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C0-RRELATION OF VITAMIN D SERUM LEVEL WITH ACUTE CORONARY SYNDROME AND MORTALITY -A PROSPECTIVE STUDY AT TERTIARY CARE HOSPITAL FROM CENTRAL INDIA

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ABSTRACT
In this study, we aimed to find out correlation of vitamin D level with acute coronary syndrome and mortality Coronary artery disease and cardiovascular death is associated with Vitamin D deficiency. Vitamin D deficiency is associated with endothelial dysfunction which plays an important role in the pathogenesis of coronary artery disease. In this study, it is aimed to assess serum 25 (OH) vitamin D and its correlation with acute coronary syndrome and analyse the vitamin D status of the study population. Serum 25 (OH) vitamin D levels were measured in 400 cases of acute coronary syndrome and 400 matched controls. The association of vitamin D deficiency with other parameters such as age, gender, body mass index, lipid profile etc were also analysed. There were 64% of the ACS cases deficient in Vitamin D Vitamin D deficiency may be an independent and potentially modifiable cardiovascular risk factor that can be easily diagnosed and corrected.

KEYWORDS: Acute coronary syndrome, Coronary Artery Disease, Vitamin D Deficiency.

INTRODUCTION

Vitamin D is metabolized by hepatic 25-hydroxylase then renal 1a-hydroxylase into its active form, calcitriol, which exerts its function on the vitamin D receptor (VDR) in nearly 30 different tissues.[1] Most of the nutritional requirements of vitamin D are derived from cutaneous solar ultraviolet radiation (80–100%)[2] and to a lesser extent from foods naturally containing or fortified with vitamin D.[3] The best measurement for vitamin D status is its metabolite 25-hydroxyvitamin D (25[OH]D) level.[4]

Vitamin D deficiency has been linked to several health outcomes[5,6] including musculoskeletal (rickets, bone fractures, osteomalacia, osteopenia, osteoporosis and muscle weakness)[3] and non-skeletal complications.[6] Non-skeletal complications include cardiovascular diseases and risk factors[8] such as congestive heart failure[9], impaired systolic and diastolic function[11], myocardial infarction[11], peripheral vascular disease[14], abdominal aortic aneurysm in older men[13], nonvalvular AF[14,15] and hypertension.[13] In addition, it was also associated with tuberculosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, cancers[1,2], schizophrenia[2], depression, cognitive deficits[17], common obesity[18], non-alcoholic fatty liver disease[19], cystic fibrosis[20], burn injuries[21], type 1 diabetes[4], type 2 diabetes[2,3], insulin resistance and metabolic syndrom25,e.[26,27]

Vitamin D deficiency is widespread, the lowest vitamin D levels are commonly found in regions such as the Middle East and South Asia and the main risk factors were attributed to elderly women, higher latitude, winter season, less sunlight exposure, skin pigmentation, dietary intake and low vitamin D fortified foods.[27] It was estimated that the prevalence of vitamin D deficiency is approximately 30–50% of the general population.[28] Furthermore, vitamin D deficiency is still common in sunshine countries.[29] In a large Middle Eastern study of 60,979 patients from 136 countries with yearlong sunlight, 82.5% of studied patients were found to have vitamin D insufficiency.[30,31]

There is an epidemic of vitamin D deficiency worldwide, which represents a major factor of many chronic diseases and has led some authors to suggest annual vitamin D measurement coupled with adequate intake and greater awareness of its consequences[4,31] In the United States, there was an increasing prevalence of vitamin D deficiency observed from a sample of 18,158 individuals between 1988 and 1994 compared with a sample of

20,289 individuals between 2000 and 2004 with 5–9 nmol/l decrease in vitamin D levels.[32]
Vitamin D levels were found to be lowest in Blacks, followed by Hispanics and Chinese, and adequate in Whites (Multi-Ethnic Study of Atherosclerosis MESA).[33] Another study done by Yetley in 2008 demonstrated that non-Hispanic blacks and Mexican Americans tend to have lower levels of vitamin D in comparison with non-Hispanic whites.[34] He also found vitamin D to be significantly lower among obese and non-college educated individuals, as well as those with poor health statuses, hypertension, low high-density lipoprotein levels and low milk consumption. Furthermore, the level of vitamin D deficiency was found to be alarmingly lower in winter and spring in a study done in British adults.[38]

