Vitamin D and cardiometabolic disorders: state of the field review

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INTRODUCTION

For some time it has been known that calcium and phosphate homeostasis is essential for normal cellular physiology as well as for skeletal integrity [1]. Several recent epidemiological, clinical and experimental studies have provided a very impressive series of information about new and different biological functions concerning vitamin D and the vitamin D receptor, in addition to those traditionally recognized. These functions include the ability to influence cellular growth and differentiation to modulate immune response and to control the activity of other hormonal systems [2].
As a result, it has been suggested that vitamin D deficiency favors the development of high prevalence cardiometabolic risk factors, such as diabetes, hypertension and associated cardiovascular events [3, 4].

THE BIOLOGY OF VITAMIN D

In humans, about 80% of vitamin D (cholecalciferol) is synthesized in the skin from 7-dehydrocholesterol and the remaining 20% from diet. Vitamin D is then activated through two hydroxylation steps at positions 1 and 25, forming calcitriol (1,25-dihydroxycalciferol).
Recent studies have disproved the previous notion that biological activation of vitamin D occurred exclusively in the kidney by showing that most human tissues and cells also express the 1α- hydroxylase enzyme. They further indicate that the vitamin D receptor (VDR), which acts as a transcription factor, is expressed in at least 36 types of human cells, where it regulates – directly or indirectly – the expression of about 3% of the entire human genome.
In light of these findings, it appears that the vitamin D – VDR system is involved in a wide range of biological activities [2].

VITAMIN D STATUS

The evaluation of vitamin D status is based on circulating 25-hydroxyvitamin D [25(OH)VitD] levels [3]. In general, vitamin D deficiency is defined as levels of 25(OH)VitD < 20 ng/mL (or 50 nmol/L). However, since levels of circulating PTH are at their nadir when levels of 25(OH)VitD < 30 ng/mL, it is believed that 25(OH)VitD levels between 21 and 29 ng/mL indicates vitamin D deficiency, while levels ≥ 30 ng/mL (74 nmol/L) are considered adequate. Based on these criteria, about 15% of the world population, including children and adolescents, is either deficient or has vitamin D insufficiency, especially in persons who are overweight or obese. In addition, more than half of elderly subjects have suboptimal levels of 25(OH)VitD [3].

VITAMIN D AND CARDIOMETABOLIC DISORDERS: PHYSIOPATHOLOGICAL CONNECTIONS

Based on widespread evidence showing that a high number of human tissues and cells, including cardiomyocytes and smooth and endothelial muscle cells, express both VDR and the 1α-hydroxylase enzyme, it has been hypothesized that the biological system of vitamin D plays a role in the pathogenesis of many cardiometabolic disorders [2]. In many studies, vitamin D deficiency and/or insufficiency led to secondary hyperparathyroidism when high levels of PTH were associated with increased cardiovascular risk. The vitamin D/VDR biological system also acts as an endocrine and paracrine negative regulator of the renin-angiotensin-aldosterone system, which plays a central role in the regulation of blood pressure, fluid volume and electrolyte metabolism. The vitamin D/VDR system also regulates insulin and insulin receptor gene expression and, through the modulation of calbindin expression, controls intracellular calcium flux in inslet cells, which in turn affects insulin release. Calcitriol synthesized in endothelial cells seems

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to have a contrasting effect with respect to the end-products of advanced glycation and of various pro-atherosclerotic metabolites.
Furthermore, calcitriol regulates the expression of factors that promote osteoblast differentiation at the vessel wall, an action that can influence the development of vascular calcification. Calcitriol also inhibits foam cell formation and macrophage cholesterol uptake in diabetic subjects. Finally, calcitriol acts as modulator of both immune response and of cytokines biosynthesis [2, 5].

