REVIEW

Low levels of vitamin D and coronary artery disease: Is it time for therapy?

Monica Verdoia[1, 2], Rocco Gioscia[1], Matteo Nardin[3], Andrea Rognoni[1], Giuseppe De Luca[4]

[1]Division of Cardiology, Ospedale degli Infermi, ASL Biella, Biella, Italy
[2]Department of Translational Medicine, Università del Piemonte Orientale, Novara, Italy
[3]Department of Medicine, Spedali Civili Brescia, Italy
[4]Clinical and Experimental Cardiology Unit, AOU Sassari, Italy

Correspondence to:
Giuseppe De Luca, MD, PhD, Director Clinical and Experimental Cardiology Unit, AOU Sassari, Sassari, Associate Professor of Cardiology, University of Sassari, Sassari, Italy, phone: +39 079 229 162, e-mail: gdeluca@uniss.it

DOI: 10.33963/KP.a2022.0079

Received:
March 20, 2022

Accepted:
March 23, 2022

Early publication date:
March 24, 2022

ABSTRACT

The association between vitamin D and the prevalence and severity of coronary artery disease (CAD), major established cardiovascular risk factors, and acute ischemic events has been consistently demonstrated in large-scale observational studies and meta-analyses, with relevant prognostic implications. The rise in prevalence of hypovitaminosis D in recent years, reaching pandemic proportions, has pointed to the importance of the identification and optimization of the indications and strategies for the therapeutic use of vitamin D, with particular relevance for cardiovascular health. However, vitamin D supplementation has provided so far inconsistent results in primary prevention, with even fewer data reported in patients with established CAD. The present review aims to provide an updated overview of the available evidence and potential therapeutic applications of vitamin D in patients with CAD.

Key words: vitamin D, atherosclerosis, inflammation, thrombosis, pharmacological therapy

INTRODUCTION

Vitamin D is a secosteroid mainly involved in the homeostasis of calcium and bone tissue but also displaying a broad spectrum of systemic hormonal effects, including both the modulation of the expression of about 3% of the human genome, and "acute", non-genomic-dependent effects, mediated by the regulation of intracellular calcium [1].

Several large-scale studies have previously demonstrated that vitamin D deficiency is associated with the development of atherosclerosis and its thrombotic complications, which increases the risk of cardiovascular events and mortality [2–5].

Inadequate levels of vitamin D deficiency or insufficiency, defined as <20 ng/ml, have reached dramatic prevalence in the last years, exceeding 50% in certain areas and subsets of population, and especially among elderly and more frail subjects, with chronic comorbidities, renal failure, diabetes, and inflammatory disease [6, 7]. This has attracted attention to the consequences of vitamin D deficiency in the pathogenesis of coronary artery disease (CAD) and potential benefits of vitamin D supplementation.

However, there is still much uncertainty about the underlying pathophysiological mechanisms. The results of the studies conducted so far to assess the cardioprotective benefits of vitamin D are still unclear and make it impossible to reach a general consensus, develop consistent guidelines, and use vitamin D on a large scale as a pharmacological therapy.

The present review provides an update on the existing evidence and the current indications for the supplementation with vitamin D in patients with CAD, focusing on potential future perspectives.

VITAMIN D DEFICIENCY: A PANDEMIC DISORDER

Severe vitamin D deficiency can cause rickets and osteomalacia, which are rarely observed in developed countries. However, less severe

Table 1. Derivates of vitamin D with clinical indications

Compound	Clinical indication
Calcidiol 3,25(OH)D3	Renal osteodystrophy
Calcitriol 4,1,25(OH)	Renal osteodystrophy
Calcipotriol 5, 22-ene-26, 27-dehydro-1,25(OH)2D3	Psoriasis
Doxercalciferol 6, 1α(OH)D2	Secondary hyperparathyroidism
Alfacalcidol 7,1α(OH)D3	Osteoporosis
Tacalcitol 8, 1α, 24(OH)2D3	Psoriasis
Oxacalcitriol 10, 22-oxa-1, 25(OH)2D3	Psoriasis
Falecalcitriol 11, 1,25(OH)2-26, 27-F6-D3	Secondary hyperparathyroidism

deficiency is more frequent and associated with osteoporosis and the risk of bone fractures [8]. Vitamin D deficiency is currently considered a global health problem [9, 10], especially in low- and middle-income countries, where it affects about 50% of adults and 90% of infants. In the USA, up to 37% of adults and up to 46% of dark-skinned infants suffer from this condition [9]. A recent analysis considering mostly Nordic and western European populations found significant variability between countries [10]. In fact, when restricted to the adult population, Nordic countries appear to have a lower incidence of vitamin D deficiency, most probably due to increased vitamin supplementation or food fortification compared to lower-latitude countries.

VITAMIN D METABOLIC PATHWAY

Cholecalciferol, the form of vitamin D named D3, is synthetized in the skin from 7-dehydrocholesterol upon irradiation with ultraviolet waves (ultraviolet B light [UV-B]) (Figure 1) [11]. 7-dehydrocholesterol is part of the metabolic pathway that controls the synthesis of cholesterol in human cells. By absorbing ultraviolet radiation, 7-dehydrocholesterol turns into pre-vitamin D3, which, because of its molecular instability, subsequently converts to cholecalciferol that is expelled in the extracellular space, binding to a carrier (vitamin D-binding protein). Although production of vitamin D3 in the skin is its primary source in humans, it can be derived from food, such as fish oil or mushrooms, in the form of ergocalciferol (Figure 2) [12]. Skin synthesis of vitamin D3 rises proportionally with the intensity of the UV radiation. It also reduces proportionally with sunblock usage or the quantity of melanin encountered in the skin, i.e., in higher-latitude-living populations, during months with reduced sun exposure, or in patients with darker skin [11, 13, 14]. However, cholecalciferol is not biologically active; thus, vitamin D is hydroxylated in the liver cells to form 25(OH)D followed by 1α-hydroxylation [11]. The active hormonal form is produced in this last step of 1α-hydroxylation mainly in the kidneys and at other extrarenal sites, resulting in a compound named 1,25(OH)2D3 [15–17].

