The article was received on September 16, 2020, and accepted for publishing on January 23, 2021.

ORIGINAL ARTICLES

The assessment of the vitamin D deficiency between the patients with acute coronary syndrome and those with stable coronary artery disease in a military hospital

Morteza Khodaparast[1]

Abstract: *Background: A few studies compared the vitamin D deficiency condition between the patients with the acute coronary syndrome (ACS) and those with stable coronary artery disease. The present comparative study aimed to assess the vitamin D deficiency status between the patients with ACS and those with stable coronary artery disease.*

Methods: This cross-sectional study was performed on 200 consecutive patients with the diagnosis of ACS or stable coronary artery disease. Serum Vitamin D level was measured by immunoassay and its serum level was categorized as normal (> 30 ng/ml), insufficient (20 to 30 ng/ml), and deficient (< 20 ng/ml).

Results: Overall, 103 patients were categorized as stable angina group, 74 had unstable angina, 10 had STEMI, and 13 had NSTEMI. There was no difference in serum vitamin D3 level across the four groups including stable angina group (13.81 ± 15.13 ng/ml), unstable angina group (15.13 ± 11.11 ng/ml), STEMI group (21.58 ± 19.87 ng/ml), and NSTEMI group (18.67 ± 13.07 ng/ml) (p = 0.276). No difference was also found in the mean vitamin D3 level between the groups with new MI (15.98 ± 12.44 ng/ml versus 14.01 ± 15.31 ng/ml, p = 0.318). In total, 8.5% had normal vitamin D levels and 9.0% had vitamin D insufficiency, while the majority of patients (82.5%) were vitamin D deficient. The vitamin D deficiency was comparable in the patients with stable angina compared to those in ACS groups. According to ROC curve analysis, measuring serum vitamin D3 had a moderate value to discriminate stable angina from ACS (AUC = 0.651). In this regard, the best cutoff point for serum vitamin D3 level to discriminate stable angina from ACS was 9.0 ng/ml yielding a sensitivity of 70.1% and a specificity of 57.3%.

Conclusion: The measurement of vitamin D and thus the presence of vitamin D deficiency have no sufficient power to discriminate ACS from stable coronary artery disease.

Keywords: *vitamin D deficiency, coronary syndrome, artery disease*

INTRODUCTION

Acute coronary syndrome (ACS) has been now known as the major cause of death whole of the world, especially in industrial countries. Potentially, the presence of various genetic, metabolic, and environmental risk factors can increase the risk for mortality and disability in affected patients [1]. In this regard, some metabolic and endocrinological factors have been identified to link the progression and severity of coronary artery disease (CAD). Within the last few years, a significant association between deficiency of some vitamins and minerals and CAD has been found [2-4]. In this regard, an association of vitamin D deficiency and different cardiovascular risk factors and

[1] Atherosclerosis Research Center, Baqyiatallah University of Medical Sciences, Tehran, Iran

Corresponding author: Morteza Khodaparast
morteza.khodaparast2020@gmail.com

diseases has been extensively evaluated. Some prospective and observational studies have addressed the possible linkage of vitamin D deficiency and the development of CAD and its risk factors [5, 6]. Thus, vitamin D deficiency not only has a major role in bone metabolism, homeostasis regulation, and immune pathways, but also the presence of vitamin D receptors on cardiomyocytes, endothelial cells, and vascular smooth muscle cells suggests the role of vitamin D in vitamin D-mediated cardiovascular system [7-9]. It has been shown that cardiac muscle functioning depends on the circulating blood concentration of calcitriol [10]. Calcitriol affects the growth, proliferation, and morphology of murine cardiomyocytes. In detail, treatment with calcitriol increased the expression of the cardiac muscle protein myotrophin. The link between vitamin D deficiency and cardiovascular risk factors has been also shown [11]. According to the Framingham Offspring Study [5], individuals with low activated vitamin D faced more with incident cardiovascular disease such as myocardial infarction, coronary insufficiency, and heart failure compared to those with a normal level of vitamin D. Thus, treatment with vitamin D supplementation could reduce cardiovascular death and length of hospitalization in ACS patients; however, a few studies compared the vitamin D deficiency condition between the patients with ACS and those with stable coronary artery disease. The present comparative study aimed to assess the vitamin D deficiency status between the patients with ACS and those with stable coronary artery disease.

