EXERCISE IMPROVES ALVEOLAR BONE LOSS AND THE INFLAMMATORY PROFILE OF PERIODONTAL DISEASE

O EXERCÍCIO MELHORA A PERDA DE OSSO ALVEOLAR E O PERFIL INFLAMATÓRIO DA DOENÇA PERIODONTAL

EL EJERCICIO MEJORA LA PÉRDIDA DE HUESO ALVEOLAR Y EL PERFIL INFLAMATORIO DE LA ENFERMEDAD PERIODONTAL

META-ANALYSIS
META-ANÁLISE
META-ANÁLISIS

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ABSTRACT

Periodontal disease (PD) is an inflammatory oral disease and alveolar bone loss is the most important sign of PD. However, the effects of exercise on inflammatory factors and alveolar bone loss in individuals with PD have been little studied. This meta-analysis assesses the effect of physical exercise on alveolar bone loss (ABL) and the inflammatory profile of PD in animal models. Relevant studies published through July 2020 in PubMed, Medline, Embase and Web of Science were searched after developing a PICOS statement. Quality assessment and risk of bias were analyzed according to the SYRCLE protocol. A total of 52 references were retrieved, 4 of which were considered eligible for inclusion. A total of thirty-four male Wistar rats from the included studies were evaluated for alveolar bone loss and assessed for inflammatory profile. The results indicated that physical exercise could reduce alveolar bone loss (95% CI -2.85 to -0.82, $p = 0.002$) and the pro-inflammatory tumor necrosis factor–α (TNF-α) in serum or gingival tissue (95% CI -0.45 to -0.24, $p < 0.00001$). Inversely, exercise increased anti-inflammatory interleukin–10 (IL-10) in serum or gingival tissue (95% CI 0.28 to 0.69, $p < 0.00001$). However, one study reported a negative result in the expression of TNF-α and IL-10. Current evidence indicates that physical exercise contributes to ameliorate PD by reducing alveolar bone loss and inflammation in animal PD models, which suggests that moderate exercise can be implemented in clinical practice to maintain periodontal health. ***Level of Evidence I; Systematic Review and Meta-analysis***

Keywords: Physical exercise; Periodontal disease; Alveolar bone loss.

RESUMO

A doença periodontal (DP) é uma doença inflamatória oral e a perda óssea alveolar é seu sinal mais importante. No entanto, os efeitos do exercício sobre os fatores inflamatórios e a perda óssea alveolar em indivíduos com DP têm sido pouco estudados. Esta metanálise avalia o efeito do exercício físico sobre a perda óssea alveolar (POA) e o perfil inflamatório da DP em modelos animais. Estudos relevantes publicados até julho de 2020 em PubMed, Medline, Embase e Web of Science foram pesquisados depois de desenvolver a pesquisa com o método PICO. A avaliação da qualidade e o risco de viés foram analisados de acordo com o protocolo SYRCLE. Um total de 52 referências foram recuperadas, quatro das quais foram consideradas elegíveis para inclusão. Um total de 34 ratos Wistar machos dos estudos incluídos foram avaliados quanto à perda de osso alveolar e avaliados quanto ao perfil inflamatório. Os resultados indicaram que o exercício físico pode reduzir a perda de osso alveolar (IC 95% -2,85 a -0,82, p = 0,002) e o fator de necrose tumoral pró-inflamatório-α (TNFα) no soro ou tecido gengival (IC 95% -0,45 a -0,24, p < 0,00001). Inversamente, o exercício aumentou a interleucina-10 anti-inflamatória (IL-10) no soro ou no tecido gengival (IC 95% 0,28 a 0,69, p < 0,00001). Contudo, um estudo relatou resultado negativo na expressão de TNFα e IL-10. As evidências atuais indicam que o exercício físico contribui para melhorar a DP, reduzindo a perda de osso alveolar e a inflamação em modelos animais de DP, o que sugere que o exercício moderado pode ser implementado na prática clínica para manter a saúde periodontal. ***Nível de Evidência I; Revisão Sistemática e Metanálise.***

