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, especially in winter, and causes several adverse outcomes, including cardiovascular diseases. Although there is conflicting information about the causes of cardiac events in VDD, the commonly accepted cause is a pathogenic relationship with hyperparathyroidism.

Aim: We aim to demonstrate the effects of hyperparathyroidism, if present, on endothelial and diastolic functions using echocardiography, carotid and brachial tissue Doppler imaging(tDi) in premenopausal women with VDD independent from other confounding risk factors.

Methods: Our study is a cross-sectional, observational study investigating premenopausal women aged 18-50 who applied to internal medicine. The patients were divided into two groups according to their parathyroid hormone(PTH) levels. While PTH levels are within the normal range in 41 patients, it was high in 29 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 diastolic blood pressures(BP) between the groups(*all p values*>0.05). Systolic BPs were significantly higher in the secondary hyperparathyroidism, no patients diagnosed with hypertension(*Mean systolic BP* 124±8, *p*=0.020). The rate of severe VDD was 78%. In terms of diastolic parameters, prolongation of A wave durations and decreased E/A ratio were observed in the secondary hyperparathyroidism(*p values are 0.043 and 0.031, respectively*). Carotid and brachial tDi; carotid intima-media thickness(IMT) is significantly higher in secondary hyperparathyroidism(*p*=0.032).

Conclusion: We showed that high PTH levels have adverse effects on diastolic functions(A wave, E/A ratio) and endothelial functions(carotid IMT) in premenopausal women 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 with effects on calcium and phosphorus metabolism(1). By binding to VitD receptors in the whole body, including endothelium, vascular smooth muscle cells, and cardiomyocytes, it also affects many vital functions such as homeostasis, autoimmunity, and inflammatory interleukins synthesis, cell proliferation and differentiation, and blood pressure regulation(2–7). The prevalence of VDD can be at 30–50%(8, 9). The main risk factors are high altitude, winter season, low sun exposure, restricted dietary intake, postmenopause, and advanced age(9, 10).

Although its pathophysiology is not fully known, VDD has been linked with various cardiovascular outcomes; hypertension, myocardial infarction complications, arterial stiffness, myocardial fibrosis,

systolic and diastolic dysfunction(1, 11–14). Hyperstimulation of the renin-angiotensin-aldosterone 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(12, 14, 15). 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(16).

Secondary hyperparathyroidism can be seen at rates 18–25% in VDD, which increases with age(17). Secondary hyperparathyroidism may be associated with disease severity in congestive heart failure, especially in older, due to bone loss and osteoporosis(18). There may be a relationship between PTH levels and arterial stiffness, coronary atherosclerosis, brachial flow-mediated dilatation(bFMD) (adversely), especially in primary hyperparathyroidism, and a regression in pulse wave velocity(PWV) with parathyroidectomy(19–22). Although this finding could not be reached with primary hyperparathyroidism in all studies, improvements in PWV were also observed using cinacalcet; a calcimimetic agent that provides a decrease in PTH levels in chronic renal failure and secondary hyperparathyroidism(23, 24).

The relationship between VDD and hyperparathyroidism with arterial stiffness has been shown one by one, as mentioned above(11, 14, 19, 22). Pirro et al. investigated independent associations between VitD and PTH with arterial stiffness in the postmenopausal stage with normal kidney functions. In this study, an inverse relationship, albeit weak, was found between VitD levels and PWV. This relation was significantly associated with PTH levels regardless of existing risk factors and factors involving bone formation(25).

The risk of cardiovascular disease increases in the postmenopausal period, especially with hormonal changes(26). Menopause can be considered as a confounding risk factor. 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.

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 8–9 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(27). Patients diagnosed with VDD

without replacement therapy were evaluated using essential echocardiographic evaluation, brachial and carotid tDi. 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 70 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 29 patients. Groups were compared regarding 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, tDi 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(28). In echocardiographic tDi evaluations, global systolic and diastolic ventricular function indicator, the myocardial performance index(MPI), also known as Tei Index, is also calculated with the formula '[Isovolumetric contraction time(IVCT) + Isovolumetric relaxation time(IVRT)]/Ejection Time(ET)' for both left ventricle lateral and septal parts(29).

Carotid systolic and diastolic diameters, 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(30).

All ultrasonic examinations were made with continuous electrocardiography 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'(31, 32).

