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ARAŞTIRMA / RESEARCH

The influence of calcium, vitamin D and parathyroid hormone levels on the prognosis of critical patients

Kalsiyum, D vitamini ve paratiroid hormon düzeylerinin kritik hastaların prognozuna etkisi

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Abstract

Purpose: There are not enough studies evaluating the change in electrolytes and hormones in patients with sepsis. The aim of our study is to evaluate the relationship between the changes in serum calcium (Ca), magnesium (Mg), phosphorus (P), 25-hydroxyvitamin D (25(OH)D) and parathyroid hormone (PTH) levels and mortality in patients with sepsis.
Materials and Methods: Our study was conducted on patients with sepsis who were hospitalized in the intensive care unit (ICU) between October 2017 and January 2019. The levels of Ca, Mg, P, 25(OH)D and PTH, together with demographic and clinical characteristics of non-survivor and survivor patients, were compared.
Results: A total of 225 patients were enrolled into the study. Of the 225 patients, 94 patients (41.2%) died and 131 patients (58.8%) were discharged. PTH and P levels were found to be significantly higher, and 25(OH)D, Ca, and Mg levels were significantly lower in non-survivor patients than in survivor patients.
Conclusions: During sepsis, the change in Ca metabolism which is in a delicate balance, in the direction of hypocalcemia, hypomagnesemia, hyperphosphatemia, low 25(OH)D and high PTH were found to be associated with mortality.
Keywords:. 25-hydroxyvitamin D, calcium, mortality, parathyroid hormone, sepsis

Öz

Amaç: Sepsisli hastalarda elektrolit ve hormonlardaki değişimi değerlendiren yeterli çalışma yoktur. Çalışmamızın amacı serum kalsiyum (Ca), magnezyum (Mg), fosfor (P), 25-hidroksivitamin D (25(OH)D) ve paratiroid hormon (PTH) düzeylerindeki değişimler ile sepsisli hastalarda mortalite arasındaki ilişkiyi değerlendirmektir.
Gereç ve Yöntem: Çalışmamız Ekim 2017-Ocak 2019 tarihleri arasında yoğun bakım ünitesinde (YBÜ) yatan sepsisli hastalar üzerinde yapılmıştır. Kalsiyum, Mg, P, 25(OH)D ve PTH düzeyleri, demografik ve klinik özellikleri ile birlikte hayatta kalan ve ölen hastalar karşılaştırıldı.
Bulgular: Çalışmaya toplam 225 hasta alındı. 225 hastanın 94'ü (%41,2) öldü ve 131'i (%58,8) taburcu edildi. Ölen hastalarda hayatta kalan hastalardan, PTH ve P seviyeleri anlamlı derecede daha yüksek, 25(OH)D, Ca ve Mg seviyeleri ise anlamlı derecede daha düşük bulundu.
Sonuç: Sepsis sırasında hassas bir denge içinde olan Ca metabolizmasının hipokalsemi, hipomagnezemi, hiperfosfatemi, düşük 25(OH)D ve yüksek PTH yönünde değişmesi mortalite ile ilişkilendirildi.

Anahtar kelimeler: 25-hidroksivitamin D, kalsiyum, mortalite, paratiroid hormon, sepsis.

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INTRODUCTION

Systemic inflammatory response syndrome (SIRS), sepsis, and septic shock are responsible for significant number of deaths. Sepsis and septic shock occur as a result of an irregular activation of the body's host defense system, in response to microbial stimulation. Despite important advances in understanding the pathophysiology of sepsis; the precise mechanisms, related cell types and mediators involved in the disease mechanism are, still speculative[1].

Calcium (Ca) circulates in the blood in three forms: the protein-bound fraction constitutes 50%, the diffusible fraction 10% and the ionized one of 40%. Ionized fraction is the only physiologically active form[2]. Calcium has widespread extra and intracellular effects, thus; the hormone secretion and responsiveness, a component of the bone matrix, enzyme activity, nerve conduction, muscle contraction, and polarization of membrane. Although there is regulated system to keep extracellular ionized Ca concentrations in a narrow physiological range, hypocalcemia is commonly seen in critically ill patients and has been associated with disease's severity[3,4]. In addition, hypocalcemia is especially common in patients with sepsis and is associated with increased mortality. The mechanisms of how critical illness leads to impaired calcium homeostasis are not well understood and controversial[2]. Magnesium (Mg) is the fourth most abundant cation in the body and the second most abundant intracellular cation in the body. Mg deficiency plays a role in the pathophysiology of some of the diseases[5].

