Review Article

Effect of Nonsurgical Periodontal Therapy in Pre and Postmenopausal Women with Periodontitis: A Systematic Review

Frank Mayta-Tovalino[1], Carlos Quispe-Vicuña[2,3], Miguel Cabanillas-Lazo[2,3], Vicente A. Benites-Zapata[4]

[1]Unidad de Revisiones Sistemáticas y Meta-análisis, Guías de Práctica Clínica y Evaluaciones de Tecnologías Sanitarias (URSIGET), Universidad San Ignacio de Loyola, [2]Sociedad Científica de San Fernando, Universidad Nacional Mayor de San Marcos, [3]Grupo Peruano de Investigación Epidemiológica, Unidad para la Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, [4]Maestría en Epidemiologia Clínica y Bioestadística, Universidad Científica del Sur, Lima, Peru

Abstract

Aim: The aim of this systematic review is to provide a comprehensive summary of the current evidence regarding the efficacy and safety of nonsurgical periodontal therapy (NSPT) in pre- and postmenopausal women. **Materials and Methods:** We performed a systematic search of five databases until May 2022 with no language or date restrictions. We included experimental or quasi-experimental clinical studies in pre- or postmenopausal female patients (≥40 years). We considered NSPT as scaling and root planning (SRP). The primary outcomes were: periodontal index (PRI) by Russell, plaque index (PI) by Löe and Silness or O'Leary and adverse events. A secondary outcome was a change in the bone mineral densitometry *T*-score. **Results:** We included three studies but did not meta-analyze the studies due to high heterogeneity. Two studies were pre–post trials, and one was a nonrandomized controlled trial. One trial included both pre- and postmenopausal women and two studies only evaluated postmenopausal women. The studies that compared the effect of SRP in pre- and postmenopausal women found a statistically significant reduction in PRI and PI according to Löe and Silness, and O'Leary. Another study found that SRP plus vitamin D and calcium supplementation decreased PI values. No study reported adverse events. The nonrandomized controlled trial reported a high risk of bias, and the two quasi-experimental studies showed high quality. **Conclusion:** All the studies included in the analysis demonstrated the effectiveness of Non-Surgical Periodontal Therapy (NSPT) in both pre- and postmenopausal patients with periodontitis. However, future studies with higher methodological quality and larger sample sizes are necessary.

Keywords: Periodontal therapy, postmenopausal women, systematic review

Received: 14-06-2023, **Revised:** 20-07-2023, **Accepted:** 27-07-2023, **Published:** 30-10-2023.

Introduction

Periodontal disease (PD) is characterized by chronic inflammation produced in response to a bacterial infection (mainly Gram-negative), which forms dental plaque in the periodontal tissues supporting the dental structures.[1,2] Among its most common characteristics are gingival inflammation, evidence of alveolar bone loss, red and swollen gums, and bleeding on probing.[1] The prevalence of PD is high, with approximately 11% of the world's population presenting the severe periodontitis.[1] Although PD is more frequent in older adults and in high-income countries.[3] In recent years, the prevalence worldwide has been decreasing, especially among young people.[4] PD is conditioned by the multiple risk factors such as smoking, genetics, socioeconomic factors, and comorbidities, such as diabetes[2,5] and hormonal changes produced during pregnancy[6] or menopause.

Access this article online

Quick Response Code:

Website: www.jioh.org

DOI: 10.4103/jioh.jioh_143_23

Address for correspondence: Dr. Frank Mayta-Tovalino, Department of Postgraduate, Universidad San Ignacio de Loyola, Av. la Fontana 550, La Molina 15024, Lima, Peru.
E-mail: fmayta@usil.edu.pe

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Mayta-Tovalino F, Quispe-Vicuña C, Cabanillas-Lazo M, Benites-Zapata VA. Effect of nonsurgical periodontal therapy in pre and postmenopausal women with periodontitis: A systematic review. J Int Oral Health 2023;15:424-30.