METHODS

This cross-sectional study was performed on 200 consecutive patients with the diagnosis of ACS or stable coronary artery disease. The ACS was diagnosed according to the ACS criteria defined based on clinical symptoms, ECG changes, and cardiac enzyme rising. Stable coronary artery disease was defined as typical exertional chest pain relieved by rest or nitroglycerin administration and a positive exertional ECG test. The exclusion criteria were history of surgery within 6 months ago or having a hematologic disease or any hemoglobinopathy or coagulopathy, history of chronic clinical conditions such as liver or kidney disease or malignancies, or history of cerebrovascular disease or other simultaneous cardiovascular disorders.

Baseline characteristics and clinical data of participants including demographics, anthropometric parameters (weight, height, and body mass index), cardiovascular risk factors (current smoking, hypertension, hyperlipidemia, and opium addiction) as well as laboratory parameters (fasting blood sugar, hemoglobin A1c, lipid profile, thyroid functional hormones, and serum creatinine) were collected from the hospital recorded files. Serum Vitamin D level was measured by immunoassay and its serum level was categorized as normal (> 30 ng/ml), insufficient (20 to 30 ng/ml), and deficient (< 20 ng/ml). The primary endpoint was to assess the relation between the type of ACS and the severity of vitamin D deficiency. The secondary endpoint was to determine the best cutoff point for vitamin D to differentiate ACS from stable coronary artery conditions. The ethical committee of Kerman University of Medical Sciences approved the study research proposal all procedures were in accord with the standards of the World Medical Association Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all study participants.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. Continuous variables were compared using t, and one-way ANOVA tests, or non-parametric Mann-Whitney U, or Kruskal-Wallis tests whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the groups. The ROC curve analysis was also used to determine the value of vitamin D measurement to predict the presence of ACS and also to determine the best cutoff value of this vitamin to discriminate ACS from stable angina. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

Overall, 103 patients were categorized as stable angina group, 74 had unstable angina, 10 had STEMI, and 13 had NSTEMI. Comparing baseline characteristics and clinical data (Table 1) across the groups showed that the patients with stable angina were older than the patients in other groups.

Also, hypertension was more frequent in those with STEMI, while hyperlipidemia was more prevalent in those with stable angina. Family history of CAD was found less and opium addiction was revealed more in the NSTEMI group when compared to other groups. Statin use, aspirin use as well as the history of prior PCI was all more in a group with stable angina than in other groups, while prior CABG was scheduled more in the NSTEMI group.

Meanwhile, there was no difference across the four groups in terms of gender, mean BMI, history of diabetes, smoking, alcohol use, thyroid dysfunction, prior SK use, and left ventricular dysfunction.

Table 1: Baseline characteristics and clinical data of study population

	Stable angina (N = 103)	Unstable angina (N = 74)	STEMI (N = 10)	NSTEMI (N = 13)	P-value
Male gender	60 (58.3)	46 (62.2)	7 (70.0)	10 (76.9)	0.555
Age, year	64.29 ± 8.85	59.92 ± 11.25	60.70 ± 12.09	61.92 ± 8.78	0.058
BMI, kg/m^2	27.92 ± 3.82	27.54 ± 2.93	26.43 ± 2.31	26.45 ± 3.94	0.333
Hypertension	87 (84.5)	46 (62.2)	10 (100)	9 (69.2)	0.002
Diabetes	34 (33.0)	33 (45.6)	5 (50.0)	6 (46.2)	0.480
Hyperlipidemia	96 (93.2)	17 (23.0)	0 (0.0)	3 (23.1)	< 0.001
Family history	44 (42.7)	31 (41.9)	4 (40.0)	3 (23.1)	0.035
Smoking	29 (28.2)	12 (16.2)	2 (20.0)	2 (15.4)	0.260
Opium use	7 (6.8)	5 (6.8)	1 (10.0)	2 (15.4)	0.033
Alcohol use	9 (8.7)	2 (2.7)	0 (0.0)	0 (0.0)	0.210
Hyperthyroidism	3 (2.9)	1 (1.4)	0 (0.0)	0 (0.0)	0.963
Hypothyroidism	7 (6.8)	1 (1.4)	0 (0.0)	0 (0.0)	0.611
CCU admission	69 (67.0)	29 (39.2)	5 (50.0)	5 (38.5)	0.011
Statin use	99 (96.1)	56 (75.7)	7 (70.0)	9 (69.2)	< 0.001
Aspirin use	90 (87.4)	53 (71.6)	8 (80.0)	9 (69.2)	0.023
NSAIDS use	2 (1.9)	2 (2.7)	0 (0.0)	0 (0.0)	0.883
Prior PCI	96 (93.2)	15 (20.3)	1 (10.0)	3 (23.1)	< 0.001
Prior SK receive	11 (10.7)	3 (4.1)	1 (10.0)	0 (0.0)	0.475
Prior CABG	3 (2.9)	13 (17.6)	3 (30.0)	2 (15.4)	0.013
LVEF	48.99 ± 8.18	47.58 ± 10.46	44.80 ± 10.29	43.85 ± 5.67	0.152