Table 2. Vitamin D and atherosclerosis: mechanistic links

Lipid profile	• Reduces total cholesterol • Reduces LDL-C • Reduces triglycerides • Increases HDL-C
Endothelial adhesion and activation	• Reduces vascular cell adhesion molecule 1 • Reduces E-selectin
Vascular tone and endothelial function	• Increases the level of nitric oxide • Reduces the level of reactive oxygen species released
Inflammation and atherosclerosis	• Reduces proinflammatory type 1 cytokines: IL-12, IL-6, IL-8, IFN-gamma, TNF-alpha • Increase anti-inflammatory type 2 cytokines: IL-4, IL-5, and IL-10 • Reduces oxidative stress through reducing cathepsin, IL-6 and adiponectin
Coagulation and platelet aggregation	• Increases trombomodulin expression • Reduces tissue factor expression • Reduces PAI-1 expression • Reduces thrombospondin expression • Increases the level of nitric oxide • Decreases ADP-induced aggregation
Arterial smooth muscle cells	• Decreases production of angiotensin II • Decreases oxidative stress • Inhibits cellular senescence • Reduces tissue factor expression

Abbreviations: ADP, adenosine diphosphate; HDL-C, high density lipoprotein cholesterol; IFN, interferon; IL, interleukin; LDL-C, low density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; TNF, tumor necrosis factor

MECHANISMS OF ACTION AND ITS IMPLICATIONS IN THE PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

The hormonal form of vitamin D, which is a lipid-soluble molecule, is transported in the blood bound to a serum protein named vitamin D-binding protein (DBP) [18]. At molecular level, vitamin D in the form of 1,25(OH)2D3 exerts its actions by binding to a membrane-bound and cytoplasmic receptor, the vitamin D receptor (VDR), which can be found in almost all human tissue, including the cardiovascular system [11, 19]. Binding of vitamin D to its VDR is critical for its action because 1.25 dihydroxy vitamin D, the active form, penetrates the cell membrane and binds to VDR [20]. This vitamin D-VDR complex acts with the retinoic acid receptor and forms important heterodimers that activate elements of vitamin D response elements by initiation of the cascade of molecular interactions regulating the suppression and transcription of specific genes [21]. In total, VDR has a direct action on the expression of more than 1000 genes [22], approximately 3% of the genome [12]. Ways in which vitamin D acts non-genomically have also been identified, such as through intracellular signaling molecules, generation of second messengers, and activation of specific protein kinases [23]. The change in the chemical structure of cholecalciferol leads to the emergence of new molecules, which, surprisingly, can bind to VDR.

Vitamin D deficiency has been consistently associated with the prevalence and severity of CAD and acute ischemic events.

In fact, vitamin D has been shown to promote endothelial function and to counteract inflammation and oxidative stress, thus preventing the development of atherosclerosis and its thrombotic complications [24–27].

In the ARIC study, vitamin D levels were measured in 11 945 participants, and an association with the incidence of coronary heart disease among white-skinned participants was reported [28].

In the LURIC Study, in a large cohort of subjects (n = 1801) referred for coronary angiography, 92% of individuals had suboptimal levels of vitamin D, which was associated with an increased all-cause mortality and cardiovascular mortality [29]. The Framingham Offspring Study found that individuals with 25(OH)D <37.5 nmol/l had a hazard ratio of 1.62 for the development of cardiovascular disease (CVD) compared to those with a level of ≥37.5 nmol/l [30].

In a large cohort study enclosing over 1400 patients undergoing coronary angiography, Verdoia et al. showed that lower circulating 25(OH)D was independently related with the prevalence and extent of CAD, especially for patients with values <10 ng/ml [3].

Furthermore, calcitriol levels have been inversely associated with coronary artery calcifications, thus serving as an early marker of coronary atherosclerosis [2].

In fact, vitamin D can directly improve the endothelial health and function, promoting the production of nitric oxide and reducing the exposure of proteins responsible for the adhesion of leukocytes and platelets. This prevents the inflammatory response and thrombotic phenomena. In addition, the inhibition of the extravasation and activation of macrophages and the antioxidant properties can prevent lipid oxidation and the production of foam cells, which contribute to plaque progression and instability [1, 24]. Indeed, levels of 25(OH)D in healthy volunteers are independently associated with various measures of endothelial function, arterial stiffness, and coronary flow reserve. In a subgroup of participants with vitamin D deficiency, normalization of 25(OH)D levels at 6 months was associated with a significant increase in reactive hyperemia indices, and in other studies, treatment with vitamin D improved arterial stiffness [2].

Moreover, vitamin D has been shown to lower tissue factor, downregulate the pro-thrombotic plasminogen activator inhibitor-1 and thrombospondin-1 mRNA expression, and upregulate thrombomodulin, thus accounting for its antithrombotic properties [31].

Additionally, the vitamin D receptor has been also identified in platelets, which suggests a direct regulatory effect. In effect, platelet activation is a calcium-dependent process, and calcitriol has been shown to display also a "rapid" non genomic action, mediated by the modulation of intracellular calcium. In fact, hypovitaminosis D has been previously linked to an enhanced platelet reactivity and a reduced effectiveness of antiplatelet drugs [25].

VITAMIN D AND CARDIOVASCULAR RISK FACTORS

Vitamin D has displayed a positive interaction with major cardiovascular risk factors and was related to the levels of blood pressure and a "healthier" metabolic profile [5, 32, 33].

A Mendelian randomization study suggested a link between vitamin D deficiency and hypertension risk [34], which was further confirmed by experimental evidence in animal studies [35]. In effect, vitamin D promotes the production of nitric oxide, a potent vasodilator, and downregulates the activity of the renin-angiotensin system, thus lowering the blood pressure and positively interacting with anti-hypertensive drugs [36].

Moreover, vitamin D has been shown to lower the glycemia levels in patients with diabetes and to protect against diabetes through the regulation of insulin synthesis and secretion or through direct action on pancreatic beta-cells function [37].

