Chronic Diseases Journal

DOI: 10.22122/cdj.v13i3.850 Published by Vesnu Publications

The effect of vitamin D3 supplementation on chronic osteomyelitis

Fatemeh Dabaghzadeh[1], Fatemeh Mehrabi[2], Farhad Sarafzadeh[3], Tania Dehesh[4]

1 Department of Clinical Pharmacy, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran
2 Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
3 Tropical and Infectious Diseases Research Center, Kerman University of Medical Sciences, Kerman, Iran
4 Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran

Original Article

Abstract

BACKGROUND: Chronic osteomyelitis is a difficult-to-treat bone infection and has frequent relapses. Vitamin D seems to have systemic antimicrobial properties and increases therapeutic response when administered with appropriate antibiotics. The aim of the present study was to evaluate the effect of vitamin D_3 supplementation on chronic osteomyelitis.

METHODS: This randomized, blinded, placebo-controlled pilot trial was conducted in Afzalipour Hospital and Besat Clinic affiliated with Kerman University of Medical Sciences, Kerman, Iran, from June 2017 to January 2020. Thirty patients with lower-extremity chronic osteomyelitis were randomly assigned to receive oral vitamin D_3 pearls or a placebo. The participants were followed for 6 months. The levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and the prevalence of osteomyelitis symptoms were recorded at baseline and 1, 3, and 6 months later. SPSS software and statistical tests such as generalized estimating equation (GEE) and mixed model analysis of variance (ANOVA) were used to analyze the data.

RESULTS: ESR (P = 0.045), CRP (P = 0.049), and the prevalence of osteomyelitis symptoms significantly decreased in the vitamin D_3 group in comparison with the placebo one during the study.

CONCLUSION: High-dose and long-term vitamin D_3 supplementation as an adjunct therapy to antibiotics may improve the outcomes of patients with chronic osteomyelitis.

KEYWORDS: Anti-Infective Agents; Osteomyelitis; Blood Sedimentation; Cholecalciferol

Date of submission: 02 Mar. 2025, ***Date of acceptance:*** 09 May 2025

Citation: Dabaghzadeh F, Mehrabi F, Sarafzadeh F, Dehesh T. **The effect of vitamin D3 supplementation on chronic osteomyelitis.** Chron Dis J 2025; 13(3): 131-7.

Introduction

Chronic osteomyelitis is a difficult-to-treat bone infection and has frequent relapses.[1,2] The most common pathogens are *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS). Besides, the pathogens with a lower prevalence include streptococci, gram-negative pathogens (*enterobacteria, pseudomonads*), and anaerobic bacteria.[3] It is managed with surgical debridement and prolonged antibiotic therapy. In several studies, the remission rate was reported as 78.8%, 84%, and 90% at 1-year, 2-year, and 5-year follow-up, respectively.[4] Consequently, this infection has significant effects on patients' morbidity, self-confidence, and socioeconomic status.[5] Moreover, some issues should be considered when treating chronic osteomyelitis including the potential toxicity of systemic antibiotics, the difficulty in achieving adequate antibiotic concentrations at the infection site, the cost of antibiotic therapy

Corresponding Author:
Fatemeh Dabaghzadeh; Department of Clinical Pharmacy, Faculty of Pharmacy, Kerman University of Medical Sciences, Kerman, Iran
Email: dabaghzadeh@kmu.ac.ir

and relapse, and the patient's compliance. As a result, finding a complementary therapy that aids the improvement of the infection plays a crucial role.[1]

Vitamin D affects bone health, serum calcium, innate immunity, and inflammatory cascade.[6-8] Moreover, vitamin D has systemic antimicrobial properties and increases therapeutic response when administered with appropriate antibiotics. *In vitro* studies show that vitamin D_3 has an antibacterial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Escherichia coli* (*E. coli*), and other bacteria.[9] Additionally, various clinical trials investigated the effect of vitamin D supplementation on the treatment or prevention of infectious diseases such as respiratory tract infections, tuberculosis (TB), human immunodeficiency virus (HIV) infection, and sepsis. The results of these studies are promising.[10] Furthermore, the prevalence of vitamin D insufficiency and deficiency is high among worldwide human populations.[11] When vitamin D levels are low, infectious diseases are more likely. Vitamin D deficiency is also associated with an increased risk of infection severity and mortality. With due attention to the above, vitamin D may be considered a cost-effective adjunct therapy to antimicrobial agents in a variety of infections.[9,10]

