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SYSTEMATIC REVIEW

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Skeletal bone density is associated with periodontitis: systematic review and metanalysis

Densidade mineral esquelética está associada com periodontite: revisão sistemática e meta-análise

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ABSTRACT

Objective: This study aimed to evaluate whether low skeletal bone density conditions, such as osteoporosis (OPR), osteopenia (OPN) and low bone mineral density (low BMD) are associated with periodontitis. **Material and Methods:** Embase, Lilacs, PubMed, Scopus, Web of Science, Livivo and Google Scholar were searched up to July 2023. Observational studies comparing different BMD levels, showing clinical data of periodontitis and with adjusted analysis for confounding factors were included. Reviewers independently conducted study selection, data extraction, methodological quality and certainty of evidence assessments. **Results:** 32 studies were included, 20 eligible for the metanalysis. Subjects with OPR/OPN/lowBMD show significantly more odds of having periodontitis (OR=1.40, 95%CI=1.26-1.53, I^2=82.9%). Association between skeletal bone density and periodontitis showed dose-response gradient, with higher effect size in osteoporotic when compared to the osteopenic subjects. Statistical association with low heterogeneity was observed in female (OR=1.42, 95%CI=1.13-1.71, I^2=20.4%), in post-menopausal women (OR=1.47, 95%CI=1.15-1.78, I^2=18.7%) and periodontitis case-definition based in clinical attachment level/alveolar bone loss (OR=1.39, 95%CI 1.16-1.62, I^2=26.5%). **Conclusion:** Routine periodontal supportive care and screening for skeletal bone diseases risk groups, may be an important tool to fully assess and care for patients with osteoporosis and osteopenia.

KEYWORDS

Metanalysis; Osteopenia; Osteoporosis; Periodontal attachment loss; Periodontitis.

RESUMO

Objetivo: Este estudo teve como objetivo avaliar se condições de baixa densidade óssea esquelética, como osteoporose (OPR), osteopenia (OPN) e baixa densidade mineral óssea (low BMD) estão associadas à periodontite. **Material e métodos:** Foram pesquisados Embase, Lilacs, PubMed, Scopus, Web of Science, Livivo e Google Scholar até julho de 2023. Estudos observacionais que comparavam diferentes níveis de BMD, apresentavam dados clínicos de periodontite e análises ajustadas para fatores de confusão foram incluídos. Revisores conduziram de forma independente a seleção de estudos, extração de dados, avaliação da qualidade metodológica e da certeza das evidências. **Resultados:** Foram incluídos 32 estudos, sendo 20 elegíveis para metanálise. Indivíduos com OPR/OPN/low BMD apresentaram significativamente mais chances de ter periodontite (OR=1.40, IC95%=1.26-1.53, I^2=82.9%). A associação entre densidade óssea esquelética e periodontite mostrou um gradiente de resposta à dose, com maior tamanho de efeito em indivíduos osteoporóticos em comparação com os osteopênicos. Foi observada associação estatística com baixa heterogeneidade em mulheres (OR=1.42, IC95%=1.13-1,71, I^2=20.4%), em mulheres pós-menopáusicas (OR=1.47, IC95%=1.15-1.78, I^2=18.7%) e na definição de casos de periodontite com base no nível clínico de inserção (OR=1.39, IC95%=1.16-1.62, I^2=26.5%). **Conclusão:**

O cuidado periodontal de rotina e a triagem para grupos de risco de doenças ósseas esqueléticas podem ser ferramentas importantes para avaliar e cuidar de pacientes com osteoporose e osteopenia.

PALAVRAS-CHAVE

Meta-análise; Osteopenia; Osteoporose; Perda de inserção periodontal; Periodontite.

INTRODUCTION

Osteoporosis (OPR), osteopenia (OPN) and low bone mineral density (BMD) are metabolic conditions that affect bone density and structure, producing an unbalanced absorption/apposition ratio [1]. In these conditions, bone mass decreased and generates a greater risk of fracture [2]. OPR affects over 200 million people worldwide [3] and causes more than 8.9 million fractures annually [4]. In the United States more than 10.2 million Americans have OPR and an additional 43.4 million have low bone density [5]. One in three women and one in five men of age over 50 years will experience osteoporotic fractures [6].

Periodontitis is an immune-inflammatory disorder initiated by dysbiosis that compromises the integrity and function of tooth-supporting structures and if not correctly treated, tooth loss may follow [7]. Notably, severe periodontitis has been ranked as the sixth most prevalent condition globally, affecting 10.8% of adult populations [8].

Periodontitis and OPR have a relatively "silent" nature leading many patients to seek "symptom-oriented" care for advanced-stage periodontitis [9] or in cases of OPR when bone fractures have already occurred [10]. Periodontitis and OPR are bone disorders associated with inflammation [11], aging [12] and share risk modifiers factors such as calcium and vitamin D deficiency [13,14] and smoking [11,15]. Considering the similarities, it raises the question whether a systemic skeletal disease like OPR could be associated to localized periodontal bone destruction.

Recently, studies using a Mendelian randomization showed no association between BMD and periodontitis [16,17]. The authors suggest caution before generalization of the findings and appoint some limitations such as: exposure and outcome summary obtained from individuals with European ancestry, case-definition of periodontitis based on different criteria including self-reported periodontitis, and because in the Mendelian randomization analysis age- and gender-data were unavailable.

In previous systematic reviews, some methodological characteristics harmed the interpretation and restricting the external validity of the findings. Among these characteristics are no information about age range or sex of the included subjects [18], inclusion of only postmenopausal women [19,20], absence assessment of risk of bias [18,20] and of certainty of evidence [18-21], and no careful about adjust to confounding variables in primary studies [18-21]. As consequence, the existing systematic evidences on the association between low BMD and periodontitis are practically restricted to the postmenopausal women [19,20] with no consideration about produced certainty of evidence.

This is the first systematic review to our knowledge to investigate the association between low skeletal bone density and periodontitis (i) including only primary studies with adjustment for covariates strengthening the effect estimate, (ii) including individuals of both sexes and without age restrictions expanding the external validity of the results, (iii) and carrying out risk of bias, publication bias and certainty of the evidence assessment. Moreover, we explored the effect of different case-definition of periodontitis and OPR on the association strength. We hypothesized that (i) Low skeletal bone density would be associated with periodontitis with dose-response gradient; and (ii) the highest effect size would be observed when periodontitis case-definition was based on destructive parameters compared to the case definition based inflammatory parameters.

MATERIAL AND METHODS

Review question

"Do subjects with low skeletal bone density have higher odds for loss of tooth-supporting structures and of teeth when compared to those with normal bone conditions?"

Protocol and registration

Our protocol was registered in the Prospective Register of Systematic Reviews (CRD42022346882). The study followed the guideline of the Preferred Reporting Items for Systematic Review and Meta-analysis checklist [22].

Inclusion criteria

The PECO(S) strategy consisted of the following acronym: Patients with any age and sex; Exposure to low BMD, OPR or OPN; Comparison with subjects showing normal BMD; Outcome representing periodontitis, clinical attachment level, alveolar bone loss, tooth loss; and Study design considering observational studies.

Eligible studies presented the following criteria: (a) observational design; (b) comparison between normal BMD and osteoporotic, osteopenic or low BMD groups; (c) clinical measure of clinical attachment level (CAL), radiographic alveolar bone loss, tooth loss, and/or periodontitis diagnosis; and (d) statistical analysis considering adjust for confounders factors.

Studies with self-report measures, reviews, case reports and clinical trials; reports without adjustment for confounding factors; and papers not written in Latin-Roman alphabet were excluded.

Search strategy

Our database search was up to July 2023. Search strategies were customized for each database considering controlled and free terms (Appendix 1). Medline/PubMed, Embase, Lilacs, Web of Science, Livivo and Scopus were searched. Grey literature was searched on Google Scholar. Reference lists of included studies and other systematic reviews were checked for additional reports. EndNote (Thomson Reuters, New York, USA) and Rayyan software [23] were used to manage references and to identify and remove duplicate hits.

Study selection and data extraction

Three independent reviewers performed the selection of studies and data extraction. In the first phase, titles and abstracts were evaluated. In the second phase, eligibility criteria were applied to the full texts. Disagreements were solved by a fourth reviewer. A standardized data extraction form was used to obtain relevant data from methodological characteristics and principal findings. If data were missing or unclear, three attempts to contact the corresponding authors were performed at an interval of 7 to 10 days via email or ResearchGate.

