UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE ODONTOLOGIA

PROGRAMA DE PÓS-GRADUAÇÃO EM ODONTOLOGIA

NÍVEL DOUTORADO

ÁREA DE CONCENTRAÇÃO EM CLÍNICA ODONTOLÓGICA

PERIODONTIA

Tese

O IMPACTO DAS REVISÕES DE LITERATURA NA CIÊNCIA ODONTOLÓGICA E NA CLÍNICA PERIODONTAL: O EXEMPLO DE UMA REVISÃO SISTEMÁTICA DE ESTATINAS COMO ADJUVANTES À TERAPIA PERIODONTAL

FRANCISCO WILKER MUSTAFA GOMES MUNIZ

Porto Alegre, novembro de 2017

Francisco Wilker Mustafa Gomes Muniz

O impacto das revisões de literatura na ciência odontológica e na clínica periodontal: o exemplo de uma revisão sistemática de estatinas como adjuvante à terapia periodontal

Tese apresentada ao Programa de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal do Rio Grande do Sul como requisito obrigatório para obtenção de título de Doutor em Odontologia, área de concentração Clínica Odontológica/Periodontia.

Orientador: Prof. Dr. Cassiano Kuchenbecker Rösing

Porto Alegre, 2017

CIP - Catalogação na Publicação

Mustafa Gomes Muniz, Francisco Wilker
O impacto das revisões de literatura na ciência odontológica e na clínica periodontal: o exemplo de uma revisão sistemática de estatinas como adjuvantes à terapia periodontal / Francisco Wilker Mustafa Gomes Muniz. -- 2017.
75 f.
Orientador: Cassiano Kuchenbecker Rösing.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Odontologia, Programa de Pós-Graduação em Odontologia, Porto Alegre, BR-RS, 2017.

1. Revisão de literatura. 2. Bibliometria. 3. Doença periodontal. 4. Estatina. I. Kuchenbecker Rösing, Cassiano, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

Agradecimentos

Em meu aniversário de sete anos, lembro de ter ganho um presente bem significativo para a minha vida. Era um quadro e uma caixa de giz. Lembro-me de forçar meu irmão mais novo a sentar na frente daquele quadro e forçá-lo a ouvir as minhas aulas de Matemática e Português. Ainda que de maneira inconsciente, ali, minha família plantou o início dos meus anseios pela docência.

Passados alguns anos, enquanto ainda estava no ensino médio, tive a oportunidade de assistir uma palestra sobre carreira odontológica da Professora Walda Viana Brígido de Moura. Naquele momento, mesmo com todas as dúvidas de um jovem de 17 anos, tive a certeza que iria fazer vestibular para Odontologia. Ali, surgiu o meu encanto pela Odontologia. Pode ter sido o destino ou mesmo o meu inconsciente trabalhando, em menos de um ano após essa palestra, fui aprovado no vestibular da Universidade Federal do Ceará e tive, como primeira orientadora, a Profa. Walda.

Após três anos, recebi o convite para participar das atividades de pesquisa com o Professor Ricardo de Souza Martins. Com isso, pude congregar as três paixões que me trouxeram até aqui: Odontologia, ensino e pesquisa. O percurso para chegar até aqui foi árduo, porém muito proveitoso. Em todo esse caminho, tive a oportunidade de ter, ao meu lado, diversas pessoas que foram fundamentais para o meu crescimento acadêmico e pessoal. A essas pessoas eu devo meus imensos agradecimentos.

Pai e mãe, **Welyton Muniz** e **Sílvia Mustafa**, vocês foram fundamentais nessa minha trajetória. Obrigado pelos incentivos constantes e por não medirem esforços, desde o princípio, em realizar meus sonhos. Nesse caminho, sei que contribuí muito para a "síndrome do ninho vazio", mas fico muito grato em saber que isso tudo só nos fortalece a cada dia. Mãe, obrigado por ter sempre as melhores palavras para me acalentar e para me motivar. Pai, obrigado por ser o exemplo de garra que me fez querer ser melhor dia após dia.

Irmãos, **Welyton Filho**, **Weyder**, **Wallace**, **Walker** e **Mariana**, em vocês tive o meu melhor porto seguro. A nossa fraternidade supera todos as barreiras do cotidiano e as geográficas. Obrigado por terem compreendido a minha ausência do dia-a-dia e pela amizade e admiração que temos.

Adilson e **Nayane**, obrigado por terem me ensinado a crer no amor familiar muito além da família tradicional. Muito mais do que estar ao seu lado dos meus pais nos momentos em que não pude, vocês me apoiaram e fizeram eu crer em mim mesmo.

A minha amada **Luísa Maurique**, boa parte do que está incluído nessa tese "tem o seu dedo". Além dos seus incentivos constantes, você me faz querer ser uma pessoa melhor a cada dia por nós dois. Você foi o meu verdadeiro porto seguro durante esses três anos. Obrigado por me mostrar sempre as minhas capacidades, mesmo quando eu quis fraquejar. Hoje tenho uma felicidade imensa no meu coração por ter, ao meu lado, a melhor companheira, a melhor amiga e a grande "incubadora de ideias acadêmicas". A nossa história está apenas no começo. Te amo!

Aos meus sogros, **Jorge** e **Beatriz Maurique**, obrigado por terem me incluído na família da melhor maneira possível. Sei que hoje tenho uma segunda família para todos os momentos da minha vida.

Aos meus eternos amigos, **Felipe**, **Irineu**, **Ivna**, **Lucas**, **Manuela**, **Mariah**, **Pedro**, **Priscilla** e **Raíssa**, por terem oferecido seus ombros em todos os momentos que necessitei. Estar longe da convivência diária de vocês foi duro, mas fico muito feliz em saber que isso não nos afetou. A ligação que nos une me faz crer que a fraternidade é algo que foge aos laços sanguíneos.

Aos grandes amigos que a Odontologia me proporcionou, **Camila Carvalho**, **Humberto Júnior**, **Karoline Sena**, **Marília Rolim**, **Myrna Arcanjo**, **Nicéa Lóssio**, **Renata Guerra**, **Sarah Guedes** e **Thayanne Brasil**, por sempre me fazerem acreditar nas minhas capacidades.

Aos amigos que a Pós-graduação me trouxe, **Ricardo Costa**, **Fernanda Milanesi**, **Keity Taminski**, **Marina Mendez**, **Tassiane Wagner**, **Stephanie Friedrich**, **Raisa Severo**, **Harry Oballe**, **Paula Amorim**, **Mirian Toniazzo**, **Belkiss Marmora, AnaCaudia Flores**, **Silvia de David**, **Silvia Zanella**, vocês transformaram a minha rotina de trabalho em um ambiente mais prazeroso e fácil de manejar. Espero levar a amizade de vocês para o resto da vida.

Ao amigo **Bruno Kauer**, por ter sido o eixo inicial e fundamental no meu vínculo com a UFRGS.

Ao Professor **Roger Celeste**, por não medir esforços em ajudar um aluno em fase de formação. Tenho um orgulho imenso em ter aprendido tanto com você nesses quatro anos.

À Professora **Patrícia Weidlich**, por ser um verdadeiro exemplo de tudo aquilo que eu quero ser na prática clínica e na docência. Sou muito grato por ter um espelho tão bom a ser seguido no meu futuro.

Ao Professor **Juliano Cavagni**, obrigado por ter sido um excelente amigo durante toda essa trajetória. Ter você ao meu lado, durante esse período de docência, foi muito enriquecedor.

Aos demais colegas de docência da Periodontia, não tenho palavras para expressar a gratidão de ter sido moldado por vocês na nossa convivência diária. Estou tendo uma experiência fantástica de docência e, boa parte disso, é por ter um grande tão coeso e excelente ao meu lado.

Aos primeiros e eternos orientadores, **Walda Viana**, **Rosimary Carvalho**, **Mônica Studart** e **Ricardo Martins**, por terem me iniciado no amor à Periodontia e por, até hoje, se preocuparem com o meu aperfeiçoamento.

Ao meu orientador, **Cassiano Rösing**, por não medir esforços em me tornar um melhor professor, pesquisador e periodontista. Sou profundamente agradecido por todas as oportunidades, por todos os ensinamentos e pelos constantes incentivos até aqui. Obrigado por ter superado todas as minhas expectativas com a Pós-Graduação e por estar sempre disponível para as minhas realizações acadêmicas. Hoje me orgulho muito do meu currículo e, boa parte disso, é mérito seu.

Agradeço à CAPES, pela concessão da bolsa de estudos durante esse período.

SUMÁRIO

RESUMO **6**

1. APRESENTAÇÃO **8**

2. INTRODUÇÃO **11**

3. PROPOSIÇÃO **14**

4. ARTIGO 1 - CITATION ANALYSIS AND TRENDS IN REVIEW ARTICLES IN DENTISTRY **15**

5. ARTIGO 2 - THE EFFECT OF STATINS ON PERIODONTAL TREATMENT – A SYSTEMATIC REVIEW WITH META-ANALYSES AND META-REGRESSION **25**

6. CONSIDERAÇÕES FINAIS **62**

ANEXOS **67**

RESUMO

As revisões sistemáticas são consideradas os desenhos experimentais capazes de guiar os cuidados em saúde. Contudo, as revisões narrativas ainda são largamente publicadas até o presente momento. No âmbito do tratamento das doenças periodontais, diversos estudos têm reportado que o uso adjuvante de estatinas à terapia periodontal mecânica pode acarretar melhorias nos parâmetros clínicos periodontais, como adicionais reduções de profundidade de sondagem e ganhos de inserção clínica. O objetivo deste trabalho é contextualizar a informação advinda de uma revisão sistemática realizada sobre um tema clínico significativo e compreender qual o seu papel como suporte da atenção ao paciente periodontal, a partir da compreensão obtida no estudo bibliométrico de revisões de literatura. No estudo bibliométrico, uma amostra representativa das revisões de literatura, publicadas na base Scopus, foi selecionada. Tipo de revisão, número de citações, ano de publicação, temática do estudo e outras variáveis foram coletadas. Nesse estudo, observou-se que o número de revisões sistemática tem aumentado significativamente ao longo dos anos quando comparados com o número de revisões narrativas. Apesar disso, o número ajustado de citações das revisões sistemáticas não difere significativamente das recebidas nas revisões narrativas. Já na revisão sistemática de uso adjuvante de estatinas, uma estratégia de busca nas bases Pubmed, Scopus e Embase foi realizada para identificar todos os ensaios clínicos que tenham utilizado estatinas como adjuvantes ao tratamento periodontal mecânico em comparação à terapia periodontal mecânica isolada ou associada a placebo. Quinze estudos foram selecionados. Observou-se que, na maioria dos estudos, o uso adjuvante de estatina apresentou adicionais reduções de profundidade de sondagem e ganhos de inserção clínica quando comparado com seus respectivos grupos controles. Contudo, a alta heterogeneidade desse resultado e o grande número de estudos ser executado por um mesmo grupo de pesquisa são fatores limitadores dessa revisão sistemática. Dessa maneira, pode-se concluir que o número de revisões sistemáticas vem aumentando a longo do tempo, porém o seu número de citações parece não acompanhar as mesmas tendências. Além disso, o uso adjuvante de estatina na terapia periodontal ainda não deve ser recomendado até a execução de outros estudos com melhor qualidade.

Palavras-chave: Revisão; Indicadores bibliométricos; Doença periodontal; Hydroxymethylglutaryl CoA Reductases.

ABSTRACT

Systematic review is considered the experimental design capable of guiding the health care. However, narrative reviews are broadly published nowadays. Regarding periodontal diseases treatment, several studies reported that the adjuvant use of statins to mechanical periodontal treatment may promote additional improvements in clinical periodontal parameters, such as additional reduction in probing depth and clinical attachment gain. This study aimed to contextualize the information obtained in a systematic review about a significant clinical thematic and comprehend is its role in the periodontal care, through information gathered in a bibliometric study of literature review studies in Dentistry. In the bibliometric study, a representative sample of literature reviews studies, published in Scopus database, was selected. Type of review, number of citations, year of publication, study thematic, and other variables were collected. It was showed that the number of systematic reviews increased throughout the years in comparison to narrative reviews. Additionally, the Dentistry clinical fields presented the highest number of published systematic reviews. Despite of that, the mean adjusted number of citations granted for systematic reviews did not differ from the narrative ones. Regarding the performed systematic review, a search strategy was conducted on Pubmed, Scopus, and Embase databases to identify all clinical trials that used statins as adjuvant to mechanical periodontal treatment in comparison to mechanical periodontal treatment alone or in association with placebo. Fifteen studies were included. It was showed that most of the included studies presented additional reduction in probing depth and clinical attachment gain in comparison to their control groups. However, the high heterogeneity among the studies and the high number of studies conducted by the same research group are limitations of the present systematic review. It was concluded that the number of systematic review are increasing dramatically throughout the years, but this trend is not followed by the number of citations granted to this type of study. Furthermore, the adjuvant use of statin in the mechanical periodontal therapy may not be recommended until further well-designed studies have been published.

Keywords: Review; Bibliometric Indicators; Periodontal disease; Hydroxymethylglutaryl CoA Reductases.

1. APRESENTAÇÃO

A presente tese intitulada "O impacto das revisões de literatura na ciência odontológica e na clínica periodontal: o exemplo de uma revisão sistemática de estatinas como adjuvante à terapia periodontal" está sendo apresentada ao Programa de Pós-Graduação em Odontologia da Universidade Federal do Rio Grande do Sul como parte dos requisitos para obtenção do título de Doutor em Clínica Odontológica/Periodontia.

A temática é de grande importância para a ciência e a prática clínica odontológica. A tese contém uma introdução geral, seguida de dois artigos e considerações finais. Nesse sentido, os dois estudos realizados, sendo um estudo de análises bibliométricas, já publicado no periódico *The Journal of Evidence-Based Denta Practice*, e uma revisão sistemática, que foi submetida ao periódico *Clinical Oral Investigations*.

Artigo 1: Citation analysis and trends in review articles in Dentistry.

Artigo 2: The effect of statins on periodontal treatment – a systematic review with meta-analyses and meta-regression.

Esta tese é parte da trajetória acadêmica do candidato. Além dos artigos científicos aqui apresentados, outras produções foram realizadas durante os períodos de mestrado e doutorado. A lista a seguir demonstra todos os artigos produzidos pelo candidato durante esse período:

1. Muniz FWMG, Celeste RK, Oballe HJR, Rösing CK. Citation analysis and trends in review articles in Dentistry. J Evid Based Dent Pract. 2017 [Epub ahead of print] doi: 10.1016/j.jebdp.2017.08.003
2. Muniz FWMG, Melo IM, Rösing CK, de Andrade GM, Martins RS, Moreira MMSM, Carvalho RS. Use of antidepressive agents as a possibility in the management of periodontal diseases: A systematic review of experimental studies. J Investig Clin Dent. 2017 Sep 1. doi: 10.1111/jicd.12291.
3. Muniz FWMG, da Silva Lima H, Rösing CK, Martins RS, Moreira MMSM, Carvalho RS. Efficacy of an unwaxed dental floss impregnated with 2% chlorhexidine on control of supragingival biofilm: A randomized, clinical trial. J Investig Clin Dent. 2017 Jul 9. doi: 10.1111/jicd.12280.
4. Rösing CK, Cavagni J, Gaio EJ, Muniz FWMG, Ranzan N, Oballe HJR, Friedrich SA, Severo RM, Stewart B, Zhang YP. Efficacy of two mouthwashes with

cetylpyridinium chloride: a controlled randomized clinical trial. Braz Oral Res. 2017 Jul 3;31:e47. doi: 10.1590/1807-3107BOR-2017.vol31.0047.

5. Toniazzo MP, Amorim PS, Muniz FW, Weidlich P. Relationship of nutritional status and oral health in elderly: Systematic review with meta-analysis. Clin Nutr. 2017 Mar 28. pii: S0261-5614(17)30105-X. doi: 10.1016/j.clnu.2017.03.014.
6. Colussi PR, Hugo FN, Muniz FW, Rösing CK. Oral Health-Related Quality of Life and Associated Factors in Brazilian Adolescents. Braz Dent J. 2017 Jan-Feb;28(1):113-120.
7. Cantarelli R, Negrini TC, Muniz FW, Oballe HJ, Arthur RA, Rösing CK. Antimicrobial potential and gustatory perception of chlorhexidine gluconate mouthwashes with or without alcohol after a single rinse - a randomized controlled crossover clinical trial. Int J Dent Hyg. 2016 Nov 7. doi: 10.1111/idh.12255.
8. Muniz FW, Friedrich SA, Silveira CF, Rösing CK. The impact of chewing gum on halitosis parameters: a systematic review. J Breath Res. 2017 Feb 17;11(1):014001. doi: 10.1088/1752-7163/aa5cc2.
9. Muniz FWMG, Cavalcante DJ, Moreira MMSM, Rodrigues LKA, de Oliveira Fernandes CA, de Almeida PC, de Sousa Carvalho R. Association Between Confidence in Smiling and Esthetic Characteristics. J Esthet Restor Dent. 2017 Apr;29(2):E56-E66.
10. Muniz FWMG, Haas AN. Preservação e aumento de rebordo alveolar após perda de implante osseointegrado. INPerio 2017; 2(1):35-42.
11. Rösing CK, Muniz FWMG. Tratamento das recessões gengivais: um desafio para a Odontologia. Clínica (São José) 2017 Jan-Mar; 13(1): 90-2.
12. Rosing CK, Cavagni J, Gaio EJ, Muniz FW, Oballe HJ, Ranzan N, Friedrich SA, Severo RM, Gittins E, Stewart B, Zhang YP. Efficacy of two soft-bristle toothbrushes in plaque removal: a randomized controlled trial. Braz Oral Res. 2016 Nov 10;30(1):e134. doi: 10.1590/1807-3107BOR-2016.vol30.0134.
13. Lopes MH, Rösing CK, Colussi PR, Muniz FW, Linden MS. Prevalence of self-reported halitosis and associated factors in adolescents from Southern Brazil. Acta Odontol Latinoam. 2016 Sep;29(2):93-103.
14. Haas AN, Wagner TP, Muniz FW, Fiorini T, Cavagni J, Celeste RK. Essential oils-containing mouthwashes for gingivitis and plaque: Meta-analyses and meta-regression. J Dent. 2016 Dec;55:7-15.

15. Cavagni J, Muniz FWMG, Rösing CK. The effect of inflammatory response modulator agents on gingivitis and periodontitis. Rev Gaúch Odontol. 2016 Jul-Sep;64(3):312-9.
16. Muniz FWMG, Vidal TC, Roger RO, Moreira MMSM, Martins RS, Carvalho RS. Perception and level of knowledge about halitosis among students and patients. Full Dent Sci. 2016; 7(26):99-103.
17. Rösing CK, Muniz FWMG. Vitamina D e saúde bucal: aspectos relevantes para conhecimento da Odontologia. Clínica (São José) 2016 Jul-Set; 12(3): 292-6.
18. Muniz FW, Nogueira SB, Mendes FL, Rösing CK, Moreira MM, de Andrade GM, Carvalho Rde S. The impact of antioxidant agents complimentary to periodontal therapy on oxidative stress and periodontal outcomes: A systematic review. Arch Oral Biol. 2015 Sep;60(9):1203-14.
19. Muniz FW, Sena KS, de Oliveira CC, Veríssimo DM, Carvalho RS, Martins RS. Efficacy of dental floss impregnated with chlorhexidine on reduction of supragingival biofilm: a randomized controlled trial. Int J Dent Hyg. 2015 May;13(2):117-24.

