ORIGINAL ARTICLE

Study of Correlation of Serum Vitamin D Levels with Arterial Stiffness and Cardiovascular Morbidity in Elderly Individuals of Western Rajasthan

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Abstract

Introduction: Vitamin D deficiency is highly prevalent condition in western countries as well as in India. Lower level of vitamin D is associated with increased arterial stiffness by activating renin–angiotensin–aldosterone system leading to increased cardiovascular morbidity and mortality including increased risk of coronary artery disease, stroke, peripheral vascular disease, hypertension, diabetes mellitus and metabolic syndrome. Our aim was to study the correlation between serum vitamin D level, various measures of arterial stiffness and cardiovascular morbidity in elderly individuals.

Material and Method: The present study was conducted in collaboration with Department of Medicine, Department of Cardiology and Regional Geriatric Centre, NPHCE, MDM Hospital attached to Dr. S.N. medical college Jodhpur. Total 100 elderly individuals 60 yrs and above attending hospital for minor short illness, acute illness or for routine health checkup or with acute coronary events are included in the study. Vitamin D level was assessed by chemiluminescent immunoassay. Pulse Wave Velocity was determined by Periscope.

Results: In subjects with coronary artery disease, 28.30% were vitamin D deficient, 49.05% were vitamin D insufficient and only 22.64% are vitamin D sufficient. In healthy subjects, 25.53% were vitamin D deficient, 23.40% were vitamin D insufficient and 51.04% were vitamin D sufficient. The difference between these groups was statistically highly significant. (p value-0.006). Various measures of arterial stiffness including Rt baPWV, Lt baPWV, cf PWV and pulse pressure are more in vitamin D deficient group as compared to vitamin D sufficient group. The difference was statistically significant.

Conclusion: Vitamin D deficiency is quite common condition in elderly individuals which besides its bone mineralization action is also involved in cardiovascular functions. Deficiency of vitamin D may cause increase in arterial stiffness and widening of pulse pressure which are the predictor of atherosclerosis and cardiovascular morbidity and mortality.

Abbreviation: NPHCE-national program for health care of elderly, Rt baPWV-Right brachio-ankle pulse wave velocity, Lt baPWV- left brachio-ankle pulse wave velocity, cfPWV- carotico-femoral pulse wave velocity

Introduction

Vitamin D deficiency is highly prevalent condition in western countries as well as in India.[1,2] However the best-characterized consequence of vitamin D deficiency involve the musculoskeletal system but many evidences suggests that low levels of vitamin D may adversely affect the cardiovascular system.[3]

There is accumulating evidences from previous studies[3,4] that suboptimal level of vitamin D is associated with increased arterial stiffness leading to cardiovascular morbidity and mortality including increased risk of coronary artery disease, stroke, peripheral vascular disease, hypertension, diabetes mellitus and metabolic syndrome. Vitamin D affects arterial stiffness by certain mechanism such as it affects vascular wall by regulating renin–angiotensin–aldosterone system (RAAS). Vitamin D inhibits renin gene expression by sequestering C-AMP response element binding protein, a necessary factor for transcription of renin mRNA. Vitamin D deficiency activates RAAS system, causes proliferation of vascular smooth muscle cells, activates macrophages invasion of vascular cell, promotes calcification and increased PTH release. These effects can be ameliorated by vitamin D supplementation. Rehman et al.[5] demonstrated that matrix metaloproteinase protein that contribute to aberrant cardiomyocytes remodeling in response to injury and atherosclerosis were up-regulated in vitamin D receptor knockout mice and impaired cardiac relaxation and contractility and developed left ventricular hypertrophy.

Vitamin D modulates endothelial function by decreasing expression of adhesion molecules, providing protection against advanced glycation products.[6]

Substantial evidence indicates that atherosclerosis is an inflammatory disease and inflammation plays a role in major CV disease events, and efforts to reduce inflammation may

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be warranted.[7] Low $25(OH)_2D$ and increased PTH levels increases the risk of inflammation, as documented by elevated levels of C-reactive protein and interleukin-10. Administration of $1,25(OH)_2D$ in the setting of vitamin D deficiency has been shown to down-regulate inflammatory biomarkers such as C-reactive protein.