Vitamin D and cardiovascular diseases
Vitamin D deficiency has been linked to several cardiovascular risk factors.[36,37] Through increased renin and angiotensin II synthesis, vitamin D deficiency can increase the production of reactive oxygen species and G protein RhoA, resulting in inhibition of the pathways necessary for intracellular glucose transporter and thus the development of insulin resistance and metabolic syndrome.[25] In addition, direct effects of vitamin D upon smooth muscle calcification and proliferation could contribute to their effects on cardiovascular health.[39] In the Inter99 study of 6784 individuals, high vitamin D level was associated with a favorable lipid profile and lower incidence of metabolic syndrome.[39]

Furthermore, in an analysis of NHANES III 1988–1994, low vitamin D was associated with cardiovascular disease (CVD)[7,33,34] and select CVD risk factors, including diabetes mellitus (DM), obesity, and hypertriglyceridemia.[24] In a prospective nested case-control study between 1993 and 1999 of 18,225 US men (Health Professionals Follow-Up Study), low vitamin D was associated with a higher risk of myocardial infarction in comparison with sufficient 25(OH)D after multivariate adjustment.[11] Kim and colleagues have found a high prevalence of hypovitaminosis D in individuals with cardiovascular diseases, namely coronary heart disease and heart failure, after controlling for age, race and gender, using data from NHANES 2001–2004.[8,37,38]

Additional prospective study of the Integrated Intermountain Healthcare system database of 41,504 patients has shown an association between vitamin D deficiency and an increase in the prevalence of DM, HTN, hyperlipidemia, and peripheral vascular disease (PVD) ($P < 0.0001$) as well as with incident death, heart failure, coronary artery disease/myocardial infarction, stroke and their composite.[40,41] Also, low serum 25(OH)D was identified as casually associated with increased risk for CVD on the basis of Hill's criteria for causality in a biological system.[41] In a meta-analysis of 19 prospective studies in 65,994 participants, Wang et al. have demonstrated a linear and inverse association between circulating vitamin D level and risk of cardiovascular diseases.[42]

The association of vitamin D deficiency with coronary artery diseases (CADs) have been investigated in many studies.[43,44,45,46] In 1978, a Danish study found that low vitamin D levels were significantly associated with angina and myocardial infarction.[47] In a multicenter US cohort study evaluating patients admitted with acute coronary syndrome (ACS), about 95% of patients were found to have low vitamin D levels.[47] In a study conducted by Dziedzie et al., low vitamin D levels were observed in patients with myocardial infarction history.[48] In a case-control study ($n = 240$), Roy et al. reported that severe vitamin D deficiency was associated with increased risk of acute myocardial infarction after adjusting for risk factors.[49] Similar findings were reported from Health Professionals Follow-up Study which included 18,225 participants. In this study, at 10-year follow-up, participants with normal vitamin D level had about half the risk of myocardial infarction.[11] In a large prospective study ($n = 10,170$), low vitamin D levels were found to be associated with increased risk of ischemic heart disease, myocardial infarction, and early death during 9 years of follow-up.[50] Additionally, in a meta-analysis of 18 studies, low vitamin D levels were found to have an increased risk of ischemic heart disease and early death.[50]

MATERIAL AND METHOD

A total of 400 consecutive patients with ACS were studied at Dr RML IMS Lucknow. The inclusion criterion was ACS and the diagnosis was made on the basis of a compatible clinical profile in combination with electrocardiographic, echocardiographic and serum troponin[9,10] while that of T2DM was made using the American Diabetes Association criteria.[11] Patients were excluded if they had chronic kidney disease, heart failure, primary hyperparathyroidism, active malignant disease, and uncontrolled hyperthyroidism or hypothyroidism. No patients were on vitamin D supplements.

We performed a prospective observational study in the patients from central India reporting to Dr RMLInstitute of Medical Sciences(DR RML IMS,LKO),India-226010. All Patients aged 45 years and above with Acute coronary syndrome over period between Apr 2017 to Dec2019(33 month) were included in the study population.Biochemical analysis of blood was performed on fresh samples at DR RML IMS LKO laboratories. These laboratories are authorized to perform tests according to the international quality standard.

