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POPULATION PHARMACOKINETICS OF 25-HYDROXY VITAMIN D IN NON-ELDERLY POSTMENOPAUSAL WOMEN

JELENA DJOKOVIC[1], ALEKSANDRA TOMIC LUCIC[2,3]*, OLIVERA Z. MILOVANOVIC[4], DANIJELA BAZIC[2,3], MIRJANA VESELINOVIC[2,3], ALEKSANDAR DJUKIC[2,3], SANDRA MATOVIC[1], RADICA ZIVKOVIC ZARIC[1], RADMILA VELICKOVIC RADOVANOVIC[5], SLOBODAN M. JANKOVIC[1] and JASMINA R. MILOVANOVIC[1]

[1]Department of Pharmacology and Toxicology, Faculty of Medical Sciences, University of Kragujevac, Serbia
[2]Department of Internal Medicine, Faculty of Medical Sciences, University of Kragujevac, Serbia
[3]Internal Clinic, Clinical Center of Kragujevac, Serbia
[4]Department of Clinical Pharmacy, Faculty of Medical Sciences, University of Kragujevac, Serbia
[5]Pharmacy Department, Medical Faculty, University of Nis, Serbia

Abstract: Vitamin D is one of the keys to bone health, and the serum levels of this vitamin are a major concern for postmenopausal women. The aims of this study were to develop a population pharmacokinetic (PPK) model for the clearance of 25-hydroxy vitamin D in non-elderly postmenopausal women and to identify the factors which have a significant influence on its clearance. The study population consisted of postmenopausal women who had been referred for evaluation of bone mineral density (BMD) by DEXA (dual-energy x-ray absorptiometry) scanner. The population pharmacokinetics modeling was conducted using the ADVAN 1 subroutine from a non-linear mixed effects (NONMEM) program, and thirty-two covariates were assessed. A total of 75 serum concentrations were obtained from the same number of postmenopausal women and used for PPK analysis. The mean value of the participants' age was 57.92 ± 3.93 years and their body weight was 69.76 ± 11.49 kg. A wide range of 25-hydroxy vitamin D concentrations was observed (from 3.41 to 61.92 ng/mL) with a mean value of 26.19 ± 10.95 ng/mL. A total of 32 covariates were examined and preliminary results suggested the influence of six covariates on 25-hydroxy vitamin D clearance. In the final PPK model, however, only one covariate was shown to have a significant impact on the clearance value – the mean daily dietary intake dose of vitamin D (DD). These findings offer a preliminary basis on which to determine the level of vitamin D supplementation required by individual postmenopausal women. It could prove particularly important in achieving optimal serum levels of vitamin D in this vulnerable population.

Keywords: women, postmenopausal women, 25-hydroxy vitamin D, population pharmacokinetics, NONMEM

Vitamin D is one of the key factors in bone health and the blood level of this vitamin is of major importance for the bone health of postmenopausal women (1). This lipophilic vitamin has multiple effects on the human body but its role in calcium and phosphorus homeostasis is essential for the preservation of bone health. Available data indicates that supplementation of vitamin D in adequate doses may prevent osteoporosis in both peri and postmenopause (2, 3). In addition to dietary intake, the impact of several other factors on vitamin D status has been examined over the past two decades, these include region, age, gender, skin type, sunscreen cream used, exposure to sun, eating habits, and season of the year, among others. Many previous studies have identified sun exposure and inadequate intake of vitamin as the most important factors influencing the development of hypovitaminosis D (4).

Vitamin D status in the human body is estimated according to the level of 25-hydroxy vitamin D in serum. The agreed values of 25-hydroxy vitamin D indicating hypovitaminosis D are less than 30 ng/mL, while values ranging from 20 to 30 ng/mL denote vitamin D insufficiency and values less than

* Corresponding author: e-mail: sanlusa@ptt.rs

20 ng/mL indicate vitamin D deficiency (5). The proven association between the decrease of BMD and vitamin D deficiency in postmenopausal women is the main reason for the recommendation of vitamin D screening tests for this population and for the use of vitamin D supplementation. Since the reduction of bone mineral density is much slower in premenopause and the early perimenopause period compared to late perimenopause and postmenopause, timely screening for vitamin D deficiency and adequate vitamin D supplementation are essential steps after the first appearance of menopausal symptoms and signs (6, 7).