In small clinical trials, vitamin D supplementation has shown reduction in blood pressure, left ventricular hypertrophy and inflammatory cytokines.[8] Population-based studies have partially, but not consistently, documented that low vitamin D status is associated with an increased risk of adverse cardiovascular events and cardiovascular mortality.[9] Meta-analyses support the finding that low 25-$(OH)_2$ D concentrations are associated with increased risk of cardiovascular diseases.[10]

However, data regarding correlation between vitamin D and arterial stiffness in elderly are lacking in context of Indian population. Our aim was to find out association between arterial stiffness and vitamin D level in elderly individuals in western Rajasthan.

Aims and Objectives

1. To study correlation between serum vitamin D level and cardiovascular morbidity.
2. To establish relationship between serum vitamin D level and various measures of arterial stiffness in elderly individuals.

Material and Method

The present study was conducted in collaboration with Department of Medicine, Department of Cardiology and Regional Geriatric Centre, NPHCE, MDM Hospital attached to Dr. S.N. medical college Jodhpur.

Participants, after making them understand study protocol and procedure, were asked to give written consent for study. It was conducted according to principles expressed in declaration of Helsinki.

Study Population

Present study was carried out in the group of elderly subjects (age>60yrs) attending MDM hospital for their acute illness (cardiac and noncardiac) or for routine health checkup.

Study Design

An observational cross-sectional hospital based study.

Inclusion Criteria

1. Healthy elderly people 60 yrs and above attending hospital for minor short illness, acute illness or for routine health checkup.
2. Elderly subjects 60 yrs and above presenting with acute coronary events.

Exclusion Criteria

1. Person <60 yr of age.
2. Previous known case of diabetes, hypertension, ischemic heart disease, chronic kidney disease, hepatic dysfunction, prior history of peripheral vascular disease, chronic obstructive pulmonary diseases, HIV etc
3. Persons on oral calcium, vitamin D, bisphosphonates supplementation, steroids treatment or on any other long term undefined medication.
4. Any past history of malignancy, sarcoidosis, tuberculosis, any chronic granulomatous diseases.

Methodology: After written informed consent from subjects comprehensive clinico-epidemiological data were collected. Diabetes, hypertension, hypercholesterolemia was defined as per ADA guidelines, JNC 8, and Adult Treatment Panel 4 respectively. Relevant laboratory investigations were done. Arterial stiffness, ABI and pulse wave velocity were accessed by Periscope – window based vascular analysis system. Vitamin D level was assessed by chemiluminescent immunoassay (CLIA).

Method: Pulse Wave Velocity was determined by Periscope[11] (M/S Genesis Medical System, Hyderabad, India). It is an 8-channel real time PC-based simultaneous acquisition and analysis system. It is dedicated hardware module connected to 4 ECG electrode and 4 blood pressure measuring cuffs. The device was validated and found to have good reproducibility in PWV measurement in healthy as well as CAD subjects.[11]

Data evaluation: In this observational study, the data was analyzed by Epi info statistical and multivariate analysis method.

Observations

The present study comprised of 100 elderly individuals who attended Medical OPD, Cardiology OPD or Geriatrics centre for their acute coronary events or minor illnesses at MDM Hospital. Jodhpur.

Result

In the study population, 21% were females and 79% were males (Table 1). Mean values of left brachio-arterial pulse wave velocity (Lt ba PWV), carotico-femoral pulse wave velocity (cf PWV) and Pulse Pressure found to increase with age with minimum value in 61-70 yrs age group (Lt ba PWV 1384.01±744.48 cm/sec, cf PWV 1095.48±694.63 cm/sec, Pulse Pressure 60.22±19.4) and maximum in >80 yr age group (Lt ba PWV 1635.74 ±1222.6 cm/sec, cf PWV 1151.83 ± 787.72cm/sec, pulse pressure 67.33 ±21.46).There was no correlation of ABI with age in our study (Table 2).

In subjects with coronary artery disease, 28.30% were vitamin D deficient, 49.05% were vitamin D insufficient and only 22.64% are vitamin D sufficient. In healthy subjects, 25.53% were vitamin D deficient, 23.40% were vitamin D insufficient and 51.04% were vitamin D sufficient. The difference between these groups was statistically highly significant (p value-0.006) (Table 3).