Variables

Independent variables

The main predictor in our study was serum 25(OH)vitamin D level recorded during the study period, with values categorized into 4 groups (<10, 10–20, 20–

30, and >30 ng/mL, respectively). The demographic covariates assessed were age group (45–64, 65–84 and >85 y), gender and population sector (general population). The 2 subgroups were targeted because they are assumed to be prone to have insufficient serum Viamin D. Clinical covariates included were body mass index (BMI; <25, 25–30, and >30 kg/m^2), smoking status (never, former or current), uncontrolled diabetes (glycosylated hemoglobin [HbA1C] groups <7, 7–9, >9), low-density lipoprotein (LDL) level (categorized as <100, ≥100), systolic blood pressure (BP; <140, 140–160 or >160.

Statistical analysis

The distribution of the sociodemographic and clinical characteristics was examined across the 4 vitamin D level groups in the study population and in the study population. Survival analysis, Kaplan-Meier and Cox proportional hazard regression were used to compare groups and estimate the hazard attributable to the combined outcome. Each participant was exposed from the time of the first vitamin D test and was right-censored on leaving the hospital at the end of the study period.

Kaplan-Meier survival curves were used to model the first occurrence of MACS between the first serum vitamin D assay and the end of the study period. Survival curves were generated for the 4 different serum vitamin concentrations for each age group and for the study population. Groups were compared using the logrank test to determine equivalence between strata.

Cox proportional hazard multivariable models generated hazard ratios (HR) to examine the nonlinear association between MACS and serum vitamin D levels between Apr 2017 to December 31, 2019, controlling for covariates that were significant in the univariate analyses (P <.05). A HR >1 is associated with an increased probability of MACS.All statistical analyses were performed using SPSS software version 21.0.

RESULT

Table 1: Descriptive Statistics of the Study Population.

	Subjects With Serum Vitamin D (ng/mL) Level in total patients(n-400)				
	<10	**10–20**	**20–30**	**>30 Total number of ACS(%)**	**ll**
Age					
45–64	58	56	52	50 216 (54%)	61
65–84	36	39	42	44 161(40.25%)	34
>85	8	5	5	5 23(5.75%)	5
Total				n-400	86 2
Gender					
Males	23	31	34	36 **n- 124 (31%)**	46
Females	77	69	66	64 **n-276 (69%)**	
Total				**no-400**	54
History of IHD					
No	96	95	95	94 n-380(95%)	95
Yes	5	5	5	5 20(5%) n-400	5
Blood pressure					
<140	84	86	88	89 n-347(86.75)	81
140–160	12	11	10	9 n-52(10.50%)	15
>160	4	3	2	2 n-11(2.75%)	4
LDL, mg/dL					
<100	37	37	41	49 n-164 (41%)	34
>100	63	63	59	51 n-236 (59%)	66
HgbA1C					
Nondiabetic	46	53	57	58 n-214 (53.5%)	73
<7	38	36	35	36 n-145(36.25%)	19
7–9	11	8	6	5 n-30 (7.5%)	6
>9	5	3	1	1 n-10(4%)	2
Smoking status					
Never	77	73	74	74 n-294(73.50%)	72
Former	9	13	13	14 n-49(12.25%)	9
Current	14 %)	14	13	12 n-39(9.75%)	19
BMI					
<25	24	28	36	44 n-132(33%)	27
25–30	35	40	41	39 n-155 (38.7%))	41

>30	41	32	23	17 n-113(28.25%)	32

Table 2: Multivariate Analysis of the Hazard Ratio for MACS among the Studied Population.