Descritores: *Exercício físico; Doença periodontal; Perda do osso alveolar.*

RESUMEN

La enfermedad periodontal (EP) es una enfermedad inflamatoria oral y la pérdida de hueso alveolar es su signo más importante. Sin embargo, los efectos del ejercicio sobre los factores inflamatorios y la pérdida ósea alveolar en individuos con EP han sido poco estudiados. Este meta-análisis evalúa el efecto del ejercicio sobre la pérdida ósea alveolar (POA) y el perfil inflamatorio de la EP en modelos animales. Se llevaron a cabo estudios relevantes publicados hasta julio de 2020 en PubMed, Medline, Embase y Web of Science tras desarrollar la investigación con el método PICO. La evaluación de la calidad y el riesgo de sesgo se analizaron según el protocolo SYRCLE. Se recuperó un total de 52 referencias, cuatro de las cuales se consideraron elegibles para su inclusión. En un total de 34 ratas Wistar macho de los estudios incluidos se evaluó la pérdida de hueso alveolar y el perfil inflamatorio. Los resultados indicaron que el ejercicio puede reducir la pérdida de hueso alveolar (IC del 95%: -2,85 a -0,82; p = 0,002) y el factor de necrosis

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tumoral proinflamatorio-α (TNFα) en suero o tejido gingival (IC del 95%: -0,45 a -0,24; p < 0,00001). Por el contrario, el ejercicio aumentó la interleucina-10 (IL-10) antiinflamatoria en el suero o en el tejido gingival (IC del 95%: 0,28 a 0,69; p < 0,00001). Sin embargo, un estudio informó de un resultado negativo en la expresión de TNFα e IL-10. Las pruebas actuales indican que el ejercicio contribuye a mejorar la EP al reducir la pérdida de hueso alveolar y la inflamación en modelos animales de EP, lo que sugiere que se puede implementar el ejercicio moderado en la práctica clínica para mantener la salud periodontal. ***Nivel de Evidencia I; Revisión Sistemática y Meta-análisis.***

Descriptores: *Ejercicio físico; Enfermedades periodontales; Pérdida de hueso alveolar.*

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INTRODUCTION

Periodontal disease (PD) is a chronic destructive inflammatory diseases that mainly affects the supporting structures of the teeth.[1] PD is one of the ten most prevalent chronic diseases, and it is the second most prevalent oral disease affecting the global population.[2,3] The symptoms and signs of PD are halitosis, swelling, gingiva bleeding, gingival recession, tooth movement, periodontal ligament destruction, alveolar bone resorption, and tooth loss ultimately.[4] PD has multifactorial etiology with a marked inflammatory gum response and eventually alveolar bone resorption.[5] In addition, PD is considered to increase several pro-inflammatory cytokines in blood,[6] which makes PD a risk factor for several chronic and systemic inflammation diseases,[7,8] and there is a possible reciprocal mechanism among them. Thus, professional and personal care may improve and adjuvant therapies to PD.

Regular physical activity plays an important role in the control of multiple diseases, particularly in several metabolic diseases, such as obesity, diabetes and nonalcoholic fatty liver disease.[9-13] The interaction between physical exercise and metabolic diseases is not clearly understood at present. Physical exercise may interfere with the several stages of the inflammatory process. It could speed up repair processes in inflammation[14] or change inflammatory markers.[15]

Additionally, regular physically active individuals are less susceptible to develop PD compared to sedentary ones.[16-19] Physical exercise protects the periodontal tissue since it declines an excessive inflammatory response.[20] However, the effects of physical exercise on inflammatory profile and alveolar bone loss in individuals with PD have been poorly studied. Herein, a systematic review with meta-analysis was performed so as to answer this question.