Some studies reported the inverse relation between the level of vitamin D and the incidence of orthopedic infections. Zargaran et al. identified a relationship between the low levels of serum 25-hydroxyvitamin D (25-OHD) and increased orthopedic infection.[12] Traven et al. reported that normal vitamin D levels resulted in fewer orthopedic infections.[13] The majority of these studies were observational rather than interventional and based on them, it could only be suggested that prophylactic vitamin D supplementation may reduce orthopedic infections. However, randomized clinical trials (RCTs) are required to establish the protective effect of vitamin D supplementation against orthopedic infections.[14] Nevertheless, there is limited research on vitamin D role in the treatment of orthopedic infections.[6] Until now, no study has been performed to investigate the effect of vitamin D on the treatment of chronic osteomyelitis. Therefore, the purpose of the present study was to evaluate the effect of vitamin D_3 supplementation on chronic osteomyelitis.

Methods

This randomized, blinded, placebo-controlled pilot trial was conducted in Afzalipour Hospital and Besat Clinic affiliated with Kerman University of Medical Sciences, Kerman, Iran, from June 2017 to January 2020. This study with registry number 91000005 was approved by the Ethical Committee of Kerman University of Medical Sciences. The ethical approval code is IR.KMU.REC.1395.786. The clinical trial was also registered at the Iranian Registry of Clinical Trials (IRCT201609026026N4). All the participants signed an informed consent form before participating in the study.

All the patients in the age range of 18-50 years with lower-extremity chronic osteomyelitis were included. Among them, those who had the same causative organisms and received the same treatment were enrolled. As recommended by an experienced infectious diseases specialist collaborating with the researchers in the current study, the patients whose bone cultures showed polymicrobial infections were selected. The causative organisms were *Enterobacteriaceae*, *Staphylococcus* spp., and *Pseudomonas aeruginosa*. After the surgery, the patients were treated with intravenous (IV) vancomycin and meropenem for six weeks, and then they received oral levofloxacin and co-trimoxazole according to antibiogram results for 12 to 24 weeks (based on clinical response). The exclusion criteria were the patients with an

underlying disease, use of vitamin D supplements during the study, pregnancy, and lactation. Demographic characteristics including sex and age were also recorded for all the patients.

Pearls of vitamin D_3 (50000 IU) and the placebo were provided by Zahravi Pharmaceutical Company, Tehran, Iran. The eligible patients were randomly assigned in a 1:1 ratio by block randomization with a block size of four to receive oral vitamin D_3 pearls or the placebo. A person (not involved in the trial) generated the assignment schedule. The patients and physicians were blinded to the treatment assignment (a double-blind study). The patients received four pearls of vitamin D_3 or the placebo after the sugary and four ones 1 month later, and then two pearls monthly for 4 months.[15]

Follow-up visits occurred at 1, 3, and 6 months after the enrollment. The presence of clinical symptoms (pain, tenderness, swelling, drainage, redness, and abscess) was recorded at baseline and follow-up visits. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), plasma calcium (corrected serum calcium levels for plasma albumin concentration), and serum 25-OHD levels were measured at baseline and 1, 3, and 6 months later. Vitamin D insufficiency and vitamin D deficiency were defined as 25-OHD levels of 12 to 20 ng/ml and less than 12 ng/ml, respectively.[16] It should be mentioned that Fatemeh Mehrabi was responsible for recording all the patients' data.

Statistical analysis: The studies evaluating the effect of complementary therapy on chronic osteomyelitis were scarce, and chronic osteomyelitis has a low prevalence. In the current study, it was tried to select patients having the same conditions such as pathogens and treatment. The study also had prolonged and frequent follow-ups. Therefore, the sample size was considered as approximately 15 patients in each group in this pilot study.[17]

The SPSS software (version 21, IBM Corporation, Armonk, NY, USA) was used for the analysis of the statistical data. An independent samples t-test and chi-square test were employed to evaluate the differences in the demographic data. A generalized estimating equation (GEE) was applied to compare the binary data (clinical symptoms) over time between the vitamin D_3 and placebo groups. A mixed model analysis of variance (ANOVA) was used to compare changes over time in the lab data. A P-value less than 0.05 was considered statistically significant.