There are two main hormones which are 1,25-dihydroxyvitamin D3 and parathyroid hormone (PTH), that regulate the levels of serum Ca, Mg and phosphorus (P)[2]. Vitamin D exerts multiple effects on innate and adaptive immune responses, endothelial function, and mucosal barrier[6]. The effect of 25-hydroxyvitamin D (25(OH)D) in infections is uncertain[6-8]. Vitamin D deficiency is thought to be associated with increased mortality in septic adults[1,7]. Various possible mechanisms, including parathyroid gland insufficiency, Vitamin D metabolism and function, and hypomagnesemia, are blamed for negative clinical results[2,3]. In addition to hypocalcemia, hypomagnesemia, low Vitamin D, hyperphosphatemia and high PTH concentrations are common findings associated with severity and mortality of disease. In addition, most of the mechanisms that lead to these abnormalities in critical diseases remain unclear[9].

There are not enough studies to examine all of calcium and related hormones in critically ill patients. The studies in the literature, separately evaluated the relationship of the above parameters with mortality. If all parameters are evaluated together, the effect on calcium metabolism and mortality in sepsis, can be better understood. The main hypothesis of our study is that, the main cause of hypocalcemia in sepsis is the decrease in level of vitamin D and high PTH level in response to hypocalcemia. Therefore, severe hypocalcemia, low vitamin D and high PTH levels during sepsis may increase mortality. The aim of this study is to evaluate the possible relationship between serum Ca, Mg, P, Vitamin D and PTH and clinical outcomes, in sepsis.

MATERIALS AND METHODS

Study design

Our study was carried out prospectively between October 2017 and January 2019 on patients hospitalized in the intensive care unit (ICU) for sepsis. The informed consent was obtained after the application was made to the local ethics committee before the study (Ankara Numune Training and Research Hospital Clinical Research Ethics Committee, ethic no: E-17-1254, date: 21/09/2017). The study was performed by the department of anesthesiology and clinical of critical care, in Ankara Numune Training and Research Hospital. The data were obtained from the hospital's electronic patient registry (Nucleus Automation System) and patient files. Both verbal and written consent was obtained from each patient or legal representative before the study. All data collected during this study were kept confidential in terms of the reliability of the records and the confidentiality and privacy of the patients included in the study and were not shared anywhere. During the study process, the authors conducted the study in accordance with the Helsinki Declaration principles.

Data collection

ICU patients with primary admission cause of sepsis were enrolled into the study. Patients hospitalized in the ICU with other causes than sepsis (intoxication, neurological and metabolic disorders, trauma, myocardial infarction, etc.) were excluded from the

study. Sepsis, the presence of suspected infection and the SIRS has been defined as having two of the four criteria [1- temperature; > 38 ° C or <36 ° C, 2- heart rate; > 90 / min, 3- respiratory rate; > 20 / min or PaCO2 <32 mmHg, 4- white blood cell count (WBC) > 12,000 / μL or <4000 / μL][10,11]. Patients diagnosed with sepsis were treated according to the "International Guidelines for Management of Sepsis and Septic Shock" guideline[12]. According to our routine protocol, all patients admitted to the ICU were diagnosed and treated according to this international guideline.

Age of patients during admission, their gender, duration of mechanical ventilation (MV), hospital stay, sepsis-related organ failure assessment (SOFA) score, acute physiology and chronic health evaluation (APACHE) II score, presence of bacteremia, C-reactive protein (CRP), WBC, and mortality data has been detailly noted[13,14]. The patients who were followed by two ICU specialists (EYC, IOT) were included in this study. Laboratory analysis was performed by two biochemists (CY, MK).

Laboratory analysis

Serum levels of CRP, WBC, and bacteremia

Venous blood samples were collected from patients with sepsis, during their admission to ICU. WBC was examined from the blood, which were obtained in tubes containing ethylenediamine tetra-acetic acid. Blood samples were centrifuged at 3000 rpm for 15 minutes. CRP were determined by a Tinaquant CRP (Latex) highly sensitive immuno-turbidimetric assay on the Roche Modular P analyzer (CRP latex HS, Roche kit, Roche Diagnostics, GmbH, Mannheim, Germany). Bacteremia were identified by using the BACTEC FX automatic blood culture detection system (Becton Dickinson, Sparks, MD, USA)[15].

