

World Journal of *Clinical Cases*

World J Clin Cases 2020 June 6; 8(11): 2066-2407



REVIEW

- 2066 Tumor circulome in the liquid biopsies for digestive tract cancer diagnosis and prognosis
Chen L, Chen Y, Feng YL, Zhu Y, Wang LQ, Hu S, Cheng P
- 2081 Isoflavones and inflammatory bowel disease
Wu ZY, Sang LX, Chang B

MINIREVIEWS

- 2092 Cytapheresis for pyoderma gangrenosum associated with inflammatory bowel disease: A review of current status
Tominaga K, Kamimura K, Sato H, Ko M, Kawata Y, Mizusawa T, Yokoyama J, Terai S
- 2102 Altered physiology of mesenchymal stem cells in the pathogenesis of adolescent idiopathic scoliosis
Ko DS, Kim YH, Goh TS, Lee JS
- 2111 Association between liver targeted antiviral therapy in colorectal cancer and survival benefits: An appraisal
Wang Q, Yu CR
- 2116 Peroral endoscopic myotomy for management of gastrointestinal motility disorder
Feng Z, Liu ZM, Yuan XL, Ye LS, Wu CC, Tan QH, Hu B

ORIGINAL ARTICLE**Case Control Study**

- 2127 Clinical prediction of complicated appendicitis: A case-control study utilizing logistic regression
Sasaki Y, Komatsu F, Kashima N, Suzuki T, Takemoto I, Kijima S, Maeda T, Miyazaki T, Honda Y, Zai H, Shimada N, Funahashi K, Urita Y
- 2137 Clinical application of ultrasound-guided selective proximal and distal brachial plexus block in rapid rehabilitation surgery for hand trauma
Zhang J, Li M, Jia HB, Zhang L
- 2144 High flux hemodialysis in elderly patients with chronic kidney failure
Xue HY, Duan B, Li ZJ, Du P
- 2150 Determination of vitamin D and analysis of risk factors for osteoporosis in patients with chronic pain
Duan BL, Mao YR, Xue LQ, Yu QY, Liu MY

Retrospective Study

- 2162 Differences in parents of pediatric liver transplantation and chronic liver disease patients
Akbulut S, Gunes G, Saritas H, Aslan B, Karipkiz Y, Demyati K, Gungor S, Yilmaz S
- 2173 Epidemiological investigation of *Helicobacter pylori* infection in elderly people in Beijing
Zhu HM, Li BY, Tang Z, She J, Liang XY, Dong LK, Zhang M
- 2181 Application of a pre-filled tissue expander for preventing soft tissue incarceration during tibial distraction osteogenesis
Chen H, Teng X, Hu XH, Cheng L, Du WL, Shen YM
- 2190 Evaluation of clinical significance of claudin 7 and construction of prognostic grading system for stage II colorectal cancer
Quan JC, Peng J, Guan X, Liu Z, Jiang Z, Chen HP, Zhuang M, Wang S, Sun P, Wang HY, Zou SM, Wang XS
- 2201 Choice and management of negative pressure drainage in anterior cervical surgery
Su QH, Zhu K, Li YC, Chen T, Zhang Y, Tan J, Guo S
- 2210 Risk scores, prevention, and treatment of maternal venous thromboembolism
Zhang W, Shen J, Sun JL
- 2219 Role of Hiraoka's transurethral detachment of the prostate combined with biopsy of the peripheral zone during the same session in patients with repeated negative biopsies in the diagnosis of prostate cancer
Pan CY, Wu B, Yao ZC, Zhu XQ, Jiang YZ, Bai S
- 2227 Efficacy of thoracoscopic anatomical segmentectomy for small pulmonary nodules
Li H, Liu Y, Ling BC, Hu B

Observational Study

- 2235 Attitudes, awareness, and knowledge levels of the Turkish adult population toward organ donation: Study of a nationwide survey
Akbulut S, Ozer A, Gokce A, Demyati K, Saritas H, Yilmaz S
- 2246 Metabolic biomarkers and long-term blood pressure variability in military young male adults
Lin YK, Liu PY, Fan CH, Tsai KZ, Lin YP, Lee JM, Lee JT, Lin GM
- 2255 Cytokines predict virological response in chronic hepatitis B patients receiving peginterferon alfa-2a therapy
Fu WK, Cao J, Mi NN, Huang CF, Gao L, Zhang JD, Yue P, Bai B, Lin YY, Meng WB

SYSTEMATIC REVIEWS

- 2266 Utilising digital health to improve medication-related quality of care for hypertensive patients: An integrative literature review
Wechkunanukul K, Parajuli DR, Hamiduzzaman M

META-ANALYSIS

- 2280** Role of *IL-17* gene polymorphisms in osteoarthritis: A meta-analysis based on observational studies
Yang HY, Liu YZ, Zhou XD, Huang Y, Xu NW

CASE REPORT

- 2294** Various diagnostic possibilities for zygomatic arch pain: Seven case reports and review of literature
Park S, Park JW
- 2305** Extensive multifocal and pleomorphic pulmonary lesions in Waldenström macroglobulinemia: A case report
Zhao DF, Ning HY, Cen J, Liu Y, Qian LR, Han ZH, Shen JL
- 2312** Lung cancer from a focal bulla into thin-walled adenocarcinoma with ground glass opacity – an observation for more than 10 years: A case report
Meng SS, Wang SD, Zhang YY, Wang J
- 2318** Pyogenic discitis with an epidural abscess after cervical analgesic discography: A case report
Wu B, He X, Peng BG
- 2325** Clinical characteristics, diagnosis, and treatment of COVID-19: A case report
He YF, Lian SJ, Dong YC
- 2332** Paraplegia after transcatheter artery chemoembolization in a child with clear cell sarcoma of the kidney: A case report
Cai JB, He M, Wang FL, Xiong JN, Mao JQ, Guan ZH, Li LJ, Wang JH
- 2339** Macrophage activation syndrome as a complication of dermatomyositis: A case report
Zhu DX, Qiao JJ, Fang H
- 2345** Serial computed tomographic findings and specific clinical features of pediatric COVID-19 pneumonia: A case report
Chen X, Zou XJ, Xu Z
- 2350** Myxofibrosarcoma of the scalp with difficult preoperative diagnosis: A case report and review of the literature
Ke XT, Yu XF, Liu JY, Huang F, Chen MG, Lai QQ
- 2359** Endoscopic pedicle flap grafting in the treatment of esophageal fistulas: A case report
Zhang YH, Du J, Li CH, Hu B
- 2364** Hemophagocytic syndrome as a complication of acute pancreatitis: A case report
Han CQ, Xie XR, Zhang Q, Ding Z, Hou XH
- 2374** Reduced delay in diagnosis of odontogenic keratocysts with malignant transformation: A case report
Luo XJ, Cheng ML, Huang CM, Zhao XP