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 $\pm$ 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, and diastolic BP between the groups (*all p values* > 0.05). The secondary hyperparathyroidism group's mean systolic BP was significantly higher than the group without hyperparathyroidism, but not high enough to diagnose hypertension (*Mean systolic BP* 124 ± 8 , 118 ± 12 , *respectively*; $p = 0.020$) (33). There were no significant differences in laboratory parameters, except for vitamin B12, which were significantly lower in the secondary hyperparathyroidism group, but the current values were within the reference range (*Mean values* 335 ± 107 , 426 ± 181 , *respectively*; $p = 0.019$). Baseline characteristics and laboratory results of the groups are shown in table 1. VitD and PTH levels are also presented in Fig. 1.

VitD levels were relatively low in the secondary hyperparathyroidism compared to the group with normal PTH levels (*mean values* 8.0 ± 4.0 , 9.3 ± 7.8 , *respectively*; $p = 0.376$). The rate of severe VDD (< 10 ng/ml) in our study's total population was 78%.

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 ($p = 0.032$).

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 (34). The removal of inhibitory effects on the RAAS system and proinflammatory cytokines can be accepted as the primary mechanism for cardiovascular involvement in VDD (12, 14, 15, 34). Hyperparathyroidism cases secondary to VDD are not uncommon and lead to adverse cardiac outcomes (17, 35).

Menopause may be considered a risk factor for VDD and, consequently, secondary hyperparathyroidism (25, 36). It is also known that cardiovascular risk increases in menopause with hormonal changes (26, 36). In postmenopausal women, Pirro M. et al. showed that VitD insufficiency was associated with arterial stiffness weakly. The main influential factor was PTH level, independent of other risk factors (25). However, possible cardiac risks due to the menopause nature can be considered a

confounding factor(26, 36). 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.

In our study, in baseline characteristics, systolic BP is higher in the secondary hyperparathyroidism group than the group with normal PTH levels($p = 0.020$). Neurohormonal effects of hyperparathyroidism may cause the difference(37). A positive correlation was found between PTH level and systolic BP, albeit standard PTH value, in a study investigating the relation of endothelial functions with VitD and PTH levels. Our findings can be evaluated in this route(38).

As stated before, secondary hyperparathyroidism prevalence is approximately 18–25% according to VitD levels, secondary hyperparathyroidism prevalence in severe VDD was also shown as 33%. In Gómez-Alonso C et al. study, the autumn-winter months covered 60% of the study period in 40°N latitude in a city 400 meters above sea level(18). However, Islam MZ. et al. showed that this prevalence could vary in the range of 16%-89%, according to ethnic differences(39). Secondary hyperparathyroidism was observed with a rate of 41% 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 0.043 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)(40). 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 these seasons, VDD lost its significance when adjusted for age and cardiovascular risks(41).

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($p > 0.05$). Also, no significant difference was found in diastolic parameters(E,A waves, IVRT, pulmonary vein atrial reversal flow) in this study(42).

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 VDD, even if there is no confounding factor.

Lim S. et al. showed VDD is associated with endothelial dysfunction and coronary atherosclerosis(43). In diabetic nephropathy patients, VDD is significantly linked with carotid IMT, but no significant relation was found for chronic renal failure(44, 45). Studies conducted with chronic renal failure and secondary hyperparathyroidism found a significant relationship between carotid thickness and PTH levels(46, 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(38).

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($p = 0.032$), no other significant difference related to carotid and brachial artery. We can say that hyperparathyroidism is an independent risk factor for carotid IMT 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 risk factors. Therefore, patients should be evaluated in terms of possible future cardiac risks by paying attention to PTH levels in diagnosing VDD. We can state that our study's findings are predictive for future studies since the significant findings were detected independently of confounding risk factors and even in young patients. The subject can be clarified with multicentric studies and advanced subgroup analyses that can be done with many patients in further studies.

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.

The difference between the vitamin B12 levels among the study groups may have affected the results, even though the vitamin levels were in the reference range.

Conclusion

Our study showed that parathormone has adverse effects on 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.

As a result of our study's findings, the importance of PTH levels in VDD should not be forgotten. An awareness should be created regarding possible cardiac risks in high PTH in VDD.

Declarations

Conflict Of Interest and Funding

No conflict of interest and financial support. Special thanks to internal medicine department for their helpfulness.