Vitamin D supplementation in postmenopausal women should be undertaken according to current recommendations, but there is no evidence that recommended doses are individualized according to the needs of each individual patient.

The aim of this study was to develop a population pharmacokinetic model for the clearance of 25-hydroxy vitamin D in postmenopausal women and to identify factors which have a significant influence on its clearance.

MATERIALS AND METHODS

Study population

Seventy-five postmenopausal women who visited the Center for Bone Densitometry at the Internal Clinic, Clinical Center Kragujevac, took part in the study over three months in 2017 (from January to March). The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Clinical Center Kragujevac (No. 01/15485, approved on 28.11. 2016.).

The participants had been referred for evaluation of bone mineral density (BMD) by their general practitioners, and the examinations were performed using a DEXA (dual-energy x-ray absorptiometry) scanner, according to the established standard. The study inclusion criteria were: women at post-menopause up to 65 years old without a previous diagnosis of any acute or chronic disease (except osteoporosis or osteopenia), who had not started taking vitamin supplements or trace elements or who used only vitamin D and calcium supplementation prescribed by their rheumatologists, without changes to their usual diet for at least 6 months and who were not following any specific dietary regime. We excluded women who were still menstruating and those with secondary osteoporosis linked to medical conditions, hormonal causes and other links to secondary osteoporosis including medication with corticosteroids, anticonvulsants and other drug classes. Women using an active form of vitamin D (1,25-dihydroxycholecalciferol) as supplementation were also excluded from the study.

The participants were given a detailed explanation of the study protocol and were included in the study after having signed an informed consent form. All the participants were asked to record accurately the amount and variety of food and drink that they consumed and the amount of time they spent outdoors daily, over the course of one month. Based on these records, we first calculated the total daily intake of vitamin D from food and drink for each day, using the USDA National Nutrient Database for Standard Reference, release 24 (8). We then calculated the average daily intake of vitamin D for one month for each patient. Next, we calculated the mean daily vitamin D supplementation intake, based on the type and number of preparations for each individual patient (prescribed by their rheumatologists and extracted from the medical records). The vitamin D content of the pharmaceutical supplements taken by our participants was clearly specified by the manufacturer on the product label. By adding the average daily intake from food to that of the supplements, we arrived at the factor used in the PPK analysis (expressed as the daily dietary intake of vitamin D, Table 1). In addition, all the participants reported their daily sun exposure over the course of one month. Based on these records we calculated the average daily sun exposure for each of them. Since the study was conducted in winter, all the women were wearing clothing which covered their arms and legs. Because sun exposure is a crucial factor for the achievement of adequate vitamin D levels, we analyzed these factors in two ways: mean daily sun exposure (expressed in hours) and category variable (less or more than two hours daily). A blood sample was taken from all the participants after the one-month period had been completed. The samples were taken in the morning, at 8.00 a.m., before the participants had eaten, and were subjected to the following analysis: biochemical (serum concentrations of 25-hydroxy vitamin D, calcium, phosphate, magnesium, bilirubin, protein, albumin, glucose, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine); the hormone tests were for triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), thyroid peroxidase antibody (TPOAb) and parathyroid hormone (PTH). Serum concentrations of 25-hydroxy vitamin D were routinely determined using the electrochemiluminescence method on Cobas®e 601 analyzer (Roche Diagnostics, Mann-

heim, Germany), according to the manufacturer's instructions. Coefficients of variation (CV) for the intra-assay and inter-assay were 4.1% and 4.8%, respectively.

According to the DEXA results based on the T score, the women were classified into one of three groups: those with normal BMD; those diagnosed with osteopenia (T-score between -1.5 and -2.5 SD); and those with osteoporosis (T score below -2.5 SD). The following data were extracted from the patients' medical records: age, body weight and height of patients, prescribed supplementation with

Table 1 Demographic, laboratory, clinical and medical data of the target population.