Menopause is a physiological state that generates adaptive changes in different parts of the body of an older adult woman. A causal mechanism between menopause and an increased risk of periodontitis has not been established; however, possible pathophysiological mechanisms that affect the gingival epithelium have been correlated with a predisposition to the inflammatory changes in menopause.[7] One of these pathophysiological mechanisms is the physiological aging of oral tissues. On the other hand, the reduction of estrogens in the body favors the development of primary osteoporosis, which also affects the maxillary teeth and could contribute to the progression of periodontitis.[8] Additionally, the change in estrogen levels interferes with immune response,[9] favoring the development of PD. All these factors create an unfavorable scenario for women with menopause, making it necessary to develop the favorable and effective treatments. Nonetheless, immunosuppressive drug treatment may predispose to a loss of periodontal tissue and a higher incidence of PD.[2] In this sense, nonsurgical periodontal therapy (NSPT), based on scaling and root planning (SRP), may be an option, with good efficacy having been reported in these patients. It is also important to recognize that miRNA expression may influence the evolution of periodontitis.[10-12]

The aim of this systematic review is to provide a comprehensive summary of the current evidence regarding the efficacy and safety of NSPT in pre- and postmenopausal women. This will facilitate a better understanding of the most appropriate treatment options for this population.

Materials and Methods

The present systematic review was reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[13] The study protocol was documented in PROSPERO with code CRD42021281297.

Data sources

We searched some databases such as PubMed, Embase, Ovid-MEDLINE, Scopus, Cochrane Library, and Web of Science until May 2022. The PubMed search strategy was adapted for use in other databases, including controlled (MeSH and Emtree) and free terms (Supplementary Table 1, electronic search strategy). There were no publication nor language date restrictions. The studies were included and eligible articles were selected.

Eligibility criteria

Manuscripts were eligible for inclusion if they met the following criteria: (1) they reported on experimental (randomized, nonrandomized, and clustered) or quasi-experimental (pre–post studies) clinical studies involving premenopausal or postmenopausal female patients. (2) The intervention being studied was NSPT, SRP. (Supplementary Table 2, List of excluded studies after full-text review).

Study selection

The results of the electronic searches were registered in Endnote X9 to eliminate the duplicate records. Then, two authors (CQV and MCL) undertook a peer review process through Rayyan QCRI (https://rayyan.qcri.org/). Any discrepancies were discussed and resolved by consensus or ultimately by a third author (FMT). Finally, these reviewers independently assessed the inclusion criteria by reading the full texts of the potentially relevant studies selected, and discrepancies were resolved according to consensus and ultimately by a third author (FMT). In addition, the bibliographic references of the included investigations were reviewed.

Outcomes

The primary outcomes were the periodontal index (PRI) by Russell,[14] the plaque index (PI) by Löe and Silness[15,16] or O'Leary[17] and safety (adverse events). A secondary outcome was change in the bone mineral densitometry (BMD) *T*-score.

Information extraction

Two reviewers (CQV and MCL) independently extracted data using an extraction spreadsheet. All disagreements were resolved by consensus involving a third author (FMT). For categorical outcomes, frequencies were obtained, while mean differences were used for numerical outcomes.

Risk of bias assessment

Two reviewers (CQV and MCL) independently assessed the risk of bias, while the third reviewer (VBZ) helped with discrepancies. The ROBINS-I (risk of bias in nonrandomized studies of interventions) tool [18] was used to assess the potential bias in nonrandomized studies and the JBI Checklist for quasi-experimental studies.[19] The ROBINS-I tool classifies study bias into low risk, high risk, and some concerns. The JBI Checklist for quasi-experimental studies classifies the quality of studies into low (1–4 points), moderate (5–6 points), and high quality (7–9 points) (Table S3, The Joanna Briggs Institute Critical Appraisal tools for quasi-experimental studies).

Data analysis

Due to the heterogeneity of the studies, the results were not meta-analyzed. For the studies that did not report standard deviations for the mean difference, an imputation was made from other available studies as recommended by the Cochrane Handbook.[20] The confidence interval for mean differences was calculated according to Chapter 7.7.3.2 of the Cochrane Handbook in the study of Higgins *et al.*[21]

Results

Study selection

We identified 2,935 studies through our systematic search. We examined 24 full-text articles and finally selected three

studies for our systematic review. The selection process is shown in Figure 1. The full list of excluded articles is provided in Table S2.