Methodological quality assessment

Three reviewers independently assessed the methodological quality using the NewCastle Ottawa Scale (NOS) for cohort, cross-sectional and case-control studies [24]. Conflicts were solved by consensus. Studies were categorized as high (≥7), moderate (4-6) or low (0-3) quality according to total score [25].

Outcomes

The main outcome was periodontitis prevalence. Additional outcomes were CAL and tooth loss.

Data synthesis and analysis

The effect measure adopted was the adjusted odds ratio (OR) and respective 95% CI. The DerSimonian and Laird's random effects model was used. Heterogeneity assessment was performed considering the direction and size of the effect estimates in the forest plot, I2 scores and Q-statistic. Heterogeneity causes were explored with subgroup analysis. A dose response gradient was assessed by subgroups analysis considering reported data from osteoporosis and osteopenia, separately, and data from studies reporting low BMD only. Case-definition of OPR and periodontitis, sex, menopause, BMD assessment tool and risk of bias [26] were analyzed. All analyses were conducted using the Stata software, version 14.0 (Stata Corporation; College Station, TX, USA). Results were reported using the informative statements to communicate the findings of systematic reviews of interventions [27] considering the magnitude of the effect and the certainty of the evidence. Effect size was reported considering outcomes with prevalence of 10% or greater, the cutoff was: trivial effect 1.1 to 1.54, small 1.53 to 2.71, moderate 2.74 to 4.01 and large >4.01) [28].

Assessment of publication bias

Publication bias was analyzed using funnel plots (visually) and Egger's statistical test was performed [29].

Assessment of quality of evidence

The GRADE (Grading of Recommendations Assessment, Development and Evaluation)

system was used to determine the certainty of the evidence gathered [30].

RESULTS

Study selection

The systematic search yielded 6,293 records; 4,312 titles/abstracts were evaluated after duplicate removal. Of this total, 212 reports were included for full text reading. Thirty-two studies were retained for qualitative analysis, 20 of which were included in the meta-analysis. The flowchart of the study selection process is presented in Figure 1. Authorship and exclusion reasons of the 180 reports are presented in Appendix 2.

Study characteristics

The characteristics of the 32 included studies are presented in the Table I. The reports included 7 cohort [38,40-42,45,46,60], 21 cross-sectional [31-37,39,43,44,47-49,51-53,56,58,59,61,62] and 4 case-control studies [50,54,55,57]. Of the 32 included studies, eighteen [31,32,35,36,38-42,44-47,50,57,58,60,61] and fourteen [33,34,37,43,48,49,51-57,59,62] were classified as low and moderate risk of bias, respectively (Appendix 3).

A total of 3.032.309 subjects aged 18 to 100 years were evaluated. Thirteen studies included males [31,35,36,38-42,44,45,47,52,55]. However, only one presented separately data from males and females [40] reporting that women with periodontitis were more likely to develop OPR [HR: 1.22, 95% CI 1.01-1.48], while no significant statistically risk was verified in men (HR 1.39, 95% CI 0.85-2.29) [40].

BMD was assessed by DXA tool in 25 studies [31-34,36,37,39,40,42,44,47-57,59-62]. Case-definition criteria of OPN and OPR according to the WHO was reported in 20 studies [31-35,37,39,42,43,49-53,55-57,59,61,62]. Fifteen studies defined a periodontitis case using CAL or radiographic bone loss [31,33,34,36,37,39,41,49,50,52-54,56,57,59].

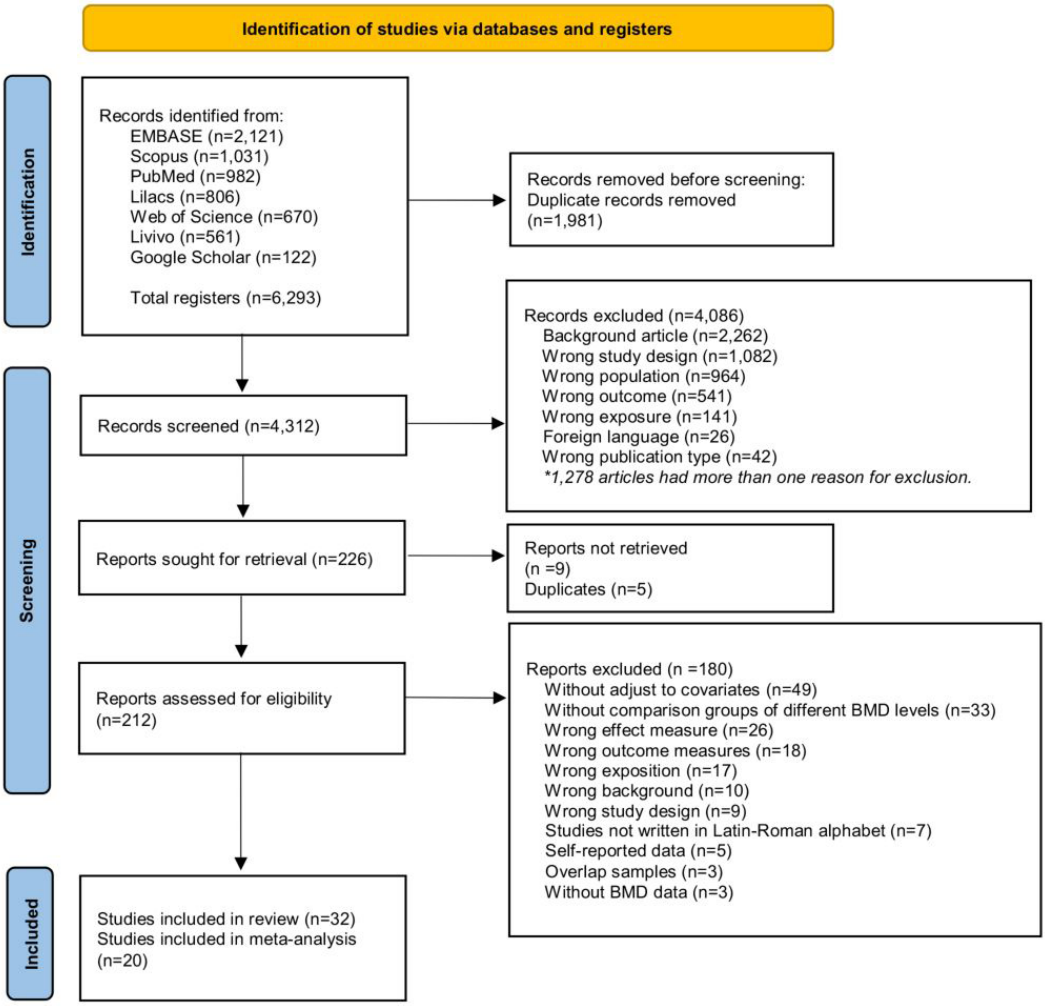

Figure 1 - Flowchart of the process of identification, screening and inclusion of studies.

Table I - The characteristic of the included studies considering the association between OPR/OPN/low BMD and periodontitis

