Original Article

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Cardiology Section

Effect of Vitamin D on Anginal Episodes in Vitamin D Deficient Patients with Chronic Stable Angina on Medical Management

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ABSTRACT

Introduction: Vitamin D deficiency has been found to contribute to various cardiac conditions, such as hypertension, coronary artery disease, stroke, and atherosclerosis. However, the clinical cardiovascular benefits after short term supplementation have not been reported.

Aim: To study the beneficial effect of Vitamin D supplementation on angina episodes in Vitamin D deficient patients with chronic stable angina on medical management.

Materials and Methods: A total of 40 patients were studied with group 1 (20 patients) with low Vitamin D levels and group 2 with normal Vitamin D levels. 60000 IU of Vitamin D supplementation was given every week for 8 weeks in group 1. Frequency of anginal episodes and use of sub-lingual nitrates were compared at base-line and after 8 weeks post supplementation.

Results: Significant 20% ($p < 0.05$) reduction in anginal episodes and 17.24% ($p < 0.05$) reduction in use of sub-lingual nitrates was noted in group1 after Vitamin D supplementation. The benefits were independent of BP, heart rate and medications, thus, attributing to supplementation. No significant change was noted in group 2.

Conclusion: Cardiovascular patients need to be evaluated for Vitamin D deficiency. Supplementation to correct Vitamin D levels may have additional cardiovascular benefits like reduction in angina episodes.

Keywords: Angina pectoris, Cardio vascular disease, Vitamin D deficiency

INTRODUCTION

Sunshine Vitamin formerly attributed with bone health is now under rigorous investigation due to expression of Vitamin D receptors found commonly in body tissues regulating gene transcription of many inflammatory factors and immune cells expression that could potentially contribute to chronic disease prognosis, recovery, or mortality [1].

Biological effects of Vitamin D are likely to be mediated by calcitriol, whether produced locally in tissues or diffusion from the blood. The fostering mechanism could be either direct, that is, when Vitamin D receptor expression affects local production of $1,25(OH)_2D3$ in pancreatic beta cells or indirect via regulation of calcium homeostasis and calcium flux through membranes [2]. Vitamin D deficiency has been found to contribute to the development of various cardiometabolic conditions such as hypertension, diabetes, and coronary artery disease. The connection between cardiovascular homeostasis and Vitamin D was first accomplished as early as 1987 [3]. Low 25 $(OH)_2$ D3 is a risk factor for stroke. Persons with low levels who are genetically predisposed to high Diastolic blood pressure (DBP) who therefore, have lower predicted bioavailable Vitamin D are at greater risk for stroke [4]. Earlier findings also suggest that serum Vitamin D levels are inversely associated with atherosclerosis in Chinese middle aged and elderly men [5]. The Vitamin D receptor has been found in many target tissues includes all the major cardiovascular cell types: endothelial cells, vascular smooth muscle cells, cardiomyocytes, platelets, and most immune cells. Gene expression is dependent on tissue specific co-activators and co-suppressors. It is estimated that the Vitamin D receptor activation may regulate about 5% of the total genome, pathway analysis suggesting effects upon regulation of cell proliferation, differentiation, apoptosis, oxidative stress, membrane transport, matrix homeostasis, tissue mineralization and cell adhesion [6-10].

Vitamin D exerts protective effects on endothelial activation/dysfunction, an inflammatory process that precedes atherosclerosis, through several mechanisms both genomic and non genomic. Among the main alterations ascribable to endothelial dysfunction are the reduced availability of nitric oxide and increased production of reactive oxygen species. Vitamin D found to stimulate nitric oxide production in human umbilical vein endothelial cells. A growing body of evidence supports that Vitamin D is a potent endocrine suppressor of Rennin angiotensin aldasterone system (RAAS) [11]. Liew et al., have studied levels of $25(OH)_2$ D in patients undergoing coronary angiogram. There was no correlation between Vitamin D and ankle brachial index or pulse wave velocity, however, low serum 25-hydroxy Vitamin D levels were associated with the presence and extent of angiographic CAD but not arterial stiffness or Peripheral artery disease (PAD) [12]. Oz et al., have reported effect of 25(OH)D levels and epicardial blood flow rate, subclinical atherosclerosis, and endothelial dysfunction. The incidence of slow coronary flow rate was significantly higher in the Vitamin D deficient group and after adjusting for cardiovascular disease risk factors, Vitamin D insufficiency was an independent risk factor for slow flow [13]. The clinical benefit of Vitamin D supplementation in chronic stable angina patients with Vitamin D insufficiency has not been reported.

