-Barthes S, Hüttenberger B, Arbeille B, Machet M, Jan V, Goga D, Lorette G. *Chronic desquamative gingivitis syndrome: retrospective analysis of 33 cases*. in *Annales de Dermatologie et de Venereologie*. 2000.
25. Yih WY, Richardson L, Kratochvil FJ, Avera SP, Zieper MBJJop (2000) Expression of estrogen receptors in desquamative gingivitis. 71:482-487. doi:
26. Karagoz G, Bektas-Kayhan K, Unur MJJoIUFoD (2016) Desquamative gingivitis: A review. 50:54. doi:
27. Sobanko JF, Alster TSJDs (2008) Efficacy of low-level laser therapy for chronic cutaneous ulceration in humans: A review and discussion. 34:991-1000. doi:
28. Jajarm HH, Asadi R, Bardideh E, Shafaee H, Khazaei Y, Emadzadeh M (2018) The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus-A systematic review and meta-analysis. Photodiagnosis and Photodynamic Therapy 23:254-260. doi: 10.1016/j.pdpdt.2018.07.001
29. Cafaro A, Arduino PG, Massolini G, Romagnoli E, Broccoletti R (2014) Clinical evaluation of the efficiency of low-level laser therapy for oral lichen planus: a prospective case series. Lasers Med Sci 29:185-190. doi: 10.1007/s10103-013-1313-6
30. Murad MH, Sultan S, Haffar S, Bazerbachi F (2018) Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 23:60-63. doi: 10.1136/bmjebm-2017-110853
31. JPT H, DG A, JAC S, *Assessing risk of bias in included studies*, in *Cochrane Handbook for Systematic Reviews of Interventions*

version 5.2.0, H. JPT, *et al*., Editors. 2017, John Wiley & Sons Ltd: England. p. 73.
32. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, Jang BH, Son HJ (2013) Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol 66:408-414. doi: 10.1016/j.jclinepi.2012.09.016
33. Thongprasom K, Luangjarmekorn L, Sererat T, Taweesap W (1992) Relative efficacy of fiuocinolone acetonide compared with triamcinolone acetonide in treatment of oral lichen planus. J Oral Pathol Med 21:456-458. doi:
34. Agha-Hosseini F, Moslemi E, Mirzaii-Dizgah I (2012) Comparative evaluation of low-level laser and CO_2 laser in treatment of patients with oral lichen planus. Int J Oral Maxillofac Surg 41:1265-1269. doi: 10.1016/j.ijom.2012.06.001

35. Derikvand N, Ghasemi SS, Moharami M, Shafiei E, Chiniforush N (2017) Management of oral lichen planus by 980 nm diode laser. Journal of Lasers in Medical Sciences 8:150-154. doi: 10.15171/jlms.2017.27
36. Dillenburg CS, Martins MAT, Munerato MC, Marques MM, Carrard VC, Sant'Ana M, Castilho RM, Martins MD (2014) Efficacy of laser phototherapy in comparison to topical clobetasol for the treatment of oral lichen planus: a randomized controlled trial. Journal of Biomedical Optics 19. doi: 10.1117/1.jbo.19.6.068002
37. Elshenawy HM, Eldin AM, Abdelmonem MA (2015) Clinical Assessment of the Efficiency of Low Level Laser Therapy in the Treatment of Oral Lichen Planus. Open Access Maced J Med Sci 3:717-721. doi: 10.3889/oamjms.2015.112
38. El Shenawy HM, Eldin AM (2015) A Comparative Evaluation of Low-Level Laser and Topical Steroid Therapies for the Treatment of Erosive-Atrophic Lichen Planus. Open Access Maced J Med Sci 3:462-466. doi: 10.3889/oamjms.2015.072
39. Fornaini C, Raybaud H, Augros C, Rocca JP (2012) New clinical approach for use of Er:YAG laser in the surgical treatment of oral lichen planus: a report of two cases. Photomedicine and laser surgery 30:234-238. doi:
40. Liu WB, Sun LW, Yang H, Wang YF (2017) Treatment of oral lichen planus using 308-nm excimer laser. Dermatologic Therapy 30. doi: 10.1111/dth.12510
41. Oliveira PC, Reis JA, Lacerda JA, Silveira NT, Santos JM, Vitale MC, Pinheiro ALB (2009) Laser light may improve the symptoms of oral lesions of cicatricial pemphigoid: A case report. Photomedicine and Laser Surgery 27:825-828. doi: 10.1089/pho.2008.2352
42. Othman NA, Shaker OG, Elshenawy HM, Abd-Elmoniem W, Eldin AM, Fakhr MY (2016) The effect of diode laser and topical steroid on serum level of TNF-alpha in oral lichen planus patients. Journal of Clinical and Experimental Dentistry 8:e566-e570. doi: 10.4317/jced.52665
43. Yilmaz HG, Kusakci-Seker B, Bayindir H, Tözüm TF (2010) Low-level laser therapy in the treatment of mucous membrane pemphigoid: A promising procedure. Journal of Periodontology 81:1226-1230. doi: 10.1902/jop.2010.100095
44. Zand N, Mansouri P, Rezaee Khiabanloo S, Fateh M, Ataie-Fashtami L, Safaee Naraghi Z, Shirkavand A (2020) The immediate pain-relieving effects of non-thermal CO2 laser therapy on genital ulcers of Behcet's disease: A case report. Journal of Lasers in Medical Sciences 11:108-111. doi: 10.15171/jlms.2020.18
45. Mutafchieva MZ, Draganova-Filipova MN, Zagorchev PI, Tomov GT (2018) Effects of Low Level Laser Therapy on Erosive-atrophic Oral Lichen Planus. Folia Med (Plovdiv) 60:417-424. doi: 10.2478/folmed-2018-0008
46. Cafaro A, Albanese G, Arduino PG, Mario C, Massolini G, Mozzati M, Broccoletti R (2010) Effect of low-level laser irradiation on unresponsive oral lichen planus: early preliminary results in 13 patients. Photomed Laser Surg 28 Suppl 2:S99-103. doi: 10.1089/pho.2009.2655
47. Trehan M, Taylor CR (2004) Low-dose excimer 308-nm laser for the treatment of oral lichen planus. Arch Dermatol 140:415-420. doi: 10.1001/archderm.140.4.415
48. Ngo ST, Steyn FJ, McCombe PA (2014) Gender differences in autoimmune disease. Front Neuroendocrinol 35:347-369. doi: 10.1016/j.yfrne.2014.04.004
49. Moulton VR (2018) Sex Hormones in Acquired Immunity and Autoimmune Disease. Front Immunol 9:2279. doi: 10.3389/fimmu.2018.02279
50. Zandman-Goddard G, Peeva E, Shoenfeld Y (2007) Gender and autoimmunity. Autoimmun Rev 6:366-372. doi: 10.1016/j.autrev.2006.10.001