- 2380** Gastric pyloric gland adenoma resembling a submucosal tumor: A case report
Min CC, Wu J, Hou F, Mao T, Li XY, Ding XL, Liu H
- 2387** Ataxia-telangiectasia complicated with Hodgkin's lymphoma: A case report
Li XL, Wang YL
- 2392** Uterine incision dehiscence 3 mo after cesarean section causing massive bleeding: A case report
Zhang Y, Ma NY, Pang XA
- 2399** Optical coherence tomography guided treatment avoids stenting in an antiphospholipid syndrome patient:
A case report
Du BB, Wang XT, Tong YL, Liu K, Li PP, Li XD, Yang P, Wang Y

LETTER TO THE EDITOR

- 2406** Macrophage activation syndrome as an initial presentation of systemic lupus erythematosus
Shi LJ, Guo Q, Li SG

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Consolato M Sergi, FRCP (C), MD, PhD, Professor, Department of Lab. Medicine and Pathology, University of Alberta, Edmonton T6G 2B7, Canada

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*
 Proofing Production Department Director: *Yun-Xiaojuan Wu*
 Responsible Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
 ISSN 2307-8960 (online)

LAUNCH DATE
 April 16, 2013

FREQUENCY
 Semimonthly

EDITORS-IN-CHIEF
 Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

EDITORIAL BOARD MEMBERS
<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE
 June 6, 2020

COPYRIGHT
 © 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS
<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS
<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT
<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE
<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS
<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION
<https://www.f6publishing.com>

Case Control Study

Determination of vitamin D and analysis of risk factors for osteoporosis in patients with chronic pain

Bao-Lin Duan, Yuan-Rong Mao, Li-Qi Xue, Qing-Yuan Yu, Mei-Yi Liu

ORCID number: Bao-Lin Duan (0000-0002-5971-6981); Yuan-Rong Mao (0000-0001-8873-7637); Li-Qi Xue (0000-0002-9424-3446); Qing-Yuan Yu (0000-0001-8868-0677); Mei-Yi Liu (0000-0002-5476-7149).

Author contributions: Duan BL performed the majority of experiments and wrote the manuscript; Liu MY designed the study and corrected the manuscript; Mao YR was involved in analytical tools; Xue LQ and Yu QY participated in the collection of data.

Supported by the 2016 Guidance Project of Qinghai Provincial Health and Family Planning Commission, No. 2016-wjzdx-14.

Institutional review board

statement: The study was approved by the ethics committee of Qinghai Provincial People's Hospital.

Informed consent statement: All patients gave informed consent.

Conflict-of-interest statement: No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at 1461519537@qq.com.

STROBE statement: The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared and

Bao-Lin Duan, Yuan-Rong Mao, Li-Qi Xue, Qing-Yuan Yu, Mei-Yi Liu, Department of Pain, Qinghai Provincial People's Hospital, Xining 810000, Qinghai Province, China

Corresponding author: Mei-Yi Liu, MD, Doctor, Department of Pain, Qinghai Provincial People's Hospital, 2 Gonghe Road Chengdong District, Xining 810000, Qinghai Province, China. 1461519537@qq.com

Abstract**BACKGROUND**

Vitamin D deficiency is common in patients with chronic pain and healthy people, but the difference between the two has not been reported; thus, whether there is a relationship between vitamin D deficiency and chronic pain remains to be confirmed. Osteoporosis is a common disease in chronic pain disorders. Understanding the relationship between vitamin D and osteoporosis will provide a basis for the rational supplementation of vitamin D to prevent osteoporosis, and to understand the risk factors of bone mass change to provide a new treatment plan for early prevention of osteoporosis.

AIM

To determine 25 hydroxy vitamin D (25OHD) level in patients with chronic pain to clarify its clinical significance. The relationship between vitamin D and bone mineral density (BMD) and the risk factors for bone mass change were also evaluated.

METHODS

In this study, 184 patients with chronic pain were included in the study group, and 104 healthy individuals who underwent routine health checkups during the same period were included in the control group. 25OHD level was detected in both groups by enzyme-linked immunosorbent assay. According to the BMD test results, the patients in the study group were further classified into three subgroups: Normal BMD group, reduced BMD group, and osteoporosis group. Age, sex, ethnicity, living altitude, body mass index, 25OHD level, parathyroid hormone (PTH), calcium (Ca) and phosphorus levels were analyzed statistically in both groups.

RESULTS

The vitamin D level in the study group was lower than that in the control group at 53.8% vs 57.7%, with no significant difference between the two groups. The proportion of patients with severe vitamin D deficiency in the study group was higher than that in the control group. The mean age was greater in the

revised according to the STROBE Statement – checklist of items.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Received: January 2, 2020

Peer-review started: January 2, 2020

First decision: February 26, 2020

Revised: April 17, 2020

Accepted: May 1, 2020

Article in press: May 1, 2020

Published online: June 6, 2020

P-Reviewer: Poturoglu S, Yu C

S-Editor: Tang JZ

L-Editor: Webster JR

E-Editor: Qi LL



osteoporosis subgroup, and the youngest in the normal BMD subgroup. Vitamin D level in the osteoporosis subgroup was lower than that in the other two subgroups, and was not specific for the diagnosis of bone mass reduction and osteoporosis. The above results were analyzed statistically and showed significant differences ($P < 0.05$). There was a positive correlation between age and BMD in patients with chronic pain ($R = 0.567$, $P < 0.001$). Age, PTH and Ca were risk factors for bone mass reduction, while age, ethnicity and altitude were risk factors for osteoporosis.