VITAMIN D AND CARDIOMETABOLIC DISORDERS: RESULTS OF OBSERVATIONAL STUDIES (TABLE I)

Many studies have provided support for the idea that vitamin D might have an impact on the risk and possibly on the course of several metabolic and cardiovascular disorders [5]. From the analysis of 28 studies on 99,745 participants, Parker et al. found that higher levels of 25(OH)VitD were associated to a significantly lower incidence of cardiovascular diseases, diabetes and metabolic syndrome, with an odds ratio (OR) of 0.57 and a confidence interval of 95% (CI 95%: 0.48-0.68) [6].
A meta-analysis conducted by Burgaz et al. on 18 studies (n = 78,028 participants) showed that 25(OH)VitD levels were inversely associated with hypertension [7]. In addition, the more recent meta-analysis by Kunutsor et al. again demonstrated an inverse correlation between 25(OH)VitD and the risk of incident hypertension in an apparently healthy population (n = 283,537), with a risk reduction equal to 12% for every increase of 10 ng/mL in vitamin D plasma levels [8]. Moreover, a meta-analysis of prospective studies by Song et al. (21 studies with 76,220 participants and 4,996 cases of incident type 2 diabetes) showed an inverse correlation between 25(OH)VitD and the risk of type 2 diabetes in different populations [9], with a risk reduction equal to 4% for every increase of 4 ng/mL 25(OH)VitD.
In the Framingham Offspring Study, Wang et al. showed that among 1,739 participants without prior cardiovascular disease (mean baseline age = 59 years; follow-up after 5.4 years) individuals with levels of 25(OH)VitD < 15 ng/mL had a multivariable hazard ratio (HR) of 1.62 (95% CI: 1.11 to 2.36) for incident cardiovascular events, including heart attack, angina pectoris, stroke, transient ischemic attack, intermittent claudication and heart failure, compared with those with 25(OH)VitD > or = 15 ng/mL. This effect was only evident in participants with hypertension [10].
In addition, a recent meta-analysis of 19 prospective studies of 65,994 participants and 6,123 cardiovascular events, performed by Wang et al., showed that there was a linear inverse association between 25(OH) VitD levels in the interval between 20 and 60 nmol/L and the risk of cardiovascular disease. In particular, comparison of the 25th and 75th percentile concentrations of 25(OH)VitD showed that the multivariable relative risk was equal to 1.38 (1.21-1.57) for coronary heart disease and to 1.64 (1.27-2.10) for stroke [11].
A recent small sample study performed by Messenger et al. on 813 males (the MrOS Study, mean baseline age = 74, median follow-up of 4.4 years) did not confirm these results: yet this study looked at a low number of subjects affected by hypovitaminosis D and a small number of incident cases of cardiovascular disease [12].
Several studies have also shown that vitamin D status might affect life expectancy in the general population. Liu et al. analyzed 13,131 subjects in the NHANES III trial (age ≥ 35 years, median follow-up of 8 years) and found that subjects with serum levels of 25(OH)VitD < 20 ng/mL had a 2.06 (1.01-4.25) higher mortality risk for heart failure than those subjects with serum levels of 25(OH)VitD ≥ 30 ng/mL. Furthermore, the risk ratio for all-causes early death (< 75 years) was 1.40 (1.17-1.68) for subjects with levels of 25(OH)VitD < 20 ng/mL, and 1.11 (0.93-1.33) for subjects with values between 20 and 29 ng/mL, compared to those with serum levels ≥ 30 ng/mL (p for trend < 0.001) [13]. The meta-analysis conducted by Wang et al., cited above, confirmed that subjects within the lowest category of 25(OH)VitD levels had an increased risk for cardiovascular disease-specific deaths, equal to 1.42 (1.19-1.71), compared to those within the highest category [11].
A meta-analysis of 14 prospective cohort studies with 62,548 participants (5,562 deaths) by Zittermann et al. confirmed a lower mortality risk for the highest compared to the lowest percentiles of 25(OH)VitD (0.71; 0.50-0.91), with optimal concentrations between 75 and 87.5 nmol/L [14]. The mortality risk related to serum levels of vitamin D was also investigated and analyzed in specific subsets of individuals. In the Whitehall study of quite elderly subjects (n = 5.409, mean baseline age = 77 years, follow-up of 13 years), an inverse correlation between 25(OH)VitD levels and relative risk of vascular and non-vascular mortality was observed. These data were confirmed in a meta-analysis by the same authors of 12 cohort studies with 42,565 participants [15]. In a small sample study on 289 patients with type 2 diabetes with a median follow-up of 15 years and 196 deaths (68%), severe vitamin D deficiency, with 25(OH) VitD < 13.9 nmol/L, was associated with an increased risk of cardiovascular (HR 1.95; 1.11-3.44) and all-causes mortality (HR 1.96; 1.29-2.98) [16]. Similar results were found by Dobnig et al. in patients who underwent coronary angiography [17].