Results

Fifteen patients (9 men and 6 women) in the vitamin D_3 group and 15 (10 men and 5 women) in the placebo group completed the study. Figure 1 shows the flowchart of the study. The mean age of the participants was 24.50 ± 4.53 and 23.87 ± 4.09 years in the vitamin D_3 and placebo groups, respectively. There were not any significant differences regarding age, sex, and baseline 25-OHD level, CRP, and ESR between the two groups. Nineteen (63.33%) out of 30 patients had vitamin D insufficiency (10 in the vitamin D_3 and 9 in the placebo group) and no one had vitamin D deficiency. The levels of calcium were in the normal range for all the participants in all the follow-up visits. The calcium levels did not significantly change between the two groups during the study.

The time-group interaction and main effect of time were statistically significant for 25-OHD level, CRP, and ESR although the time-group interaction was borderline significant for CRP and ESR. The effect of the group reached statistical significance only for the 25-OHD level. Table 1 demonstrates changes in ESR, CRP, and 25-OHD levels in the vitamin D_3 and placebo groups throughout the study.

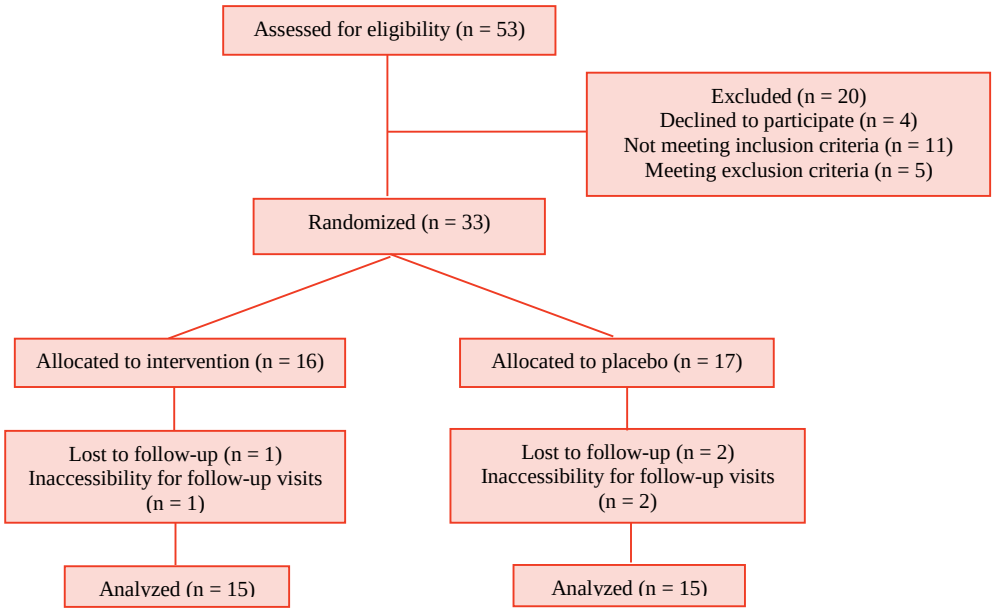

Figure 1. Flowchart of the participants in this pilot study

The prevalence of osteomyelitis symptoms significantly decreased after 1, 3, and 6 months following the treatment initiation in the vitamin D_3 in comparison with the placebo group (Table 2). Additionally, no adverse effect was reported during the study.

Discussion

The present study was designed to evaluate the effect of vitamin D_3 supplementation as an adjunct treatment to antibiotics on chronic osteomyelitis. The results of this study suggest that high-dose and long-term vitamin D_3 supplementation as an adjunct therapy to antibiotics could decrease CRP and ESR and also improve the clinical symptoms of chronic osteomyelitis. Vitamin D plays multiple important roles in the musculoskeletal system including the regulation of bone health, fracture healing, and soft tissue healing.

