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General Medicine

ROLE OF VITAMIN D IN PERIPHERAL VASCULAR DISEASES

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ABSTRACT **BACKGROUND –** Peripheral vascular disease (PVD) is currently a leading cause of morbidity and mortality. More than 200 million people globally have been estimated to be affected by PVD. Recent evidence has shown that Vitamin D deficiency plays a causal role in various systemic disorders specially in PVD. Vitamin D deficiency affects almost 50% of the population worldwide. Low serum 25-hydroxyvitamin D levels were particularly associated with a higher prevalence of PVD.

OBJECTIVE – To study the relation between serum Vitamin D levels and peripheral vascular diseases.

MATERIAL AND METHODS – Study subjects comprised 100 patients of Peripheral Vascular Disease, aged 18 - 70 years, enrolled from OPD and indoor of L.P.S. Institute of Cardiology & K.P.S Institute of Medicine. Their detailed physical examination and investigations was done including serum vitamin D levels.

RESULTS – The results showed that majority of the patients (70%) with PVD were having vitamin D deficiency (S. Vit D <20ng/ml). The prevalence of PVD increases with increasing age of the subjects but the association was statistically insignificant. There was no significant association of PVD with any socio-demographic factors.

CONCLUSION – The study showed that vitamin D deficiency was present in majority of subjects (70%) establishing its significant association with PVD ($p<0.05$).

KEYWORDS : PVD, Vitamin D, deficiency,

BACKGROUND

Peripheral vascular disease (PVD) is currently a leading cause of morbidity and mortality. More than 200 million people globally have been estimated to be affected by PVD. Peripheral vascular diseases (PVD) are caused due to narrowing, blockage or spasm of the blood vessels outside of the heart and brain. PVD also known as arteriosclerosis obliterans is mainly the result of atherosclerosis. In atherosclerosis, atheroma or plaques build up in a vessel wall, narrowing the lumen of artery and limiting the flow of blood. The atheroma is an abnormal accumulation of cells, cholesterol with a fibrous connective tissue covering. Atherosclerosis may gradually progress to completely occlude the lumen or clots may develop due to injury to vessel wall, thereby obstructing the blood flow. This leads to development of ischaemia and necrosis of tissues which causes symptoms of pain, discoloration, weakness and in chronic conditions may cause amputation of limbs or fingers. The primary risk factors of atherosclerosis are smoking, hypertension, diabetes and dyslipidemia.
Peripheral arterial disease (PAD) is the most common form of PVD, which affects only the arteries. Peripheral arterial occlusive disease (PAOD) occurs due to blockage of the blood flow to the lower extremities and manifests as intermittent claudication (IC) or leg pain during walking and critical limb ischemia (CLI) where there is tissue loss. Severity of PAOD is assessed by measuring the ankle-brachial pressure index (ABPI).

The prevalence of PVD being greater in the elderly, is also increasing with an increase in aging population. It has been projected to rise further in forthcoming years and is expected that the PVD prevalence will double by 2040. More than 200 million people globally have been estimated to be affected by PVD with a current prevalence rates estimated at 4% of the general population older than 40, 16% of those individuals older than 55 and a prevalence of 30% in subjects aged over 70 years.

While patients with PVD often have a sedentary lifestyle with limited exposure to sunlight, age may also be a factor, reducing the exposure to sunlight. The capacity of UV-mediated vitamin D synthesis was previously reported to be reduced in aged skin, with an associated reduced expression of the vitamin D receptor in aged human muscle.

Recent evidence has shown that Vitamin D deficiency plays a causal role in various systemic disorders specially in PAD. Vitamin D deficiency affects almost 50% of the population worldwide. Low serum 25-hydroxyvitamin D levels were particularly associated with a higher prevalence of PAD. Vitamin D deficiency is mainly caused by inadequate cutaneous synthesis secondary to decreased exposure to sunlight. Serum level of 25-OH vitamin D < 20 ng/ml are diagnostic of vitamin D deficiency. Serum levels of 25(OH)D > 30 ng/mL are likely optimal for bone health. Parathyroid hormone (PTH) suppression appears to plateau at levels between 30 and 40 ng/mL (Holick M.F. et al., 2011). There has been no agreement on optimum 25(OH)D levels required for purported health benefits beyond skeletal health. One study suggested that 25(OH)D levels below 11–14 ng/mL signify increased CVD risk(Tepper S. et al., 2014) .

