Abstract: The purpose of this study was to investigate the effects of vitamin D in rat models of chronic obstructive pulmonary disease (COPD) and periodontitis. Animals with both periodontitis and COPD, or with periodontitis only, were established. Once the animal model was established, experimental groups received intraperitoneal injections of 25-hydroxyvitamin D3 (25-OHD3) for 8 weeks, while control groups received refined peanut oil. After sacrifice, inflammatory status was examined in terms of the serum levels of receptor activator of the nuclear factor κB ligand (RANKL), tumor necrosis factor alpha (TNF-α) and interleukins (IL-1 and IL-10), as well as alveolar bone loss, forced expiratory volume (0.20) (FEV0.20), and the ratio of FEV0.2 to forced vital capacity. The results showed that 25-OHD3 treatment significantly alleviated inflammation by decreasing the serum levels of RANKL, TNF-α and IL-1 and increasing that of IL-10, while reducing alveolar bone loss and slightly improving lung function. These findings suggest that vitamin D supplementation could be a new clinical approach for the treatment of COPD and periodontitis.

Keywords: chronic obstructive pulmonary disease; periodontitis; vitamin D.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung condition characterized by progressive, irreversible airway obstruction. It is predicted to become the third leading cause of death worldwide by 2020 (1). Mostly due to the high prevalence of cigarette smoking in China, the incidence rate of COPD in seven Chinese provinces is reported to be 8.2%, associated with a significant corresponding increase in per-patient healthcare costs (2). In recent years it has been recognized that periodontitis is linked to the severity of COPD through microbial colonization of the respiratory system by dental plaque or airway inflammation caused by periodontal pathogens (3). Oral pathogens may be related to elevated circulating levels of cytokines and systemic inflammation, which has been implicated in the pathogenesis of COPD (4).

Previous evidence has suggested that vitamin D could reduce the risk of many chronic diseases such as cancer, myopathy, autoimmune disease, diabetes and metabolic...
syndrome, infections, and cardiovascular disease (5). Vitamin D has also received considerable attention as a modulator of immune function and inflammation (6). Vitamin D not only functions as a hormone for bone maintenance but also may be a potential therapeutic target for many non-skeletal chronic diseases including COPD (7,8). Vitamin D can be produced in the skin by exposure to sunlight or obtained from dietary components (fatty fish, fish liver oils, and dairy products) (9). Vitamin D deficiency appears to be a risk factor for COPD (10,11). The relationship between periodontitis and vitamin D has also been reported recently (12-14). These findings suggest that the anti-inflammatory and immune-modulating properties of vitamin D may be crucial for alleviating periodontitis and reducing the severity of COPD (8,12); by reducing periodontal inflammation, it should be possible to prevent the progressive deterioration of pulmonary function.

In the present study, therefore, the animal models of COPD with periodontitis were established to investigate the impact of intraperitoneal administration of vitamin D on inflammation status as well as periodontal and lung function parameters. The present study provides some insight into a potential treatment for periodontitis and COPD and its underlying mechanisms.

**Materials and Methods**

**Animals**

Fifty 4-week-old male SD rats were obtained from Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). The animal treatment protocol was reviewed and approved by the institutional committee for animal use and care in the Medical Research Center affiliated to Beijing Chao-Yang Hospital (2013). Animals were housed under conventional conditions with free access to water and food. Five groups were planned: a normal group (N), a periodontitis group (P), a COPD and periodontitis group (CP), a periodontitis with 25-OHD3 treatment group (PV), and a COPD and periodontitis with 25-OHD3 treatment group (CPV). There were 10 rats in each group. All animals were sacrificed by the age of 21 weeks. Their lungs were then excised and fixed for hematoxylin and eosin (H&E) staining.

**Experimental COPD induction**

COPD induction was started when the animals were 5 weeks old. The rats were placed in smoke chambers and passively exposed to cigarette smoke using snout-only exposure units. Zhongnanhai cigarettes (14 mg of tar, 1.2 mg of nicotine, and 14 mg of nitric oxide per cigarette) were placed in the fuming device and ignited one by one. For each cigarette, 30 mL of smoke was taken each time (totally 20-25 times) and mixed with 50% air at a flow rate of 0.90 L/min (20-25 times). The rats were exposed to cigarette smoke for 60 min each time and twice a day for a total of 8 weeks (15). The evaluation criteria used to determine whether establishment of the COPD rat model had been successful were based on observations of H&E-stained lung tissue and lung function (16).