2. INTRODUÇÃO

A construção do conhecimento nas ciências da saúde tem passado por evolução ao longo dos anos. Isso se dá frente aos novos conhecimentos propiciados pela pesquisa científica. Assim, as abordagens baseadas em conhecimentos populares, em informações não testadas sistematicamente, perdem espaço para abordagens que apresentam suporte científico.

Surge, a partir desse entendimento, um movimento denominado "Medicina baseada em evidências" que, por analogia, suscita a criação do movimento "Odontologia baseada em evidências" (Dodson, 1997). Essa nova forma de encarar a ciência foi definida como o "uso consciente, explícito e prudente da melhor evidência disponível para o cuidado em saúde" (Dodson, 1997). A partir desse entendimento, muitas modificações do fazer em saúde aconteceram. Esse movimento alertou a comunidade científica a respeito de diferentes tipos de desenhos de pesquisa que teriam menores ou maiores capacidades de geração de evidência (Healey e Lyons, 2002). Assim, entende-se que, na pirâmide da evidência científica, a opinião de especialistas apresenta a menor capacidade de geração de evidência e as revisões sistemáticas da literatura, principalmente aquelas que são estatisticamente analisadas (com metanálises ou outras formas de análise) aparecem como o desenho de pesquisa com maior capacidade de geração de evidências (Brignardello-Petersen *et al.*, 2014).

Essa forma de encarar a ciência, em um primeiro momento, acabou por gerar grandes críticas às revisões narrativas da literatura, pois, viriam carregadas fortemente da opinião de quem as escreve (Cook, 2008). Em contrapartida, as revisões sistemáticas, por apresentarem métodos explícitos, dificultariam pelo menos a inclusão/exclusão de artigos com base somente na opinião dos autores da revisão (Higgins e Green, 2011). Por um tempo, parecia que as revisões narrativas deveriam ser descartadas. Entretanto, não se pode negar que os capítulos de livro-texto, que sempre apoiaram o ensino dos profissionais da saúde, sempre foram revisões narrativas. Da mesma forma, os periódicos historicamente publicaram e publicam revisões narrativas (algumas a convite e outras por submissão de autores), que facilitam muito a atualização dos profissionais da saúde. Essas revisões têm sido substancialmente citadas e têm contribuído para o cuidado em saúde.

Com o entendimento das limitações eventuais das revisões narrativas, muitas críticas passaram a ser feitas às mesmas e uma controvérsia acaba por ser estabelecida,

confrontando revisões sistemáticas e narrativas (Dijkers e Guidelines, 2009). Na verdade, entende-se que há espaço para ambas as formas de realização de revisão, uma vez que as revisões sistemáticas são delineadas com finalidade de responder a perguntas específicas e as revisões narrativas apresentam um espectro mais amplo (Cook, 2008; Dijkers e Guidelines, 2009). Em ambas podem-se encontrar viéses, equívocos ou até mesmo tendências. A interpretação da informação escrita deve ser realizada pelo leitor que, no caso dos profissionais da saúde, deve ser crítico e reflexivo quanto ao estado da arte para a atenção em saúde daqueles que dele necessitam.

Uma forte característica surgiu na ciência que é sempre buscar somente revisões sistemáticas para responder a uma determinada dúvida. Isso potencialmente levaria que os estudos mais citados e, portanto, mais impactantes, seriam as revisões sistemáticas. A análise encontrada nesta tese amplia um pouco o horizonte do olhar minimalista para a questão das revisões. Assim, a partir de uma análise bibliométrica de revisões de literatura, sugere-se uma reflexão sobre a informação não embasada de que revisões sistemáticas seriam os estudos com maior impacto.

No âmbito prático, está incluída neste trabalho uma revisão sistemática sobre o uso de estatinas como coadjuvantes ao tratamento periodontal. Nessa revisão, a seguinte pergunta clínica focada foi: “Em pacientes com periodontite crônica/agressiva, o quão efetivas são as estatinas, quando utilizadas como adjuvantes ao tratamento periodontal mecânico em comparação ao tratamento periodontal mecânico isolado ou associado a um placebo?”. Até o presente momento, o controle mecânico do biofilme, em associação a uma terapia de suporte periodontal, é considerado o procedimento padrão-ouro para o tratamento das periodontites (Graziani *et al.*, 2017). Contudo, em alguns pacientes, essa terapia parece ser ineficiente, pois alguns sítios continuam a perder inserção periodontal após a terapia mecânica (Slots *et al.*, 1985; Dye, 2012).

Nesse contexto, o uso adjuvante de outras substâncias, como antibióticos, tem sido proposto na literatura (Muniz *et al.*, 2013). A literatura reporta que esses fármacos apresentam, quando administrados de forma adjuvante à terapia periodontal, um efeito clínico significativamente maior que a terapia periodontal associado a placebo (Smiley *et al.*, 2015; Zandbergen *et al.*, 2016). Entretanto, a relevância clínica desses achados têm sido questionada na literatura (Walters e Lai, 2015; Assem *et al.*, 2017).

Outras substâncias farmacológicas clinicamente testadas como adjuvantes à terapia periodontal são as estatinas. Esses fármacos são largamente utilizados na redução dos níveis de colesterol sanguíneo, sendo rotineiramente utilizados no tratamento das hiperlipidemias e da aterosclerose. Além disso, apresenta-se como uma das principais terapias para a prevenção secundária de desfechos adversos cardiovasculares (Adams *et al.*, 2014; Adams *et al.*, 2015). As estatinas são inibidoras da 3-hidroxi-3-metilglutaril Coenzima A redutase (HMG-CoA redutase), uma importante enzima envolvida na síntese do colesterol. Além desses efeitos, as estatinas apresentam os chamados efeitos pleiotrópicos, que são efeitos adicionais não relacionados com o efeito hipolipidêmico, incluindo ações antiinflamatórias, antioxidantes, angiogênese, aumento da função endotelial e aumento da formação óssea (Mcfarlane *et al.*, 2002; Adam e Laufs, 2008; Sadowitz *et al.*, 2010; Cicek Ari *et al.*, 2016; Tsujinaka *et al.*, 2017).

Diversos ensaios clínicos randomizados têm demonstrado resultados superiores do uso adjuvante de estatinas à terapia mecânica periodontal (Pradeep e Thorat, 2010; Pradeep *et al.*, 2012; Pradeep *et al.*, 2013; Rao *et al.*, 2013; Pradeep *et al.*, 2015; Pradeep *et al.*, 2016). Contudo, até o presente momento, nenhuma revisão sistemática foi publicada analisando as diversas formas de administração desse fármaco em pacientes submetidos à terapia periodontal.

Com base na ideia de que as revisões de literatura são importantes na construção de informações para a prática, esta tese vai analisar criticamente um exemplo de uma revisão sistemática, procurando contextualizar as suas vantagens e limitações em termos de aplicação prática. Na verdade, o objetivo deste trabalho é contextualizar a informação advinda de uma revisão sistemática realizada sobre um tema clínico significativo e compreender qual o seu papel como suporte da atenção ao paciente periodontal, a partir da compreensão obtida no estudo bibliométrico de revisões da literatura.

3. PROPOSIÇÃO

A presente tese teve por objetivo avaliar o impacto das revisões na ciência e na clínica periodontal. Para tanto, dois estudos foram delineados. Os objetivos desses estudos foram:

1. Descrever tendências em artigos de revisão de literatura em Odontologia, assim como comparar os padrões de citação entre revisões narrativas e tradicionais.
2. Revisar sistematicamente a literatura sobre o uso adjuvante de estatinas, associadas ao tratamento periodontal mecânico, em relação a parâmetros periodontais, como profundidade de sondagem, perda de inserção clínica e defeito intraósseos, em comparação à terapia periodontal mecânica isolada ou em associação a um placebo.

4. ARTIGO 1 - CITATION ANALYSIS AND TRENDS IN REVIEW ARTICLES IN DENTISTRY

Artigo aceito no periódico “The Journal of Evidence-Based Dental Practice”.

The Journal of EVIDENCE-BASED DENTAL PRACTICE

FEATURE ARTICLE

CITATION ANALYSIS AND TRENDS IN REVIEW ARTICLES IN DENTISTRY

FRANCISCO WILKER MUSTAFA GOMES MUNIZ, DDS, MSc[a], ROGER KELLER CELESTE, DDS, MSc, PhD[b], HARRY JUAN RIVERA OBALLE, DDS, MSc, PhD[a], AND CASSIANO KUCHENBECKER RÖSING, DDS, MSc, PhD[a]

[a]Department of Periodontology, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil
[b]Department of Preventive and Social Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil

ABSTRACT

Objective
This study aimed to describe the trends in dentistry article reviews as well as to compare citation patterns between systematic and narrative reviews.

Methods
A search strategy was developed, in Scopus database, in order to identify all narrative and systematic reviews published between 2000 and 2015. Original research studies, letters to the editor, editorials, book chapters, and case reports were excluded. From the list of studies available, 30 reviews per year were randomly chosen. The review type, year of publication, number of authors, country of the first author, open access, language, main topic of interest, journal's H index, number of references, and number of citations were extracted by 2 researchers. The number of citations was extracted from the Scopus database. Multivariable regression analysis was used in order to detect the association between citation rate and the independent variables.

Results
Overall, 118 and 362 systematic and narrative reviews were included in this study. Throughout the years, the number of systematic reviews has increased from 5.8% to 53.3%. However, the mean number of citations has significantly decreased, and this is affected by the review's year of publication. A trend for lower citation in systematic reviews (Relative risk [RR]: 0.79; 95% confidence interval: 0.75-0.84) has been demonstrated; however, the number of citations of narrative reviews has been increasing over the years (RR: 1.14; 95% confidence interval: 1.08-1.21).

Conclusion
From 2000 to 2015, the number of systematic reviews increased substantially. On the other hand, a trend for lower citations of these studies has been observed that is affected over time.

INTRODUCTION

Publishing is an important step in order to spread research findings in the scientific community. Furthermore, the number of citations of an article may reflect the dissemination and popularity of its results among other researchers. Quantitative measures of citations are related to quality and impact of an article.[1] It is well established that the high journal prestige, publications in English, and review articles are associated with a higher number of citations.[2,3] In addition,

CORRESPONDING AUTHOR:
Roger Keller Celeste, Department of Preventive and Social Dentistry, Federal University of Rio Grande do Sul, Rua Ramiro Barcelos 2492, 3rd floor, Porto Alegre, Rio Grande do Sul, Brazil 90035-003.
E-mail: roger.keller@ufrgs.br

KEYWORDS
Bibliometrics, Reviews, Dentistry, Citation, Trends

Source of funding: This study is self-funded.
Conflict of interest: Roger Keller Celeste and Cassiano Kuchenbecker Rösing hold a Productivity-quality (PQ) fellowship from the Brazilian Science and Technology Council (CNPq). Other authors have no conflicts of interest to disclose.

Received 1 August 2017; revised 18 August 2017; accepted 19 August 2017

J Evid Base Dent Pract 2017: [1-9]
1532-3382/$36.00

doi: http://dx.doi.org/10.1016/j.jebdp.2017.08.003

the number of authors and country of publication can also help dissemination among peers, therefore influencing the number of citations.

In dentistry, few studies have assessed citation patterns and have mainly focused in specific subareas. In endodontics, for instance, the most cited articles are all published in English,[4] and low citation is attributed to case report studies in the oral and maxillofacial surgery field.[5] On the other hand, case series and cohort studies are the most cited methodological studies in implant dentistry.[6]

Systematic reviews are considered the highest level of scientific evidence; however, they have not appeared very often among the list of most cited articles.[4,6,7] Indeed, narrative reviews were ranked higher among top cited articles, and this may reveal that authors frequently use articles that bring expert opinions about future research or yet articles describing theories and specific hypotheses, which may be the case of narrative reviews. On the other hand, a more pragmatic explanation is that narrative reviews have been more frequently published, especially among older articles.[8] It could be hypothesized that systematic reviews would have higher mean citations and may become more frequently published over time. Nonetheless, to the best of our knowledge, those hypotheses have not been evaluated in the dental literature or in other fields. Therefore, the objectives of this study were to describe trends in dentistry review articles and compare citation patterns between systematic and narrative reviews. The null hypothesis under study is that there is no significant difference between the citation rates between narrative and systematic reviews.

MATERIAL AND METHODS

Data Sources and Design

In this study, only systematic and narrative reviews in dentistry were retrieved and included in data analyses. Original research studies, letters to the editor, editorials, and book chapters were excluded. Additionally, case reports were excluded, even if they were accompanied by a literature review. The following search strategy was performed on Scopus database in order to identify only the studies published between 2000 and 2015:

((TITLE-ABS-KEY(review*) AND SUBJAREA (DENT)) AND NOT SUBJAREA(MULT OR AGRI OR BIOC OR VETE OR CENG OR CHEM OR COMP OR EART OR ENER OR ENGI OR ENVI OR MATE OR MATH OR PHYS OR IMMU OR NEUR OR PHAR OR MEDI OR NURS OR HEAL)) AND (LIMIT-TO (PUBYEAR,2015) OR LIMIT-TO (PUBYEAR,2014) OR LIMIT-TO (PUBYEAR,2013) OR LIMIT-TO (PUBYEAR,2012) OR LIMIT-TO (PUBYEAR,2011) OR LIMIT-TO (PUBYEAR,2010) OR LIMIT-TO (PUBYEAR,2009) OR LIMIT-TO (PUBYEAR,2008) OR LIMIT-TO (PUBYEAR,2007) OR LIMIT-TO (PUBYEAR,2006) OR LIMIT-TO (PUBYEAR,2005) OR LIMIT-TO (PUBYEAR,2004) OR LIMIT-TO (PUBYEAR,2003) OR LIMIT-TO (PUBYEAR,2002) OR LIMIT-TO (PUBYEAR,2001) OR LIMIT-TO (PUBYEAR,2000))

The diagnostic accuracy (sensitivity and specificity) of this search strategy was determined in a sample of a specific journal and year (*Journal of Clinical Periodontology*, 2005). High sensitivity (0.97) and specificity (1.0) were demonstrated.

Randomization Process and Studies Selection

From this search strategy, 12,341 studies were available for eligibility in the elected years in dentistry. Using the command "sort on relevance" on Scopus database, these studies were numerically identified from 1 to 12,341. Then, a stratified randomization by the year of publication was performed by one of the researchers (F.W.M.G.M.), using random numbers obtained from the software R version 3.3, to identify a total of 30 systematic or narrative reviews per year.

Two researchers (F.W.M.G.M. and H.J.R.O.) have independently classified the study type as "systematic review," "narrative review," or "other studies." Those authors extensively discussed the study type classification until an agreement was achieved. When a study was classified as "other studies," a new randomization process, also stratified by year, was performed until 30 systematic or narrative reviews per year were included in the present study.

Independent Variable and Predictors

The dependent variable–the number of citations per article–was automatically extracted from Scopus dataset on April 6, 2017. Our main exploratory variable was the type of review article (systematic review or narrative review). In addition, 8 other covariates were collected for each study as follows: the year of publication, authors' names (from which the number of authors was derived), country of the first author, type of access (open access: yes or no), language of publication (that was categorized as only English or other languages), main topic of interest was classified after reading titles and abstracts (basic/lab sciences, cariology, dental materials, endodontics, gerodontology, implantology, operative dentistry, oral microbiology, oral and maxillofacial surgery, oral pain, oral pathology, orthodontics, pediatric dentistry, periodontology, prosthodontics, public health, or other), journal's H index, and number of references. The journal's H index was extracted from the Scimago Journal & Country Rank Web site (www.scimagojr.com). These variables were independently extracted by 2 researchers (F.W.M.W.G. and H.J.R.O.). Each variable was discussed extensively until an agreement was possible.

Statistical Analysis

Mean citations were presented in tables with standard deviation for descriptive purposes as well as percentage of systematic reviews among each category of covariates. Bivariate analyses were conducted in order to test for differences among categories of covariates. The chi-square test was used for categorical variables, and Mann–Whitney or Kruskal–Wallis test was used to compare differences in ranking of citations.

The number of citations was highly skewed with the presence of overdispersion 53 times higher than expected for a Poisson distribution (likelihood ratio test of alpha $P < .0001$). Therefore, negative binomial regression was used to model predictors of mean citation rates. Interaction between the types of review was tested with all covariates. Linear regression was used in order to estimate absolute difference in number of citations between systematic and narrative reviews. However, due to the asymptotic nature of the distributions, confidence intervals (CIs) were calculated based on bootstrap with 500 repetitions. All analyses were carried out in Stata 13.1.

RESULTS

This study included 118 and 362 systematic and narrative reviews, respectively. Totally, 714 studies were retrieved, and the main reasons for exclusion are expressed in Figure 1. Table 1 shows the main characteristics and percentage of systematic reviews, for each variable, in the selected studies. Overall, a significantly higher number of systematic reviews was found in European countries (other than the United Kingdom and Ireland), periodontology/implantology themes, with the journal's H-index >100, with the number of references between 26 and 50, and more than 5 authors ($P < .01$). Throughout the year, the

Figure 1. Flowchart of the included studies.

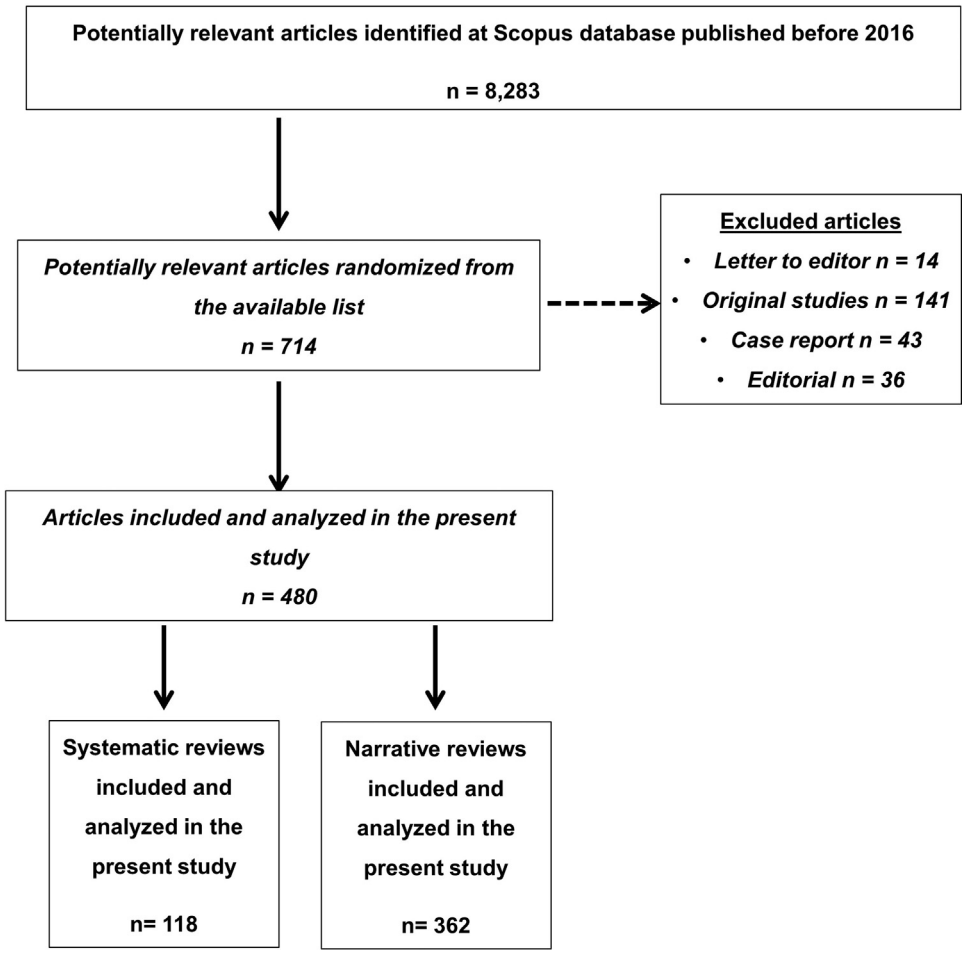

Table 1. Frequency of published articles and percentage of systematic reviews (SRs) by article categories.