METHODS

Protocol and study design

We searched the relevant studies published in PubMed, Medline, Embase, and Web of Science until 28 July 2020. A systematic literature search strategy was employed using (PICOS) the participants, intervention, comparison, outcome, and study design principle. Searching and data extraction were conducted by following PRISMA guidelines. We used combined key phrases and Medical Subject Heading (MeSH) terms as follows: "exercise" or "physical activity" and "periodontitis" or "periodontal disease" or "gingivitis." Relevant articles were further cross-checked to search for articles that were cited in the relevant journals and references to be considered eligible studies.

Selection of studies and data extraction

A bibliographic reference manager (EndNote X8) was used to save retrieved citations in all databases and remove duplicate results. After screening the titles and abstracts, the studies that did not meet our eligibility criteria were excluded. The remaining studies were evaluated by reading their full-texts and making a final decision. All differences between the reviewer viewpoints were resolved through discussions or consultation with a third reviewer.

The data were extracted from each study following the predesigned guideline on unified standardization by two independent reviewers. The following data were extracted: first author's name, publication year, species of animals, animal models of periodontal disease, number of animals, intervention protocols (aerobic exercise), and main outcomes (alveolar bone loss and expression of TNF-α and IL-10).

Risk of bias assessment

The methodological quality of the included studies was evaluated by two independent authors (LY and YY). The authors used SYRCLE's tool to check for random sequence generation, blinding, incomplete outcome data, selective reporting, and other biases. The evaluation results were categorized into high-risk, low-risk, and unclear grades.[21]

Quality assessment analysis

We designed a 10-item rating system to assess the methodological quality of the included animal experimental studies based on the recommendations published in 2014.[21] Ten aspects of each study were evaluated as follows: (1) randomization of animal grouping, (2) baseline characteristics, (3) random housing, (4) blind trial of caregivers and researchers, (5) random outcome assessment, (6) blind outcome of assessors, (7) incomplete outcome data, (8) assessment of at least 2 outcomes (alveolar bone loss and expression of TNF-α and IL-10), (9) types of exercise (aerobic exercise), and (10) animal species. The points were granted when in the study report these items were mentioned, and the studies in three categories: category I (7 to 10 items), category II (4 to 6 items), and category III (0 to 3 items).

Statistical analysis

Briefly, outcome measures were calculated by standardized weighted mean difference (SMD). All analyses were carried out with Revman Manager 5.3.5. Lastly, we set a significance level of *P* less than 0.05 as a statistical significance.

RESULTS

Study selection

A total of 52 studies were identified in accordance with our search strategy. Among the 52 studies, 14 duplicates were removed. After reading titles and abstracts, 23 out of 38 references were excluded based on the eligibility criteria. Thus, 15 references were selected for full-text appraisal. Among these full-text references, one reference was a conference article,[22] two articles were excluded due to the lack of the main outcomes,[23,24] six articles were excluded because the experimental animals were not rat or mouse,[25-30] two studies did not included since the exercise was not belong to aerobic exercise.[31,32] Finally, four articles were eligible for qualitative assessment. The selection process of identifying eligible studies is shown in Figure 1.

Study characteristics

The primary characteristics of the included studies are shown in Table 1. Among our included studies, all used animals were male Wistar rats and the periodontitis models were ligation. In the four reports, only one report that exercise was treadmill exercise,[33] the others were swimming. The exercise intervention lasted for four weeks or more in all reports. In the involved experiments, one reported the outcomes only had the result of alveolar bone loss,[34] and one only had the result of the expression of TNF-α and IL-10.[33] The others reported complete results. All animal models included in the experiments mentioned weight (100 -250 g).

Alveolar bone loss

Alveolar bone loss (ABL) is a main sign of PD, and may result in tooth loss. Out of four studies, three studies assessed the effects of exercise on ABL, as measured by the distance between the cementum-enamel junction (CEJ) and alveolar bone crest (ABC) using digital images (n ≥ 3). Animals submitted to exercise presented lower ABL than those from non-trained groups (95% CI -2.85 to -0.82, $p = 0.002$), which showed a positive effect of exercise on ABL (Figure 2). Although alveolar bone loss measured by imaging method in all experiments, the measuring unit demonstrated was different. Two experiments used millimeter,[35,36] while one experiment used pixel.[34] The results indicated that physical exercise reduces ABL during PD, which was contribute to prevent the development of PD.