**Induction of experimental periodontitis**

*Porphyromonas gingivalis* strain ATCC 33277 was purchased from the Dental Research Institute of Beijing Stomatology Hospital (Beijing, China) and grown anaerobically in blood-agar (Oxoid, Oxoid Ltd., Hampshire, UK) with hemin/ menadione (Sigma-Aldrich, Sigma-Aldrich Co., St. Louis, MO, USA). At 12 weeks of age, the rats in the P, CP, PV, and CPV groups were intraperitoneally injected with anesthetic and inoculated with *P. gingivalis* into the subgingiva of the first maxillary molars as follows: 10^9 colony-forming units of live bacteria were dispersed in 100 µL of phosphate-buffered saline (PBS) containing 2% carboxymethyl cellulose, and orally inoculated three times every other day within 5 days. Rats in the normal control group received the same volume of PBS alone (100 µL, with 2% carboxymethyl cellulose).

**Intraperitoneal treatment with 25-OHD3**

Rats in the PV and CPV groups received intraperitoneal injections of 25-OHD3 (Sigma-Aldrich) at a dose of 5 µg/kg at 2-day intervals from 13 weeks of age, and received the last injection 1 day before sacrifice. The 25-OHD3 was dissolved in refined peanut oil (Sigma-Aldrich). Rats in the control groups (N, P, and CP) received intraperitoneal injection of refined peanut oil alone.

**Measurement of lung function**

Lung function measurement was performed using a whole-body flow plethysmography system calibrated by measuring basal ventilatory parameters such as airway pressure and pulmonary volume. After calibration, the rats were weighed and anesthetized by intraperitoneal injection of 4% pentobarbital sodium. An inverted T-shaped incision was made in the third and fourth tracheal rings followed by intubation. The rats were then placed in the plethysmograph and the endotracheal cannula was connected to the plethysmograph and ventilator by a three-way pipe. The plethysmograph was then closed to prevent leakage. The respiratory frequency was 60 times per minute and the respiratory ratio is 2:1. Normal respiration was recorded for a while to establish
the forced vital capacity (FVC) using a controller set at a tidal volume of 1 mL (5 mL/kg) and FVC 4-6 times the tidal volume. Forced inhalation and expiration were achieved using the input FVC and a negative pressure system (-25 cmH₂O), respectively. Recordings were made as one lung function measurement with a 20-s interval of normal respiration between next measurement. Results were recorded at least 5 times per rat and analyzed with AniRes2005 software. The indicators of pulmonary function included the value of FEV0.2 (forced expiratory volume in 0.20 s) and the percentage of forced vital capacity. The ratio of FEV0.2/FVC represents the degree of bronchoconstriction.

Serum measurements
At sacrifice, blood was collected from the abdominal aorta, and serum was separated for determination of RANKL, TNF-α, IL-1, and IL-10 levels using the corresponding ELISA kits (BlueGene, Shanghai, China). Experiments were conducted in accordance with the manufacturer’s instructions.

Assessment of alveolar bone loss
After sacrifice, the maxillae were dissected from their surrounding soft tissues. Alveolar bone loss for the first molars was monitored using a stereomicroscope with an attached digital camera (Olympus, Tokyo, Japan). The degree of bone loss was defined by measuring the area bordered by the cementum-enamel junction, the alveolar bone crest, and the mesial and distal line angles on the lingual side of the maxillary first molar. The measurements were performed on 7-fold-magnified pictures of bones and repeated three times. The data from both maxillae were averaged to represent the bone loss per animal.

Statistical analysis
Data were analyzed using the SPSS statistical package (Version18.0; SPSS Inc., Chicago, IL, USA) and shown as mean ± SEM. For multiple group comparisons, the significance of differences was analyzed using one-way analysis of variance (ANOVA) followed by SNK-q test. Differences were considered to be significant at \( P < 0.05 \).

Results
25-OHD3 treatment significantly improves the periodontal index in model rats with COPD and periodontitis
The COPD and periodontitis models were established by cigarette smoke exposure and \( P. gingivalis \) infection alone or in combination. In the present study, periodontal bone loss was successfully induced by repeated subgingival inoculation of live \( P. gingivalis \). The average bone loss induced in the P group and CP group was 388 ± 17 μm and 411 ± 13 μm, respectively. At 21 weeks of age, all the animals were sacrificed for further study (Fig. 1A). The severity of periodontitis in terms of alveolar bone loss was examined, as shown in Fig. 1B. Treatment with 25-OHD3 obviously decreased the degree of alveolar
bone loss in the PV group relative to the P group, and in the CPV group relative to the CP group (Fig. 1B).

