Vitamin D, cardiovascular and bone health in postmenopausal women with metabolic syndrome

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Advances in Clinical and Experimental Medicine, ISSN 1899-5276 (print), ISSN 2451-2680 (online) *Adv Clin Exp Med*. 2018;27(11):1555–1560

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Funding sources
None declared

Conflict of interest
None declared

Received on November 5, 2016
Reviewed on January 24, 2017
Accepted on June 20, 2017

Abstract

Background. The evidence highlights the importance of improving vitamin D levels in the general population for the prevention of adverse long-term health risks, including cardiovascular events, metabolic syndrome, cancer, anxiety and depression, and overall mortality, although controversies in the research are common.

Objectives. The purpose of this study was to investigate the relationship between vitamin D and vascular and bone health among postmenopausal metabolic women, controlling for traditional cardiovascular factors, and thus seeking to explore their plausible relation. The secondary aim was to look specifically for the relation between artery stiffness and bone health.

Material and methods. This is a cross-sectional study designed to evaluate the relation between vitamin D level and vascular and bone health among women with metabolic syndrome. Two hundred and ten women visiting a cardiologist were recruited consecutively into the study. The study variables included clinical examination, laboratory findings, measurements of vascular stiffness, and bone turnover markers.

Results. We found 126 (60%) metabolic women with a vitamin D deficiency (50 nmol/L) among the study group. We discovered no statistically significant correlation between vitamin D and vascular stiffness. Vitamin D was not associated neither with femoral neck bone mineral density (BMD) and T score, nor with lumbar spine BMD and T score. Nevertheless, there was an indirect weak correlation between vascular stiffness, in particular the augmentation index (AIx), and all bone health markers, including BMD and T score in both the femur head and lumbar spine.

Conclusions. We showed a high proportion of postmenopausal metabolic women with a vitamin D deficiency, but there was no relation between vitamin D and vascular health or vitamin D and bone health. Nevertheless, the relation between vascular health and bone health exists, although the role of vitamin D in this link has not yet been established.

Key words: metabolic syndrome, vitamin D, bone mineral density, vascular stiffness

DOI
10.17219/acem/75147

Introduction

There is sufficient evidence that vitamin D is related to bone health in children and the elderly, while the benefit for middle-aged people still needs to be proven.[1] The emerging evidence highlights the importance of normalizing vitamin D levels in the general population, as it may prevent long-term health problems, including cardiovascular events, metabolic syndrome, cancer, overall health, anxiety and depression, and overall mortality, although controversies in the literature are common and the data is inconclusive.[2,3] Our own previous experience from a cross-sectional study with 100 postmenopausal metabolic women revealed a favorable correlation between vitamin D concentrations and mean blood pressure and high density lipoproteins.[4] We showed that normalizing vitamin D level may lower the mean blood pressure. Similar evidence has mostly been based on cross-sectional studies, less in observational longitudinal studies, while randomized controlled studies in general have denied the beneficial effect of vitamin D.[5] In addition, studies with higher sample sizes, which is often the case in cross-sectional studies, are more powerful in proving the relation, while randomized controlled trials with small groups mostly fail. The aim of this cross-sectional analytic study was to investigate if there is a relationship between vitamin D (25(OH)D) and vascular health and bone health among postmenopausal metabolic women, taking into consideration traditional cardiovascular factors, and thus to explore their plausible relation. The secondary aim was to look specifically for the relation between artery stiffness and bone health.

Material and methods

Study design

A total of 210 women attending Vilnius University Hospital Santariskiu Klinikos, Lithuania, according to the Lithuanian high cardiovascular risk primary prevention program, signed the informed consent form and were enrolled into the study consecutively, after meeting the following inclusion criteria: age between 50 and 65 years, diagnosis of metabolic syndrome and being in menopausal period.[6] Metabolic syndrome was diagnosed if at least 3 out of 5 symptoms were present: waist circumflex >88 cm; systolic blood pressure (SBP) ≥130 mm Hg and/or diastolic blood pressure (DBP) ≥85 mm Hg; fasting glycemia >5.6 mmol/L or type 2 diabetes mellitus; triacylglyceride (TG) concentration >1.7 mmol/L or special treatment prescribed to reduce the TG concentration; high-density lipoprotein cholesterol (HDL-C) <1.2 mmol/L.[7] The exclusion criteria were: vitamin D supplements currently or at least half a year before the study, diagnosed coronary heart disease, malignant disease currently, kidney or liver failure, other advanced somatic or mental disease. The approval was obtained from the Lithuanian Bioethics Committee (158200-14-724-240). The enrollment period lasted 2 years, from March 2014 until March 2016.