Expression of TNF-α and IL-10

Tumor necrosis factor–α (TNF-α) is a pro-inflammatory cytokines and plays an important role in the development of PD.[37] Out of three studies, two studies showed that physical training reduces TNF-α levels in serum or gingival tissue than those without training[35,36] (Figure 3A). Unfortunately, one study showed that there was no significant difference between training and non-training groups in TNF-α serum level.[33] Unlike TNF-α, interleukin -10 (IL-10) exerts a strong anti-inflammatory role. Its increase is related to bone preservation, mainly by inhibiting osteoclastogenesis.[38] The results showed that exercise increases levels of IL-10 in serum or gingival tissue of PD groups in two studies[35,36] (Figure 3B). However, only one study showed that expression of IL-10 decreased in serum after exercise intervention, but the level of IL-10 maintained high levels in the exercise group.[33] Both results of TNF-α and IL-10 confirmed the positive effect of exercise on PD. These results indicated that exercise attenuates PD by increasing the expression of an anti-inflammatory mediator and reducing the expression of a pro-inflammatory mediators.

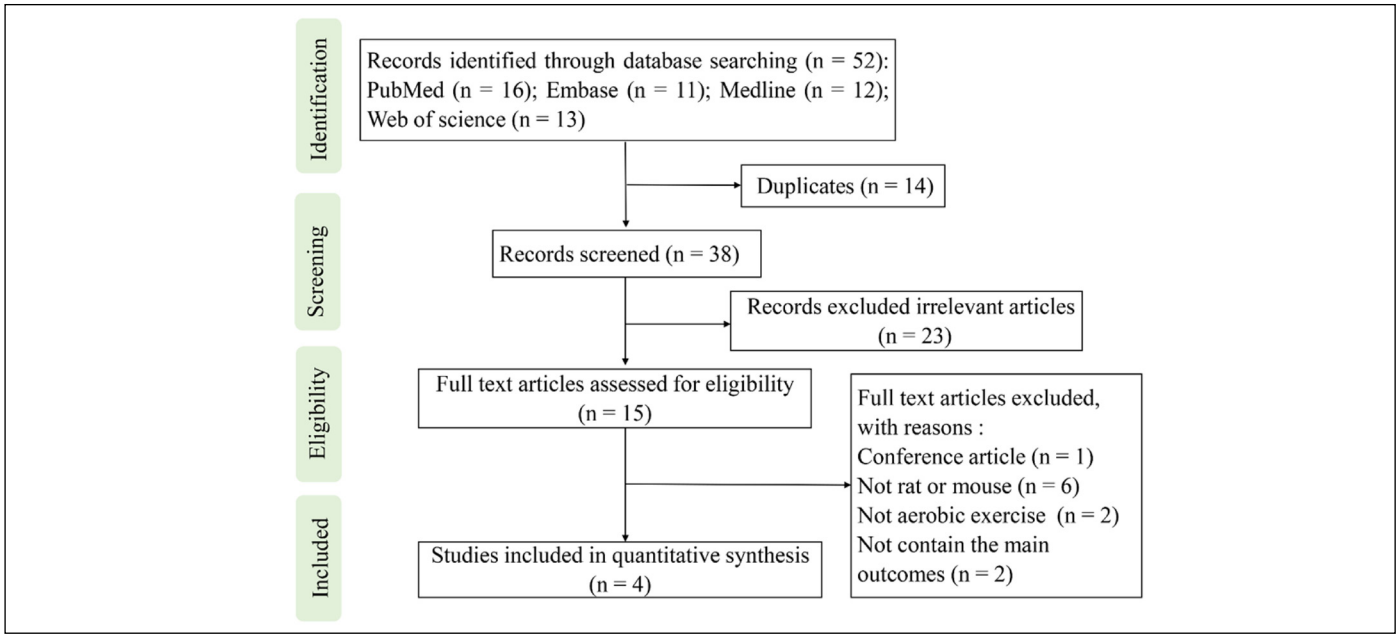

Figure 1. Selection process of eligible studies.