**Histological assessment of lung tissues after 25-OHD3 treatment**

In order to investigate the effects of 25-OHD3, lung tissues were harvested for H&E staining. The normal group (Fig. 2A) showed a normal lung architecture whereas the periodontitis (P) group (Fig. 2B) and COPD with periodontitis (CP) group (Fig. 2C) showed bronchial narrowing, thickening of the airway epithelium, and infiltration of inflammatory cells (black frame). After 25-OHD3 treatment, the infiltration of inflammatory cells was reduced in the PV and CPV groups (bars: 100 µm).

**Effect of 25-OHD3 treatment on lung function**

The effects of 25-OHD3 treatment on lung function using resistance inspiration (RI) (Fig. 3A), resistance expiration (RE) (Fig. 3B), forced expiratory volume in 0.2 s (FEV0.2) (Fig. 3C) and the ratio of FEV0.2 to forced vital capital (Fig. 3D) were evaluated in the five groups.

The values of FEV0.2 and FEV0.2/FVC in the P and CP groups were significantly lower than in the N group. Both values in the CP group were significantly lower than in the P group. After intraperitoneal treatment with 25-OHD3, the values of FEV0.2 and FEV0.2/FVC in the CPV group were significantly higher than in the CP group, which indicated improved pulmonary function (**P < 0.01**). Data are expressed as mean ± SD.

**Effect of 25-OHD3 treatment on serum cytokine levels**

To investigate the effect of vitamin D on systemic inflammation in periodontitis and COPD, the levels of cytokines in serum, including the pro-inflammatory cytokines receptor activator of the nuclear factor κB ligand (RANKL) (Fig. 4A), tumor necrosis factor (TNF-α) (Fig. 4B) and interleukin (IL-1) (Fig. 4C), and the anti-inflammatory cytokine IL-10 (Fig. 4D) were measured. It is found that the serum levels of RANKL, TNF-α, and IL-1 were significantly higher in the P and CP group than in the N group, and were significantly reduced by 25-OHD3 treatment when compared with the PV and CPV groups. On the other hand, the serum level of the
anti-inflammatory cytokine IL-10 was significantly reduced in the P and CP group relative to the N group, and was significantly increased by 25-OHD3 treatment when compared with the PV and CPV groups. Notably, in comparison with the P group, the serum levels of RANKL, TNF-α, and IL-1 were significantly higher, and that of IL-10 was significantly lower in the CP group, suggesting that periodontitis might exacerbate inflammation in COPD. Consistent with the findings obtained in H&E-stained lungs, 25-OHD3 treatment appeared to have ameliorated the systemic inflammatory response in both periodontitis and COPD with periodontitis.

Discussion
In the present study, it is shown that 25-OHD3 significantly reduced bone loss in rats with periodontitis alone, or in those with COPD and periodontitis. 25-OHD3 treatment significantly alleviated inflammation by decreasing the serum levels of RANKL, TNF-α, and IL-1 and increasing that of IL-10, while at the same time slightly improving lung function. These findings indicate that 25-OHD3 has beneficial effects on either periodontitis alone or COPD with periodontitis.

Previous studies have shown that *P. gingivalis* is associated with human periodontal disease, and experimental periodontitis can also be induced with this organism in animals. Rat models of *P. gingivalis*-induced periodontitis have been widely used in many studies (17). In the present study, periodontal bone loss was successfully induced in all rats by repeated subgingival inoculation of live *P. gingivalis*. Therefore, the periodontal model established in this study is valid. COPD is a lung disorder characterized by progressive airway obstruction. The present study established a COPD rat model assessed on the basis of two aspects: lung histomorphology and lung function (16). Histopathological changes provide a gold standard for the diagnosis of COPD. The parameters measured by plethysmography system gave us a reference standard, while the reduction of both Fev0.2 and Fev0.2/FVC suggested obstructive lesions. All rats in the CP and CPV groups developed COPD as defined by the standards described previously.

