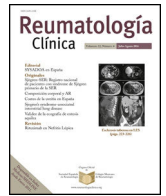




Sociedad Española
de Reumatología -
Colegio Mexicano
de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org



Review Article

Is There Really a Relationship Between Serum Vitamin D (25OHD) Levels and the Musculoskeletal Pain Associated With Statin Intake? A Systematic Review[☆]



Claudia Alejandra Pereda,^{a,*} Maria Betina Nishishinya^b

^a Hospital Mediterráneo, Almería, Spain

^b Instituto Traumatológico Quirón, Barcelona, Spain

ARTICLE INFO

Article history:

Received 23 November 2015

Accepted 10 March 2016

Available online 27 October 2016

Keywords:

Vitamin D

Statins

Musculoskeletal pain

ABSTRACT

Introduction: Musculoskeletal pain associated to statin use, is the most common adverse event, leading to cessation of treatment. Several studies proposed Vitamin D deficiency to increase the risk of pain associated to statin intake.

Objectives: To evaluate whether vitamin D status is linked to musculoskeletal pain associated to statin use.

Methods: We performed a systematic review based on electronic searches through MEDLINE, Cochrane Central and EMBASE to identify studies that (1) included patients on statin therapy, (2) with vitamin D serum levels assessment, (3) in relation to musculoskeletal pain.

Results: The electronic search identified 127 potentially eligible studies, of which three were included and analyzed in the present study. The heterogeneity of studies did not allow metaanalysis. A systematic review and two cohort studies not included in the previous systematic review, revealed a statistically significant association of vitamin D deficit in patients with musculoskeletal pain on statin therapy.

Conclusion: The displayed evidence suggests a significant association between 25OHD serum levels <30 ng/ml and the presence of musculoskeletal pain in patients on statin therapy.

© 2015 Elsevier España, S.L.U. and Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. All rights reserved.

¿Existe relación entre los niveles séricos de vitamina D (25OHD) y el dolor musculoesquelético relacionado con la ingesta de estatinas? Revisión sistemática

RESUMEN

Introducción: El dolor musculoesquelético (DME) asociado a estatinas es el efecto adverso más frecuente y responsable de su abandono. Diversos trabajos sugieren que el déficit de vitamina D incrementa el riesgo de padecer dolor asociado a estatinas.

Objetivos: Evaluar una posible asociación entre el nivel de vitamina D y la presencia de DME en pacientes en tratamiento con estatinas.

Métodos: Se realizó una búsqueda bibliográfica en Medline, Cochrane Central y EMBASE para identificar estudios que: 1) incluyeran pacientes tratados con estatinas; 2) en los que valoraran niveles séricos de vitamina D, 3) en relación con DME.

Resultados: Se identificaron 127 estudios de los que se incluyeron y analizaron finalmente 3. La heterogeneidad de los estudios no permitió realizar metaanálisis. Una revisión sistemática y 2 estudios de cohorte no incluidos en la revisión previa mostraron una asociación significativa entre el déficit de vitamina D y el DME.

Palabras clave:

Vitamina D

Estatinas

Dolor musculoesquelético

[☆] Please cite this article as: Pereda CA, Nishishinya MB. ¿Existe relación entre los niveles séricos de vitamina D (25OHD) y el dolor musculoesquelético relacionado con la ingesta de estatinas? Revisión sistemática. Reumatol Clin. 2016;12:331–335.

* Corresponding author.

E-mail addresses: cpereda@ser.es, pereda063@gmail.com (C.A. Pereda).

Conclusiones: La evidencia sugiere una asociación significativa entre niveles séricos de 25OHD <30 ng/ml y la presencia de DME.

© 2015 Elsevier España, S.L.U.

y Sociedad Española de Reumatología y Colegio Mexicano de Reumatología. Todos los derechos reservados.