25(OH) D, PTH, Ca, Mg and P serum levels

25 (OH) D analysis was analyzed using a Nexera XR HPLC system coupled with a Shimadzu Liquid Chromatograph Mass Spectrometer 8045 (Shimadzu Corporation, Kyoto, Japan) triple quadrupole mass spectrometer (reference range: 20-50 ng/mL). PTH measurements were made immunoenzymatically on UniCel DxI 800 autoanalyzer (Beckman Coulter, Inc., Fullerton, U.S.A.) (reference range: 12-88 pg/mL). Ca, Mg and P levels were measured by colorimetric/fluorescent method with Beckman Coulter AU5800 (Beckman Coulter AU5800, Brea, CA USA) device. Reference range for Ca, Mg and P, respectively; It is 7.6-10.4 mg/dL, 1.80-2.60 mg/dL, and 2.50-4.50 mg/dL. Demographic and clinical characteristics and laboratory parameters were compared for non-survivor and survivor patients with sepsis.

Statistical analysis

As statistical analysis, SPSS program 17.0 (SPSS, Chicago, IL) was used for data analysis. Histogram and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk Test) were used to evaluate the variables in terms of compliance with normal distribution. We used Mann Whitney's U test or T test to compare non-parametric continuous (laboratory) variables of independent samples, and used Fisher's exact test or chi-square test for categorical (demographic and clinical) variables. The result was reported as the median (minimum-maximum) of continuous variables. The categorical variables were represented as frequency and percentage distributions. Receiver operating characteristic (ROC) analysis was carried out to determine mortality in patients with sepsis. After ROC analysis, area under the curve (AUC), 95% confidence interval, cut off values, sensitivity and specificity values were calculated for Ca, Mg, P, Vitamin D and PTH. If the p value was less than 0.05 after the analysis, it was considered statistically significant. The sample size calculated at a power of 90% and a significance level of 5% by using G*Power software (version 3.1.9.4, Kiel University, Kiel, Germany), was approximately 86 patients per group, with an effect size of 0.80 for statistical significance.

RESULTS

A total of 722 patients were admitted to the ICU during the study period. According to the exclusion criteria, 497 patients with a reason for hospitalization other than sepsis, were excluded from the study. During the study period, 225 patients were enrolled into the study according to the inclusion criteria. Mortality rate was found as 41.6% (94/225) for all of the study patients. Of the 225 patients, 94 patients (41.2%) died, and 131 patients (58.8%) were discharged. Bacteremia rate in blood culture for all patients was found to be 34.6% (78/225). 25 (OH) D levels of all study patients were found to be 12.03 ± 10.1 ng / mL, lower than normal ranges; and PTH levels were 108.21 ± 95.70 pg / mL higher than normal ranges. Results were similar in terms of age, sex, duration of MV, hospital stay and WBC in non-

survivor and survivor patients (p> 0.05). APACHE II and SOFA scores, bacteremia ratio, CRP, PTH, P levels were significantly higher in non-surviving patients compared to surviving patients, while 25(OH)D, Ca, and Mg levels were found to be significantly lower (p <0.05) (Table 1) (Figure 1).

Table 1. Comparison of demographic and clinical features between survivors and non-survivors

Variables	Survivors (n=131)	Non-survivors (n=94)	P value
Age, (years), [a]	77 (29-96)	76 (52-94)	0.546
Male gender, n (%)	72 (54.9)	41 (43.6)	0.061
APACHE II score, [a]	20 (8-33)	24 (11-48)	<0.001*
SOFA score, [a]	6 (3-17)	9 (5-24)	<0.001*
Bacteremia, n (%)	26 (19.8)	52 (55.3)	<0.001*
White blood cell, (x103/µL) [a]	8.8 (1.3 -16.5)	10.4 (1.9-27.0)	0.496
C-reactive protein, (mg/L) [a]	86 (12-270)	154 (23-269)	<0.001*
Duration of MV, (days), [a]	4 (2-41)	7 (1-39)	0.112
Hospital stay, (days), [a]	11 (5-46)	19 (4-50)	0.949
Calcium, mg/dL, [a]	8.9 (6.9-10.9)	7.4 (5.3-8.9)	<0.001*
Magnesium, mg/dL, [a]	2 (1-2.9)	1.8 (0.9-2.9)	0.003*
Phosphorus, mg/dL, [a]	3.2 (2.5-6.2)	3.9 (2.3-8.8)	<0.001*
25-dihydroxyvitamin D, ng/mL, [a]	14 (0.94-71)	3.1 (0.2-26.1)	<0.001*
Parathyroid hormone, pg/mL, [a]	57 (11-266)	120 (9-999)	<0.001*