Patients characteristics	Index data set (mean value and SD)	Range of index data set
Number of patients	75	
Number of observations	75	
Age (years)	57.92 ± 3.93	48 - 64
Body weight (kg)	69.76 ± 11.49	45 - 103
Daily dietary intake of vitamin D (from foods and supplementations) (µg/day)	24.01 ± 15.3	1.6 - 70,06
25,OH vit D serum concentration (ng/mL)	26.19 ± 10.95	3.45 - 61.92
Serum calcium levels (mmol/L)	2.38 ± 0.13	2.0 - 2.7
Serum phosphate levels (mmol/L))	1.11 ± 0.19	0.7 - 1.81
Serum magnesium levels (mmol/L)	0.86 ± 0.08	0.66 - 1.05
Total serum bilirubin (mmol/L)	9.15 ± 3.66	3.8 - 20.7
Total serum protein (g/L)	70.89 ± 4.4	63 - 82
Total serum albumin (g/L)	43.07 ± 4.34	16 - 50
Glukose (mmol/L)	5.14 ± 0.82	3.5 - 9.09
Urea (mmol/L)	5.32 ± 1.64	3.1 - 10.2
CLcr (mL/min)	85.84 ± 17.3	58 - 127
AST (IU/L)	21.87 ± 4.22	13 - 37
ALT (IU/L)	20.19 ± 7.42	7 - 54
TSH (mIU/L)	2.05 ± 1.22	0.3 - 5.4
T4 (pg/mL)	10.99 ± 3.24	2.1 - 19.3
T3 (pg/mL)	3.95 ± 6.93	1.9 - 62.9
TPOAb (IU/mL)	506.30 ± 1592.79	1 - 8901
PTH (pg/mL)	37.54 ± 14.4	10.2 - 82.4
Daily sun exposure (h)	2.69 ± 1.34	0.78 - 6.7
Daily sun exposure (< 2 h/> 2 h)	42/33	
T score (SD): - normal - osteopenia - osteoporosis	 - 30/75 - 36/75 - 9/75	
Coffee (> 3 cups/≤ 3 cups)	22/53	
Alcohol (> 3 cups/≤ 3 cups)	10/65	
Smokers (yes/no)	37/48	
Hereditary predisposition (yes/no)	20/55	
Skin types (2/3)	23 /52	
Comedications (yes/no): - Bisphoshponates - Calcium - Statins - Benzodiazepines	 -35/40 - 12/63 - 13/62 - 20/55	

calcium and vitamin D (daily dose, dosage regimens and types of vitamin D supplements and calcium) and drug classes for the treatment of osteoporosis. The women's life habits (consumption of coffee, alcohol, smoking status), their hereditary predisposition (i.e. absence/presence of a family history of osteoporosis). Skin type and co-medication were noted on the same day using an unstructured questionnaire filled out by the researchers.

Population pharmacokinetic analysis

The population pharmacokinetics (PPK) modeling was conducted using the ADVAN 1 subroutine from the non-linear mixed effects (NONMEM) program version 7.3.0 (Icon Development Solution, USA). To form a structural base model, we selected a one-compartment model without absorption based on our previous reports with regard to the clearance of 25-hydroxy vitamin D. The inter-individual variability of the examined pharmacokinetic parameters was compared between the additive and exponential error models. Residual variability of serum concentration was tested using an additive, exponential, constant coefficient of variation (CCV) and combined (additive and CCV) error models. To assess the influence of a potential covariate on the clearance of 25-hydroxy vitamin D we performed a sequential univariate analysis which included one-by-one addition of variables in the base model. In this process, we examined the influence of 32 variables (Table 1). The results of the covariate analysis were interpreted through differences in the minimum of objective function (MOF) between the base and individual covariate model, and better congruency on diagnostic plots: population predicted or individual predicted concentrations versus measured concentrations of 25-hydroxy vitamin D. A significant influence of each covariate on CL/F was assumed using the difference in MOF value (Δ MOF > 3.84 for $p < 0.05$, df = 1) in the forward stepwise inclusion process. The results were confirmed by the backward stepwise elimination method with a higher statistical threshold for previously marked covariates (Δ MOF > 6.6 for $p < 0.01$, df = 1). The final model included all covariates that were statistically significant by both the aforementioned methods.

