Study of the Relation between Peripheral Arterial Disease and Vitamin D Level among Maintenance Hemodialysis Patients

Ashraf Hassan Abdelmobdy*[1], Amr Abd Elshafy Aboud[2], Walid Ahmed Bichari[1]
[1]Internal Medicine and Nephrology Department, Faculty of Medicine Ain Shams University, Cairo, Egypt
[2]Internal Medicine and Nephrology Department, Faculty of Medicine, Kafr El-Sheikh University, Cairo, Egypt
***Corresponding author:** Ashraf Hassan Abdelmobdy, **Mobile:** 01093989048, **Email:** ashrafnephro@med.asu.edu.eg

ABSTRACT

Background: Worldwide, chronic kidney disease (CKD) is a major public health issue. The Global Burden of Disease study stated that, worldwide mortality attributed to renal failure showed a tremendous rise with around 1.2 million deaths from renal failure in 2015. Atherosclerosis, especially peripheral arterial disease (PAD), is more common in people undergoing hemodialysis (HD). However, there are some correlations that appear to be unique to dialysis patients when it comes to risk factors for peripheral artery disease.

Objective: To study the relation between PAD assessed by ankle brachial index (ABI) and serum level of 25(OH) vitamin D among maintenance HD patients from multiple dialysis centers in Kafr El-Sheikh Governorate, Egypt.

Patients and Methods: From the dialysis centers in Kafr El-Sheikh Governorate, Egypt, a total of 90 ESRD patients on maintenance HD were recruited for this study and were divided into two groups, 45 with PAD assessed by ABI (value less than 0.9) and 45 without PAD assessed by ABI (value more than or equal 0.9). Study was done over six months starting from April 2019 till end of October 2019.

Results: Serum 25(OH) vitamin D levels differed statistically significantly between the two groups ($P< 0.001$). Patients and control groups both showed a statistically significant positive connection between ABI and their serum vitamin D level ($P< 0.001$).

Conclusion: PAD is linked to vitamin D insufficiency in people who are on maintenance hemodialysis.

Keywords: Chronic kidney disease, Peripheral arterial disease, Vitamin D.

INTRODUCTION

Chronic kidney disease (CKD) is a main medical concern globally and is causing significant increase in morbidity and mortality [(1)]. End-stage renal disease (ESRD) affects around 675,000 people in the United States, costing the healthcare system more than $32 billion a year. Despite therapeutic improvements, mortality and morbidity rates for hemodialysis (HD) patients remain high [(2)]. The death rate was high among maintenance HD patients and the major reason of death was cardiovascular (CV) diseases [(3)].

Patients with peripheral arterial disease are classified as those who have atherosclerotic or thrombi-embolic processes in their lower limb arteries, which are major health-care issues [(4)]. There are a variety of symptoms associated with peripheral artery disease (PAD), ranging from the nonexistence of symptoms to those that are uncommon, such as an inability to do strenuous activities, typical intermittent claudication, or lower-limb ischemia discomfort and ulceration [(5)].

Subclinical and symptomatic PAD can both be detected with high accuracy and reliability using the ankle–brachial index (ABI) [(6)]. PAD can be diagnosed by comparing it to the gold standard, arteriography. PAD patients can be accurately identified with 95% sensitivity and 100% specificity using the ABI value. An ABI of less than 0.9 has been associated with an increased risk of clinical PAD, myocardial infarction, composite cardiovascular disease and all-cause mortality in individuals with chronic renal failure [(7)]. However, there are some correlations that appear to be unique to dialysis patients when it comes to risk factors for peripheral artery disease (PAD).

The current work aims to study the relation between PAD assessed by ABI and serum level of 25(OH) vitamin D among maintenance HD patients.

PATIENTS AND METHODS

90 ESRD patients on maintenance HD were selected from multiple dialysis centers in Kafr El-Sheikh Governorate, Egypt and were divided into two groups: **Patient group** included 45 with PAD (ABI value less than 0.9), and **Control group** included 45 without PAD (ABI value more than or equal 0.9).

The study population selected included subjects who were 18 years old or above and maintained on regular hemodialysis for more than six months with dialysis regimen of 3 sessions per week, bicarbonate containing dialysate and using heparin anticoagulation.