Table 1. Characteristics of the included animal studies.

Author, year of publication	Animal (treated/control), n	Periodontitis model	Method of administration	Outcome measures	Quality category (score)
Andrade et al.[35]	Male Wistar rats (6/6)	Ligature placed around each first mandibular molars	Swimming without a load until each animal swam for 60 min (7 days). Swimming with 5% of body weight load 60 min/d for 8 weeks (5 days a week).	Alveolar bone loss, expression of TNF-α and IL-10 in gingival tissue.	II (6)
Andrade et al.[36]	Male Wistar rats (5/5)	Ligature placed around each first molars.	Swimming without a load until each animal swam for 60 min (7 days). Swimming with 5% of body weight load 60 min/ day for 8 weeks (5 days a week).	Alveolar bone loss, expression of TNF-α and IL-10 in serum.	II (6)
Bortolini et al.[34]	Male Wistar rats (6/6)	Ligature placed around the first right molar.	Each animal swam 15 min/day for 3 days in the first week. And then each animal swam with a gradual increase in time until 60 min/day for 4 weeks (5 days a week).	Alveolar bone loss.	II (5)
de Souza et al.[33]	Male Wistar rats (6/6)	Ligature placed around the first molars.	The treadmill exercise with a gradual increase in speed until approximately 70% of the speed capability of the animal. Exercise lasted for 8 weeks (5 days a week).	Expression of TNF-α and IL-10 in serum.	I (7)

Category I: 7 to 10 items, category II: 4 to 6 items, category III: 0 to 3 items.

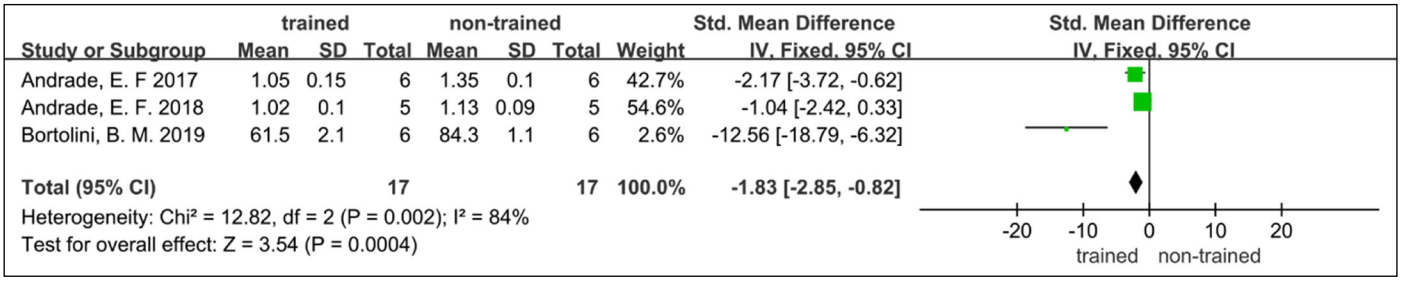

Figure 2. Forest plot for changes in alveolar bone loss.