Pulse Pressure was abnormal in 66.66% of vitamin D deficient individuals, 43.24% vitamin D insufficient individuals and in only 25% of vitamin D sufficient individuals. Correlation of Pulse Pressure with serum vitamin D level was statistically significant (p value 0.004) (Table 4).It was highest in vitamin D deficient group (mean value-70±19.93) and lowest in vitamin D sufficient group (mean value-56.05±14.02). Pulse Pressure was 56.05±14.02 in vitamin D insufficient group. The difference between these groups was statistically highly significant (p value-0.0132).

In this study, right brachioarterial pulse wave velocity (Rt ba PWV) was abnormal in 55.55% of vitamin D deficient individuals, 43.24% of vitamin D insufficient individuals and in only 25% of vitamin D sufficient individuals. Correlation of Rt ba PWV with serum vitamin D level was statistically

Table 1: Topographic details of study population

	Male	Female	Total
Age	Mean: 73 ± 6.7 yrs		
61-70 yrs	48 (84.2%)	9 (15.8%)	57
71-80 yrs	22 (78.6%)	6 (21.4%)	28
≥ 81 yrs	9 (60%)	6 (40%)	15
Rural	64 (78%)	18 (22%)	82
Urban	15 (83.3%)	3	18
Smoker	44	0	44
Non-smoker	35	21	56

Table 2: Distribution of serum vitamin D level according to age, sex and residence

	Low vitamin D		Normal vitamin D	Total
	Deficient	Insufficient	Sufficient	
Age				
61-70 yrs	15 (26.3%)	19 (33.3%)	23 (40.35%)	57
71-80 yrs	9 (32.1%)	9 (32.1%)	10 (35.71%)	28
≥81 yrs	3 (20%)	9 (60%)	3 (20%)	15
Rural	21 (25.6%)	37 (45.12%)	24 (29.26%)	82
Urban	6 (33.33%)	-	12 (66.66%)	18
Male	15 (18.98%)	34 (43.03%)	30 (37.97%)	79
Female	12 (57.14%)	3 (14.28%)	6 (28.57%)	21

Table 3: Distribution of serum vitamin D level according to cardiovascular involvement

CV status	Vitamin D deficient (n=27)	Vitamin D insufficient (n=37)	Vitamin D sufficient (n=36)	P value
CAD	15 (28.30%)	26 (49.05%)	12 (22.64%)	0.006
Healthy	12 (25.53%)	11 (23.40%)	24 (51.04%)	

Table 4: Distribution of pulse pressure according to sr. vitamin D level

Pulse pressure	Vitamin D deficient (n=27)	Vitamin D insufficient (n=37)	Vitamin D sufficient (n=36)	P value
Abnormal	18 (66.66%)	16 (43.24%)	9 (25%)	0.004
Normal	9 (33.33%)	21 (56.75%)	27 (75%)	
Total	27	37	36	
Mean ± SD	70 ± 19.93	66.4 ± 23.43	56.05 ± 14.02	0.0132

Table 5: Distribution of pulse wave velocity according to serum vitamin D level –

Vit D	Rt ba PWV			Lt ba PWV			cf PWV		
	Abn	Norm	Mean ± SD	Abn.	Norm	mean ± SD	Abn.	norm	Mean± SD
Def.	15 (55.55%)	12 (44.44%)	1846.9 ± 1679	22 (81.48%)	5 (18.51%)	1827.64 ± 713.89	15 (55.55%)	12 (44.44%)	1363.67 ± 824.75
Insuff.	16 (43.24%)	21 (56.75%)	1430.92 ± 790.6	19 (51.35%)	18 (48.64%)	1448.54 ± 788.85	15 (40.54%)	22 (59.45%)	22 (59.45%)
Suf	9 (25%)	27 (75%)	1184.5 ± 664.9	9 (25%)	27 (75%)	1217.8 ± 715.45	6 (16.66%)	30 (83.33%)	796.78 ± 490.58
P value	0.044		0.0563	<0.0001		0.0071	0.005		0.0014

significant (p value 0.044). Mean of Rt ba Pulse Wave Velocity according to serum vitamin D level in study population was highest in vitamin D deficient group (mean value-1846.9 ± 1679.2 cm/sec) and lowest in vitamin D sufficient group (mean value-1184.5 ± 664.92 cm/sec) but difference between these groups was statistically not significant (p value-0.0563) (Table 5).