Introduction

Statins have demonstrated their efficacy both in the prevention of cardiovascular mortality and its overall reduction.¹ As a consequence, the number of patients receiving statin therapy has grown substantially and continues to increase. However, nearly 15%–30% of them will develop musculoskeletal pain (MSP) as the major adverse effect, which often leads to their discontinuing the treatment.² The mechanism of the production of the pain is unknown and, potential factors include genetic predisposition, a possible mitochondrial dysfunction, a dysfunction involving coenzyme Q synthesis and/or cholesterol.³

Recent studies have suggested that vitamin D deficiency would be associated with MSP induced by statins and, that this could be reversible with vitamin D supplementation and the subsequent normalization of serum 25-hydroxyvitamin d (25OHD) levels.^{4,5}

We performed the present systematic review of the literature for the purpose of determining whether serum 25OHD levels were associated or not with a higher prevalence of MSP related to the intake of statins.

Materials and Methods

Source of Data and Search Strategy

A systematic search was performed in 3 databases: Medline, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (up to October 2015), through the documentation service of the Sociedad Española de Reumatología (SER).

Moreover, we performed a manual search of the abstracts from meetings of the American College of Rheumatology (ACR) and the European League Against Rheumatology (EULAR) of the last 3 years. We included studies in English and Spanish.

See the search strategy (Appendix A) (available at the website).

Inclusion Criteria

- *By population:* adult patients (≥ 18 years) with any underlying disease being treated with statins (of any type or dose).
- *By factor:* evaluation of serum 25OHD levels.
- *By outcome:* musculoskeletal pain.
- *By type of study:* systemic reviews (SR), cohort and/or longitudinal studies that have been published after the most recently updated SR. Designs that evaluate risk factors (association).
- *By sample number:* >20 per group.

Review Methodology

Independently, 2 reviewers (CAP/MBN) reviewed the identified abstracts (inclusion criteria and quality of the selected studies), and differences in criteria were resolved by consensus. The citations were handled using ENDNOTE X, version 7.2.

The quality of the studies was evaluated utilizing New Castle-Ottawa Scale (NOS)⁶ and the Checklist SIGN (SR). Differences in criteria were resolved by consensus.

Statistical Analysis

We did not perform a meta-analysis, but did identify a SR^2 that utilized weighted mean difference, and used the statistical heterogeneity measured by Cochran Q test and I^2 .

The results are presented in narrative form.

Results

The combined search identified 127 studies, 119 of which were excluded as they did not meet the inclusion criteria, and another 5 were ruled out as they were duplicates. Finally, 3 studies were included (Fig. 1): 1 of which was a SR, by Michalska-Kasiczak et al.,² that contained 7 studies,^{1,7–12} as well as, another 2 that were cohort studies, which had been published more recently, Mergenhausen et al.¹³ and Morioka et al.¹⁴

With regard to quality, the SR is acceptable (SIGN), as are the cohort studies (NOS 6–7) (Table 1).

The total population of the studies was 3927 patients, 1038 of whom (26.43%) had MSP, whereas the rest, 2889 (73.53%), were asymptomatic. The mean age of the patients was 61.7 years, and ranged between 58 and 69 years. There were 1026 women and 1527 men; there were no population-based data from the 3 studies.^{1,7,12}

The drug most widely used was simvastatin^{2,12,13}; it was followed in frequency by atorvastatin,^{2,12} pravastatin,^{2,8} and

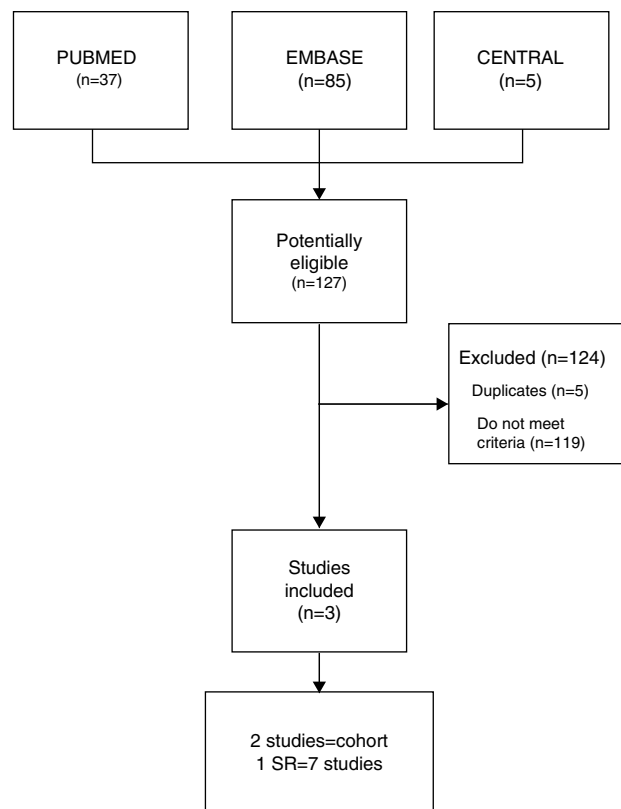


Fig. 1. Flow chart. SR, systemic review.