Patients with active infection, malignancy, decompensated liver disease, autoimmune disease were excluded. Diabetes mellitus is an important risk factor for PAD, so we also excluded diabetic HD patients from our trial in order to assess the only effects of vitamin D on ABI. Study was done over six months starting from April 2019 till end of October 2019.

Personal and family histories, smoking habits, and past cardiovascular disease, like cerebrovascular disease, peripheral vascular disease, as well as coronary artery disease, were gathered from all participants in the study.

Heart rate, systolic and diastolic blood pressure, and height/weight measurements were taken before each HD session to ensure that the patient was healthy enough to participate in the treatment. When a person has hypertension, their blood pressure was either

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consistently over 140 mm Hg systolic or consistently over 90 mm Hg diastolic.

For both groups, the blood creatinine and urea levels were assessed as well as the calcium and phosphorus levels, alkaline phosphatase levels, parathyroid hormone levels, C-reactive protein levels, serum 25(OH) vitamin D levels, and the serum lipid profile.

There was a range of 20-100 ng/ml of 25-OHD vitamin D in the blood. Serum 25(OH)D levels of 20-29 ng/ml have been classified as vitamin D insufficiency, whereas levels of fewer than 20 ng/ml have been classified as vitamin D deficiency.

An automated, non-invasive waveform analysis instrument was used to determine the ABI. During the first two hours of a normal HD session, we measured the ABI level of exposure. The dorsalis pedis and posterior tibial arteries' blood flow was monitored using a Doppler ultrasonography blood flow detector. We also utilized a sphygmomanometer with an ankle cuff to measure blood pressure. In order to detect the artery Doppler signal, the sphygmomanometer was inflated to a pressure 20–30 mmHg above that. Systolic blood pressure was the first evidence of arterial activity that we heard when we deflated the cuff.

Ethical consent:

An approval of the study was obtained from Kafr El-Sheikh University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

We used IBM SPSS version 23 (IBM SPSS) for data collection, revision, coding, and entry into the database. Quantitative data were represented by means, standard deviations, and ranges. There were also numbers and percentages for qualitative characteristics, which were compared by chi-square tests and Fisher exact tests.

For quantitative data with parametric distribution, the independent t-test was employed, while the Mann-Whitney test was utilized for comparisons between groups without parametric distribution. The correlation between two quantitative variables was examined using Spearman correlation coefficient. Multivariate linear regression analysis was used to find the most important factors affecting the value of ABI. P value < 0.05 was considered significant and <0.01 was considered highly significant.

RESULTS

Regarding the age, there was insignificant difference between the 2 groups. With relation to the two groups' blood pressure measures (systolic and diastolic) and smoking history, there was no significant difference. In the patients group, the mean serum vitamin D Level was significantly lower than the control group (Table 1).

Table (1): Comparison of the two groups based on their performance on various studied metrics

		Control group	Patients group	P-value
		No. = 45	No. = 45	
Age (years)	Mean ± SD	47.67 ± 12.85	46.49 ± 13.53	0.673
Gender	Female Male	18 (40.0%) 27 (60.0%)	15 (33.3%) 30 (66.7%)	0.512
Smoking history	Non-smoker Smoker	15 (33.3%) 30 (66.7%)	18 (40.0%) 27 (60.0%)	0.512
BMI (kg/m²)	Mean ± SD	23.63 ± 2.92	25.08 ± 3.78	0.045
SBP (mm Hg)	Mean ± SD	136.33 ± 22.42	139.44 ± 18.16	0.471
DBP (mm Hg)	Mean ± SD	80.00 ± 12.25	81.11 ± 9.65	0.634
TC (mg/dl)	Mean ± SD	140.20 ± 23.71	150.96 ± 32.05	0.074
LDL (mg/dl)	Mean ± SD	72.00 ± 6.56	99.40 ± 23.23	< 0.001
HDL (mg/dl)	Mean ± SD	40.36 ± 9.15	42.13 ± 10.06	0.383
TG (mg/dl)	Mean ± SD	107.02 ± 25.44	109.47 ± 8.32	0.754
Vitamin D (ng/mg)	Mean ± SD	19.20 ± 4.36	13.88 ± 4.66	< 0.001
CRP (mg/l)	Mean ± SD	5 ± 1.12	26 ± 5.45	< 0.001
Albumin (g/dL)	Mean ± SD	3.56 ± 0.58	2.88 ± 0.35	< 0.001

TC: total cholesterol, TG: triglyceride

No significant difference between both groups was found as regard etiology of renal failure and duration of dialysis (Table 2).