In the study, Lt ba PWV was abnormal in 81.48% of vitamin D deficient individuals, 51.35% vitamin D insufficient individuals and in only 25% of vitamin D sufficient individuals. Correlation of Lt ba PWV with serum vitamin D level was statistically highly significant (p value <0.0001). Mean of Lt ba Pulse Wave Velocity according to serum vitamin D level in study population was highest in vitamin D deficient group (mean value-1827.64 ± 713.89 cm/sec) and lowest in vitamin D sufficient group (mean value-1217.8 ± 715.45 cm/sec). The difference between these groups was statistically significant (p value-0.0071).

It was found that cf PWV was abnormal in 55.55% of vitamin D deficient individuals, 40.54% vitamin D insufficient individuals and in only 16.66% of vitamin D sufficient individuals. Correlation of cf PWV with serum vitamin D level was statistically highly significant (p value 0.005). It was highest in vitamin D deficient group (mean value-1363.67 ± 824.75 cm/sec) and lowest in vitamin D sufficient group in (mean value-796.78 ± 490.58 cm/sec). The difference between these groups was statistically highly significant (p value-0.0014).

Discussion

Vitamin D deficiency is highly prevalent condition in India as well as worldwide. Besides its function of bone mineralization, now a-days research has explored its involvement in variety of others functions affecting cardiovascular system. Vitamin D affects blood pressure, insulin resistance, cytokine profile as well as psychological functions which ultimately affect arterial stiffness, predisposed individuals for various adverse cardiovascular events and increases morbidity and mortality.

In recent years, with development of readily available non-invasive techniques of measuring arterial stiffness, especially of large and medium arteries, has gathered pace. These include measurement of PWV, use of ultrasound and applanation tonometer to detect arterial waveforms. Most widely used technique is to estimate the distensibility and stiffness of aorta and proximal vessels by PWV and pulse pressure. In our study we used Periscope, which records simultaneously pressure wave forms from all four limbs to calculate PWV. The device was validated and found to have good reproducibility in PWV measurement in healthy as well as CAD subjects.

The correlation between vitamin D level and pulse wave velocity was validated in Baltimore longitudinal study of ageing[12] in 1228 healthy volunteers (50% males; age, 70±12 yr). There was a significant inverse association between central PWV and 25-OH D levels.

In a study, Lee *et al.*[13] reported that low 25-OH D levels independently predicted PWV ($P < 0.001$) in individuals with type 2 diabetes (n = 305) after adjustment for other risk factors such as age, smoking, hypertension, C-reactive protein, diabetes duration, hypertension duration, glycosylated hemoglobin, and BMI.

Ageing characterized by widening of Pulse Pressure and in older subjects Pulse Pressure relates more closely to cardiovascular events than systolic or diastolic blood pressure. Third national health and nutrition exam survey[14] found increased pulse pressure, a nonspecific marker of arterial compliance and vitamin D deficiency. ABI has been suggested to be unsuitable for assessing PAD

in subjects with diabetes, older age, history of intervention for PAD, or advanced chronic kidney disease (CKD).[15] In particular, increased arterial stiffness might interfere with ABI measurements and affect the sensitivity of ABI for detecting PAD among dialysis subjects.

Vitamin D deficiency is more common in acute myocardial infarction. S Karur et al.[16] found that 83.5% of acute MI subjects had low Vitamin D level. Chowdhury et al.[17] showed in a meta-analysis of seven studies, including 47,809 individuals and 926 cerebrovascular events that, under consideration of established cardiovascular risk factors, the risk for cerebrovascular disease was significantly lower in subjects with high 25(OH)D levels compared to those with insufficient vitamin D status.

Conclusion

Vitamin D deficiency is quite common condition in elderly individuals which besides its bone mineralization action is also involved in cardiovascular functions. Deficiency of vitamin D may cause increase in arterial stiffness and widening of pulse pressure which are the predictor of atherosclerosis and cardiovascular morbidity and mortality. Supplementation of vitamin D may be helpful in old age.

Study Limitations

Our study was a cross-sectional, observational study which precludes definitive conclusions regarding the causal relationship between arterial stiffness and vitamin D levels. In addition, we did not explore the putative mediating effect of alcohol consumption and inflammatory status. Despite the aforementioned limitations, our study has several unique strengths. First, this study measured carotid-femoral PWV, which is the "gold standard" for the noninvasive assessment of arterial stiffness. Second, this study was performed in the context of a normative aging study that included both sexes with careful assessment of several potential confounders of the arterial stiffness/vitamin D status relationship.

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