Authorship, Country, design study	Sample, Sex, Age	Groups	OPR/OPN case definition, BMD tool	Periodontitis	Results
Peng et al. [31], USA, cross-sectional	6,377 Male/female, 45-60y	Normal BMD, OPN, OPR	WHO, DXA	CAL, PD	OR for periodontitis in whole sample: OPN: OR 1.08 (0.86-1.36), OPR: OR 1.66 (1.00-2.77)
Lee [32], South Korea, cross-sectional	2,573 Female, 45-60y	Normal BMD, OPR	WHO, DXA	CPITN	OR for periodontitis: OPR: OR 1.25 (1.00-1.6)
Zamani et al. [33], Iran, cross-sectional	94 Female, 50-75y	Normal BMD, OPN, OPR	WHO, DXA	CAL, Bone loss	β for alveolar bone loss: BMD: β - 1.122 (SE 0.35; p=0.002)
Baldodia et al. [34], India, cross-sectional	112 Female, 52-59y	Normal BMD, OPN	WHO, DXA	CAL, PD, BOP	β for CAL: OPN ß 0.206; SE 0.045
Chou et al. [35], Taiwan, cross-sectional	7,298 Male/female, 40-44y	Normal BMD, OPN, OPR	WHO, Ultrasound	CPI>3	OR for periodontitis: OPN/ OPR: OR 1.13 (1.02-1.26)
Costa et al. [36], Brazil, cross-sectional	2,032 Male/female, 18-19y	Normal BMD, low BMD	BMD Z score, DXA	CAL, PD	OR for severe periodontitis: Low BMD: OR 2.08 (1.12-3.85)
Gil-Montoya et al. [37], Spain, cross-sectional	173 Female, 45-72y	Normal BMD, OPN, OPR	WHO, DXA	CAL	β for percentage of sites with CAL≥6mm: Women≤58y: OPR: β 0.37 (-9.6 to10.4), OPN: β 3.63, (-10.7 to 17.9) Women>58 y: OPR: β 27.06 (11.31 to 42.81), OPN: β 30.12 (-2.14 to 62.4)
Lee et al. [38], South Korea, cohort	558,147 Male/female, ≥ 60y	Healthy oral, Period	ICD-11	Periodontal therapy type	OR for periodontitis: OPR: OR 1.37 (1.35-1.40)
Mongkornkarn et al. [39], Taiwan, cross-sectional	3,282 Male/female, 30-82y	Normal BMD, OPN, OPR	WHO, DXA	CAL, PD	OR for periodontitis: OPR: OR 0.98 (0.67-1.44), OPN: OR 0.99 (0.82-1.21)
Choi et al. [40], South Korea, cohort	13,464 Male/female, 30-60+y	No Period, Period	ICD-10, DXA	Periodontal therapy type	HR for OPR: Males with periodontitis: HR 1.39 (0.85-2.29), Female with periodontitis: HR 1.22 (1.01-1.48)
Lee et al. [41], South Korea, retrospective	354,850 Male/female, 40-79y	Healthy oral, Period	ICD-10 (codes M08-M82)	CAL	OR for periodontitis: OPR: OR 1.22 (1.18-1.27)
Mau et al. [42], Taiwan, cohort	88,389 Male/female, 40-65+y	Period, Control	WHO, DXA	Periodontal therapy type	HR for the development of OPR: Mild periodontitis HR 1.56 (1.30-1.76), Moderate: HR 2.09 (1.60-2.72)
Richa et al. [43], India, cross-sectional	600 menopausal women, 45-65y	Non-Period, Period	WHO, QUS	CPI≥3	OR for osteoporosis: Periodontitis OR 0.92 (0.53-1.60)
Huang et al. [44], Taiwan, cross-sectional	85,583 Male/female, <50-80+y	No- Period, Period	ICD-9-CM 733.0, DXA	Periodontal therapy type	OR for osteoporosis: Good OH/periodontitis: OR 1.29 (1.12-1.49); Poor OH/ periodontitis: OR 6.02 (4.65-7.81)
Lin et al. [45], Taiwan, cohort	1,878,401 Male/female	No- Period, Period	ICD-9-CM code 733.0	Periodontal therapy type	OR for osteoporosis: OR 2.03 (1.29-3.20) Male OR 2.37 (0.88-6.39), Female OR 1.96 (1.17-3.26)
Chang et al. [46], Taiwan, cohort	10,102 Male/female, 50-100y	OPR, Non OPR	ICD-9-CM code 733.0 to 733.90	ICD-9-CM.	Stratified Cox proportional-hazards regression. Periodontitis incidence: OPR: HR 1.14 (1.05-1.24)
Kim et al. [47], South Korea, cross-sectional	9,977 Male/female, 40+y	No- Period, Period	DXA	CPI≥ 3	OR for periodontitis: OPN: OR 1.30 (1.15-1.47), OPR: OR 2.26 (1.83-2.78)
Iwasaki et al. [48], Japan, cross-sectional	397 women, 60-80y	Normal BMD, OPN, OPR	OPN: 70%-80% yan, OPR ≤70% yan. DXA	NA	β for CAL mean: OPN: ß 0.18, SD 0.08, p=0.022 OPR: ß 0.26, SD 0.09, p=0.003.

Abbreviations: BMD: bone mineral density; OPR: osteoporosis; OPN: osteopenia; Period: periodontitis; WHO: world health organization; DXA: dual-energy x-ray absorptiometry; QUS: quantitative ultrasound technique; PD: probing depth; CAL: clinical attachment level; BOP: bleeding on probing; CPI: community periodontal index; CPITN: community periodontal index of treatment needs. NA: Not applicable.

Table I - Continued...

Authorship, Country, design study	Sample, Sex, Age	Groups	OPR/OPN case definition, BMD tool	Periodontitis	Results
Marjanovic et al. [49], UK, cross-sectional	380 female, 45-65y	Non-OPR, OPR	WHO, DXA	CAL, PD	OR for periodontitis: OPR: OR 1.17 (0.67-2.05).
Passos et al. [50], Brazil, case-control	521 postmenopausal women, 50-87y	No- Period, Period	DXA, WHO	CAL, PD	OR for periodontitis: OPN/ OPR: OR 2.24 (1.24-4.06)
Pepelassi et al. [51], Greece, cross-sectional	90 women with periodontitis, 45-70y	Normal BMD, OPN, OPR	WHO, DXA	NA	β for CAL mean adjusted for menopause: OPR: β 0.69 p=0.03, OPN: B β 0.12 p=0.55 Adjusted for smoking: OPR: β 0.63 p=0.05, OPN: β 0.12 p=0.54
Moedano et al. [52], Mexico, cross-sectional	166 Male/female, 60- 85y	Normal BMD, OPN, OPR	WHO, DXA	CAL	OR for periodontitis severity: OPR: OR 1.36 (0.80-2.31)
Al Habashneh et al. [53], Jordan, cross-sectional	400 postmenopausal women, 50-75y	Normal BMD, OPN, OPR	WHO, DXA	CAL, PD	OR for periodontitis: OPR: OR 2.45 (1.38-4.34), OPN: OR 1.35 (0.78-2.35)
Passos et al. [54], Brazil, case-control	139 postmenopausal women, >50y	No- Period, Period	DXA	CAL, PD, BOP	OR for periodontitis: OR 2.02 (0.79-5.19)
Shum et al. [55], China, case-control	200 male, 69-78y	Control, OPN, OPR	WHO, DXA	NA	Percentage of sites CAL≥6 mm: OPR: coef 5.3 (0.1-10) p=0.045, OPN: coef -0.8 (-6.0 to 4.4) p=0.757.
Brennan et al. [56], USA, cross-sectional	1,256 post-menopausal women	Normal BMD, OPN, OPR	WHO, DXA	Alveolar crestal height	OR for clinical oral bone loss: OPR: OR 1.75 (1.09-2.82), OPN: OR 1.09 (0.78-1.52)
Gomes-Filho et al. [57], Brazil, case-control	139 postmenopausal women, 50-80y	No periodontal disease, Period	WHO, DXA	CAL, PD, BOP, radiographic bone loss	OR for periodontitis: OPR: OR 2.71 (1.12-6.55)
Inagaki et al. [58], Japan, cross-sectional	356 Female, Pre- and post-menopausal	No/mild Period, moderate/ severe Period	OPN: 70%-80% yan, OPR ≤70% yan, CXD	CPITN	OR for OPR/OPN Moderate/severe periodontitis: OR 2.0 (1.1-3.7)
Wactawski-Wende et al. [59], USA, cross-sectional	1,341 postmenopausal women, 53.2-85.1y	Normal, Low, Moderate, and Osteoporotic T-score	WHO, DXA	Alveolar crestal height	OR for alveolar crestal height: OPR: OR 1.90 (1.19-3.05)

Abbreviations: BMD: bone mineral density; OPR: osteoporosis; OPN: osteopenia; Period: periodontitis; WHO: world health organization; DXA: dual-energy x-ray absorptiometry; QUS: quantitative ultrasound technique; PD: probing depth; CAL: clinical attachment level; BOP: bleeding on probing; CPI: community periodontal index; CPITN: community periodontal index of treatment needs. NA: Not applicable.

Five studies that used multivariate linear regression [33,34,37,48,51], and three population-based cohort studies from South Korea [40] and Taiwan [42,46] that reported hazard ratio as an effect measure, were not included in our metanalysis. All them demonstrated a statistical association between OPR and loss of periodontal support tissue (CAL or bone loss) [33,34,37,48,51], and between OPR and periodontitis [40,42,46]. Four studies reported the association between low BMD and tooth loss [58,60-62], with two of them observing no significant association between OPR and tooth loss [58,61]. Twenty studies reporting OR as effect measures for the association between OPR/OPN/ low BMD and periodontitis were included in the present metanalysis [31,32,35,36,38,39,41,43-45,47,49,50,52-54,56-59].

Metanalysis

Among the 20 metanalysis studies, 15 reported data from OPR or OPN cases [31,32,38,39,41,43-45,49,52-54,56,57,59], while 5 studies reported a general low BMD status, without a clearly defined category such as OPR or OPN [35,36,47,54,58]. Subjects with OPR/OPN/low BMD show significantly more odds of periodontitis (OR 1.40, 95% CI 1.26-1.53, I^2=82.9%, p=0.000, prediction interval 1.03 to 1.77) with low certainty of evidence (Figure 2).