PAD manifestations including claudication, rest pain, and tissue loss are less likely to be explained by vascular occlusion alone. Increasing evidence suggests that a myopathy is present which contributes to and determines the pathogenesis of PAD. A state of repetitive cycles of exercise-induced ischemia followed by reperfusion at rest in patients with PAD may mediate a large number of structural and metabolic changes in the muscle, resulting in reduced strength and function. In this setting, vitamin D may exert a fundamental role. Vitamin D status is significantly associated with muscle strength, and a lack of vitamin D can cause myopathy, which tends to be more marked in the proximal muscles. Vitamin D is reported to mediate protein synthesis and cellular adenosine triphosphate accumulation, increase troponin C, and increase actin and sarcoplasmic protein expression in striated muscles.

In the present study we analyzed the association of vitamin D levels with peripheral vascular diseases, the socio demographic profile of PVD patients.

MATERIAL AND METHODS

The present Hospital based cross sectional study was conducted over 100 Peripheral arterial disease (PAD) patients in GSVM Medical College (L.P.S Institute of Cardiology & L.L.R Hospital), Kanpur with age between 18 years to 70 years, of both sex (male and female). After obtaining the consent form, a detailed comprehensive history was obtained pertaining to symptoms of PAD. All patients in OPD, indoor were enrolled in this study.

STUDY POPULATION: Patients with chronic Peripheral arterial disease (PAD).

STUDY DESIGN: Hospital based cross sectional study.

STUDY LOCATION: This was a tertiary care teaching hospital based cross sectional study done in K.P.S Institute of Medicine and L.P.S Institute of Cardiology, GSVM Medical College, Kanpur (Uttar Pradesh).

STUDY PERIOD: 22 months (January 2019 to October 2020)

SAMPLE SIZE: 100 patients

INCLUSION CRITERIA
- Patients with chronic PAD (defined as an ankle-brachial index50% stenosis or occlusion in a leg artery) ➢ Unchanged medication in the 6 weeks prior to the study,
- No vascular interventions in the 2 months preceding the study.
- Patients who had given informed written consent

EXCLUSION CRITERIA
- Acute intercurrent illness,
- Renal insufficiency defined as serum creatinine >130 µmol/l
- Acute myocardial infarction or stroke within 2 months,
- Current oral anticoagulation medication,
- Liver cirrhosis
- Presence of any malignancy

Screening/ Survey: A total of 109 patients were screened, 6 were rejected to participate in the study and 3 were not fit according to inclusion criteria and finally 100 patients were fulfilling diagnostic criteria of Peripheral arterial disease and were found fit according to inclusion criteria.

PROCEDURE METHODOLOGY

Method of collection of data: A written consent was taken from all potentially eligible subjects and excluded from the study if they were not matched with inclusion criteria of the study. Detailed history and physical examination was performed and recorded on predesigned proforma from each patient. Patient's personal history, physical examination findings like name, age, sex, demographic profile, socio economic status, education, occupation, Height, Weight and BMI were recorded. At baseline a clinical examination including measurement of Ankle Brachial Index (ABI), modified Rankin Scale (mRS), blood collection and specific tests were performed in all patients.

ABI was calculated by dividing the higher systolic Ankle (Posterior Tibial or Dorsalis pedis) pressure by the higher brachial artery systolic pressure. Patients with an ABI <0.9 (or angiographically based verification of a > 50% stenosis or occlusion in a leg artery) were considered to have PAD and they were screened for serum vitamin D level.

MRS is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered with a stroke, PAD or other causes of neurological disability.

Table no. 1

Modified Rankin Scale (MRS)
0 No symptoms
1 No significant disability, despite symptoms; able to perform all usual duties and activities
2 Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3 Moderate disability; requires some help, but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6 Death

Patients were divided in two group as group I (Serum vitamin D ≤20 ng/ml) and group II (Serum vitamin D >20 ng/ml).

Hemodynamic measurements
- Routine blood investigations – CBC, LFT, KFT, S. Electrolytes, Blood sugar (Fasting, P.P, and RBS) Values
- Serum Vitamin D levels

Radiological Investigations
- Colour Doppler
- USG with duplex scanning
- X-Ray
- CT angiography
- MRI Angiography

STATISTICALANALYSIS

Data was analyzed using Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL). Results for continuous variables are presented as mean ± standard deviation, whereas results for categorical variables are presented as number (percentage). For baseline variables, continuous variables were compared using an independent t-test and categorical variables were compared using the chi-square test. The level $P < 0.05$ was considered as the cutoff value or significance.

RESULTS

In this longitudinal prospective study all the patients with chronic PAD (ABI was calculated by dividing the higher systolic ankle (posterior tibial or dorsalis pedis) pressure by the higher brachial artery systolic pressure. Patients with an ABI <0.9 (or angiographically based verification of a > 50% stenosis or occlusion in a leg artery) were considered to have PAD and they were screened for vitamin D deficiency and it was found that the majority of the patients with PAD were having vitamin D deficiency (70.0%). We have divided the 100 studied patients in two group as group I (Serum vitamin D ≤20 ng/ml) and group II (Serum vitamin D >20 ng/ml) on the basis of previous study done by Rahman MAA et al., (2015) who has taken 20 ng/ml as the reference range for vitamin D level.