51. Quintero OL, Amador-Patarroyo MJ, Montoya-Ortiz G, Rojas-Villarraga A, Anaya JM (2012) Autoimmune disease and gender: plausible mechanisms for the female predominance of autoimmunity. J Autoimmun 38:J109-119. doi: 10.1016/j.jaut.2011.10.003
52. Herrmann M, Scholmerich J, Straub RH (2000) Stress and rheumatic diseases. Rheum Dis Clin North Am 26:737-763, viii. doi: 10.1016/s0889-857x(05)70167-8
53. Stojanovich L, Marisavljevich D (2008) Stress as a trigger of autoimmune disease. Autoimmun Rev 7:209-213. doi: 10.1016/j.autrev.2007.11.007
54. Chen HX, Blasiak R, Kim E, Padilla R, Culton DA (2017) Triggers of oral lichen planus flares and the potential role of trigger avoidance in disease management. Oral Surg Oral Med Oral Pathol Oral Radiol 124:248-252. doi: 10.1016/j.oooo.2017.05.508
55. Moccia L, Janiri D, Pepe M, Dattoli L, Molinaro M, De Martin V, Chieffo D, Janiri L, Fiorillo A, Sani G, Di Nicola M (2020) Affective temperament, attachment style, and the psychological impact of the COVID-19 outbreak: an early report on the Italian general population. Brain Behav Immun 87:75-79. doi: 10.1016/j.bbi.2020.04.048
56. Vissink CE, van Hell HH, Galenkamp N, van Rossum IW (2021) The effects of the COVID-19 outbreak and measures in patients with a pre-existing psychiatric diagnosis: A cross-sectional study. J Affect Disord Rep 4:100102. doi: 10.1016/j.jadr.2021.100102
57. Routray S, Mishra P (2020) A probable surge in oral lichen planus cases under the aura of coronavirus in females in India. Oral Oncol 109:104714. doi: 10.1016/j.oraloncology.2020.104714
58. Capuano R, Altieri M, Bisecco A, d'Ambrosio A, Docimo R, Buonanno D, Matrone F, Giuliano F, Tedeschi G, Santangelo G, Gallo A (2021) Psychological consequences of COVID-19 pandemic in Italian MS patients: signs of resilience? J Neurol 268:743-750. doi: 10.1007/s00415-020-10099-9
59. Stojanov A, Malobabic M, Milosevic V, Stojanov J, Vojinovic S, Stanojevic G, Stevic M (2020) Psychological status of patients with relapsing-remitting multiple sclerosis during coronavirus disease-2019 outbreak. Mult Scler Relat Disord 45:102407. doi: 10.1016/j.msard.2020.102407
60. Garlet GP (2010) Destructive and protective roles of cytokines in periodontitis: a re-appraisal from host defense and tissue destruction viewpoints. J Dent Res 89:1349-1363. doi: 10.1177/0022034510376402
61. Nakasone N, Kubota T, Hoshino C, Nohno K, Itagaki M, Shimizu T, Yoshie H (2009) Differential gene and protein expression of tissue inhibitors of metalloproteinases (TIMP)-3 and TIMP-4 in gingival tissues from drug induced gingival overgrowth. Arch Oral Biol 54:634-641. doi: 10.1016/j.archoralbio.2009.04.002
62. Xu HH, Werth VP, Parisi E, Sollecito TP (2013) Mucous membrane pemphigoid. Dent Clin North Am 57:611-630. doi: 10.1016/j.cden.2013.07.003
63. Nisengard RJ, Rogers RS, 3rd (1987) The treatment of desquamative gingival lesions. J Periodontol 58:167-172. doi: 10.1902/jop.1987.58.3.167
64. Motta AC, Domaneschi C, Komesu MC, Souza Cda S, Aoki V, Migliari DA (2009) Double-blind, crossover, placebo-controlled clinical trial with clobetasol propionate in desquamative gingivitis. Braz Dent J 20:231-236. doi: 10.1590/s0103-64402009000300011
65. Mollaoglu N (2000) Oral lichen planus: a review. Br J Oral Maxillofac Surg 38:370-377. doi: 10.1054/bjom.2000.0335

66. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR (2012) The nuts and bolts of low-level laser (light) therapy. Ann Biomed Eng 40:516-533. doi: 10.1007/s10439-011-0454-7
67. Farhi D, Dupin N (2010) Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies. Clin Dermatol 28:100-108. doi: 10.1016/j.clindermatol.2009.03.004
68. Elsabagh HH, Gaweesh YY, Ghonima JK, Gebril M (2021) A novel comprehensive scoring system for oral lichen planus: A validity, diagnostic accuracy, and clinical sensitivity study. Oral Surg Oral Med Oral Pathol Oral Radiol 131:304-311. doi: 10.1016/j.oooo.2020.12.016
69. Chiarotto A, Maxwell LJ, Ostelo RW, Boers M, Tugwell P, Terwee CB (2019) Measurement Properties of Visual Analogue Scale, Numeric Rating Scale, and Pain Severity Subscale of the Brief Pain Inventory in Patients With Low Back Pain: A Systematic Review. J Pain 20:245-263. doi: 10.1016/j.jpain.2018.07.009
70. Sung YT, Wu JS (2018) The Visual Analogue Scale for Rating, Ranking and Paired-Comparison (VAS-RRP): A new technique for psychological measurement. Behav Res Methods 50:1694-1715. doi: 10.3758/s13428-018-1041-8
71. Heller GZ, Manuguerra M, Chow R (2016) How to analyze the Visual Analogue Scale: Myths, truths and clinical relevance. Scand J Pain 13:67-75. doi: 10.1016/j.sjpain.2016.06.012

REFERÊNCIAS[1]

AKRAM, Z. *et al*. Photodynamic therapy in the treatment of symptomatic oral lichen planus: A systematic review. **Photodermatology Photoimmunology and Photomedicine**, [*s. l.*], v. 34, n.3,p. 167-174, 2018.

ARDUINO, P. G. Oral Complications of Dermatologic Disorders. **Atlas of the Oral and Maxillofacial Surgery Clinics of North America**, [*s. l.*], v. 25, n.2, p. 221-228, 2017.