Variables	N	%	% of SR	*P* value[a]
Total	480	100		
Country of publication of the first author				
Oceania	32	6.7	12.5	<.01
Other European	113	23.5	51.3	
Other countries	22	4.6	36.4	
BRICS	62	12.9	35.5	
USA/Canada	203	42.3	8.9	
UK/Ireland	48	10.0	16.7	
Main thematic of the article				
Basic/lab sciences	87	18.1	5.8	<.01
Other clinical sciences	240	50.0	23.3	
Periodontology/implantology	134	27.9	41.0	
Dental Public Health	19	4.0	10.5	
Year of publication				
2000-2003	120	25.0	5.8	<.01
2004-2007	120	25.0	10.0	
2008-2011	120	25.0	29.2	
2012-2015	120	25.0	53.3	
Language of the article				
Non-English/dual	24	5.0	16.7	.36
Only English	456	95.0	25.0	
Journal H-index				
0-25	67	14.0	22.4	<.01
26-50	173	36.0	7.5	
51-75	80	16.7	22.5	
76-100	84	17.5	25.0	
>100	75	15.8	66.1	
Open access?				
No	373	77.7	25.2	.56
Yes	107	22.3	22.4	
Number of references				
0-25	99	20.8	9.1	<.01
26-50	140	29.2	32.9	
51-75	107	22.3	30.8	
76-100	59	12.4	30.5	
>100	75	15.6	16.0	
Number of authors				
1 author	109	22.7	0.9	<.01
2-5 authors	328	68.3	29.3	
>5 authors	43	9.0	48.8	

[a] Chi-squared test.

number of systematic reviews increased from 5.8% (between 2000 and 2003) to 53.3% (between 2012 and 2015), and this difference is statistically significant ($P < .01$). On the other hand, in comparison to narrative reviews, no statistically significant difference was demonstrated for the number of systematic reviews in the following variables: open access and the language of the articles ($P > .05$).

Table 2 shows the overall mean citation of all the narrative and systematic reviews included in the present study. A significantly higher mean citation was demonstrated in studies with periodontology/implantology themes and in studies published in the earlier 2000s in all review types ($P < .05$). On the other hand, the type of access did not result in a significant difference in the mean citation number in all review types ($P > .05$).

Table 2. Mean citation and standard deviation (± SD) among systematic reviews (SRs) and narrative reviews (NRs) according to article categories.

Variables	Overall	±SD	*P* value[a]	SR	±SD	*P*-value[a]	NR	± SD	*P* value[a]
Total	30.0	43.7		36.9	51.9		27.7	40.6	
Country of publication of the first author									
Oceania	34.0	39.1	<.01	43.5	66.9	0.33	32.7	35.2	<.01
Other European	39.6	43.7		39.4	47.7		39.9	39.5	
Other countries	23.2	26.3		16.6	21.6		27.0	28.7	
BRICS	18.9	32.1		27.0	42.2		14.4	24.4	
USA/Canada	28.2	48.4		44.9	73.4		26.6	45.2	
UK/Ireland	29.3	42.5		45.1	67.8		26.2	35.9	
Main thematic of the article									
Basic/lab sciences	33.4	51.0	<.01	14.8	11.3	0.02	34.5	52.3	<.01
Other clinical sciences	22.6	32.1		30.8	43.9		20.0	27.2	
Perio/implants	44.4	54.2		46.3	60.4		43.1	49.9	
Dental Public Health	5.4	6.8		4.0	1.4		5.5	7.2	
Year of publication									
2000-2003	39.9	48.2	<.01	92.0	110.7	<0.01	36.7	40.3	<.01
2004-2007	38.6	57.5		77.4	77.1		34.3	53.7	
2008-2011	28.8	35.3		52.1	44.7		19.2	25.2	
2012-2015	12.6	18.6		15.0	21.3		9.8	14.7	
Language of the article									
Non-English/dual	5.8	15.1	<.01	16.3	32.5	0.07	3.7	9.0	<.01
Only English	31.2	44.4		37.6	52.4		29.1	41.2	
Journal H-index									
0-25	3.1	4.6	<.01	2.8	3.7	<0.01	3.2	4.9	<.01
26-50	16.5	22.3		22.2	40.1		16.0	20.4	
51-75	36.1	48.0		36.4	68.8		36.1	40.8	

(*continued*)

Table 2. (Continued)

Variables	Overall	±SD	*P* value[a]	SR	±SD	*P*-value[a]	NR	± SD	*P* value[a]
76-100	51.4	54.0		45.9	53.1		53.3	54.5	
>100	54.0	56.5		47.2	51.2		67.9	65.0	
Open access?									
No	31.3	46.7	.99	39.3	55.2	0.19	28.7	43.3	.32
Yes	25.2	30.9		27.8	35.7		24.4	29.5	
Number of references									
0-25	9.7	21.8	<.01	7.4	7.1	<0.01	9.9	22.8	<.01
26-50	20.3	32.4		30.3	50.0		15.4	16.8	
51-75	31.9	48.5		37.3	57.0		29.6	44.5	
76-100	43.4	39.8		60.0	47.4		36.1	34.1	
>100	61.4	57.4		48.8	59.4		63.7	57.2	
Number of authors									
1 author	19.2	26.9	<.01	33.0	0.0	0.50	19.1	26.9	<.01
2-5 authors	32.9	46.5		39.5	55.2		30.1	42.2	
>5 authors	35.0	52.2		25.2	33.0		44.3	64.9	

[a] Kruskal–Wallis or Mann–Whitney test for variables with multiple or two categories, respectively.

Table 3 shows the adjusted mean citation rate according to the study characteristics. In the year 2000, the mean adjusted difference between systematic and narrative reviews was 50.1 citations (95% CI = +0.77 to +99.5) more for systematic reviews, whereas in the year 2015, the difference was −12.5 (95% CI = −25.7 to +0.7), meaning that systematic reviews presented a predicted value of 12.5 fewer citations. It was also demonstrated that studies with basic/lab sciences and periodontology/implantology themes presented a significantly higher mean citation rate than Dental Public Health (DPH) studies ($P < .05$). Table 4 summarizes the main finding of present study, stating both pros and cons.

DISCUSSION

This study aimed to analyze the trend in review articles in dentistry as well as to compare the citation patterns between narrative and systematic reviews. The number of systematic reviews has substantially increased throughout the years; meanwhile, the adjusted number of citations granted to systematic reviews has declined notably in comparison to narrative reviews. It was confirmed that many other factors may predict the probability of receiving more citations. Importantly, the effect of the main theme of the article, of which studies in the periodontology/implantology themes received higher number of citations, was the highlight.

Systematic reviews and meta-analyses are useful study designs, as they may guide clinical practice and health policies. These types of studies are very attractive to perform, mainly due to their low cost, power to suggest the pathways for new investigations,[9] and the higher chances to be cited in comparison to other study designs.[10,11] It is also reported that before starting a new study, the researchers must assess the literature systematically.[12] Additionally, when the literature is assessed in a nonsystematic approach, the

Table 3. Adjusted mean citation rate (Relative risk [RR] and 95% CI) of review articles from negative binomial regression according to article characteristics.

Variables	Relative risk [RR] (95% CI)
Type of review by year	
Difference at year 2000	
Narrative review	1
Systematic review	4.24 (2.23-8.06)
Annual decrease in difference (systematic review by each year)	0.87 (0.82-0.92)
Difference at year 2015	
Narrative review	1
Systematic review	0.56 (0.37-0.86)
Country of publication of the first author	
Other European	1
Oceania	0.91 (0.62-1.34)
Other countries	0.65 (0.42-1.00)
BRICS	0.74 (0.54-1.02)
USA/Canada	0.63 (0.49-0.82)
UK/Ireland	0.74 (0.53-1.05)
Main thematic of the article	
Dental Public Health	1
Basic/lab sciences	2.24 (1.32-3.79)
Other clinical sciences	1.60 (0.98-2.63)
Perio/implants	2.13 (1.27-3.57)
Language of the article	
Non-English/dual	1
Only English	5.94 (3.46-10.23)
Journal H-index	
0-25	1
26-50	2.60 (1.86-3.65)
51-75	4.66 (3.20-6.78)
76-100	5.34 (3.63-7.87)
>100	6.47 (4.37-9.57)
Open access?	
No	1
Yes	1.36 (1.08-1.71)
Number of references	
0-25	1
26-50	2.14 (1.63-2.80)
51-75	2.91 (2.20-3.85)
76-100	3.44 (2.50-4.75)
>100	4.22 (3.10-5.74)
Number of authors	
1 author	1
2-5 authors	1.26 (1.01-1.58)
>5 authors	1.77 (1.24-2.53)

CI, confidence interval.

synthesis of information may be inaccurate or suboptimal[13] and may present researcher bias in the qualitative analyses.[9] Other disadvantages are also associated with nonsystematic reviews, such as financial competing interest and favorable conclusions.[14] However, the literature reports that these study designs answer different questions and should be complementary in biomedical science.[9,15]

Table 4. Summary of the present study main findings, stating the pros and cons of both systematic reviews (SRs) and narrative reviews (NRs).

Summary of the findings	
Pros	**Cons**
• There is an increase in SR from 5.8% (in 2000-2003) to 53.3% (in 2012-2015). • The overall mean citation number is significantly higher for SR. • At the year 2015, the adjusted mean citation for NR was double of the citations received by SR.	• The current high number of SR makes it difficult for clinicians to find appropriate SR for their needs. • It may be unlikely the current level of SR covers all health care demands from policy makers. • We did not assess quality of the reviews. Although it is possible, we cannot be sure that the highly cited reviews are the most useful guide for clinicians. Looking for highly cited is an easier step.

The present study showed an increase in systematic reviews from 5.8% (in 2000-2003) to 53.3% (in 2012-2015). The substantial increase in the number of systematic reviews was already demonstrated in a previous study, which showed that, in the PubMed database, the number of studies tagged as systematic reviews increased 2728% between 1991 and 2014, whereas for all PubMed-indexed items, the increase was 153%.[16] This study also demonstrated that the higher amount of systematic review studies may be a result of redundant and nonuseful studies,[16] which partially support our findings that systematic reviews are receiving fewer citations.

On average, the mean number of citations for systematic reviews is significantly higher than that for narrative reviews. However, over time, the adjusted number of citations granted to systematic reviews has decreased, and the citation gap between systematic and narrative reviews has reversed. For instance, in 2015, the mean citation rate for systematic reviews was half of that received by narrative reviews (RR: 0.56, 95% CI: 0.37-0.86). It may be supposed that the increase in the number of published systematic reviews was followed by a decrease in the quality and utility in those studies.

On the other hand, the 2 review types may present different patterns in the citation peak. The literature reports that the peak citation rate has differed across many fields.[17] Unfortunately, the peak rate for citations has not been assessed in reviews in dentistry. Therefore, it may be hypothesized that systematic reviews have a longer citation life, having a citation peak years after narrative reviews, as obsolescence of systematic reviews may not occur quickly. A narrative review is useful to generate hypotheses, and presents its results in a rich and critical way.[9] This may be one of the reasons for the higher citation trend in the years after publication. It is important to emphasize that this study does not recommend a nonsystematic approach to all reviews conducted in the future.

Another important finding of this study is that more than 50% of the systematic reviews published are from dental clinical sciences, especially in the periodontology and implantology fields. On the other hand, only 10.5% of the systematic reviews published in the dental literature were identified as DPH, although not necessarily in DPH core journals.[18] Initially, the majority of the systematic reviews, as advocated by the Cochrane Collaboration, were based on intervention reviews, which are not common in DPH.[18] The need for evidence-based public policy may require community interventions.

This study showed that a significantly higher citation rate was observed for reviews published in English and more than 90% of them were written in English. These results are consistent in the literature, as other studies have similar results.[3,19,20] As more visibility and a higher number of citations is expected for articles in English, most of the researchers tend to publish their studies in English, even when they are non-native English speakers. Additionally, English is recognized as the lingua franca for the scientific world. However, non-English native speakers still publish studies in their native language, perhaps due to local or regional interest, explaining lower citation rates.

The presented study used a stratified random method in order to identify all narrative and systematic reviews published between 2000 and 2015, without limits in the search strategy of selection. Therefore, the sample allows for representativeness of the dentistry field, and it must be

pointed out as a strength in this study. One study has shown that, in radiology journals, there is a positive correlation between the quality of reporting in systematic reviews and meta-analysis and citation rate.[21] Despite that, the literature reports that the assessment of a study by quality checklist may be inaccurate or not meaningful.[22,23] Quality assessment, the number of self-citations, and the H-index of the reviews' authors were not performed in the present study. Additionally, direct comparison to other fields, even in the biomedical sciences, may be inappropriate. These are the limitations of the present study.

CONCLUSION

In conclusion, it was observed that the number of systematic reviews published in dentistry increased from 2000 to 2015. This type of study still shows an overall higher mean number of citations in comparison to narrative reviews. However, there is a trend for systematic reviews to receive fewer citations in recent years.

REFERENCES

1. Seglen PO. Citations and journal impact factors: questionable indicators of research quality. Allergy 1997;52:1050-6.
2. Callaham M, Wears RL, Weber E. Journal prestige, publication bias, and other characteristics associated with citation of published studies in peer-reviewed journals. JAMA 2002;287:2847-50.
3. Di Bitetti MS, Ferreras JA. Publish (in English) or perish: the effect on citation rate of using languages other than English in scientific publications. Ambio 2017;46:121-7.
4. Fardi A, Kodonas K, Gogos C, Economides N. Top-cited articles in endodontic journals. J Endod 2011;37:1183-90.
5. Nabil S, Samman N. The impact of case reports in oral and maxillofacial surgery. Int J Oral Maxillofac Surg 2012;41:789-96.
6. Alarcon MA, Esparza D, Montoya C, Monje A, Faggion CM Jr. The 300 most-cited articles in Implant dentistry. Int J Oral Maxillofac Implants 2017;32:e1-8.
7. Feijoo JF, Limeres J, Fernandez-Varela M, Ramos I, Diz P. The 100 most cited articles in dentistry. Clin Oral Investig 2014;18:699-706.
8. Pitak-Arnnop P. The 100 most cited articles in dentistry–some discussions. Clin Oral Investig 2014;18:683-4.
9. Cook DA. Narrowing the focus and broadening horizons: complementary roles for systematic and nonsystematic reviews. Adv Health Sci Educ Theor Pract 2008;13:391-5.
10. Bhandari M, Busse J, Devereaux PJ, et al. Factors associated with citation rates in the orthopedic literature. Can J Surg 2007;50:119-23.
11. Patsopoulos NA, Analatos AA, Ioannidis JP. Relative citation impact of various study designs in the health sciences. JAMA 2005;293:2362-6.
12. Clarke M, Alderson P, Chalmers I. Discussion sections in reports of controlled trials published in general medical journals. JAMA 2002;287:2799-801.
13. Mulrow CD. The medical review article: state of the science. Ann Intern Med 1987;106:485-8.
14. Dunn AG, Zhou X, Hudgins J, et al. Financial competing interests were associated with favorable conclusions and greater author productivity in nonsystematic reviews of neuraminidase inhibitors. J Clin Epidemiol 2016;80:43-9.
15. Ercikan K, Roth W. What good is polarizing research into qualitative and quantitative? Educ Res 2006;35:14-23.
16. Ioannidis JP. The Mass Production of redundant, Misleading, and conflicted systematic reviews and meta-analyses. Milbank Q 2016;94:485-514.
17. Colledge L, de Moya-Anegón F, Guerrero-Bote V, López-Illescas C, El Aisati M, Moed H. SJR and SNIP: two new journal metrics in Elsevier's Scopus. Serials 2010;23:215-21.
18. Celeste RK, Broadbent JM, Moyses SJ. Half-century of Dental Public Health research: bibliometric analysis of world scientific trends. Community Dent Oral Epidemiol 2016;44:557-63.
19. Eshraghi A, Osman NA, Gholizadeh H, Ali S, Shadgan B. 100 top-cited scientific papers in limb prosthetics. Biomed Eng Online 2013;12:119.
20. Hamel R. The dominance of English in the international scientific periodical literature and the future of language use in science. AILA Rev 2007;20:53-71.
21. van der Pol CB, McInnes MD, Petrcich W, Tunis AS, Hanna R. Is quality and completeness of reporting of systematic reviews and meta-analyses published in high impact radiology journals associated with citation rates? PLoS One 2015;10:e0119892.
22. Berlin JA, Rennie D. Measuring the quality of trials: the quality of quality scales. JAMA 1999;282:1083-5.
23. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999;282:1054-60.

5. ARTIGO 2 - The effect of statins on periodontal treatment – a systematic review with meta-analyses and meta-regression

Artigo submetido no periódico “Clinical Oral Investigations”.

THE EFFECT OF STATINS ON PERIODONTAL TREATMENT – A SYSTEMATIC REVIEW WITH META-ANALYSES AND META-REGRESSION

Short Title: Statins and periodontal treatment

Francisco Wilker Mustafa Gomes MUNIZ[a], **Keity TAMINSKI**[a], **Juliano CAVAGNI**[a], **Roger Keller CELESTE**[b], **Patrícia WEIDLICH**[a], **Cassiano Kuchenbecker RÖSING**[a]

[a]Department of Periodontology, Faculty of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. Rua Ramiro Barcelos, 2492, Porto Alegre/RS, Brazil, ZIP Code: 90035-003.

[b]Department of Preventive and Social Dentistry, Faculty of Dentistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil. Rua Ramiro Barcelos, 2492, Porto Alegre/RS, Brazil, ZIP Code: 90035-003.

