Vitamin D Deficiency in Premenopause: Endothelial and Diastolic Functions With Hyperparathyroidism

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Abstract

Introduction: Vitamin D deficiency(VDD) is a common condition in all ages worldwide, especially in winter, and causes several adverse cardiovascular outcomes. Although there is conflicting information about the causes of adverse cardiac events in VDD, the accepted leading cause is a pathogenic relationship with hyperparathyroidism. Aim: We aim to demonstrate hyperparathyroidism's effects, if present, on endothelial and diastolic functions using echocardiography, carotid, and brachial tissue Doppler imaging (tDi) in premenopausal women with VDD independent from confounding risk factors. Methods: Our study is a cross-sectional, observational study investigating premenopausal women aged 18-50 who applied to internal medicine department. The patients are divided into two groups according to parathyroid hormone(PTH) levels (Normal PTH 41 patients, abnormal PTH 27 patients). Study groups are analyzed for basal characteristics, standard echocardiographic evaluation, carotid, and brachial artery tDi features. Results: There were no significant differences in age, height, weight, body mass index(BMI), and blood pressures between the groups (all p values>0.05). The rate of severe VDD was 76%. In terms of diastolic parameters, prolongation of A wave durations and decreased E/A ratio were observed in the secondary hyperparathyroidism (p values 0.042 and 0.031, respectively). Also, carotid IMT is significantly higher in secondary hyperparathyroidism(p=0.034). Conclusion: Our study showed that high PTH levels have adverse effects on diastolic(A wave, E/A ratio) and endothelial functions(carotid IMT) in premenopausal women diagnosed with VDD, even in the absence of other confounding risk factors. We can state that our study's findings will contribute to the literature and are predictive for future studies.

Introduction

Vitamin D (VitD) is an important steroid hormone in bone and mineral physiology, mainly due to its effects on calcium and phosphorus metabolism (1). By binding to VitD receptors in the whole body, including endothelium, vascular smooth muscle cells, and cardiomyocytes of its active metabolite, it also affects many vital functions such as homeostasis, autoimmunity, synthesis of inflammatory interleukins, cell proliferation, and differentiation, and blood pressure regulation (2-8). The prevalence of VDD can be at 30-50% (9,10). The main risk factors are high altitude, winter season, low sun exposure, restricted dietary intake, and advanced age(especially in postmenopausal women) (10,11).

Although its pathophysiology is not fully known, VDD has been linked with various cardiovascular outcomes; hypertension, adverse cardiac events, acute myocardial infarction complications, arterial stiffness, and inverse cardiac remodeling processes cause myocardial fibrosis, systolic and diastolic dysfunction (1,12-15). Hyperstimulation of the renin-angiotensin-aldosteron system(RAAS) and sympathetic nervous system, consequently increasing systemic inflammation, fluid-electrolyte balance distortions, and continuing these conditions in a vicious circle, can be considered as the underlying mechanism (13, 15, 16). Sunbul M. et al. showed that basal VitD values might adversely associated with left ventricular basal global longitudinal strain values. VitD therapy may have positive effects on myocardial deformation (17). But in Omidi F. et al study, the global longitudinal subendocardial deformations were not statistically significantly correlated

with the presence or absence of VDD (18). In addition, it was stated in a letter to the editor that age and renal insufficiency may play a role in the background of myocardial deformation in VDD (19).

Secondary hyperparathyroidism can be seen at rates 18-25% in VDD, which increases with age (20). Secondary hyperparathyroidism may be associated with disease severity in congestive heart failure, especially in older, due to bone loss and osteoporosis (21). When the literature is reviewed, there may be a relationship between PTH levels and arterial stiffness, coronary atherosclerosis, abnormal left ventricular function (global longitudinal strain), LV asynchrony, brachial flow-mediated dilatation (bFMD) (adversely), especially in primary hyperparathyroidism; a regression in pulse wave velocity and improvement in global longitudinal strain with parathyroidectomy (22-25). Although this finding could not be reached with primary hyperparathyroidism in a different study, improvements in pulse wave velocity were also observed using cinacalcet; a calcimimetic agent that provides a decrease in PTH levels in chronic renal failure and secondary hyperparathyroidism, in literature (26,27).