Characteristics of the studies included

Of the three studies, two were pre–post trials,[22,23] and one was an NRCT.[24] Two studies were conducted in India and one in Iran. One trial included both pre- and postmenopausal women and two studies only evaluated postmenopausal women. The sample size ranged from 38 to 62 participants. The follow-up period ranged from 3 to 6 months. Two trials included only SRP as an intervention, while one also included vitamin D and calcium supplementation. The outcomes analyzed were heterogeneous among the studies. Further information on the manuscripts included is provided in Table 1.

Risk of bias assessment

One trial was at high risk of bias [Figure 2], and two were of high quality (Table S3). The trial at high risk of bias did not report a control for confounding variables and no protocol was found, and thus, the outcome reporting domain was assessed as "no information."

Scaling and root planning in pre- and postmenopausal women

One trial[22] compared the effect of SRP in both pre- and postmenopausal women. This study reported a statistically significant reduction after PRI treatment (premenopausal [mean difference: MD]: -3.14, 95% confidence interval [CI]: -3.38 to -2.90; postmenopausal [MD]: -3.53, 95% CI: -3.70 to -3.36) and PI according to Löe and Silness (premenopausal [MD]: -0.93, 95% CI: -0.99 to -0.87; postmenopausal [MD]: -0.86, 95% CI: -0.97 to -0.76) compared to baseline measures. Faramarzi *et al.*[23] described a statistically significant decrease in PI, according to O'Leary, in postmenopausal women ([MD]: -46.31, 95% CI: -50.25 to -42.37). None of the trials reported information on adverse events [Table 2].

Scaling and root planning versus vitamin D and calcium supplementation

One trial[24] compared with SRP plus supplementation (vitamin D and calcium) versus supplementation alone. This study showed that the SRP plus supplementation statistically decreased the PI values ([MD]:-1.15, 95% CI:-1.31 to -0.99) and increased BMD ([MD]: 0.14, 95% CI: 0.07 to 0.21). No adverse events were reported [Table 2].

Discussion

Our study aimed to describe the clinical effectiveness and safety of NSPT in pre- and postmenopausal women with periodontitis. Two of the studies included were from India, and one was from Iran and reported that the PRI and PI are reduced after the application of nonsurgical therapy in periods of 3–6 months. Our study provides evidence of the effectiveness of NSPT and the possible effects of pre- and postmenopausal hormonal alterations on the treatment.