Table 1
General Features of the Studies.

Study Country	Studies (included in SR) Country	Study design Registry (years)	Total n MSP (%)	Population Sex (M/W) Age (years)	Statins Doses	MSP 25OHD ng/mL Mean (SD)	Asymptomatic 25OHD ng/mL Mean (SD)
Michalska-Kasieczak et al., 2015	Duell and Connor 2008 ND Ahmed et al., 2009 United States Linde et al., 2010 United States Backes et al., 2011 United States Riphagen et al., 2012 The Netherlands Eisen et al., 2014 Israel Palamaner Subash Shanta et al., 2014 United States	Cross-sectional ND Cross-sectional 2007–08 Cohort, retrospective Cohort, retrospective Prospective, observational 2009–10 Cohort, retrospective 2007–10 Cohort, retrospective 2005–12	n=99 (38.4)	Sex: ND 58–59.3	All Doses: ND	20.5 (10)	30.1 (12.5)
			n=621 (20.6)	MSP=128 (52/76) 58–60	All Doses: ND	28.6 (13.2)	34.2 (13.8)
			n=64 (60.9)	MSP=39 (21/18) 59	All Doses: 5–80 mg	28.2 (11.6)	24.3 (10.5)
			n=129 (44.2)	MSP=57 (26/31) 58–62.4	All Doses: ND	21.4 (9.7)	21.8 (12.1)
			n=75 (29.3)	Sex: ND 65	All Doses: ND	18	15.2
			n=272 (39)	MSP=106 (52/54) 66–69	All Doses: ND	19.1 (4.1)	20.2 (6.0)
			n=1160 (27.8)	Sex: ND 55.9	Atorvastatin/ Simvastatin Doses: ND	22.3 (7.1)	33.8 (4.5)
			n=450 (11.1)	MSP=50 (45/5) 65–69	Simvastatin Doses: 80 mg	26.2 (12.9)	36.3 (11.8)
			n=1057 (30.5)	M: 565/W: 492 62.8	ND	25OHD <15 OR: 1.90 (1.18–3.05)	25OHD ≥15 OR: 0.91 (0.71–1.16)
			Mergenhagen et al., 2014 United States	Cohort, retrospective 2006–11			
Morioka et al., 2015 United States	Cross-sectional, National Health Nutrition Examination Survey (NHNES) 2001–2004						

M, man; MSP, musculoskeletal pain; ND, no data; OR, odds ratio; SD, standard deviation; SR, systematic review; W, woman.

rosuvastatina.^{1,2} The doses used and the duration of the treatment were specified in only 1 of the cohort studies,¹³ in which simvastatin was employed at 80 mg/day.

With respect to cointerventions, the authors of a single study,⁹ mention the utilization of other drugs like niacin, fenofibrate, diltiazem and verapamil.

In the SR² (which included 7 studies; n=2420 patients) 27.5% patients had MSP, probably related to the intake of statins. The comparison of the mean serum levels of 25OHD in patients with MSP and asymptomatic patients, there was a mean of 28.4 ng/mL in the first group vs 34.8 ng/mL in the asymptomatic group. The weighted mean difference was: -9.41 ng/mL (-10.17 to -8.64), with an elevated heterogeneity test ($I^2=94%$; $P=.00001$).

In the study by Mergenhagen et al.¹³ (n=450), 11.1% of the patients had MSP. In the comparison of the mean serum 25OHD level in patients with MSP and those who were asymptomatic, there was a mean of 26.2 ng/mL in the group with pain vs 36.3 ng/mL in the asymptomatic patients, with a mean difference of 10 ng/mL ($P=.0003$).