UPPER case letters means author's last name

Corresponding Author:

Francisco Wilker Mustafa Gomes Muniz

Universidade Federal do Rio Grande do Sul

Rua Ramiro Barcelos, 2492, Porto Alegre/RS, Brazil, ZIP Code: 90035-003

Phone/Fax: +55 51 3308 5318

Email: wilkermustafa@gmail.com (email can be published)

The effect of statins on periodontal treatment – a systematic review with meta-analyses and meta-regression

ABSTRACT

Objective: This study aimed to systematically review clinical trials about the effect of statins as adjunct to mechanical periodontal therapy, on probing pocket depth, clinical attachment level and intrabony defects, in comparison to mechanical periodontal therapy alone or in association with placebo. **Material and methods:** Medline, SCOPUS, and EMBASE databases were searched for controlled clinical trials that used any locally delivered or systemically statin as a sole adjunctive therapy to mechanical periodontal treatment. Weighted mean differences between baseline and 6 months after periodontal treatment for clinical attachment level (CAL), probing pocket depth (PPD), and intrabony defect (IBD) were calculated. A high heterogeneity was detected. Therefore, a meta-regression adjusted for type of statin and year of publication was performed. **Results:** Fifteen studies were included in the systematic review, and ten studies were included in the meta-analysis. In the meta-regression, the adjunct use of simvastatin, rosuvastatin, and atorvastatin additionally reduced PPD in comparison to mechanical periodontal therapy and a placebo gel (2.90±0.35mm, 3.90±0.77mm, 3.06±0.71mm, respectively – $p<0.05$). Regarding the resolution of IBD, simvastatin and rosuvastatin significantly improved in comparison to control group (0.89±0.35mm and 1.93±0.77mm, respectively – $p<0.05$). No statistically significant difference was found between the statins for both PPD and IBD ($p<0.05$). Regarding CAL gain, simvastatin provided a statistically significant improvement as compared to the control group (2.02±0.79mm – $p=0.043$). **Conclusions:** The use of statins, used as sole adjuncts to mechanical periodontal treatment, improved the periodontal parameters. In the quantitative analyses, simvastatin was the only drug that showed additional benefits in all evaluated parameters. Due to the higher heterogeneity and the number of studies by the same research group, treating only few tooth site per patient, further well-designed studies are recommended prior to its use in periodontal treatment.

Clinical relevance: Statins promote significantly clinical periodontal improvements when administered in association with non-surgical scaling and root planning (SRP), when compared to SRP alone or in association with a placebo.

KEY WORDS: Periodontal disease; Periodontitis; Hydroxymethylglutaryl CoA Reductases.

INTRODUCTION

Statins are inhibitors of the 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase), which is an important enzyme related to the synthesis of cholesterol [1]. Statins are widely used because of their effectiveness on reducing the blood cholesterol levels, excellent tolerability, safety and low cost [2]. The use of statins is an established therapy for hyperlipidemia and arteriosclerosis and it is the primary and secondary prevention of coronary artery diseases, mainly due to lowering of low-density lipoprotein cholesterol (LDL-C) [3, 4].

So far, the control of biofilms, along with proper periodontal supportive therapy, are the gold-standard procedures to prevent and treat periodontal diseases [5]. Several treatment modalities are reported in the literature, such as surgical periodontal therapy and scaling and root planing (SRP), both of them alone or with adjunct antimicrobial/several other pharmacological agents [6, 7]. When successful, all those therapies lead to reduction of probing pocket depth (PPD) and gain of clinical attachment. Furthermore, it is known that the healing process after conventional therapy is mainly due to repair, including establishment of a long junctional epithelium [8]. However, as some sites continue to experience periodontal breakdown, despite the conventional treatment [9], recent studies are exploring new strategies to manage periodontal diseases [10, 11].

Additional to its hypolipidemic effects, statins present the pleiotropic mechanisms, which have pharmacologic effects not directly related to the lipid lowering profile, such as antioxidant and anti-inflammatory properties, angiogenesis, improvements in the endothelial function, and increased bone formation [12-15]. The literature also suggests that statins may attenuate periodontal inflammation by decreasing interleukin (IL)-1β and increasing IL-10 levels in gingival crevicular fluid of patients with periodontitis [16]. Positive outcomes of simvastatin in patients with chronic periodontitis were demonstrated in observational studies [17-19]. Periodontitis patients treated with statins presented less periodontal pockets in comparison to those that did not use statin [17, 19]. Furthermore, a retrospective cohort study showed that chronic periodontitis patients under statin presented 48% decreased tooth loss rate in comparison to those that did not use the medication [18]. On the other hand, this finding is not consistent in the literature[20].

A previous systematic review about the effects of statins on the treatment of chronic periodontitis included cohort, cross-sectional, and clinical trial studies, but it did not perform a quantitative analysis of the selected clinical trials [11]. Therefore, this study

aimed to systematically review clinical trials about the effect of statins in conjunction with mechanical periodontal therapy on probing pocket depth, clinical attachment level and intrabony defects.

MATERIAL AND METHODS

The focused question for this systematic review was: "In patients with chronic/aggressive periodontitis, how effective are statins, when used as adjuncts to mechanical periodontal therapy, when compared to mechanical periodontal treatment alone or associated with placebo?" The PICO question comprised patients with chronic or aggressive periodontitis (P), mechanical periodontal treatment with statins (I), compared to mechanical treatment alone or placebo (C) and probing pocket depth, clinical attachment level and intrabony defect alterations (O).

Search strategy

The search for this systematic review was performed in MEDLINE-Pubmed, Scopus, and EMBASE databases. Search strategy for Pubmed database was developed as follows:

#1: periodontal disease[Title/Abstract] OR periodontal diseases[MeSH Terms]) OR periodontal treatment[Title/Abstract] OR periodontal therapy[Title/Abstract] OR subgingival curettage[MeSH Terms] OR periodontal intervention[Title/Abstract] OR periodontium[MeSH Terms] OR periodontics[MeSH Terms] OR wound healing[MeSH Terms] OR periodontal repair[Title/Abstract] OR periodontal regeneration[Title/Abstract] OR chronic periodontitis [Title/Abstract]

#2: dyslipidemias[MeSH Terms] OR hyperlipidemia[Title/Abstract] OR higher cholesterol[Title/Abstract] OR statin[Title/Abstract] OR hydroxymethylglutaryl-coareductase[MeSH Terms] OR anticholesteremic agents[MeSH Terms] OR cholesterol reductase[MeSH Terms] OR lovastatin[MeSH Terms] OR provastatin[Title/Abstract] OR atorvastatin[Title/Abstract] OR Rosuvastatin [Title/Abstract]

#3: #1 and #2

The search strategy for Scopus and EMBASE databases is an adaptation of the above and the literature was searched up to July 2016.

Selection criteria and risk of bias assessment

Titles and abstracts resulting from the search as described were screened independently by two reviewers (FWMGM and KT). Any discrepancies with regard to

the exclusion/inclusion of the studies of any study were solved by extensive discussion between the two reviewers. When any doubt was still remaining, another investigator (JC) was involved in these processes.

Full text reading and data extraction was performed when the titles or abstracts fulfilled the following criteria:

- Clinical trials with at least 1-month follow-up;
- Patients with diagnosis of chronic or aggressive periodontitis;
- Intervention group should use any statin, as any form of administration, as a solely adjunct to non-surgical mechanical periodontal treatment;
- The comparison group should comprise non-surgical mechanical periodontal therapy alone or associated with placebo;
- The outcome should include at least one clinical periodontal measurement, such as probing depth, clinical attachment level, and intrabony defect.

No language or publication date restrictions were applied. However, the studies were excluded, after full text reading, if they presented one of the following characteristics:

- Observational and experimental animal studies.
- Case reports, letters and reviews.
- Included only patients younger than 18 years old.
- Those that did not perform any mechanical periodontal therapy.
- Studies that used statin and any other drug/biomaterial in the same study group.
- Studies that reported only a secondary analysis of a previously included study.

Studies without abstracts but whose titles suggested that they could be related to the objective of this systematic review were selected, so the full text could be screened for eligibility. All references of related reviews [11, 21] and of the studies included during the electronic search were screened for eligibility. Additionally, after the electronic first screening and selection, all the studies that have cited the included articles, in Scopus database, were also screened for eligibility

The grey literature was also search through contact with the corresponding author of the included studies and in the following databases: trip database, NYAM grey literature report, Centre for Reviews and Dissemination, and Google scholar. Furthermore, the register of the Clinical Trial website was also screened for eligibility. The above mentioned databases were searched using an adaptation of the search strategy previously described.

The risk of bias of the non-randomized clinical trials was assessed by the ROBINS-I tool, developed by the Cochrane Group [22]. In this tool, different bias are assessed: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, selection of the reported result, and overall bias. The risk of bias of the randomized clinical trials was assessed according to the criteria defined by the Cochrane Collaboration [23]. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias were evaluated. When sufficient information description was provided, a positive mark was attributed to each item, indicating low risk of bias. In case of missing information, a negative mark was recorded to each of the seven items, indicating high risk of bias. When both low and high risk of bias could not be assessed, the item was classified as unclear. To both tools, each selected study was evaluated independently by two reviewers (FWMGM and JC). Any discrepancies in this regard were solved by extensive discussion between the two reviewers.

Data extraction

The data extraction was performed in a spreadsheet specifically developed for this study. The data extraction included the following variables: authors, year of publication, country of the patients, sample size, statin used, mean or range age, the percentage of male/female, and the results of the periodontal outcomes assessed.

When some of the necessary data were missing in the original studies, a contact with the authors was made by e-mail. Through the same contact, the corresponding authors were asked if they knew any other trial that may fulfill the objectives of this systematic review. All the authors were contacted; however, none of them answered the contact. Studies with missing data were maintained in the systematic review, but not included in the quantitative analysis.

Data synthesis

Due to the larger number of statin locally delivered in periodontal pockets, the quantitative analysis was performed only for these studies, despite the type of statin used. In order to standardize data synthesis, mean alterations in probing pocket depth (PPD), intrabony defect assessed radiographically (IBD), and clinical attachment level (CAL), from baseline to 6 months were included in the meta-analysis. When two different statins

were evaluated in the same study, both statin groups were included in the analysis, but the sample size in the group without statin was divided by two.

Statistical Analysis: Meta-analyses and Meta-regression

Meta-analyses were performed using the weighted mean difference (WMD) between baseline and 6 months after periodontal therapy. When difference between 6 months and baseline was not presented in the article, the study was not eligible for meta-analysis. Quantitative analyses were conducted for PPD, IBD, and CAL applying linear meta-analyses. The primary outcome for the meta-analysis was mean alterations in CAL and secondary outcomes were alterations in PPD and IBD. Heterogeneity was assessed by the Q test and quantified with the I^2 statistic. Publication bias was assessed using the Egger's and Begg's test. Additionally, the overall quality of evidence for each of the main outcomes included in the meta-analyses was rated using the GRADE approach [24].

When high heterogeneity was found (I^2>40%), sources of effect modification of the pooled WMD were investigated using linear meta-regression [25]. Due to the number of studies (only one/two studies, respectively), we could not test effect modification by diabetes or smoking status. Therefore, only the following study characteristics were included in the meta-regression: year of publication and type of statin.

The heterogeneity parameter (tau^2), which denotes the standard deviation of the true between-groups variance, was calculated using the method of moment and p-values were estimated with MonteCarlo simulation from 1000 permutations. The analyses were adjusted for the year 2010, as the first study was published in this year. Meta-analyses and meta-regression were conducted using Stata13.1 software [26, 27].

RESULTS

Studies selection

One thousand three hundred and sixty-three (1363) titles/abstracts were retrieved from the search, of which 15 were selected based on the criteria previously described (Figure 1) [28-42]. One study reported a secondary analysis of an included clinical trial, and was excluded [43]. The additional searches resulted in 393 studies, but did not increase the number of selected studies. All the selected studies were written in English, the demographic sample characteristics and the main results of these studies are shown in Table 1.

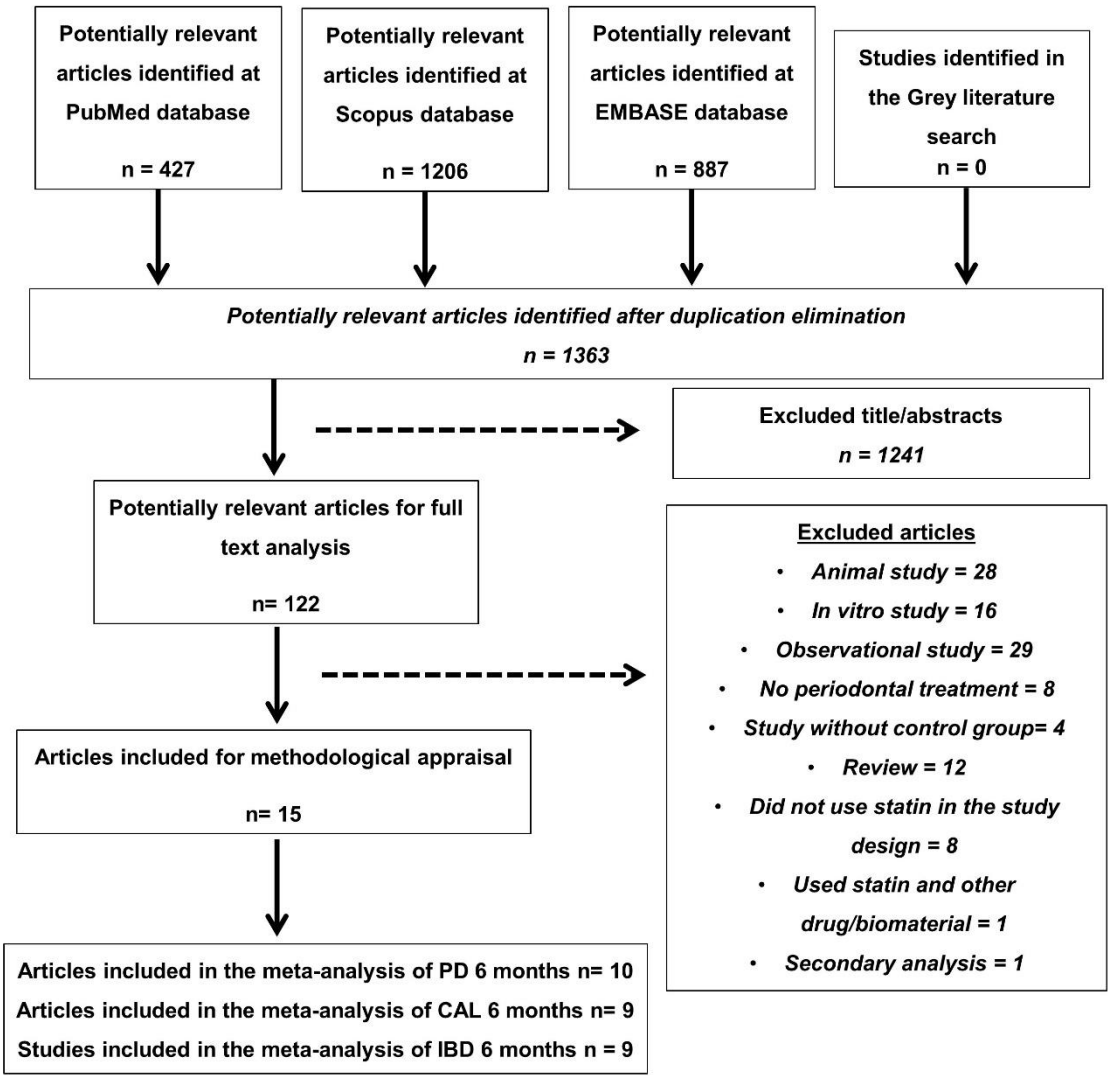

Figure 1. Flow of the studies during the review.

Characteristics of included studies

Among the included studies, 3 were non-randomized clinical trials [29, 30, 39], and 12 were randomized clinical trials [28, 31-38, 40-42]. All the studies included in the systematic review comprised chronic periodontitis patients. Statins used were atorvastatin, simvastatin, and rosuvastatin. Eleven studies used locally delivered statins with a 1.2% concentration [32-42]. From these, 5 used simvastatin [32-35, 37], 3 used atorvastatin [36, 40, 42], 1 used rosuvastatin [38]. Furthermore, one study used rosuvastatin and atorvastatin [41] and another used simvastatin and atorvastatin in different patients [39]. All these studies used statins as adjunct to site specific mechanical periodontal treatment and compared to a placebo gel plus site specific mechanical periodontal treatment. One study used 2% atorvastatin in a dentifrice compared to a control dentifrice [31]. Atorvastatin was the only drug used systemically as adjunctive to

whole-mouth scaling and root planing in three studies. In one study it was compared to placebo pills [28] and in the two others the comparison was solely with mechanical treatment [29, 30].

Two studies treated patients with both periodontitis and hyperlipidemia [29, 30]. Another study treated only patients with type 2 diabetes [35], and Rosenberg et al. (2015) [31] included patients without diabetes and well-controlled diabetics. The others studies included only systemically healthy patients with no use of systemic statin [28, 32-34, 36-42]. Furthermore, only two studies included smokers with periodontitis [31, 37]. Regarding to the side effects of statins, 13 studies reported no adverse effects in any patient [28, 31-42]. However, two studies did not report adverse events [29, 30].

Risk of bias assessment

Figure 2 presents the quality analysis of the RCT included in the present systematic review [28, 31-38, 40-42]. Only one study fulfilled all criteria with low risk of bias [28]. The majority of the studies did not provide any explanation of how allocation concealment was performed [31-38, 40-42]. Despite of that, all RCT had low risk of bias for random sequence generation [28, 31-38, 40-42]. Additionally, all RCT had low risk of bias for incomplete outcome data. No study had unclear risk of bias. Overall, this analysis showed that there is a moderate heterogeneity in the risk of bias in the selected studies, ranging from zero negative marks (low risk of bias) to four negative marks (high risk of bias).

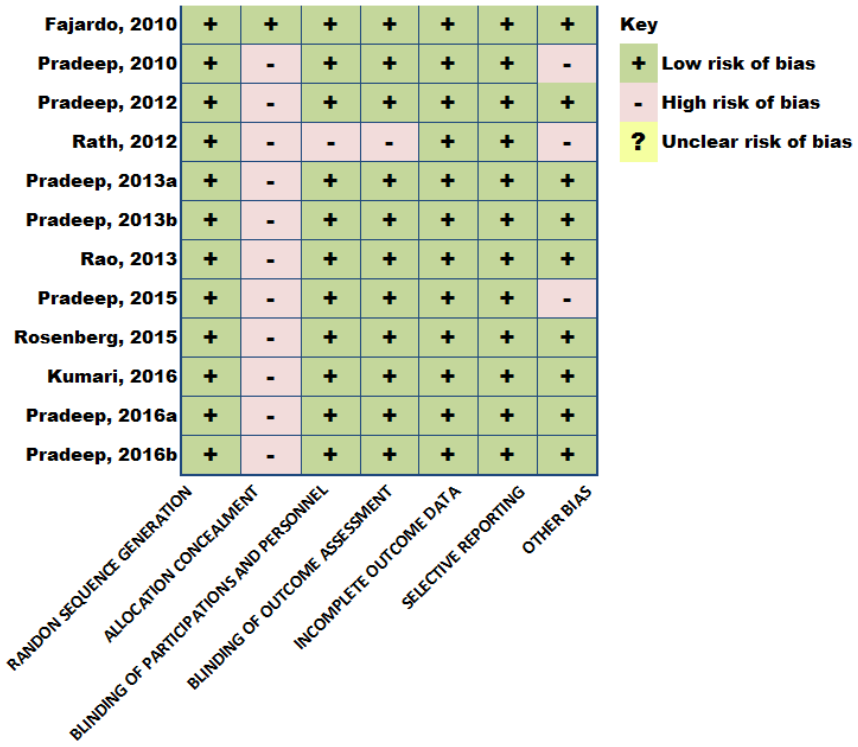

Figure 2. Risk of bias of the included studies.

Table 2 shows the risk of bias of the non RCT included in the present systematic review. All studies presented an overall bias ranging from moderate [29, 30] to critical [39]. Risk of bias due to confounding were classified as moderate in all non RCT. One study was classified in the other domains as low risk of bias [30], meanwhile another study presented a moderate risk of bias only in measurement of outcomes [29]. The other non RCT was evaluated as critical/serious in almost all domains [39].