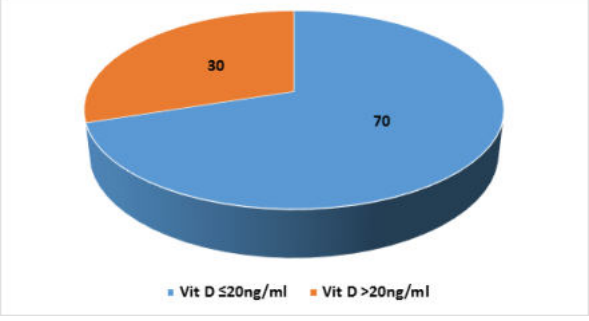
Table No. 2 Distribution of patients on the basis of their vitamin D status

Vitamin D level	Number of patients	%	Mean ± S.D.
≤20 ng/ml	70	70%	13.80±3.83
>20 ng/ml	30	30%	24.39±2.27
Total	100	100%	

Chi square; Unpaired Student's t test, P<0.05, C.I. 95%

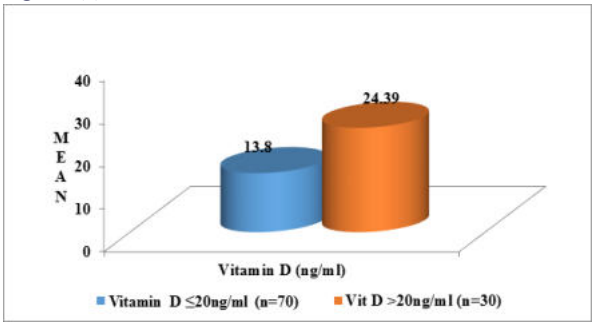
The above table shows the distribution of study subjects on the basis of their vitamin D levels. There were 70 patients having vitamin D levels Deficient (≤20 ng/ml) with a mean value of 14.9 ± 4.12. There were 30 patients having vitamin D levels sufficient (>20 ng/ml) with a mean value of 25.43 ± 2.86. On applying unpaired student's t test between means of vitamin D deficient and sufficient group, p value was found to be <0.5 at 95% C.I. Hence the association was statistically significant.

Figure no. 1(a): Distribution of patients on the basis of vitamin D levels



The above figure shows majority (70%) of the PAD patients belong to vitamin D deficient group (≤20 ng/dl).

Figure 1(b) : Mean vitamin D levels



The above figure shows the mean levels of vitamin D was significantly lower in vitamin D deficient group as compared to the sufficient group.

Table No. 3: Distribution of patients on the basis of their socio demographic profile

Variables		Distribution of patients		
		Vitamin D (≤20 ng/ml) (n=70) No. (%)	Vitamin D (>20 ng/ml) (n=30) No. (%)	p-value
Age in years	≤30	5 (7.1)	1 (3.3)	0.848*
	31-45	18 (25.7)	8 (26.7)	
	46-60	33 (47.1)	16 (53.4)	
	>60	14(20.0)	5 (16.7)	
	Mean age	49.61±13.45	50.9±11.19	0.646**
Gender	Male	40 (57.1)	21 (70.0)	0.227*
	Female	30 (42.9)	9 (30.0)	
Religion	Hindu	56 (80.0)	28 (93.3)	0.096*
	Muslim	14 (20.0)	2 (6.7)	
Area of residence	Urban	43 (61.4)	15 (50.0)	0.288*
	Rural	27 (38.6)	15 (50.0)	
Socio Economic Status	Lower	21 (30.0)	10 (33.3)	0.461*
	Lower Middle	22 (31.4)	9 (30.0)	
	Upper Middle	27 (38.6)	10 (33.3)	
	Upper	0 (0)	1 (3.3)	
Education	Graduation	11 (15.7)	9 (30.0)	0.117*
	Secondary Education	42 (60.0)	18 (60.0)	
	Primary Education	17 (24.3)	3 (10.0)	
Occupation	Employed	43 (61.4)	16 (53.3)	0.451*
	Unemployed	27 (38.6)	14 (46.7)	

*chi square ** student's t test

The above table shows the distribution of patients with PAD on the basis of their socio-demographic factors in vitamin D sufficient and deficient group and there was no statistically significant association of vitamin D status with any of the factors.