Study variables

The clinical, laboratory and instrumental measurements were obtained during the 2nd visit to a cardiologist. These included clinical examination and measurements of laboratory markers: fasting cholesterol, glucose, C-reactive protein (CRP), creatinine, albumin, 25(OH) vitamin D, and ionized calcium. Vitamin D level was considered deficient when it was <50 nmol/L.[8] The physical activity index was obtained from the questionnaires containing information on intensity, duration and frequency of current exercise program, which was then entered into the equation (intensity × duration × frequency = total score).

Vascular health measurements

We applied 3 non-invasive techniques to examine the vascular health of 210 women enrolled in the study: pulse wave velocity (PWV), flow-mediated dilatation (FMD) and carotid artery intima-media thickness (IMT) measurements. All 3 measurements were carried out in the early morning hours and the participants were asked to refrain from drinking and eating for at least 12 h before the examination.

Pulse wave velocity was obtained by measuring the carotid-to-radial (PWVcr) and carotid-to-femoral (PWVcf) pulse wave flow. Mainly, the transit time of the wave from the sternal notch to the radial or femoral artery was used to estimate the path length between the carotid and radial or femoral arteries, using applanation tonometry with a high-fidelity micromanometer (SphygmoCor, Sydney, Australia). The augmentation index (AIx) adjusted for 75 beats/min was calculated from PWVcr, using an integrated software program. This technique was described by Kelly et al. in 1989 and later elaborated by Wilkinson et al. and O'Rourke and Gallagher.[9–11] A detailed description of the arterial stiffness measuring technique, as it was performed in a local clinical setting, was described in detail in the publication by our group.[12]

The endothelium-dependent FMD test in a brachial artery was measured on B-mode imaging by an ultrasound system (Logiq 7; GE Healthcare, Waukesha, USA) based on the recommendations by Celermajer et al.[13] Scans were taken twice, before the inflation and after deflation, and were carried out in the longitudinal plane, 1–8 cm above the antecubital fossa. The inflation of a pneumatic tourniquet to a suprasystolic pressure of 100 mm Hg was kept for 5 min, and the 2nd scan was taken within the first 15 s after the cuff release.

The intima-media thickness was measured in the common carotid artery, 1–2 cm from the bifurcation on the bottom wall, in a live 2-dimensional view, which comprised

4 cm automatic recognition, using a high-resolution ALOKA ultrasound system (Hitachi, Tokyo, Japan). The mean carotid IMT was calculated as the average from the means of the left and right common carotid artery IMT.

Bone health measurements

Bone mineral density (BMD) of the femoral neck and lumbar spine in region L1-L4 was measured by the dual-photon energy absorptiometry method (Hologic, Massachusetts, USA). T scores were calculated for each anatomical site. Osteopenia was defined when T score was below –1 but above –2.5, and osteoporosis was defined when T score was ≤–2.5.

Statistical analysis

Quantitative variables were presented as means and standard deviation (SD) or median and min–max, depending on normality. Qualitative variables were expressed as numbers and percentages. Quantitative comparisons were computed with an independent Student's t-test if they were normally distributed or the Mann-Whitney test if the normal distribution was violated. Pearson's or Spearman's correlation analyses were used for establishing the relations between the variables. Multivariate linear regression analysis (stepwise model) was performed separately for vitamin D (dependent variable) and vascular health measurements, and for vitamin D (dependent variable) and bone health measurements. The traditional cardiovascular factors were included into the multivariate analysis as important covariates: age, body mass index (BMI), waist circumflex, smoking, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, TG, fasting glucose, CRP, and the albumin/creatinine ratio. The p-values <0.05 were considered statistically significant.