Qualitative results – statins used systemically

Considering the three studies that used systemic administration of atorvastatin, only one demonstrated significant improvements in PPD and dental mobility, favoring the group that used statin [28]. The two remaining studies included hyperlipidemic patients with prescribed atorvastatin and compared with normolipidemic patients [29, 30]. In one study, no statistically significant differences between both groups for all periodontal parameters was shown [30]. Comparisons between groups with and without atorvastatin as adjunct to mechanical periodontal treatment in relation to periodontal parameters are not reported in the other study [29].

Qualitative results – statins used in a dentifrice

One of the selected studies reported one-month follow-up results of a 2% atorvastatin dentifrice compared with a placebo dentifrice [31]. Both groups showed

improvements in periodontal parameters after non-surgical periodontal treatment. Furthermore, when compared to a placebo dentifrice, atorvastatin dentifrice was able to additionally enhance CAL gain, reduce PPD and bleeding on probing.

Qualitative results – statins used locally

Eleven studies used locally delivered statins adjunctive to periodontal therapy [32-42], of which nine were performed by the same research group [32, 33, 35-38, 40-42]. All studies, but one [39], showed statistically significant reduction in PPD, favoring the statin group. Similarly to PPD, only one study [39] showed no statistically significant improvements in the IBD favoring the statin group. Regarding the CAL gain, only two studies did not demonstrate statistically significant differences between groups with and without statin [34, 39]. All of these studies performed intraoral radiographic analyses.

Meta-analyses and meta-regression for alterations in probing pocket depth

From the 15 selected studies, ten were included in the quantitative analysis of PPD [32-38, 40-42]. For PPD at 6 months, this analysis showed a pooled WMD of 1.93 mm (95% CI:1.44;2.41), favoring the statin group (FigureS1). However, this analysis showed a high heterogeneity (93.9%, $p<0.001$). No publication bias was shown in both tests for this analysis ($p=0.213$ and $p=0.146$ for Begg's and Egg's tests, respectively) (Figure S2). In the sensitivity analysis, no major changes were detected for the pooled WMD ranging from 1.81 mm (95% CI: 1.44;2.18) to 2.04 mm (95%CI: 1.62;2.47) (Figure S3).

The cumulative meta-analysis showed that over the years the effect size was decreasing significantly across the published studies ($p=0.041$). For each year, a mean decrease of 0.21 mm on PPD was observed. On the other hand, the meta-regression showed that all statins, when associated to SRP, reduced significantly PPD in comparison to SRP plus placebo (Table 3). When controlling for the year of publication, rosuvastatin demonstrated numerically the higher coefficient of PPD reduction. However, no statistically significant differences were found between the statins.

Meta-analyses and meta-regression for alterations in intrabony defect

Nine studies were included in the quantitative analysis of alterations in IBD [32, 34-38, 40-42]. The resolution of IBD 6 months after periodontal therapy was also included in the meta-analysis. It was showed a pooled WMD of 1.54 mm (95% CI:1.24;1.84), favoring the statin group. High heterogeneity was also found in this analysis (96.5%, $p<0.001$) (Figure S4). No publication bias was observed in both tests for this analysis ($p=0.721$ and $p=0.661$ for Begg's and Egg's tests, respectively) (Figure S5).

No major changes were detected for the pooled WMD ranging from 1.40 mm (95% CI: 1.16;1.65) to 1.65 mm (95%CI: 1.36;1.94) in the sensitivity analysis (Figure S6).

The year of publication presented a positive statistically significant effect, with each year increment promoting a decrease of 0.20 mm in the IBD (p=0.041). In the meta-regression, when the year of publication (at year 2010) and the type of statin were considered, both rosuvastatin and simvastatin showed significantly more resolution of IBD in comparison to the group without statin (p=0.047 and p=0.044, respectively). However, no statistically significant differences between the three statin were found (Table 3).

Meta-analyses and meta-regression for alterations in clinical attachment level

Nine studies were included in the quantitative analysis of alterations in CAL [32, 34-38, 40-42]. Regarding CAL gain 6 months after the therapy, the pooled WMD found was 1.82 mm (95% CI: 1.24; 2.41), also favoring the statin group (Figure S7). However, a high heterogeneity (96.5%, p<0.001) was observed. Publication bias was found with the Egger's test (p=0.024) (Figure S8) but not with the Begg's test(p=0.592). The sensitivity analysis showed a ranged of pooled WMD of 1.70 mm (95% CI: 1.22;2.19) to 2.01 mm (95%CI: 1.44;2.58) (Figure S9).

In the meta-regression, this periodontal outcome did not show statistically significant correlation with year of publication (p=0.951). When statins where compared to the groups without statin, simvastatin was the only statin to promote significantly CAL gain, when adjusted for the year of publication (p=0.043; Table 3). The comparison among statin groups failed to show statistically significant differences between them. Furthermore, the inclusion of type of statin and year of publication in the meta-regression included more confounders in the model, as the adjusted R^2 was -43.59%.

Quality of evidence at the review level.

The GRADE quality of evidence of both primary and secondary outcomes performed in the meta-analyses is presented in Table 4. To all outcomes assessed, the quality of evidence was rated as low.

DISCUSSION

This systematic review aimed to analyze the effect of statins, in any form of administration, as a solely adjuvant to the mechanical periodontal treatment. Generally, most of the included studies showed additional periodontal clinical benefits when statins were used in along with mechanical periodontal treatment. Meta-analyses were performed using locally delivered statins as an adjunct to mechanical periodontal

treatment and showed high heterogeneity. Meta-regression showed that simvastatin, atorvastatin, and rosuvastatin significantly reduced PPD in comparison to the group without statin. Simvastatin and rosuvastatin gel significantly decreased IBD when compared to a placebo gel. Regarding CAL gain, the meta-regression showed that only simvastatin was able to significantly improve this periodontal parameter in comparison to a placebo group.

Statins are important drugs used in the treatment of hypercholesterolaemia that act through the inhibition of the HMG-CoA reductase. By inhibiting this enzyme, the mevalonate synthesis is reduced, and consequently, other isoprenoid pathways are affected [44]. Therefore, cholesterol is lowered and many cardiovascular diseases may be prevented [1, 44]. Additional to their lipid lowering effect, statins present the pleiotropic effects, which are dependent of their direct activity in a target site or as consequence to their inhibition on the biosynthesis of cholesterol. These pleiotropic effects include anti-inflammatory, antioxidant effects and increase bone formation [15, 45, 46]. In this respect, an interest raised in assessing the possible effects of statins in periodontal treatment outcomes.

The literature showed that statins are able to significantly reduce the expression of IL-6, IL-8, IL-1β, and tumor necrosis factor-α levels [14, 47]. These drugs also showed an *in vitro* activity against Gram-positive and Gram-negative bacteria [48]. It is also reported a decrease on the release of matrix metalloproteinase-1 (MMP-1) and MMP-3 from macrophages and endothelial cells [14, 49]. Furthermore, simvastatin reduced the levels of inducible nitric oxide synthase (iNOS), receptor activator of nuclear factor κB (RANK), RANK ligand (RANKL) and increased the level of osteoprotegerin (OPG) in periodontal tissues [50].

These important pleiotropic effects may be the main reason why statin showed additional improvements in PPD reduction, CAL gain and IBD decrease in most of the included studies in this systematic review. The beneficial effects of statins on the periodontal tissues were also reported on others literature reviews [11, 21]. However, to the best of the authors' knowledge, this is the first study to show a quantitative analysis of these studies. Additionally, this is the first systematic review to report the risk of bias of the included studies.

Regarding the studies that used systemically statin, only one study showed additional improvements in PPD in normolipidemic patients, favoring the group that used atorvastatin [28]. The atorvastatin anti-inflammatory effect may be responsible for this

additional improvement [51]. Two other studies used systemically atorvastatin in patients with hyperlipidemia [29, 30]. The literature shows a significantly association between altered lipid profile and periodontal disease [52, 53]. Therefore, it may be hypothesized that the use of statins, in patients with altered lipid profile, may not promote additionally reduction of PPD when compared to normolipidemics without statins use.

After an oral administration, statins are quickly absorbed because of their higher liver specificity, making their bioavailability very low (approximately 5-30% of the administered dose) [44]. Therefore, it may be important to have a higher drug concentration in the target site. Locally delivered drug is an approach that presents the advantage of achieving high intrasucular drug concentration directly in the target site with a reduced dosage, better patient compliance and reduced side effects in comparison to its systemically administration [54, 55]. Due to the higher number of studies using locally delivered statins, a meta-analysis was performed only on those studies.

Three different meta-analyses were performed, and demonstrate that statins, when used as adjunct to mechanical treatment, promote additional improvements in clinical parameters. The pooled WMD (95% CI) for PPD, IBD, and CAL were, respectively, 1.93mm (1.44;2.41), 1.54 mm (1.24;1.84), and 1.82 mm (1.24;2.41) (Figure S1, S4 and S7). Despite these interesting findings, a higher heterogeneity was detected in all the analyses. Therefore, due to the lack of consistency, the clinical relevance of these results should be interpreted with caution, as it may not be directly translated into the clinical practice. Additionally, the GRADE evaluation showed that evidence provided for the studies included in the meta-analyses was ranked as low quality. Another point to be raised is statistical versus clinical significance. This fact needs to be individually interpreted. However, a statistically significant difference in such a pool of studies at least points out for a strong tendency of better results. The clinical extrapolation of them needs to consider other points of evidence-based approaches, such as the skills of the professional and the preferences and beliefs of the patients.

Overall, in the meta-regression, all the tested statins (simvastatin, atorvastatin and rosuvastatin) showed additional benefits in reducing PPD. However, simvastatin was the only drug able to additionally improve CAL gain when compared to a placebo gel. The higher number of studies using this statin may explain this result.

The use of other drugs as an adjunct to mechanical periodontal treatment is also reported in the literature. Local and systemic antibiotics are largely studied. Overall, despite of their statistically significant improvements in periodontal parameters, this

additional benefit is small and may not represent a clinical benefit. For example, a systemic review with meta-analysis showed that the use of systemic amoxicillin/metronidazole, as adjunct to mechanical periodontal treatment, promote significantly CAL gain (WMD = 0.21; 95% CI = 0.02 to 0.4) and PPD reduction (WMD = 0.43; 95% CI = 0.24 to 0.63) [56]. Additionally, the subgingival application of antimicrobials, adjunctive to periodontal treatment, also showed a significantly improvement in PPD reduction and CAL gain, with a WMD of 0.407 and 0.310, respectively [57]. Comparing with these results of the present meta-analyses, the magnitude of CAL gain and PPD reduction was higher with the adjunct use of statins than with the adjunct use of antimicrobials.

All kinds of statin administration were included to give a broader view of this drug when associated with mechanical periodontal therapy. Of the 15 studies included in this systematic review, 11 used locally delivered statin. From these, 9 were performed by the same research group in India. All those studies were included in at least one of the performed meta-analyses/meta-regression. Additionally, these 11 studies performed periodontal treatment and the gel application in only one/two sites of each participant. These facts should be put in perspective when analyzing the quantitative data presented in this study, as a research center-effect may be expected and one/two sites treatment may not represent the periodontal treatment as a whole.

The study of Surve et al. (2015) [39] was the only study included in this systematic review that did not show an additional benefit of locally delivered statin to any periodontal parameter evaluated. This study was not included in the quantitative analysis, as the data extraction could not be performed in a standardized manner. Despite its methodology similarities to the included ones, this study did not present a sample size calculation, and used only 15 sites on each group. Additionally, it should be highlighted that this study presented a critical/serious risk of bias in several domains of the ROBINS-I tool (Table 2). Those observations may explain the discrepancies between the studies.

The most common side effects related to statin are muscle toxicity with myopathy and rhabdomyolysis, which occurs in patients using higher statin doses or drugs that interact with the hepatic metabolism [58]. Almost of all the included studies in the systematic review showed no adverse events related to use of statin either locally delivered or systemically. This is in agreement with the literature that states that statins are well tolerated and the adverse events are rare [59].

The results herein presented are challenging in terms of interpretation. However, the possible benefits of the adjunct use of statins in periodontal therapy should be considered, with further clinical studies exploring this hypothesis, especially due to some of the limitations of the included studies, with a high degree of heterogeneity and the possible strong research center-effect.

CONCLUSION

It was concluded that statins, used as sole adjuncts to mechanical periodontal treatment, additionally improved at least one of the following periodontal parameters: probing pocket depth, clinical attachment level, and intrabony defect. The use of locally delivered statins in periodontal pockets is largely studied. Within the limits of this review, in the meta-regression analyses, simvastatin was the only drug that showed additional benefits in probing depth, clinical attachment level, and intrabony defect, when compared to the groups without statin. However, further well-designed studies are recommended prior to its use in periodontal treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest: The authors declare no conflicts of interest related to this study.

Funding: This study was self-funded by the authors.

Ethical approval: Does not apply to systematic reviews.

Informed consent: Does not apply to systematic reviews.

REFERENCES

[1] Baigent C, Keech A, Kearney PM et al (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 366:1267-1278.

[2] Maron DJ, Fazio S, Linton MF (2000) Current perspectives on statins. Circulation 101: 207-213.

[3] Todd PA, Goa KL (1990) Simvastatin. A review of its pharmacological properties and therapeutic potential in hypercholesterolaemia. Drugs 40: 583-607.

[4] Zhou Q, Liao JK (2009) Statins and cardiovascular diseases: from cholesterol lowering to pleiotropy. Curr Pharm Des 15: 467-478.

[5] Ramfjord SP, Knowles JW, Nissle RR, Burgett FG, Shick RA (1975) Results following three modalities of periodontal therapy. J Periodontol 46: 522-526.
[6] Deas DE, Moritz AJ, Sagun RS, Gruwell SF, Powell CA (2016) Scaling and root planing vs. conservative surgery in the treatment of chronic periodontitis. Periodontol 2000 71: 128-139.
[7] Muniz FW, de Oliveira CC, de Sousa Carvalho R, Moreira MM, de Moraes ME, Martins RS (2013) Azithromycin: a new concept in adjuvant treatment of periodontitis. Eur J Pharmacol 705: 135-139.
[8] Caton JG, Greenstein G (1993) Factors related to periodontal regeneration. Periodontol 2000 1: 9-15.
[9] Dye BA (2012) Global periodontal disease epidemiology. Periodontol 2000 58: 10-25.
[10] Chen J, Chen Q, Hu B, Wang Y, Song J (2016) Effectiveness of alendronate as an adjunct to scaling and root planing in the treatment of periodontitis: a meta-analysis of randomized controlled clinical trials. J Periodontal Implant Sci 46: 382-395.
[11] Estanislau IM, Terceiro IR, Lisboa MR, Teles PB, Carvalho RS, Martins RS, Moreira MM (2015) Pleiotropic effects of statins on the treatment of chronic periodontitis--a systematic review. Br J Clin Pharmacol 79: 877-885.
[12] Mundy G, Garrett R, Harris S et al (1999) Stimulation of bone formation in vitro and in rodents by statins. Science 286: 1946-1949.
[13] Mennickent CS, Bravo DM, Calvo MC, Avello LM (2008) Pleiotropic effects of statins. Rev Med Chil 136: 775-782.
[14] Kavalipati N, Shah J, Ramakrishan A, Vasnawala H (2015) Pleiotropic effects of statins. Indian J Endocrinol Metab 19: 554-562.
[15] Adam O, Laufs U (2008) Antioxidative effects of statins. Arch Toxicol 82: 885-892.
[16] Cicek Ari V, Ilarslan YD, Erman B et al (2016) Statins and IL-1β, IL-10, and MPO Levels in Gingival Crevicular Fluid: Preliminary Results. Inflammation 39: 1547-1557.
[17] Lindy O, Suomalainen K, Mäkelä M, Lindy S (2008) Statin use is associated with fewer periodontal lesions: A retrospective study. BMC Oral Health doi: 10.1186/1472-6831-8-16.
[18] Cunha-Cruz J, Saver B, Maupome G, Hujoel PP (2006) Statin use and tooth loss in chronic periodontitis patients. J Periodontol 77: 1061-1066.

[19] Saxlin T, Suominen-Taipale L, Knuuttila M, Alha P, Ylöstalo P (2009) Dual effect of statin medication on the periodontium. J Clin Periodontol 36: 997-1003.
[20] Saver BG, Hujoel PP, Cunha-Cruz J, Maupomé G (2007) Are statins associated with decreased tooth loss in chronic periodontitis? J Clin Periodontol 34: 214-219.
[21] de Mones E, Schlaubitz S, Catros S, Fricain JC (2015) Statins and alveolar bone resorption: a narrative review of preclinical and clinical studies. Oral Surg Oral Med Oral Pathol Oral Radiol 119: 65-73.
[22] Sterne JA, Hernán MA, Reeves BC (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355: i4919. doi: 10.1136/bmj.i4919.
[23] J.P. Higgins, D.G. Altman, P.C. Gøtzsche, P. Jüni, D. Moher, A.D. Oxman, J. Savovic, K.F. Schulz, L. Weeks, J.A. Sterne, C.B.M. Group, C.S.M. Group, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, BMJ 343 (2011) d5928.
[24] Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A (2011) GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 64: 380-382.
[25] Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Chichester, UK: John Wiley & Sons, Ltd. [Acessed on November 22th, 2016].
[26] Harbord R, Higgins J. Meta-regression in Stata. Stata Journal 2008;8:493-519.
[27] Sterne J, Bradburn M, Egger M. Meta-analysis in StataTM. Systematic review in health care, BMJ Publishing Group, 2008.
[28] Fajardo ME, Rocha ML, Sanchez-Marin FJ, Espinosa-Chavez EJ (2010) Effect of atorvastatin on chronic periodontitis: a randomized pilot study. J Clin Periodontol 37: 1016-1022.
[29] Fentoglu O, Kirzioglu FY, Ozdem M, Kocak H, Sutcu R, Sert T (2012) Proinflammatory cytokine levels in hyperlipidemic patients with periodontitis after periodontal treatment. Oral Dis 18: 299-306.
[30] Sangwan A, Tewari S, Singh H, Sharma RK, Narula SC (2016) Effect of hyperlipidemia on response to nonsurgical periodontal therapy: Statin users versus nonusers. Eur J Dent 10: 69-76.

[31] Rosenberg DR, Andrade CX, Chaparro AP et al (2015) Short-term Effects of 2% Atorvastatin Dentifrice as an Adjunct to Periodontal Therapy: A Randomized Double Blind Clinical Trial. J Periodontol 86: 623-630.

[32] Pradeep AR, Thorat MS (2010) Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. J Periodontol 81: 214-222.

[33] Pradeep AR, Priyanka N, Kalra N, Naik SB, Singh SP, Martande S (2012) Clinical efficacy of subgingivally delivered 1.2-mg simvastatin in the treatment of individuals with Class II furcation defects: a randomized controlled clinical trial. J Periodontol 83: 1472-1479.

[34] Rath A, Mahenra J, Thomas L, Sandhu M, Namasi A, Ramakrishna T (2012) A clinical, radiological and IL-6 evaluation of subgingivally delivered simvastatin in the treatment of chronic periodontitis. Int J Drug Deliv 4: 70-81.

[35] Pradeep AR, Rao NS, Bajaj P, Kumari M (2013) Efficacy of subgingivally delivered simvastatin in the treatment of patients with type 2 diabetes and chronic periodontitis: a randomized double-masked controlled clinical trial. J Periodontol 84: 24-31.