Finally, in the report by Morioka et al.¹⁴ (n=5907), 1057 (18%) of whom received statins, and 30.5% of this group, had MSP. Of these symptomatic patients, 43.8% (33.5%–54.6%) had 25OHD <15 ng/mL vs 28% (23.4%–33.2%) who had levels >15 ng/mL ($P=.01$).

These authors calculate the odds ratio (OR) of patients who are taking statins of developing MSP: if the 25OHD level is <15 ng/mL, the OR=1.90 (1.18–3.05; $P=.01$), and if the 25OHD level is >15 ng/mL, the OR=0.91 (0.71–1.16; $P=.43$) (Table 2).

Table 2
Serum 25OHD Levels in Patients With and Without Musculoskeletal Pain.

Author/year	Studies included in SR	Population (n)	Musculoskeletal pain n (%)		25OHD level ng/mL Mean (SD)		P
			With MSP	Without MSP	With MSP	Without MSP	
Michalska-Kasieczak et al., 2015	Duell and Connor 2008 Ahmed et al., 2009 Linde et al., 2010 Backes et al., 2011 Riphagen et al., 2012 Palamaner Subash Shanta et al., 2014 Eisen et al., 2014	99	38 (38.8)	61 (61.6)	20.5 (±10)	30.1 (±12.5)	<.05
		621	128 (20.6)	493 (79.3)	28.6 (±13.2)	34.2 (±13.8)	.0001
		64	39 (60.9)	25 (39.0)	28.2 (±11.6)	24.3 (±10.5)	NS
		129	57 (44.1)	72 (55.8)	21.4 (±9.7)	21.8 (±12.1)	NS
		75	22 (29.3)	53 (70.6)	18.0	15.2	NS
		1160	276 (24.2)	864 (75.7)	22.3 (±7.1)	33.8 (±4.5)	.01
		272	106 (38.9)	166 (61.0)	19.1 (±4.1)	20.2 (±6)	NS
Mergenhagen et al., 2014	450	50 (11.1)	400 (88.9)	26.2 (±12.9)	36 (±11.8)	.0003	
Morioka et al., 2015	1057	322.3 (30.4)	734.7 (69.5)	25OHD (ng/mL) with MSP <15 (ng/mL) 43.8% (33.5–54.6) >15 (ng/mL) 28% (23.4–33.2)		.01	
n Total		3927 (100%)	1038 (26.5%)	2889 (73.5%)			

MSP, musculoskeletal pain; NS, not significant; SD, standard deviation; SR, systematic review.

Discussion

The present systemic review suggests the existence of an association between vitamin D deficiency and MSP. Therefore, about 1 out of every 4 patients who were receiving statins in the present work, will manifest MSP. In this respect, the definition of MSP related to statins is somewhat confusing and quite vague,¹⁵ as there is no internationally standardized classification.¹⁶ Its clinical form encompasses, from simple myalgia or muscle weakness, and even rhabdomyolysis. Thus, its most frequently observed presentation is muscle pain that is not associated with an elevation in creatine phosphokinase.^{16,17} Likewise, it is well-known that reduced serum vitamin D levels are also the cause of generalized MSP,¹⁸ and possibly, the presence of vitamin D receptor (VDR) in muscle cells supports this principle.¹⁹ The relationship between serum 25OHD levels <30 ng/mL and MSP associated with statins has been reported in certain uncontrolled series.^{8,20} Although, in a speculative manner, it has been estimated that the mechanism of interaction between MSP and statins and vitamin D deficiency could have a relationship with the activation of cytochromes CYP3A4, CYP2B6 and CYP2C9 in hepatocytes.³ Thus, vitamin D is an activator of these cytochromes, which, in turn, are responsible for metabolism of different statins, especially the lipophilic type (atorvastatin, simvastatin, lovastatin, fluvastatin and pravastatin).^{3,21} Their deficiency could explain a prolongation of the half-life of these drugs and their possible toxicity, resulting in MSP. The muscle fibers affected would be type II, which are also implicated in the myalgia caused by alcohol.²² Moreover, it is suggested that low vitamin D levels could reduce the transcriptional gene linked to VDR, decreasing the synthesis of proteins to repair the t-tubular system and prevent the subsarcolemmal rupture of those fibers.²² The combination of these 2 causal factors, the vitamin D deficiency and statins, would potentiate the involvement in type II muscle fibers, favoring the development of pain. This symptomatology appears to extend even to patients who receive statins on alternate days. Thus, the study of Minissian et al.²³ demonstrated that patients with MSP caused by statins, who also received treatment on alternate days for intolerance to these drugs, had significantly decreased serum vitamin D levels when compared with those patients who were tolerant to the daily therapies. In contrast, studies like those of Eisen et al.,¹¹ Kurnik et al.,²⁴ and Backes et al.,¹⁰ found no connection among serum vitamin D levels and risk of MSP in patients receiving statins. Possibly, this divergence corresponds to differences in the type of population studied, ethnic groups, type and dose of statins employed or the nutritional status of the patients, etc. Once again, in none of these studies is the season of the year mentioned or are the methods used to assess serum 25OHD levels. In this respect, it is important to point out that vitamin D level deficiency (<30 ng/mL or 75 nmol/L)^{25,26} is a prevalent condition in different populations and regions of the world.^{27–29} Moreover, this situation is becoming more extended and more profound in recent years.³⁰ For this reason, it is appropriate to mention, although it is not within the scope of this analysis, that uncontrolled studies have evaluated the response of patients with MSP due to statins to vitamin D supplementation, with encouraging results.^{4,5,8}