Regarding laboratory parameters (Table 2), mean serum FBS was significantly lower in the group with stable angina, while serum HDL level was higher among those with stable angina than other patients. The highest liver enzymes were revealed in those with STEMI. The patients with stable angina had a significantly higher level of T3 than other ones.

Table 2: Baseline laboratory indices in the study population

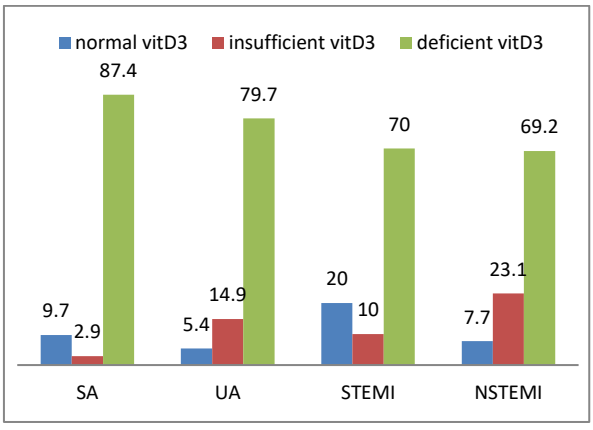
	Stable angina	Unstable angina	STEMI	NSTEMI	P-value
Hemoglobin	14.77 ± 2.89	13.89 ± 1.60	14.73 ± 1.12	14.16 ± 2.20	0.106
Hematocrit	48.61 ± 36.91	40.85 ± 4.46	41.78 ± 3.46	41.09 ± 6.48	0.258
Platelet	226.21 ± 65.72	218.84 ± 58.57	195.70 ± 48.04	223.54 ± 73.51	0.495
ESR	15.17 ± 6.46	16.14 ± 15.67	13.10 ± 7.56	14.69 ± 15.00	0.848
CRP	0.97 ± 8.36	0.32 ± 0.47	0.50 ± 0.52	0.62 ± 0.51	0.918
FBS	115.27 ± 36.98	143.47 ± 61.22	170.70 ± 68.86	166.85 ± 71.98	< 0.001
Creatinine	3.25 ± 14.27	1.33 ± 0.97	1.14 ± 0.21	1.19 ± 0.20	0.613
Uric acid	7.83 ± 11.78	5.59 ± 1.93	4.74 ± 1.44	6.45 ± 2.09	0.317
Triglyceride	157.69 ± 71.86	148.07 ± 86.70	137.50 ± 68.42	105.87 ± 93.43	0.153
Cholesterol	183.37 ± 50.72	171.80 ± 52.83	170.10 ± 40.04	170.23 ± 50.33	0.433
LDL	98.46 ± 30.33	105.40 ± 42.09	100.34 ± 25.09	105.91 ± 42.84	0.609
HDL	46.43 ± 30.16	36.38 ± 8.52	36.90 ± 7.91	34.54 ± 10.22	0.018
AST	21.36 ± 7.96	24.38 ± 19.29	65.40 ± 42.45	34.38 ± 26.31	< 0.001