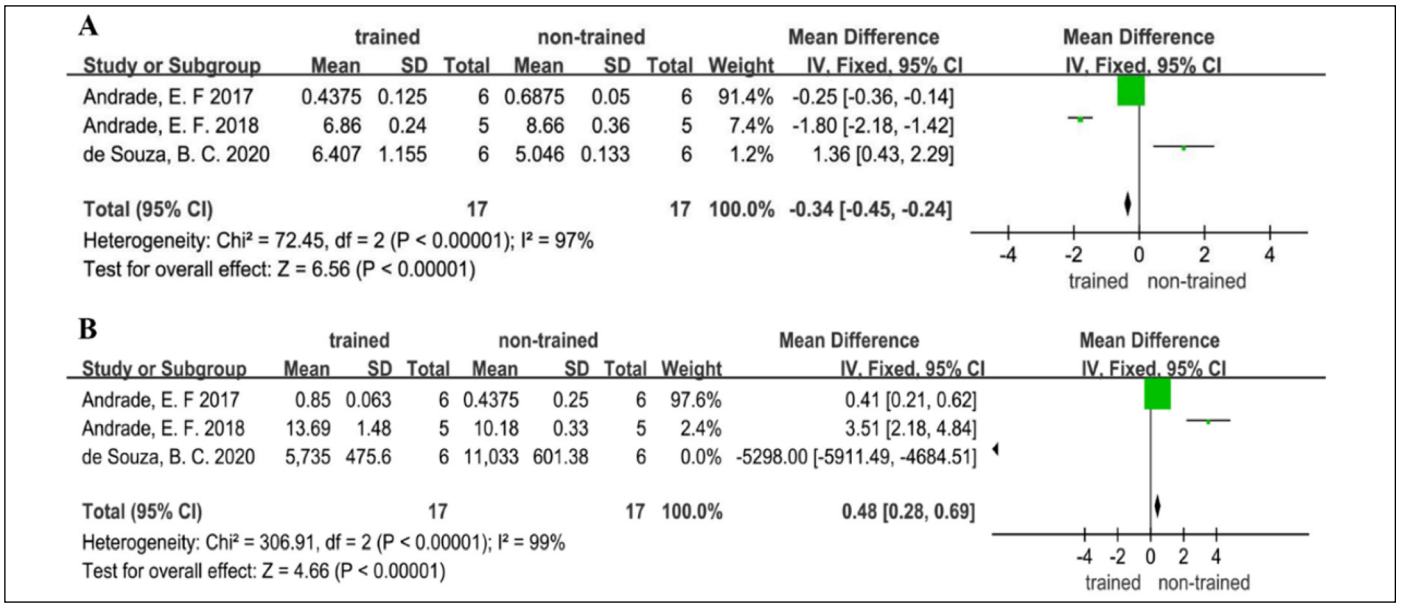

Figure 3. Forest plot for changes in expression of (A) TNF-α and (B) IL-10.

Risk of bias

All included studies were assessed according to related assessment criteria and the evaluation results are shown in Table 2. All the studies clearly stated the baseline characteristics, random housing, aerobic exercise and experimental animal species. Only one study reported incomplete outcomes data and the method of randomization of animal grouping.[33] Among the included studies, three experiments did not employ assessor blinding.[33-35] None of the studies were clearly stated feeders or experimenter blinding. However, all included studies were classified as having a low risk of bias according to the assessment criteria and quality category (Table 1).[21,39]

Table 2. SYRCLE's tool for assessing risk of bias.

Type of bias	Description of domain	Results of assessment
Selection bias	Randomization of animal grouping	Andrade, 2017 (U); Andrade, 2018 (U); Bortolini, 2019 (U); de Souza, 2020 (Y)
Selection bias	Relevant baseline characteristics in the intervention and control groups (such as sex, weight, age, healthy or not)	Andrade, 2017 (Y); Andrade, 2018 (Y); Bortolini, 2019 (Y); de Souza, 2020 (Y)
Performance bias	Random housing	Andrade, 2017 (Y); Andrade, 2018 (Y); Bortolini, 2019 (Y); de Souza, 2020 (Y)
Performance bias	Blinding (feeders or experimenters)	Andrade, 2017 (U); Andrade, 2018 (U); Bortolini, 2019 (U); de Souza, 2020 (U)
Detection bias	Random outcome assessment	Andrade, 2017 (Y); Andrade, 2018 (U); Bortolini, 2019 (U); de Souza, 2020 (U)
Detection bias	Blinding (assessors).	Andrade, 2017 (U); Andrade, 2018 (Y); Bortolini, 2019 (U); de Souza, 2020 (U)
Attrition bias	incomplete outcome data	Andrade, 2017 (U); Andrade, 2018 (U); Bortolini, 2019 (U); de Souza, 2020 (Y)
Reporting bias	Selective outcome reporting (alveolar bone loss, expression of TNF-α and IL-10)	Andrade, 2017 (Y); Andrade, 2018 (Y); Bortolini, 2019 (Y); de Souza, 2020 (Y)
other	Exercise types (aerobic exercise) and time	Andrade, 2017 (Y); Andrade, 2018 (Y); Bortolini, 2019 (Y); de Souza, 2020 (Y)
other	Species (rats and mice)	Andrade, 2017 (Y); Andrade, 2018 (Y); Bortolini, 2019 (Y); de Souza, 2020 (Y)