Table (2): Comparison between the two groups according to the etiology of ESRD and dialysis duration

		Control group	Patients group	P-value
		No. = 45	No. = 45	
Etiology of ESRD	HTN	27 (60.0%)	30 (66.7%)	0.685
	Reflux	9 (20.0%)	6 (13.3%)	
	Obstructive	9 (20.0%)	9 (20.0%)	
Dialysis duration (months)	Mean ± SD Range	7.60 ± 2.83 2 – 14	7.09 ± 3.07 1 – 14	0.31

Both groups were statistically significantly different as regard alphacalcidol medication to be higher percentage in patient group (Table 3).

Table (3): Comparison between the two groups according to drug history

		Control group	Patients group	P-value
		No. = 45	No. = 45	
Vasodilators /Anti HTN	No Yes	14 (31.1%) 31 (68.9%)	16 (35.6%) 29 (64.4%)	0.655
Statins	No Yes	36 (80.0%) 9 (20.0%)	34 (75.6%) 11 (24.4%)	0.612
Alphacalcidol	No Yes	9 (20.0%) 36 (80.0%)	40 (88.9%) 5 (11.1%)	< 0.001

Patients were found to have a significantly greater rate of cardiovascular events than the control group (Table 4).

Table (4): Comparison between the two groups according to cardiovascular events

		Control group	Patients group	P-value
CV Event	Stroke	0 (0.0%)	2 (22.2%)	0.003
	MI	0 (0.0%)	4 (44.4%)	
	TIA	0 (0.0%)	3 (33.3%)	

In both patient and control groups, we identified a statistically significant negative connection between ABI and age, as well as systolic and diastolic blood pressure readings, serum LDL, serum total cholesterol, and CRP levels. Patients and control groups showed a statistically significant positive connection between ABI and serum vitamin D concentration and HDL concentration (Table 5).

Table (5): Correlation between ABI and other parameters

	ABI	
	R	P-value
Age (years)	**-0.631**	**< 0.001**
BMI (kg/m²)	-0.116	0.448
Ca (mg/dl)	0.200	0.188
PO_4 (mg/dl)	0.182	0.232
Vitamin D (ng/mg)	**0.316**	**0.034**
CRP (mg/l)	**-0.322**	**0.031**
Albumin(g/dl)	**0.491**	**0.001**
TC (mg/dl)	**-0.415**	**0.005**
LDL (mg/dl)	**-0.707**	**< 0.001**
HDL (mg/dl)	**0.301**	**0.044**
TG (mg/dl)	0.013	0.934
SBP (mm/Hg)	**-0.684**	**< 0.001**
DBP (mm/Hg)	**-0.336**	**0.024**

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, CRP: C-reactive protein

Multivariate linear regression analysis of the correlated parameters showed that calcium phosphorus product, vitamin D, CRP, TC, LDL, HDL and TG were the most important factors affecting the value of ABI (Table 6).

Table (6): Multivariate linear regression analysis for the factors affecting level of ABI

	Unstandardized Coefficients		Standardized Coefficients	P
	B	Std. Error	Beta	
(Constant)	1.340	0.267		< 0.001
Age (years)	-0.001	0.001	-0.057	0.368
Dialysis duration (years)	0.000	0.005	-0.001	0.983
Ca×Po4	-0.007	0.001	-0.344	< 0.001
Vitamin D (ng/mg)	0.018	0.003	0.453	< 0.001
CRP (mg/l)	-0.003	0.001	-0.176	0.019
Alb (g/dl)	0.051	0.040	0.122	0.202
TC (mg/dl)	0.003	0.001	0.392	0.002
LDL (mg/dl)	-0.008	0.001	-0.840	< 0.001
HDL (mg/dl)	-0.007	0.002	-0.269	0.003
SBP (mm/Hg)	-0.001	0.001	-0.095	0.277
DBP (mm/Hg)	0.002	0.002	0.102	0.219

DISCUSSION

The present study included 90 subjects, 45 ESRD patients on maintenance HD with PAD assessed (with ABI less than 0.9) and 45 ESRD patients on maintenance HD without peripheral arterial disease by (ABI more than or equal 0.9).