During the development of the final model, we evaluated the model fitting data through visual inspection of the diagnostic plots previously mentioned. To evaluate the stability and predictive performances of the derived model, bootstrapping analysis was performed as internal validation. This analysis is a resampling technique which includes several hundred or thousand data replicates with replacement from the original data set using the individual patients as the sampling unit. Each of the bootstrap samples was fitted to the final model with estimated values of clearance and variability using NONMEM software. The mean value of estimated PK parameters (CL/F and Vd/F), the standard deviation and 95% confidence interval for each parameter were calculated and compared with their values of the final derived model.

RESULTS

The characteristics of the study population are summarized in Table 1. A total of 75 serum concentrations were obtained from the participants and used in the PPK analysis. The mean value of the participant's age was 57.92 ± 3.93 years and body weight had a value of 69.76 ± 11.49 kg. A wide range of 25-hydroxy vitamin D concentrations was observed in our population (from 3.41 to 61.92 ng/mL) with a mean value of 26.19 ± 10.95 ng/mL. Forty-four women (60%) from the study population had osteopenia (n = 35.48%) or osteoporosis (n = 9.12%) according to the DEXA results (T score). Moreover, 55 women (73.33%) had no history of hereditary predisposition in the family. A one-compartment model with ADVAN1 subroutine described the concentrations of 25-hydroxy vitamin D well, and an exponential error model for inter-individual variability and an additive model for residual variability gave a better model fit. In the base model, the mean population value of the clearance of 25-hydroxy vitamin D was 0.0722 L/h with a reported value of 695.112 units for the minimum of an objective function.

The effects of the following covariates were estimated in the analysis: patient's age and body weight, the mean daily dietary intake of vitamin D, the mean daily sun exposure (the time spent outside, expressed in two ways: as a continuous variable (average number of hours per day) or a category variable (categorized to less than or more than 2 hours daily with values 0 or 1), serum calcium, phosphate, magnesium, bilirubin, total protein, albumin, glucose, urea, AST and ALT, creatinine clearance, TSH, PTH, T3, T4 and TPO antibody, the presence of osteopenia/osteoporosis (T score), hereditary predisposition, skin type, usage of coffee, alcohol or cigarettes and concomitant therapy with bisphosphonates, calcium, statins or benzodiazepines. The results of covariate analysis after the forward inclusion step suggested the significant influence of six covariates: the mean daily dietary intake of vitamin D (from foods and supplementa-

tions), both variables linked to the mean daily sun exposure (as a continuous and category variable), TPO antibody, coffee usage and co-medication with benzodiazepines. Backward elimination showed that the clearance of 25-hydroxy vitamin D was significantly affected by the mean daily dietary intake of vitamin D. The equation of the final PPK model was as follows:

$$CL\ (L/h) = 0.0886 + 0.00097 \times DD$$

In the final model, the MOF value decreased by 191.477 units; decreases were also observed in both variability, inter-individual and residual variability of 24.01% and 15.26%, respectively. Moreover, improvement of the final model fit was expressed through the diagnostic plot of individual predicted values versus measured serum concentrations of 25-hydroxy of vitamin D in the target population (Fig. 1). To evaluate the predictive performance of the derived model, bootstrap analysis was performed, the results of which are shown in Table 2. It can be seen that the bootstrapping yielded similar results to those obtained in the initial development of the model, which indicates that the final model is accurate and stable.

DISCUSSION

The population pharmacokinetic model of 25-hydroxy vitamin D in women at postmenopause examined the influence of 32 covariates on the population clearance value. Preliminary results pointed to six covariates that may influence 25-hydroxy vitamin D clearance (the mean daily dietary intake of vitamin D, mean daily sun exposure expressed as a continuous and category variable, level of TPOAb, coffee consumption and use of benzodiazepines), but in the final PPK model only one covariate had a significant impact on the clearance. To our knowledge, this is the first report on the population pharmacokinetics of vitamin D in postmenopausal women.

The intake of vitamin D from food is essential for reaching an adequate physiological level of 25-hydroxy vitamin D in the human body. Since food is a poor source of vitamin D, taking into account that

Table 2. Parameter estimates evaluated by NONMEM and bootstrap analysis for the final model.