Yes (Y) indicates low risk of bias, no (N) indicates high risk of bias, and unclear (U) indicates an unclear risk of bias.

DISCUSSION

This meta-analysis is the first study to systematically assess the effect of physical exercise on alveolar bone loss and inflammatory profile in animal models of PD. The results showed that physical exercise reduced ABL in PD. Furthermore, the meta-analysis revealed that exercise was an effective interventions in the reduction of pro-inflammatory TNF-α and increase anti-inflammatory IL-10. These findings indicated that exercise is an appropriate prevention and therpeutic modality for improving PD.

We found meaningful reductions from exercise intervention to the non- intervention of -1.83 in ABL in the trained and non-trained groups. As we known, if ABL decrease, PD will improve. Therefore, exercise may be an effective method to improve periodontitis in this respect. The rise of pro-inflammatory mediators in individuals with periodontitis is one aspect that contributes to increase ABL.[40] Our studies indicated that exercise led to a small but significant reduction in pro-inflammatory TNF-α level serum or gingival tissue, which may

have a positive effect on lessening the ABL and preventing PD. As well as TNF-α, the levels of other pro-inflammatory biomarkers such as IL-6 and IL-1β also decreased after exercise training.[41] Regretfully, only one including study presented the changes of IL-6 and IL-1β intervened by exercise, respectively.[33,35] Thus, this data was absent in our studies. In addition, one article's findings were inconsistent with others, which reported that there was no significant difference between trained and non-trained groups in TNF-α level of serum.[33] It may indicate that TNF-α contributes to the regeneration process after tibialis anterior and gastrocnemius injury. But the inflammatory cells such as lymphocytes, and neutrophils monocytes and eosinophils changed in the tibialis anterior and gastrocnemius.

As mentioned above, the increase of anti-inflammatory contributes to bone preservation. However, IL-10 is a cytokine produced by a several cells and presents low levels in patients with PD.[42] In our findings, there was a significant increase of IL-10 in serum or gingival tissue of trained groups. These results were consistent with the results of previous studies, which showed that exercise can cause an increase of anti-inflammatory IL-10.[43] These results indicated that the increase of IL-10 and the reduction of pro-inflammatory TNF-α cooperated to improve PD. However, heterogeneity of ABL and inflammatory cytokines among the included studies was large, which may be related to the different measuring unit used. It is a problem of experiment measure in different area, which implied that it is essential to use uniform and standard measuring unit globally.

There were methodological problem (eg. randomization, assessor blinding, and feeders or experimenters blinding) in our analysis, which is known to affect the risk of bias in animal studies.[21] Nevertheless, the quality score ranged from 5 to 7 (according to the 10-item quality scale) in the meta-analysis. More good-quality studies should be conducted in the future. Recruitment of different animal specises including large animals and application of different types of exercise regimes are important for translational results.

CONCLUSION

This meta-analysis supports the positive effects of physical exercise on ABL and inflammatory profile in animal models of PD. These findings indicate that physical exercise is contribute to improve PD via ameliorating alveolar bone loss and inflammatory profile, and moderate exercise can be implemented in clinical practice to maintain periodontal health.

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