[a] median (minimum-maximum), APACHE II: acute physiology and chronic health evaluation score, SOFA: sepsis-related organ failure assessment score, MV: mechanical ventilation ; *Statistically significant p values are highlighted.

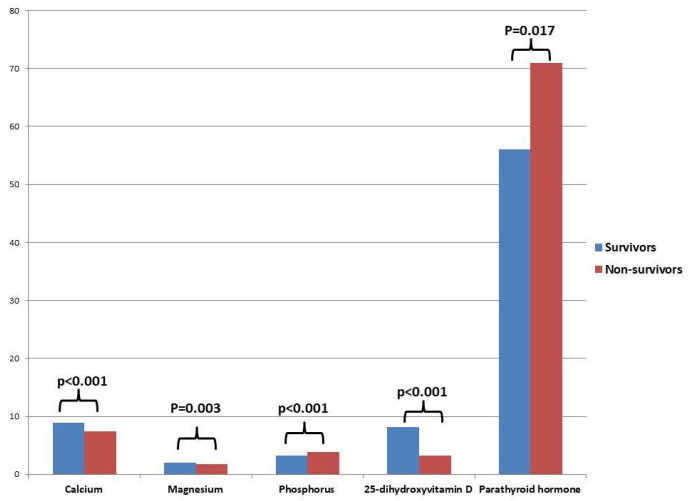
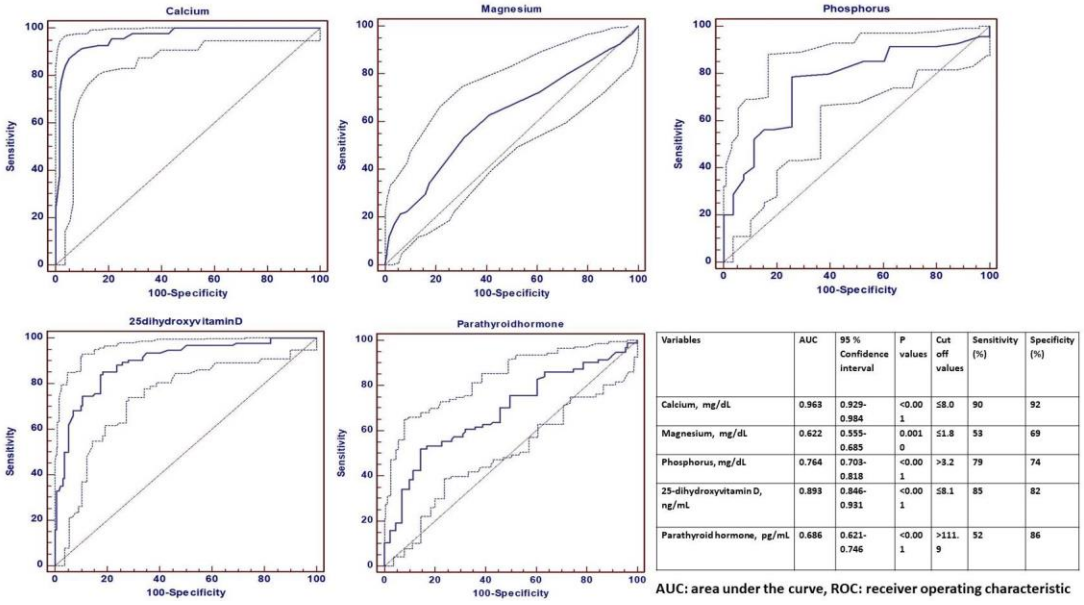


Figure 1. Calcium, magnesium, phosphorus, vitamin D and parathyroid hormone levels in the groups

The cut-off values for mortality in sepsis were ≤8.0 mg/dL for Ca levels (AUC:0.963), ≤1.8 mg/dL for Mg (AUC:0.622), >3.2 mg/dL for P (AUC:0.764), ≤8.1 ng/mL for 25(OH)D levels (AUC:893) and >111.9 pg/mL for PTH levels (AUC:0.686) (p<0.001, p=0.001, p<0.001, p<0.001, and <0.001, respectively). The results are presented in the Figure 2 as AUC, confidence interval, p values, sensitivity, specificity and ROC curves.