Parameter	NONMEM		Bootstrap analysis	
	Estimate	95% CI*	Estimate	95% CI‡
CL/F (L/h)	0.0886	0.071 – 0.106	0.0888	0.0807 - 0.096
Mean daily dietary intake of vitamin D	0.00097	0.00075 - 0.00119	0.00098	0.00081 - 0.00115
Inter-individual variance of CL- ω^2_{CL}	0.0237	0.0171 - 0.0303	0.0235	0.019 - 0.028
Residual variance - σ^2	0.0838	0.0618 - 0.1058	0.0841	0.0595 - 0.1087

* (Estimate) ± 1.96 x (standard error of the estimate); ‡ 2.5th and 97.5th percentile of the ranked bootstrap parameter estimates

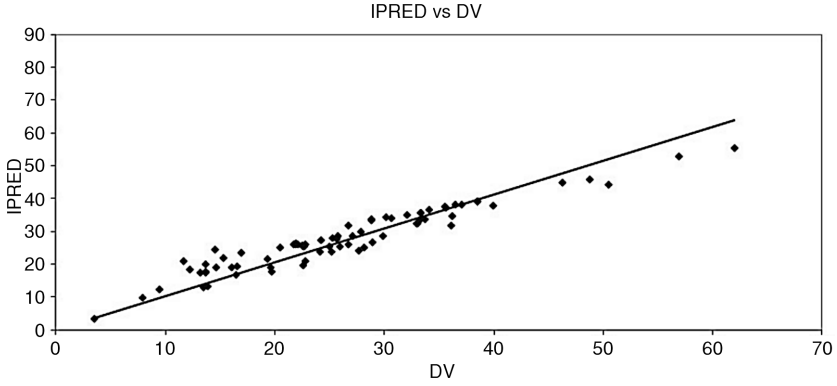

Figure 1. Scatter-plot of individual predicted (IPRED) 25-hydroxy vitamin D concentrations versus observed concentrations (DV) of the final model

only a limited number of foods have a significant amount of this vitamin, intake of food fortified with this vitamin or supplementation is a sensible choice. In Serbia, only a few food products are fortified with vitamin D, such as milk, butter, some breakfast cereals, orange juice, and certain pasta products. The mean daily dietary intake of vitamin D in our patients was 24.01 ± 15.3 μg with a wide range between 1.06 μg and 70.06 μg. Such a high value of the mean daily dietary intake of vitamin D is a consequence of supplementation, as significantly lower values of vitamin D daily dietary intake were observed in our two previous studies conducted on the Serbian population: 2.57 ± 2.53 μg and 1.55 ± 0.87 μg, respectively (9, 10). A similar situation was reported for other European countries: a high prevalence of vitamin D deficiency and very low vitamin D intake from food (11). However, there are differences in the vitamin D supplementation rate, as northern countries are characterized by the highest rate of vitamin D supplementation, almost 61.7%, while the data from Italy, France and Germany show lower ranges (from 6.7 to 27%). On the other hand, 80% of our participants took supplementation because they had a diagnosis of osteopenia or osteoporosis in 60% of cases. The influence of mean daily dietary intake of vitamin D on 25-hydroxy vitamin D clearance could be understood from MOF reduction in the final PPK model of 191.477 units and is in accordance with the previous PPK analysis from Serbia (9, 10).

In the past few decades, it has been stressed in a large number of scientific reports that exposure to the sun is essential for achieving a sufficient level of 25-hydroxy vitamin D and the manifestation of its beneficial effects in the human body. In spite of this growing body of evidence we still do not know precisely what duration of sun exposure is adequate for optimal vitamin D synthesis in the skin. Two factors have a notable impact on the effectiveness of exposure to the sun; the geographical position of the population and the season of the year when the person is exposed to the sun. Serbia lies at geographical latitudes above 35^{o} which stops natural skin production of vitamin D during a large part of the year, from as early as October, until April, implying the need for vitamin D supplementation. The time frame for our study was the period from January to March, which explains why the four-fifths of the study population used vitamin D supplements. The results of a cross-sectional study in Turkish woman clearly indicated the influence of a low level of life-long sun exposure on earlier onset of menopause (12). Other benefits of sun exposure were shown in a cohort study with postmenopausal woman where the results suggested a positive correlation between serum concentration of 25-hydroxy vitamin D and period of sun exposure (13). Our observations are in accordance with previous studies where mean daily sun exposure time was 2.69 ± 1.34 h while 56% of the study population spent less than 2 h daily exposed to the sun, however, neither covariate had a significant impact on 25-hydroxy vitamin D clearance in the final PPK model.