This review has certain limitations: limitations inherent in the type of design and the biases of the studies included (retrospective designs, duration of the registry of inaccurate data, etc.). Likewise, there is little information concerning the types, doses and duration of statin therapy on the part of the patients, and too few references on the presence of comorbidities and/or cointerventions. One particularity to be taken into account is the updated definition of statin-induced MSP, which, in our opinion, is very vague and can lead to confusion. Finally, we understand that it is very important to define the methodology for measuring vitamin D, as well as the

season of the year in which the sample is collected and is analyzed, and its evaluation according to age group.

We can conclude that the available evidence (a systematic review and 2 cohort studies) shows a prevalence of MSP associated with statins that ranges between 11% and 30%. There is also a significant association between decreased serum 25OHD levels, and a higher prevalence of statin-related MSP.

Well-designed, long-term, prospective studies are needed to confirm these results.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflict of Interest

The authors declare they have no conflict of interest.

Acknowledgements

The authors thank Dr. Loreto Carmona for her collaboration in the review of this article, and Ms. Mercedes Guerra, manager of documents and archives of the Research Unit of the Sociedad Española de Reumatología (SER), for her help in the literature search strategy and her assistance in obtaining the articles.

Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.reumae.2016.03.001>.

References

- Riphagen IJ, van der Veer E, Muskiet FA, DeJongste MJ. Myopathy during statin therapy in the daily practice of an outpatient cardiology clinic: prevalence, predictors and relation with vitamin D. *Curr Med Res Opin.* 2012;28:1247–52.
- Michalska-Kasiczak M, Sahebkar A, Mikhailidis DP, Rysz J, Muntner P, Toth PP, et al. Analysis of vitamin D levels in patients with and without statin-associated myalgia – a systematic review and meta-analysis of 7 studies with 2420 patients. *Int J Cardiol.* 2015;178:111–6.
- Bhattacharyya S, Bhattacharyya K, Maitra A. Possible mechanisms of interaction between statins and vitamin D. *Q J Med.* 2012;105:487–91.
- Glueck CJ, Budhani SB, Masineni SS, Abuchaibe C, Khan N, Wang P, et al. Vitamin D deficiency, myositis-myalgia, and reversible statin intolerance. *Curr Med Res Opin.* 2011;27:1683–90.
- Khayznikov M, Hemachandra K, Pandit R, Kumar A, Wang P, Glueck C. Statin intolerance because of myalgia, myositis, myopathy, or myonecrosis can in most cases be safely resolved by vitamin D supplementation. *N Am J Med Sci.* 2015;7:86–93.
- Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses; 2009. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [accessed 16.02.16].
- Duell B, Connor WE. Vitamin D deficiency is associated with myalgias in hyperlipidemic subjects taking statins. *Circulation.* 2008;118:S470.
- Ahmed W, Khan N, Glueck CJ, Pandey S, Wang P, Goldenberg N, et al. Low serum 25 (OH) vitamin D levels (<32 ng/mL) are associated with reversible myositis-myalgia in statin-treated patients. *Transl Res.* 2009;153:11–6.
- Linde R, Peng L, Desai M, Feldman D. The role of vitamin D and SLC01B1*5 gene polymorphism in statin-associated myalgias. *Dermatoendocrinology.* 2010;2:77–84.
- Backes JM, Barnes BJ, Rusinger JF, Moriarty PM. A comparison of 25-hydroxyvitamin D serum levels among those with or without statin-associated myalgias. *Atherosclerosis.* 2011;218:247–9.