The risk factors linked with coronary artery disease, such as age, gender, diabetes, cigarette use, hypertension, and hyperlipidemia, are also present in peripheral atherosclerosis [(8)]. Regarding the age, **Laghari *et al.*** [(9)] stated results similar to our results with no significant difference as regard age between the two studied groups, however, these results were different from those stated by **Matsuzawa *et al.*** where there was a considerable age disparity between patients with PAD and those without the disease [(10)].

In both the patient and control groups, we discovered a statistically significant inverse relationship between ABI and age. This is similar to that found by **Arroyo *et al.*** study [(11)], which showed that for atherosclerosis, age has been found to be the strongest predictor.

When it comes to gender, smoking history, lipid profile, and blood pressure, we found no significant differences between the two groups, while the **Arroyo *et al.*** study [(11)] showed that there was a substantial difference in the former parameters between both groups. The explanation is that the studies by **Matsuzawa et al** [(10)] **and Arroyo et al** [(11)]**,** were both cross-sectional studies, which aimed mainly at detection of PAD prevalence among HD patients while our study is a case-control study in which matching was done between the two groups as regard age, gender, smoking history, dialysis duration and blood pressure measurements to eliminate the effect of these major cofounding risk factors and to study the sole impact of vitamin D on PAD.

In both the patient and control groups, we discovered a statistically significant link between ABI and HDL-C levels in the blood. **Kronenberg and colleagues**[(12)] **and Vaziri and colleagues** [(13)] stated that low HDL is often already present in an early stage of CKD and could be considered one of the factors that accelerate atherosclerosis in patients on dialysis.

In both patient and control groups, we identified a statistically significant inverse correlation between ABI and blood CRP levels. As a result of uremia-related inflammation and immunological dysfunction, HDL dysfunction, and uremic vasculopathy, patients with end-stage renal disease (ESRD) have an increased risk of atherosclerosis and peripheral arterial disease (PAD) [(14)].

Differences between the two groups were statistically significant as regard cardiovascular events being significantly higher in the patients group in comparison to the control group. This is comparable to the findings of **Matsuzawa *et al.*** [(10)]**,** who observed that the prevalence of CVD and CAD was considerably greater in the PAD group**.** A low ABI (0.9) was shown to be related with a 60% increased risk of all-cause mortality and a 96% greater risk of cardiovascular mortality after controlling for age and gender as well as the conventional cardiovascular risk variables [(15)].

ABI and serum vitamin D levels had a statistically significant beneficial relationship in our study, both in patients and in the control group. Lower 25(OH) D levels have been linked to an increased risk of PAD in studies like those conducted by **Melamed *et al.*** [(16)] who found that there was a gradated connection between decreased 25(OH) D levels and an increased prevalence of PAD.

Numerous hypotheses exist to explain the link between low 25(OH) D levels and PAD. First of all, peripheral arterial disease (PAD) has been linked to vitamin D deficiency, which may explain why vitamin D indicators are lower in individuals with PAD at the time of presentation. Second, vitamin D insufficiency in persons with pre-existing PAD may lead to complications such as atherosclerotic plaque instability or thrombosis, which can lead to disease progression and finally critical limb ischemia (CLI). CLI and intermittent claudication (IC) patients exhibited lower

25(OH) vitamin D concentrations than either controls or patients in the included studies, which lends credence to this hypothesis. Thirdly, Low 25(OH) D levels may potentially be an outcome of PAD rather than a cause of the illness itself. Due to their decreased mobility, people with peripheral artery disease (PAD) may have low levels of 25(OH) D.

A study by **Riek and colleagues**[17] demonstrated that 1; 25-OHD affects macrophages by decreasing the uptake of acetylated and oxidized low-density lipoprotein in type 2 diabetes patients, therefore reducing the production of foam cells and atherosclerosis**. Takeda *et al*[18].** stated that mice fed oral vitamin D3 showed a reduction in atherosclerosis due to a decrease of inflammatory cells; human trials are needed to corroborate these results**.** According to **Somjen *et al.*[19],** one alpha hydroxylase enzyme was detected within vascular smooth muscle cells that locally activate circulating vitamin D.

Multivariate linear regression analysis of the correlated parameters showed that calcium phosphorus product, vitamin D, CRP, TC, LDL, HDL and TG were the most important factors affecting the value of ABI.

This finding is comparable to that of **Arroyo *et al.*[11],** who reported that 25-hydroxivitamin D levels were lower, high-sensitivity C-reactive protein (hsCRP) levels and triglyceride levels were greater, all were the primary predictors of a low ABI.