Variables	AUC	95 % Confidence interval	P values	Cut off values	Sensitivity (%)	Specificity (%)
Calcium, mg/dL	0.963	0.929-0.984	<0.001	≤8.0	90	92
Magnesium, mg/dL	0.622	0.555-0.685	0.0010	≤1.8	53	69
Phosphorus, mg/dL	0.764	0.703-0.818	<0.001	>3.2	79	74
25-dihydroxyvitamin D, ng/mL	0.893	0.846-0.931	<0.001	≤8.1	85	82
Parathyroid hormone, pg/mL	0.686	0.621-0.746	<0.001	>111.9	52	86

AUC: area under the curve, ROC: receiver operating characteristic

Figure 2. ROC curves for calcium, magnesium, phosphorus, 25-hydroxyvitamin D and parathyroid hormone in the prediction of mortality in sepsis.

DISCUSSION

In our study, low 25 (OH) D, Ca, Mg levels and high CRP, PTH and P levels were found to be associated with mortality in patients with sepsis who were hospitalized in ICU. In addition to the increased CRP which is assumed to be a marker of higher inflammation in patients with mortality, lower levels of Ca, Mg, and Vitamin D is thought to be the result of higher inflammatory response[16]. APACHE II, SOFA score and bacteremia rate were also found to be higher in patients who lost their lives, compared to patients who were discharged, similar to some previous studies[1,17,18].

During critical illness, systemic electrolyte concentrations are often disturbed. These electrolyte irregularities have been classically considered as harmful and therefore require closely follow-up and treatment[4]. The main ones of these electrolytes are Ca, Mg and P [2,4,5]. Hypocalcemia is common in critical illness and especially in septic conditions. Hypocalcemia in septic ICU patients can occur without an increase in bone resorption and urinary calcium excretion[16]. The reason for the decrease in serum Ca in sepsis, is due to intracellular migration, decreased parathyroid function, renal 1-α hydroxylase deficiency, vitamin D deficiency and calcitriol resistance. Resuscitation with large volumes of liquid, crystalloid and albumin solutions may also cause hypocalcemia[19]. In our results, it was found that there is a relationship between hypocalcemia and mortality. Supporting our results, some previous studies show that the development of hypocalcemia is a risk factor for increased mortality[1,4]. However, a causal relationship between mortality and hypocalcemia has not been completely revealed. The clinical benefit of Ca supplementation in the case of hypocalcemia in critically ill patients is also controversial[4]. Irregular intracellular calcium use and rapid calcium entry into the cytoplasm are thought to be the cause of the potential harm of parenteral Ca supplementation[4,16]. These changes in intracellular Ca are thought to contribute to increased inflammatory response, cellular death, and subsequent organ dysfunction[4,20]. Supporting this information, we found lower serum Ca levels in patients who died. Therefore, although hypocalcemia increases the negative results, uncertainties about the treatment approach still persist.

Mg is required for energy metabolism, nucleic acid transcription, messenger RNA translation, protein synthesis, and is responsible for the regulation of

mitochondrial function. Immunologically, Mg ions have an important role in macrophage activation, adhesion and bactericidal activity of granulocyte oxidative burst, lymphocyte proliferation and endotoxin binding to monocytes[21]. Mg deficiency plays a role in the pathophysiology of same diseases and has been associated with increased mortality[22]. Mg's critical role in sepsis is due to the immune system effects that are important in sepsis pathogenesis. Hypomagnesemia depletes endogenous antioxidants and predisposes myocardium to reperfusion injury with the accumulation of inflammatory cells. In our results, the lower Mg level in patients with mortality, can be explained by the critical tasks of the Mg ion. For all these reasons, Mg deficiency may be associated with poor outcomes in critically ill patients with sepsis. Because of this, recognition and treatment of hypomagnesemia is of great importance. ICU clinicians should pay attention to the evaluation and treatment of hypomagnesemia[5].