In summary, the results from subgroup analysis (Table II) showed that patients with OPR/OPN/low BMD have statistically higher odds for periodontitis when compared to the patients with normal BMD, independently of the periodontitis case-definition, OPR case-

definition, sex, tool type used to evaluate BMD, study design and risk of bias of the included studies and if the diagnosis was osteoporosis or osteopenia. The association observed in the pre-menopause women subgroup was non-significant, but only 2 studies were available for metanalysis. We observed a heterogeneity reduction between females (OR 1.42, 95% CI 1.13-1.71, I2=20.4%, p=0.255) when compared overall estimate. Grouped data from female/male showed high heterogeneity. Unfortunately, data from males only was not available. Lower heterogeneity was also observed in post-menopausal women (OR 1.47, 95% CI 1.15-1.78, I^2 18.7%, p=0.271) when compared to the overall estimates. A dose response gradient of the association between skeletal bone density and periodontitis was observed in subgroups analysis. OPR maintained the effect estimate (OR 1.43, 95% CI 1.27-1.58, I2=84.4%, p=0.000) when compared to the overall estimate, while OPN reduced the estimate (OR 1.14 95% CI 1.02-1.27, I2=24.4%, p=0.251), and low BMD without defined diagnosis lost statistical significance (OR 1.61 95% CI 0.94-2.28, I2=48.5%, p=0.120.

Criteria to define OPN/OPR diagnosis (WHO or others) did not change the effect size and maintained the heterogeneity. Tool type to evaluate BMD did not explain the heterogeneity. However, BMD evaluation using DXA tool increased the effect size (OR 1.94, 95% CI 1.50-2.37) when compared to the overall estimate, while other tools, such as ultrasound, QUS or not reported (OR 1.25, 95% CI 1.11-1.38) reduced the size effect. Studies that classified periodontitis using CAL/Bone Loss (CAL/PD and CDC/AAP) maintained the effect size in comparison to the general aggregated analysis and reduced heterogeneity (OR 1.39, 95% CI 1.16 to 1.62, I^2=26.5%,).

Regarding the study design, low heterogeneity was verified only in case-control studies (I^2 0.0%, p=0.927), despite of the imprecision highlighted by the amplitude of the confidence intervals when compared to the other study design. In studies with moderate and low risk of bias, OPR/OPN/low BMD remained statistically associated with periodontitis.

Sensitivity analysis omitting one by one of the studies demonstrated no change in the statistical significance and estimate direction (Appendix 4).

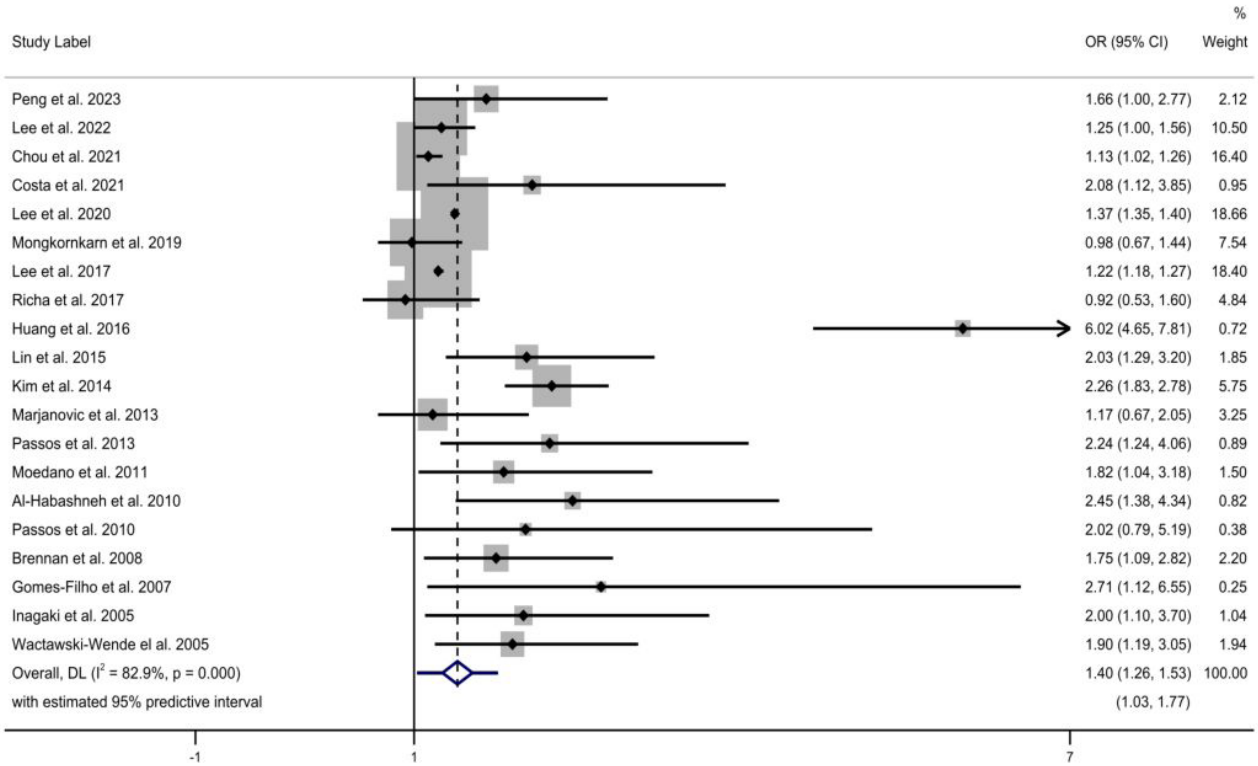

Figure 2 - Forest plot of OPR/OPN/low BMD and periodontitis in a random effects model meta-analysis.

Table II - Subgroups analysis

Subgroups	Number of studies	Pooled OR (95% CI)	I^2	p (heterogeneity)
All studies	20	1.40 (1.26-1.53)	82.9%	0.000
BMD category				
Osteoporosis	16	1.43 (1.27-1.58)	84.4%	0.000
Osteopenia	6	1.14 (1.02-1.27)	24.4%	0.251
Low BMD	4	1.61 (0.94-2.28)	48.5%	0.120
Periodontitis definition				
CAL/Bone loss	12	1.39 (1.16-1.62)	26.5%	0.184
Others	8	1.55 (1.27-1.83	89.7%	0.000
OPR definition				
WHO	14	1.46 (1.20-1.72)	63.2%	0.001
Others	6	1.43 (1.23-1.63)	92.9%	0.000
Sex subgroups				
Female/male	10	1.40 (1.24-1.56)	91%	0.000
Female	10	1.42 (1.13-1.71)	20.4%	0.255
Menopause				
Post-menopause	10	1.47 (1.15-1.78)	18.7%	0.271
Pre-menopause	2	1.46 (0.72-2.21)	34.6%	0.216
Tool type to evaluate BMD				
DXA	15	1.94 (1.50-2.37)	76.1%	0.000
Others	5	1.25 (1.11-1.38)	91.6%	0.000
Study design				
Cross-sectional	14	1.67 (1.33-2.01)	81.4%	0.000
Cohort	3	1.31 (1.17-1.46)	94.2%	0.000
Case-control	3	2.26 (1.17-3.35)	0.0%	0.927
Risk of bias				
Moderate	7	1.47 (1.07-1.87)	25.8%	0.232
Low	13	1.39 (1.24-1.54)	88.3%	0.000

Assessment of publication bias

Although Egger's test has indicated no significant publication bias (p=0.228), we observed, in the visual analysis of the funnel plot, asymmetric distribution of the effect estimates (Appendix 5). Trim and fill sensibility analysis was performed to measure the impact of publication bias on the metanalysis (Appendix 6). Eight studies were filled, although a reduction of effect size was observed, statistical significance remained in the filled meta-analysis (OR 1.28, 95% CI 1.13-1.42).

Assessment of certainty of evidence

No major problems were observed regarding risk of bias, inconsistency, indirectness and imprecision. Studies showed an inversely proportional relationship between BMD categories and periodontitis in the dose-response gradient domain. Although publication bias was detected, trim and fill sensibility analysis revealed a slight reduction of effect size and no significant changes to statistical significance. Thus, certainty of evidence was graded low (Table III).