MATERIALS AND METHODS

The study was conducted in Rajiv Gandhi Super Speciality Hospital, Raichur Institute of Medical Sciences, Raichur, Karnataka, India between November 2013 and November 2015. Patients attending the outpatient clinics of investigators were enrolled after informed consent. Patients with known CAD (previous myocardial infarction, angioplasty, coronary artery bypass grafting) with chronic stable angina on medical management were included. Patients with recent acute coronary syndromes, recent Vitamin D supplementation,

scheduled for revascularization were excluded from the study. All patients underwent Vitamin D estimation. They were divided into two groups (group 1 with low Vitamin D levels and group 2 with normal Vitamin D levels). Vitamin D supplementation (60000 IU chewable tablets every week for 8 weeks) was given to group 1. All other medications were continued as per treating physician's discretion.

All patients age, sex, risk factors (smoking, diabetes, hypertension, dyslipidemia, obesity), height, weight, body mass index, drug status, angina episodes, use of sub-lingual nitrates, ECG, echocardiography were recorded. Patients were assessed between 8 to 10 weeks.

Vitamin D total (25 hydroxy Vitamin D) was estimated by electro-Chemiluminiscence immuno Assay (ECLIA). Vitamin D level > 30 ng/ml was considered optimal, < 30 ng/ml was considered insufficient, < 10 ng/ml severe deficiency was considered.

This study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the hospital. Written informed consents were obtained from all the patients prior to their inclusion into the study.

STATISTICAL ANALYSIS

The primary objective was to assess the decrease in angina episodes after Vitamin D supplementation. The basic descriptive statistics were calculated and expressed as mean ± SD. The data at baseline and after supplementation were compared by using t-tests with a level of significance of 0.05. The statistical analysis was performed by using the software, Minitab 16.

RESULTS

During the study period [Table/Fig-1], total 40 patients were included, 20 patients with low levels of Vitamin D (group 1) and 20 patients with normal levels of Vitamin D (group 2). Group 1 and Group 2 were comparable in regard to age, sex and risk factors, and angina episodes. Vitamin D levels were 16.11±10.22 in group 1 and 39.10 ± 2.89ng/ml in group 2 and five patients had severe Vitamin D deficiency. After 8 weeks of Vitamin D supplementation in group 1 there was significant reduction in angina episodes, 20% from baseline, p<0.05, and use of sub-lingual nitrate, 17.24% reduction from baseline, p <0.05 [Table/Fig-2]. There was no significant difference in heart rate and BP after Vitamin D supplementation. There was no significant difference in angina episodes in group 2 at the end of the study.

DISCUSSION

Involvement of Vitamin D in numerous imperative metabolic pathways has been found to mediate health benefits by reducing risk through its effects on confounders in cardiovascular disease.

	Group 1(20)	Group 2 (20)	p
Age (mean ± SD), years	59.65±3.91	58.35±4.69	NS
Sex (M:F)	11:9	12:8	
Diabetes (N, %)	05 (25)	06 (33.3)	
HTN (N, %)	06 (33.3)	05 (25)	
Current smoking (N, %)	4 (20)	05 (25)	
SBP (mean ± SD) mmHg	133.05±7.83	132.10±6.94	NS
DBP (mean ± SD) mmHg	81.35±3.52	80.10±5.52	NS
LVEF (%)	40.10±3.90	40.25±4.51	NS
Heart rate (per minute)	72.00±6.55	71.40±7.19	NS
Anginal episodes (cumulative 14 days)	560	549	NS
Sublingual nitrate use (cumulative 14 days)	290	301	NS
Vitamin D (ng/ml)	16.11±10.22	39.10±2.89	<0.05

[Table/Fig-1]: Baseline characteristics.