	Stable angina	Unstable angina	STEMI	NSTEMI	P-value
ALT	26.89 ± 17.69	28.46 ± 24.30	52.00 ± 33.04	34.46 ± 22.99	0.005
ALKP	181.25 ± 73.84	185.70 ± 60.70	170.40 ± 30.67	225.92 ± 79.55	0.144
Calcium	13.56 ± 19.05	8.98 ±0.61	8.86 ± 0.33	9.16 ± 0.47	0.141
Phosphorus	4.16 ± 1.25	3.99 ± 0.58	3.38 ± 0.71	3.83 ± 0.72	0.091
PTH	30.48 ± 30.51	47.81 ± 21.74	43.29 ± 11.42	49.96 ± 15.40	0.227
T3	2.99 ± 3.86	0.89 ± 0.97	0.70 ± 0.14	0.68 ± 0.17	< 0.001
T4	45.44 ± 47.98	62.71 ± 19.19	65.74 ± 11.80	61.28 ± 11.44	0.102
TSH	4.19 ± 14.30	2.64 ± 4.32	2.14 ± 1.59	1.62 ± 1.18	0.698
HbA1C	6.33 ± 1.36	14.88 ± 70.03	7.99 ± 2.01	7.61 ± 2.63	0.622

There was no difference in serum vitamin D3 level across the four groups including stable angina group (13.81 ± 15.13 ng/ml), unstable angina group (15.13 ± 11.11 ng/ml), STEMI group (21.58 ± 19.87 ng/ml), and NSTEMI group (18.67 ± 13.07 ng/ml) (p = 0.276). No difference was also found in the mean vitamin D3 level between the groups with new MI (15.98 ± 12.44 ng/ml versus 14.01 ± 15.31 ng/ml, p = 0.318).

In total, 8.5% had normal vitamin D levels and 9.0% had vitamin D insufficiency, while the majority of patients (82.5%) were vitamin D deficient. As shown in Figure 1, the vitamin D deficiency was comparable in the patients with stable angina compared to those in other ACS groups (p = 0.338). However, vitamin D deficiency was more prevalent in the old MI group compared to the new MI group (87.0% versus 78.0%, p = 0.011).

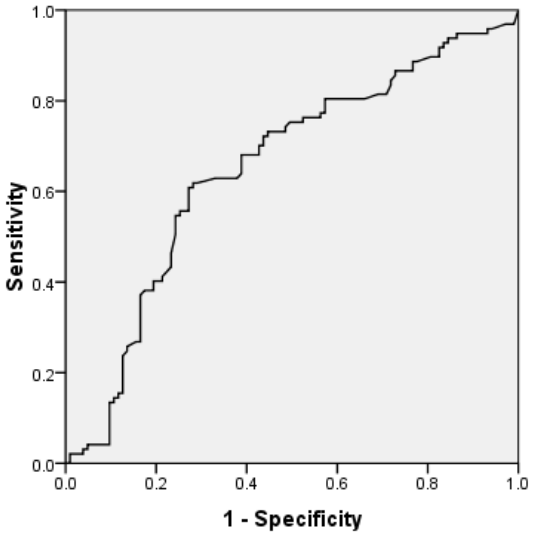
Figure 1: Vitamin D deficiency in ACS subgroups



The level of vitamin D was similar in the patients with and without hypertension (15.04 ± 14.56 ng/ml versus 14.88 ± 11.93 ng/ml, p = 0.9450), the groups with and without diabetes mellitus (13.46 ± 4.17 ng/ml versus 15.35 ± 15.08 ng/ml, p = 0.760), and those with and without hypertriglyceridemia (13.29 ± 4.02 ng/ml versus 15.03 ± 12.49 ng/ml, p = 0.714).

According to ROC curve analysis, measuring serum vitamin D3 had a moderate value to discriminate stable angina from ACS (AUC = 0.651, 95% CI: 0.573 – 0.728, P < 0.001) (Figure 2). In this regard, the best cutoff point for serum vitamin D3 level to discriminate stable angina from ACS was 9.0 ng/ml yielding a sensitivity of 70.1% and a specificity of 57.3%.

Figure 2: ROC curve analysis to determine the value of vitamin D level to discriminate stable angina from ACS



Diagonal segments are produced by ties.