The relationship between VDD and hyperparathyroidism with arterial stiffness has been shown separately, as mentioned above (12,15,22,23). Pirro et al. investigated independent associations between VitD, PTH levels, and arterial stiffness in the postmenopausal stage with normal kidney functions. In this study, an inverse relationship, albeit weak, was found between VitD levels and pulse wave velocity. This relation was significantly associated with PTH levels regardless of existing risk factors and factors involving bone formation (28).

The risk of cardiovascular disease increases in the postmenopausal period, especially hormonal changes (29). Menopause can be considered as a confounding factor in terms of cardiac risks. In the light of these pieces of information and taking into account the missing points, our study aims to reveal the differences that secondary hyperparathyroidism will create on endothelial and diastolic functions, if present, using echocardiography, carotid, and brachial tDi in premenopausal women with VDD independent of confounding risk factors.

Materials and Methods

Our study is a cross-sectional, observational study, includes premenopausal women aged 18-50 who applied to internal disease and were diagnosed with VDD. Our study was carried out in Bilecik City in the period November-December 2020. Bilecik, located at an approximate altitude of 500 meters and a latitude of 40°N, is a small city in Turkey. During the study period, the average temperature in Bilecik city was determined as 8.5 degrees Celsius (maximum 13°C, minimum 2°C).

The fasting routine blood samples (including PTH levels) were investigated of these patients' internal medicine records. In evaluating VitD, the serum circulating 25-hydroxyvitamin D [25(OH)D] level was measured. VDD was defined as a serum 25-hydroxyvitamin D level of $<$20 ng/ml, and severe VDD was also defined as a serum 25-hydroxyvitamin D level of $<$10 ng/ml (30). Patients diagnosed with VDD who have not yet started replacement therapy were evaluated using essential echocardiographic evaluation, brachial and carotid tissue doppler, and flow-mediated dilatation. Local ethics committee approval was obtained.

Patients diagnosed with diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, peripheral artery disease, moderate-severe heart valve disease, cardiomyopathies, thyroid dysfunction, chronic obstructive pulmonary disease, malignancy, rheumatological disease, active infection, kidney failure, liver disease, hormonal diseases (affecting calcium level, including primary hyperparathyroidism), obesity (BMI$>$30), drug usage (including beta-blockers and medications affect calcium level), menopause, pregnancy, and heavy alcohol users and smokers were excluded from the study. A total of 68 patients were included in the survey by excluding patients with low echogenicity.

Patients were divided into two groups according to their PTH levels. While PTH levels were in the normal reference range ($<$65 pg/ml) in 41 patients, it was high in 27 patients. Groups were compared in terms of basal demographic characteristics, standard echocardiographic evaluation, carotid and brachial artery tDi features.

Image Recordings and Analysis

Standard echocardiographic measurements; left ventricular ejection fraction(EF) with modified Simpson method, tissue Doppler measurements, and cardiac valve evaluations performed with transthoracic echocardiography (EPIQ 7 echocardiography device (Philips, Amsterdam, Netherlands)) with reference of 2015 ASE (American Society of Echocardiography) guideline (31). In echocardiographic tissue Doppler evaluations, global systolic and diastolic ventricular function indicator, the myocardial performance index(MPI), also known as Tei Index, is also calculated. The formula '[Isovolumetric contraction time(IVCT)+Isovolumetric relaxation time(IVRT)]/Ejection Time(ET)' is used for both left ventricle lateral and septal parts(32,33).

Carotid systolic and diastolic diameters, intima-media thickness (IMT), and bFMD performed with duplex ultrasound (Toshiba Sonolayer SSA 270 A equipped with a 7.5 Mhz linear array transducer, Toshiba Medical Systems, Japan). The distal 1 cm of each common carotid artery's far wall and plaque-free segments were used for carotid IMT measurements. The mean carotid IMT value was derived from the measurements made in both carotid arteries' locations (34).

All ultrasonic examinations were made with continuous electrocardiography (ECG), in a semi-dark room. Brachial artery measurements were made by keeping the patient's left arm steady in a horizontal plane, approximately 2 cm above the elbow, in the longitudinal plane at the diastolic phase. Basal measurements were taken after 15 minutes of rest in the fasted state. The appropriate sphygmomanometer cuff located in the patient's upper arm inflated to the level of 200 mmHg and waited for 5 minutes, and recordings will be continued until 2 minutes after cuff deflation. The maximum rate of change, which is also named as peak bFMD was calculated in a percentage(%) with the formula '[(maximum diameter - basal diameter)/basal diameter]*100' (35,36).