[36] Pradeep AR, Kumari M, Rao NS, Martande SS, Naik SB (2013) Clinical efficacy of subgingivally delivered 1.2% atorvastatin in chronic periodontitis: a randomized controlled clinical trial. J Periodontol 84: 871-879.

[37] Rao NS, Pradeep AR, Bajaj P, Kumari M, Naik SB (2013) Simvastatin local drug delivery in smokers with chronic periodontitis: a randomized controlled clinical trial. Aust Dent J 58: 156-162.

[38] Pradeep AR, Karvekar S, Nagpal K, Patnaik K, Guruprasad CN, Kumaraswamy KM (2015) Efficacy of locally delivered 1.2% rosuvastatin gel to non-surgical treatment of patients with chronic periodontitis: a randomized, placebo-controlled clinical trial. J Periodontol 86: 738-745.

[39] Surve SM, Acharya AB, Thakur SL (2015) Efficacy of subgingivally delivered atorvastatin and simvastatin as an adjunct to scaling and root planing. Drug Metabol Personal Ther 30: 263-269.

[40] Kumari M, Martande SS, Pradeep AR (2016) Subgingivally delivered 1.2% atorvastatin in the treatment of chronic periodontitis among smokers: a randomized, controlled clinical trial. J Investig Clin Dent doi: 10.1111/jicd.12213.

[41] Pradeep AR, Garg V, Kanoriya D, Singhal S (2016) 1.2% Rosuvastatin Versus 1.2% Atorvastatin Gel Local Drug Delivery and Re-Delivery in Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Placebo Controlled Clinical Trial. J Periodontol 87: 756-762.

[42] Pradeep AR, Kanoriya D, Singhal S, Garg V, Manohar B, Chatterjee A (2016) Comparative evaluation of subgingivally delivered 1% alendronate versus 1.2% atorvastatin gel in treatment of chronic periodontitis: a randomized placebo-controlled clinical trial. J Investig Clin Dent doi: 10.1111/jicd.12215.

[43] Fentoğlu Ö, Kirzioğlu FY, Tözüm Bulut M et al (2015) Serum Lp-PLA2: as a novel viewpoint in periodontal treatment of hyperlipidaemics. Turk J Med Sci 45: 619-626.

[44] Sirtori CR (2014) The pharmacology of statins. Pharmacol Res 88: 3-11.

[45] Viereck V, Gründker C, Blaschke S et al (2005) Atorvastatin stimulates the production of osteoprotegerin by human osteoblasts. J Cell Biochem 96: 1244-1253.

[46] Blanco-Colio LM, Tuñón J, Martín-Ventura JL, Egido J (2003) Anti-inflammatory and immunomodulatory effects of statins. Kidney Int 63: 12-23.

[47] Sakoda K, Yamamoto M, Negishi Y, Liao JK, Node K, Izumi Y (2006) Simvastatin decreases IL-6 and IL-8 production in epithelial cells. J Dent Res 85: 520-523.

[48] Jerwood S, Cohen J (2008) Unexpected antimicrobial effect of statins. J Antimicrob Chemother 61: 362-364.

[49] Kamio K, Liu XD, Sugiura H et al (2010) Statins inhibit matrix metalloproteinase release from human lung fibroblasts. Eur Respir J 35: 637-646.

[50] Dalcico R, de Menezes AM, Deocleciano OB et al (2013) Protective mechanisms of simvastatin in experimental periodontal disease. J Periodontol 84: 1145-1157.

[51] Goes P, Lima NA, Rodrigues JA, Benevides NM, Brito GA, Lima V (2016) Anti-inflammatory and Anti-resorptive Effects of Atorvastatin on Alveolar Bone Loss in Wistar Rats. Braz Dent J 27: 267-272.

[52] Thapa S, Wei F (2016) The Association Between High Serum Total Cholesterol and Periodontitis - An NHANES 2011-2012 Study of American Adults. J Periodontol 87:1286-1294.

[53] Zhou X, Zhang W, Liu X, Li Y (2015) Interrelationship between diabetes and periodontitis: role of hyperlipidemia. Arch Oral Biol 60: 667-674.

[54] Pragati S, Ashok S, Kuldeep S (2011) Recent advances in periodontal drug delivery systems. Int J Drug Deliv 1:1-14.
[55] Needleman IG, Pandya NV, Smith SR, Foyle DM (1995) The role of antibiotics in the treatment of periodontitis (Part 2--Controlled drug delivery). Eur J Prosthodont Restor Dent 3: 111-117.
[56] Sgolastra F, Gatto R, Petrucci A, Monaco A (2012) Effectiveness of systemic amoxicillin/metronidazole as adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis: a systematic review and meta-analysis. J Periodontol 83: 1257-1269.
[57] Matesanz-Pérez P, García-Gargallo M, Figuero E, Bascones-Martínez A, Sanz M, Herrera D (2013) A systematic review on the effects of local antimicrobials as adjuncts to subgingival debridement, compared with subgingival debridement alone, in the treatment of chronic periodontitis. J Clin Periodontol 40: 227-241.
[58] Jeger R, Dieterle T (2012) Statins: have we found the Holy Grail?. Swiss Med Wkly 142: w13515.
[59] Schachter M (2005) Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol 19: 117-125.

Table 1. Country, demographic characteristics, number of subjects per groups, statins used, and main results of the selected studies.

Author, year; Country; study design	**Groups with and without statin**	**Sample size Age; Male/female Sample characteristics Smoking exposure**	**Main results**	
		Statin systemically delivered		
Fajardo, 2010; Mexico; RCT [28]	Group with statin: atorvastatin, 20 mg; Group without statin: placebo	Group with statin: 19; Group without statin: 19 Whole-sample (range) – 40 to 60 years; 6/32 Good general health No smokers	Both groups improved after therapy. **Mean±SD decrease in PPD (in mm) – from baseline to 3 months** **Mean±SD CAL gain (in mm) – from baseline to 3 months** **Mean±SD decrease in BOP (%)– from baseline to 3 months**	Group with statin: 1.79±0.57 Group without statin: 1.47±0.36 p-value: 0.03 Group with statin: 1.58±1.2 Group without statin: 1.26±1.0 p-value: 0.46 Group with statin: 0.4±0.15 Group without statin: 0.5±0.25 p-value: 0.18
Fentoglu, 2012; Turkey; nRCT [29]	Group with statin: atorvastatin 10/20mg; Group	Hyperlipidaemic patients with statin: 28; Group without statin: 28	All groups improved after therapy, except for CAL. **Median (min – max) PPD (in mm) 3 months after therapy**	Hyperlipidaemic with statin: 2.30 (1.84 – 2.67)

	without statin: systemically health with no additional therapy	Group without statin: range – 30 to 57; 14/14 Hyperlipidaemic: range – 31 to 54; ?/? Hyperlipidemic/good general health No smokers	**Median (min – max) BOP (%) 3 months after therapy**	Group without statin: 2.38 (1.96 – 3.50) p-value: not reported Hyperlipidaemic with statin: 15.60 (5.79 – 32.69) Group without statin: 45.00 (0.23 – 100) p-value: not reported
Sangwan, 2016; India; nRCT [30]	Group with statin: atorvastatin 20mg; Group without statin: systemically health with no additional therapy	Hyperlipidaemic patients with statin: 36; Group without statin: 35 Hyperlipidaemic with statin: 44.56±10.44; 24/12 – Group without statin: 43±10.73; 17/18 Hyperlipidemic/good general health No smokers	All groups improved after therapy	
			Mean±SD PPD (in mm) 3 months after therapy	Hyperlipidaemic with statin: 2.46±0.68 Group without statin:2.27±0.54 p-value: 0.447
			Mean±SD CAL (in mm) 3 months after therapy	Hyperlipidaemic with statin: 3.63±1.07 Group without statin: 3.14±0.71 p-value: 0.616
		Statin in a dentifrice		
Rosenberg, 2015; Chile; RCT [31]	Group with statin: 2% atorvastatin in dentifrice; Group	Group with statin: 19; Group without statin: 19	One month after therapy, statically significant differences in the group with statin, when compared to the group without statin, were showed to: Mean decrease in PPD – p-value: 0.02*	

	without statin: Placebo dentifrice	Whole-sample (mean): 45.28; Group with statin: 4/14 - Group without statin: 7/11 Good general health/Patients with well-controlled diabetes No smokers/Smokers	Mean decrease in CAL – p-value: 0.001* Decrease of percentage of sites with BOP – p-value: <0.001*	
		Statin locally delivered		
Pradeep, 2010; India; RCT [32]	Group with statin: 1.2 mg Simvastatin gel; Group without statin: placebo gel	Group with statin: 30; Group without statin: 30 Whole sample (mean): 30.5±4.1; 33/31 (before exclusions) Good general health No smokers	Both groups improved after therapy. **Mean±SD decrease in PPD (in mm) – from baseline to 6 months** **Mean±SD CAL gain (in mm) – from baseline to 6 months** **Mean±SD decrease in IBD (%)– from baseline to 6 months**	Group with statin: 4.26±1.59 Group without statin: 1.20±1.24 P-value: 0.001 Group with statin: 4.36±1.92 Group without statin: 1.63±1.99 P-value: 0.001 Group with statin: 1.41±0.74 Group without statin: 0.09±0.58 P-value: <0.05
Pradeep, 2012; India; RCT [33]	Group with statin: 1.2 mg Simvastatin gel;	Group with statin: 18; Group without statin: 18	Both groups improved after therapy. **Mean±SD decrease in PPD (in mm) – from baseline to 6 months**	Group with statin: 4.05±1.31 Group without statin: 1.30±1.01

	Group without statin: Placebo gel	Whole-sample (range) – 30 to 50; Sample screening: 38/34 (before exclusions) Good general health No smokers	**Mean±SD gain in RVAL (in mm) – from baseline to 6 months**	P-value: 0.001 Group with statin: 4.63±1.01 Group without statin: 2.46±1.49 P-value: 0.001
			Mean±SD gain in RHAL (in mm) – from baseline to 6 months	Group with statin: 4.33±1.42 Group without statin: 2.43±1.66 P-value: 0.001
Rath, 2012; India; RCT [34]	Group with statin: 1.2% Simvastatin gel; Group without statin: Placebo gel	Group with statin: 30; Group without statin: 30 Whole-sample (range) – 25 to 45 years; Group with statin: 18/12 - Group without statin: 15/15 Good general health No smokers	Both groups improved after therapy.	
			Mean±SD decrease in PPD (in mm) – from baseline to 6 months	Group with statin: 4.00±1.6 Group without statin: 2.1±0.8 P-value: <0.01
			Mean±SD CAL gain (in mm) – from baseline to 6 months	Group with statin: 4.6±1.5 Group without statin: 4.6±1.5 P-value: 1.00
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 0.57±1.0 Group without statin: 0.08±0.1 P-value: 0.02
Pradeep, 2013a; India; RCT [35]	Group with statin: 1.2% simvastatin gel;	Group with statin: 17; Group without statin: 18	Both groups improved after therapy.	
			Mean±SD decrease in PPD (in mm) – from baseline to 6 months	Group with statin: 3.79±1.15 Group without statin: 1.69±0.76

	Group without statin: Placebo gel	Whole-sample (range) – 30 to 50; 20/18 (before exclusions) Patients with diabetes No smokers	**Mean±SD CAL gain (in mm) – from baseline to 6 months**	P-value: <0.01 Group with statin: 3.83±0.97 Group without statin: 1.38±0.56 P-value: <0.01
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 1.38±0.73 Group without statin: 0.19±0.37 P-value: <0.01
Pradeep, 2013b; India; RCT [36]	Group with statin: 1.2% atorvastatin gel; Group without statin: Placebo gel	Group with statin: 30; Group without statin: 30 Whole-sample (range) – 30 to 50; Sample screening: 35/32 (before exclusions) Good general health No smokers	Both groups improved after therapy.	
			Mean±SD decrease in PPD (in mm) – from baseline to 6 months	Group with statin: 3.40±0.56 Group without statin: 1.56±0.53 P-value: <0.001
			Mean±SD CAL gain (in mm) – from baseline to 6 months	Group with statin: 4.20±0.60 Group without statin: 2.36±0.51 P-value: <0.001
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 1.60±0.24 Group without statin: 0.13±0.25 P-value: <0.001
Rao, 2013; India; RCT [37]	Group with statin: 1.2% simvastatin gel;	Group with statin: 17; Group without statin: 18 Whole-sample (range) – 30 to 50; 35/0	Both groups improved after therapy.	
			Mean±SD decrease in PPD (in mm) – from baseline to 6 months	Group with statin: 3.37±1.27 Group without statin: 1.90±1.32

	Group without statin: Placebo gel	Good general health Smokers	**Mean±SD CAL gain (in mm) – from baseline to 6 months**	P-value: <0.01 Group with statin: 3.20±1.32 Group without statin: 1.67±1.18 P-value: <0.01
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 1.17±0.45 Group without statin: 0.13±0.26 P-value: <0.01
Pradeep, 2015; India; RCT [38]	Group with statin:1.2% rosuvastatin gel; Group without statin: Placebo gel	Group with statin: 32; Group without statin: 33 Whole-sample (range) – 22 to 55 years; 33/37 (before exclusions) Good general health No smokers	Both groups improved after therapy.	
			Mean±SD decrease in PPD (in mm) – from baseline to 6 months	Group with statin: 4.04±0.34 Group without statin: 1.31±0.24 P-value: <0.01
			Mean±SD CAL gain (in mm) – from baseline to 6 months	Group with statin: 4.2±0.17 Group without statin: 1.4±0.15 P-value: <0.01
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 2.23±0.32 Group without statin: 0.46±0.02 P-value: <0.01
			All groups improved after therapy.	

Surve, 2015; India; nRCT [39]	Group with statin: 1.2% atorvastatin and 1.2% simvastatin gel; Group without statin: Placebo gel	Atorvastatin group: 15; Simvastatin group: 15 Group without statin: 15 Whole-sample (range) – 35 to 55 years; Not reported Good general health No smokers	**Mean±SD PPD (in mm) 6 months after therapy**	Atorvastatin group: 3.43±0.75 Simvastatin group: 3.33±0.62 Group without statin: 3.23±0.59 P-value (all groups): >0.05
			Mean±SD RAL (in mm) 6 months after therapy	Atorvastatin group: 9.19±1.35 Simvastatin group: 9.07±1.66 Group without statin: 9.61±1.12 P-value (all groups): >0.05
			Both groups improved after therapy.	
Kumari, 2016; India; RCT [40]	Group with statin: 1.2% atorvastatin gel; Group without statin: placebo gel	Group with statin: 33; Group without statin: 33 Whole-sample (range) – 30 to 50 years; Not reported Good general health Smokers	**Mean±SD decrease in PPD (in mm) – from baseline to 6 months**	Group with statin: 2.66±1.34 Group without statin: 1.00±0.93 P-value: <0.001
			Mean±SD CAL gain (in mm) – from baseline to 6 months	Group with statin: 3.61±1.41 Group without statin: 1.91±1.24 P-value: <0.001
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 1.44±0.41 Group without statin: 0.14±0.09 P-value: <0.001
			All groups improved after therapy.	

Pradeep, 2016; India; RCT [41]	Rosuvastatin group: 1.2% rosuvastatin gel; Atorvastatin group: 1.2% atorvastatin gel; Group without statin: placebo gel	Rosuvastatin group: 27; Atorvastatin group: 27; Group without statin: 27 Whole-sample (range) – 25 to 45 years; 45/45 (before exclusions) Good general health No smokers	**Mean±SD decrease in PPD (in mm) – from baseline to 6 months**	Rosuvastatin group: 3.03±0.43 Atorvastatin group: 2.33±0.48 Group without statin: 1.47±0.50 P-value (in comparison to group without statin): <0.001
			Mean±SD CAL gain (in mm) – from baseline to 6 months	Rosuvastatin group: 2.88±0.42 Atorvastatin group: 2.33±0.48 Group without statin: 1.37±0.49 P-value (in comparison to group without statin): <0.001
			Mean±SD decrease in IBD (%)– from baseline to 6 months	Rosuvastatin group: 2.83±0.53 Atorvastatin group: 2.29±1.06 Group without statin: 0.07±0.26 P-value (in comparison to group without statin): <0.001
Pradeep, 2016; India; RCT [42]	Group with statin: 1.2% atorvastatin gel; Group without statin: Placebo gel	Group with statin: 30; Group without statin: 30 Whole-sample (range) – 30 to 50 years; 53/51 (before exclusions)	Both groups improved after therapy. **Mean±SD decrease in PPD (in mm) – from baseline to 6 months**	Group with statin: 2.46±0.97 Group without statin: 1.06±0.90 P-value: <0.001

	Good general health No smokers	**Mean±SD CAL gain (in mm) – from baseline to 6 months**	Group with statin: 3.7±0.91 Group without statin: 1.16±0.94 P-value: <0.001
		Mean±SD decrease in IBD (%)– from baseline to 6 months	Group with statin: 1.90±0.44 Group without statin: 0.09±0.17 P-value: <0.001

Legend: RCT: randomized clinical trial; nRCT: non-randomized clinical trial; PPD: probing pocket depth; CAL: clinical attachment level; BOP: bleeding on probing; IBD: intrabony defect; RVAL: relative vertical attachment level; RHAL: relative horizontal attachment level; RAL: relative attachment level; * mean values were not reported; ? not reported.

Table 2. Risk of bias of the non-randomized clinical trial, assessed by ROBINS-I tool, included in the present systematic review.

Author, Year	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall bias**
Fentoglu, 2012 [29]	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Surve, 2015 [39]	Moderate	Critical	Serious	Serious	Serious	Critical	Low	Critical

Sangwan, 2016 [30]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Table 3. Meta-regression of clinical trials for three periodontal outcomes using different types of statin adjusted for year of publication (at year 2010).

References of the included studies	Type of statin	Coefficient±SE (in mm when compared to control)	95% CI	Adjusted R^2	P-values in comparison to			
					Without statin	Atorvastatin	Rosuvastatin	Simvastatin
Reduction on PPD at 6 months								
[32-38, 40-42]	**Simvastatin**	2.90±0.35	2.06 – 3.74	25.76%	<0.001	0.768	0.128	-
	Atorvastatin	3.06±0.71	1.38 – 4.74		0.004	-	0.056	0.768
	Rosuvastatin	3.90±0.77	2.09 – 5.72		0.001	0.056	-	0.128
CAL gain at 6 months								
[32, 34-38, 40-42]	**Simvastatin**	2.02±0.79	0.89 – 3.96	-43.59%	0.043	0.658	0.480	-
	Atorvastatin	2.56±1.57	-1.29 – 6.42		0.155	-	0.624	0.658
	Rosuvastatin	3.01±1.71	-1.18 – 7.20		0.130	0.624	-	0.480
Decrease on IBD at 6 months								
[32, 34-38, 40-42]	**Simvastatin**	0.89±0.35	0.33 – 1.76	47.19%	0.044	0.404	0.136	-
	Atorvastatin	1.37±0.71	-0.36 – 3.10		0.102	-	0.213	0.404

Rosuvastatin	1.93±0.77	0.30 – 3.82	0.047	0.213	-	0.136

Legend: SE: Standard error; PPD: probing pocket depth; CAL: clinical attachment level; IBD: intrabony defect.

Table 4. Summary of the quality assessement to all outcomes included in the meta-analyses.

