

RELATIONSHIP BETWEEN VITAMIN (D) LEVEL AND CARDIAC DYSFUNCTION IN HEMODIALYSIS PATIENT

By

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ABSTRACT

Background: Vitamin D deficiency has been associated with inflammation and endothelial and platelet dysfunction, which favours the risk of cardiovascular complications.

Objective: To study the correlation between serum vitamins 25(OH)-VD level and cardiac dysfunction in end stage renal disease patients on regular hemodialysis.

Patients and Methods: This was a cross-sectional study which done in Mustafa Kamel Military hospital an on 50 hemodialysis patients on regular hemodialysis for > 6 months to assess the correlation between serum vitamin D level and cardiac dysfunction in end stage renal disease patients on hemodialysis.

Results: In our patients, we discovered that there was a highly significant relation between vit D deficiency and cardiac dysfunction in HD patients we found strong relation between Vitamin D deficiency with coronary heart disease, decrease Ejection fraction (EF%), increase Left ventricular mass index (LVMI), End diastolic and End systolic and, Diastolic dysfunction and valvular calcification in HD patients with 25-hydroxyvitamin D insufficiency and deficiency.

Conclusion: Clinical studies among patients with CKD on HD have largely that a poor vitamin D status is an independent risk factor for prevalent and incident heart disease, including coronary vascular calcification, heart failure, and CV mortality.

Keywords: Chronic kidney disease, cardiovascular, vitamin D deficiency.

INTRODUCTION

Chronic kidney disease (CKD) is a global health burden estimated to affect up to 15% of adult populations and is independently associated with increased cardiovascular (CV) disease risk similar to the risk of diabetes mellitus or coronary heart disease. This risk increases as CKD

advances and is evidenced by worsening excretory function, usually manifest as declining glomerular filtration rate, and increasing proteinuria. The overall cost of CKD accounts for 1.3% of healthcare budgets of which 13% is related to the excess myocardial infarctions and strokes associated with CKD (*Major et al., 2018*).

Several studies have demonstrated that individuals with CKD are at high risk of vitamin D deficiency (VDD). *Gonzalez et al. (2004)* reported that 97% of the patients on hemodialysis presented inadequate levels of 25(OH)-VD. In a cross-sectional analysis of a cohort study including 1056 United States dialysis units, *Bhan et al. (2010)* showed that 79% and 57% out of 908 individuals on chronic hemodialysis (HD) had 25(OH)-VD levels of <30 and <20 ng/mL, respectively. Hypoalbuminemia, and dialysis initiation during the winter are strong predictors of VDD, whereas VDD was universal in patients presenting with all these three predictors (*Jean et al., 2017*).

Vitamin D deficiency has been associated with inflammation and endothelial and platelet dysfunction, which favor the risk of cardiovascular complications (*Mozos and Marginean, 2015*).

1,25 (OH)₂D has a direct action on myocardial cells, smooth muscle fibres and vascular endothelial cells stimulating the calcium ATPase activity, promoting the calcium transfer to the intracellular space (*Diaz et al., 2015*).

Vitamin D appears to play a more extensive role as a cell differentiates and antiproliferative factor with actions in a variety of tissues including the renal, cardiovascular, and immune systems. As new evidence has improved our understanding of classical, as well as the non-classical, functions for vitamin D, it has become apparent that the autocrine role of vitamin D is an important modulator of several systems including the immune, renal and cardiovascular systems (*Umar et al., 2018*).

In patients with CKD, the new non-classical role of vitamin D also encompasses regulation of the renin-angiotensin system (RAS) and the nuclear factor (NF) κ B pathway.³ These emerging findings establish a new paradigm in approaching treatment to address both the classical and non-classical effects of vitamin D in patients affected by vitamin D deficiency, particularly those with CKD (*Williams et al., 2009*).

Emerging evidence suggests that the progression of CKD and many of the cardiovascular complications may be linked to hypovitaminosis D. So we will study the correlation between serum vitamin 25(OH)-VD level and cardiac dysfunction in end stage renal disease patients on regular hemodialysis.