Statistical Analysis

Statistical analysis was performed by the SPSS version 20.0 (IBM, Armonk, New York, United States). The normality of distribution was examined by using both the Shapiro-Wilk W test. Descriptive statistical methods, including percent and mean ± standard deviation(SD) or median (interquartile range[IQR]), were used to provide the basic features of the data. Mann-Whitney U test was used for non-normally distributed continuous variables for normal PTH levels group and secondary hyperparathyroidism group. A p-value less than 0.05 was accepted as significant.

Results

There were no significant differences in age, height, weight, BMI, blood pressures, and laboratory parameters between the groups *(all p values>0.05)* . Baseline characteristics and laboratory results of the groups are shown in Table 1. Vitamin D and PTH levels are demonstrated in Figure 1.

Vit D levels were relatively low in the secondary hyperparathyroidism compared to the group with normal PTH levels *(mean values 8.1+-4.1, 9.3+-7.8, respectively; p=0.369)* . The rate of severe VDD in our study's total population was 76%.

Echocardiographic and peripheral tDi findings are shown in Table 2. Some significant differences related to diastolic parameters are observed, which will explain in the discussion section in detail. Other echocardiographic parameters were similar, including EF *(p values>0.05)* . Regarding carotid and brachial tDi, only a significant difference was observed according to carotid IMT (*p=0.034)* .

Discussion

VDD is a common condition that can be seen in all age groups worldwide, especially in winter, and causes several adverse outcomes, including cardiovascular diseases (38). The removal of inhibitory effects on the RAAS system and proinflammatory cytokines can be accepted as the primary mechanism for cardiovascular involvement in VDD (13,15,16,37). Hyperparathyroidism cases secondary to VDD are not uncommon and lead to adverse cardiac outcomes (20,38).

Menopause may be considered a risk factor for VDD and, consequently, secondary hyperparathyroidism (28,39). It is also known that cardiovascular risk increases in menopause with hormonal changes (29,39). Therefore regardless of the confounding factors, we aimed to reveal the differences that secondary hyperparathyroidism will create on endothelial and diastolic functions, if present, using echocardiography, carotid and brachial tDi in premenopausal women with VDD.

As stated before, the prevalence of secondary hyperparathyroidism is approximately 18-25% according to vitamin D levels, the prevalence of secondary hyperparathyroidism in severe VDD (<10 ng/ml) was shown as 33%. In Gomez-Alonso C et al. study, the autumn-winter months covered 60% of the study period in 40degN latitude in a city 400 meters above sea level (20). However, Islam MZ. et al. showed that this prevalence could vary in the range of 16% and 89%, according to ethnic differences (40). Secondary hyperparathyroidism was observed with a rate of 39.7% in our study. Ethnic differences, characteristics of the city, and the time interval may have influenced these differences.

In the secondary hyperparathyroidism group, A wave durations were longer, and E/A ratios were lower than the group with normal PTH levels*(p values are 0.042 and 0.031, respectively)* . It can be accepted that the prolongation of the A wave duration is effective in decreasing the E/A ratio. In Pandit A. et al. study investigating VDD and left ventricular diastolic dysfunction in a population of 67% women, there was no significant relationship between vitamin D levels and diastolic parameters (Deceleration time, e' wave, E/A, and E/e' ratios) (41). In Pilz S. et al. study, which evaluated approximately 600 patients over 65 years of age, the prevalence of diastolic dysfunction might increase seasonally in VDD. Even in the seasons with high risk, VDD lost its significance when adjusted for age and cardiovascular risks (42).

In 'the fifth Tromso study,' myocardial systolic contraction rates were significantly lower in the secondary hyperparathyroidism group (approximately 100 patients), even after adjustments for covariables*(for lateral s' and septal e ', s' waves; p <0.05)* . In the follow-up of these patients 6-12 months later, in case of persistently elevated PTH, a similar trend was observed in myocardial systolic contraction velocities, but the significance is lost. This study's difference from our study was that the mean VitD values after the relevant unit conversions(nmol/l to ng/ml) were 17.2+-5.0 in the high PTH group and 18.7+-5.4 ng/ml in the normal PTH group*(p>0.05) (In our study VitD levels 8.1+-4.1 and 9.3+-7.8 ng/ml; respectively)* . Also, no significant difference was found in diastolic parameters (E, A waves, IVRT, pulmonary vein atrial reversal flow) in 'the fifth Tromso study.' (43).