	Group 1 before supplementation	Group 1 after supplementation	Group 2 after follow up	p Group 1 before vs after	p Group 1 (after) vs Group 2 follow up
SBP (mean ± SD) mmHg	133.05±7.83	133.15±7.93	131.10±6.84	NS	NS
DBP (mean ± SD) mmHg	81.35±3.52	81.65±3.62	80.20±5.42	NS	NS
Heart rate (per minute)	72.00±6.55	71.00±6.45	71.50±7.29	NS	NS
Anginal episodes (cumulative 14 days)	560	448	535	<0.05	<0.05
Sublingual nitrate use (cumulative 14 days)	290	240	298	<0.05	<0.05

[Table/Fig-2]: After supplementation.

Signalling via both Vitamin D and the Rennin Angiotensin System (RAS) plays important roles in physiological processes. Evidence has mounted linking cardiovascular disease to both increased activity of RAS and Vitamin D deficiency. Several studies have established functional relationships between the RAS and Vitamin D. Defective Vitamin D signalling can promote vascular damage by inducing premature senescence of smooth muscle cells due to elevated local production of angiotensin II and reactive oxygen species and up regulation of tumor suppressor [14]. Oh J et al., in their model have shown deletion of Vitamin D receptors sufficient to programme a sustained, pro-atherogenic monocyte/macrophage phenotype, confirmed by the transplantability of the cardiometabolic outcome. Chronic excess of cytokines, glucose, and lipid triggers Endoplasmic reticulum (ER) stress, provoking inflammatory signalling, macrophage cholesterol uptake, or macrophage death, key mechanisms in insulin resistance and atherosclerosis [15].

Our study has suggested beneficial effect of Vitamin D supplementation in chronic stable angina patients who have low Vitamin D levels, which is independent of changes in BP and /or heart rate. The significant change compared to baseline as well as with group 2 having normal Vitamin levels points definitely towards effect of Vitamin D supplementation. The beneficial effects may be mediated by multiple mechanisms as previously described [14-19]. The incidence of slow coronary flow rate was significantly higher in the Vitamin D deficient group and after adjusting for cardiovascular disease risk factors Vitamin D insufficiency was an independent risk factor for slow flow [13]. Whether slow flow noticed in Vitamin D deficient patients improves after adequate supplementation needs to be studied angiographically.

Earlier studies have reported that Vitamin D deficiency may lead to impaired vascular function and abnormalities in central arterial stiffness. Effect of two different doses of Vitamin on arterial stiffness was reported by Macgreevy et al., [20]. A total of 119 known Vitamin D deficient subjects were randomized to receive 50,000 IU or 1,00,000 IU single IM Vitamin D3. In the group that received 1,00,000 IU median pulse wave velocity decreased significantly after 8 weeks. A mean decrease in augmentation index which is a measure of systemic stiffness was also noted in their study [20]. In a double blind randomized placebo controlled study Martin et al., evaluated the effect of a monthly dose of 1,00,00 IU of Vitamin D for three months. There was significant increase in the serum 25(OH)D levels. The increase in 25(OH)D was associated with a significant decrease in Parathyroid Hormone (PTH), mean urinary isoprostane and adipocyte cytokine expression. There was significant decrease in augmentation index among the participants with the highest tertile of urinary isoprostane [21]. We have used 60000 IU per week for 8 weeks which is a preferred

method at present. Among the Vitamin D3 studies, participants in the intervention arm have received Vitamin D3 supplementation ranging from 10 to 6000 IU per day, and oral tablets were the principle form of supplementation [22].

LIMITATION

Small sample size is a limitation of the study. Subjective assessment of angina episodes is not a hard end point. The objective assessment of angina with stress test or myocardial perfusion imaging is more useful in interpretation of results.

CONCLUSION

Vitamin D deficiency is very prevalent and modest improvements might make substantial health gains with a low risk of adverse outcome. Vitamin D deficiency has been associated with various cardiovascular conditions. Cardiovascular patients need to be evaluated for Vitamin D deficiency. Supplementation to correct Vitamin D levels may have additional cardiovascular benefits. More trials are needed in this direction.

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