The levels of 25(OH)D have also been shown to condition the lipid asset, which is associated with lower levels of circulating cholesterol and a less atherogenic lipid profile and prevents the formation of foam cells with potentiating the effectiveness of statins [38–40],

Furthermore, vitamin D deficiency could be even more frequent among subjects at increased cardiovascular risk, due to comorbidities, aging or renal failure, or unhealthy lifestyle. In fact, low 25(OH)D concentrations can be enhanced by obesity, air pollution, or limited outdoors activity, which are associated with worse cardiovascular outcomes [41].

VITAMIN D SUPPLEMENTATION IN CAD: CURRENT EVIDENCE

Although several studies have linked lower levels of vitamin D with more severe cardiovascular disease and increased mortality [42–44], controversies still exist about using vitamin D supplementation in cardiovascular prevention [45, 46].

The ViDA (Vitamin D Assessment) study in New Zealand, which randomized over 5 000 subjects, showed an increase in serum 25(OH)D concentrations with the supplementation, although it was ineffective in reducing the primary outcome of incident CVD and death [47].

In the recent VITAL trial [48], which randomized over 25 000 healthy subjects to two groups with either n–3 fatty acid or vitamin D3 supplementation, no prognostic difference was observed at a 5-year follow-up.

However, heterogeneity in these strategies, with inadequate dosing and duration of the treatment and the failure to achieve optimal levels of vitamin D, as summarized in Table 3, could have determined the negative findings of most of the trials.

Moreover, increased benefits could be expected when focusing on higher-risk populations, such as patients with

Table 3. Vitamin D supplementation in primary and secondary prevention

Study name	Patients (n)	Inclusion criteria	Vitamin D dosing	Follow-up duration	Study outcome and results
Secondary prevention					
Sokol et al. [49]	90	CAD (angiographic) and vitamin D <30 ng/ml	ergocalciferol (50 000 IU/week)	12 weeks	No difference in blood pressure and all markers of endothelial function
Bahrami et al. [50]	80	CAD (angiographic) and vitamin D <30 ng/ml	Vitamin D 50 000 IU/ week	8 weeks	Decreased systolic and diastolic blood pressure, waist circumference and fat percentage
Aslanabadi et al. [51]	99	Patients undergoing elective PCI	300 000 IU dose of cholecalciferol given before PCI	In-hospital	Periprocedural myocardial injury: no difference
Wu et al. [29]	90	CAD (angiographic)	Calcitriol (0.5 µg/day)	6 months	CAD (SYNTAX score) and C-reactive protein significantly decreased
Shaseb et al. [52]	95	T2DM with ischemic heart disease	Single dose of chole-calciferol (300 000 IU, i.m.)	8 weeks	Glycemic status: HbA1c was reduced by 0.48%
Witham et al. [53]	75	Patients with a prior history of MI	Two high-doses of orally administered cholecalciferol (100 000 IU)	6 months	Vascular function (reactive hyperemia index, systolic BP, diastolic BP) and cholesterol levels: no difference. C-reactive protein: reduced significantly
Farrokhian et al. [54]	60	T2DM patients with coronary artery disease.	50 000 IU cholecalciferol every second week	6 months	Significant attenuation in vascular inflammation and improved glycemic status
Schleithoff et al. [55]	123	Participants with heart failure	Vitamin D3, 2000 IU/d	Average 1.3 years	Reduced the inflammatory milieu
Primary prevention					
Aloia et al. [56]	27	Postmenopausal women	Vitamin D3, 400 IU/d	2 years	No difference in MACE
Ott et al. [57]	86	Postmenopausal women	Vitamin D3, 1000 mg/d	2 years	No difference in MACE
Komulainen et al. [58]	227	Women in early postmenopause who were non-osteoporotic	Vitamin D3, 300 and 100 IU/d	5 years	No difference in MACE
STOP IT/Gallagher et al. [59]	489	Women aged 65-77 years with femoral neck density in normal range (SD, ≤2) for their age	Calcitriol, 0.25 µg twice daily	3 years	No difference in MACE
Trivedi et al. [60]	2686	Participants aged 65–85 years	Vitamin D3, 100 000 IU/4 months	5 years	No difference in MACE
RECORD/Grant et al. [26]	5292	Participants aged ≥70 years who had had a low trauma, osteoporotic fracture in the previous 10 years	Vitamin D3, 800 IU daily	Median (IQR), 3.8 (3.1–4.3) years	No difference in MACE
Brazier et al. [61]	172	Ambulatory women aged >65 years	Vitamin D3, 400 IU twice daily	1 years	No difference in MACE
WHI/Jackson et al. [62]	36282	Women aged 50–79 years with no evidence of a medical condition	Vitamin D3, 400 IU/d	12 years	No difference in MACE, improvement in hip bone density
Berggren et al. [63]	199	Participants aged ≥70 years who had femoral neck fractures	Vitamin D3, 800 IU/d	1 year	No difference in MACE
Zhu et al. [64]	120	Women aged 70–80 years	Vitamin D3, 1000 IU/d	5 years	No difference in MACE
Prince et al. [65]	302	Women aged 70–90 years	Vitamin D3, 1000 IU/d	1 year	No difference in MACE, reduction in falls
Vital D/Sanders et al. [66]	2256	Women aged ≥70 years at high risk of fracture	Vitamin D3, 500 000 IU/year	Median (IQR), 2.96 (2.92–3.00)	Increased falls, no difference in MACE
Lehouck et al. [67]	182	Current of former smokers with COPD	Vitamin D, 100 000 IU/ month	1 year	Reduced COPD exacerbations in vitamin D deficient patients
VITDISH/Witham et al. [68]	159	Participants aged ≥70 years with isolated systolic hypertension	Vitamin D, 100 000 IU/month	1 year	MACE, blood pressure, arterial stiffness, endothelial function, cholesterol level, glucose level, and walking distance: no difference
OPERA/Wang et al. [69]	60	Stages 3–5 chronic kidney disease and left ventricle hypertrophy	Paricalcitol, 1 µg/d	1 year	No impact of left ventricular mass, improved secondary hyperparathyroidism
Baron et al. [70]	2259	Participants aged 45–75 years who had ≥1 colorectal adenoma	Vitamin D3, 1000 IU\d	3 years	Adverse events: no difference
EVITA/Zitterman et al. [71]	400	Participants aged 18–79 years who were classified as having New York Heart Association functional class ≥II	Vitamin D3, 4000 IU/d	3 years	No difference in mortality
VIDA/Scragg et al. [47]	5110	Vitamin D insuficient patients	Cholecalciferol (100 000 IU/month)	Median follow-up = 3.3 years	No beneficial effects of cholecalciferol supplementation on CVD risk or mortality