Hyperphosphatemia is also common in severe sepsis and septic shock. Excess phosphate can lead to severe cell death in ongoing septic shock. In addition, hyperphosphatemia may also cause direct toxicity. Although data on hyperphosphatemia in critically ill patients are limited, possible mechanisms include vascular inflammation, reactive oxygen types caused by mitochondrial dysfunction, ischemia, and exacerbation of cardiovascular disease[23]. Consistent with this information, we found an increment in serum P levels in patients with mortality. Patients with sepsis who were hospitalized in ICU, should be evaluated, in terms of serum Ca, Mg and P levels in addition to clinical parameters and should be followed closely in terms of treatment.

In addition to the regulation of Ca homeostasis, vitamin D has broad biological effects which are nuclear transcription, regulation of cell cycle, differentiation, apoptosis, regulation of inflammation and protection from infection, induction of cathelicidin, an antimicrobial peptide, changes in glutathione and glutamate pathway metabolic profiles[1,24, 25]. As in other studies highlighting its potential role in the regulation of inflammation, low levels of 25(OH)D3 are associated with reduced survival in ICU[26,27]. Our data confirm these studies. The cause of increased mortality with low 25(OH)D is impaired metabolism, fluid resuscitation, decreased Vitamin D serum levels during the acute phase of sepsis, decreased Vitamin D binding protein synthesis due to liver dysfunction, interstitial extravasation caused by increased vascular permeability and renal registration of Vitamin D. In septic patients, there is also a decrease in the conversion of 25(OH)D to 1.25 (OH) D3 in the kidneys[26]. However, no benefit was seen on severe infection or sepsis, after Vitamin D supplementation in patients with Vitamin D deficiency. This may be due to the small number of low doses, short supplementation times, and possibly conversion of Vitamin D to alternative metabolites and epiforms[7,26]. On the contrary, Vitamin D supplementation may be beneficial as a potential therapeutic agent in hospitalized patients[24]. The causal relationship is not fully known. Although Vitamin D is thought to help prevent secondary complications and reduce mortality in high-risk patients, there is no rationale cause suggesting that Vitamin D supplementation may be beneficial in patients with Vitamin D deficiency and sepsis hospitalized in ICU[26]. Therefore, clinical studies investigating Vitamin D deficiency and the effects of Vitamin D supplementation on sepsis and mortality are needed. In addition, Vitamin D levels of healthy individuals should be carefully monitorized and if necessary be improved in terms of public health.

Another regulator of Ca, Mg and P regulation is hormone PTH. PTH increases in response to hypocalcemia and hyperphosphatemia[28]. We found that patients with mortality had lower levels of Ca, Mg, 25 (OH) D and higher levels of P, PTH and these results were consistent with the severity of the inflammatory response in sepsis. The reason for hypocalcemia for patients with sepsis is due to the decrease in PTH's effect on both the kidney and bone[16].

Our study has limitations in some aspects. We could not evaluate the volume of fluid resuscitation given to the patients and the ionized Ca and calcitonin levels. The parameters examined are only the values at the time of hospitalization and we do not know the levels during hospitalization period. Finally, our results cannot be reflected in general since the data is from a single center.

In conclusion, studies investigating entire electrolytes and hormones -but especially calcium- related to mortality in sepsis, are insufficient. Our study showed how the changes in hormones affecting calcium and calcium affect mortality in sepsis. Hypocalcemia, hypomagnesemia, hyperphospatemia, Vitamin D deficiency and PTH increase were found to be

associated with mortality in patients with critical sepsis. Therefore, Ca metabolism and related hormones can provide information about the clinical outcomes of patients with sepsis or keeping them at normal levels with close monitoring can improve clinical results. Vitamin D supplementation is not recommended as panacea. However, Vitamin D plays an important pleiotropic role in the emergence of critical illness and may support recovery from serious acute illnesses. More clinical studies should be conducted to determine the potential Vitamin D level target and dose strategies required to achieve the benefit.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EYC, CY; Veri toplama: EYC, CY; Veri analizi ve yorumlama: CY, MK; Yazı taslağı: EYC; İçeriğin eleştirel incelenmesi: IOT; Son onay ve sorumluluk: EYC, CY, MK, IOT; Teknik ve malzeme desteği: CY, MK; Süpervizyon: IOT; Fon sağlama (mevcut ise): yok.
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