The study's design differences, the population, the city where the study was conducted, and some other factors may have been influential in these differences. Suppose we interpret the findings of diastolic parameters in our study; there may be additional impairment in diastolic functions due to PTH levels in vitamin D deficiency, even if there is no confounding factor.

Lim S. et al. showed VDD is associated with endothelial dysfunction and coronary atherosclerosis (44). In diabetic nephropathy patients, VDD is significantly linked with increase in carotid IMT, but no significant relation was found in chronic renal failure patients (45,46). Studies conducted with chronic renal failure and secondary hyperparathyroidism found a significant relationship between carotid thickness and PTH levels (47). In Yankouskaya L. et al. study, which investigates women with arterial hypertension, the effects on endothelial dysfunction were explained by the pathogenic relationship between VDD and PTH levels, not a single factor (48).

Our study carotid IMT mean values are 0.6+-0.1 mm in secondary hyperparathyroidism and 0.5+-0.1 mm in the group with normal PTH levels*(p=0.034)* , no other significant difference related to carotid and brachial artery. We can say that hyperparathyroidism may cause an increase in carotid intima thickness independent of other risk factors in VDD.

As a result, we observed a significant relationship between PTH levels and endothelial (carotid IMT) and diastolic functions (A wave duration, E/A ratio) in premenopausal women with VDD, independent of all other confounding factors. Therefore, patients should be evaluated in terms of possible future cardiac risks by paying attention to PTH levels in diagnosing VDD.

Limitations

A limited number of patients could be included in our study. Our study population may not fully reflect the target population due to the pandemic process, the inclusion of patients in a limited time frame (it may have helped clarify the findings.), and the recruitment of only patients referred to cardiology.

Conclusion Our study showed that PTH might adversely affect diastolic functions (A wave, E/A ratio) and endothelial functions (carotid IMT) in premenopausal women with VDD, independent of other confounding risk factors. We can state that our results will contribute to the literature since conflicting information in the literature and confounding factors are included in these studies. The recent literature is insufficient, and there is a need for further, multicentric studies with advanced subgroup analyses and longer follow-up periods also with other multi-modality imaging methods.

As a result of our study's findings, an awareness should also be created regarding possible cardiac risks in high parathyroid hormone in VDD.

Declarations

Conflict Of Interest and Funding

There is no conflict of interest and no financial support in our study. We want to thank our hospital's internal diseases departments for their helpfulness in conducting our study.

Availability Data and Material

The data that support the findings of this study are available on request from the corresponding author (Onur Akhan, akhanonur@gmail.com). The data are not publicly available due to privacy or ethical restrictions.

Author contributions

Concept/design: Onur Akhan, Data collection: Onur Akhan, Data analysis/interpretation: Onur Akhan, Mustafa Dogdus, Drafting article: Onur Akhan, Critical revision of article: Onur Akhan, Mustafa Dogdus: Approval of article: Onur Akhan, Mustafa Dogdus