→

Table 3 (cont.). Vitamin D supplementation in primary and secondary prevention

Study name	Patients (n)	Inclusion criteria	Vitamin D dosing	Follow-up duration	Study outcome and results
J-DAVID/Shoji et al. [72]	954	Patients on hemodialysis	Alfacalcidol, 0.5 μg/d	Median (IQR), Vitamin D: 4.0 (2.6–4.0)a; Placebo: 4.0 (3.5–4.0)	no difference in selected cardiovascular events
VITAL/Manson et al. [25]	754	All women	Calcium (1000 mg/day) + cholecalciferol (400 IU/day)	Average of seven years	No significant changes in CAC score
Gulseth et al. [73]	62	Subjects with T2DM	Single dose of 400,000 IU oral vitamin D3	4 weeks	No change in insulin sensitivity or insulin secretion
Jorde et al. [74]	438	Overweight or obese subjects	Vitamin D (3) 40 000 IU per week (DD group), vitamin D 20 000 IU per week (DP group)	12 months	Glucose tolerance, blood pressure or serum lipids: no change
BEST-D trial /Clarke et al. [75]	305	Elderly	cholecalciferol (4000 IU or 2000 IU)	12 months	No significant changes in CVD risk factors
Seibert et al. [76]	106	Healthy subjects	cholecalciferol (2000 IU/day)	12 weeks	No difference in mortality, major cardiovascular events and invasive cancer
Forouhi et al. [77]	340	Patients with high risk of diabetes type 2	Ergocalciferol (100,000 IU/month) or cholecalciferol (100 000 IU/month)	4 months	Improvements in pulse wave velocity, no difference in other cardiometabolic parameters

Abbreviations: CVD, cardiovascular disease; IQR, interquartile range; IU, international units; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; S, supplementary; T2DM, type 2 diabetes mellitus

Endothelial adhesion and activation # reduces vascular cell adhesion molecule 1 (VCAM-1) # reduces E-selectin Vascular tone and endothelial function • increases the level of nitric oxide • reduces the level of reactive oxygen species released Inflammation and atherosclerosis # reduces proinflammatory type 1 cytokines: IL-12, IL-6, IL-8, IFN-gamma, TNF-alpha # increase anti-inflammatory type 2 cytokines: IL-4, IL-5, and IL-10 # reduces oxidative stress through reducing cathepsin, IL-6 and adiponectin Arterial smooth muscle cells • decreases production of angiotensin II • decreases oxidative stress • inhibits cellular senescence • reduces tissue factor expression

established cardiovascular disease. In the randomized controlled trial: the Randomised Evaluation of Calcium Or vitamin D (RECORD), treatment with cholecalciferol prevented cardiac failure among 5292 older people but did not appear to protect against myocardial infarction or stroke [78].

In addition, Le et al. [79] explored the effects of vitamin D on cardiac function in mice with post-myocardial infarction, showing a significant reduction in the fibrotic scar area and wall thinning in the animals receiving calcitriol supplementation, mediated by a reduction of fibrosis and enhanced myocytes differentiation. Thus, these data could further reinforce the incoming evidence of the potential benefits of using vitamin D in patients with left ventricular dysfunction and heart failure [80].

In a study in which calcitriol was administered over 6 months (0.5 mg/day) in patients with stable CAD, improvements were noted in the SYNTAX score and cardiometabolic variables [81].

Moreover, Bonakdaran et al. [82] reported that calcitriol supplementation could improve metabolic parameters and the control of cardiovascular risk factors among 119 patients with diabetes, suggesting that inadequate activation of vitamin D to its active metabolite, calcitriol, could represent a cause of the failure of major trials.

In fact, Saghir Afifeh et al. [83] previously reported a prevalence of calcitriol deficiency of about 10% in the patients with CAD, even despite adequate levels of vitamin D.

FUTURE PERSPECTIVES

Thus, future trials specific for subsets of higher-risk patients are certainly warranted to define whether a more tailored approach with vitamin D supplementation could be beneficial. Nevertheless, considering the positive effects on reducing overall mortality, cancer and functional status, consistently demonstrated in different trials and meta-analyses, and the safety, tolerability and low cost of vitamin D supplementation, such a strategy should certainly be considered, in particular in subjects at higher risk of deficiency [46, 84].

Such strategy should certainly be further reinforced in the context of the ongoing COVID-19 pandemic. In fact, the role of vitamin D in the modulation of the immune system and inflammation, and the prevention of thrombotic events, has been suggested. Vitamin D was reported to lower the rate of complications and improve the outcomes for infected patients [85]. Moreover, in addition to empowering the immune defense, vitamin D could prevent of contagion, by lowering the expression of the ACE-2 enzyme [86], thus leading the scientific societies to recommend the maintenance of adequate levels of vitamin D, and especially among subjects with increased risk for complications, as in patients with CAD [87, 88].

Moreover, the exact definition of the optimal vitamin D levels to reduce the cardiovascular risk and the appropriate dosing of pharmacological therapy, still need to be settled by experts' agreement. Possibly, the achievement of levels higher than expected is required to observe the cardioprotective effects of vitamin D, especially in those severely deficient subjects [89].