Whether coffee, alcohol and nicotine are factors which may influence serum concentration of 25-hydroxy vitamin D is still a matter of controversy. In our study 49.3% of the participants were smokers, 13.3% consumed more than 3 alcoholic drinks weekly and 29.3% more than 3 cups of coffee daily. However, our final PPK model did not recognize any of these three covariates as important elements in 25-hydroxy vitamin D clearance, an observation which is in accordance with the results of previous PPK analysis in a healthy, young population (10). The effects of caffeine consumption in amounts larger than 300mg/day on the serum level of 25-hydroxy vitamin D has been studied in a large number of epidemiological and experimental trials and the results provide a much clearer picture of this correlation. Yang et al. analyzed the influence of coffee consumption on osteoporosis in postmenopausal women and they concluded that osteoporosis prevalence was higher in women who did not consume coffee (14). The results of a meta-analysis in which the authors wanted to determine the influence of coffee consumption on the risk of fracture showed that coffee intake increased the risk of fracture in 4.9% of women with each additional cup of coffee per day, through the influence of coffee on mineral homeostasis, which can be reflected in decreased levels of 25-hydroxy vitamin D (15). An experimental study explained the influence of caffeine on 25-hydroxy vitamin D through changes in the expression of vitamin D receptors (VDR) (16). Rupury et al. showed that caffeine dose-dependently decreased VDR expression by 50-70% (17). Other studies demonstrated that smoking can decrease the serum level of 25-hydroxy vitamin D by 9% (18).

Thyroid gland function markers were also included in our study and the results showed that they had no significant impact on the pharmacokinetic model of 25-hydroxy vitamin D. The presence of vitamin D receptors in many tissues and organs explains the multiple effects of this vitamin in the human body including immunomodulatory effects. Some studies have revealed a strong correlation between low levels of 25-hydroxy vitamin D and

autoimmune thyroid disease because antithyroid antibodies are more common in persons with vitamin D deficiency or insufficiency (19). An additional observation from this study was that this factor was more influential in females (20), suggesting a need for supplementation. Chaudhary et al. conducted a study where they examined the influence of vitamin D supplementation on thyroid autoimmunity and results from this open-labeled randomized control study strongly indicated that vitamin D decreases the level of TPOAb (21). Our results show that parameters linked to thyroid gland function do not affect the pharmacokinetics of 25-hydroxy vitamin D.

The metabolism of vitamin D can be affected by certain drugs, and this has been a topic in vitamin D research over the past few years. For this reason, we included some concomitant therapy in our PPK analysis such as the use of bisphosphonates, calcium, statins, and benzodiazepines. Our study failed to detect any significant impact from these drugs on clearance of 25-hydroxy vitamin D. Of our patients, 26.7% used benzodiazepines, 12 were taking bromazepam and 8 lorazepam. Orten-Luiten and colleagues made a review of observational and experimental studies where they summarized the influence of several drugs on vitamin D status; this report reached different conclusions on the influence of benzodiazepines on 25-hydroxy vitamin D serum levels (22). The decreased level of vitamin D induced by drugs can be very harmful to for postmenopausal women when bone health status is endangered by changes in hormonal status. One of the potential explanations of how benzodiazepines change serum levels of vitamin D is the pharmacokinetic interactions involving liver metabolism. This, however, was not confirmed in our study, and it has previously been shown that while bromazepam is metabolized by CYP1A2 and CYP2D6 isoforms and lorazepam by UGT2B15 isoform, vitamin D is predominantly metabolized by CYP27A1, CYP27B1 and CYP24A1.