CONCLUSION

PAD is correlated with cardiovascular events among hemodialysis patients with higher cardiovascular events among those with peripheral arterial disease. Most of peripheral arterial disease patients are asymptomatic. Vitamin D deficiency and higher levels of CRP are major non-traditional factors found in ESRD patients for PAD. Most of ESRD patients are suffering from vitamin D deficiency with lower levels among those with PAD.

Limitations of the study: Our investigation was limited by a small sample size.

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Conflicts of interest: The authors of this research appear to have no conflicts of interest.

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REFERENCES

1. **Coresh J, Selvin E, Stevens L *et al.* (2007):** Prevalence of chronic kidney disease in the United States. JAMA., 298(17):2038–47.
2. **Saran R, Robinson B, Abbott K *et al.* (2017):** US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis., 69(3): 7-8.
3. **Guérin A, Pannier B, Marchais S *et al.* (2006):** Cardiovascular disease in the dialysis population: prognostic significance of arterial disorders. Current Opinion in Nephrology and Hypertension, 15(2):105-10.
4. **Siddiqi R, Paracha M (2010):** Frequency of peripheral arterial disease in patients presenting with acute coronary syndrome at a tertiary care centre in Karachi. J Pak Med Assoc., 60:171-4.
5. **Berger J, Hiatt W (2012):** Medical therapy in peripheral artery disease. Circulation, 126:491–500.
6. **Diehm C, Lange S, Darius H *et al.* (2006):** Association of low ankle brachial index with high mortality in primary care. Eur Heart J., 27:1743-9.
7. **Jing C (2016):** Ankle brachial index and subsequent cardiovascular disease risk in patients with chronic kidney disease. J Am Heart Assoc., 5:003339 – 003339.
8. **Garcia L (2006):** Epidemiology and pathophysiology of lower extremity peripheral arterial disease. Journal of Endovascular Therapy, 13(2): 1-3.
9. **Laghari S, Ullah K, Masroor I *et al.* (2015):** Prevalence of peripheral arterial disease diagnosed by ankle brachial index among chronic kidney disease patients in a tertiary care unit. Saudi Journal of Kidney Diseases and Transplantation, 26(5):924-29.
10. **Matsuzawa R, Aoyama N, Yoshida A (2015):** Clinical characteristics of patients on hemodialysis with peripheral arterial disease. Angiology, 66(10):911-7.
11. **Arroyo D, Betriu A, Valls J *et al.* (2016):** Factors influencing pathological ankle-brachial index values along the chronic kidney disease spectrum: the NEFRONA study. Nephrology Dialysis Transplantation, 32(3):513-20.
12. **Kronenberg F, Lingenhel A, Neyer U *et al.* (2003):** Prevalence of dyslipidemic risk factors in hemodialysis and CAPD patients. Kidney Int., 84: 113–116.
13. **Vaziri N, Liang K, Parks J (2001):** Down-regulation of hepatic lecithin: cholesterolacyltransferase gene expression in chronic renal failure. Kidney Int., 59:2192–2196.
14. **Betjes M (2013):** Immune cell dysfunction and inflammation in end-stage renal disease. Nature Reviews Nephrology, 9(5):255-58.
15. **Chen H, Wei F, Wang L *et al.* (2017):** Abnormal ankle-brachial index and risk of cardiovascular or all-cause mortality in patients with chronic kidney disease: a meta-analysis. Journal of Nephrology, 30(4):493-501.
16. **Melamed M, Muntner P, Michos E *et al.* (2008):** Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. Arteriosclerosis, Thrombosis, and Vascular Biology, 28(6):1179-85.
17. **Riek A, Oh J, Bernal-Mizrachi C (2010):** Vitamin D regulates macrophage cholesterol metabolism in diabetes. The Journal of Steroid Biochemistry and Molecular Biology, 121(1-2):430-3.
18. **Takeda M, Yamashita T, Sasaki N *et al.* (2010):** Oral administration of an active form of vitamin D3 (calcitriol) decreases atherosclerosis in mice by inducing regulatory T cells and immature dendritic cells with tolerogenic functions. Arteriosclerosis, Thrombosis, and Vascular Biology, 30(12):2495-503.
19. **Somjen D, Weisman Y, Kohen F *et al.* (2005):** 25-Hydroxyvitamin D3-1α-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation, 111(13):1666-71.