VITAMIN D AND CARDIOMETABOLIC DISORDERS: EVIDENCE FROM INTERVENTIONAL STUDIES (TABLE II)

While observational studies have almost uniformly found inverse correlations between circulating levels of 25(OH)VitD and the risk of metabolic and/or cardiovascular diseases, only recently has evidence for a correlation between vitamin D and cardiometabolic disorders been found through randomized controlled trials and relative meta-analyses.
The meta-analysis by Li et al. provided evidence for the effects of vitamin D supplementation in patients with type 2 diabetes on the most important glycol metabolic parameters [18]. Analysis of 20 randomized controlled trials over 2 to 6 months on 2,703 patients showed a significant reduction in the HOMA index of insulin resistance in patients with hypovitaminosis D, without, however, significant improvements for other variables, such as body weight, fasting blood sugar levels or glycated hemoglobin. It is important to note that the quality of the evidence provided by the above-mentioned studies was on average considered low.
Another meta-analysis by Swart et al. examined randomized controlled trials concerning vitamin D supplementation in population samples of great heterogeneity (n = 2,994). Ranging in duration from 16 weeks to 1 year, these trials used individual data and set blood pressure and glycated hemoglobin levels as the main outcomes. Results from this meta-analysis showed that there were no significant effects of vitamin D supplementation on either of these two outcomes, while a significant reduction of LDL cholesterol levels was found [19].

TABLE I.
Vitamin D and Cardiometabolic Disorders: results from most important observational studies.

Author [ref.]	Type of study	Characteristics	Main results
Parker [6]	Meta-analysis	28 studies (n = 99,745 participants)	Inverse association between 25(OH)D and prevalence of cardiovascular diseases, diabetes and metabolic syndrome
Burgaz [7]	Meta-analysis	18 studies (n = 78,028 participants)	Inverse association between 25(OH)D and prevalence of hypertension
Kunutsor [8]	Meta-analysis	8 prospective studies (n = 283,537; 55,816 incident cases)	Reduction of incident hypertension risk equal to 12% for each 10 ng/mL 25(OH) D increment
Song [9]	Meta-analysis	21 prospective studies (n = 76,220 participants; 4,996 incident cases)	Reduction of diabetes risk equal to 4% for each 4 ng/mL 25(OH)D increment
Wang [10]	Prospective study	*Framingham Offspring Study* (n = 1,739 clinically healthy participants, mean age 59 years, medium follow-up 5.4 years)	For levels of 25(OH)D < 15 ng/mL HR multivariate of 1.62 (CI 95% 1.11-2.36) for incident cardiovascular events *vs* 25(OH) D ≥ 15 ng/mL (only in subjects with hypertension)
Wang [11]	Meta-analysis	19 prospective studies (n = 65,994 participants; 6,123 events)	For lowest category of 25(OH)D compared to highest category, RR equal to 1.52 (1.30-1.77) for all cardiovascular diseases, 1.42 (1.19-1.71) for cardiovascular deaths, 1.38 (1.21-1.57) for coronary disease and 1.64 (1.27-2.10) for stroke
Messenger [12]	Prospective study	MrOS study (n = 813 males, mean age 74 years, medium follow-up 4.4 years)	No association between 25(OH)D and incidence of cardiovascular diseases
Liu [13]	Prospective study	NHANES III (n = 13,131; age ≥ 35 years, medium follow-up 8 years)	For levels of 25(OH)D < 20 ng/mL, RR of heart failure death equal to 2.06 (1.01-4.25) compared to 25(OH)D ≥ 30 ng/mL Risk ratio for all-cause premature deaths equal to 1.40 (1.17-1.68) for 25(OH)D < 20 ng/mL and 1.11 (0.93-1.33) for values between 20 and 29 ng/mL, *vs* 25(OH)D ≥ 30 ng/mL (p for trend < 0.001)
Zittermann [14]	Meta-analysis	14 prospective studies (n = 62,548 and 5,562 deaths)	Mortality reduced risk (0.71, 0.50-0.91) for subjects in highest category *vs* those in lowest category of 25(OH)D, with an optimal concentration of 25(OH)D between 75 and 87.5 nmol/L
Tomson [15]	Prospective study	Whitehall (n = 5,409, mean age 77 years, medium follow-up 13 years)	Inverse correlation between 25(OH)D and relative risk of vascular and non-vascular death
Tomson [15]	Meta-analysis	12 prospective studies (n = 42,565)	For subjects in the highest quartile of 25(OH)D, reduction of mortality for vascular causes equal to 21% (13-28%) and of all mortality equal to 28% (24-32%) *vs* subjects in the lowest quartile
Joergensen [16]	Prospective study	(289 patients with type 2 diabetes, medium follow-up 15 years, 196 deaths)	For levels of 25(OH)D < 10th percentile (13.9 nmol/L), HR for cardiovascular deaths equal to 1.95 (1.11-3.44) and for all-cause deaths equal to 1.96 (1.29-2.98), compared to subjects with levels of equal to 25(OH)D > 13.9 nmol/L
Dobnig [17]	Prospective study	3,258 patients, mean age 62 years, scheduled for coronary angiography, medium follow-up 7.7 years, 737 deaths	For subjects in the lowest quartile of 25(OH)D, HR for all deaths equal to 2.08 (1.60-2.70) and for cardiovascular deaths equal to 2.22 (1.57-3.13)