References

1. Jorge AJL, Cordeiro JR, Rosa MLG, et al. Vitamin D Deficiency and Cardiovascular Diseases. Int. J. Cardiovasc. Sci. Aug 2018;31(4)422-432 https://doi.org/10.5935/2359-4802.20180025.
2. Nibbelink KA, Tishkoff DX, Hershey SD, et al. 1,25(OH)2-vitamin D3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. J Steroid Biochem Mol Biol 2007;103:533–537.
3. Wu-Wong JR, Nakane M, Ma J, et al. Effects of Vitamin D analogs on gene expression profiling in human coronary artery smooth muscle cells. Atherosclerosis 2006 May;186(1):20–8.
4. Merke J, Milde P, Lewicka S, et al. Identification and regulation of 1,25-dihydroxyvitamin D3 receptor activity and biosynthesis of 1,25-dihydroxyvitamin D3. Studies in cultured bovine aortic endothelial cells and human dermal capillaries. J Clin Invest 1989 Jun;83(6):1903–15.
5. Cantorna MT, Mahon BD. D-hormone and the immune system. J Rheumatol Suppl. 2005;76:11-20.
6. Li YC, Qiao G, Uskokovic M, et al. Vitamin D: a negative endocrine regulator of the rennin-angiotensin system and blood pressure. J Steroid Biochem Mol Biol. 2004 May;89-90(1-5):387-92.
7. Deeb KK, Trump DL, Johnson CS. Vitamin D signaling pathways in cancer: potential for anticancer therapeutics. Nat Rev Cancer. 2007 Sep;7(9):684-700.
8. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008 Jan 29;117(4):503-11.
9. Lee JH, Keefe JHO, Bell D, et al. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol. 2008 Dec 9;52(24):1949-56.
10. Kheiri B, Abdalla A, Osman M, et al. Vitamin D deficiency and risk of cardiovascular diseases: a narrative review. Clin Hypertens. 2018 Jun 22;24:9.

11. Mithal A, Wahl DA, Burckhardt P, et al. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009 Nov;20(11):1807–20.
12. Van Ballegooijen AJ, Kestenbaum B, Sachs MC, et al. Association of 25-hydroxyvitamin D and parathyroid hormone with incident hypertension: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2014 Apr 1;63(12):1214-22.
13. McMurray JJ. Clinical practice. Systolic heart failure. N Engl J Med. 2010 Jan 21;362(3):228–38.
14. Gullestad L, Ueland T, Vinge LE, et al. Inflammatory cytokines in heart failure: mediators and markers. Cardiology. 2012;122(1):23–35.
15. Yuan W, Pan W, Kong J, et al. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem. 2007 Oct 12;282(41):29821-30.
16. Connell JM, Mackenzie SM, Freel EM, et al. A lifetime of aldosterone excess: long-term consequences of altered regulation of aldosterone production for cardiovascular function. Endocr. Rev. 2008 Apr; 29(2):133-54.
17. Sunbul M, Bozbay M, Mammadov C, et al. Effect of vitamin D deficiency and supplementation on myocardial deformation parameters and epicardial fat thickness in patients free of cardiovascular risk. Int J Cardiovasc Imaging. 2015 Apr;31(4):765-72.
18. Omidi F, Hosseinsabet A. Is the longitudinal deformation of the left ventricle affected by vitamin D deficiency in nondiabetics? A 2D speckle-tracking echocardiographic study. Echocardiography. 2019 Jan;36(1):67-73.
19. Davarpasand T. Vitamin D deficiency as a seed in a fertile soil: A proposed hypothesis. Echocardiography. 2019 May;36(5):1019.
20. Gomez-Alonso C, Naves-Diaz ML, Fernandez-Martin JL, et al. Vitamin D status and secondary hyperparathyroidism: the importance of 25-hydroxyvitamin D cut-off levels. Kidney Int Suppl. 2003 Jun;(85):S44-8.
21. Terrovitis J, Zotos P, Kaldara E, et al. Bone mass loss in chronic heart failure is associated with secondary hyperparathyroidism and has prognostic significance Eur J Heart Fail. 14(3):326-32
22. Schillaci G, Pucci G, Pirro M, et al. Large-artery stiffness: A reversible marker of cardiovascular risk in primary hyperparathyroidism. Atherosclerosis, 2011;218:98-101
23. Rosa J, Raska I Jr, Wichterle D, et al. Pulse wave velocity in primary hyperparathyroidism and effect of surgical therapy. Hypertens Res, 2011 Mar,34(3);296-300.
24. Atasever A, Ozdemir E, Acar T, et al. The effect of successful parathyroid surgery on left ventricle function in patients with primary hyperparathyroidism evaluated with strain echocardiography. Echocardiography. 2020 May;37(5):670-677.
25. Kırış A, Erem C, Kırış G, et al. The assessment of left ventricular systolic asynchrony in patients with primary hyperparathyroidism. Echocardiography. 2011 Oct;28(9):955-60.
26. Smith JC, Page MD, John R, et al. Augmentation of central arterial pressure in mild primary hyperparathyroidism. J Clin Endocrinol Metab, 2000 Oct;85(10):3515-9.
27. Rothe HM, Liangos O, Biggar P, et al. Cinecalcet Treatment of primary hyperparathyroidisim. Int J Endocrinol, 2011; 2011:415719.
28. Pirro M, Manfredelli MR, Helou RS, et al. Association of parathyroid hormone and 25-OH-vitamin D levels with arterial stiffness in postmenopausal women with vitamin D insufficiency. J Atheroscler Thromb. 2012;19(10):924-31.
29. El Khoudary SR. Age at menopause onset and risk of cardiovascular disease around the world. Maturitas. 2020 Nov;141:33-38.
30. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2011 Jul;96(7):1911–1930.
31. Lang RM, Badano LP, Mor-avi V. et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015 Jan;28(1):1–39.e14.