The present study aimed to study the correlation between serum vitamin 25(OH)-VD level and cardiac dysfunction in end stage renal disease patients on regular hemodialysis.

PATIENTS AND METHODS

Our study was a cross-sectional study which was done in Mustafa Kamel Military Hospital, and conducted on 50 hemodialysis patients on regular hemodialysis for > 6 months to assess the correlation between serum vitamin 25(OH)-VD level and cardiac dysfunction in end stage renal disease patients on hemodialysis.

A written consent was obtained from each patient and the study protocol was approved from the Medical Ethical Committee of the hospital.

Inclusion criteria: Patients >18 y old. Patients on hemodialysis > 6 months.

Exclusion criteria: Decompensated cardiac disease, severely anemic patients (Hb < 7gm/dL) patients who had any malignancy, patients on regular hemodialysis < 6 months.

Patients were subjected to the following: History taking, Clinical examination including measurement of mean arterial blood pressure and Body Mass Index (BMI). Laboratory work-up: Blood samples were collected pre-dialysis for assessment of the following: Serum vitamin 25(OH)-VD level. Serum Creatinine, blood Urea. CBC. Fasting blood glucose. Lipid profile (serum A

Echocardiography: 2D targeted M-mode echocardiography was used to assess different cardiac parameters:

Left ventricular mass index (LVMI): $LVMI(g/m^2) = (1.04 [(IVST + LVID + PWT)^3 - LVID^3] - 14g) / \text{Body surface area}$. According to this formula, LVMI is increased if >134/m² in men and >110 g/m² in women: End diastolic diameter (EDD). Ejection fraction (EF%). Diastolic dysfunction. Valvular calcification. Statistics was done using SPSS program version 20 to evaluate the results.

Statistically method:

The following were done:

1. Descriptive data expressed as mean \pm standard deviation for quantitative

values and as frequency and percentage for qualitative data.

2. Paired sample t-test and one way ANOVA (including post-hoc test) to perform comparison analysis of mean as regard two intervals of time or more within the same group.

P-value >0.05= -significant difference (N.S).

P-value <0.05= significant difference (S).

P-value >0.01= highly significant difference (H.S).

3. Bivariate correlations to study the correlations between different parameters

P-value >0.05=Non-significant correlation.

P-value <0.05= significant correlation.

P-value >0.01= highly significant correlation.

Survival analysis including Kaplan Meier test and Cox regression analysis to assess predictive effect of different factors.

RESULTS

Our sample included 50 patients diagnosed with CKD and on regular hemodialysis, sample included equal number of males and females 1:1, 58% of the sample were diagnosed with DM, while 26% were diagnosed with hypertension, and 54% were diagnosed

with ischemic heart disease (IHD). After assessment of serum vitamin D level using quantitative ELISA test, 78% (n=39) were deficient in vitamin D. Included patients had a mean BMI 25.5 ± 0.75 , MBP 98.1 ± 13.3 mmHg, and HD duration in months (mean 25.9 ± 7.75 months) (**Table 1**).

Table (1): Demographic and clinical data of the studied groups

Clinical data	Parameters	
Age (years)	18±65	
Mean ±SD	25–25	
Range		
	No	%
Sex		
Male	25	50
Female	25	50
DM	29	58
HTN	18	36
IHD	27	54
Prevalence of vit d deficiency	39	78
BMI (kg/m²)		
Mean ±SD	25.5 ± 0.75	
Range	23.8 – 27.1	
MBP (mmHg)		
Mean ±SD	98.1 ± 13.26	
Range	69 – 119	
Hemodialysis duration (months)		
Mean ±SD	25.9 ± 7.75	
Range	11 – 37	

Serum vitamin D level had a mean 16.8 ± 13.16 IU/dl, TLC 6.9 ± 1.49 106/L, serum creatinine 5.4 ± 1.07 mg/ dL and blood urea 151.5 ± 159.29 mg/ dL, regarding lipid profile for the included patient's serum cholesterol had a mean

199.5 ± 30.93 mg/ dL, serum triglycerides 57.2 ± 21.19 mg/ dL, while CRP level was 3.2 ± 1.07 mg/dl and finally Hemoglobin level had a mean of 12.5 ± 6.61 gm/dl. (Table 2).