Another meta-analysis which included observational and interventional studies on the correlation between 25(OH)VitD levels and fat mass percentage confirmed an inverse correlation between the latter and circulating levels of vitamin D; it did not, however, highlight any significant effect of vitamin D supplementation on fat mass percentage [20].
In another randomized controlled trial, vitamin D supplementation was given for 48 weeks to 127 type 2 diabetes patients (mean average age = 60 years) who were not selected for hypovitaminosis D and who had good glycol-metabolic control with metformin. Results did not show significant ef-

TABLE II.
Vitamin D and Cardiometabolic Disorders: results from most important observational studies.

Author [ref.]	Type of study	Characteristics	Main results
Li [18]	Meta-analysis	20 randomized controlled trials of vitamin D supplementation (n = 2,703 patients with type 2 diabetes, for a period of 2-6 months)	Supplementation with vitamin D followed by reduction of insulin-resistance HOMA index, particularly in patients with hypovitaminosis D, without, though, improvements in body weight, fasting blood sugar and glycated hemoglobin.
Swart [19]	Meta-analysis	12 randomized controlled trials of vitamin D supplementation (n = 2,994, length of therapy between 16 weeks and 1 year)	Ineffective supplementation for two main outcomes (blood pressure and glycated hemoglobin) Reduction of cholesterol LDL
Golzarand [20]	Meta-analysis	Observational studies and controlled clinical trials on relation between vitamin D supplementation and percentage of body fat.	Inverse correlation between levels of 25(OH)D and percentage of body fat, but no relation between vitamin D and percentage of body fat
Angellotti [21]	RCT	Randomized controlled trial on vitamin D supplementation for 48 weeks (n = 127 patients with type 2 diabetes, mean age 60 years, not selected for hypovitaminosis D and with good glycol metabolic control with metformin)	No effect on glycated hemoglobin and insulin secretion velocity
Cefalo [22]	RCT	Randomized controlled trial on 18 overweight, nondiabetic, vitamin D deficient volunteers following hypocaloric regime and vitamin D supplementation for 3 months	Increase of insulin sensitivity measured using hyperinsulinemic-euglycemic clamp in treated subjects but not in control group, with equal weight loss in both groups
Bislev [23]	RCT	Randomized controlled trial with vitamin D supplementation (n = 81 females in post-menopausal age with hypovitaminosis D and secondary hyperparathyroidism for 12 weeks)	Reduced PTH levels but no reduction in renin-angiotensin-aldosterone system activity or in levels of blood pressure, glycated hemoglobin, plasma lipids or vascular stiffness
Sluyter [24]	RCT	ViDA Study Randomized controlled trial with vitamin D supplementation (n = 517 adult subjects, for 1.1 years)	No significant effect on blood pressure parameters for all subjects, but significant favorable changes in vascular stiffness and central blood pressure parameters among a subset of participants with severe vitamin D deficiency
Manson [25]	RCT	VITAL Study (*Vitamin D and Omega 3 Trial*) Randomized controlled trial with vitamin D supplementation and/or omega 3 fatty acids (n = 25,871 subjects, age > 50 years, for over 5 years)	No significant effects on the incidence of overall or specific cardiovascular events, even in participants with levels of 25(OH)D < 20 ng/mL

fects on either glycated hemoglobin levels or on insulin secretion velocity, in spite of the significantly higher levels of circulating 25(OH)VitD [21].