Results

Differences of health characteristics between women with and without a vitamin D deficiency

The average level of vitamin D was 48.01 nmol (±16.95) in the whole cohort (Table 1). We found 126 (60%) women with metabolic syndrome with a vitamin D deficiency and a minor proportion of them – 84 (40%) – had normal vitamin D levels. On average, the women were obese (BMI = 32.42 kg/m^2) with a low index of physical activity around 18. No clinically significant differences were observed when comparing the laboratory data between the 2 groups. Differences in early markers of atherosclerosis were unremarkable, except for PWVcr being higher in the group with normal vitamin D concentration. Almost a quarter of the women had osteoporosis or osteopenia. Bone health status, including BMD in the lumbar and femur area, was quite similar in different vitamin D level groups.

The relation between vitamin D and vascular health

We did not find a significant relation between vitamin D concentration and early atherosclerosis markers in a simple Spearman's correlation. However, after adjustment for age, mean blood pressure, BMI, waist circumflex, physical activity index, smoking, TC, LDL-C, HDL-C, TG, fasting glucose, CRP, and the albumin/creatinine ratio, the association between vitamin D levels and PWVcf became significant (p = 0.049) (Table 2). We consider it coincidental and it is doubtful whether it is clinically important.

The relation between vitamin D and bone health

In this study we failed to show an association between vitamin D and femoral neck BMD or its T score or with lumbar spine BMD and T score in a simple linear regression (Table 2). No association was found between vitamin D and bone health markers in multiple linear regression after adjusting for traditional markers for atherosclerosis.

Early atherosclerosis markers and bone health

Though an association between vitamin D and vascular health or bone health was not proven, we found an important link between AIx and bone health. There was an indirect weak correlation between AIx (adjusted for heart rate) and all bone health markers, including BMD and T score in both the femur head and lumbar spine (Table 3). We presume that when BMD decreases, the stiffening of the arteries becomes more pronounced. Therefore, keeping the bone structure healthy may prevent vascular stiffening. In other words, what is good for bone health is also good for blood vessels, though it is not that straightforward. We did not find vitamin D being somehow interrelated with this.

Discussion

We found 126 (60%) women with metabolic syndrome who had vitamin D deficiency (<50 nmol/L) and a minor proportion of 84 (40%) had normal vitamin D levels (>50 nmol/L). This cut-off was chosen following the recommendations developed by a consensus agreement of a Polish multidisciplinary group and it targeted the Central European population.[8] In this cross-sectional study, when applying multiple linear regression, we found no statistically significant relation between vitamin D and arterial stiffness. Furthermore, vitamin D was not associated with

Table 1. The characteristics of 210 metabolic women according to vitamin D levels