COPD is the fourth leading cause of death worldwide, and is associated with an increasing economic cost and social burden (18). Periodontitis is a common oral infectious disease that is associated with poor oral hygiene. It is characterized by inflammation of the periodontium induced by subgingival plaque bacteria such as anaerobic gram-negative rods (19), which can also be associated with COPD exacerbation (20). The prevalence of periodontitis increases together with COPD severity (21). Accumulating reports have confirmed the association between the two diseases (22,23). One possible explanation for this association is an amplified inflammatory state. Cigarette smoke initially induces lung epithelial cell injury and activation of toll-like receptors (TLRs), and subsequent production of chemokines and cytokines results in further inflammation and tissue injury (24,25). Similarly, periodontopathic bacteria activate TLRs and subsequent inflammation in the periodontium (26).

Vitamin D is a potent modulator of innate immunity, suggesting its roles in multiple immune-mediated disorders (27). Low serum levels of 25-OHD3 are reportedly associated with the risk of COPD and chronic periodontitis (28,29).

25-OHD3, the major circulating vitamin D metabolite, is converted to 1,25(OH)2D3, the physiologically active metabolite of vitamin D, by 1α-hydroxylase (CYP27B1) upon TLR activation (30). 1,25(OH)2D3 further binds to the vitamin D receptor (VDR) to mediate biologic effects through transcriptional regulation (31). In macrophages and monocytes, the 1,25(OH)2D3/VDR complex
promotes innate immunity by increasing chemotactic and phagocytic activity and production of the antimicrobial peptide cathelicidin (32). Vitamin D metabolites can also enhance interleukin-1 (IL-1) secretion through activation of inflammasomes (33). However, the present data provided further evidence for the therapeutic benefits of 25-OH3D on COPD and periodontitis through its anti-inflammatory activity. It is shown that 25-OH3D treatment significantly reduced the levels of the inflammatory cytokines tumor necrosis factor-alpha (TNF-α) and IL-1 and increased that of the anti-inflammatory cytokine IL-10. Previous research has demonstrated that the VDR is present in many cells, including pulmonary and gingival epithelial cells (34,35). Wang et al. used immunohistochemical staining technology and Western blotting to detect VDR expression in mouse maxilla and gingival tissues, separately. Their data clearly showed that such vitamin D treatment significantly increased VDR expression (36). Although the blood concentrations of vitamin D to assess its interventional effects were evaluated, the research protocol fully conformed to that in the previous study. The results of this study and others suggest cell type-dependent regulatory effects of vitamin D on inflammatory responses.

In this study, it is also shown that 25-OH3D significantly reduced bone loss in either periodontitis or COPD with periodontitis, suggesting the beneficial effects of 25-OH3D on both diseases. However, although a moderate improvement has been observed, the effect of 25-OH3D on lung function did not reach statistical significance. One possible reason might be that the present study only observed the changes within a 2-month period after 25-OH3D treatment. Further investigation will be needed to determine whether prolongation of the observation time will reveal more significant effects. Due to the complexity of the periodontal architecture, traditional scaling instruments sometimes cannot access every facet. Some patients have difficulty with mechanical treatment and prefer non- or low-invasive therapy. Therefore, although a further clinical study is needed, the present study suggest that increasing vitamin D levels through strategies such as food fortification or supplementation might be feasible for the treatment of periodontitis and COPD.

Through its calcemic effect, vitamin D is well known to mediate multiple biological functions, especially in bone biology (37). Vitamin D not only maintains calcium balance by facilitating calcium absorption in the intestine, but also stimulates mineralization of human osteoblasts to increase bone density (38). Therefore, vitamin D analogs are used for treatment of osteoporosis and reduce the risk of bone fracture (39,40). A link between osteoporosis and COPD has also been reported (41), and the present results showed that treatment with 25-OH3D significantly reduced alveolar bone loss in rat models of periodontitis or COPD with periodontitis. Since 1,25(OH)2D3 is a potent modulator of receptor activator of the nuclear factor κB ligand (RANKL) expression (42), as expected, the vitamin D treatment significantly reduced the expression of RANKL in either the periodontitis group or the COPD with periodontitis group. RANKL is a major osteoclastogenesis factor that might be up-regulated in TLR-activated neutrophils (43). Neutrophils have been shown to be important mediators in periodontitis (44,45). Consistent with the results for RANKL, the vitamin D treatment reduced the expression of TNF-α, which has been shown to be involved in periodontal alveolar bone loss (46). Both results might be partly attributable to the protection of pulmonary and periodontal tissues by 25-OH3D.

Taken together, the present study provides evidence for the therapeutic benefits and anti-inflammatory effects of 25-OH3D. Further clinical studies are needed to confirm the potential therapeutic role of vitamin D in this setting. It is suggested that increasing vitamin D levels through strategies such as food fortification or supplementation might be feasible for the treatment of patients with periodontitis and COPD.