In another clinical trial, 18 nondiabetic volunteers with both obesity and vitamin D deficiency were fed a hypocaloric diet combined with either a weekly administration of 25,000 IU of 25(OH)-hydroxycholecalciferol or a placebo for three months. A significant rise in vitamin D concentrations was associated with a considerable increase in insulin sensitivity, measured using a hyperinsulinemic-euglycemic clamp in subjects under active treatment compared to the placebo group. Body weight in both groups decreased equally [22].

In a controlled clinical trial on 81 postmenopausal women with hypovitaminosis D and secondary hyperparathyroidism, treatment with vitamin D for 12 weeks reduced PTH levels but did not reduce renin-angiotensin-aldosterone system activity or lower levels of blood pressure, glycated hemoglobin, lipids, lipoproteins or vascular stiffness [23].

As part of the ViDA Study, a total of 517 adults were recruited to receive, for 1.1 years, either an initial dose of 200,000 IU of vitamin D3 followed by monthly 100,000 IU doses, or a placebo. Results showed no significant changes in hemodynamic parameters in the total sample; among a subset of participants with severe vitamin D deficien-

cy, however, statistically significant favorable changes in vascular stiffness and central blood pressure parameters were observed [24].

Recently, results from VITAL (Vitamin D and Omega 3 Trial) have been published, a trial investigating the effects of daily vitamin D3 administration (2,000 IU) and/or omega 3 fatty acids (1 g) in 25,871 subjects for a period of over 5 years; the group studied was composed of men 50 years of age or older and women 55 or older. The primary endpoints were the incidence of cancer and of major cardiovascular events. These results showed that vitamin D supplementation was not associated with a lower risk of either of the primary or secondary endpoints (the latter represented by specific forms of cancer and cardiovascular events), even in the subset of participants with baseline values of 25(OH)VitD < 20 ng/mL [25].

CONCLUSIONS

Most observational studies, both transversal and prospective, suggest that there is an inverse correlation between vitamin D status (expressed as plasma levels of 25-hydroxycholecalciferol), on one hand, and cardiometabolic risk factors and cardiovascular morbidity and mortality, on the other, both in samples of the general population and in high risk patients (such as the elderly and patients with diabetes, hypertension and/or chronic kidney disease).

Results from several experimental studies provide biological plausibility for such statistical and epidemiological associations and for the hypothesis of the metabolic and cardiovascular effects of vitamin D.

Recently, many randomized controlled studies have been performed in the attempt to confirm this hypothesis. Some of these trials examined samples of people taken from the general population while others examined smaller groups of patients affected by specific morbid conditions. While on one hand some of these studies corroborated the possible positive effect of vitamin D supplementation in subjects with vitamin D deficiency relative to some risk factors (particularly high blood pressure and insulin resistance), on the other hand the largest trials did not confirm the positive effect of vitamin D supplementation on cardiovascular morbidity and mortality. At the same time, some possibility of a positive effect of vitamin D cannot be completely excluded for specific subsets of patients, or in therapeutic treatments of longer duration based on innovative approaches. At present, then, there is a clear need for further experimental research and for more controlled studies with specific aims.