Table No. 8: ABI, % stenosis and mRS of patients

	Vitamin D deficient (≤20 ng/ml) (n=70)	Vitamin D (>20 ng/ml) (n=30)	p-value
ABI	0.53 ± 0.18	0.55 ± 0.23	0.463
Stenosis (in%)	71.78 ± 11.68	71.69 ± 11.62	0.691
mRS	2.32 ± 1.02	2.33 ± 1.20	0.752

The above table shows the Ankle Brachial Index (ABI), % stenosis of peripheral artery and Modified Rankin Scale disability score for PAD in Vitamin D deficient subjects (n=70) and sufficient subjects and the association was statistically insignificant among the groups (p>0.05).

DISCUSSION

Vitamin D is an essential micronutrient required for calcium metabolism. Recent research suggests that vitamin D may possess a wide range of biological effects beyond its classically recognized function in bone and mineral homeostasis [Christakos et al., 2016). Indeed, deficiency of vitamin D has been associated with increased prevalence of multiple diseases including osteoporosis, a number of autoimmune diseases, many different cancers and conditions such as hypertension and cardiovascular diseases (CVDs) (Bendik I et al., 2014). Apart from its well-known role in bone and calcium metabolism, vitamin D deficiency has recently received widespread attention for its potential role as a risk factor in cardiovascular disease and for its association with traditional cardiovascular risk factors. Particularly, low serum 25- hydroxyvitamin D (25-OH vitamin D) levels were associated with a higher prevalence of PAD[6]. Previous clinical studies have indicated that low vitamin D (defined as serum calcifediol/25-hydroxyvitamin D (25-(OH) D) concentration below 50 nmol/l [=20 ng/ml] as according to The Endocrine Society guidelines (Rosen. C.J. et al., 2019) can impair vascular function which may compromise vascular compliance (the elastic property of blood vessels) manifesting as increased arterial stiffness (Melamed M.L. et al., 2008). Observational studies have suggested that vitamin D deficiency or insufficiency is associated with a poorer vascular profile including increased stiffness(Andrade J et al., 2008). No causal relationship has been established. In this longitudinal prospective study all the patients with chronic PAD were screened for vitamin D level and it was found that the majority of the patients with PAD were having vitamin D deficiency (70.0%) adding more data to other studies that did not confirm a causal role of vitamin D in cardiovascular disease.

In the present study it was seen that as the age increases the problem of PAD also increases while the association was found to be statistically insignificant (p>0.05). The majority of the patients were in the age group ranging from 46 to 60 years and the mean age for the patients with Vitamin D ≤20 ng/ml was 49.61±13.45 and that of Vitamin D >20 ng/ml it was 50.9±11.19 (p>0.05). Our findings were consistent with Stricker H et al (2012) who reported the insignificant association between the ages among the two groups but the mean age was higher in their study which may be because their sample size was smaller than our study. Van de Luijtgaarden KM et al. (2012) in their study based on Vitamin D Deficiency as an Independent Risk Factor for Arterial Disease reported the mean age of the studied patients with severely deficient vitamin-D as 64.3 ± 11.6 while the overall mean age was 66.8 ± 10.7 years which was slightly more than the present study but the association was statistically insignificant which was similar to the present study. Bonatto S et al. (2020) reported that both the method for PAD diagnosis as well as the participants' mean age were similar to those in their study (p>0.05).

In our study it was seen that the majority of the studied patients were males than females in both the groups and the association was found to be statistically insignificant (p>0.05). Also, all the other demographic parameters (Area of residence, socio economic status, religion, education and occupation) show no statistically significant difference among the two group (p>0.05) Van de Luijtgaarden KM et al (2012) supported our findings in their study on vitamin D deficiency as an independent risk factor for arterial disease and reported that male were more prone to vascular disease and were in higher number in their study than females (p>0.05). Stricker H et al (2012) reported 61.0% males in their which was in accordance to the present study and the association was statistically insignificant (p>0.05). Yuan J et al (2019)[12] and Satilmis S et al (2015) also reported similar finding as in the present study.

In the present study Ankle Brachial Index (ABI), % stenosis of peripheral artery and Modified Rankin Scale disability score for PAD in Vitamin D deficient subjects (n=70) was measured and the association was statistically insignificant among the groups (p>0.05). ABI was the measurement used to diagnose PAD in our institute and these are the novel findings of our study which shows that vitamin-D status does not affect the peripheral vascular disease parameters (p>0.05)

CONCLUSION

Results of our study show that PAD patients in India had lower mean levels of 25-hydroxy vitamin D. Vitamin D deficiency was found in majority of PAD patients and the association was statistically significant. (p<0.05). Our findings support the association between deficient vitamin D serum levels and PAD, and, as far as we know, this is the first north Indian study to research such association. In this study, most patients with PAD (n=70) were vitamin D deficient.

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