Finally, a tailored approach to vitamin D supplementation, accounting for the differential mechanisms of deficiency and comorbidities conditioning its effectiveness [90], certainly represents a promising option, which should be further assessed in future randomized trials.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

REFERENCES

1. Rosen CJ, Adams JS, Bikle DD, et al. The nonskeletal effects of vitamin D: an Endocrine Society Scientific statement. Endocr Rev. 2012; 33(3): 456–492, doi: 10.1210/er.2012-1000, indexed in Pubmed: 22596255.
2. Norman PE, Powel JT. Vitamin D and cardiovascular disease. Circ Res. 2014; 114(2): 379–393, doi: 10.1161/CIRCRESAHA.113.301241, indexed in Pubmed: 24436433.
3. Verdoia M, Schaffer A, Sartori C, et al. Vitamin D deficiency is independently associated with the extent of coronary artery disease. Eur J Clin Invest. 2014; 44(7): 634–642, doi: 10.1111/eci.12281, indexed in Pubmed: 24829065.
4. Verdoia M, Schaffer A, Barbieri L, et al. Novara Atherosclerosis Study Group (NAS). Impact of gender difference on vitamin D status and its relationship with the extent of coronary artery disease. Nutr Metab Cardiovasc Dis. 2015; 25(5): 464–470, doi: 10.1016/j.numecd.2015.01.009, indexed in Pubmed: 25791862.
5. Lavie CJ, DiNicolantonio JJ, Milani RV, et al. Vitamin D and cardiovascular health. Circulation. 2013; 128(22): 2404–2406, doi: 10.1161/CIRCULATIONAHA.113.002902, indexed in Pubmed: 24276875.
6. Wahl DA, Cooper C, Ebeling PR, et al. A global representation of vitamin D status in healthy populations. Arch Osteoporos. 2012; 7: 155–172, doi: 10.1007/s11657-012-0093-0, indexed in Pubmed: 23225293.
7. Isaia G, Giorgino R, Rini GB, et al. Prevalence of hypovitaminosis D in elderly women in Italy: clinical consequences and risk factors. Osteoporos Int. 2003; 14(7): 577–582, doi: 10.1007/s00198-003-1390-7, indexed in Pubmed: 12856111.
8. Chang SW, Lee HC. Vitamin D and health — the missing vitamin in humans. Pediatr Neonatol. 2019; 60(3): 237–244, doi: 10.1016/j.pedneo.2019.04.007, indexed in Pubmed: 31101452.
9. Roth DE, Abrams SA, Aloia J, et al. Global prevalence and disease burden of vitamin D deficiency: A roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018; 1430(1): 44–79, doi: 10.1111/nyas.13968, indexed in Pubmed: 30225965.
10. Cashman KD, Dowling KG, Škrabáková Z, et al. Vitamin D deficiency in Europe: pandemic? Am J Clin Nutr. 2016; 103(4): 1033–1044, doi: 10.3945/ajcn.115.120873, indexed in Pubmed: 26864360.
11. Christakos S, Dhawan P, Verstuyf A, et al. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev. 2016; 96(1): 365–408, doi: 10.1152/physrev.00014.2015, indexed in Pubmed: 26681795.
12. Bouillon R, Marcocci C, Carmeliet G, et al. Skeletal and extraskeletal actions of vitamin D: current evidence and outstanding questions. Endocr Rev. 2019; 40(4): 1109–1151, doi: 10.1210/er.2018-00126, indexed in Pubmed: 30321335.
13. Hsu S, Hoofnagle AN, Gupta DK, et al. Race, ancestry, and vitamin D metabolism: the multi-ethnic study of atherosclerosis. J Clin Endocrinol Metab. 2020; 105(12): e4337–e4350, doi: 10.1210/clinem/dgaa612, indexed in Pubmed: 32869845.
14. Weishaar T, Rajan S, Keller B. Probability of vitamin D deficiency by body weight and race/ethnicity. J Am Board Fam Med. 2016; 29(2): 226–232, doi: 10.3122/jabfm.2016.02.150251, indexed in Pubmed: 26957379.
15. Jones G, Prosser DE, Kaufmann M. The activating enzymes of vitamin D metabolism (25- and 1α-hydroxylases). In: Feldman D, Pike WJ, Bouillon R, Giovannucci E, Goltzman D, Hewison M. ed. Vitamin D, 4th ed. Academic Press, Cambridge 2018.
16. Saponaro F, Saba A, Zucchi R. An update on vitamin D metabolism. Int J Mol Sci. 2020; 21(18): 6573, doi: 10.3390/ijms21186573, indexed in Pubmed: 32911795.
17. Haussler MR, Whitfield GK, Haussler CA, Sabir MS, Khan Z, Sandoval R, Jurutka PW. 1, 25- dihydroxyvitamin d and klotho: a tale of two renal hormones coming of age. In: Litwack G. ed. Vitamins & hormones: vitamin D hormone. Academic Press, Cambridge 2016: 165–230.
18. Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014; 21(3): 319–329, doi: 10.1016/j.chembiol.2013.12.016, indexed in Pubmed: 24529992.
19. Bouillon R, Pauwels S. The Vitamin D-Binding Protein. In Vitamin D, 4th ed.; Feldman, D., Pike, W.J., Bouillon, R., Giovannucci, E., Goltzman, D., Hewison, M., Eds. In: Feldman D, Pike WJ, Bouillon R, Giovannucci E, Goltzman D, Hewison M. ed. Vitamin D, 4th ed. Academic Press, Cambridge 2018.
20. Carlberg C. Nutrigenomics of vitamin D. Nutrients. 2019; 11(3): 676, doi: 10.3390/nu11030676, indexed in Pubmed: 30901909.
21. De Castro LCG. The vitamin D endocrine system [article in Portuguese]. Arq Bras Endocrinol Metabol. 2011; 55(8): 566–575, doi: 10.1590/s0004-27302011000800010, indexed in Pubmed: 22218438.
22. Carlberg C. Vitamin D: a micronutrient regulating genes. Curr Pharm Des. 2019; 25(15): 1740–1746, doi: 10.2174/1381612825666190705193227, indexed in Pubmed: 31298160.
23. Hii CS, Ferrante A. The non-genomic actions of vitamin D. Nutrients. 2016; 8(3): 135, doi: 10.3390/nu8030135, indexed in Pubmed: 26950144.
24. Verdoia M, De Luca G. Potential role of hypovitaminosis D and vitamin D supplementation during COVID-19 pandemic. QJM. 2021; 114(1): 3–10, doi: 10.1093/qjmed/hcaa234, indexed in Pubmed: 32735326.
25. Verdoia M, Pergolini P, Rolla R, et al. Novara Atherosclerosis Study Group (NAS). Vitamin D levels and high-residual platelet reactivity in patients receiving dual antiplatelet therapy with clopidogrel or ticagrelor. Platelets. 2016; 27(6): 576–582, doi: 10.3109/09537104.2016.1149159, indexed in Pubmed: 27540959.
26. Verdoia M, Nardin M, Rolla R, et al. Novara Atherosclerosis Study Group (NAS). Cholecalciferol levels, inflammation and leukocytes parameters: results from a large single-centre cohort of patients. Clin Nutr. 2021; 40(4): 2228–2236, doi: 10.1016/j.clnu.2020.09.054, indexed in Pubmed: 33121835.
27. de la Guía-Galipienso F, Martínez-Ferran M, Vallecillo N, et al. Vitamin D and cardiovascular health. Clin Nutr. 2021; 40(5): 2946–2957, doi: 10.1016/j.clnu.2020.12.025, indexed in Pubmed: 33397599.
28. Michos ED, Misialek JR, Selvin E, et al. 25-hydroxyvitamin D levels, vitamin D binding protein gene polymorphisms and incident coronary heart disease among whites and blacks: The ARIC study. Atherosclerosis. 2015; 241(1): 12–17, doi: 10.1016/j.atherosclerosis.2015.04.803, indexed in Pubmed: 25941991.
29. Thomas GN, ó Hartaigh B, Bosch JA, et al. Vitamin D levels predict all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. Diabetes Care. 2012; 35(5): 1158–1164, doi: 10.2337/dc11-1714, indexed in Pubmed: 22399697.

30. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008; 117(4): 503–511, doi: 10.1161/CIRCULATIONAHA.107.706127, indexed in Pubmed: 18180395.
31. Aihara K, Azuma H, Akaike M, et al. Disruption of nuclear vitamin d receptor gene causes enhanced thrombogenicity in mice. J Biol Chem. 2004; 279(34): 35798–35802, doi: 10.1074/jbc.M404865200, indexed in Pubmed: 15205460.
32. Verdoia M, Nardin M, Rolla R, et al. Novara Atherosclerosis Study Group (NAS). Association of lower vitamin D levels with inflammation and leucocytes parameters in patients with and without diabetes mellitus undergoing coronary angiography. Eur J Clin Invest. 2021; 51(4): e13439, doi: 10.1111/eci.13439, indexed in Pubmed: 33112413.
33. Nardin M, Verdoia M, Schaffer A, et al. Novara Atherosclerosis Study Group (NAS). Vitamin D status, diabetes mellitus and coronary artery disease in patients undergoing coronary angiography. Atherosclerosis. 2016; 250: 114–21, doi: 10.1016/j.atherosclerosis.2016.05.019, indexed in Pubmed: 27205868.
34. Vimaleswaran KS, Cavadino A, Berry DJ, et al. LifeLines Cohort Study investigators. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian randomisation study. Lancet Diabetes Endocrinol. 2014; 2(9): 719–729, doi: 10.1016/S2213-8587(14)70113-5, indexed in Pubmed: 24974252.
35. Li YC, Kong J, Wei M, et al. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest. 2002; 110(2): 229–238, doi: 10.1172/JCI15219, indexed in Pubmed: 12122115.
36. Verdoia M, Nardin M, Rolla R, et al. Novara Atherosclerosis Study Group (NAS). Vitamin D levels condition the outcome benefits of renin-angiotensin system inhibitors (RASI) among patients undergoing percutaneous coronary intervention. Pharmacol Res. 2020; 160: 105158, doi: 10.1016/j.phrs.2020.105158, indexed in Pubmed: 32841717.
37. Wolden-Kirk H, Overbergh L, Christesen HT, et al. Vitamin D and diabetes: its importance for beta cell and immune function. Mol Cell Endocrinol. 2011; 347(1-2): 106–120, doi: 10.1016/j.mce.2011.08.016, indexed in Pubmed: 21889571.
38. Verdoia M, Viglione F, Boggio A, et al. Novara Atherosclerosis Study Group (NAS). Relationship between vitamin D and cholesterol levels in STEMI patients undergoing primary percutaneous coronary intervention. Nutr Metab Cardiovasc Dis. 2021, doi: 10.1016/j.numecd.2021.11.014, indexed in Pubmed: 35078678.
39. Oh J, Weng S, Felton SK, et al. 1,25(OH)2 vitamin D inhibits foam cell formation and suppresses macrophage cholesterol uptake in patients with type 2 diabetes mellitus. Circulation. 2019; 120(8): 687–698, doi: 10.1161/CIRCULATIONAHA.109.856070, indexed in Pubmed: 19667238.
40. Verdoia M, Pergolini P, Rolla R, et al. Novara Atherosclerosis Study Group (NAS). Impact of high-dose statins on vitamin D levels and platelet function in patients with coronary artery disease. Thromb Res. 2017; 150: 90–95, doi: 10.1016/j.thromres.2016.12.019, indexed in Pubmed: 28068529.
41. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000; 72(3): 690–693, doi: 10.1093/ajcn/72.3.690, indexed in Pubmed: 10966885.
42. Verdoia M, Nardin M, Rolla R, et al. Novara Atherosclerosis Study Group (NAS). Prognostic impact of Vitamin D deficiency in patients with coronary artery disease undergoing percutaneous coronary intervention. Eur J Intern Med. 2020; 83: 62–67, doi: 10.1016/j.ejim.2020.08.016, indexed in Pubmed: 32830035.
43. Verdoia M, Schaffer A, Sartori C, et al. Vitamin D deficiency is independently associated with the extent of coronary artery disease. Eur J Clin Invest. 2014; 44(7): 634–642, doi: 10.1111/eci.12281, indexed in Pubmed: 24829065.
44. Kunadian V, Ford GA, Bawamia B, et al. Vitamin D deficiency and coronary artery disease: a review of the evidence. Am Heart J. 2014; 167(3): 283–291, doi: 10.1016/j.ahj.2013.11.012, indexed in Pubmed: 24576510.
45. Mao X, Hu B, Zhou Z, et al. Vitamin D levels correlate with lymphocyte subsets in elderly patients with age-related diseases. Sci Rep. 2018; 8(1): 7708, doi: 10.1038/s41598-018-26064-6, indexed in Pubmed: 29769621.
46. Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. BMJ. 2019; 366: l4673, doi: 10.1136/bmj.l4673, indexed in Pubmed: 31405892.
47. Khaw KT, Stewart AW, Waayer D, et al. Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomised, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017; 5(6): 438–447, doi: 10.1016/S2213-8587(17)30103-1, indexed in Pubmed: 28461159.
48. Manson JE, Cook NR, Lee IM, et al. VITAL Research Group. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med. 2019; 381(1): 33–44, doi: 10.1056/NEJMoa1809944, indexed in Pubmed: 30415629.
49. Sokol SI, Srinivas V, Crandall JP, et al. The effects of vitamin D repletion on endothelial function and inflammation in patients with coronary artery disease. Vasc Med. 2012; 17(6): 394–404, doi: 10.1177/1358863X12466709, indexed in Pubmed: 23184900.
50. Bahrami LS, Ranjbar G, Norouzy A, et al. Vitamin D supplementation effects on the clinical outcomes of patients with coronary artery disease: a systematic review and meta-analysis. Sci Rep. 2020; 10(1): 12923, doi: 10.1038/s41598-020-69762-w, indexed in Pubmed: 32737345.
51. Aslanabadi N, Jafaripor I, Sadeghi S, et al. Effect of vitamin D in the prevention of myocardial injury following elective percutaneous coronary intervention: a pilot randomized clinical trial. J Clin Pharmacol. 2018; 58(2): 144–151, doi: 10.1002/jcph.989, indexed in Pubmed: 28841229.
52. Shaseb E, Tohidi M, Abbasinazari M, et al. The effect of a single dose of vitamin D on glycemic status and C-reactive protein levels in type 2 diabetic patients with ischemic heart disease: a randomized clinical trial. Acta Diabetol. 2016; 53(4): 575–582, doi: 10.1007/s00592-016-0843-3, indexed in Pubmed: 26873242.
53. Witham MD, Dove FJ, Khan F, et al. Effects of vitamin D supplementation on markers of vascular function after myocardial infarction — a randomised controlled trial. Int J Cardiol. 2013; 167(3): 745–749, doi: 10.1016/j.ijcard.2012.03.054, indexed in Pubmed: 22459388.
54. Farrokhian A, Raygan F, Bahmani F, et al. Long-term vitamin D supplementation affects metabolic status in vitamin D-deficient type 2 diabetic patients with coronary artery disease. J Nutr. 2017; 147(3): 384–389, doi: 10.3945/jn.116.242008, indexed in Pubmed: 28122931.
55. Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006; 83(4): 754–759, doi: 10.1093/ajcn/83.4.754, indexed in Pubmed: 16600924.
56. Aloia JF, Dhaliwal R, Shieh A, et al. Calcium and vitamin d supplementation in postmenopausal women. J Clin Endocrinol Metab. 2013; 98(11): E1702–E1709, doi: 10.1210/jc.2013-2121, indexed in Pubmed: 24064695.
57. Ott SM, Chesnut CH. Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med. 1989; 110(4): 267–274, doi: 10.7326/0003-4819-110-4-267, indexed in Pubmed: 2913914.
58. Komulainen M, Kröger H, Tuppurainen MT, et al. Prevention of femoral and lumbar bone loss with hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. J Clin Endocrinol Metab. 1999; 84(2): 546–552, doi: 10.1210/jcem.84.2.5496, indexed in Pubmed: 10022414.
59. Gallagher JC, Fowler SE, Detter JR, et al. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab. 2001; 86(8): 3618–3628, doi: 10.1210/jcem.86.8.7703, indexed in Pubmed: 11502787.
60. Trivedi M, Faridi MM, Aggarwal A, et al. Oral vitamin D supplementation to mothers during lactation-effect of 25(OH)D concentration on exclusively breastfed infants at 6 months of age: a randomized double-blind placebo-controlled trial. Breastfeed Med. 2020; 15(4): 237–245, doi: 10.1089/bfm.2019.0102, indexed in Pubmed: 32181677.
61. Brazier M, Grados F, Kamel S, et al. Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2005; 27(12): 1885–1893, doi: 10.1016/j.clinthera.2005.12.010, indexed in Pubmed: 16507374.
62. Jackson RD, Wright NC, Beck TJ, et al. Calcium plus vitamin D supplementation has limited effects on femoral geometric strength in older postmenopausal women: the Women's Health Initiative. Calcif Tissue Int. 2011; 88(3): 198–208, doi: 10.1007/s00223-010-9449-x, indexed in Pubmed: 21253715.
63. Berggren M, Stenvall M, Olofsson B, et al. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-year follow-up.