Quality assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins adjunct to mechanical therapy**	**Placebo or mechanical therapy alone**	**Absolute (95% CI)**	**Quality**	**Importance**
Probing pocked depth alterations (follow up: mean 6 months; assessed with: periodontal probing in millimeters; Scale from: 1 to maximum)											
10	randomized trials	serious [a]	very serious [a]	not serious	not serious	All plausible residual confounding would reduce the demonstrated effect.	306	267	WMD **1.93 higher** (1.44 to 2.41)	⊕⊕◯◯ LOW	CRITICAL
Intrabony defect alterations (follow up: mean 6 months; assessed with: radiographically; Scale from: 1 to maximum)											
9	randomized trials	serious [a]	very serious [a]	not serious	not serious	All plausible residual confounding would reduce the demonstrated effect.	273	249	WMD **1.54 mm higher** (1.24 to 1.84)	⊕⊕◯◯ LOW	CRITICAL
Clinical attachment level alterations (follow up: mean 6 months; assessed with: level of attachment in millimeters; Scale from: 1 to maximum)											

Quality assessment							№ of patients		Effect		
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Statins adjunct to mechanical therapy**	**Placebo or mechanical therapy alone**	**Absolute (95% CI)**	**Quality**	**Importance**
9	randomized trials	serious [a]	very serious	not serious	not serious	All plausible residual confounding would reduce the demonstrated effect.	273	249	WMD **1.82 mm higher** (1.24 to 2.41)	⊕⊕◯◯ LOW	IMPORTANT

Legend: CI: Confidence interval; **WMD:** Weighted Mean difference. **Explanations:** [a.]In all studies, mechanical therapy (control arm) did not provide the results commonly demonstrated by this therapy modality. It can be inferred by the results that mechanical therapy performed in all studies was suboptimal, thus leading to a false impression that test treatment was superior to control

Figure legends

Figure 1. Flow of the studies during the review.

Figure 2. Risk of bias of the included studies.

Figure S1. Forest plot of PPD reduction.

Figure S2. Funnel plot of the risk of bias analysis of pocket depth at 6-months follow-up.

Figure S3. Cumulative meta-analysis of pocket depth at 6-months follow-up.

Figure S4. Forest plot of IBD decrease.

Figure S5. Funnel plot of the risk of bias analysis of intrabony defect at 6-months follow-up.

Figure S6. Cumulative meta-analysis of intrabony defect at 6-months follow-up.

Figure S7. Forest plot of CAL gain.

Figure S8. Funnel plot of the risk of bias analysis of clinical attachment level at 6-months follow-up.

Figure S9. Cumulative meta-analysis of clinical attachment level at 6-months follow-up.

6. CONSIDERAÇÕES FINAIS

A literatura odontológica carece de estudos com metodologias específicas para avaliar o que é produzido dentro da própria ciência. Esses estudos podem elucidar questões essenciais para a construção do conhecimento em Odontologia, sendo as análises bibliométricas consideradas as metodologias padrão-ouro para avaliar e predizer a evolução da ciência (Glänzel, 2003). Apesar disso, desenhos metodológicos específicos não têm sido descritos na literatura.

As revisões sistemáticas são consideradas o maior nível de evidência disponível na literatura científica em saúde e, potencialmente, apresentam-se com um maior número de citações (Patsopoulos *et al.*, 2005; Brignardello-Petersen *et al.*, 2014). O número de revisões sistemáticas tem aumentado exponencialmente ao longo dos anos, e as áreas odontológicas eminentemente clínicas têm se beneficiado desse tipo de estudo em maior escala (Ioannidis, 2016; Muniz *et al.*, 2017). No estudo reportado nesta tese, houve a confirmação desses achados, com as revisões sistemáticas apresentando o maior número de citações que revisões narrativas, e as áreas de Periodontia/Implantodontia apresentando o maior número de revisões sistemáticas (Muniz *et al.*, 2017). Contudo, observou-se que esse tipo de desenho experimental tem recebido um menor número de citações nos últimos anos. As razões subjacentes a esta constatação são ainda desconhecidas, sendo se suma importância que se possa fazer tentativas de compreender tal situação.

A análise da qualidade dessa evidência científica pode ser um dos primeiros passos a serem considerados para melhor compreensão desses achados. O impacto do pesquisador na literatura odontológica e o índice de autocitação também podem ser considerados na elucidação desses fatos. Mesmo com o alto número de revisões sistemáticas publicadas, é improvável que elas consigam abordar todas as demandas clínicas e de políticas de saúde necessárias (Cook, 2008). Somado a isso, os resultados conflitantes dos estudos também podem ser fatores contribuintes para essa constatação (Ioannidis, 2016). Além disso, em alguns casos, pode não estar claro a relação entre os achados das revisões sistemáticas e sua transferência direta para a rotina clínica (Ioannidis, 2016).

Na revisão sistemática demonstrada nesta tese, o uso de adjuvante de estatinas, especialmente do gel de sinvastatina localmente aplicado, pode apresentar efeitos benéficos adicionais ao tratamento periodontal. Reduções adicionais de profundidade de

sondagem e ganhos clínicos de inserção adicionais são reportados quando se compara essa nova modalidade terapêutica ao tratamento mecânico isolado ou associado a um placebo. Esse fármaco possui diversos efeitos pleiotrópicos, que podem ser importantes para o manejo da doença periodontal (Kavalipati *et al.*, 2015).

Entretanto, o grande número de estudos executados apenas por um grupo de pesquisa, o tratamento periodontal empregado realizado em apenas um ou poucos sítios por indivíduo e a grande heterogeneidade dos resultados são limitações importantes ressaltadas no estudo contido nessa tese. Dessa maneira, a incorporação dessa nova modalidade de terapia periodontal deve ser vista com cautela.

Futuros ensaios clínicos randomizados envolvendo essa temática e contornando os problemas aqui apresentados são fortemente indicados no intuito de validar ou refutar essa nova modalidade terapêutica periodontal. Além disso, a avaliação dos impactos sistêmicos dessa terapia são recomendados.

Assim, esta tese demonstra que as revisões sistemáticas têm um impacto no direcionamento da ciência, entretanto ainda não podem ser consideradas o único esteio da prática em saúde. Isso porque muitas das mesmas concluem que não há evidências em quantidade e qualidade suficientes para dar uma resposta clínica precisa, gerando espaço para outros delineamentos na pirâmide de evidências. Nesse contexto, é importante que se tenha claro que, em que se pese serem as revisões sistemáticas o mais alto grau de evidências, nem sempre elas são passíveis de serem realizadas ou estão disponíveis para determinada pergunta. Assim, tão importante quanto a existência e o uso de revisões sistemáticas da literatura, é imperioso que os profissionais de saúde sejam capacitados em leitura crítica de toda a informação científica, para que possam ser sujeitos ativos na interpretação da evidência, construindo sua prática da forma mais competente possível.

7. REFERÊNCIAS BIBLIOGRÁFICAS

ADAM, O.; LAUFS, U. Antioxidative effects of statins. **Arch Toxicol,** v. 82, n. 12, p. 885-92, Dec 2008.

ADAMS, S. P.; SEKHON, S. S.; WRIGHT, J. M. Lipid-lowering efficacy of rosuvastatin. **Cochrane Database Syst Rev**, n. 11, p. CD010254, Nov 2014.

ADAMS, S. P.; TSANG, M.; WRIGHT, J. M. Lipid-lowering efficacy of atorvastatin. **Cochrane Database Syst Rev**, n. 3, p. CD008226, Mar 2015.

ASSEM, N. Z. et al. Antibiotic therapy as an adjunct to scaling and root planing in smokers: a systematic review and meta-analysis. **Braz Oral Res,** v. 31, p. e67, Jul 2017.

BRIGNARDELLO-PETERSEN, R. et al. A practical approach to evidence-based dentistry: How to search for evidence to inform clinical decisions. **J Am Dent Assoc,** v. 145, n. 12, p. 1262-7, Dec 2014.

CICEK ARI, V. et al. Statins and IL-1β, IL-10, and MPO Levels in Gingival Crevicular Fluid: Preliminary Results. **Inflammation,** v. 39, n. 4, p. 1547-57, Aug 2016.

COOK, D. A. Narrowing the focus and broadening horizons: complementary roles for systematic and nonsystematic reviews. **Adv Health Sci Educ Theory Pract,** v. 13, n. 4, p. 391-5, Nov 2008.

DIJKERS, M. P.; GUIDELINES, T. F. O. S. R. A. The value of traditional reviews in the era of systematic reviewing. **Am J Phys Med Rehabil,** v. 88, n. 5, p. 423-30, May 2009.

DODSON, T. B. Evidence-based medicine: its role in the modern practice and teaching of dentistry. **Oral Surg Oral Med Oral Pathol Oral Radiol Endod,** v. 83, n. 2, p. 192-7, Feb 1997.

DYE, B. A. Global periodontal disease epidemiology. **Periodontol 2000,** v. 58, n. 1, p. 10-25, Feb 2012.

GLÄNZEL, W. **Bibliometrics as a research field**: a course on theory and application of bibliometric indicators. Ed.1 . Budapeste: Magyar Tudományos Akadémia, 2003.

GRAZIANI, F. et al. Nonsurgical and surgical treatment of periodontitis: how many options for one disease? **Periodontol 2000,** v. 75, n. 1, p. 152-188, Oct 2017.

HEALEY, D.; LYONS, K. Evidence-based practice in dentistry. **N Z Dent J,** v. 98, n. 432, p. 32-5, Jun 2002.

IOANNIDIS, J. P. The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses. **Milbank Q,** v. 94, n. 3, p. 485-514, Sep 2016.

HIGGINS, J.P.T.; GREEN, S. **Cochrane Handbook for Systematic Reviews of Interventions**. Version 5.1. Chichester, UK: John Wiley & Sons, Ltd, 2011. Disponível em: [http://onlinelibrary.wiley.com/book/10.1002/9780470712184]. Acessado em: 9 de outubro de 2017.

KAVALIPATI, N. et al. Pleiotropic effects of statins. **Indian J Endocrinol Metab,** v. 19, n. 5, p. 554-62, 2015 Sep-Oct 2015.

MCFARLANE, S. I. et al. Clinical review 145: Pleiotropic effects of statins: lipid reduction and beyond. **J Clin Endocrinol Metab,** v. 87, n. 4, p. 1451-8, Apr 2002.

MUNIZ, F. W. et al. Citation analysis and trends in review articles in Dentistry. **Evidence-based Dental Practice**, 2017. DOI: 10.1016/j.jebdp.2017.08.003 [Epub ahead of print].

MUNIZ, F. W. et al. Azithromycin: a new concept in adjuvant treatment of periodontitis. **Eur J Pharmacol,** v. 705, n. 1-3, p. 135-9, Apr 2013.

PATSOPOULOS, N. A.; ANALATOS, A. A.; IOANNIDIS, J. P. Relative citation impact of various study designs in the health sciences. **JAMA,** v. 293, n. 19, p. 2362-6, May 2005.

PRADEEP, A. R. et al. 1.2% Rosuvastatin Versus 1.2% Atorvastatin Gel Local Drug Delivery and Re-Delivery in Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Placebo Controlled Clinical Trial. **J Periodontol**, p. 1-9, Feb 2016.

PRADEEP, A. R. et al. Efficacy of locally delivered 1.2% rosuvastatin gel to non-surgical treatment of patients with chronic periodontitis: a randomized, placebo-controlled clinical trial. **J Periodontol,** v. 86, n. 6, p. 738-45, Jun 2015.

PRADEEP, A. R. et al. Clinical efficacy of subgingivally delivered 1.2-mg simvastatin in the treatment of individuals with Class II furcation defects: a randomized controlled clinical trial. **J Periodontol,** v. 83, n. 12, p. 1472-9, Dec 2012.

PRADEEP, A. R. et al. Efficacy of subgingivally delivered simvastatin in the treatment of patients with type 2 diabetes and chronic periodontitis: a randomized double-masked controlled clinical trial. **J Periodontol,** v. 84, n. 1, p. 24-31, Jan 2013.

PRADEEP, A. R.; THORAT, M. S. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. **J Periodontol,** v. 81, n. 2, p. 214-22, Feb 2010.

RAO, N. S. et al. Simvastatin local drug delivery in smokers with chronic periodontitis: a randomized controlled clinical trial. **Aust Dent J,** v. 58, n. 2, p. 156-62, Jun 2013.

SADOWITZ, B.; MAIER, K. G.; GAHTAN, V. Basic science review: Statin therapy--Part I: The pleiotropic effects of statins in cardiovascular disease. **Vasc Endovascular Surg,** v. 44, n. 4, p. 241-51, May 2010.

SLOTS, J. et al. Relationship between some subgingival bacteria and periodontal pocket depth and gain or loss of periodontal attachment after treatment of adult periodontitis. **J Clin Periodontol,** v. 12, n. 7, p. 540-52, Aug 1985.

SMILEY, C. J. et al. Systematic review and meta-analysis on the nonsurgical treatment of chronic periodontitis by means of scaling and root planing with or without adjuncts. **J Am Dent Assoc,** v. 146, n. 7, p. 508-24.e5, Jul 2015. ISSN 1943-4723.

TSUJINAKA, H. et al. Statins decrease vascular epithelial growth factor expression via down-regulation of receptor for advanced glycation end-products. **Heliyon,** v. 3, n. 9, p. e00401, Sep 2017.

WALTERS, J.; LAI, P. C. Should Antibiotics Be Prescribed to Treat Chronic Periodontitis? **Dent Clin North Am,** v. 59, n. 4, p. 919-33, Oct 2015.

ZANDBERGEN, D. et al. The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planing alone in treating periodontitis: a systematic review. **BMC Oral Health,** v. 16, p. 27, Feb 2016.

ANEXOS

Os anexos inseridos, na presente tese, são referentes ao material suplementar do artigo 2.

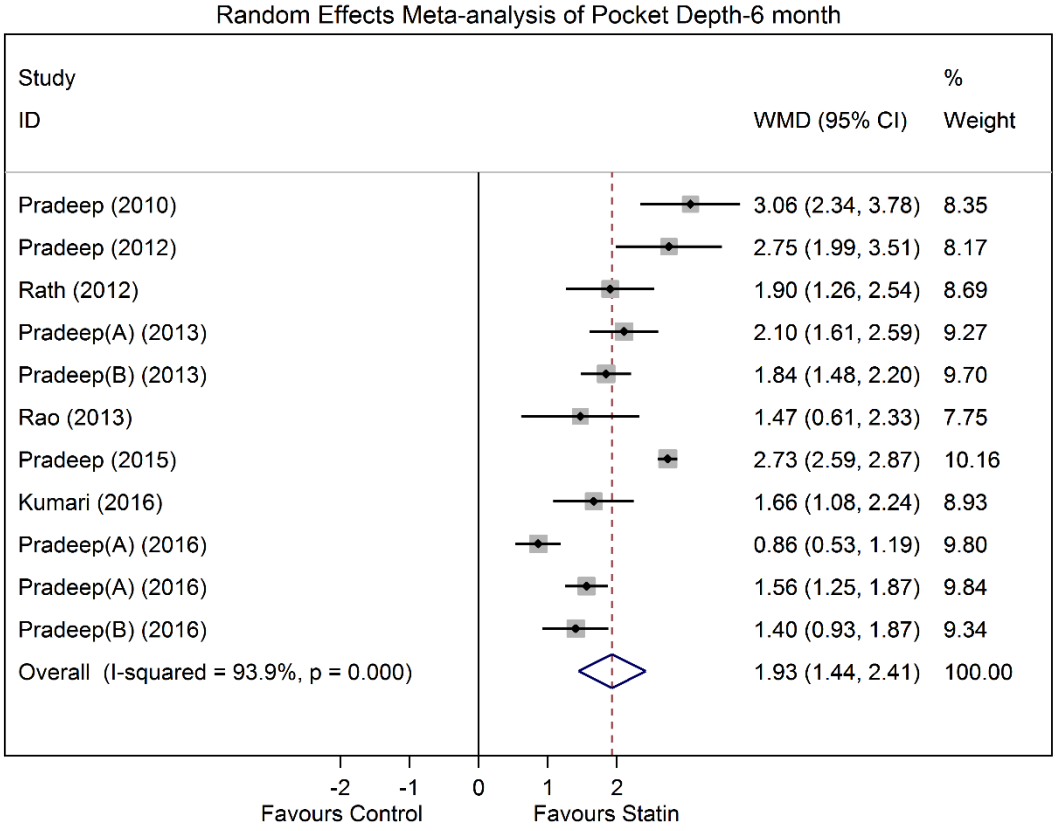

Figure S1. Forest plot of PPD reduction.

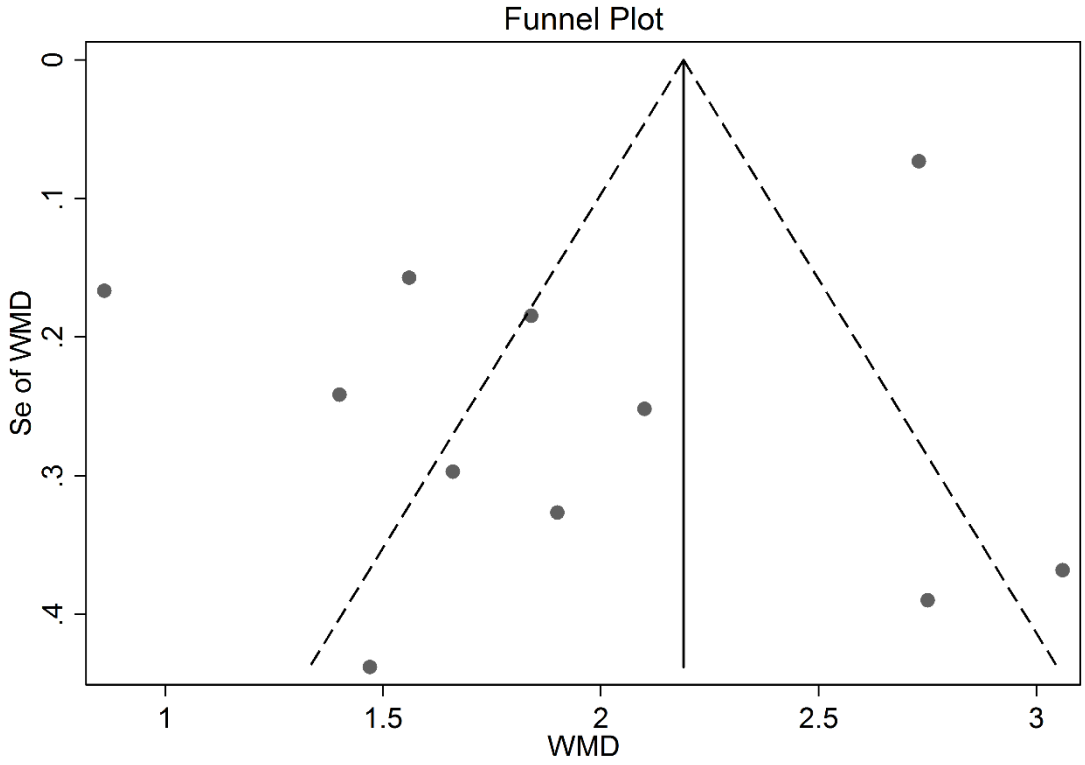

Figure S2. Funnel plot of the risk of bias analysis of pocket depth at 6-months follow-up.