Bibliography

1. Civitelli R, Ziambaras K. *Calcium and phosphate homeostasis: concerted interplay of new regulators*. J Endocrinol Invest 2011;34(Suppl 7):3-7.
2. Lockau L, Atkinson SA. *Vitamin D's role in health and disease: how does the present inform our understanding of the past?* Int J Paleopathol 2018;23:6-14.
3. Holick MF. *The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention*. Rev Endocr Metab Disord 2017;18:153-65.
4. Zittermann A. *Vitamin D status, supplementation and cardiovascular disease*. Anticancer Res 2018;38:1179-86.
5. Rendina D, De Filippo G, Muscariello R, et al *Vitamin D and cardiometabolic disorders*. High Blood Press Cardiovasc Prev 2014;21:251-6.
6. Parker J, Hashmi O, Dutton D, et al. *Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis*. Maturitas 2010;65:225-36.
7. Burgaz A, Orsini N, Larsson SC, et al. *Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis*. J Hypertens 2011;29:636-45.
8. Kunutsor SK, Apekey TA, Steur M. *Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants*. Eur J Epidemiol 2013;28:205-21.
9. Song Y, Wang L, Pittas AG, et al. *Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies*. Diabetes Care 2013;36:1422-8.
10. Wang TJ, Pencina MJ, Booth SL, et al. *Vitamin D deficiency and risk of cardiovascular disease*. Circulation 2008;117:503-11.
11. Wang L, Song Y, Manson JE, et al. *Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies*. Circ Cardiovasc Qual Outcomes 2012;5:819-29.
12. Messenger W, Nielson CM, Li H, et al. *Serum and dietary vitamin D and cardiovascular disease risk in elderly men: a prospective cohort study*. Nutr Metab Cardiovasc Dis 2012;22:856-63.
13. Liu L, Chen M, Hankins SR, et al.; Drexel Cardiovascular Health Collaborative Education, Research, and Evaluation Group. *Serum 25-hydroxyvitamin D concentration and mortality from heart failure and cardiovascular disease, and premature mortality from all-cause in United States adults*. Am J Cardiol 2012;110:834-9.
14. Zittermann A, Iodice S, Pilz S, et al. *Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies*. Am J Clin Nutr 2012;95:91-100.
15. Tomson J, Emberson J, Hill M, et al. *Vitamin D and risk of death from vascular and non-vascular causes in the Whitehall study and meta-analyses of 12,000 deaths*. Eur Heart J 2013;34:1365-74.
16. Joergensen C, Gall MA, Schmedes A,et al. *Vitamin D levels and mortality in type 2 diabetes*. Diabetes Care 2010;33:2238-43.
17. Dobnig H, Pilz S, Scharnagl H, et al. *Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality*. Arch Intern Med 2008;168:1340-9.
18. Li X, Liu Y, Zheng Y, et al. *The effect of vitamin D supplementation on glycemic control in type 2 diabetes patients: a systematic review and meta-analysis*. Nutrients 2018;10:375. doi: 10.3390/nu10030375.
19. Swart KM, Lips P, Brouwer IA, et al. *Effects of vitamin D supplementation on markers for cardiovascular disease and type 2 diabetes: an individual participant data meta-analysis of randomized controlled trials*. Am J Clin Nutr 2018;107:1043-53.
20. Golzarand M, Hollis BW, Mirmiran P, et al. *Vitamin D supplementation and body fat mass: a systematic review and meta-analysis*. Eur J Clin Nutr 2018;72:1345-57.
21. Angellotti E, D'Alessio D, Dawson-Hughes B, et al. *Vitamin D supplementation in patients with type 2 diabetes: the vitamin D for established type 2 diabetes (DDM2) study*. J Endocrine Soc 2018;2:310-21.
22. Cefalo CMA, Conte C, Sorice GP, et al. *Effect of Vitamin D Supplementation on obesity-induced insulin resistance: a double-blind, randomized, placebo-controlled trial*. Obesity 2018;26:651-7.
23. Bislev LS, Langagergaard Rødbro L, Bech JN, et al. *The effect of vitamin D3 supplementation on markers of cardiovascular health in hyperparathyroid, vitamin D insufficient women: a randomized placebo-controlled trial*. Endocrine 2018;62:182-94.

[24] Sluyter JD, Camargo, Jr CA, et al. *Effect of monthly, high-dose, long-term vitamin D supplementation on central blood pressure parameters: a randomized controlled trial substudy.* J Am Heart Assoc 2017;6:e006802. doi: 10.1161/JAHA.117.006802.

[25] Manson JE, Cook NR, Lee I-Min, et al. for the VITAL Research Group. *Vitamin D supplements and prevention of cancer and cardiovascular disease.* N Engl J Med 2019;380:33-44.