ARDUINO, P. G. *et al*. Subgingival Microbiota in White Patients With Desquamative Gingivitis: A Cross-Sectional Study. **J Periodontol**, [*s. l.*], v. 88, n.7, p. 643-650, 2017.

CAFARO, A. *et al*. Clinical evaluation of the efficiency of low-level laser therapy for oral lichen planus: a prospective case series. **Lasers Med Sci**, London, v. 29, n.1, p. 185-190, 2014.

CAFARO, A. *et al*. Low-level laser therapy for oral mucous membrane pemphigoid. **Lasers Med Sci**, London, v. 27, n.6, p. 1247-1250, 2012.

CHAN, L. S. Mucous membrane pemphigoid. **Clin Dermatol**, [*s. l.*], v. 19, n.6, p. 703-711, 2001.

CHAN, L. S. *et al*. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. **Arch Dermatol**, [*s. l.*], v. 138, n.3, p. 370-379, 2002.

CHENG, Y. S. *et al*. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. **Oral Surg Oral Med Oral Pathol Oral Radiol**, [*s. l.*], v. 122, n.3, p. 332-354, 2016.

DAL PRÁ, K. J. *et al*. Oral management of pemphigus vulgaris in the intensive care unit. **Spec Care Dentist**, [*s. l.*], v. 40, n.3, p. 280-284, 2020.

DANIELLI, J. *et al*. Protocolo de atendimento e acompanhamento do paciente com líquen plano oral (LPO) / Protocol of care and patient follow-up monitoring with oral lichen planus (OLP). **Rev Odontol Bras Central**, [Brasil] v. 19, n.50, p. 233-238, 2010.

[1] Referências da introdução expandida de acordo com o Manual de normalização para elaboração de trabalhos acadêmicos, dissertações e teses da UNIFAL-MG.

DILLENBURG, C. S. *et al*. Efficacy of laser phototherapy in comparison to topical clobetasol for the treatment of oral lichen planus: a randomized controlled trial. **J Biomed Opt**, [*s. l.*], v. 19, n.6, p. 068002, 2014.

EL SHENAWY, H. M.; ELDIN, A. M. A Comparative Evaluation of Low-Level Laser and Topical Steroid Therapies for the Treatment of Erosive-Atrophic Lichen Planus. **Open Access Maced J Med Sci**, [Macedonia], v. 3, n.3, p. 462-466, 2015.

EL SHENAWY *et al*. Clinical Assessment of the Efficiency of Low Level Laser Therapy in the Treatment of Oral Lichen Planus. **Open Access Maced J Med Sci**, [Macedonia],v. 3, n.4, p. 717-721, 2015.

FITZPATRICK, S. G.; HIRSCH, S. A.; GORDON, S. C. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. **J Am Dent Assoc**, [*s. l.*], v. 145, n.1, p. 45-56, 2014.

GARCIA-POLA, M. J. *et al*. Oral hygiene instructions and professional control as part of the treatment of desquamative gingivitis. Systematic review. **Med Oral Patol Oral Cir Bucal**, [*s. l.*], v. 24, n.2, p. e136-e144, 2019.

GORSKY, M. *et al*. Clinical characteristics and treatment of patients with oral lichen planus in Israel. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod**, [*s. l.*], v. 82, n.6, p. 644-649,1996.

GRANDO, L. J. *et al*. Carcinoma de seno maxilar en paciente con liquen plano oral: Presentación de un caso clínico. **Av Odontoestomatol**, [*s. l.*], v. 29, n.4, p. 185-190, 2013.

JAJARM, H. H. *et al*. The effects of photodynamic and low-level laser therapy for treatment of oral lichen planus-A systematic review and meta-analysis. **Photodiagnosis PhotodynTher**, [*s. l.*], v. 23, p. 254-260, 2018.

JASCHOLT, I. *et al*. Periodontitis in oral pemphigus and pemphigoid: A systematic review of published studies. **J Am Acad Dermatol**, [*s. l.*], v. 76, n.5, p. 975-978 e973, 2017.

KARAGOZ, G. *et al*. Desquamative gingivitis: A review. **J Istanbul Univ Fac Dent**, Istanbul, v. 50, n.2, p. 54, 2016.

KAZANCIOGLU, H. O.; ERISEN, M. Comparison of Low-Level Laser Therapy versus Ozone Therapy in the Treatment of Oral Lichen Planus. **Ann Dermatol**, [*s. l.*] v. 27, n.5, p. 485- 491, 2015.

LAVAEE, F.; SHADMANPOUR, M. Comparison of the effect of photodynamic therapy and topical corticosteroid on oral lichen planus lesions. **Oral Dis**, [*s. l.*], v. 25, n.8, p. 1954-1963, 2019.

LO RUSSO, L. *et al*. Diagnostic pathways and clinical significance of desquamative gingivitis. **J Periodontol**, [*s. l.*], v. 79, n.1, p. 4-24, 2008.

LO RUSSO, L. *et al*. Epidemiology of desquamative gingivitis: evaluation of 125 patients and review of the literature. **Int. J. Dermatol.**, [*s. l.*], v. 48, p. 1049–1052, 2009.

MADERAL, A. D. *et al*. Desquamative gingivitis: Clinical findings and diseases. **J Am Acad Dermatol**, [*s. l.*], v. 78, n.5, p. 839-848, 2018.

MUSTAFA, M. B. *et al* Oral mucosal manifestations of autoimmune skin diseases. [*s. l.*], v. 14,n.10, p. 930-951, 2015.

NEVILLE, B. W. *et al*. **Patologia Oral e Maxilofacial**. 3 ed. Rio de Janeiro: Elsevier Editora Ltda., 2009.

NICO, M. M. S. *et al*. Oral lichen planus. **An Bras Dermatol**, [Brazil] v. 86, n.4, p. 633-643, 2011.

ORTONA, E. *et al*. Sex-based differences in autoimmune diseases. **Ann Ist Super Sanita**, [Italy], v.52, n.2, p. 205-212, 2016.

PAIVA, S. N. *et al*. Oral Lichen Planus: Clinical Profile and Determination of Oral Epithelial Dysplasia. **International journal of odontostomatology**, [*s. l.*], v. 10, n.1, p. 99-106, 2016.

PARASHAR, P. Oral lichen planus. **Otolaryngol Clin North Am**, [*s. l.*], v. 44, n.1, p. 89-107, vi,2011.

PORRO, A. M. *et al*. Pemphigus vulgaris. **An Bras Dermatol**, [Brazil], v. 94, n.3, p. 264-278, 2019.