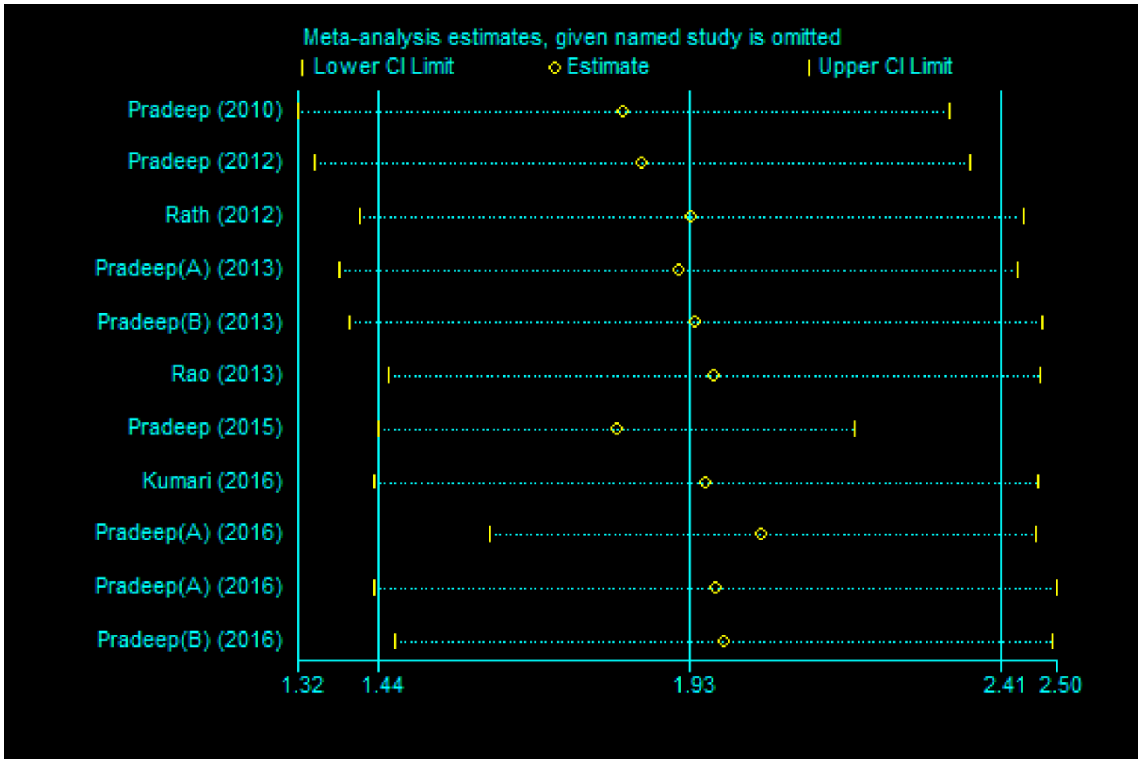

Figure S3. Cumulative meta-analysis of pocket depth at 6-months follow-up.

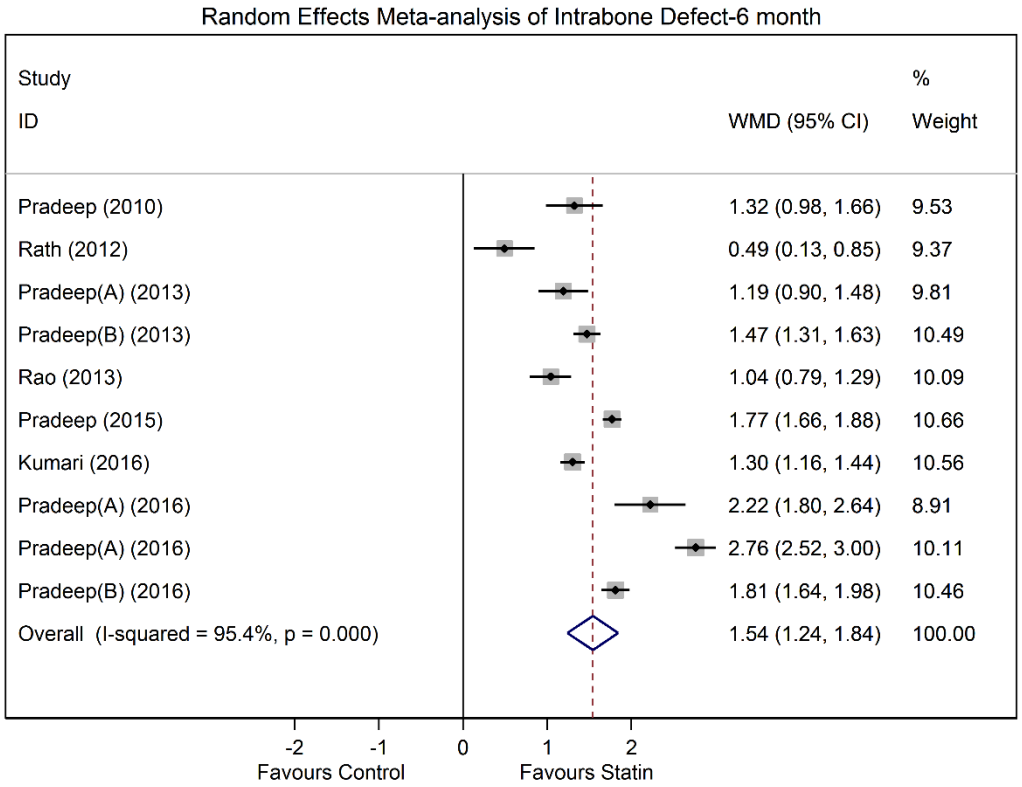

Figure S4. Forest plot of IBD decrease.

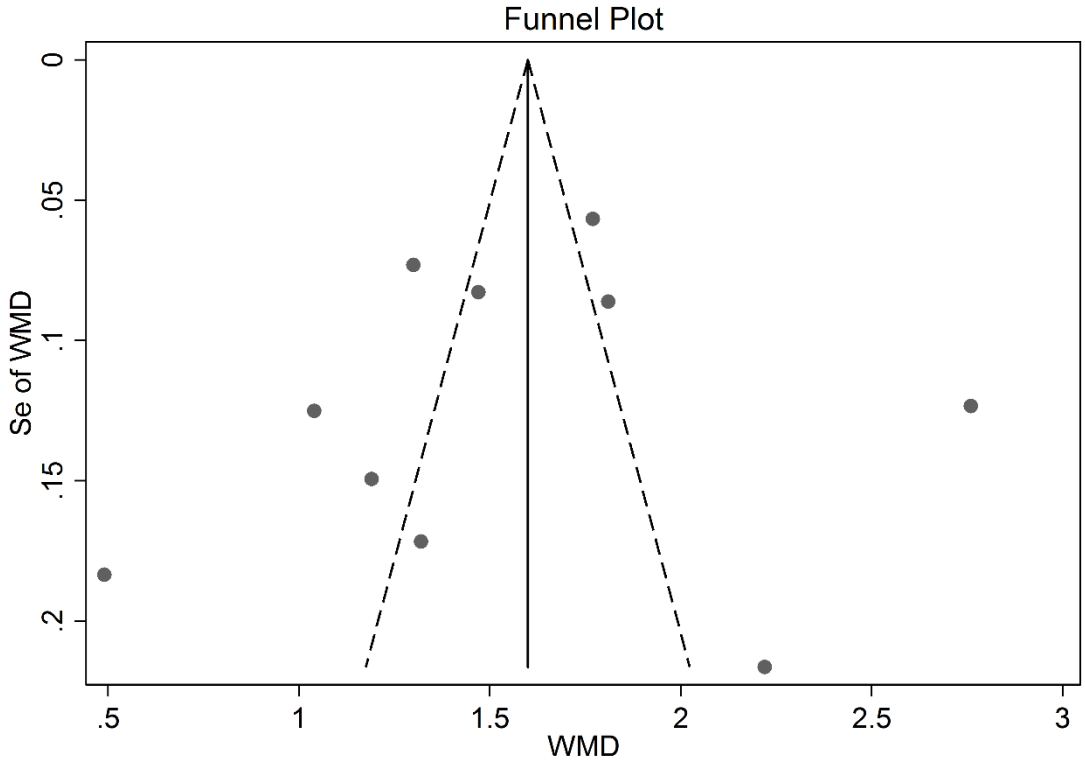

Figure S5. Funnel plot of the risk of bias analysis of intrabony defect at 6-months follow-up.

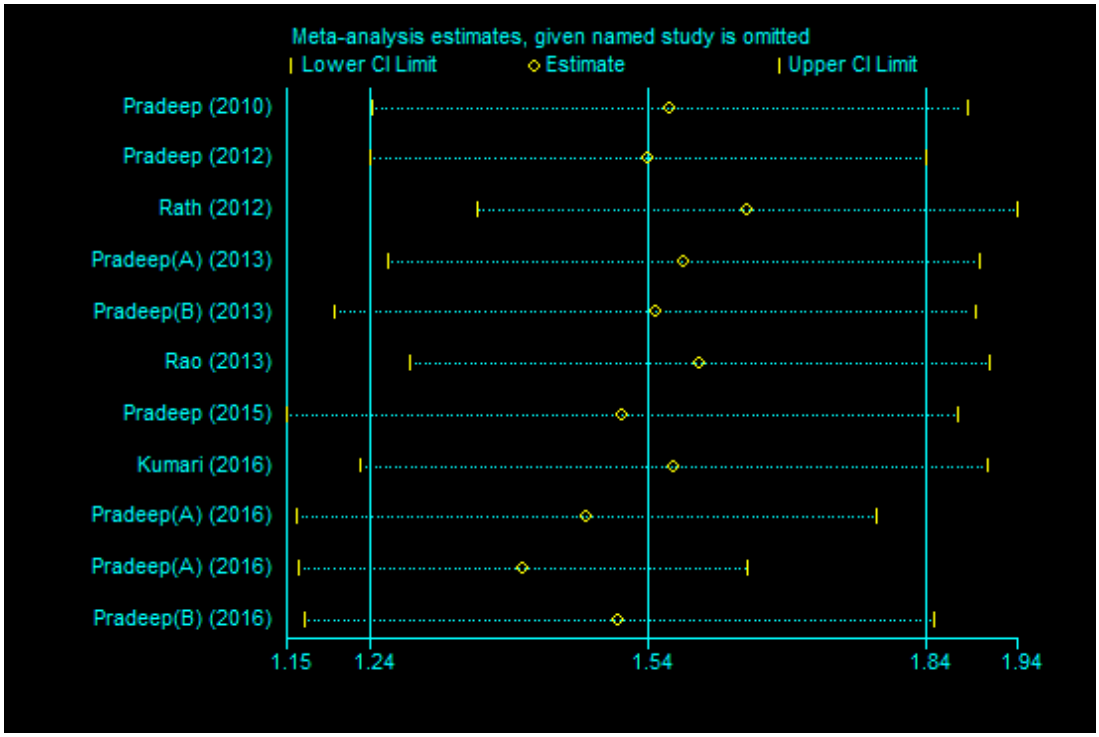

Figure S6. Cumulative meta-analysis of intrabony defect at 6-months follow-up.

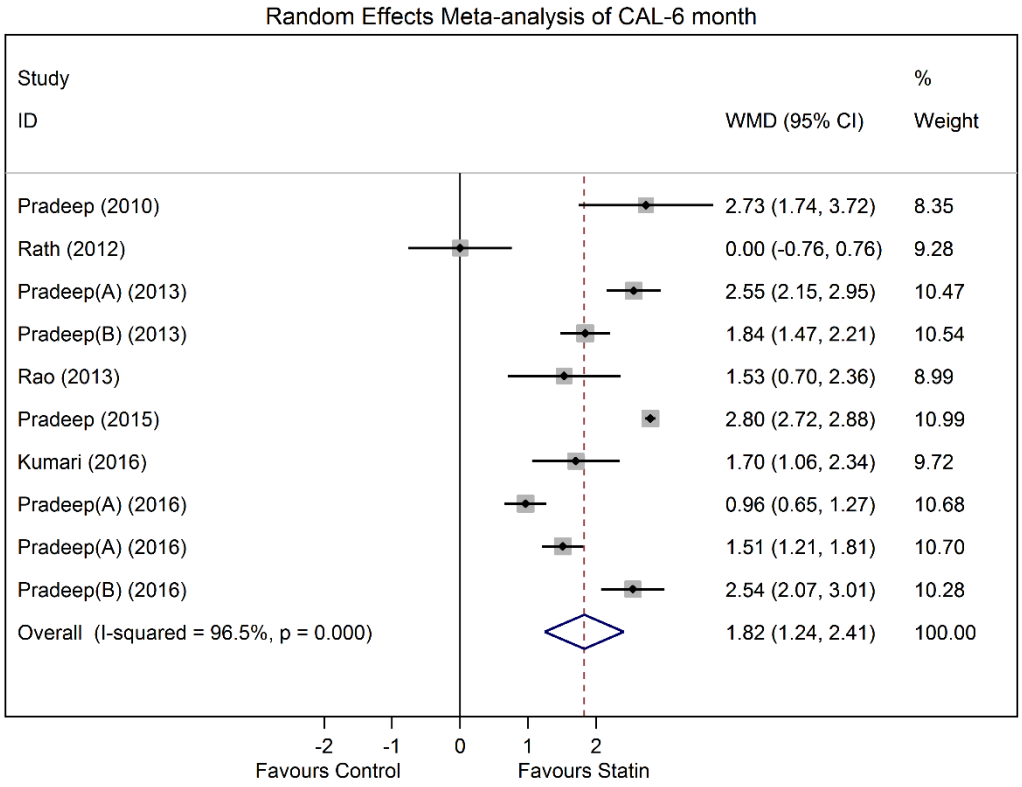

Figure S7. Forest plot of CAL gain.

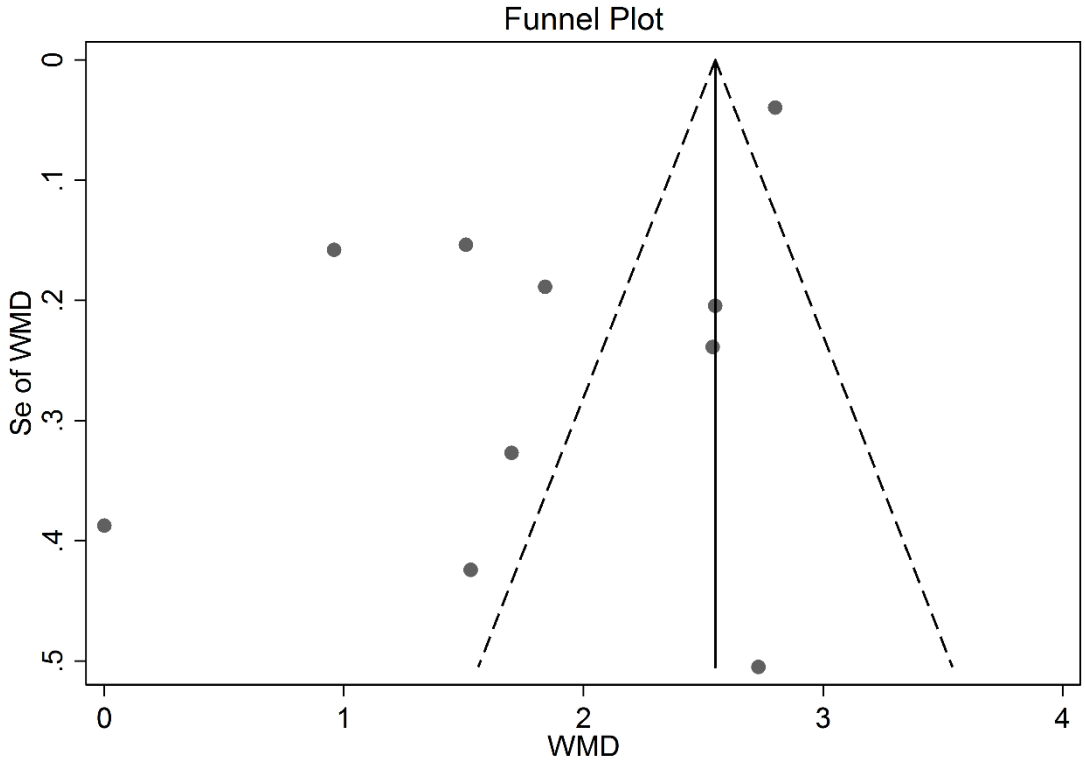

Figure S8. Funnel plot of the risk of bias analysis of clinical attachment level at 6-months follow-up.

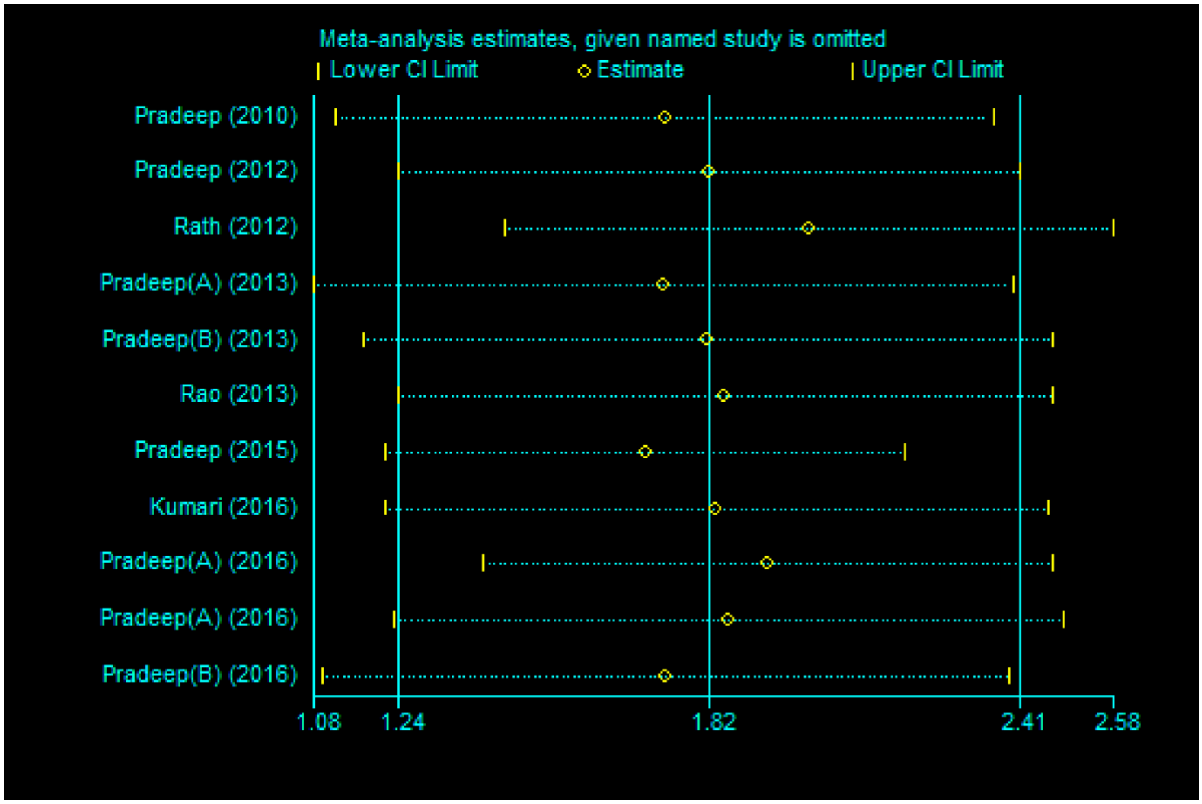

Figure S9. Cumulative meta-analysis of clinical attachment level at 6-months follow-up.