Table 1. Changes in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum 25-hydroxyvitamin D (25-OHD) in the vitamin D_3 and placebo groups during the study

Variables	Time	Vitamin D_3 group (mean ± SD)	Placebo group (mean ± SD)	P[1] (time-group interaction)	P[1] (time effect)	P[1] (group effect)
ESR	At the baseline	29.96 ± 21.76	26.63 ± 22.85	0.0450	0.0150	0.5200
	After 1 month	22.79 ± 18.61	25.50 ± 20.37			
	After 3 months	14.15 ± 16.89	25.75 ± 17.37			
	After 6 months	11.78 ± 8.98	24.75 ± 15.84			
CRP	At the baseline	6.78 ± 6.06	4.38 ± 4.62	0.0490	0.0420	0.9600
	After 1 month	4.22 ± 4.41	3.63 ± 3.82			
	After 3 months	2.78 ± 4.23	4.25 ± 4.11			
	After 6 months	2.33 ± 3.94	4.20 ± 4.09			
25-OHD	At the baseline	18.12 ± 3.91	17.77 ± 4.64	0.0001	0.0001	0.0040
	After 1 month	29.75 ± 4.19	17.71 ± 4.31			
	After 3 months	35.33 ± 4.51	17.14 ± 4.22			
	After 6 months	34.25 ± 3.69	16.43 ± 3.87			

[1]Based on mixed model analysis of variance (ANOVA)
ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; 25-OHD: 25-hydroxyvitamin D; SD: Standard deviation

Table 2. Prevalence of osteomyelitis symptoms over time in the vitamin D_3 and placebo groups

Time point	Group	Presence of symptoms (%)	Exp(B)	95% CI for Exp(B)	P[1]
At baseline	Vitamin D_3	75.9	1.11	0.89-2.14	0.325
	Placebo	66.7	1		
After 1 month	Vitamin D_3	28.9	0.54	0.17-0.91	0.001
	Placebo	52.9	1		
After 3 months	Vitamin D_3	9.2	0.38	0.12-0.81	0.015
	Placebo	30.2	1		
After 6 months	Vitamin D_3	4.8	0.16	0.06-0.49	< 0.001
	Placebo	29.4	1		

[1]Based on a generalized estimating equation (GEE)
Exp(B): Exponential beta; CI: Confidence interval

Moreover, Vitamin D supplementation improves the neuromuscular function and neuroprotective effects. It has also immunomodulatory and anti-infective activity.[18-20] Vitamin D signaling seems to reduce susceptibility to and severity of bacterial and viral infections via several mechanisms including its direct effects on producing antimicrobial peptides and cytokines, and its regulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway during infections. Furthermore, there is a strong relationship between vitamin D status and susceptibility to infectious and autoimmune diseases.[21]

Vitamin D supplementation was used for the treatment of infectious diseases in many clinical trials. It is difficult to compare the results of these studies due to different methodologies, different infections, and different doses, frequencies, and routes of vitamin D administration. In addition, many of these trials did not measure baseline 25-OHD levels. Thus, further research should be undertaken before recommending vitamin D supplementation for routine treatment of infections. Furthermore, several studies with vitamin D sufficient and nearly sufficient populations had negative results, and an inverse relationship between baseline 25-OHD level and response to vitamin D supplementation may be suggested. Finally, it is not clearly determined whether vitamin D supplementation has any beneficial effects on the treatment of infectious diseases in patients with normal 25-OHD levels.[10] In the present study, 63.33% of the patients had vitamin D insufficiency; therefore, it may be a reason for a good response.