Acknowledgments
This study was supported by grants from the National Natural Science Foundation of China (NSFC) (81000449) (81670989).

Conflict of interest
No conflict of interest has been reported by the authors or by any individual in control of the content of this article.

References
1. Kuebler KK, Buchsel PC, Balkstra CR (2008) Differentiating chronic obstructive pulmonary disease from asthma. J Am Acad Nurse Pract 20, 445-454.
2. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S et al. (2007) Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med 176, 753-760.
3. Wang Z, Zhou X, Zhang J, Zhang L, Song Y, Hu FB et al. (2009) Periodontal health, oral health behaviours, and chronic obstructive pulmonary disease. J Clin Periodontol 36, 750-755.
4. Terpenning MS (2001) The relationship between infections and chronic respiratory diseases: an overview. Ann Periodontol 6, 66-70.
5. Bouillon R, Bischoff-Ferrari H, Willett W (2008) Vitamin D
and health: perspectives from mice and man. J Bone Miner Res 23, 974-979.
6. Calton EK, Keane KN, Newsholme P, Soares MJ (2015) The impact of vitamin D levels on inflammatory status: a systematic review of immune cell studies. PLoS One 10, e0141770.
7. Janssens W, Lehouck A, Carremans C, Bouillon R, Mathieu C, Debeer M (2009) Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. Am J Respir Crit Care Med 179, 630-636.
8. Solidoro P, Bellocchia M, Facchini F (2016) The immunobiological and clinical role of vitamin D in obstructive lung diseases. Minerva Med 107, 12-19.
9. van Etten E, Mathieu C (2005) Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts. J Steroid Biochem Mol Biol 97, 93-101.
10. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357, 266-281.
11. Gilbert CR, Arum SM, Smith CM (2009) Vitamin D deficiency and chronic lung disease. Can Respir J 16, 75-80.
12. Goldstein MR, Mascitelli L, Pezzetta F (2009) Periodontitis, atherosclerotic cardiovascular disease and vitamin D. Am J Cardiol 104, 1164.
13. Jimenez M, Giovannucci E, Krall Kaye E, Joshipura KJ, Dietrich T (2014) Predicted vitamin D status and incidence of tooth loss and periodontitis. Public Health Nutr 17, 844-852.
14. Lee HJ, Je DI, Won SJ, Paik DI, Bae KH (2015) Association between vitamin D deficiency and periodontal status in current smokers. Community Dent Oral Epidemiol 43, 471-478.
15. Davis BB, ShenYH, Tancredi DJ, Flores V, Davis, RP, Pinkerton, KE (2012) Leukocytes are recruited through the bronchial circulation to the lung in a spontaneously hypertensive rat model of COPD. PLoS One 7, e33304.
16. Nie YC, Wu H, Li PB, Luo YL, Zhang CC, Shen JG et al. (2012) Characteristic comparison of three rat models induced by cigarette smoke or combined with LPS: to establish a suitable model for study of airway mucus hypersecretion in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 25, 349-356.
17. Han X, Lin X, Yu X, Lin J, Kawai T, LaRosa KB et al. (2013) Porphyromonas gingivalis infection-associated periodontal bone resorption is dependent on receptor activator of NF-kB ligand. Infect Immun 81, 1502-1509.
18. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A et al. (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187, 347-365.
19. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtet EE et al. (1994) Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol 65, 260-267.
20. Brook I, Frazier EH (2003) Immune response to Fusobacterium nucleatum and Prevotella intermedia in the spumum of patients with acute exacerbation of chronic bronchitis. Chest 124, 832-833.
21. Deo V, Bhongade ML, Ansari S, Chavan RS (2009) Periodontitis as a potential risk factor for chronic obstructive pulmonary disease: a retrospective study. Indian J Dent Res 20, 466-470.
22. Zhou X, Wang Z, Song Y, Zhang J, Wang C (2011) Periodontal health and quality of life in patients with chronic obstructive pulmonary disease. Respir Med 105, 67-73.