CONCLUSION

Vitamin D deficiency is a common phenomenon in patients with chronic pain, and severe vitamin D deficiency is not uncommon. Vitamin D level is not a risk factor for bone mass reduction and osteoporosis. Bone mass reduction is correlated with age, PTH and Ca, while osteoporosis is correlated with age, ethnicity and altitude.

Key words: Chronic pain; Vitamin D deficiency; Bone mass reduction; Osteoporosis; Bone mineral density

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Vitamin D deficiency is common in chronic pain patients and healthy people, and its level is not different between the two, but severe deficiency is more common in patients with chronic pain. Vitamin D is not a risk factor for bone loss and osteoporosis. Age, parathyroid hormone, and calcium are risk factors for bone loss. Age, ethnicity, and altitude are risk factors for osteoporosis.

Citation: Duan BL, Mao YR, Xue LQ, Yu QY, Liu MY. Determination of vitamin D and analysis of risk factors for osteoporosis in patients with chronic pain. *World J Clin Cases* 2020; 8(11): 2150-2161

URL: <https://www.wjnet.com/2307-8960/full/v8/i11/2150.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i11.2150>

INTRODUCTION

Chronic pain is one of the most challenging clinical problems for clinicians. Patients with chronic pain not only have to endure somatic pain but also bear a huge psychological burden due to behavioral responses. Some studies have demonstrated that vitamin D deficiency is associated with non-specific musculoskeletal pain^[1], knee osteoarthritis^[2], migraine^[3], chronic cervical pain^[4], and other multiple chronic pains. It is also a risk factor for various chronic diseases such as osteoporosis, hypertension and cardiovascular disease^[5].

Vitamin D deficiency is not only present in patients with chronic pain but also a common phenomenon in healthy populations. It is estimated that more than 50% of the world's population have vitamin D deficiency^[6]. A recent multi-center survey in China showed that the prevalence of vitamin D deficiency in Chinese urban residents is approximately 55.9%^[7]. Vitamin D is a pro-hormone that regulates the calcium (Ca) and phosphorus (P) balance and skeletal structures. Vitamin D deficiency increases the risk of osteoporosis^[8]. The occurrence of osteoporosis is a silent and imperceptible process, and is often ignored until fragile fracture occurs. For osteoporotic patients, early detection, diagnosis and treatment are of primary importance. Currently, the diagnosis of osteoporosis mainly depends on bone mineral density (BMD) measured by dual-energy X-ray absorptiometry. Many studies have reported the relationship between vitamin D and BMD, but the conclusions are controversial.

The aim of the present study was to determine the changes in vitamin D level in patients with chronic pain, clarify the relationship between vitamin D and BMD, and explore the risk factors for bone mass reduction and osteoporosis in patients with chronic pain, in an attempt to provide experimental clues for the prevention and treatment of osteoporosis.

MATERIALS AND METHODS

General data

In this study, 184 patients with chronic pain who were admitted to the Pain Department of Qinghai People's Hospital (Xining, China) between May and September 2017 were enrolled. These patients consisted of 49 males and 135 females with a mean age of 57.62 ± 13.79 years. An additional 104 healthy individuals who underwent routine health checkups in the same hospital during the same period were enrolled as controls, including 25 males and 79 females with a mean age of 56.52 ± 13.66 years. According to the BMD test results, the patients in the study group were further classified into three subgroups: Normal BMD group ($n = 55$), reduced BMD group ($n = 74$) and osteoporosis group ($n = 55$). The exclusion criteria were as follows: Patients with endocrine and autoimmune diseases; malignant tumors; chronic liver disease, chronic obstructive pulmonary disease and chronic kidney disease; sequelae of cardio-cerebrovascular disease affecting extremity function; skin diseases who could not be exposed to sunlight; those using active vitamin D, steroids, sex hormones, parathyroid hormone (PTH), calcitonin, diphosphate and other drugs that may affect bone metabolism within 6 mo before initiation of the study.

The research protocol was approved by Qinghai People's Hospital, and informed consent was obtained from all participants in the study on the principle of voluntary participation. Of the initially recruited 346 patients with chronic pain, 103 patients with complicated autoimmune, cardiovascular, endocrine and chronic kidney diseases, malignant tumors, and those who had a history of using anti-osteoporosis drugs or Ca supplements, and 59 patients who lacked BMD, PTH and other key data were excluded from the study. In total, 184 patients were included in this study for analysis.

Methods

Criteria for test index evaluation: Venous blood samples were collected at 7:00-8:00 AM from all participants under fasting conditions and sent to our laboratory for analysis. 25 hydroxy vitamin D (25OHD) and PTH were measured by a Cobas 8000 electrochemiluminescence immunoassay kit. Ca and P levels were detected using an automatic biochemical analyzer and the required kit (Hitachi, Japan). BMD of the L1-4 and femoral neck, Ward's triangle and trochanter was measured by dual-energy X-ray absorptiometry (Hologic Q DR 2000, United States). Other general data of the participants including age, height, weight, body mass index (BMI), living altitude, past medical history and drug administration were also recorded for analysis.

The vitamin D status was assessed by measuring the serum level of 25OHD, and was classified as severe vitamin D deficiency (< 10 ng/mL), vitamin D deficiency ($\geq 10 < 20$ ng/mL), vitamin D insufficiency ($\geq 20 < 30$ ng/mL), and vitamin D sufficiency (≥ 30 ng/mL).