11. Eisen A, Lev E, Iakobishvili Z, Porter A, Brosh D, Hasdai D, et al. Low plasma vitamin D levels and muscle-related adverse effects in statin users. *Isr Med Assoc J*. 2014;16:42–5.
12. Palamaner Subash Shantha G, Ramos J, Thomas-Hemak L, Pancholy SB. Association of vitamin D and incident statin induced myalgia – a retrospective cohort study. *PLOS ONE*. 2014;9:e88877.
13. Mergenhagen K, Ott M, Heckman K, Rubin LM, Kellick K. Low vitamin D as a risk factor for the development of myalgia in patients taking high-dose simvastatin: a retrospective review. *Clin Ther*. 2014;36:770–7.
14. Morioka TY, Lee AJ, Bertisch S, Buettner C. Vitamin D status modifies the association between statin use and musculoskeletal pain: a population based study. *Atherosclerosis*. 2015;238:77–82.
15. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. *J Clin Lipidol*. 2014;8 Suppl. 3: S58–71.
16. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy – European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015;36:1012.
17. Argov Z. Statins and the neuromuscular system: a neurologist's perspective. *Neurology*. 2015;22:31–6.
18. Bischoff-Ferrari HA, Giovannucci E, Willet WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr*. 2006;84:18–28.
19. Bischoff HA, Borchers M, Gudat F. In situ detection of 1-25-dihydroxyvitamin D3 receptor in human skeletal muscle tissue. *Histochem J*. 2001;33:19–24.
20. Lee P, Greenfield JR, Campbell LV. Vitamin D insufficiency – a novel mechanism of statin-induced myalgia? *Clin Endocrinol (Oxf)*. 2009;71:154–5.
21. Magni P, Macchi C, Morlotti B, Sirtori CR, Ruscica M. Risk identification and possible countermeasures for muscle adverse effects during statin therapy. *Eur J Intern Med*. 2015;26:82–8.
22. Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. *Atherosclerosis*. 2011;215:23–9.
23. Minissian M, Agarwal M, Shufelt C, Mehta PK, Waldman T, Lentz G, et al. Do women with statin-related myalgias have low vitamin D levels? *BMC Res Notes*. 2015;8:449.
24. Kurnik D, Hochman I, Vesterman-Landes J, Kenig T, Katzir I, Lomnicki Y, et al. Muscle pain and serum creatine kinase are not associated with low serum 25(OH) vitamin D levels in patients receiving statins. *Clin Endocrinol (Oxf)*. 2012;77:36–41.
25. Gómez-Alonso C, Naves-Díaz ML, Fernández-Martin JL, Díaz-López JB, Fernández-Coto MT, Cannata-Andía JB. Vitamin D status and secondary hyperparathyroidism: the importance of 25-hydroxyvitamin D cut-off levels. *Kidney Int*. 2003;63 Suppl. 85:S44–8.
26. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. *Osteoporos Int*. 2005;16:713–6.
27. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2011;95:91–100.
28. Gagnon C, Baillargeon JP, Desmarais G, Fink GD. Prevalence and predictors of vitamin D insufficiency in women of reproductive age living in northern latitude. *Eur J Endocrinol*. 2010;163:819–24.
29. Gonzalez G. Vitamin D status among healthy postmenopausal women in South America. *Dermatoendocrinology*. 2013;5:117–20.
30. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch Intern Med*. 2009;169:626–32.