23. Si Y, Fan H, Song Y, Zhou X, Zhang J, Wang Z (2012) Association between periodontitis and chronic obstructive pulmonary disease in a Chinese population. J Periodontol 83, 1288-1296.
24. Cosio MG, Saetta M, Agusti A (2009) Immunologic aspects of chronic obstructive pulmonary disease. N Engl J Med 360, 2445-2454.
25. Tudor RM, Petracchi I (2012) Pathogenesis of chronic obstructive pulmonary disease. J Clin Invest 122, 2749-2755.
26. Song B, Zhang Y, Chen L, Zhou T, Huang W, Zhou X (2017) The role of toll-like receptors in periodontitis. Oral Dis 23, 168-180.
27. Baike F, van Etten E, Gyssemans C, Overbergh L, Mathieu C (2008) Vitamin D signaling in immune-mediated disorders: evolving insights and therapeutic opportunities. Mol Aspects Med 29, 376-387.
28. Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I et al. (2010) Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax 65, 215-220.
29. Zhou X, Han J, Song Y, Zhang J, Wang Z (2012) Serum levels of 25-hydroxyvitamin D, oral health and chronic obstructive pulmonary disease. J Clin Periodontol 39, 350-356.
30. Chun RF, Liu PT, Modlin RL, Adams JS, Hewison M (2014) Impact of vitamin D on immune function: lessons learned from genome-wide analysis. Front Physiol 5, 151.
31. Lin R (2016) Crosstalk between Vitamin D Metabolism, VDR Signalling, and Innate Immunity. Biomed Res Int 2016, 1375858.
32. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR et al. (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311, 1770-1773.
33. Tulk SE, Liao KC, Muruve DA, Li Y, Beck PL, MacDonald JA (2015) Vitamin D, metabolites enhance the NLRP3-dependent secretion of IL-1β from human THP-1 monocytes. J Cell Biochem 116, 711-720.
34. Rehan VK, Torday JS, Peleg S, Gennaro L, Vourou P, Padbury J et al. (2002) 1,25-dihydroxy-3-epi-vitamin D3, a natural metabolite of 1alpha,25-dihydroxy vitamin D3: production and biological activity studies in pulmonary alveolar type II cells. Mol Genet Metab 76, 46-56.
35. McMahon L, Schwartz K, Yilmaz O, Brown E, Ryan LK, Diamond G (2011) Vitamin D-mediated induction of innate immunity in gingival epithelial cells. Infect Immun 79, 2250-2256.
36. Wang Q, Li H, Xie H, Fu M, Guo B, Ding Y et al. (2013) 25-Hydroxyvitamin D3 attenuates experimental periodontitis.
through downregulation of TLR4 and JAK1/STAT3 signaling in diabetic mice. J Steroid Biochem Mol Biol 135, 43-50.
37. Wintermeyer E, Ihle C, Ehner S, Stöckle U, Ochs G, de Zwart P et al. (2016) Crucial role of vitamin D in the musculoskeletal system. Nutrients, doi: 10.3390/nu8060319
38. van de Peppel J, van Leeuwen JP (2014) Vitamin D and gene networks in human osteoblasts. Front Physiol 5, 137.
39. Hagino H (2015) Vitamin D3 analogs for the treatment of osteoporosis. Can J Physiol Pharmacol 93, 327-332.
40. Thomas T, Briot K (2016) Vitamin D, bone metabolism and fracture risk. Geriatr Psychol Neuropsychiatr Vieil 14, 122-126.
41. Okazaki R, Watanabe R, Inoue D (2016) Osteoporosis associated with chronic obstructive pulmonary disease. J Bone Metab 23, 111-120.
42. Feng X, Lv C, Wang F, Gan K, Zhang M, Tan W (2013) Modulatory effect of 1,25-dihydroxyvitamin D 3 on IL1β-induced RANKL, OPG, TNF α , and IL-6 expression in human rheumatoid synoviocyte MH7A. Clin Dev Immunol 2013, 160123.
43. Chakravarti A, Raquil MA, Tessier P, Poubelle PE (2009) Surface RANKL of Toll-like receptor 4-stimulated human neutrophils activates osteoclastic bone resorption. Blood 114, 1633-1644.
44. Hajishengallis G, Chavakis T, Hajishengallis E, Lambris JD (2015) Neutrophil homeostasis and inflammation: novel paradigms from studying periodontitis. J Leukoc Biol 98, 539-548.
45. Hienz SA, Paliwal S, Ivanovski S (2015) Mechanisms of bone resorption in periodontitis. J Immunol Res 2015, 615486.
46. Algare K, Haynes DR, Bartold PM, Crotti TN, Cantley MD (2016) The effects of tumour necrosis factor-α on bone cells involved in periodontal alveolar bone loss; osteoclasts, osteoblasts and osteocytes. J Periodontal Res 51, 549-566.