The criteria for BMD assessment were as follows: Patients with a BMD T value > 1 in any of the L1-4, total hip and femoral neck were included in the normal BMD group, -1 to 2.5 were included in the reduced BMD group, and ≤ -2.5 were included in the osteoporosis group.

The criteria for PTH assessment were as follows: Serum PTH < 15 pg/mL was considered reduced, ≥ 15 pg/mL ≤ 65 pg/mL was considered normal, and > 65 pg/mL was considered increased.

The criteria for P assessment were as follows: Serum P < 0.85 mmol/L was considered reduced, ≥ 0.85 mmol/L ≤ 1.51 mmol/L was considered normal, and > 1.51 mmol/L was considered increased.

The criteria for Ca assessment were as follows: Serum Ca < 2.2 mmol/L was considered reduced, ≥ 2.2 mmol/L ≤ 2.7 mmol/L was considered normal, and > 2.7 mmol/L was considered increased.

Statistical analysis

All statistical analyses were performed using SPSS 17.0. Quantitative data are expressed as $\bar{x} \pm s$. Comparisons between two groups were performed using the independent sample t test; comparisons between three groups were performed by one way ANOVA; and comparisons between multiple groups were performed by LSD. Counting data are expressed as c^2 . Two sets of ordered counting data were analyzed by Mantel-Haenszel test for linear trend. Risk factors were analyzed by binary logistic regression. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Comparison of the general data and vitamin D concentrations between the study and control groups

Comparisons of the general data indicated no significant difference in age and sex between the two groups. The vitamin D concentration in the study group was significantly lower than that in the control group ($P < 0.05$) (Table 1).

Comparison of the percentage of vitamin D concentration between the study and control groups

Vitamin D deficiency was predominant in both groups, accounting for 53.8% and 57.7%, respectively, with no significant difference between the two groups. The proportion of patients with severe vitamin D deficiency in the study group was significantly higher than that in the control group ($P < 0.05$) (Table 2).

Comparison of vitamin D concentrations between the normal BMD group, reduced BMD group and osteoporosis group, and the diagnostic value of vitamin D concentration on osteoporosis

Two-group comparisons showed a significant difference in age between the normal BMD, reduced BMD and osteoporosis groups, with the oldest patients in the osteoporosis group and the youngest in the normal BMD group. There was no significant difference in sex between the three groups. The vitamin D level in the osteoporosis group was lower than that in the other two groups (Table 3).

The area under the receiver operating characteristic curve of vitamin D concentration in the reduced BMD and osteoporosis groups was 0.487 and 0.417, respectively, suggesting that it was significant for the diagnosis of bone mass reduction and osteoporosis (Table 4, Figure 1).

Relationship between BMD and vitamin D concentrations in terms of age in the study group

The relationship between age and BMD was analyzed by the Mantel-Haenszel chi-square test, and the results showed a linear correlation between age and BMD in patients with chronic pain ($\chi^2 = 58.933$, $P < 0.001$). Pearson correlation analysis showed that $R = 0.567$ and $P < 0.001$, indicating that BMD decreased gradually with increased age in chronic pain patients (Table 5).

There was no significant difference in vitamin D change between the different age groups in the study group ($P > 0.05$) (Table 6).

Analysis of risk factors for bone mass reduction in the study group

Ten factors including age, sex, ethnicity and BMI in the normal and reduced BMD groups were analyzed by univariate analysis and the results showed that age, sex, ethnicity, PTH and Ca showed statistical significance ($P < 0.05$) (Table 7).

Of the above results, age, sex, ethnicity, PTH, and Ca were entered into binary logistic analysis, and the results showed that age, PTH and Ca were risk factors for bone mass reduction (Table 8).

Analysis of risk factors for osteoporosis in patients with chronic pain

Univariate analysis of 10 factors including age, sex, ethnicity and BMI in the osteoporosis and normal BMD subgroups showed significant differences in age, sex, ethnicity and altitude between these two subgroups ($P < 0.05$) (Table 9).

Of the above results, age, sex, ethnicity and altitude were entered into binary logistic analysis, and the results showed that age, ethnicity and altitude were risk factors for osteoporosis (Table 10).

DISCUSSION

Vitamin D is a hormone synthesized in the skin during sunlight exposure. It not only participates in bone and cellular metabolism but plays a role in the regulation of autoimmune disease, inflammation, neuromuscular and other immune functions. During the process of vitamin D metabolism, serum 25OHD concentration is the optimal marker for evaluating vitamin D status^[9]. A number of studies have demonstrated the deficiency or insufficiency of vitamin D in multiple chronic pain disorders including non-specific musculoskeletal pain, chronic generalized pain, fibromuscular pain, lower back pain, headache and lumbar canal stenosis. In addition, the results of vitamin D surveys in healthy populations worldwide are not optimistic, with the prevalence of vitamin insufficiency reaching 30%-50%^[10]. In the present

Table 1 Comparison of the general data and vitamin D concentrations between the study and control groups

Group	n	Age (yr)	Sex (M/F)	Vitamin D (ng/mL)
Study	184	57.62 ± 13.79	49/135	13.76 ± 7.15
Control	104	56.52 ± 13.66	25/79	20.12 ± 7.59
t (c ²)		0.656	0.234	7.085
P value		0.512	0.629	0.000

M: Male; F: Female.

study, it was found that vitamin deficiency was generally present in both chronic pain patients and healthy individuals, although the overall vitamin D level in chronic pain patients was lower than that in healthy individuals, especially in those with vitamin D deficiency or severe vitamin D insufficiency. Some studies showed that vitamin D supplements could alleviate pain^[11-14]. However, three meta-analyses found no significant correlation between vitamin D supplementation and pain relief in their randomized study and placebo control groups^[15-17]. Serum 25OHD concentration is affected by multiple host and environmental factors, including age, sex, diet, sunlight exposure, physical activity, body weight, skin pigmentation, and genetic factors. Whether there is a relationship between vitamin D deficiency/severe insufficiency and chronic pain requires further studies.