Availability Data and Material

This study's data are available on request from the corresponding author(Onur Akhan, akhanonur@gmail.com), not publicly available due to privacy or ethical restrictions.

Author contributions

Concept/design:OA, Data collection:OA, Data analysis/interpretation:OA, MD, Drafting:OA, Critical revision:OA, MD: Approval:OA, MD

References

1. Jorge AJL, Cordeiro JR, Rosa MLG, et al. Vitamin D Deficiency and Cardiovascular Diseases. *Int J Cardiovasc Sci* 2018(Aug);31(4)422-432
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;103:533–7.
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;186:20–8.
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;83:1903–15.
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;89-90(1-5):387-92.
7. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation.* 2008(Jan)29;117(4):503-11.
8. Lee JH, Keefe JHO, Bell D, et al. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2017;52:1949–56.
9. 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.
10. Mithal A, Wahl DA, Burckhardt P, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int* 2009;20:1807–20.
11. 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;63(12):1214-22.
12. McMurray JJ. Clinical practice. Systolic heart failure. *N Engl J Med* 2010;362(3):228–38.

13. Gullestad L, Ueland T, Vinge LE, et al. Inflammatory cytokines in heart failure: mediators and markers. *Cardiology* 2012;122(1):23–35.
14. 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;282(41):29821-30.
15. 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;29(2):133-54.
16. 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.
17. Gómez-Alonso C, Naves-Díaz ML, Fernández-Martín 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.
18. Terrovitis J, Zotos P, Kaldara E, et al. Bone mass loss in chronic heart failure is associated with secondary hyperparathyroidism and has prognostic significance [European Journal of Heart Failure](#)14(3):326-32
19. 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
20. Kepez A, Harmanci A, Hazirolan T, et al., "Evaluation of subclinical coronary atherosclerosis in mild asymptomatic primary hyperparathyroidism patients," *Int J Cardiovasc Imaging* 2009(vol.25),pp.187-193
21. Baykan M, Erem C, Erdoğan T, et al. Impairment of flow mediated vasodilatation of brachial artery in patients with primary hyperparathyroidism. *Int J Cardiovasc Imaging* 2007(Jun);23(3):323-8.
22. Rosa J, Raska I Jr, Wichterle D, et al. Pulse wave velocity in primary hyperparathyroidism and effect of surgical therapy. *Hypertens Res* 2011,34;296-300.
23. Smith JC, Page MD, John R, et al. Augmentation of central arterial pressure in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 2000;85:3515-3519.
24. Rothe HM, Liangos O, Biggar P, et al. Cinacalcet Treatment of primary hyperparathyroidism. *Int J Endocrinol* 2011;41:5719
25. 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.
26. El Khoudary SR. Age at menopause onset and risk of cardiovascular disease around the world. *Maturitas* 2020(Nov);141:33-38.
27. 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;96:1911–1930.

28. Lang RM, Badano LP 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)28(1):1–39.
29. 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* Volume 11, Issue 10, December 2010, Pages 829–833.
30. 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.
31. 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* Volume 39, Issue 2, 2002, Pages 257-265.
32. 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.
33. Williams B, Mancia G, Spiering W, et al. ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018(Sep 1);39(33):3021-3104.
34. Holick MF High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006(81),353–373.
35. 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.
36. Schnatz PF, Nudy M, Jiang X, et al. Vitamin D deficiency and cardiovascular disease in postmenopausal women: contributions from human and nonhuman primate studies. *Menopause*. 2015(May);22(5):554-63.
37. 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.
38. Yankouskaya L, Snezhitskiy V. Relationship between vascular endothelial function and vitamin D and parathyroid hormone levels in women with arterial hypertension. *Pol Arch Med Wewn* 2014;124(10):532-9.
39. 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.
40. Pandit A, Mookadam F, Boddu S, et al. Vitamin D levels and left ventricular diastolic function. *Open Heart* 2014(Feb)15;1(1):e000011.
41. 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.

42. 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.

43. 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.

44. 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.

45. 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.

46. Ardahanli I, Cengizhan MS, Celik M, et al. Carotid Artery Intima-Media Thickness and Heart Valve Calcifications in Hemodialysis Patients with Hyperparathyroidism (A Pilot Study). *Archives of Nephrology and Urology* 2(2019):052-061.

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.