To our knowledge, up to now, no studies have evaluated the effect of vitamin D_3 supplementation on chronic osteomyelitis. However, some studies have investigated the effect of baseline 25-OHD on clinical outcomes in orthopedic infections. Marschall et al. reported that there was no association between low vitamin D serum levels at the start of antibiotic therapy and the outcomes of osteoarticular infections when the patients received vitamin D supplementation along with antimicrobial therapy. They mentioned that hypovitaminosis D is prevalent and may be a modifiable risk factor for poor clinical outcomes in patients with osteoarticular infections. In their study, 75% of the patients had 25-OHD levels < 30 ng/ml.[20] In another study, Signori et al. investigated vitamin D status in patients undergoing orthopedic surgery for prosthetic or bone tissue infections and compared baseline 25-OHD levels between these patients and non-infected ones. Higher 25-OHD levels were observed in the patients with prosthetic joint infection (significant) and in those with osteomyelitis and aseptic arthritis (non-significant) compared to non-infected patients. It was proposed that the higher levels of 25-OHD may be the result of the infectious process not

a predisposing factor for infection. They reported 79% of the study population were vitamin D deficient (25-OHD levels < 20 ng/ml).[6] Moreover, Maier et al. found that low vitamin D levels were inversely associated with the length of hospital stay in orthopedic patients receiving elective hip or knee arthroplasty. In this study, 86% and 63% of the patients were vitamin D insufficient (25-OHD levels < 30 ng/ml) and vitamin D deficient (25-OHD levels < 20 ng/ml), respectively.[22] Besides, in another study, Maier et al. showed that the prevalence of vitamin D deficiency in the patients treated for periprosthetic joint infection was high. Sixty-four percent of the study population had 25-OHD levels less than 20 ng/ml.[23] All the above-mentioned studies demonstrated a possible association between low vitamin D levels and orthopedic diseases, particularly orthopedic infections. The reasons for some differences in the results of the aforementioned studies are as follows: patients with different orthopedic infections, small sample size, and also differences and limitations in methodology.[14] These results may confirm the need for vitamin D supplementation in this population.

It is worth mentioning that Jiang et al. have indicated that vitamin D receptor *TaqI*, *BsmI*, *FokI*, and *ApaI* gene polymorphisms may contribute to the increased risk of chronic osteomyelitis in the Chinese population. The vitamin D receptors are responsible for the endocrine action of vitamin D.[24] This study also emphasized the special role of vitamin D in chronic osteomyelitis.

Long-term and frequent follow-ups were the limitations of the current study. However, this is a pilot study and the results are encouraging. Moreover, due to the coronavirus disease 2019 (COVID-19) epidemic and issues arising from it, there was not enough time to report the results of the current study earlier. Large trials with a longer duration and different doses of vitamin D are suggested to be conducted for future studies.

Conclusion

High-dose and long-term vitamin D_3 supplementation as an adjunct therapy to antibiotics may improve the outcomes of patients with chronic osteomyelitis. The vitamin D_3 supplementation could decrease CRP and ESR and also improve the clinical symptoms of chronic osteomyelitis in the patients. Moreover, the number of patients with vitamin D insufficiency was high in the current study. However, this is a pilot study, a small-scale trial, and large-scale trials should be performed to reach robust results.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

The authors are grateful to Ehsan Mehrabi Kermani for editing the English text.

Financial support and sponsorship

The study was supported by Kerman University of Medical Sciences.

References

1. Naderi Nabi B, Sedighinejad A, Mirbolouk A, Farzi F, Haghighi M, Atrkarroushan Z, et al. The effectiveness of ozone therapy in chronic osteomyelitis: A randomized controlled clinical trial. Arch Clin Infect Dis. 2018; 13(2): e61320.
2. Fantoni M, Taccari F, Giovannenze F. Systemic antibiotic treatment of chronic osteomyelitis in adults. Eur Rev Med Pharmacol Sci. 2019; 23(2 Suppl): 258-70.
3. Arshad Z, Lau EJ, Aslam A, Thahir A, Krkovic M. Management of chronic osteomyelitis of the femur and tibia: A scoping review. EFORT Open Rev. 2021; 6(9): 704-15.
4. Marais LC, Ferreira N, Aldous C, Le Roux TL. The outcome of treatment of chronic osteomyelitis according to an integrated approach. Strategies Trauma Limb Reconstr. 2016; 11(2): 135-42.
5. Geurts J, Hohnen A, Vranken T, Moh P. Treatment strategies for chronic osteomyelitis in low- and