Vitamin D is a pro-hormone that regulates Ca and P balance and skeletal structures, and has an adverse impact on skeletal health and neuromuscular function. Vitamin D deficiency increases the risk of osteoporosis. Serum 25OHD level lower than 20 ng/mL was reported to be associated with defective bone mineralization^[8,18]. In our study, it was found that vitamin D concentration was lowest in osteoporotic patients but was not a risk factor for bone mass reduction and osteoporosis, suggesting that they are not correlated. This finding is consistent with the results of a large-scale cross-sectional study conducted in Northwest China^[19]. However, the role of vitamin D in the basic treatment of osteoporosis should not be questioned. A large number of studies have confirmed that vitamin D alone cannot reduce the risk of bone fracture, but combined use of vitamin D and Ca supplements can reduce the risk of hip and non-vertebral fractures^[20-22]. The anti-osteoporosis treatment guidelines from multiple different countries and regions maintain that sufficient Ca uptake plus the vitamin D status is a precondition of any regimen for the prevention and treatment of osteoporosis regardless of which drug is used^[23-25]. Thus, questions arise as to what amount of vitamin D supplementation can maximally increase the serum 25OHD concentration and at the same time ensure that the concentration will not be excessive? In other words, what is the optimal vitamin D supplement concentration required for the 25OGD target for general populations? One study set up the general practical criteria and the latest suggestions for preventive administration of vitamin D for newborns, infants, children, adolescents and adults (including pregnant women, lactating mothers and older people) in central European areas, in which the vitamin D concentration < 20 ng/mL is defined as deficiency, 20-30 ng/mL as the sub-healthy state, and 30-50 ng/mL as the optimal target concentration of vitamin D action and the range of serum 25OHD concentration. It also suggests that all individuals with serum 25OHD lower than 20 ng/mL should be supplemented or corrected for vitamin D, and 30 ng/mL is the target most suitable for infirm, osteoporotic and senile patients^[26].

Osteoporosis is one of the main health concerns worldwide. With increasing age, bone mass decreases gradually, leading to bone mass reduction and osteoporosis. The differential diagnosis of bone mass reduction and osteoporosis is based on the BMD level. The main goal of osteoporosis screening and treatment is to prevent fracture by reducing bone mass loss. It is therefore extremely important to recognize risk factors associated with bone mass change in order to identify high risk populations and take early preventive strategies to reduce the occurrence of osteoporosis. With increasing age, the risk of bone mass reduction and fracture is generally increased, especially in menopausal women whose estrogen level and liver/kidney function in synthesizing active vitamin D are both reduced, leading to reduced absorption of Ca in the gut. In addition, a reduction in estrogen level activates PTH, thus increasing the activity of osteoclasts, increasing bone absorption, and quickening bone turnover and bone mass loss. As a result, the bone trabecula becomes thinner, the bone cortex is structurally damaged and becomes progressively thinner, and the bone density is decreased. Undoubtedly, age is an important risk factor for bone mass change, which is

Table 2 Comparison of the percentage of vitamin D concentration between the study and control groups

Vitamin D level	Study group (n = 184), n (%)	Control group (n = 104), n (%)	χ^2	P value
< 10	55 (29.9)	1 (1.0)	35.502	0.000
10-20	99 (53.8)	60 (57.7)	0.406	0.524
20-30	25 (13.6)	33 (31.7)	13.600	0.000
≥ 30	5 (2.7)	10 (9.6)	6.404	0.011

consistent with related reports^[23]. What is different is that we failed to find a significant correlation between bone mass loss and BMI. Lifestyle factors associated with the risk of osteoporosis include alcohol consumption, diet, hormones, sports and smoking. In addition, Ca and vitamin D are extremely important in age-related BMD and skeletal muscle mass reduction^[27]. It was observed in our study that PTH and Ca were risk factors contributing to bone mass reduction, while ethnicity and altitude were risk factors contributing to osteoporosis. Whether this phenomenon is due to the relatively small sample size or reflects intrinsic differences remains to be confirmed in future studies.

Multiple individual factors should be considered in the treatment of osteoporosis. Personalized treatment strategies should be built on disease severity, patient sex, complications and adverse effects that the drug(s) may produce^[28]. Differences in related risk factors should also be included in the selection of therapies.

Table 3 Comparison of vitamin D concentrations between the normal bone mineral density group, reduced bone mineral density group, and osteoporosis group

Group	n	Age (yr)	Sex (M/F)	Vitamin D (ng/mL)
Normal BMD	55	49.18 ± 11.29	20/35	14.20 ± 7.48
Reduced BMD	74	62.29 ± 12.28 ¹	19/55	14.12 ± 6.71
Osteoporosis	55	67.48 ± 9.20 ²	10/45	12.94 ± 7.00 ²
F(c ²)		2108.770	4.711	35.824
P value		0.000	0.095	0.000

¹Compared with the normal bone mineral density group, *P* < 0.05.

²Compared with the reduced bone mineral density group, *P* < 0.05. M: Male; F: Female; BMD: Bone mineral density.

Table 4 The diagnostic value of vitamin D concentration on bone mass reduction and osteoporosis

Group	n	AUC	SD	P value	95%CI
Reduced BMD	74	0.487	0.056	0.820	0.379-0.596
Osteoporosis	55	0.417	0.055	0.134	0.309-0.525

CI: Confidence interval; BMD: Bone mineral density; AUC: Area under curve; SD: Standard deviation.

Table 5 Relationship between age groups and bone mineral density in patients with chronic pain

Age group (yr)	n	Normal BMD (%)	Reduced BMD (%)	Osteoporosis (%)	c ²	P value
< 45	32	27 (49.09)	4 (5.41)	1 (1.82)		
45-64	86	24 (43.63)	43 (58.11)	19 (34.55)	58.933	0.000
≥ 65	66	4 (7.27)	27 (36.49)	35 (63.64)		
Total	184	55 (100)	74 (100)	55 (100)		

BMD: Bone mineral density.

