



Is Severe Vitamin D Deficiency an Independent Risk Factor for Critical Limb Ischemia of Patients Diagnosed to Have Atherosclerotic Peripheral Arterial Occlusive Disease?

KEYWORDS

Peripheral arterial disease, vitamin D deficiency

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ABSTRACT *Objectives:* The aim of this study was to assess vitamin D status in patients with atherosclerotic peripheral arterial occlusive disease (PAOD) in relation to the severity of disease

Methods: This was a prospective cohort study. Patients with symptomatic PAOD were divided into claudicants and patients with critical limb ischemia. Patient demography, risk factor profile, ABPI and vitamin D levels were assessed.

Results: Of the cohort of 100 patients, 24 patients were severely vitamin D deficient, 36 patients had moderate deficiency, 23 patients had mild deficiency and 17 patients had normal vitamin levels. There was a statistically significant difference of severe vitamin D deficiency in the critical limb group compared to the claudicants (32% vs 14%) ($p = 0.004$). Low ankle brachial index (<0.4) was associated with more severe vitamin D deficiency.

Conclusion: Severe vitamin deficiency appears to be an independent risk factor in critical limb ischemia.

Introduction:

Peripheral arterial occlusive disease (PAOD) results from gradual occlusion of the peripheral arteries. Atherosclerosis is the commonest etiology especially in the elderly. Patients commonly present with claudication pain those progresses to rest pain with or without ulcers (critical limb ischemia).

The role of several risk factors like smoking, diabetes, and hyperlipidemia has been well established. It is also well known that modifying these risk factors slow the progression of atherosclerosis. The role of vitamin D as an independent risk factor has gained interest recently. Several large epidemiological studies have concluded that vitamin D deficiency is associated with increasing mortality(1). The prevalence of vitamin D deficiency in patients with PAOD and coronary artery disease has been reported(2).

Many studies have suggested that low vitamin D levels promote atherosclerosis(3). The exact mechanism seems unclear. Moreover it is also not well known if low vitamin levels actually correspond to an increase in severity of the disease.

Materials and methods

This study is a prospective cohort study. This study was conducted between 2013 and 2015 at the department of vascular surgery, Christian Medical College Vellore, India. There were a total of 100 patients with PAOD. They were divided into two groups. One group of claudicants and another with severe disease (critical limb ischemia). Patients with critical limb ischemia were defined as having rest pain with or without tissue loss in the form of ulceration or gangrene with an ankle brachial pressure index (ABPI) of less than 0.4. All these patients underwent a thorough history and examination followed by Ankle-brachial

pressure index evaluation. The ABPI was measured at using a portable 8MHz vascular Doppler. The ABPI was calculated according to the Trans Atlantic Inter-society consensus management guidelines (TASC).

Vitamin D assay: Serum vitamin D was measured in fresh blood samples using a 25-hydroxyvitamin D radioimmunoassay (Diasorin Inc, Stillwater, MN, USA). Any level less than 30ng per milliliter was considered deficient. Levels between 20-30ng per milliliter were considered as mild deficiency. The levels between 10-20ng per milliliter were considered as moderate deficiency and any level less than 10ng per milliliter was severely deficient(4).

The Institutional review board approved the study. The study complies with the Declaration of Helsinki. Statistical analyses was done using Chi square test.

RESULTS:

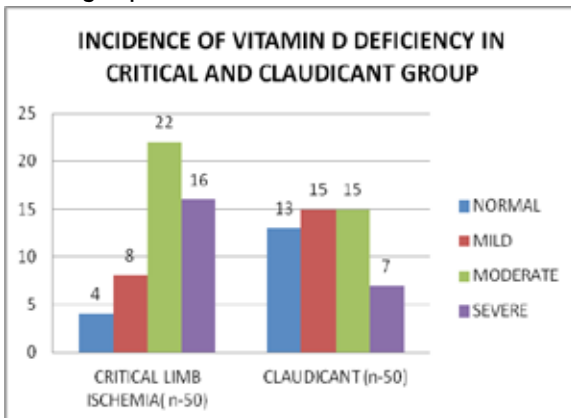
Demography Table 1 :

	Total N = 100	Severe vitamin D deficiency	Moderate vitamin D deficiency	Mild/ normal vitamin D levels
Mean Vitamin D levels	20.4	6.09	15.13	33.72
BASELINE CHARACTERISTICS				
Male	81	8	48	25
Female	19	9	5	5
RISK FACTORS				
Diabetes	47	14	18	15

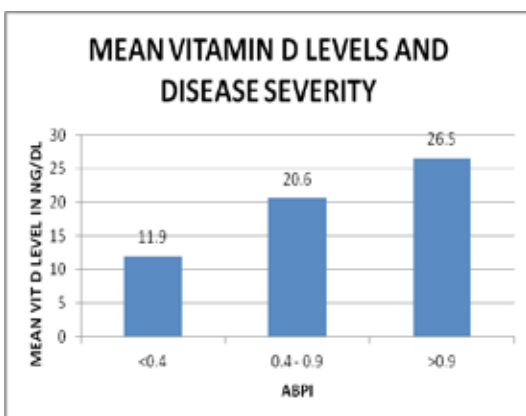
	Total N = 100	Severe vitamin D deficiency	Moderate vitamin D deficiency	Mild/ normal vitamin D levels
Hypertension	41	11	16	14
Dyslipidemia	27	8	9	10
Smoking	55	12	12	31
MARKER OF ATHEROSCLEROSIS				
ABPI				
Mild disease	40	3	23	14
Moderate disease	36	9	16	11
Severe disease	24	9	13	2

A total of 100 patients were included in the study. 50 patients had critical limb ischemia and 50 patients were diagnosed to have claudication. There were 80 men and 20 women. The mean age of the population was 58.9 years. A total of 24 patients were severely deficient, 36 were moderately deficient and 23 had mild deficiency, 17 patients had normal vitamin D levels. The incidence of severe vitamin D deficiency in the critical limb ischemia group was 32% while in the claudicant group it was 14%. This difference in vitamin D levels was statistically significant (p value-0.004). (Graph 1).