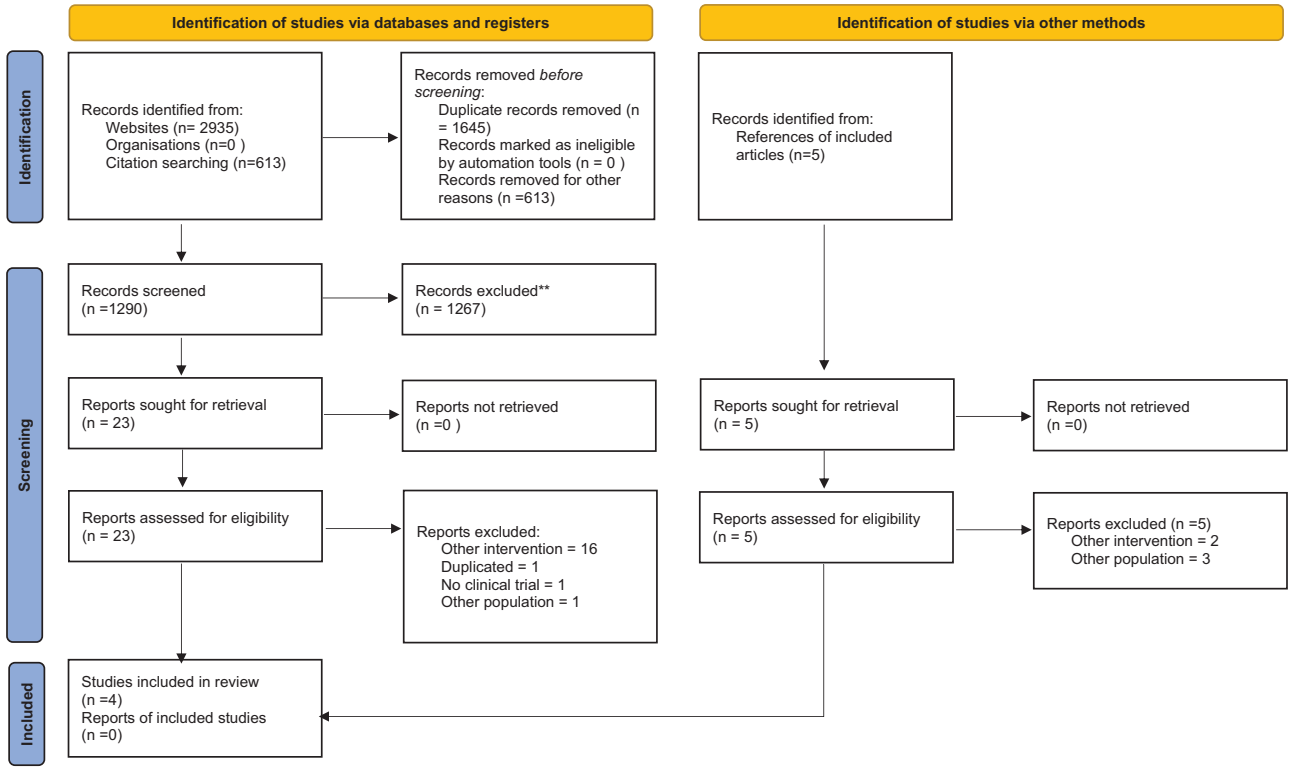


Figure 1: Flowchart of study selection PRISMA 2020

Table 1: Characteristics of studies included evaluating the effect of nonsurgical periodontal treatment in pre- and postmenopausal women with periodontitis ($n = 4$)

Study	Country	Study design	Follow-up (months)	Sample size	Population	Intervention	Control	Age range (years)	Funding
Prasanna-2017 [22]	India	Pre–post trial	3	30 30	Premenopause Postmenopause	SRP	None	40–60	NR
Baldodia-2017 [24]	India	Nonrandomized controlled trial	6	32 30	Postmenopause	SRP + vitamin D + calcium	Vitamin D + calcium	52–59	NR
Farmarzi-2021 [23]	Iran	Pre–post trial	3	38	Postmenopause	SRP	None	>50	Tabriz University of Medical Sciences

SRP = scaling and root planing, NR = not reported

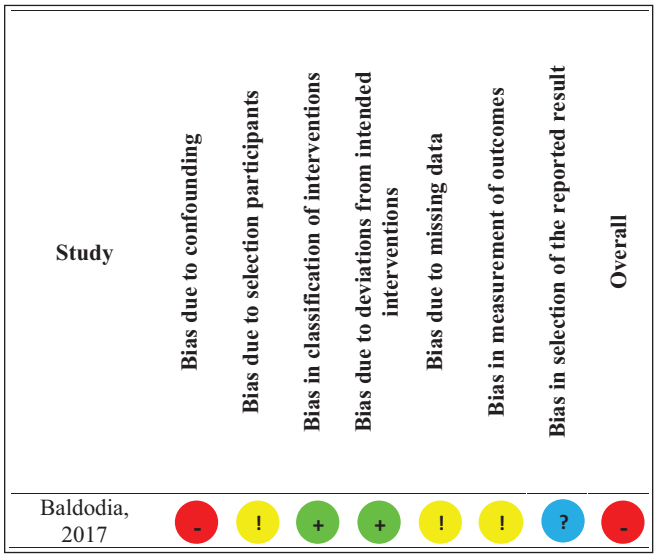


Figure 2: Risk of bias of nonrandomized trials. risk of bias in nonrandomized studies of interventions (ROBINS-I)

In this regard, we evidenced an apparent better response in premenopausal compared to postmenopausal women. However, randomized clinical trials are necessary to ratify these promising results.