DISCUSSION

The present study shows statistical association between low skeletal bone density and periodontitis with dose-response gradient, OPR is associated with periodontitis, while a weaker association between OPN and periodontitis was found. The heterogeneity was explained by subgroups analyses, particularly by women, presence of menopause and by periodontitis case-definition from destructive parameters (CAL and alveolar bone loss). BMD assessment using DXA increased the effect size. These findings partially confirmed our initial hypothesis, since that

Table III - GRADE certainty of evidence assessment

Certainty assessment									
Periodontitis (Assessed with: Clinical or Radiographic measurement based on attachment level or bone level)									
N studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other domains	Effect size (95% CI)	Certainty	Importance
20	observational studies	not serious	not serious	not serious	not serious	publication bias, gradient dose-response	OR 1.40 (1.26 to 1.53)	Low	Important

periodontitis case-definition based on destructive parameters did not increase the effect estimate size, although it reduced the heterogeneity in comparison to the overall estimate.

Independently of the case-definition of OPR and of periodontitis, the association between OPR and periodontitis remained statistically significant. OPR case-definitions following WHO criteria compared to others, as well as periodontitis case-definition from destructive parameters (CAL, alveolar bone loss) rather than by inflammatory parameters (CPITN) reduced heterogeneity. Periodontal parameters that indicate destructive process of support tissue reflects the lifetime experience of periodontitis and is a critical outcome measure for diagnosing and staging periodontitis [7]. Although subgroups analysis according the equipment type used to evaluate the BMD did not explain the heterogeneity, DXA strengthened the effect estimate. DXA is considered the gold-standard to evaluate BMD and to establish OPR and OPN diagnosis [63].

Comparison of female with female/male data indicated that female have higher odds of periodontitis particularly after menopause. Unfortunately, only one study reported separately data according to sex showing no association between OPR and periodontitis in males [40]. Men lose 15-45% of cancellous bone and 5-15% of cortical bone with advancing age, whereas women lose 35-50% of cancellous bone and 25-30% of cortical bone. Besides, men have shorter life expectancy means being exposed for a shorter period to the low BMD and its consequences [64]. In previous systematic reviews [21], OPR was associated with periodontitis in women and men, with a larger effect size in women. Male data were obtained from only 3 studies, more substantial evidence for the association of osteoporosis in men and periodontitis is still needed.

No previous systematic review explored the association between OPR and periodontitis in pre- and post-menopausal women. Here, we observed association in post-menopausal, but no statistical association in pre-menopause women. Several mechanistic links can take part in this phenomenon, such as ageing process, oxidative stress, hormonal changes and cellular senescence [11,65]. During menopause, women estrogen levels are reduced, this hormonal imbalance is associated with a gap between bone resorption and formation, as well as lower calcium absorption [66], these metabolic changes in menopause, together with ageing and exposure to risk factors such as smoking and vitamin deficiencies can upregulate the production of inflammatory mediators, impairing bone remodeling and promoting osteoclast activity, weakening skeletal bone structure, leading to the risk of fractures [67]. These systemic changes in homeostasis, bone density and structure are hypothesized to take part in the association between osteoporosis and periodontitis, exacerbating the local progression of active periodontal tissue destruction [68]. In this context, antiresorptive medication may be an important modulating factor to the association between OPR and periodontitis in postmenopausal women. In a case-control study including 521 postmenopausal women, the odds having of periodontitis were of 2.51 (95%CI 1.33-4.72) and of 1.17 (95%CI 0.19-7.36) in osteopenic/osteoporotic women non-users and users of antiresorptive medication, respectively [54]. Further studies have reported that treatment for osteoporosis may lead to improvements in periodontal attachment loss parameters in post-menopausal women [69,70]. Additionally, addressing shared risk factors such as smoking cessation and nutritional deficiencies may also be strategic as part of a common risk factor approach for both diseases [11,68].

Previous metanalysis found higher effect measure to association between OPR and periodontitis than those reported here. Xu et al. [21] reported an OR of 1.96 (95%CI 1.50-2.54), while we found an OR of 1.40 (95%CI 1.26-1.53) resulting in a trivial effect size [28]. This discordance can be explained because

we included only studies with adjusted effect measured, due the difference in other inclusion criteria and an update of studies from 2021.

As a strength, our systematic review used a sensitive search strategy across six databases and gray literature, which allowed us to reach a large number of results. We examined 4,312 reports, while previous systematic reviews examined 145 to 1,206 records [18-21]. In addition, we included only studies with adjusted effect measures, minimizing the interference of potential confounders on the effect estimate. With broad inclusion criteria, we could explore the role of the case-definition of OPR and periodontitis, of the menopause presence and of the equipment type used to evaluate BMD on the effect estimates. Finally, in the quantitative analysis, we found significant values for the prediction interval, which indicates that in new studies similar to those included in our review, the possible effect will be the same as reported here.

Notably, this is the first systematic review to investigate the association between skeletal bone density conditions such as OPR, OPN and low BMD and periodontitis including studies with adjustment for covariates and presenting both, risk of bias and certainty of evidence assessment. Besides, this is the first systematic review to our knowledge, to investigate the impact of case-definition of osteoporosis and periodontitis, even as to directly compare pre- and post-menopausal women on the association estimate. However, some limitations must be considered when interpreting our findings. First, although there were no restrictions regarding sex, only one study reported adjusted estimates in males only [55] impairing the external validity of our findings. Second, although we included only studies with adjusted analysis, we realized that some important confounders were explored in few studies. For example, of the 20 studies included in the metanalysis, hormone replacement therapy [49,56,59], vitamin D [31,53,56,59], obesity/weight/BMI [31,32,35,36,38,39,44,47,56,59] were variables included in the regression model in, 3, 4 and 10 studies, respectively. Smoking, a recognized factor of risk at OPR and periodontitis, was included in 13 studies [31,32,35,36,39,41,47,49,50,54,56,57,59]. Therefore, future studies should explore more complex analysis models to determine the true size effect of the association between OPR and periodontitis. Finally, a risk for publication bias was detected in a funnel plot analysis, this bias occurs when there is an over representation of published studies with statistically significant results, while studies with non-significant or negative findings are less likely to be published. When trim and fill sensibility analysis was performed, only a small reduction of effect size was observed, with no important changes related to statistical significance.

CONCLUSION

The main finding of our study is that osteoporotic and osteopenic individuals have higher odds of periodontitis when compared to individuals with normal BMD. Then, dentists must be attentive to patients with risk to develop skeletal bone diseases to promote preventive care for periodontitis. Routine oral supportive care and screening for risk groups, may be an important tool to fully assess and care for patients with osteoporosis and osteopenia.

As implications to future research, we highlight that the evidences of association between low BMD and periodontitis are scarce in male, and studies should explore more complex analysis models considering important confounding factors, for example smoke, hormone replacement therapy, vitamin D, obesity/weight/BMI.

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Author's Contributions

FLK: Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation. OFFB: Investigation, Data Curation, Formal Analysis, Writing – Original Draft Preparation. JCU: Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing – Original Draft Preparation. KZK: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Review & Editing, Supervision, Project Administration. All authors approved of the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Regulatory Statement

This systematic review was conducted through a search strategy in electronic databases. The approval for ethics committee for the reviewed studies were obtained in their original work.

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Appendix 1. Search strategy according to database