SHIVHARE, P. *et al*. Evaluation of different diagnostic criteria of diseases manifesting the oral cavity - A review. Part-1. **J Oral Biol Craniofac Res**, [*s. l.*], v. 6, n.2, p. 135-141, 2016.

SOBANKO, J. F.; ALSTER, T. S. J. D. s. Efficacy of low-level laser therapy for chronic cutaneous ulceration in humans: A review and discussion. [*s. l.*], v. 34, n.8, p. 991-1000, 2008.

SOUSA, F. A. C. G. *et al*. Estudo Comparativo entre o Líquen Plano e o Carcinoma Epidermóide em Mucosa Bucal. **Cienc Odontol Bras**, [Brasil], v. 8, n.1, p. 55-60, 2005.

SUGERMAN, P. B. *et al*. The Pathogenesis of Oral Lichen Planus. **Crit Rev Oral Biol Med**, [*s. l.*], v. 13, n.4, p. 350-365, 2002.

TAKAHASHI, H. *et al*. Autoimmunity and immunological tolerance in autoimmune bullous diseases. **Int Immunol**, [*s. l.*], v. 31, n.7, p. 431-437, 2019.

TAYLOR, J. *et al*. World Workshop on Oral Medicine VI: a systematic review of thetreatment of mucous membrane pemphigoid. **Oral Surg Oral Med Oral Pathol Oral Radiol**, [*s. l.*], v. 120, n.2, p. 161-171 e120, 2015.

THORNE, J. E. et al. Mucous membrane pemphigoid and pseudopemphigoid. **Ophthalmology**, [*s. l.*], v. 111, n.1, p. 45-52, 2004.

TOFAN, E. C. *et al*. Desquamative Gingivitis - A Clinicopathological Review. **Curr Health Sci J**, [*s. l.*], v. 44, n.4, p. 331-336, 2018.

VÉLEZ, J. J. U. Estudio inmunohistoquímico del liquen plano bucal. **Rev haban cienc méd**, La Habana, v. 11, n.4, p. 457-463, 2012.

VENUGOPAL, S. S.; MURRELL, D. F. Diagnosis and clinical features of pemphigus vulgaris. **Dermatol Clin**, [*s. l.*], v. 29, n.3, p. 373-380, vii, 2011.

WANG, L. *et al*. Human autoimmune diseases: a comprehensive update. [*s. l.*], v. 278, n.4, p. 369- 395, 2015.

WERNECK, J. T. *et al*. Oral lichen planus: study of 21 cases. **An Bras Dermatol**, [Brazil] v. 90, n.3, p. 321-326, 2015.

XU, H. H. *et al*. Mucous membrane pemphigoid. **Dent Clin North Am**, [*s. l.*], v. 57, n.4, p. 611- 630, 2013.

ZAKRZEWSKA, J. M. Re: Mollaoglu N. Oral lichen planus: a review. Br J Oral Maxillofac Surg 2000; 38: 370-377. **Br J Oral Maxillofac Surg**, [England], v. 39, n.5, p. 407, 2001.

ZAND, N.; SHIRKAVAND, A. Letter regarding “Effect of laser on pain relief and wound healing of recurrent aphthous stomatitis: a systematic review”. **Lasers Med Sci**, [*s. l.*], v. 32, n.8, p. 1941, 2017.

APÊNDICE A: Metodologia detalhada da pesquisa[2]

4.1 Pergunta Principal

Esta revisão sistemática foi registrada no Registro Prospectivo Internacional de Revisões Sistemáticas (PROSPERO - CRD42020200843). Estabelecemos nossa questão de pesquisa usando as diretrizes dos Itens de Relatório Preferenciais para Revisão Sistemática e Meta-Análise (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses* - PRISMA) (MOHER *et al*., 2010) e de acordo com o princípio PICO (Participantes, Intervenções, Controle e Desfecho). A questão de interesse em foco foi: "A FBM é eficaz para tratar lesões gengivais autoimunes?".

População: pacientes com lesões gengivais devido a doenças autoimunes, incluindo LPO, PMM oral e PV oral;

Intervenção: lesões autoimunes gengivais tratadas com FBM;

***Comparação*:** lesões gengivais autoimunes tratadas com terapia medicamentosa convencional ou outra modalidade de tratamento (quando existirem grupos comparativos);

Desfecho (Outcome): verificar a eficácia da FBM em lesões gengivais autoimunes;

4.2 Estratégia de Busca

Foram realizadas pesquisas eletrônicas nos bancos de dados PubMed, Web of Science, EMBASE e Scopus. As palavras-chave foram selecionadas de acordo com *Medical Subject Headings* [MeSH — *National Center for Biotechnology Information* (NCBI)] e considerando os critérios PICO. Os artigos relevantes foram identificados através da combinação das palavras da seguinte forma:

[2] De acordo com as normas acadêmicas do Programa de Pós-Graduação em Ciências Odontológicas (RESOLUÇÃO no 05/2021, DE 28 DE ABRIL DE 2021).

- Para **líquen plano oral** e **fotobiomodulação**: “lichen planus, oral” OR “Oral lichen planus” AND “photobiomodulation therapy” OR “Photobiomodulation Therapies” OR “Low-Level Light Therapy” OR “Low-Level Light Therapies” OR “Light Therapies, Low-Level” OR “Light Therapy, Low-Level” OR “Therapies, Low-Level Light” OR “Therapy, Low-Level Light” OR “Therapies, Photobiomodulation” OR “Therapy, Photobiomodulation” OR “LLLT” OR “Laser Therapy, Low-Level” OR “Laser Therapies, Low-Level” OR “Laser Therapy, Low Level” OR “Low-Level Laser Therapies” OR “Laser Irradiation, Low-Power” OR “Irradiation, Low-Power Laser” OR “Laser Irradiation, Low Power” OR “Low-Power Laser Therapy” OR “Low Power Laser Therapy” OR “Laser Therapy, Low-Power” OR “Laser Therapies, Low- Power” OR “Laser Therapy, Low Power” OR “Low-Power Laser Therapies” OR “Low-Level Laser Therapy” OR “Low Level Laser Therapy” OR “Low-Power Laser Irradiation” OR “Low Power Laser Irradiation” OR “Laser Biostimulation” OR “Biostimulation, Laser” OR “Laser Phototherapy” OR “Phototherapy, Laser”;
- Para **penfigoide das membranas mucosas** e **fotobiomodulação**: “Mouth” or “Oral” AND “Pemphigoid, Benign Mucous Membrane” OR “Benign Mucosal Pemphigoid” OR “Benign Mucosal Pemphigoids” OR “Mucosal Pemphigoid, Benign” OR “Mucosal Pemphigoids, Benign” OR “Pemphigoid, Benign Mucosal” OR“Pemphigoids, Benign Mucosal” OR “Pemphigoid, Cicatricial” OR “Cicatricial Pemphigoid” OR “Benign Mucous Membrane Pemphigoid” OR “Mucous Membrane Pemphigoid, Benign” OR “Ocular Cicatricial Pemphigoid” OR “Cicatricial Pemphigoids, Ocular” OR “Ocular Cicatricial Pemphigoids” OR “Pemphigoids, Ocular Cicatricial” OR “Pemphigoid, Ocular Cicatricial” OR “Cicatricial Pemphigoid,Ocular” AND “photobiomodulation therapy” OR “Photobiomodulation Therapies”OR “Low-Level Light Therapy” OR “Low-Level Light Therapies” OR “Light Therapies, Low-Level” OR “Light Therapy, Low-Level” OR “Therapies, Low-Level Light” OR “Therapy, Low-Level Light” OR “Therapies, Photobiomodulation” OR “Therapy, Photobiomodulation” OR LLLT OR “Laser Therapy, Low-Level” OR “Laser Therapies, Low-Level” OR “Laser Therapy, Low Level” OR “Low-LevelLaser Therapies” OR “Laser Irradiation, Low-Power” or “Irradiation, Low-PowerLaser” OR “Laser Irradiation, Low Power” OR “Low-Power Laser Therapy” OR“Low Power Laser Therapy” OR “Laser Therapy, Low-Power” OR “Laser Therapies,