	β (SE)	Hazard Ratio [95% CI]	*P* Value
Serum vitamin D, ng/mL			
<10	0.63 (0.02)	1.91 (1.83–2.00)	<.001
10–20	0.23 (0.02)	1.26 (1.22–1.31)	<.001
20–30		1.40(1.12-1.20	<.002
>30	0.12 (0.04)	1.13 (1.04–1.22)	<.003
Age group			
45–64	1.25(0.01)	2.62(2.65-2.78)	<.001
65–84	1.31 (0.02)	3.71 (3.55–3.87)	<.001
>85	2.61 (0.03)	13.6 (12.9–14.3)	<.001
Gender			
Female	0.49(0.018)	1.65(1.63-1.72)	<.001
Male	0.58 (0.02)	1.79 (1.73–1.85)	<.001
History of IHD			
No		1 (Reference)	
Yes	0.48 (0.02)	1.61 (1.54–1.69)	<.001
Blood pressure			
<140	0.06(0.018)	1.05(1.018-1.09)	<.002
140–160	0.07 (0.02)	1.07 (1.02–1.12)	<.003
>160	0.24 (0.04)	1.27 (1.18–1.36)	<.001
LDL, mg/dL			
<100	0.10(0.02)	0.77(0.71-0.80)	<.001
>100	−0.14 (0.02)	0.87 (0.83–0.91)	<.001
HgbA1C			
Nondiabetic	0.20(.02)	1.20(1.14-1.16)	<0.001
<7	0.22 (0.02)	1.24 (1.20–1.28)	<.001
7–9	0.53 (0.03)	1.70 (1.61–1.79)	<.001
>9	0.86 (0.04)	2.36 (2.17–2.55)	<.001
Smoking status			
Never	0.09(0.018)	1.09(1.04-1.10)	<.001
Former	0.10 (0.02)	1.10 (1.06–1.15)	<.001
Current	0.34 (0.03)	1.40 (1.34–1.47)	<.001
BMI			
<25		1 (Reference)	<.001
25–30	−0.22 (0.02)	0.80 (0.77–0.83)	<.001
>30	−0.14 (0.02)	0.87 (0.83–0.91)	

A subdivision of the serum vitamin D concentration levels found that the vitamin D level above 30 ng/mL was associated with the lowest risk of having a MACS This model was then stratified by gender; the results for men and women were similar, although the relative risk of MACS among those with the lowest vitamin D levels (below 10 ng/mL), as compared to normal levels, was greater among women. The lowest HR for MACS was found in those whose vitamin D level was above 30 ng/mL for both genders.

DISCUSSION

In our comprehensive database, we have determined the safe range of serum vitamin D levels and suggested a threshold for low vitamin D, beyond which there are at increased risk for MACS (all-cause mortality and/or cardiovascular events). We defined a safe level of serum vitamin D more than 30 ng/mL. This finding is also corroborated by other studies, which describe a similar level of vitamin D level, centered around 30 to 40 ng/mL.[2,9,35] This safe range also applies to all-cause mortality; in the MACS outcome, 76% of the events were due to acute coronary with Vitamin D bellow 30 ng/mL syndrome, whereas 24% pertained to all-cause mortality.

Our findings also corroborated the expected association between typical risk factors (and potential confounders), such as age, gender, IHD history, hypertension, serum cholesterol, diabetes, smoking, and BMI, and the risk of MACS Furthermore, only about 35% of the patients fell into the safe vitamin D range, which is further corroborated by other studies.[9,16,36] Furthermore, women were tested for serum vitamin D at a rate nearly twice that of men. This is not surprising, because women tend

to visit their family doctors more. Compared to other studies, the duration of our study (33 month) may be too short to capture acute coronary syndrome and mortality related to vitamin D blood levels adequately. Finally, individual polymorphic effects may affect the optimal serum vitamin-D, which may require personalized targets.

In conclusion, we identified a safe target level of above 30 ng/mL for serum vitamin D, which minimizes the risk for acute coronary syndrome and all-cause mortality, during a 33-month time period.

A 12-year prospective cohort in the United States showed that those with vitamin D <30 ng/mL had a higher HR than those with >30 ngmLFurthermore, the odds ratio of >2.3 associated with low serum levels of vitamin D for acute coronary syndrome described by Zitterman etal[36] further supports the burden and the risk of low serum vitamin D concentrations.[40.41]

Abbreviations

- **BMI-**body mass index.
- **BP-**blood pressure.
- **CI-**confidence interval.
- **HbA1C-**glycosylated hemoglobin.
- **HR-**hazard ratios.
- **IHD-**ischemic heart disease.
- **LDL-**low-density lipoprotein.
- **MACS-**mortality in acute coronary syndrome.
- **QC-**quality control.

CONCLUSION

Vitamin D in the more than 30 ng/mL was associated with the lowest risk for morbidity and mortality and less than 10ng/mL with highest morbidity and mortality The hazard ratio above more than 30ng/mL and and below 10ng/mL increases significantly.