middle-income countries: systematic review. Trop Med Int Health. 2017; 22(9): 1054-62.
6. Signori V, Romanò CL, De Vecchi E, Mattina R, Drago L. May osteoarticular infections be influenced by Vitamin D status? An observational study on selected patients. BMC Musculoskelet Disord. 2015; 16: 183.
7. Ismailova A, White JH. Vitamin D, infections and immunity. Rev Endocr Metab Disord. 2022; 23(2): 265-77.
8. Athanassiou L, Mavragani CP, Koutsilieris M. The immunomodulatory properties of Vitamin D. Mediterr J Rheumatol. 2022; 33(1): 7-13.
9. Youssef DA, Miller CW, El-Abbassi AM, Cutchins DC, Cutchins C, Grant WB, et al. Antimicrobial implications of vitamin D. Dermatoendocrinol. 2011; 3(4): 220-9.
10. Kearns MD, Alvarez JA, Seidel N, Tangpricha V. The impact of Vitamin D on infectious disease: A systematic review of controlled trials. Am J Med Sci. 2015; 349(3): 245-62.
11. Ghazizadeh H, Rezayi M, Emadzadeh M, Tayefi M, Abdollahi Z, Timar A, et al. Prevalence of Vitamin D deficiency in Iran: A systematic Review and meta-analysis. J Cardio-Thorac Med. 2022; 10(2): 945-73.
12. Zargaran A, Zargaran D, Trompeter A. The relationship between serum 25[OH]D concentration and orthopaedic infection: A case-control study. Orthop Res Rev. 2020; 12: 121-5.
13. Traven SA, Chiaramonti AM, Barfield WR, Kirkland PA, Demos HA, Schutte HD, et al. Fewer complications following revision hip and knee arthroplasty in patients with normal Vitamin D levels. J Arthroplasty. 2017; 32(9s): S193-s6.
14. Zargaran A, Zargaran D, Trompeter AJ. The role of Vitamin D in orthopaedic infection: A systematic literature review. Bone Jt Open. 2021; 2(9): 721-7.
15. Murdoch DR, Slow S, Chambers ST, Jennings LC, Stewart AW, Priest PC, et al. Effect of Vitamin D3 supplementation on upper respiratory tract infections in healthy adults: The VIDARIS randomized controlled trial. Jama. 2012; 308(13): 1333-9.
16. Giustina A, Adler RA, Binkley N, Bouillon R, Ebeling PR, Lazaretti-Castro M, et al. Controversies in Vitamin D: Summary statement from an international conference. J Clin Endocrinol Metab. 2019; 104(2): 234-40.
17. Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016; 25(3): 1057-73.
18. Moon AS, Boudreau S, Mussell E, He JK, Brabston EW, Ponce BA, et al. Current concepts in Vitamin D and orthopaedic surgery. Orthop Traumatol Surg Res. 2019; 105(2): 375-82.
19. Machaj D, Cyboran K, Płaczek A, Baran M, Wojnowski M. The importance of Vitamin D3 supplementation in orthopedics-literature review. J Educ Health Sport. 2020; 10(5): 118-22.
20. Marschall J, Lewis JW, Warren DK, Babcock HM, Barrack RL, Fraser VJ. Baseline hypovitaminosis D is not associated with poor clinical outcomes in osteoarticular infections. Int J Infect Dis. 2014; 26: 98-102.
21. Bishop EL, Ismailova A, Dimeloe S, Hewison M, White JH. Vitamin D and immune regulation: antibacterial, antiviral, anti-inflammatory. JBMR Plus. 2021; 5(1): e10405.
22. Maier GS, Maus U, Lazovic D, Horas K, Roth KE, Kurth AA. Is there an association between low serum 25-OH-D levels and the length of hospital stay in orthopaedic patients after arthroplasty? J Orthop Traumatol. 2016; 17(4): 297-302.
23. Maier GS, Horas K, Seeger JB, Roth KE, Kurth AA, Maus U. Is there an association between periprosthetic joint infection and low Vitamin D levels? Int Orthop. 2014; 38(7): 1499-504.
24. Jiang N, Zhao XQ, Qin CH, Hu YJ, Wang L, Xie GP, et al. Association of Vitamin D receptor gene TaqI, BsmI, FokI and ApaI polymorphisms and susceptibility to extremity chronic osteomyelitis in Chinese population. Injury. 2016; 47(8): 1655-60.