Low-Power" OR "Laser Therapy, Low Power" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Biostimulation, Laser" OR "Laser Phototherapy" OR "Phototherapy, Laser";

- Para **pênfigo vulgar** e **fotobiomodulação**: "Mouth" OR "Oral" AND "Pemphigus" or "Pemphigus Vulgaris" AND "photobiomodulation therapy" OR "Photobiomodulation Therapies" OR "Low-Level Light Therapy" OR "Low-Level Light Therapies" OR "Light Therapies, Low-Level" OR "Light Therapy, Low-Level" OR "Therapies, Low-Level Light" OR "Therapy, Low-Level Light" OR "Therapies, Photobiomodulation" OR "Therapy, Photobiomodulation" OR "LLLT" OR "Laser Therapy, Low-Level" OR "Laser Therapies, Low-Level" OR "Laser Therapy, Low Level" OR "Low-Level Laser Therapies" OR "Laser Irradiation, Low-Power" or "Irradiation, Low-Power Laser" OR "Laser Irradiation, Low Power" OR "Low-Power Laser Therapy" OR "Low Power Laser Therapy" OR "Laser Therapy, Low-Power" OR "Laser Therapies, Low-Power" OR "Laser Therapy, Low Power" OR "Low-Power Laser Therapies" OR "Low-Level Laser Therapy" OR "Low Level Laser Therapy" OR "Low-Power Laser Irradiation" OR "Low Power Laser Irradiation" OR "Laser Biostimulation" OR "Biostimulation, Laser" OR "Laser Phototherapy" OR "Phototherapy, Laser".

A busca em todos os bancos de dados eletrônicos foi exportada para o software EndNote Program ™ X7(Thomson Reuters, Nova York, NY, EUA), a fim de eliminar as referências duplicadas.

4.3 Critérios de Elegibilidade e Seleção dos Estudos

Foram selecionados artigos de pesquisa originais de acordo com os seguintes critérios de inclusão: (I) relatos de casos, séries de casos, estudos longitudinais e ensaios clínicos randomizados/aleatórios (ECA), (ii) nos quais os pacientes apresentem lesões gengivais por doenças autoimunes, incluindo LPO, PMM e PV, (iii) e que foram tratados com FBM. Foram excluídos estudos com crianças, gestantes e pacientes apenas com lesões cutâneas, oculares ou genitais, estudos laboratoriais (*in vitro* e *in vivo*), artigos de revisão, anais de conferências,

artigos de protocolo e estudos com dados insuficientes ou publicados em um idioma diferente do inglês.

Os estudos foram selecionados para elegibilidade por dois pesquisadores independentes (MMC e MLC), analisando títulos e resumos considerando os critérios de inclusão / exclusão descritos acima, e os estudos que não preencheram os critérios foram excluídos. Na sequência, os textos completos dos estudos que atenderam aos critérios de elegibilidade foram acessados pelos dois autores para inclusão. As discordâncias entre os investigadores foram resolvidas por consenso ou encaminhadas ao terceiro autor da revisão para a decisão final. Os estudos que atenderam aos critérios de seleção seguiram para extraçãode dados.

4.4 Extração de Dados

Dois revisores (MMC e MLC) extraíram os dados de forma independente. Os seguintes parâmetros foram extraídos de cada estudo selecionado: (i) tipo de estudo; (ii) número da amostra; (iii) média de idade; (iv) sexo dos sujeitos; (v) diagnóstico; (vi) método de diagnóstico utilizado; (vii) período de acompanhamento; (viii) métodos de avaliação e (ix) principais desfechos. Além disso, os parâmetros do laser dos estudos incluídos também foram coletados. Nessa etapa, também foram acessados os dados quantitativos dos desfechos (média e desvio padrão) para posterior realização da meta-análise.

4.5 Avaliação de Qualidade

Dois autores (SCP e MMC) avaliaram separadamente a qualidade dos estudos incluídos. Desacordos foram discutidos com um terceiro revisor. A qualidade metodológica dos relatos de casos e séries de casos foi avaliada utilizando a estrutura de avaliação sugerida por Murad e colaboradores (2018) com base nos domínios de seleção, apuração, causalidade erelato. Os estudos clínicos randomizados, por sua vez, foram avaliados usando a ferramenta de colaboração Cochrane (DE CARVALHO *et al*., 2013) e para estudos não randomizados,

foi empregada a escala RoBANS (ferramenta de avaliação de risco de viés para estudos não randomizados) (KIM *et al*., 2013).

O julgamento dos relatos e séries de casos foi feito com base nas questões consideradas mais críticas. Seis pontos foram concedidos para estudos da mais alta qualidade. Uma pontuação total abaixo de 2, será determinada como "baixa qualidade", uma pontuação de 3 ou 4, como "qualidade moderada" e uma pontuação acima de 5 como "alta qualidade". Por sua vez, os estudos clínicos foram avaliados quanto ao risco de viés em seis domínios, julgados como incertos, de baixo ou alto risco.