Tables

Table 1: Basal Characteristics and Laboratory Parameters

	Normal PTH Level (n=41) (mean±SD)	Secondary Hyperparathyroidism (n=29) (mean±SD)	P
Age (year)	36.8±7.3	38.9±9.1	0.277
Height (cm)	1.62±0.1	1.61±0.1	0.860
Weight (kg)	69.8±9.5	71.1±10.5	0.623
BMI (kg/m ²)	26.5±3.1	27.1±3.1	0.509
Systolic BP (mmHg)	118±12	124±8	0.020
Diastolic BP (mmHg)	80±13	83±12	0.413
Laboratory measurements			
PTH (pg/dl)	58.4±5.4	94.9±25.3	<0.001
Vitamin D (ng/ml)	9.3±7.8	8.0±4.0	0.376
Blood glucose* (mg/dl)	90±6.9	92.8±5.9	0.077
Creatinine (mg/dl)	0.73±0.05	0.76±0.6	0.146
BUN (mg/dl)	11±3.1	12±3.1	0.144
Corrected Calcium (mg/dl)	9.2±0.3	9.3±0.2	0.705
Phosphate (mg/dl)	3.2±0.4	3.2±0.6	0.729
Magnesium (mg/dl)	1.8±0.2	1.9±0.3	0.375
HDL (mg/dl)	50±8.4	49±6.9	0.630
LDL (mg/dl)	113±16	118±13	0.141
Vitamin B12 (pg/ml)	426±181	335±107	0.019
TSH (IU/L)	1.8±0.9	1.6±0.8	0.211
<i>SD: standard deviation, BMI: body-mass index BP: blood pressure, PTH: Parathormon, BUN: blood urea nitrogen, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TSH: thyroid stimulating hormone</i>			

Table 2: Echocardiographic and Peripheral Tissue Doppler Parameters

	Normal PTH Level (n=41) (mean±SD)	Secondary Hyperparathyroidism (n=29) (mean±SD)	P
LVEF (Simpson Method - %)	69±7	71±7	0.436
HR (/min)	78±11	79±11	0.621
E (cm/s)	73±12	77±16	0.213
A (cm/s)	53±14	62±19	0.043
Deceleration Time (ms)	216±49	223±42	0.495
E/A	1.4±0.3	1.3±0.6	0.031
E/E'	3.7±0.9	4.2±1.1	0.097
Lat. s (cm/s)	16±4.1	15±4.9	0.249
Lat. e (cm/s)	20±4.8	19±4.7	0.360
Lat. a (cm/s)	17±5.7	15±4.9	0.208
Lat. IVRT (ms)	92±17	83±19	0.062
Lat. IVCT (ms)	81±22	73±31	0.229
Lat. Ejection time (ms)	269±30	255±29	0.078
Lat (mpi)	0.6±0.1	0.6±0.2	0.622
Sep. s (cm/s)	14±2.8	16±3.6	0.128
Sep. e (cm/s)	18.6±3.2	18±4.3	0.500
Sep. a (cm/s)	16±5	17±6	0.473
Sep. IVRT (ms)	95±25	91±22	0.531
Sep. IVCT (ms)	93±21	87±18	0.164
Sep. Ejection Time (ms)	263±22	263±24	0.939
Sep (mpi)	0.7±0.1	0.6±0.1	0.221
RVSm (cm/s)	19±2.8	18±4.6	0.762
Carotid syst. diameter (cm)	0.56±0.03	0.57±0.06	0.549
Carotid diast. diameter (cm)	0.51±0.03	0.52±0.05	0.437
Carotid IMT (mm)	0.5±0.1	0.6±0.1	0.032

Basal Brachial diameter (cm)	0.28±0.03	0.29±0.04	0.537
Peak Brachial diameter (cm)	0.31±0.04	0.31±0.04	0.685
bFMD (%)	0.09±0.04	0.08±0.04	0.436
<i>SD.: Standard deviation, LVEF: left ventricular ejection fraction, HR: Heart rate, Lat: Lateral, Sep.: Septal, mpi: myocardial performance index(TEI-Doppler Index), IVRT: Isovolumetric relaxation time, IVCT: Isovolumetric contraction time, RVS_m: Right ventricular peak systolic myocardial velocity, syst.: systolic, diast: diastolic, IMT: Intima-media thickness, bFMD: Brachial flow-mediated dilatation</i>			

Figures

Figure 1

Vitamin D and PTH levels of the patients