The efficacy of NSPT in the treatment of chronic periodontitis has been previously described. A systematic review by Akram *et al.*[25] compared the efficacy of nonsurgical therapy in obese versus nonobese patients but found inconsistent and nonsignificant results due to the heterogeneity and a small number of studies. In addition, previous studies reported the efficacy of nonsurgical therapy with adjuvant supplements. Castro Dos Santos *et al.*[26] reported that omega-3 as supplemental therapy provides a clinical attachment level gain of 0.58 mm (95% CI: 0.24–0.92) and a reduction in probing pocket depth of 0.42 mm (95% CI: 0.15–0.68). Liu *et al.*[27] reported that melatonin adjunctive therapy significantly increased probing depth (PD) (weighted mean difference [WMD] = -1.18, 95 % CI (-1.75, -0.62)), while clinical attachment loss had a WMD = -1.16, 95% CI (-1.60, -0.72)) and the gingival index had a WMD = -0.29, 95% CI (-0.48, -0.11)). Similarly, other studies evaluating intervention with hyaluronic acid [28] and azithromycin[29] reported an increase in the level of clinical attachment and an improvement in PD. Although these studies were not performed in a population of pre- and postmenopausal women, they are consistent with our results on the efficacy of nonsurgical therapy in the treatment of chronic periodontitis.

Regarding vitamin D and calcium supplementation, we found a statistically significant decrease in PI and an increase in BMD, in accordance with results in the literature. A systematic review reported some studies evidencing a perio-protective role of vitamin D in patients with chronic periodontitis.[30] Similarly, another systematic review reported that vitamin D deficiency during periodontal therapy negatively affects the outcomes.[31]

Our results evidenced the efficacy of NSPT in pre- and postmenopausal patients. These results include the efficacy reported for other alternatives used for the treatment of PD in pre- and postmenopausal women. One alternative is hormone replacement therapy which, although no direct effects on periodontal status have been reported,[32] it has been related to a 21% lower risk of periodontitis in postmenopausal women[33] and a reduction in the number of periodontal pathogens.[34] Similarly, local adjuvant drug therapy, such as minocycline microspheres, has been reported to reduce bacteria.[35] Despite the efficacy of NSPT, this treatment has several limitations, such as the maximum PD that can be reached, and thus, surgical therapy may be necessary to control PD.[2] Although this surgical therapy has been reported to be less cost-effective than NSPT, in the long term it significantly reduces the additional therapies such as the need for supportive care and antibiotics.[36] In this context, what could give value to NSPT is its greater short-term cost-effectiveness for nonadvanced periodontitis cases, which are more prevalent than severe cases.[4] NSPT is less expensive because it does not require specialized equipment or training and is less invasive.[37] The characteristics of NSPT could

Table 2: Characteristics of studies included evaluating the effect of nonsurgical periodontal treatment on outcomes

Study	Sample size	Population	Intervention arm	PRI Mean difference (95% CI)	PI Mean difference (95% CI)	BMD Mean difference (95% CI)	Adverse events n (%)
Prasanna-2017 (22)	30	Premenopause	SRP	-3.14 (-3.38 to -2.90)	-0.93 (-0.99 to -0.87)*	NR	NR
	30	Postmenopause	SRP	-3.53 (-3.70 to -3.36)	-0.86 (-0.97 to -0.76)*	NR	NR
Baldodia-2017 (24)	32	Postmenopause	SRP + vitamin D + calcium	NR	-1.15 (-1.31 to -0.99)*	0.14 (0.07 to 0.21)	None
	30		Vitamin D + calcium	NR			None
Faramarzi-2021 (23)	38	Postmenopause	SRP	NR	-46.31 (-50.25 to -42.37)**	NR	NR