4.6 Medidas de Efeito do Tratamento

Os efeitos foram medidos por meio da escala visual analógica de dor (EVA) e evolução clínica da lesão (escala de Thongprasom) (THONGPRASOM *et al*., 1992).

4.7 Síntese dos Dados

Uma meta-análise foi realizada para comparar a FBM com a terapia medicamentosa em lesões gengivais autoimunes. Os estudos foram separados em laser com controle e laser sem controle para análise dos resultados e, para os estudos sem controle, foi feita a comparação do efeito do laser ao longo do tempo. Na meta-análise, foram avaliados o númerode indivíduos por grupo, a idade de cada grupo (média e desvio padrão) e os valores numéricos da média e desvio padrão dos critérios de avaliação. Os estudos sem controle foram agrupados considerando os escores EVA e os escores clínicos de Thongprasom. Devidoà semelhança entre EVA e *Numerical Rating Scale* (*NRS System*), essas duas ferramentas foram agrupadas em uma análise separada. O tamanho do efeito foi estimado e relatado como a diferença média (DM). O software estatístico Review Manager [RevMan] (Versão 5.1. Copenhagen: *The Nordic Cochrane Centre, The Cochrane Collaboration*, 2011) foi usadopara reunir os dados e produzir os gráficos *forest plot*. Além disso, foi realizada uma análise narrativa para explorar a relação entre os estudos.

REFERÊNCIAS

DE CARVALHO, A.; SILVA, V.; GRANDE, A. J. D. T. Avaliação do risco de viés de ensaios clínicos randomizados pela ferramenta da colaboração Cochrane. [Brasil], v. 18, n.1, p. 38-44, 2013.

KIM, S. Y.; PARK, J. E.; LEE, Y. J.; SEO, H.-J.; SHEEN, S.-S.; HAHN, S.; JANG, B.-H.; SON, H.-J. J. J. o. c. e. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. [*s. l.*], v. 66, n.4, p. 408-414, 2013.

MOHER, D.; SCHULZ, K. F.; SIMERA, I.; ALTMAN, D. G. J. P. m. Guidance for developers of health research reporting guidelines. [*s. l.*], v. 7, n.2, p. e1000217, 2010.

MURAD, M. H. *et al*. Methodological quality and synthesis of case series and case reports. **BMJ evidence-based medicine**, [*s. l.*], v. 23, n. 2, p. 60-63, 2018.

THONGPRASOM, K.; LUANGJARMEKORN, L.; SERERAT, T.; TAWEESAP, W. Relative efficacy of fiuocinolone acetonide compared with triamcinolone acetonide in treatment of oral lichen planus. **J Oral Pathol Med**, [*s. l.*], v. 21, n.10, p. 456-458, 1992.

ANEXO A: Normas da Revista *Clinical Oral Investigations*[3]

Submission guidelines

Instructions for Authors

Types of papers

Papers may be submitted for the following sections:

- Original articles
- Invited reviews
- Short communications – with up to 2000 words and up to two figures and/or tables
- Discussion paper
- Letters to the editor

It is the general policy of this journal not to accept case reports and pilot studies.

Manuscript Submission

MANUSCRIPT SUBMISSION

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be heldlegally responsible should there be any claims for compensation.

PERMISSIONS

[3] De acordo com as normas acadêmicas do Programa de Pós-Graduação em Ciências Odontológicas (RESOLUÇÃO no 05/2021, DE 28 DE ABRIL DE 2021).

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

ONLINE SUBMISSION

Please follow the hyperlink “Submit manuscript” on the right and upload all of your manuscript files following the instructions given on the screen.

Please ensure you provide all relevant editable source files. Failing to submit these source files might cause unnecessary delays in the review and production process.

The Springer Author Academy is a set of comprehensive online training pages mainly geared towards first-time authors. At this point, more than 50 pages offer advice to authors on how to write and publish a journal article.

Title Page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)

The e-mail address, telephone and fax numbers of the corresponding author

Abstract

Please provide a structured abstract of 150 to 250 words which should be divided into the following sections:

- Objectives (stating the main purposes and research question)
- Materials and Methods

- Results
- Conclusions
- Clinical Relevance

These headings must appear in the abstract.

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

Text

TEXT FORMATTING

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX. We recommend using Springer Nature's LaTeX template.

HEADINGS

Please use no more than three levels of displayed headings.

ABBREVIATIONS

Abbreviations should be defined at first mention and used consistently thereafter.

FOOTNOTES

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

ACKNOWLEDGMENTS

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

References

CITATION

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

REFERENCE LIST

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

The entries in the list should be numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

- Journal article

Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

Ideally, the names of all authors should be provided, but the usage of “*et al*” in long author lists will also be accepted:

Smith J, Jones M Jr, Houghton L *et al* (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

- Book

South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation

Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

Authors preparing their manuscript in LaTeX can use the bibliography style file sn-basic.bst which is included in the Springer Nature Article Template.

Tables

All tables are to be numbered using Arabic numerals.

Tables should always be cited in text in consecutive numerical order.

For each table, please supply a table caption (title) explaining the components of the table.

Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and Illustrations Guidelines

ELECTRONIC FIGURE SUBMISSION

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

LINE ART

Definition: Black and white graphic with no shading.

Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.

All lines should be at least 0.1 mm (0.3 pt) wide.

Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.

Vector graphics containing fonts must have the fonts embedded in the files.

HALFTONE ART

Definition: Photographs, drawings, or paintings with fine shading, etc.

If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.

Halftones should have a minimum resolution of 300 dpi.

COMBINATION ART

Color art is free of charge for online publication.

If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.

If the figures will be printed in black and white, do not refer to color in the captions.

Color illustrations should be submitted as RGB (8 bits per channel).

FIGURE LETTERING

To add lettering, it is best to use Helvetica or Arial (sans serif fonts).

Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).

Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

Avoid effects such as shading, outline letters, etc.

Do not include titles or captions within your illustrations.

FIGURE NUMBERING

All figures are to be numbered using Arabic numerals.

Figures should always be cited in text in consecutive numerical order.

Figure parts should be denoted by lowercase letters (a, b, c, etc.).

If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

FIGURE CAPTIONS

Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.

Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.

No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.

Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.

Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

FIGURE PLACEMENT AND SIZE

Figures should be submitted separately from the text, if possible.

When preparing your figures, size figures to fit in the column width.

For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.

For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

PERMISSIONS

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

ACCESSIBILITY

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that:

All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)

Any figure lettering has a contrast ratio of at least 4.5:1.

Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as Supplementary Information, authors should read the journal's Research data policy. We encourage research data to be archived in data repositories wherever possible

SUBMISSION

Supply all supplementary material in standard file formats.

Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.

To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

High resolution (streamable quality) videos can be submitted up to a maximum of 25GB; low resolution videos should not be larger than 5GB.

AUDIO, VIDEO, AND ANIMATIONS

Aspect ratio: 16:9 or 4:3

Maximum file size: 25 GB for high resolution files; 5 GB for low resolution files

Minimum video duration: 1 sec

Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

TEXT AND PRESENTATIONS

Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.

A collection of figures may also be combined in a PDF file.

SPREADSHEETS

Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

SPECIALIZED FORMATS

Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

COLLECTING MULTIPLE FILES

It is possible to collect multiple files in a .zip or .gz file.

NUMBERING

If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.

Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.

Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

CAPTIONS

For each supplementary material, please supply a concise caption describing the content of the file.

PROCESSING OF SUPPLEMENTARY FILES

Supplementary Information (SI) will be published as received from the author without any conversion, editing, or reformatting.

ACCESSIBILITY

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

The manuscript contains a descriptive caption for each supplementary material

Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk).

Clinical Trial Registration

Clinical trials must be registered prior to submission of manuscripts. The registration site must be publicly available in English.

Recommended sites are: https://www.isrctn.com ; https://www.clinicaltrialsregister.eu; https://clinicaltrials.gov or similar.

The registration number is required for the submission and must appear on the title page

English Language Editing

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should consider:

Getting a fast, free online grammar check.

Asking a colleague who is proficient in English to review your manuscript for clarity.

Visiting the English language tutorial which covers the common mistakes when writing in English.

Using a professional language editing service where editors will improve the English to ensure that your meaning is clear and identify problems that require your review. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts. Springer authors are entitled to a 10% discount on their first submission to either of these services, simply follow the links below.

Free online grammar check

English language tutorial

Nature Research Editing Service

American Journal Experts

Please note that the use of a language editing service is not a requirement for publication in this journal and does not imply or guarantee that the article will be selected for peer review or accepted.

If your manuscript is accepted it will be checked by our copyeditors for spelling and formal style before publication.

Ethical Responsibilities of Authors

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation ishelped by following the rules of good scientific practice, which include*:

The manuscript should not be submitted to more than one journal for simultaneous consideration.

The submitted work should be original and should not have been published elsewhere in any form or language (partially or in full), unless the new work concerns an expansion of previous work. (Please provide transparency on the re-use of material to avoid the concerns about text-recycling (‘self-plagiarism’).

A single study should not be split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (i.e. ‘salami-slicing/publishing’).

Concurrent or secondary publication is sometimes justifiable, provided certain conditions are met. Examples include: translations or a manuscript that is intended for a different group of readers.

Results should be presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation (including image based manipulation). Authors should adhere to discipline-specific rules for acquiring, selecting and processing data.

No data, text, or theories by others are presented as if they were the author’s own (‘plagiarism’). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks (to indicate words taken from another source) are used for verbatim copying of material, and permissions secured for material that is copyrighted.

Important note: the journal may use software to screen for plagiarism.

Authors should make sure they have permissions for the use of software, questionnaires/(web) surveys and scales in their studies (if appropriate).

Research articles and non-research articles (e.g. Opinion, Review, and Commentary articles) must cite appropriate and relevant literature in support of the claims made. Excessive and inappropriate self-citation or coordinated efforts among several authors to collectively self-cite is strongly discouraged.

Authors should avoid untrue statements about an entity (who can be an individual person or a company) or descriptions of their behavior or actions that could potentially be seen as personal attacks or allegations about that person.

Research that may be misapplied to pose a threat to public health or national security should be clearly identified in the manuscript (e.g. dual use of research). Examples include creation of harmful consequences of biological agents or toxins, disruption of immunity of vaccines, unusual hazards in the use of chemicals, weaponization of research/technology (amongst others).

Authors are strongly advised to ensure the author group, the Corresponding Author, and the order of authors are all correct at submission. Adding and/or deleting authors during the revision stages is generally not permitted, but in some cases may bewarranted. Reasons for changes in authorship should be explained in detail. Pleasenote that changes to authorship cannot be made after acceptance of a manuscript.

*All of the above are guidelines and authors need to make sure to respect third parties rights such as copyright and/or moral rights.

Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results presented. This could be in the form of raw data, samples, records, etc. Sensitive information in the form of confidential or proprietary data is excluded.

If there is suspicion of misbehavior or alleged fraud the Journal and/or Publisher will carry out an investigation following COPE guidelines. If, after investigation, there are valid concerns, the author(s) concerned will be contacted under their given e-mail address and given an opportunity to address the issue. Depending on the situation, this may result in the Journal's and/or Publisher's implementation of the following measures, including, but not limited to:

If the manuscript is still under consideration, it may be rejected and returned to the author.

If the article has already been published online, depending on the nature and severity of the infraction:

- an erratum/correction may be placed with the article

- an expression of concern may be placed with the article

The reason will be given in the published erratum/correction, expression of concern or retraction note. Please note that retraction means that the article is maintained on the platform, watermarked "retracted" and the explanation for the retraction is provided in a note linked to the watermarked article.

The author's institution may be informed

A notice of suspected transgression of ethical standards in the peer review system may be included as part of the author's and article's bibliographic record.

FUNDAMENTAL ERRORS

Authors have an obligation to correct mistakes once they discover a significant error or inaccuracy in their published article. The author(s) is/are requested to contact the journal and explain in what sense the error is impacting the article. A decision on how to correct the literature will depend on the nature of the error. This may be a correction or retraction. The retraction note should provide transparency which parts of the articleare impacted by the error.

SUGGESTING / EXCLUDING REVIEWERS

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

Authorship principles

These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

AUTHORSHIP CLARIFIED

The Journal and Publisher assume all authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, before the work is submitted.

The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

DISCLOSURES AND DECLARATIONS

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

DATA TRANSPARENCY

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

ROLE OF THE CORRESPONDING AUTHOR

One author is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;

managing all communication between the Journal and all co-authors, before and after publication;*

providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;

making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

AUTHOR CONTRIBUTIONS

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

Examples of such statement(s) are shown below:

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commentedon previous versions of the manuscript. All authors read and approved the finalmanuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

For review articles where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the student's dissertation or thesis, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

Affiliation

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

CHANGES TO AUTHORSHIP

Authors are strongly advised to ensure the correct author group, the Corresponding Author, and the order of authors at submission. Changes of authorship by adding or

deleting authors, and/or changes in Corresponding Author, and/or changes in the sequence of authors are not accepted after acceptance of a manuscript.