Graph 1: Mean vitamin D levels in the critical and claudicants group.

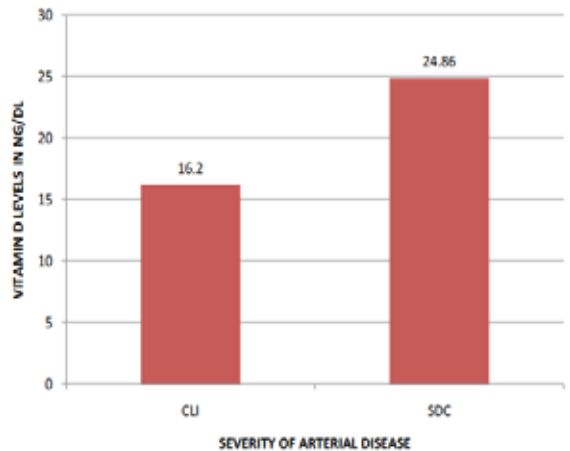


Graph 2: Mean Vitamin D level in patient with severe , moderate and mild disease based on ABPI



Graph 3: number of patients with severe vitamin D deficiency in both the groups. (N = 50 both critical limb ischaemia (CLI) and short distance claudicants (SDC).

MEAN VITAMIN D LEVELS IN BOTH THE ARTERIAL GROUPS



Moreover it was also noticed that as the severity of the disease increases, the deficiency levels worsen. (Graph 2). The mean vitamin D value in the critical limb ischemia group was 16.2ng/ml while the mean in the claudicant group was 24.86ng/ml. This difference in vitamin D Levels was also statistically significant. (Graph 3)

The cardiovascular morbidities assessed in the two groups were diabetes, hypertension and hyperlipidemia. These showed a similar distribution between the two groups. Overall lower vitamin D levels seemed to be associated with more risk factors. There seemed to be more current smokers in the group with severe deficiency and critical limb ischemia.

In our study we have considered ABPI as a marker for atherosclerotic disease. Decreasing ABPI has been associated with an increasing hazard ratio in the Framingham study. The mean vitamin D level in the (<0.4) ABPI group was 11.9ng/dl and in the ABPI group (0.4 to 0.9) was 20.6ng/dl and the mean in the normal ABPI group was 26.5ng/dl. The correlation between low vitamin D levels and low ABPI was also statistically significant (p value-0.02).

DISCUSSION -

PAOD (peripheral arterial occlusive disease) is common in the community. Many patients with claudication are symptomatic but manage their life by altering their activities. They visit their physician only when their disability becomes a handicap. Pain is always their first and foremost complaint. The Edinburgh arterial study found that 4.5 % men and women over the age of 55 years had intermittent claudication, but a good 25% had asymptomatic disease(5). This study strongly indicates that there is window for altering the course of the disease by modifying the risk factors. However another important finding was that many of these patients do not actually deteriorate to the point of limb loss. In fact only 1 % - 2 % actually end up with an amputation(6). The rate of cardiovascular events among these patients is higher. If these patients are compared

to normal individuals the rate of cardiovascular mortality is almost 6 times higher. 1 in 5 of the patients with critical limb ischemia will die within 1 year of diagnosis.(reference) These observations have resulted in a paradigm shift of treatment strategy which is now aimed at modifying risk factors.

Our study seems to show a strong association between the vitamin D status and severity of PAOD. This seems to be independent of the other cardiovascular risk factors. The prevalence of vitamin D deficiency in these patients seems to be very high. Moreover as the severity of the disease increases the vitamin D status also worsens. This is probably due to poor dietary and socioeconomic status. Moreover we also noticed that deteriorating ABPI which is a marker for atherosclerotic disease is associated with low vitamin D status. There are very few studies that have mentioned ABPI status in patients with vitamin D deficiency. We also found that the association between the low vitamin D status and severity of the PAOD was independent of hypertension, diabetes and dyslipidemia.

Low vitamin D status seems to have an independent effect on atherosclerotic arteries resulting in disease progression(7). The vitamin D receptors which are ubiquitous may play an important role by interacting with the endothelial cells and vascular smooth muscles. The low levels of vitamin D seem to cause inflammation and vascular calcification (8),(9).

Low vitamin D is more common in adults with type 2 diabetic and is independently related to higher carotid intima-media thickness (10). While this is not a definite evidence of the effect vitamin D levels on atherosclerotic disease it seems to point towards a causal relationship. A study published in the European Journal of vascular and Endovascular surgery in 2011 showed that vitamin D was associated with more aortic stiffness and calcification of the peripheral arteries(11). This was followed by another study from the Erasmus University Rotterdam, Netherlands that said Vitamin D might actually be an independent risk factor for arterial disease (12). The prevalence of vitamin D deficiency in the Indian population is quite significant with range from 50 %to 90% over all age groups and populations(13),(14),(15),(16). Independent cohorts studied in our hospital have shown a 20% prevalence of severe vitamin D deficiency.

CONCLUSION -

This study clearly demonstrates that low vitamin D status is a risk factor for atherosclerotic peripheral arterial disease independent of established risk factors like smoking, hypertension, dyslipidemia and diabetes. The question of whether this association is influenced by other confounding factors like melatonin levels, ethnicity, poor living conditions, socioeconomic scores, and diet and drug interaction has not been studied. The question of whether supplementation of vitamin D in asymptomatic or symptomatic PAOD patients actually delays progression of the disease needs further randomized trials.

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