32. Shingu Y, Amorim P, Nguyen TD, et al. Myocardial performance (Tei) index is normal in diastolic and systolic heart failure induced by pressure overload in rats, Eur J Echocardiogr, 2010 Dec;11(10):829-33.
33. Tafreshi RI, Human N, Otukesh H, et al. Evaluation of combined left ventricular function using the myocardial performance index in children with chronic kidney disease. Echocardiography. 2011 Jan;28(1):97-103.
34. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. J Am Soc Echocardiogr. 2008 Feb;21(2):93-111; quiz 189-90.
35. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force, J Am Coll Cardiol. 2002 Jan 16;39(2):257-65.
36. Bots ML, Westerink J, Rabelink TJ, et al. Assessment of flow-mediated vasodilatation (FMD) of the brachial artery: effects of technical aspects of the FMD measurement on the FMD response, European Heart Journal, Volume 26, Issue 4, February 2005, Pages 363–368.
37. Holick MF (2006) High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006 Mar;81(3):353-73.
38. Saiki H, Kuwata S, Kurishima C, et al. Aldosterone-cortisol imbalance immediately after Fontan operation with implications for abnormal fluid homeostasis. Am J Cardiol 2014;114:1578–1583.
39. Schnatz PF, Nudy M, Jiang X, et al. Vitamin D deficiency and cardiovascular disease in post-menopausal women: contributions from human and nonhuman primate studies. Menopause. 2015 May;22(5):554-63.
40. Islam MZ, Viljakainen HT, Kärkkäinen MU, et al. Prevalence of vitamin D deficiency and secondary hyperparathyroidism during winter in premenopausal Bangladeshi and Somali immigrant and ethnic Finnish women: associations with forearm bone mineral density. Br J Nutr. 2012 Jan;107(2):277-83.
41. Pandit A, Mookadam F, Boddu S, et al. Vitamin D levels and left ventricular diastolic function. Open Heart. 2014 Feb 15;1(1):e000011.
42. Pilz S, Henry RM, Snijder MB, et al. Vitamin D deficiency and myocardial structure and function in older men and women: the Hoorn study. J Endocrinol Invest. 2010 Oct;33(9):612-7.
43. Iqbal A, Jorde R, Lunde P, et al. Left ventricular dysfunction in subjects with mild secondary hyperparathyroidism detected with pulsed wave tissue Doppler echocardiography. Cardiology. 2006;105(1):1-8.
44. Lim S, Shin H, Kim MJ, et al. Vitamin D inadequacy is associated with significant coronary artery stenosis in a community-based elderly cohort: the Korean Longitudinal Study on Health and Aging. J Clin Endocrinol Metab. 2012 Jan;97(1):169-78.
45. Zang L, Fu P, Huang YQ, et al. [Vitamin D deficiency and carotid artery intima-media thickness and coronary calcification in patients with diabetic nephropathy]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2012 May;43(3):420-4, 450. Chinese.
46. Ng YM, Lim SK, Kang PS, et al. Association between serum 25-hydroxyvitamin D levels and carotid atherosclerosis in chronic kidney disease patients. BMC Nephrol. 2016 Oct 18;17(1):151.
47. Costa AF, Barufaldi F, Silveira MA, et al. Association of PTH and carotid thickness in patients with chronic kidney failure and secondary hyperparathyroidism. J Bras Nefrol. 2014 Jul-Sep;36(3):315-9. English, Portuguese.
48. Anderson JL, Vanwoerkom RC, Horne BD, et al. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent factors? Am Heart J 2011; 162:331–339.