DISCUSSIONS

There is modest evidence that lower vitamin D levels are associated with an increased risk of CAD. However, few studies have researched CAD as a separate disease entity from cardiovascular disease. It has been now suggested that people with low vitamin D levels had twice the risk of developing a heart attack compared to those with adequate vitamin D levels, but it has remained uncertain the effect of vitamin D levels on CAD risk particularly in variant angina.

Hence, we attempted to compare the value of vitamin D measurement and thus vitamin D deficiency in differentiating stable coronary conditions from ACS variants. In this regard, we could demonstrate a similar incidence of vitamin D deficiency in stable coronary arteries and those without this condition. Even, using ROC curve analysis, it was shown that the measuring vitamin D level could discriminate stable coronary involvement and ACS variants with moderate power. However, a higher incidence of vitamin D3 might be predicted in those with old MI than in patients that newly suffered MI. In a study by Raina et al [12] in India, it was suggested a significant correlation between vitamin D deficiency and chronic stable angina. In India, results similar to the pointed were seen by Sanjeev Kumar et al. [13] who studied 100 patients undergoing CAG. They found that the mean 25(OH) D level was 14.8 ng/mL; vitamin D deficiency was present in 80% and only 7% had an optimal 25(OH) D level that was near to our result. More interestingly, another study that divided 2910 patients with coronary artery disease history (acute myocardial infarction – unstable angina – stable angina) into three groups based on their angiography results showed that although vitamin D deficiency is prevalent in all groups, it is more prevalent in patients with stable angina and also it is indicative of a worse prognosis [14] that was numerically near to our results.

The similarity in incidence of vitamin D deficiency in our study subgroups may be due to this fact that the majority of patients included into the study had vitamin D deficiency so 82.5% were vitamin D deficient that is a considerable finding. Another reason for the insignificant association between vitamin D level and the ACS variants could be related to no significant association between the level of vitamin D and various cardiovascular risk subgroups. As we assessed this association, the level of vitamin D was similar in cardiovascular risk subgroups. In fact, because of a probable causative relation between cardiovascular risk factors and vitamin D deficiency, our finding can be explained. Another reason for paradoxical results across the studies may be due to the different cutoff points for defining vitamin D deficiency. During a Framingham–Off spring study on 1739 participants who were followed up within 5.4 years Wang and colleagues [15] revealed that vitamin D deficiency is associated with cardiovascular disease. However in the mentioned study levels < 15 ng/ml were considered as vitamin D deficiency. Also, in Siadat et al study [16], it was considered levels lower than 30 ng/ml as vitamin D deficiency, while in our study, vitamin D deficiency was defined as the levels of lower than 20 30 ng/ml.

It seems that the effect of vitamin D on cardiovascular risk can be mediated by some mechanisms including reduction of the risk for underlying metabolic disorders such as diabetes and high blood pressure, lowering the thickening of the arterial walls, reduces the risk of respiratory infections, suppression of inflammatory pathways, and reduction the risk of arterial calcification or hardening [17-21]. Furthermore, some studies are indicative of a relation between vitamin D deficiency and cardiovascular disease, increased blood pressure, increased insulin resistance, heart failure, and fatal strokes [22-26] that can explain the association between CAD risk and vitamin D deficiency; however, this association was not proved in our study population.

As a new result, the best cutoff value for differentiating stable angina from ACS conditions was 9.0 that considerably lower than the cutoff values defined for vitamin D deficiency. We could not find a similar study on determining the best cutoff values for vitamin D to predict stable angina and thus the obtained result on this subject should be more assessed in further studies.

References:

1. Michos ED, Melamed ML: Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care 11: 7–12, 2008

2. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, Steele D, Chang Y, Camargo CA Jr, Tonelli M, Thadhani R: Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int 72: 1004–1013, 2007

3. Ravani P, Malberti F, Tripepi G, Pecchini P, Cutrupi S, Pizzini P, Mallamaci F, Zoccali C: Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int 75: 88–95, 2009.

4. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS: Vitamin D deficiency and risk of cardiovascular disease. Circulation 117: 503–511, 2008

5. Giovannucci E, Liu Y, Hollis BW, Rimm EB: 25-Hydroxyvitamin D and risk of myocardial infarction in men: A prospective study. Arch Intern Med 168: 1174–1180, 2008

6. Bouillon, R.; Carmeliet, G.; Verlinden, L.; van Etten, E.; Verstuyf, A.; Luderer, H.F.; Lieben, L.; Mathieu, C.; Demay, M. Vitamin D and human health: Lessons from vitamin D receptor null mice. Endocr. Rev. 2008, 29, 726–776.