Characteristics	All (n = 210)	25 (OH) vitamin D (<50 nmol/L) (n = 126)	25 (OH) vitamin D (>50 nmol/L) (n = 84)	p-value
Age [years]	57.89 ±3.91	57.94 ±3.84	57.82 ±4.01	0.835
Current smokers, n (%)	33 (15.7)	20 (15.9)	13 (15.5)	0.938
BMI [kg/m^2]	32.42 ±4.12	32.58 ±4.37	32.19 (3.74)	0.498
Waist circumflex [cm]	103.83 ±9.39	104.08 ±9.25	103.46 ±9.66	0.645
Physical activity index (1–100; 100 – the highest)	18 (1–100)	16 (1–100)	20 (1–80)	0.348
TC [mmol/L]	6.54 ±1.37	6.58 ±1.37	6.49 ±1.36	0.619
LDL-C [mmol/L]	4.33 ±1.19	4.37 ±1.16	4.28 ±1.27	0.576
HDL-C [mmol/L]	1.31 ±0.30	1.29 ±0.30	1.35 ±0.29	0.146
TG [mmol/L]	1.75 (0.57–6.98)	1.8 (0.61–6.98)	1.78 (0.57–6.85)	0.777
Fasting glycemia [mmol/L]	5.91 (4.68–15.20)	5.75 (4.68–13.43)	5.97 (5.02–15.20)	0.064
CRP [mmol/L]	2.20 (0.30–23.80)	2.55 (0.40–15.50)	1.85 (0.30–23.80)	0.035
The albumin/creatinine ratio	0.58 (0.17–86.39)	0.60 (0.17–86.39)	0.56 (0.18–11.61)	0.411
FMD [%]	3.08 ±2.15	3.23 ±2.19	2.83 ±2.07	0.219
PWVcr [m/s]	8.80 (6–108)	8.65 (6–13)	8.95 (7–14)	0.049
PWVcf [m/s]	8.86 ±1.48	8.89 ±1.43	8.82 ±1.55	0.737
AIx (adjusted for 75 heart rate)	27.91 ±8.97	27.44 ±7.37	28.53 ±10.74	0.474
Mean arterial pressure [mm Hg]	105.59 ±12.61	106.74 ±13.70	103.88 ±10.64	0.109
IMF [μm]	685.64 ±95.82	673.70 ±83.41	703.98 ±110.30	0.026
25(OH) vitamin D [nmol/L]	48.01 ±16.95	37.72 ±8.70	63.81 ±14.13	–
Ionized calcium [mmol/L]	1.170 ±0.083	1.160 ±0.093	1.180 ±0.063	0.123
Total femur BMD [g/cm^2]	1.06 ±0.13	1.06 ±0.14	1.06 ±0.11	0.895
Total femur T score	0.48 ±1.07	0.49 ±1.16	0.47 ±0.94	0.866
Total lumbar spine BMD [g/cm^2]	1.14 ±0.16	1.14 ±0.17	1.16 ±0.15	0.475
Total lumbar spine T score	−0.28 ±1.35	−0.32 ±1.44	−0.21 ±1.21	0.574
Normal bone status, n (%)	152 (72.3)	87 (69.0)	81 (77.4)	0.290
Osteopenia, n (%)	52 (24.8)	34 (27.0)	18 (21.4)	
Osteoporosis, n (%)	6 (2.9)	5 (4.0)	1 (1.2)	

BMI – body mass index; TC – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triacylglycerides; CRP – C-reactive protein; FMD – flow-mediated dilatation; PWVcr – pulse wave velocity (carotid-to-radial); PWVcf – pulse wave velocity (carotid-to-femoral); AIx – the augmentation index; IMF – intima-media thickness; BMD – bone mineral density.

femoral neck BMD and T score, nor with lumbar spine BMD and T score. In both models, the adjustment for age, mean blood pressure, BMI, waist circumflex, physical activity index, smoking, TC, LDL-C, HDL-C, TG, fasting glucose, CRP, and the albumin/creatinine ratio was made. This led to the conclusion that the association in simple or more sophisticated models between an independent factor – vitamin D – and vascular health markers or bone health markers cannot be proven.

It is known that vitamin D is predominantly synthetized in the skin or obtained with food or supplements, and these physiological functions go far beyond the regulation of calcium and phosphorus uptake, and extend to immunomodulatory effects, effects on the renin-angiotensin system, insulin secretion, and the apoptosis of malignant cell proliferation. Vitamin D deficiency (<50 nmol/L) is a worldwide epidemic with multiple implications on human health, due to its role in various physiological systems.[14] It is generally considered that vitamin D plays an important role in overall health and it is important to have adequate vitamin D.[2] The overall enthusiasm to search and to find links between disease and vitamin D deficiency has changed with the evolving paradox: the optimistic findings from observational studies were not supported by interventional studies.[5,15] This may be explained by the study duration, design and sample size, as it may take a longer time for the cardiovascular outcome to occur than the duration of a clinical trial. The classical observational Framingham Offspring Study showed an increase in the number of cardiovascular events when vitamin D was deficient.[16] A Norwegian study showed that all-cause mortality, as well as cardiovascular mortality, may be higher with vitamin D deficiency,and it is also applicable to a non-Caucasian population.[17,18] Clinical trials usually take under consideration the endothelial