Although our research has led us to some specific conclusions, there were some limitations that should be highlighted. The study was conducted in the winter when vitamin D supplementation is certainly needed. Further research should be conducted during a different season of the year to establish precisely what influence the weather has on vitamin D status, and also to make possible generalization of this conclusion to the Balkan region, as a whole. Another important limitation for this study was the self-reported approach for daily vitamin D intake and sun exposure time, but this was unavoidable due to the type of participants taking part in the study.

CONCLUSION

According to the presented results, we may conclude that the mean daily dietary intake dose of vitamin D is the only factor with an important influence on the clearance of 25-hydroxy vitamin D in non-elderly postmenopausal women. These findings could help when individualizing vitamin D intake in the form of supplements in order to achieve the required blood levels in postmenopausal women.

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Conflict of interest

All authors have no conflicts of interest.

REFERENCES

1. Milovanovic O.: Ser. J. Exp. Clin. Res. 18, 3 (2017).
2. Purdue-Smithe A.C., Whitcomb B.W., Szegda K.L., Boutot M.E., Manson J.E. et al.: Am. J. Clin. Nutr. 105, 1493 (2017).
3. Chon S.J., Koh Y.K., Heo J.Y., Lee J., Kim M.K. et al.: Obstet. Gynecol. Sci. 60, 53 (2017).
4. Nair-Shalliker V., Clements M., Fenech M., Armstrong B.K.: Photochem. Photobiol. 89, 208 (2013).
5. Makariou S., Liberoupolos E., Elisaf M., Challa A.: Eur. J. Inter. Med. 22, 355 (2011).
6. Monteleone P., Mascagni G., Giannini A., Genazzani A.R., Simoncini T.: Nat. Rev. Endocrinol. 14, 199 (2018).
7. Zhou P., Hu J., Xi P., Zhang N., Yang B. et al.: PLoS One. 12, e0180366 (2017).
8. http://www.ars.usda.gov/ba/bhnrc.ndl. (accessed on 15. 03. 2018.)
9. Matovic S., Milovanovic J.R., Dajic K., Stojkovic A., Jankovic S.M.: Int. J. Clin. Pharmacol. Ther. 56, 169 (2018).
10. Milovanovic O., Milovanovic J.R., Djukic A., Matovic M., Lucic A.T. et al.: Int. J. Clin. Pharmacol. Ther. 53, 1 (2015).
11. Spiro A., Buttriss J.L.: Nutr. Bull. 39, 322 (2014).

12. Aydin D., Erbas B., Karakus N., Aydin O., Ozkan S.: Maturitas 52, 235 (2005).
13. Cheng T.Y., Millen A., Wactawski-Wende J., Beresford S.A., LaCroix A.Z., Zheng Y., Goodman G.E., Thornquist M.D., Neuhouser ML.: J. Nutr. 144, 681 (2014).
14. Yang P., Zhang X.Z., Zhang K., Tang Z.: Int. J. Clin. Exp. Med. 8, 15958 (2015).
15. Liu H., Yao K., Zhang W., Zhou J., Wu T., He C.: Arch. Med. Sci. 8, 776 (2012).
16. Rapuri B., Gallagher C., Kinyamu K., Ryschon K.: Am. J. Clin. Nutr. 74, 694 (2001).
17. Rapuri P.B., Gallagher J.C., Nawaz Z.: J. Steroid. Biochem. Mol. Biol. 103, 368 (2007).
18. Brot C., Jorgensen N.R., Sorensen O.H.: Eur. J. Clin. Nutr. 53, 920 (1999).
19. Shin D.Y., Kim K.J., Kim D., Hwang S., Lee E.J.: Yonsei. Med. J. 55, 476 (2014).
20. Canaris G.J., Manowitz N.R., Mayor G., Ridgway E.C.: Arch. Intern. Med. 160, 526 (2000).
21. Chaudhary S., Dutta D., Kumar M., Saha S., Mondal S.A. et al.: Indian. J. Endocrinol. Metab. 20, 391 (2016).
22. Van Orten-Luiten A.C., Janse A., Dhonukshe-Rutten R.A., Witkamp R.F.: Drugs. Aging. 31, 111 (2014).

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