7. Wacker, M.; Holick, M.F. Vitamin D—Effects on skeletal and extraskeletal health and the need for supplementation. Nutrients 2013, 5, 111–148.

8. Souberbielle, J.-C.; Body, J.-J.; Lappe, J.M.; Plebani, M.; Shoenfeld, Y.; Wang, T.J.; Bischoff-Ferrari, H.A.; Cavalier, E.; Ebeling, P.R.; Fardellone, P.; et al. Vitamin D and musculoskeletal health, cardiovascular disease, autoimmunity and cancer: Recommendations for clinical practice. Autoimmun. Rev. 2010, 9, 709–715.

9. Muscogiuri, G.; Sorice, G.P.; Ajjan, R.; Mezza, T.; Pilz, S.; Prioletta, A.; Scragg, R.; Volpe, S.L.; Witham, M.D.; Giaccari, A. Can vitamin D

deficiency cause diabetes and cardiovascular diseases? Present evidence and future perspectives. Nutr. Metab. Cardiovasc. Dis. 2012, 22, 81–87.

10. Pilz, S.; Tomaschitz, A.; März, W.; Drechsler, C.; Ritz, E.; Zittermann, A.; Cavalier, E.; Pieber, T.R.; Lappe, J.M.; Grant, W.B.; et al. Vitamin D, cardiovascular disease and mortality. Clin. Endocrinol. (Oxf.) 2011, 75, 575–584.

11. Kunutsor, S.K.; Apekey, T.A.; Steur, M. Vitamin D and risk of future hypertension: Meta-analysis of 283,537 participants. Eur. J. Epidemiol. 2013, 28, 205–221.

12. Raina A, Allai MS, Shah ZA, Changal KH, Raina MA, Bhat FA. Association of low levels of vitamin D with chronic stable angina: A prospective case-control study. North Am J Med Sci 2016;8:143-50

13. Syal SK, Kapoor A, Bhatia E, Sinha A, Kumar S, Tewari S, et al. Vitamin D deficiency, coronary artery disease, and endothelial dysfunction: Observations from a coronary angiographic study in Indian patients. J Invasive Cardiol 2012;24:385-9

14. Lee JH, Okefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficienc an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol. 2008;52:1949–56.

15. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503–11

16. Siadat ZD1, Kiani K, Sadeghi M, Shariat AS, Farajzadegan Z, Kheirmand M. Association of vitamin D deficiency and coronary artery disease with cardiovascular risk factors. J Res Med Sci. 2012 Nov;17(11):1052-5.

17. Yusupov, E. Li-Ng, M. Pollack, S. Yeh, J. K. Mikhail, M. Aloia, J. F. Vitamin d and serum cytokines in a randomized clinical trial. Int J Endocrinol. 2010; 2010

18. Zittermann, A. Koerfer, R. Vitamin D in the prevention and treatment of coronary heart disease. Curr Opin Clin Nutr Metab Care. 2008 Nov; 11 (6): 752-7.

19. Targher, G. Bertolini, L. Padovani, R. Zenari, L. Scala, L. Cigolini, M. Arcaro, G. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. Clin Endocrinol (Oxf). 2006 Nov; 65 (5): 593-7.

20. Reddy Vanga, S. Good, M. Howard, P. A. Vacek, J. L. Role of vitamin D in cardiovascular health. Am J Cardiol. 2010 Sep 15; 106 (6): 798-805.

21. Pittas, A. G. Chung, M. Trikalinos, T. Mitri, J. Brendel, M. Patel, K. Lichtenstein, A. H. Lau, J. Balk, E. M. Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med. 2010 Mar 2; 152 (5): 307-14.

22. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure.Lancet. 1998;352:709–10.

23. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr. 2004;79:820–5.

24. Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes Care.2006;29:722–4.

25. Targher G, Bertolini L, Padovani R, Zenari L, Scala L, Cigolini M, et al. Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. Clin Endocrinol.2006;65:593–7.

26. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503–11.