Table 2. The relation between vitamin D, vascular health and bone health

Dependent variables	r	p-value	Beta	p-value (adjusted model)
Vascular health variables				
AIx (adjusted for 75 heart rate)	0.013	0.875	0.143	0.251
PWVcr [m/s]	0.087	0.314	–0.029	0.825
PWVcf [m/s]	–0.005	0.948	0.233	0.049
IMF [μm]	0.080	0.252	0.144	0.232
FMD [%]	–0.054	0.471	0.008	0.947
Bone health variables				
Total femur BMD [g/cm^2]	–0.024	0.746	–0.033	0.972
Total femur T score	–0.027	0.721	–0.005	0.956
Total lumbar spine BMD [g/cm^2]	0.96	0.195	0.035	0.716
Total lumbar spine T score	0.107	0.151	0.036	0.713
Ionized calcium [mmol/L]	0.130	0.062	0.124	0.199

Model adjusted for age, mean blood pressure, body mass index (BMI), waist circumflex, smoking, total cholesterol (TC), low-density lipoproteins, high-density lipoproteins, triacylglycerides (TG), fasting glucose, C-reactive protein, the albumin/creatinine ratio, and physical activity index; AIx – augmentation index; PWVcr – pulse wave velocity (carotid to radial); PWVcf – pulse wave velocity (carotid to femoral); IMF – intima-media thickness; FMD – flow-mediated dilatation; BMD – bone mineral density.

Table 3. The relation between the augmentation index (AIx) and bone health

Augmentation index/ bone health	r	p-value
Total femur BMD [g/cm^2]	–0.229	0.010
Total femur T score	–0.222	0.013
Total lumbar spine BMD [g/cm^2]	–0.287	0.001
Total lumbar spine T score	–0.301	0.001

*adjusted for 75 heart rate; BMD – bone mineral density.

functioning parameters as the main outcome rather than cardiovascular events, and it is due to the accepted agreement that the endothelial function itself may serve as an independent predictor of future cardiovascular events.[13] Several controlled clinical trials have shown that vitamin D supplementation improves the endothelial function, while others have not.[19–22] Therefore, there is not enough evidence to decide whether the substitution of low vitamin D would prevent cardiovascular events in the future. Our cross-sectional observational study did not show meaningful results concerning the endothelial functioning and vitamin D.

There is considerable evidence regarding the benefit of vitamin D in the prevention of rickets in children and osteomalacia in the senior population, but the benefit for the middle-aged population remains unclear and controlled clinical trials are needed in this setting of patients.[23] In a meta-analysis by Reid et al., 23 studies were included, and no evidence was gained suggesting that taking vitamin D prevents osteoporosis developing in the middle-aged population, with only a small effect on increasing BMD in the femoral neck.[24] These findings are in line with the systematic review by Cohrane collaboration, which came to the conclusion that vitamin D alone is unlikely to prevent fractures in older people when taken in the recommended daily dose. However, in combination with calcium, it may be helpful in preventing hip or any type of fracture in postmenopausal women or older men.[25] Our study did not show any link between vitamin D and BMD or T score, likewise other, more powerful studies.

On the other hand, by carrying out the main aim of this study, we examined the link between arterial stiffness and bone health in a simple linear regression model and it was obvious that there was an indirect weak correlation between AIx and bone health markers, including BMD and T score in the femur head and even more in the lumbar spine. Our data shows that higher arterial stiffness may be associated with a higher risk of osteopenia in postmenopausal women with metabolic syndrome, but it is not necessarily associated with vitamin D deficiency. A very recent study by Ye et al. looked into 25 studies and pooled data on 10,299 patients. The calcification of carotid arteries, the incidence of cardiovascular disease and coronary artery disease were taken into account and were significantly higher in numbers in low BMD patients compared to normal BMD patients. The same trend for BMD being related to arterial stiffness was observed in different settings of the population, including postmenopausal women, and persisted after the adjustments for gender, age, weight, and other vascular risk factors. In the quoted study, BMD was proven to be an independent risk factor that may increase the risk of arterial stiffness and atherosclerosis.[26] The results of our study are in line with the findings of this meta-analysis; however, the limitations of our study should be pointed out: cross-sectional study design and relatively small sample size. Both of them make this study less compelling when compared to other observational study designs.

Conclusions

In this cross-sectional study, we showed a high proportion of postmenopausal women with metabolic syndrome with vitamin D deficiency, but there was no relation between vitamin D and vascular health or vitamin D and bone health. Nevertheless, the relation between vascular health and bone health exists, but it is unlikely due to vitamin D.

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