Table 6 Comparison of vitamin D concentrations between different age groups in the study group

Age group (yr)	n	Vitamin D (ng/mL)
< 45	32	13.23 ± 5.58
45-64	86	1.64 ± 7.06
≥ 65	66	14.15 ± 8.00
F		0.189
P value		0.28

Table 7 Univariate analysis of various factors in the normal and reduced bone mineral density groups of the study group

Factor	Reduced BMD (%)	Normal BMD (%)	χ^2	P value
Age (yr)			37.533	0.000
< 45	4	27		
45-64	43	24		
≥ 65	27	4		
Sex			23.334	0.000
M	19	20		
F	55	35		
Ethnicity			8.407	0.038
Tibetan	3	10		
Han	60	37		
Hui	7	7		
Others	4	1		
BMI			2.302	0.512
< 18.5	3	4		
18.5-22.9	38	33		
24-27	22	11		
≥ 28	11	7		
Occupation			0.144	0.704
Farmer	18	15		
Non-farmer	56	40		
Vitamin D			1.323	0.724
< 10	21	15		
10-20	38	32		
20-30	13	6		
≥ 30	2	2		
PTH			7.503	0.023
< 15	1	0		
15-65	41	43		
> 65	32	12		
Ca			21.396	0.000
< 2.2	39	26		
2.2-2.7	17	29		
> 2.7	18	0		
P			1.312	0.519
< 0.85	5	3		
0.85-1.51	61	49		
> 1.51	8	3		
Altitude			2.988	0.224
1500-2500	58	40		
2500-3500	15	11		
3500-5800	1	4		

BMD: Bone mineral density; PTH: Parathyroid hormone; BMI: Body mass index; M: Male; F: Female.

Table 8 Binary logistic analysis of multiple factors for bone mass reduction

Factor	B value	SD (S.E.)	Wald value	Variance	P value	OR value	OR, 95%CI
Age	2.670	0.473	31.868	1	0.000	14.440	5.714-36.488
PTH	2.210	0.546	16.387	1	0.000	9.119	3.127-26.592
Ca	0.717	0.363	3.906	1	0.048	2.048	1.006-4.171
constant	-1.298	2.135	28.008	1	0.000	0.000	

PTH: Parathyroid hormone; SD: Standard deviation; OR: Odds ratio; S.E.: Standard error; CI: Confidence interval.

Table 9 Univariate analysis of multiple factors in the osteoporosis and normal bone mineral density subgroups of the study group

Factor	Osteoporosis, (%)	Normal BMD (%)	χ^2	P value
Age (yr)			49.365	0.000
< 45	1	27		
45-64	19	24		
≥ 65	35	4		
Sex			4.583	0.032
M	10	20		
F	45	35		
Ethnicity			9.913	0.019
Tibetan	2	10		
Han	38	37		
Hui	8	7		
Others	7	1		
BMI			0.777	0.855
< 18.5	5	4		
18.5-23.9	36	33		
24-27	9	11		
> 28	5	7		
Occupation				
Farmer	10	15	1.294	0.255
Non-farmer	45	40		
Vitamin D			0.959	0.811
< 10	19	15		
10-20	29	32		
20-30	6	6		
≥ 30	1	2		
PTH			0.767	0.381
< 15	0	0		
15-65	39	43		
> 65	16	12		
Ca			0.146	0.703
< 2.2	28	26		
2.2-2.7	27	29		
> 2.7	0	0		
P			1.942	0.379
< 0.85	7	3		
0.85-1.51	46	49		
> 1.51	2	3		
Altitude			6.381	0.041
1500-2500	49	40		
2500-3500	6	11		
3500-5800	0	4		

BMD: Bone mineral density; PTH: Parathyroid hormone; BMI: Body mass index; M: Male; F: Female.

Table 10 Binary logistic regression analysis of multiple factors for osteoporosis

Factor	B value	SD (S.E.)	Wald value	Variance	P value	OR value	OR 95%CI
Age	3.976	0.846	22.062	1	0.000	53.305	10.144-280.095
Ethnicity	1.262	0.521	5.871	1	0.015	5.531	1.273-9.797
Altitude	-2.049	0.514	15.871	1	0.000	0.129	0.047-0.353
Constant	-8.343	2.141	15.186	1	0.000	0.000	

SD: Standard deviation; OR: Odds ratio; S.E.: Standard error; CI: Confidence interval.

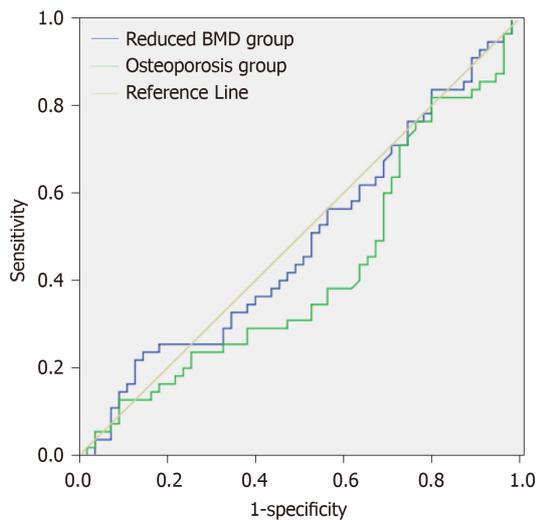


Figure 1 The diagnostic value of vitamin D concentration on bone mass. BMD: Bone mineral density.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is common in chronic pain patients and healthy people, but the difference between the two has not been reported. The relationship between vitamin D, chronic pain and bone mineral density (BMD) is controversial. The aim of the present study was to observe changes in vitamin D levels in patients with chronic pain, clarify the relationship between vitamin D and BMD, and explore risk factors for bone mass reduction and osteoporosis.

Research motivation

To understand the relationship between vitamin D and chronic pain, clarify the relationship between vitamin D and bone density, analyze the risk factors of bone mass reduction and osteoporosis, and provide a basis for early treatment of osteoporosis.