PRI = periodontal index, PI = plaque index, BMD = bone mineral density, CI = confidence interval, SRP = scaling and root planning, NR = not reported

* Löe y Silness index

** O´Leary index

favor greater access and outreach in low- and middle-income regions, especially in the population of pre- and postmenopausal women diagnosed with nonadvanced periodontitis. Importantly, certain miRNAs in gingival crevicular fluid (GCF) in patients with periodontitis may be increased. These miRNAs could be valuable indicators to identify the presence and severity of periodontitis in pre- and postmenopausal women.[12]

One of our included studies presented a high risk of bias due to the lack of information on the control of confounding variables and participant selection. This agrees with the review by Muniz *et al.*,[38] who evaluated the effect of statins as an adjunct to periodontal therapy. This review included 15 studies, among which 3 were nonrandomized trials. One of these three studies.[39] reported a high risk of bias in the domains of participant selection bias and outcome measurement bias. In addition, only one outcome (PI) was reported in more than one study. Although the other two studies in our review reported high quality, as they were studies without a control group, their results should be corroborated by the future research. Therefore, our results should be interpreted with caution, and we recommend conducting randomized controlled trials in pre- and postmenopausal women with low risk of bias and high-methodological quality.

It is important to highlight that we found a greater effect on the PI in premenopausal than in postmenopausal women. One possible reason could be the biological role that menopause plays at the oral level. Menopause produces a deficiency of estrogen and progesterone which not only diminishes the anti-inflammatory effect of these hormones on the periodontium but also alters alveolar bone resorption and formation,[7,40] which, in the long term, decreases the physiological response of periodontal tissue to the development of microbial plaque and favors the risk of more severe PD.[41] These biological effects could be diminished by nonsurgical treatment, as adequate and consistent maintenance of oral hygiene and control of microbial plaque can counteract the effects caused by menopausal hormonal dysfunction on alveolar tissue.[42] Our results not only support evidence of the influence of sex hormones on treatment, but also promote the idea of supporting strategies for the prevention and early management of chronic periodontitis in pre- and postmenopausal women. Nonetheless, to be conclusive, these values need to be explored in further clinical trials.

There are some limitations that should be considered in our systematic review. First, we did not find any randomized controlled studies that responded to our study objective. Second, the risk of bias in the studies included was critical in the domain of confounder control and thus, the actual effect size may differ from that reported. In addition, although two studies had a sample size of greater than or equal to 30 persons per group, neither included sample size calculations. Third, the studies were conducted in populations in India and Iran, making it necessary to conduct the research in various geographical areas of the world for the generalization of the findings. Finally, a quantitative synthesis could not be conducted due to the methodological and clinical heterogeneity of the studies, making it necessary to standardize future research. Although only a few studies have been published on this topic, the systematic review allows us to illustrate that there is a lack of solid evidence to make decisions; however, it provides us with patterns of trends in the data. This systematic review provides an understanding of what has been published so far and thus allows us to be cautious when indicating one or another treatment.

Conclusions

In conclusion, within the scope of this systematic review, although the studies included demonstrated a potential beneficial effect of NSPT in pre- and postmenopausal patients, more studies with better scientific rigor and methodological quality with a larger sample size are needed to confirm these promising results.

Acknowledgments

The authors would like to thank the Universidad San Ignacio de Loyola and Universidad Cientifica del Sur for all the support provided in the development of this review.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Authors contributions

Not applicable.

Ethical policy and institutional review board statement

Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

The data for supporting this review were taken from previous studies. Data are available upon request to the corresponding author.

Supplementary Material

A series of tables are presented below as supplementary material to support the results of the systematic review.