Database	Search strategy
Pubmed	#1"bone diseases, metabolic"[MeSH Terms] OR "osteoporosis, postmenopausal"[MeSH Terms] OR ("osteoporosis, postmenopausal"[MeSH Terms] OR "osteoporosis"[MeSH Terms]) OR "bone density"[MeSH Terms] OR "fractures, bone"[MeSH Terms] OR "Low Bone Mineral Density"[All Fields] OR "Low Bone Densities"[All Fields] OR "Low Bone Density"[All Fields] OR "Bone Mineral Density"[All Fields] OR ("bone diseases, metabolic"[MeSH Terms] OR ("bone"[All Fields] AND "diseases"[All Fields] AND "metabolic"[All Fields]) OR "Metabolic Bone Diseases"[All Fields] OR "osteopenia"[All Fields] OR "osteopenias"[All Fields]) OR ("bone diseases, metabolic"[MeSH Terms] OR ("bone"[All Fields] AND "diseases"[All Fields] AND "metabolic"[All Fields]) OR "Metabolic Bone Diseases"[All Fields] OR "osteopenia"[All Fields] OR "osteopenias"[All Fields]) OR "Metabolic Bone Diseases"[All Fields] OR "Metabolic Bone Disease"[All Fields] OR "Perimenopausal Bone Loss"[All Fields] OR "Post-Menopausal Osteoporosis"[All Fields] OR "Postmenopausal Osteoporosis"[All Fields] OR "Postmenopausal Osteoporoses"[All Fields] OR "Postmenopausal Bone Loss"[All Fields] OR ("osteoporosis"[MeSH Terms] OR "osteoporosis"[All Fields] OR "osteoporoses"[All Fields] OR "osteoporosis, postmenopausal"[MeSH Terms] OR ("osteoporosis"[All Fields] AND "postmenopausal"[All Fields]) OR "Postmenopausal Osteoporosis"[All Fields]) OR "Post-Traumatic Osteoporosis"[All Fields] OR "Senile Osteoporosis"[All Fields] OR "Age-Related Bone Loss"[All Fields] OR "Age-Related Bone Losses"[All Fields] OR "age related osteoporosis"[All Fields] OR "age related osteoporosis"[All Fields] OR "Age-Related Osteoporoses"[All Fields] OR "Bone Densities"[All Fields] OR "Bone Mineral Density"[All Fields] OR "Bone Mineral Densities"[All Fields] OR "Bone Mineral Content"[All Fields] OR "Bone Mineral Contents"[All Fields] OR "Bone Fracture"[All Fields] #2"Periodontal Diseases"[MeSH Terms] OR "periodontal attachment loss"[MeSH Terms] OR "alveolar bone loss"[MeSH Terms] OR "periodontitis"[MeSH Terms] OR "Chronic Periodontitis"[MeSH Terms] OR "Aggressive Periodontitis"[MeSH Terms] OR "Tooth Loss"[MeSH Terms] OR "Tooth Mobility"[MeSH Terms] OR "Clinical Attachment Loss"[All Fields] OR "Clinical Attachment Level"[All Fields] OR "Alveolar Bone Losses"[All Fields] OR "Alveolar Resorption"[All Fields] OR "Periodontal Bone Losses"[All Fields] OR "Periodontal Bone Loss"[All Fields] OR "Periodontal Resorption"[All Fields] OR "Adult Periodontitis"[All Fields] OR "Prepubertal Periodontitis"[All Fields] OR "early onset periodontitis"[All Fields] OR "early onset periodontitis"[All Fields] OR "Juvenile Periodontitis"[All Fields] OR "Tooth Mobilities"[All Fields] OR "Probing Depth"[All Fields] OR "Periodontal Pocket"[All Fields] #3 "absorptiometry, photon"[MeSH Terms] OR "Densitometry"[All Fields] OR "Bone densitometry"[All Fields] OR "Dual-Energy X-Ray Absorptiometry"[All Fields] OR "DXA"[All Fields] OR "DEXA"[All Fields] OR "DXA Scan"[All Fields] OR "DEXA Scan"[All Fields] OR "t score"[All Fields] OR "t score"[All Fields] OR "Frax"[All Fields] OR "Frax Tool"[All Fields] OR "BMD"[All Fields] OR "BMD Test"[All Fields] OR "Dual Photon Absorptiometry"[All Fields] OR "x ray densitometry"[All Fields] OR "x ray densitometry"[All Fields] OR "x ray photodensitometry"[All Fields] OR "x ray photodensitometry"[All Fields] OR "Dual Photon Absorptiometry"[All Fields] OR "Dual Energy"[All Fields] OR "Bone Mineral Density"[All Fields] OR "fractures, bone"[MeSH Terms] #4: #1 AND #2 AND #3
EMBASE *	#1 "bone density" OR "bone disease" OR "bone densitometry" OR "metabolic bone disease" OR "osteopenia" OR "involutional osteoporosis" OR "low bone mineral density" OR osteoporosis OR "postmenopause osteoporosis" OR "fragility fracture" OR "senile osteoporosis" OR "posttraumatic osteoporosis" OR "bone demineralization" #2 Periodontitis OR "periodontal disease" OR "periodontal disease assessment" OR "Alveolar Bone Loss" OR "Chronic Periodontitis" OR "aggressive periodontitis" OR "Clinical attachment loss" OR "Clinical attachment level" OR "probing depth" OR "tooth loss" OR "Tooth Mobility" #3 "bone densitometry" OR "dual energy X ray absorptiometry" OR "frax tool" OR "bone density" OR "DXA" OR "T score" #4: #1 AND #2 AND #3
Web of Science	#1 "osteoporosis postmenopausal" OR "osteoporosis" OR "senile osteoporosis" OR "age related bone loss" OR "age related osteoporosis" OR "bone density" OR "bone densities" OR "bone mineral density" OR "osteopenia" OR "age related osteoporosis" OR "bone mineral densities" OR "bone mineral content" OR "low bone density" #2 "periodontal attachment loss" OR "clinical attachment level" OR "periodontal diseases" OR "periodontal disease" OR "periodontitis" OR "periodontal bone loss" OR "probing depth" OR "alveolar bone loss" OR "tooth loss" #3 "densitometries" OR "Dual-Energy X-Ray Absorptiometry" OR "dual energy" OR "DXA scans" OR "DEXA scans" OR "absorptiometry" OR "bone mineral density" OR "fracture" OR "DXA" OR "DEXA" OR "T score" #4: #1 AND #2 AND #3
Scopus	#1 TITLE-ABS-KEY "osteoporosis postmenopausal" OR "osteoporosis" OR "senile osteoporosis" OR "age related bone loss" OR "age related osteoporosis" OR "bone density" OR "bone densities" OR "bone mineral density" OR "osteopenia" OR "age related osteoporosis" OR "bone mineral densities" OR "bone mineral content" #2 TITLE-ABS-KEY "periodontal attachment loss" OR "clinical attachment level" OR "periodontal diseases" OR "periodontal disease" OR "periodontitis" OR "clinical attachment level" OR "periodontal bone loss" OR "probing depth" OR "tooth loss" #3 TITLE-ABS-KEY "densitometries" OR "Dual-Energy X-Ray Absorptiometry" OR "dual energy" OR "DXA scans" OR "DEXA scans" OR "absorptiometry" OR "bone mineral density" OR "fracture" OR "DXA" OR "DEXA" OR "T score" #4: #1 AND #2 AND #3
LILACS **	(osteoporosis OR "bone mineral density" OR "bone density" OR "osteoporose") AND (Periodontitis OR "periodontal diseases" OR "alveolar bone loss" OR "periodontite" OR "doença periodontal" OR "tooth loss" OR "perda dentária")
LIVIVO ***	("osteoporosis" OR "age related bone loss" OR "bone density" OR "bone mineral density" OR "osteopenia" OR "low bone density") AND ("clinical attachment level" OR "periodontal diseases" OR "periodontal disease" OR "periodontitis" OR "probing depth" OR "alveolar bone loss" OR "tooth loss")
Google Scholar	allintitle: osteoporosis OR osteopenia OR "bone mineral density" OR "bone density" AND Periodontitis OR "periodontal diseases" OR "alveolar bone loss" OR "tooth loss"

*Embase, we used Emtree terms with explode function and added all synonymous. **Lilacs, we applied filters to remove: systematic review, overview, case report, qualitative research and clinical practice guidelines. ***Livivo, we removed the books and included only articles.

Appendix 2. Records and exclusion reason after the full-text reading

	Authors and year	Reason for exclusion
1.	Agrawal, Richa et al. 2021	1
2.	Aguilera-Barreiro et al. 2014	2
3.	Akram et al. 2018	2
4.	Al-Rawi 2007	2
5.	Alli et al. 2013	3
6.	Alli et al. 2015	2
7.	Al-Sosowa et al. 2022	1
8.	Antonenko et al. 2011	4
9.	Aspalli et al. 2014	2
10.	Ateeq et al. 2021	5
11.	Atrushkevich et al. 2014	4
12.	Ayed et al. 2018	2
13.	Ayed et al. 2019	2
14.	Barros et al. 2012	2
15.	Bertulucci et al. 2012	2
16.	Brennan et al. 2007	5
17.	Bullon et al. 2005	2
18.	Calciori et al. 2022	6
19.	Darcey et al. 2013	2
20.	Darcey et al. 2013 b	6
21.	Dargahi et al. 2018	2
22.	Dhandapani et al. 2023	2
23.	Dietrich et al. 2004	5
24.	Drozdzowska et al. 2006	7
25.	Duncea et al. 2022	8
26.	Earnshaw et al. 1998	7
27.	Ehsanpour & Etemadi 2018	2
28.	Elders et al. 1992	7
29.	Erdogan et al. 2009	2
30.	Famili et al. 2005	5
31.	Farcas et al. 2019	7
32.	Ferreira et al. 2008	7
33.	Garnier Rodriguez et al. 2017	3
34.	Geary et al. 2013	4
35.	Geary et al. 2015	4
36.	Gondin et al. 2013	5
37.	Grgić et al. 2017	2
38.	Grocholewicz et al. 2012	7
39.	Gur et al. 2003	5.
40.	Haerian et al. 2019	2
41.	Haerian-Ardakani et al. 2014	9
42.	Haghighati et al. 2007	9
43.	Hanai et al. 2015	3
44.	Hassanvad et al. 2016	2
45.	Hattatoğlu-Sönmez et al. 2008	2
46.	Henriques & Neto 2011	5
47.	Hérnandez-Vigueras et al. 2016	2
48.	Hildebolt et al. 1997	5
49.	Hildebolt et al. 2000	5
50.	Hong et al. 2021	10
51.	Ignasiak et al. 2016	7
52.	Inagaki et al. 2001	11 (Sample overlap from Inagaki et al. 2005, which was included).
53.	Iwasaki et al. 2021	4
54.	Jang et al. 2015	5
55.	Jin et al. 2022	5
56.	Juluri et al. 2015	2
57.	Kapoor et al. 2017	10
58.	Kaye et al. 2017	5

1: Without BMD data; 2: Without adjust to covariates; 3: Wrong exposition; 4: Wrong background; 5: Without comparison groups according to different BMD levels; 6: Wrong study design; 7: Wrong effect measure; 8: Wrong outcome measures; 9: Studies not written in Latin-Roman alphabet; 10: Self-reported data; 11: Overlap samples.