Research objectives

Vitamin D deficiency is very common in patients with chronic pain and healthy people, but severe vitamin D deficiency is more likely to occur in patients with chronic pain. Vitamin D is not a risk factor for bone mass changes. Age, parathyroid hormone (PTH) and calcium (Ca) were risk factors for bone mass reduction, while age, ethnicity and altitude were risk factors for osteoporosis.

Research methods

25 hydroxy vitamin D and PTH were determined by a Cobas 8000 electrochemical luminescence immunoassay kit. Ca and P levels were detected using a fully automated biochemical analyzer and the relevant kit (Hitachi). BMD of 1-1-4, femoral neck, Ward's triangle, and femoral trochanter was measured by dual-energy X-ray absorptiometry. General patient information was collected including age, height, weight, body mass index, altitude of residence, previous medical history and medication use. All statistical analyses were performed using SPSS 17.0. Quantitative data are expressed as $\bar{x} \pm s$. Comparisons between two groups were performed using the independent sample *t* test; comparisons between three groups were performed by one way

ANOVA; and comparisons between multiple groups were performed by LSD. Counting data are expressed as c^2 . Two sets of ordered counting data were analyzed by the Mantel-Haenszel test for linear trend. Risk factors were analyzed by binary logistic regression. Values of $P < 0.05$ were considered statistically significant.

Research results

Both chronic pain patients and healthy people were mainly deficient in vitamin D, but the proportion of severe vitamin D deficiency in chronic pain patients was significantly higher than that in the healthy group. Patients with chronic pain were more likely to suffer from vitamin D deficiency or severe deficiency, the causes of which require further study. The levels of vitamin D in the osteoporosis group were lower than those in the groups with normal bone mass and reduced bone mass, but vitamin D levels were not a risk factor for changes in bone mass. Age, PTH and Ca were risk factors for bone mass loss. Age, sex, ethnicity, and altitude were risk factors for osteoporosis.

Research conclusions

Vitamin D deficiency is common among patients with chronic pain, and severe vitamin D deficiency is more likely to occur. Although vitamin D levels are lowest during osteoporosis, they are not a risk factor for changes in bone mass. According to the different risk factors of bone mass change, independent treatment methods can be adopted clinically.

Research perspectives

Chronic pain patients are more likely to have severe vitamin D deficiency, and the reason for this is not clear. Vitamin D is not a risk factor for osteoporosis. Whether vitamin D supplementation is beneficial requires further study. Whether early monitoring of PTH and Ca levels has an effect on the prevention of bone mass change, and which age group can effectively prevent osteoporosis requires further investigation.

REFERENCES

- 1 **Knutsen KV**, Brekke M, Gjelstad S, Lagerlöv P. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway. *Scand J Prim Health Care* 2010; **28**: 166-171 [PMID: 20642395 DOI: 10.3109/02813432.2010.505407]
- 2 **Al-Jarallah KF**, Shehab D, Al-Awadhi A, Nahar I, Haider MZ, Moussa MA. Are 25(OH)D levels related to the severity of knee osteoarthritis and function? *Med Princ Pract* 2012; **21**: 74-78 [PMID: 22024977 DOI: 10.1159/000330025]
- 3 **Song TJ**, Chu MK, Sohn JH, Ahn HY, Lee SH, Cho SJ. Effect of Vitamin D Deficiency on the Frequency of Headaches in Migraine. *J Clin Neurol* 2018; **14**: 366-373 [PMID: 29971976 DOI: 10.3988/jcn.2018.14.3.366]
- 4 **Eloqayli H**, Al-Yousef A, Jaradat R. Vitamin D and ferritin correlation with chronic neck pain using standard statistics and a novel artificial neural network prediction model. *Br J Neurosurg* 2018; **32**: 172-176 [PMID: 29447493 DOI: 10.1080/02688697.2018.1436691]
- 5 **Ortega Anta RM**, González-Rodríguez LG, Jiménez Ortega AI, Estaire Gómez P, Rodríguez-Rodríguez E, Perea Sánchez JM, Aparicio Vizuete A, Grupo de Investigación N° 920030. [Insufficient intake of vitamin D in spanish schoolchildren: determinants of the problem and basis for its improvement]. *Nutr Hosp* 2012; **27**: 1437-1443 [PMID: 23478689 DOI: 10.3305/nh.2012.27.5.5900]
- 6 **Wimalawansa SJ**, Razzaque MS, Al-Daghri NM. Calcium and vitamin D in human health: Hype or real? *J Steroid Biochem Mol Biol* 2018; **180**: 4-14 [PMID: 29258769 DOI: 10.1016/j.jsbmb.2017.12.009]
- 7 **Yan X**, Thomson JS, Zhao R, Zhu R, Wang Z, Zhang N, Coad J. Vitamin D Status of Residents in Taiyuan, China and Influencing Factors. *Nutrients* 2017; **9** [PMID: 28820448 DOI: 10.3390/nu9080898]
- 8 **Yuan R**, Ma S, Zhu X, Li J, Liang Y, Liu T, Zhu Y, Zhang B, Tan S, Guo H, Guan S, Ao P, Zhou G. Core level regulatory network of osteoblast as molecular mechanism for osteoporosis and treatment. *Oncotarget* 2016; **7**: 3692-3701 [PMID: 26783964 DOI: 10.18632/oncotarget.6923]
- 9 **Tsugawa N**. [Vitamin D and osteoporosis: current topics from epidemiological studies]. *Rinsho Byori* 2010; **58**: 244-253 [PMID: 20408443]
- 10 **Emini-Sadiku M**, Morina-Kuqi N. Concealing Clothing Leading to Severe Vitamin D Deficiency, Osteomalacia and Muscle Weakness. *Open Access Maced J Med Sci* 2019; **7**: 2146-2149 [PMID: 31456842 DOI: 10.3889/oamjms.2019.584]
- 11 **Bergman P**, Sperner S, Höjjer J, Bergqvist J, Björkhem-Bergman L. Low vitamin D levels are associated with higher opioid dose in palliative cancer patients--results from an observational study in Sweden. *PLoS One* 2015; **10**: e0128223 [PMID: 26018761 DOI: 10.1371/journal.pone.0128223]
- 12 **Björkhem-Bergman L**, Bergman P. Vitamin D and patients with palliative cancer. *BMJ Support Palliat Care* 2016; **6**: 287-291 [PMID: 27084421 DOI: 10.1136/bmjspcare-2015-000921]
- 13 **Gendelman O**, Itzhaki D, Makarov S, Bennun M, Amital H. A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. *Lupus* 2015; **24**: 483-489 [PMID: 25801891 DOI: 10.1177/0961203314558676]
- 14 **Ovesjö ML**, Skilving I, Bergman P, Rane A, Ekström L, Björkhem-Bergman L. Low Vitamin D Levels and Genetic Polymorphism in the Vitamin D Receptor are Associated with Increased Risk of Statin-Induced Myopathy. *Basic Clin Pharmacol Toxicol* 2016; **118**: 214-218 [PMID: 26423691 DOI: 10.1111/bcpt.12482]
- 15 **Shipton EE**, Shipton EA. Vitamin D Deficiency and Pain: Clinical Evidence of Low Levels of Vitamin D and Supplementation in Chronic Pain States. *Pain Ther* 2015; **4**: 67-87 [PMID: 25920326 DOI: 10.1007/s40122-015-0036-8]
- 16 **Straube S**, Andrew Moore R, Derry S, McQuay HJ. Vitamin D and chronic pain. *Pain* 2009; **141**: 10-13 [PMID: 19084336 DOI: 10.1016/j.pain.2008.11.010]
- 17 **Straube S**, Derry S, Straube C, Moore RA. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev* 2015; CD007771 [PMID: 25946084 DOI: 10.1002/14697528.cd007771]