References

1. Kwon T, Lamster IB, Levin L. Current concepts in the management of periodontitis. Int Dent J 2021;71:462-76.
2. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Primer 2017;3:17038.
3. Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Almas K. Global prevalence of periodontal disease and lack of its surveillance. Sci World J 2020;2020:2146160.
4. Frencken JE, Sharma P, Stenhouse L, Green D, Laverty D, Dietrich T. Global epidemiology of dental caries and severe periodontitis—A comprehensive review. J Clin Periodontol 2017;44:S94-S105.
5. Wu CZ, Yuan YH, Liu HH, Li SS, Zhang BW, Chen W, *et al*. Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. BMC Oral Health 2020;20:204.
6. Silva de Araujo Figueiredo C, Gonçalves Carvalho Rosalem C, Costa Cantanhede AL, Abreu Fonseca Thomaz EB, Fontoura Nogueira da Cruz MC. Systemic alterations and their oral manifestations in pregnant women. J Obstet Gynaecol Res 2017;43:16-22.
7. Ciesielska A, Kusiak A, Ossowska A, Grzybowska ME. Changes in the oral cavity in menopausal women—A narrative review. Int J Env Res Public Health 2021;19:253.
8. Cj W, Lk M. Osteoporosis and periodontitis. Curr Osteoporos Rep [Internet] 2016;14.
9. Kovats S. Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol 2015;294:63-9.
10. Cobb CM. Clinical significance of non-surgical periodontal therapy: An evidence-based perspective of scaling and root planing. J Clin Periodontol 2002;29:6-16.
11. Van der Weijden GAF, Dekkers GJ, Slot DE. Success of non-surgical periodontal therapy in adult periodontitis patients: A retrospective analysis. Int J Dent Hyg 2019;17:309-17.
12. Isola G, Santonocito S, Distefano A, Polizzi A, Vaccaro M, Raciti G, *et al*. Impact of periodontitis on gingival crevicular fluid miRNAs profiles associated with cardiovascular disease risk. J Periodontal Res 2023;58:165-74.
13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
14. Russell AL. A system of classification and scoring for prevalence surveys of periodontal disease. J Dent Res 1956;35:350-9.
15. Silness J, Loe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condtion. Acta Odontol Scand 1964;22:121-35.
16. Löe H. The gingival index, the plaque index and the retention index systems. J Periodontol 1967;38:610-6.
17. O'Leary TJ, Drake RB, Naylor JE. The plaque control record. J Periodontol 1972;43:38.
18. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al*. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
19. Aromataris E, Munn Z, Editors. JBI Manual for Evidence Synthesis. JBI, 2020. Available from: https://synthesismanual.jbi.global. [Last accessed 2 Apr 2023].
20. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing Effect Measures and Computing Estimates of Effect. Imputing Standard Deviations for Changes from Baseline. En: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019. p. 143-76. (6.5.2.8).
21. Higgins JP, Li T, Deeks JJ. Chapter 6: Choosing Effect Measures and Computing Estimates of Effect. Obtaining Standard Deviations from Standard Errors and Confidence Intervals for Group Means. En: Cochrane Handbook for Systematic Reviews of Interventions [Internet]. John Wiley & Sons, Ltd; 2019. p. 143-76. (6.5.2.2).
22. Prasanna JS, Sumadhura C, Karunakar P. A comparative analysis of pre- and postmenopausal females with periodontitis and its response to a non invasive clinical approach. J Menopausal Med 2017;23:202-9.
23. Faramarzi M, Shirmohammadi A, Khorramdel A, Sadighi M, Bargahi E. Effect of non-surgical periodontal therapy on serum ferritin levels in postmenopausal women with chronic periodontitis. J Dent Res Dent Clin Dent Prospects 2021;15:178-82.
24. Baldodia A, Sharma RK, Tewari S, Narula SC. Effect of periodontitis on bone mineral density in postmenopausal women: A non-randomized interventional study. Quintessence Int 2017;48:113-22.
25. Akram Z, Safii SH, Vaithilingam RD, Baharuddin NA, Javed F, Vohra F. Efficacy of non-surgical periodontal therapy in the management of chronic periodontitis among obese and non-obese patients: A systematic review and meta-analysis. Clin Oral Investig 2016;20:903-14.
26. Castro Dos Santos NC, Furukawa MV, Oliveira-Cardoso I, Cortelli JR, Feres M, Van Dyke T, *et al*. Does the use of omega-3 fatty acids as an adjunct to non-surgical periodontal therapy provide additional benefits in the treatment of periodontitis? A systematic review and meta-analysis. J Periodontal Res 2022;57:435-47.
27. Liu RY, Li L, Zhang ZT, Wu T, Lin S, Zhang XT. Clinical efficacy of melatonin as adjunctive therapy to non-surgical treatment of periodontitis: A systematic review and meta-analysis. Inflammopharmacology 2022;30:695-704.
28. Eliezer M, Imber JC, Sculean A, Pandis N, Teich S. Hyaluronic acid as adjunctive to non-surgical and surgical periodontal therapy: A systematic review and meta-analysis. Clin Oral Investig 2019;23:3423-35.
29. Renatus A, Herrmann J, Schönfelder A, Schwarzenberger F, Jentsch H. Clinical efficacy of azithromycin as an adjunctive therapy to non-surgical periodontal treatment of periodontitis: A systematic review and meta-analysis. J Clin Diagn Res 2016;10:ZE01-07.
30. Perić M, Cavalier E, Toma S, Lasserre JF. Serum vitamin D levels and chronic periodontitis in adult, Caucasian population—A systematic review. J Periodontal Res 2018;53:645-56.
31. Fakheran O, Khodadadi-Bohlouli Z, Khademi A. Effect of vitamin D level on periodontal treatment outcomes: A systematic review. Gen Dent 2019;67:64-7.