Please note that author names will be published exactly as they appear on the accepted submission!

Please make sure that the names of all authors are present and correctly spelled, and that addresses and affiliations are current.

Adding and/or deleting authors at revision stage are generally not permitted, but in some cases it may be warranted. Reasons for these changes in authorship should be explained. Approval of the change during revision is at the discretion of the Editor-in- Chief. Please note that journals may have individual policies on adding and/or deletingauthors during revision stage.

AUTHOR IDENTIFICATION

Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

DECEASED OR INCAPACITATED AUTHORS

For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

AUTHORSHIP ISSUES OR DISPUTES

In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

CONFIDENTIALITY

Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

Compliance with Ethical Standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

Disclosure of potential conflicts of interest

Research involving Human Participants and/or Animals

Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of a real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. Examples of potential conflicts of interests that are directly or indirectly related to the research may include but are not limited to the following:

Research grants from funding agencies (please give the research funder and the grant number)

Honoraria for speaking at symposia

Financial support for attending symposia

Financial support for educational programs

Employment or consultation

Support from a project sponsor

Position on advisory board or board of directors or other type of management relationships

Multiple affiliations

Financial relationships, for example equity ownership or investment interest

Intellectual property rights (e.g. patents, copyrights and royalties from such rights)

Holdings of spouse and/or children that may have financial interest in the work

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but

are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.

The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it,it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found here:

The corresponding author will include a summary statement in the text of the manuscript in a separate section before the reference list, that reflects what is recorded in the potential conflict of interest disclosure form(s)

Please make sure to submit all Conflict of Interest disclosure forms together with the manuscript.

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of Interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving human participants, their data or biological material

ETHICS APPROVAL

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was

performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 HelsinkiDeclaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

RETROSPECTIVE ETHICS APPROVAL

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

ETHICS APPROVAL FOR RETROSPECTIVE STUDIES

Although retrospective studies are conducted on already available data or biologicalmaterial (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of acountry. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

ETHICS APPROVAL FOR CASE STUDIES

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on Informed Consent.

CELL LINES

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

RESEARCH RESOURCE IDENTIFIERS (RRID)

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

Examples:

Organism: Filip1tm1a(KOMP)Wtsi RRID:MMRRC_055641-UCD

Cell Line: RST307 cell line RRID:CVCL_C321

Antibody: Luciferase antibody DSHB Cat# LUC-3, RRID:AB_2722109

Plasmid: mRuby3 plasmid RRID:Addgene_104005

Software: ImageJ Version 1.2.4 RRID:SCR_003070

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

CLINICAL TRIAL REGISTRATION

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

Standards of reporting

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal's Instructions for Authors.

Checklists are available for a number of study designs, including:

Randomised trials (CONSORT) and Study protocols (SPIRIT)

Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

SUMMARY OF REQUIREMENTS

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No.).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No.).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number:).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are

in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as toany photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether oftheir whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymizedand the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

- Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

- Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant information regarding consent. Authors should provide the appropriate attribution for republished images.

CONSENT AND ALREADY AVAILABLE DATA AND/OR BIOLOGIC MATERIAL

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

DATA PROTECTION, CONFIDENTIALITY AND PRIVACY

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered “informed”. However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

CONSENT TO PARTICIPATE

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors

must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

CONSENT TO PUBLISH

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper to a journal. This is in particular applicable to case studies. A consent to publish form can be found here. (Download docx, 36 kB)

SUMMARY OF REQUIREMENTS

The above should be summarized in a statement and placed in a ‘Declarations’ section before the reference list under a heading of ‘Consent to participate’ and/or ‘Consent to publish’. Other declarations include Funding, Competing interests, Ethics approval, Consent, Data and/or Code availability and Authors’ contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for "Consent to participate":

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for “Consent to publish”:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason forremoval.

Research Data Policy

This journal operates a type 1 research data policy. The journal encourages authors, where possible and applicable, to deposit data that support the findings of their research in a public repository. Authors and editors who do not have a preferred repository should consult Springer Nature’s list of repositories and research data policy.

List of Repositories

Research Data Policy

General repositories - for all types of research data - such as figshare and Dryad may also be used.

Datasets that are assigned digital object identifiers (DOIs) by a data repository may be cited in the reference list. Data citations should include the minimum information recommended by DataCite: authors, title, publisher (repository name), identifier.

DataCite

If the journal that you're submitting to uses double-blind peer review and you are providing reviewers with access to your data (for example via a repository link, supplementary information or data on request), it is strongly suggested that the authorship in the data is also blinded. There are data repositories that can assist with this and/or will create a link to mask the authorship of your data.

Authors who need help understanding our data sharing policies, help finding a suitable data repository, or help organising and sharing research data can access our AuthorSupport portal for additional guidance.

After Acceptance

Upon acceptance, your article will be exported to Production to undergo typesetting. Once typesetting is complete, you will receive a link asking you to confirm your affiliation, choose the publishing model for your article as well as arrange rights and payment of any associated publication cost.

Once you have completed this, your article will be processed and you will receive the proofs.

ARTICLE PUBLISHING AGREEMENT

Depending on the ownership of the journal and its policies, you will either grant the Publisher an exclusive licence to publish the article or will be asked to transfercopyright of the article to the Publisher.

OFFPRINTS

Offprints can be ordered by the corresponding author.

COLOR ILLUSTRATIONS

Publication of color illustrations is free of charge.

PROOF READING

The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor.

After online publication, further changes can only be made in the form of an Erratum, which will be hyperlinked to the article.

ONLINE FIRST

The article will be published online after receipt of the corrected proofs. This is the official first publication citable with the DOI. After release of the printed version, the paper can also be cited by issue and page numbers.

Open Choice

Open Choice allows you to publish open access in more than 1850 Springer Nature journals, making your research more visible and accessible immediately onpublication.

Article processing charges (APCs) vary by journal – view the full list

Benefits:

Increased researcher engagement: Open Choice enables access by anyone with an internet connection, immediately on publication.

Higher visibility and impact: In Springer hybrid journals, OA articles are accessed 4 times more often on average, and cited 1.7 more times on average*.

Easy compliance with funder and institutional mandates: Many funders require openaccess publishing, and some take compliance into account when assessing future grant applications.

It is easy to find funding to support open access – please see our funding and support pages for more information.

*) Within the first three years of publication. Springer Nature hybrid journal OA impact analysis, 2018.

Open Choice

Funding and Support pages

Open access publishing

To find out more about publishing your work Open Access in Clinical Oral Investigations, including information on fees, funding and licenses, visit our Open access publishing page.