- 10.1002/14651858.CD007771.pub3]
- 18 **Rizzoli R**, Stevenson JC, Bauer JM, van Loon LJ, Walrand S, Kanis JA, Cooper C, Brandi ML, Diez-Perez A, Reginster JY; ESCEO Task Force. The role of dietary protein and vitamin D in maintaining musculoskeletal health in postmenopausal women: a consensus statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Maturitas* 2014; **79**: 122-132 [PMID: 25082206 DOI: 10.1016/j.maturitas.2014.07.005]
 - 19 **Zhen D**, Liu L, Guan C, Zhao N, Tang X. High prevalence of vitamin D deficiency among middle-aged and elderly individuals in northwestern China: its relationship to osteoporosis and lifestyle factors. *Bone* 2015; **71**: 1-6 [PMID: 25284157 DOI: 10.1016/j.bone.2014.09.024]
 - 20 **Tang BM**, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 2007; **370**: 657-666 [PMID: 17720017 DOI: 10.1016/s0140-6736(07)61342-7]
 - 21 **Avenell A**, Mak JC, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures in postmenopausal women and older men. *Cochrane Database Syst Rev* 2014; CD000227 [PMID: 24729336 DOI: 10.1002/14651858.CD000227.pub4]
 - 22 **Weaver CM**, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, Liu S, Looker AC, Wallace TC, Wang DD. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. *Osteoporos Int* 2016; **27**: 367-376 [PMID: 26510847 DOI: 10.1007/s00198-015-3386-5]
 - 23 **Tarantino U**, Iolascon G, Cianferotti L, Masi L, Marcucci G, Giusti F, Marini F, Parri S, Feola M, Rao C, Piccirilli E, Zanetti EB, Cittadini N, Alvaro R, Moretti A, Calafiore D, Toro G, Gimigliano F, Resmini G, Brandi ML. Clinical guidelines for the prevention and treatment of osteoporosis: summary statements and recommendations from the Italian Society for Orthopaedics and Traumatology. *J Orthop Traumatol* 2017; **18**: 3-36 [PMID: 29058226 DOI: 10.1007/s10195-017-0474-7]
 - 24 **Compston J**, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis JA, McCloskey EV, Poole KES, Reid DM, Selby P, Thompson F, Thurston A, Vine N; National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2017; **12**: 43 [PMID: 28425085 DOI: 10.1007/s11657-017-0324-5]
 - 25 **Al-Saleh Y**, Sulimani R, Sabico S, Raef H, Fouda M, Alshahrani F, Al Shaker M, Al Wahabi B, Sadat-Ali M, Al Rayes H, Al Aidarous S, Saleh S, Al Ayoubi F, Al-Daghri NM. 2015 Guidelines for Osteoporosis in Saudi Arabia: Recommendations from the Saudi Osteoporosis Society. *Ann Saudi Med* 2015; **35**: 1-12 [PMID: 26142931 DOI: 10.5144/0256-4947.2015.1]
 - 26 **Al-Daghri NM**, Al-Saleh Y, Aljohani N, Sulimani R, Al-Othman AM, Alfawaz H, Fouda M, Al-Amri F, Shahrani A, Alharbi M, Alshahrani F, Tamimi W, Sabico S, Rizzoli R, Reginster JY. Vitamin D status correction in Saudi Arabia: an experts' consensus under the auspices of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO). *Arch Osteoporos* 2017; **12**: 1 [PMID: 28004295 DOI: 10.1007/s11657-016-0295-y]
 - 27 **Erem S**, Atfi A, Razzaque MS. Anabolic effects of vitamin D and magnesium in aging bone. *J Steroid Biochem Mol Biol* 2019; **193**: 105400 [PMID: 31175968 DOI: 10.1016/j.jsbmb.2019.105400]
 - 28 **Schulz K**, Kalscheuer H, Lehnert H. Personalized Therapy In Osteoporosis. *Dtsch Med Wochenschr* 2019; **144**: 1111-1119 [PMID: 31416102 DOI: 10.1055/a-0841-8336]



Published by Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