32. Pizzo G, Guiglia R, Licata ME, Pizzo I, Davis JM, Giuliana G. Effect of hormone replacement therapy (HRT) on periodontal status of postmenopausal women. Med Sci Monit 2011;17:PH23-27.
33. Lee Y, Kim I, Song J, Hwang KG, Choi B, Hwang SS. The relationship between hormone replacement therapy and periodontal disease in postmenopausal women: A cross-sectional study the Korea National Health and Nutrition Examination Survey from 2007 to 2012. BMC Oral Health 2019;19:151.
34. Tarkkila L, Kari K, Furuholm J, Tiitinen A, Meurman JH. Periodontal disease-associated micro-organisms in peri-menopausal and post-menopausal women using or not using hormone replacement therapy. A two-year follow-up study. BMC Oral Health 2010;10:10.
35. Laza GM, Sufaru IG, Martu MA, Martu C, Diaconu-Popa DA, Jelihovschi I, *et al*. Effects of locally delivered minocycline microspheres in postmenopausal female patients with periodontitis: A clinical and microbiological study. Diagn Basel 2022;12:1310.
36. Miremadi SR, De Bruyn H, Steyaert H, Princen K, Sabzevar MM, Cosyn J. A randomized controlled trial on immediate surgery versus root planing in patients with advanced periodontal disease: A cost-effectiveness analysis. J Clin Periodontol 2014;41:164-71.
37. Bowen DM. Is non-surgical periodontal therapy cost effective? J Dent Hyg 2015;89:6-10.
38. Muniz FWMG, Taminski K, Cavagni J, Celeste RK, Weidlich P, Rösing CK. The effect of statins on periodontal treatment—A systematic review with meta-analyses and meta-regression. Clin Oral Investig 2018;22:671-87.
39. Surve SM, Acharya AB, Thakur SL. Efficacy of subgingivally delivered atorvastatin and simvastatin as an adjunct to scaling and root planing. Drug Metab Ther 2015;30:263-9.
40. Sathish AK, Varghese J, Fernandes AJ. The impact of sex hormones on the periodontium during a woman's lifetime: A concise-review update. Curr Oral Health Rep 2022;9:146-56.
41. Dutt P, Chaudhary S, Kumar P. Oral health and menopause: A comprehensive review on current knowledge and associated dental management. Ann Med Health Sci Res 2013;3: 320-3.
42. Yakar N, Türedi A, Emingil G, Şahin C, Köse T, Silbereisen A, *et al*. Oral health and emotional well-being in premenopausal and postmenopausal women: A cross-sectional cohort study. BMC Womens Health 2021;21:338.