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REFERENCE

1. Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? *Br J Nutr*, 2003; 89: 552–572.
2. Kimlin MG. Geographic location and vitamin D synthesis. *Mol Aspects Med*, 2008; 29: 453–461.
3. Holick MF. Vitamin D deficiency. *N Engl J Med*, 2007; 357: 266–281.
4. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*, 2004; 79: 362–371.
5. Basit S. Vitamin D in health and disease: a literature review. *Br J Biomed Sci*, 2013; 70: 161–172.
6. Judd SE, Tangpricha V. Vitamin D Deficiency and Risk for cardiovascular disease. *Am J Med Sci*, 2010; 117: 503–511.
7. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the third National Health and nutrition examination survey. *Atherosclerosis*, 2009; 205: 255–260.
8. Kim D, Sabour S, Sagar U, Adams S, Whellan D. Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and nutrition examination survey 2001 to 2004) *Am J Cardiol*, 2008; 102: 1540–1544.
9. Zittermann A, Schleithoff SS, Koerfer R. Vitamin D insufficiency in congestive heart failure: why and what to do about it? *Heart Fail Rev*, 2006; 11: 25–33.
10. Pekkanen MP, Ukkola O, Hedberg P, Piira OP, Lepojärvi S, Lumme J, Tulppo M, Huikuri H. Serum 25-hydroxyvitamin D is associated with major cardiovascular risk factors and cardiac structure and function in patients with coronary artery disease. *Nutr Metab Cardiovasc Dis*,2015; 25: 471–478.
11. Giovannucci E, Liu Y, Hollis B, Rimm E. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Arch Intern Med*, 2008; 168: 1174–1180.
12. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease: a narrative review. *Ann Intern Med*, 2011; 155: 820–826.
13. Wong YYE, Flicker L, Yeap BB, McCaul KA, Hankey GJ, Norman PE. Is hypovitaminosis D associated with abdominal aortic aneurysm, and is there a dose-response relationship? *Eur J Vasc Endovasc Surg*, 2013; 45: 657–664.
14. Demir M, Uyan U, Melek M. The effects of vitamin D deficiency on atrial fibrillation. *Clin Appl Thromb Hemost*, 2014; 20: 98–103.
15. Ozcan OU, Gurlek A, Gursoy E, Gerede DM, Erol C. Relation of vitamin D deficiency and new-onset atrial fibrillation among hypertensive patients. *J Am Soc Hypertens*, 2015; 9: 307–312.
16. Pavlovic D, Josipovic J, Pavlovic N. Vitamin D and hypertension. *Period Biol*, 2011; 113: 299–302.
17. Barnard K, Colón-emeric C. Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition. *Am J Geriatr Pharmacother*, 2010; 8: 4–33.
18. Foss YJ. Vitamin D deficiency is the cause of common obesity. *Med Hypotheses*, 2009; 72: 314–321.
19. Küçükazman M, Ata N, Dal K, Yeniova A, Kefeli A, Basyigit S, Aktas B, Akin K, Ağladıoğlu K, Üre Ö, Topal F, Nazligül Y, Beyan E, Ertugrul D. The association of vitamin D deficiency with non-alcoholic fatty liver disease. *Clin (Sao Paulo)*, 2014; 69: 542–546.
20. Donovan DS, Papadopoulos A, Staron RB, Addesso V, Schulman L, Gregor CMC, Cosman F, Lindsay RL, Shane E. Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung

disease. *Am J Respir Crit Care Med*, 1998; 157: 1892–1899.
21. Klein GL, Chen TC, Holick MF, Langman CB, Price H, Celis MM, Herndon DN. Synthesis of vitamin D in skin after burns. *Lancet*, 2004; 363: 291–292.
22. Liu E, Meigs JB, Pittas AG, Economos CD, Mckeown NM, Booth SL, Jacques PF. Predicted 25-hydroxyvitamin D score and incident type 2 diabetes in the Framingham offspring study. *Am J Clin Nutr*, 2010; 91: 1627–1633.
23. Baz-hecht M, Goldfine AB. The impact of vitamin D deficiency on diabetes and cardiovascular risk. *Curr Opin Endocrinol Diabetes Obes*, 2010; 17: 113–119.
24. Martini LA, Wood RJ. Vitamin D status and the metabolic syndrome. *Nutr Rev*, 2006; 64: 479–486.
25. Rammos G, Tseke P, Ziakka S. Vitamin D, the renin-angiotensin system, and insulin resistance. *Int Urol Nephrol*, 2008; 40: 419–426.
26. Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. *Am J Clin Nutr*, 2004; 79: 820–825.
27. Mithal A, Wahl DA, Burckhardt P, Eisman JA, Fuleihan GE, Josse RG, Lips P, Morales-Torres J. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int*, 2009; 20: 1807–1820.
28. Lee JH, Keefe JHO, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol*, 2017; 52: 1949–1956.
29. Prentice A. Vitamin D deficiency: a global perspective. *Nutr Rev*, 2008; 66: 153–164.
30. Haq A, Svobodová J, Imran S, Stanford C, Razzaque MS. Journal of Steroid Biochemistry & Molecular Biology Vitamin D de fi ciency: A single centre analysis of patients from 136 countries. *J Steroid Biochem Mol Biol*, 2016; 164: 209–213.
31. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. *Nutr J*, 2010; 9: 1–13.
32. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano F, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. *Am J Clin Nutr*, 2008; 88: 1519–1527.
33. Robinson-cohen C, Hoofnagle AN, Ix JH, Kestenbaum R, de Boer IH. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. *JAMA*, 2013; 310: 179–188.
34. Yetley EA. Assessing the vitamin D status of the US population. *Am J Clin Nutr*, 2008; 88: 558s–564s.
35. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. *Am J Clin Nutr*, 2007; 85: 860–868.
36. Lavie CJ, Lee JH, Milani RV. Vitamin D and Cardiovascular disease: will it live up to its hype? *J Am Coll Cardiol*, 2011; 58: 1547–1556.
37. Wang L, Song Y, Manson J, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal S, Barrett-Connor E, Zhang C, Eaton C, May H, Anderson J, Sesso H. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes*, 2012; 5: 819–829.
38. Heston TF. Hypovitaminosis D in hypertension. *South Med J*, 2010; 103: 723–724.
39. Skaaby T, Nystrup L, Pisinger C, Jørgensen T, Thuesen B, Fenger M, Linneberg A. Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population. *Cardiology*, 2012; 123: 62–70.
40. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, Carlquist JF, Lappé DL, Muhlestein JB. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol*, 2010; 106: 963–968.
41. Weyland PG, Grant WB, Howie-Esquivel J. Does sufficient evidence exist to support a causal association between vitamin D status and cardiovascular disease risk? An assessment using Hill's criteria for causality. *Nutrients*, 2014; 6: 3403–3430.
42. Pilz S, Tomaschitz A, Drechsler C, Zittermann A, Dekker J, März W. Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. *Curr Drug Targets*, 2011; 12: 88–96.
43. Milazzo V, De Metrio M, Cosentino N, Marenzi G, Tremoli E. Vitamin D and acute myocardial infarction. *World J Cardiol*, 2017; 9: 14–20.
44. Anderson J, May H, Horne B, Bair T, Hall N, Carlquist J, Lappé D, Muhlestein J. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. *Am J Cardiol*, 2010; 106: 963–968.
45. Aleksova A, Belfiore R, Carriere C, Kassem S, La Carrubba S, Barbati G, Sinagra G. Vitamin D deficiency in patients with acute myocardial infarction: an Italian single-center study. *Int J Vitam Nutr Res*, 2015; 85: 23–30.
46. Lund B, Badskjaer J, Lund B, Soerensen O. Vitamin D and ischaemic heart disease. *Horm Metab Res*, 1978; 10: 553–556.
47. Lee JH, Gadi R, Spertus JA, Tang F, O'Keefe JH. Prevalence of vitamin D deficiency in patients with acute myocardial infarction. *Am J Cardiol.* 2011; 107: 1636–1638.
48. Dziedzic E, Gąsior J, Pawłowski M, Dąbrowski M. Association of Vitamin D Deficiency and Degree of coronary artery disease in cardiac patients with type 2 diabetes. *J Diabetes Res*, 2017; 2017: 1–11.
49. Roy A, Lakshmy R, Tarik M, Tandon N, Reddy KS, Prabhakaran D. Independent association of severe

vitamin D deficiency as a risk of acute myocardial infarction in Indians. *Indian Heart J*, 2015; 67: 27–32.

50. Brøndum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG. 25-Hydroxyvitamin D levels and risk of ischemic heart disease, myocardial infarction, and early death, Arter. *Thromb Vasc Biol*, 2012; 32: 2794–2802.