Appendix 2. Continued...

	Authors and year	Reason for exclusion
59.	Khorsand et al. 2006	9
60.	Kim et al. 2016	8
61.	Klemetti et al. 1994	7
62.	Koduganti et al. 2009	6
63.	Krall et al. 1994	5
64.	Krall et al. 1996	5
65.	Krall et al. 2005	6
66.	Krall et al. 2006	6
67.	Kules et al. 2021	6
68.	Kribbs et al. 1990	7
69.	Kulikowska-Bielaczyc et al. 2006	7
70.	Lafzi et al. 2012	2
71.	LaMonte et al. 2013	2
72.	LaMonte et al. 2021	5
73.	Lee 2015	11[Korea NHANES 2010-2011, sample overlap from Ji et al. 2016 (NHANES 2011-2012), which was included].
74.	Lee & Myong 2022	8
75.	Lekamwasam & Lenora 2006	5
76.	Lenora & Lekamwasam 2003	5
77.	Lohana et al. 2015	7
78.	Lopes et al. 2006	2
79.	Lopes et al. 2008a	2
80.	Lopes et al. 2008b	2
81.	Mafetano et al. 2007	2
82.	Manjunath et al. 2019	7
83.	Martinez-Maestre et al. 2013	3
84.	Mashalkar et al. 2018	2
85.	Masulili et al. 2016	2
86.	Mazur & Bilozetskyi 2016	3
87.	Mochizuki, Takeshi et al. 2023	9
88.	Moeintaghavi et al. 2013	2
89.	Moghadam et al. 2016	4
90.	Mohammad et al. 1996	7
91.	Mohammad et al. 1997	7
92.	Mohammad et al. 2003	2
93.	Mohammad Gorji-nejad et al. 2023	9
94.	Mohiuddin et al. 2023	2
95.	Mouli et al. 2021	8
96.	Munhoz et al. 2019	8
97.	Murrieta et al. 2016	8
98.	Nayak et al. 2020	7
99.	Nicopoulou-Karayianni et al. 2009	5
100.	Niramitchainon et al. 2020	11 (Overlap sample from Mongkornkarn et al. 2019, which was included).
101.	Öçaka et al. 2015	3
102.	Oztürk Tonguç et al. 2012	2
103.	Oz et al. 2010	2
104.	Pan et al. 2019	2
105.	Pallos et al. 2006	2
106.	Pavičin et al. 2013	8
107.	Pavičin et al. 2017	7
108.	Payne et al. 1999	2
109.	Pejčić et al. 2005	2
110	Penoni et al. 2016	7
111.	Penoni et al. 2018	5
112.	Penoni et al. 2019	2
113.	Pereira et al. 2014	2
114.	Persson et al. 2011	8
115.	Phipps et al. 2007	7

1: Without BMD data; 2: Without adjust to covariates; 3: Wrong exposition; 4: Wrong background; 5: Without comparison groups according to different BMD levels; 6: Wrong study design; 7: Wrong effect measure; 8: Wrong outcome measures; 9: Studies not written in Latin-Roman alphabet; 10: Self-reported data; 11: Overlap samples.

Appendix 2. Continued...

	Authors and year	Reason for exclusion
116.	Piatek et al. 2013	2
117.	Pilgram et al. 2002	5
118.	Pourjavad et al. 2012	2
119.	Priebe et al. 2017	3
120.	Preda et al. 2022	2
121.	Preda et al. 2022b	6
122.	Reinhardt et al. 1999	2
123.	Renvert et al. 2011	2
124.	Rieuwpassa et al. 2019	4
125.	Ronderos et al. 2000	7
126.	Sawy et al. 2010	8
127.	Shen et al. 2004	2
128.	Shrout et al. 2000	8
129.	Shu-Nyu Tang et al. 2022	9
130.	Silveira et al. 2016	3
131.	Singh et al. 2011	5
132.	Singh et al. 2012	8
133.	Singh et al. 2014	7
134.	Sire et al. 2021	8
135.	Slaidina et al. 2011	8
136.	Sperr et al. 2018	10
137.	Stagraczynski et al. 2015	7
138.	Streckfus et al. 1997	7
139.	Sultan & Rao 2011	5
140.	Suresh et al. 2010	2
141.	Svedha et al. 2017	2
142.	Taguchi et al. 1995	5
143.	Taguchi et al. 1995b	4
144.	Taguchi et al. 1999	7
145.	Taguchi et al. 2004	5
146.	Taguchi et al. 2007	3
147.	Taguchi et al. 2022	6
148.	Tak et al. 2014	5
149.	Takahashi et al. 2012	5
150.	Takaishi et al. 2005	7
151.	Takaishi et al. 2012	2
152.	Tanaka et al. 2020	7
153.	Tanriover et al. 2014	8
154.	Tezal et al. 2000	5
155.	Touger et al. 2005	6
156.	Ursărescu et al. 2012	7
157.	Ursărescu et al. 2016	8
158.	Vescini et al. 2005	3
159.	Vishwanath et al. 2011	3
160.	Vlasiadis et al. 2008	8
161.	Vlasiadis et al. 2007	5
162.	von Wovern et al. 1977	3
163.	von Wovern et al. 1992	3
164.	von Wovern et al. 1994	3
165.	von Wovern et al. 1996	3
166.	von Wovern et al. 2001	4
167.	Wakai et al. 2013	8
168.	Wang et la. 2013	3
169.	Weyant et al. 1999	5
170.	Yakar et al. 2021	1
171.	Yasar et al. 2006	8
172.	Ye et al. 2020	4

1: Without BMD data; 2: Without adjust to covariates; 3: Wrong exposition; 4: Wrong background; 5: Without comparison groups according to different BMD levels; 6: Wrong study design; 7: Wrong effect measure; 8: Wrong outcome measures; 9: Studies not written in Latin-Roman alphabet; 10: Self-reported data; 11: Overlap samples.

Appendix 2. Continued...

	Authors and year	Reason for exclusion
173.	Yoshihara et al. 2003	5
174.	Yoshihara et al. 2004	3
175.	Yoshihara et al. 2005	5
176.	Yu et al. 2021a	10
177.	Yu et al. 2021b	10
178.	Zhang et al. 2010	5
179.	Zhu et al. 2019	9
180.	Zhu et al. 2020	9