Osteoporos Int. 2008; 19(6): 801–809, doi: 10.1007/s00198-007-0507-9, indexed in Pubmed: 18030411.
64. Zhu K, Austin N, Devine A, et al. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. J Am Geriatr Soc. 2010; 58(11): 2063–2068, doi: 10.1111/j.1532-5415.2010.03142.x, indexed in Pubmed: 21054285.
65. Lewis JR, Radavelli-Bagatini S, Rejnmark L, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res. 2015; 30(1): 165–175, doi: 10.1002/jbmr.2311, indexed in Pubmed: 25042841.
66. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010; 303(18): 1815–1822, doi: 10.1001/jama.2010.594, indexed in Pubmed: 20460620.
67. Lehouck An, Mathieu C, Carremans C, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2012; 156(2): 105–114, doi: 10.7326/0003-4819-156-2-201201170-00004, indexed in Pubmed: 22250141.
68. Witham MD, Price RJG, Struthers AD, et al. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension: the VitDISH randomized controlled trial. JAMA Intern Med. 2013; 173(18): 1672–1679, doi: 10.1001/jamainternmed.2013.9043, indexed in Pubmed: 23939263.
69. Wang AY, Fang F, Chan J, et al. Effect of paricalcitol on left ventricular mass and function in CKD — the OPERA trial. J Am Soc Nephrol. 2014; 25(1): 175–186, doi: 10.1681/ASN.2013010103, indexed in Pubmed: 24052631.
70. Baron JA, Barry EL, Mott LA, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. N Engl J Med. 2015; 373(16): 1519–1530, doi: 10.1056/NEJMoa1500409, indexed in Pubmed: 26465985.
71. Zittermann A, Ernst JB, Prokop S, et al. Effect of vitamin D on all-cause mortality in heart failure (EVITA): a 3-year randomized clinical trial with 4000 IU vitamin D daily. Eur Heart J. 2017; 38(29): 2279–2286, doi: 10.1093/eurheartj/ehx235, indexed in Pubmed: 28498942.
72. Shoji T, Inaba M, Fukagawa M, et al. J-DAVID Investigators. Effect of oral alfacalcidol on clinical outcomes in patients without secondary hyperparathyroidism receiving maintenance hemodialysis: the J-DAVID randomized clinical trial. JAMA. 2018; 320(22): 2325–2334, doi: 10.1001/jama.2018.17749, indexed in Pubmed: 30535217.
73. Gulseth HL, Wium C, Angel K, et al. Effects of vitamin D supplementation on insulin sensitivity and insulin secretion in subjects with type 2 diabetes and vitamin d deficiency: a randomized controlled trial. Diabetes Care. 2017; 40(7): 872–878, doi: 10.2337/dc16-2302, indexed in Pubmed: 28468770.
74. Jorde R, Sneve M, Figenschau Y, et al. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. J Intern Med. 2008; 264(6): 599–609, doi: 10.1111/j.1365-2796.2008.02008.x, indexed in Pubmed: 18793245.
75. Clarke R, Newman C, Tomson J, et al. Estimation of the optimum dose of vitamin D for disease prevention in older people: rationale, design and baseline characteristics of the BEST-D trial. Maturitas. 2015; 80(4): 426–431, doi: 10.1016/j.maturitas.2015.01.013, indexed in Pubmed: 25721698.
76. Seibert E, Lehmann U, Riedel A, et al. Vitamin D3 supplementation does not modify cardiovascular risk profile of adults with inadequate vitamin D status. Eur J Nutr. 2017; 56(2): 621–634, doi: 10.1007/s00394-015-1106-8, indexed in Pubmed: 26621634.
77. Forouhi NG, Menon RK, Sharp SJ, et al. Effects of vitamin D2 or D3 supplementation on glycaemic control and cardiometabolic risk among people at risk of type 2 diabetes: results of a randomized double-blind placebo-controlled trial. Diabetes Obes Metab. 2016; 18(4): 392–400, doi: 10.1111/dom.12625, indexed in Pubmed: 26700109.
78. Ford JA, MacLennan GS. RECORD Trial Group. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr. 2014; 100(3): 746–755, doi: 10.3945/ajcn.113.082602, indexed in Pubmed: 25057156.
79. Le TYL, Ogawa M, Kizana E. Vitamin D improves cardiac function after myocardial infarction through modulation of resident cardiac progenitor cells. Heart Lung Circ. 2018; 27(8): 967–975, doi: 10.1016/j.hlc.2018.01.006, indexed in Pubmed: 29573957.
80. Busa V, Dardeir A, Marudhai S, et al. Role of vitamin D supplementation in heart failure patients with vitamin d deficiency and its effects on clinical outcomes: a literature review. Cureus. 2020; 12(10): e10840, doi: 10.7759/cureus.10840, indexed in Pubmed: 33173646.
81. Wu Z, Wang T, Zhu S, et al. Effects of vitamin D supplementation as an adjuvant therapy in coronary artery disease patients. Scand Cardiovasc J. 2016; 50(1): 9–16, doi: 10.3109/14017431.2015.1103893, indexed in Pubmed: 26440923.
82. Bonakdaran S, Nejad AF, Abdol-Reza V, et al. Impact of oral 1,25-dihydroxy vitamin D (calcitriol) replacement therapy on coronary artery risk factors in type 2 diabetic patients . Endocr Metab Immune Disord Drug Targets. 2013; 13(4): 295–300, doi: 10.2174/18715303113136660047, indexed in Pubmed: 24180458.
83. Saghir Af, Verdoia M, Nardin M, et al. Novara Atherosclerosis Study Group (NAS). Determinants of vitamin D activation in patients with acute coronary syndromes and its correlation with inflammatory markers. Nutr Metab Cardiovasc Dis. 2021; 31(1): 36–43, doi: 10.1016/j.numecd.2020.09.021, indexed in Pubmed: 33308994.
84. Amrein K, Schnedl C, Holl A, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014; 312(18): 1932, doi: 10.1001/jama.2014.13204, indexed in Pubmed: 25268295.
85. Kaya MO, Pamukçu E, Yakar B. The role of vitamin D deficiency on COVID-19: a systematic review and meta-analysis of observational studies. Epidemiol Health. 2021; 43: e2021074, doi: 10.4178/epih.e2021074, indexed in Pubmed: 34607398.
86. Ferrario CM, Jessup J, Chappell M, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005; 111(20): 2605–2610, doi: 10.1161/CIRCULATIONAHA.104.510461, indexed in Pubmed: 15897343.
87. Annweiler C, Souberbielle JC. Vitamin D supplementation and COVID-19: expert consensus and guidelines [article in French]. Geriatr Psychol Neuropsychiatr Vieil. 2021; 19(1): 20–29, doi: 10.1684/pnv.2020.0907, indexed in Pubmed: 33350389.
88. Ulivieri FM, Banfi G, Camozzi V. Vitamin D in the Covid-19 era: a review with recommendations from a G.I.O.S.E.G. expert panel . Endocrine. 2021; 72(3): 597–603, doi: 10.1007/s12020-021-02749-3, indexed in Pubmed: 33999367.
89. Michos ED, Cainzos-Achirica M, Heravi AS, et al. Vitamin D, calcium supplements, and Implications for cardiovascular health: JACC focus seminar. J Am Coll Cardiol. 2021; 77(4): 437–449, doi: 10.1016/j.jacc.2020.09.617, indexed in Pubmed: 33509400.
90. Bilezikian JP, Formenti AM, Adler RA, et al. Vitamin D: dosing, levels, form, and route of administration: does one approach fit all? Rev Endocr Metab Disord. 2021; 22(4): 1201–1218, doi: 10.1007/s11154-021-09693-7, indexed in Pubmed: 34940947.