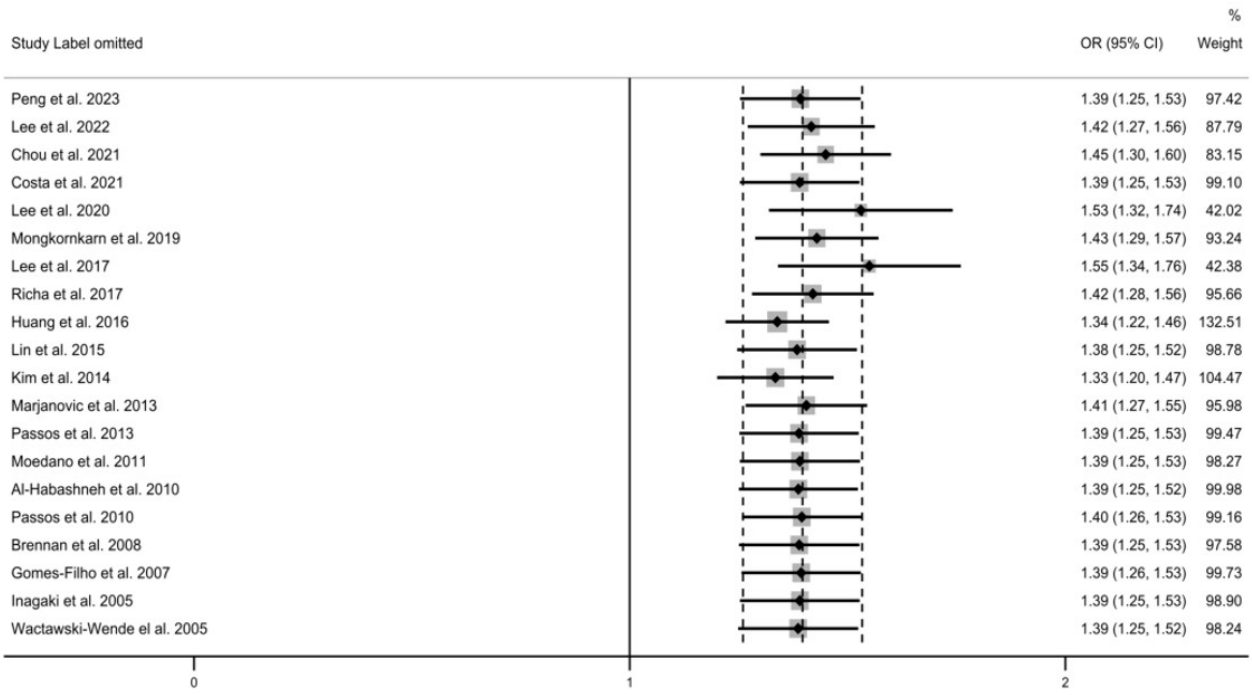
1: Without BMD data; 2: Without adjust to covariates; 3: Wrong exposition; 4: Wrong background; 5: Without comparison groups according to different BMD levels; 6: Wrong study design; 7: Wrong effect measure; 8: Wrong outcome measures; 9: Studies not written in Latin-Roman alphabet; 10: Self-reported data; 11: Overlap samples.

Appendix 3. Newcastle-Ottawa scale quality assessment of included studies

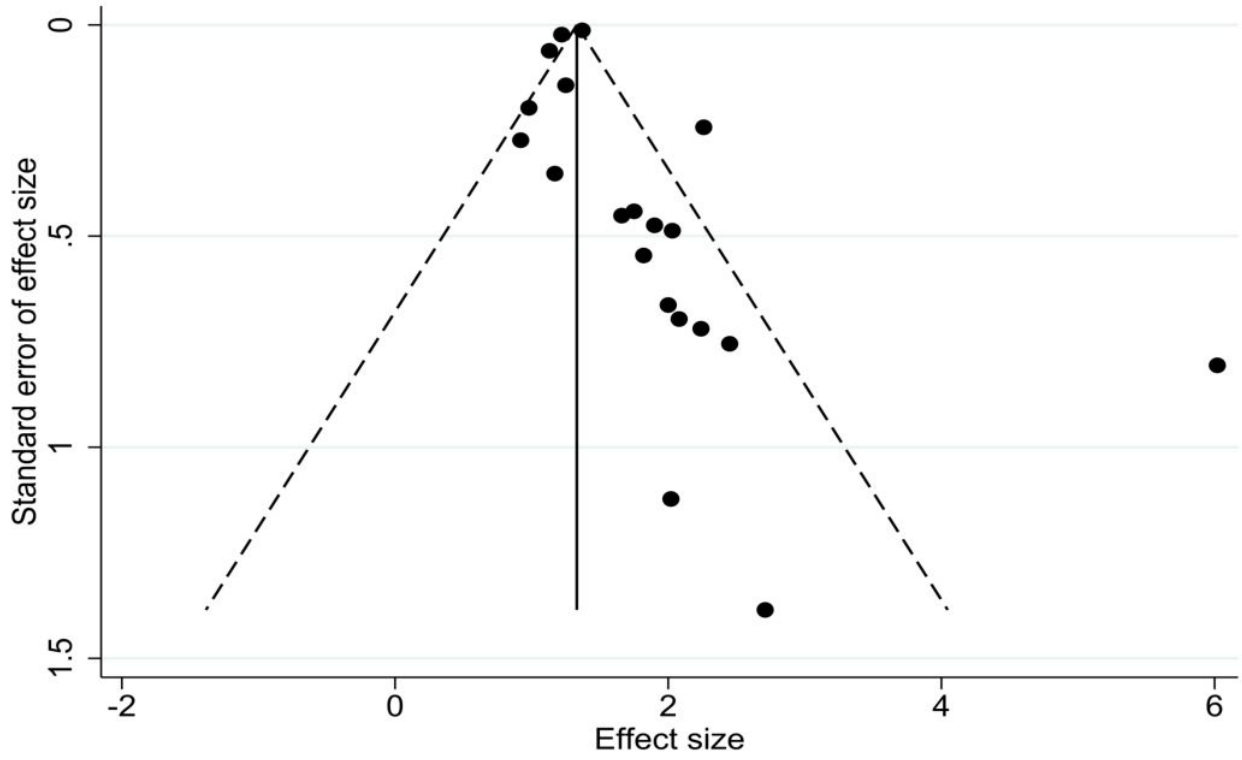
Cross-sectional Studies	Selection	Comparability	Outcome	Max 9*	Max 100%	Risk of bias
Peng et al. 2023	***	**	**	7/9	77.77%	Low
Lee et al. 2022	***	**	**	7/9	77.77%	Low
Zamani et al. 2022	*	*	**	4/9	44.44%	Moderate
Baldodia et al. 2021	**	*	***	6/9	66.66%	Moderate
Chou et al. 2021	***	**	**	7/9	77.77%	Low
Costa et al. 2021	***	**	***	8/9	88.88%	Low
Gil-Montoya et al. 2021	*	**	***	6/9	66.66%	Moderate
Lee et al. 2020	***	**	**	7/9	77.77%	Low
Mongkornkarn et al. 2019	****	**	***	9/9	100%	Low
Richa et al. 2017	**	*	**	5/9	55.55%	Moderate
Huang et al. 2016	***	**	**	7/9	77.77%	Low
Ji et al. 2016	***	**	**	7/9	77.77%	Low
Kim et al. 2015	**	*	**	5/9	55.55%	Moderate
Kim et al. 2014	***	**	**	7/9	77.77%	Low
Iwasaki et al. 2013	**	**	**	6/9	66.66%	Moderate
Marjanovic E. J. 2013	**	**	**	6/9	66.66%	Moderate
Papelassi et al. 2012	**	*	***	6/9	66.66%	Moderate
Moedano et al. 2011.	**	**	**	6/9	66.66%	Moderate
Al Habashneh et al. 2010	*	**	**	5/9	55.55%	Moderate
Shum et al. 2010	*	**	**	5/9	55.55%	Moderate
Brennan et al. 2008	**	**	**	6/9	66.66%	Moderate
Inagaki et al. 2005	**	**	***	7/9	77.77%	Low
Wactawski-Wende et al. 2005	**	**	**	6/9	66.66%	Moderate
Case-control Studies	Selection	Comparability	Outcome	Max 9*	Max 100%	Risk of bias
Passos et al. 2013	***	**	**	7/9	77.77%	Low
Passos et al. 2010	**	**	**	6/9	66.66%	Moderate
Gomes-Filho et al. 2007	***	**	**	7/9	77.77%	Low
Cohort Studies	Selection	Comparability	Outcome	Max 9 *	Max 100%	Risk of bias
Lee et al. 2020	***	**	**	7/9	33.33%	Low
Choi et al. 2017	****	**	***	9/9	100%	Low
Lee et al. 2017	***	**	***	8/9	88.88%	Low
Mau et al. 2017	***	**	***	8/9	88.88%	Low
Chang et al. 2014	****	**	***	9/9	100%	Low
Iwasaki et al. 2012	***	**	**	7/9	33.33%	Low

Classified according to the risk of bias: (a) high (0-3 stars); (b) medium (4-6 stars); or (c) low (≥7 stars). Asterisks represent the number of stars, * (1 star), ** (2 stars), *** (3 stars), **** (4 stars).

Appendix 4. Forest plot of OPR/OPN/low BMD and periodontitis in a random effects model meta-analysis.



Appendix 5. Funnel Plot with pseudo 95% confidence limits for exploring publication bias. Each point represents a separate study effect size and standard of error plotted.



Appendix 6. Trim and Fill Funnel Plot with pseudo 95% confidence limits for exploring publication bias. Each point represents a separate study effect size and standard of error plotted.