Table (2): Laboratory data of the studied groups

Variables	Minimum	Maximum	Mean ±S.D.
Serum VIT D level (IU/dl)	5	45	16.8 ± 13.16
TLC (106/L)	4	11	6.9 ± 1.49
Serum creatinine (mg/dl)	3.0	7.0	5.4 ± 1.07
Blood urea (mg/dl)	91	1251	151.5 ± 159.29
Fasting blood sugar (mg/dl)			
Serum Cholesterol (mg/dl)	147	256	199.5 ± 30.93
Serum Triglycerides (mg/dl)	122	211	157.2 ± 21.19
CRP level (mg/dl)	1.0	5.0	3.2 ± 1.07
HB% (g/dl)	11.0	58.0	12.5 ± 6.61

All patients underwent ECHO examination, evaluations of LVMI had a mean of 130.5 ± 37.28 g/m², EDD 5.8 ± 1.17 , EF 41.2 ± 7.92 % and valvular

calcification 38% (n= 19), regarding diastolic dysfunction grade 1 represented 16%, grade 2 22% and grade 3 50% Table (3).

Table (3): Echocardiographic data of the studied groups

Echo data	Parameter		
LVMi (g/m²)			
Mean ±SD	130.5± 37.28		
Range	55 – 167		
EDD (Cm)			
Mean ±SD	5.8 ± 1.17		
Range	3 – 8		
EF %			
Mean ±SD	41.2 ± 7.92		
Range	31 – 56		
Diastolic dysfunction		No	%
	No	8	16
	Grade 1	11	22
	Grade 2	6	12
Valvular calcification	19		38

We defined two groups based on vitamin D level, group 1 has normal vitamin D level and group 2 was vitamin D deficient. Hypertension was significantly more common in patients of

group 2 with p value <0.01, moreover the prevalence of IHD was higher in group 2 with p value <0.01. In addition, MBP was significantly higher in group 1 with p value <0.01 (**Table 4**).

Table (4): Comparison between the two groups as regard demographic and clinical data

Parameters	Group N 1(25)		Group N 2(25)		P value
	No	%	No	%	
Age (years)					>0.05
Mean ±SD	25.3 ± 8.25		28 ± 5.44		
Range	18–60		18–65		
	No	%	No	%	
Sex					>0.5
Male	20	51.3	5	45.5	
Female	19	48.7	6	54.5	
DM	22	56.4	7	63.6	>0.05
HTN	7	17.9	11	100	< 0.01
IHD	16	41	11	100	< 0.01
BMI (kg/m²)					>0.05
Mean ±SD	25.6 ± 0.81		25.5 ± 0.51		
Range	23.8 – 27.1		24.8 – 26.5		
MBP (mmHg)					< 0.01
Mean ±SD	100.7 ± 13.66		89.1 ± 6.12		
Range	69 – 119		79 – 99		
Hemodialysis duration (months)					>0.05
Mean ±SD	25.3 ± 8.25		28 ± 5.44		
Range	11 – 37		19 – 36		

Regarding laboratory tests of both groups, there was no significant difference between both groups in terms of TLC,

serum cholesterol level, serum triglycerides and CRP levels (**Table 5**).

Table (5): Comparison between the two groups as regard laboratory data

Parameters \ Groups	Group 1	Group 2	P value
TLC (106/L)			
Mean \pm SD	6.9 \pm 1.48	6.7 \pm 1.62	0.711
Range	5 – 11	14 – 9	
Serum Cholesterol (mg/dl)			
Mean \pm SD	202.1 \pm 33.62	190.3 \pm 16.55	0.425
Range	147 – 256	168 – 217	
Serum Triglycerides (mg/dl)			
Mean \pm SD	155.7 \pm 22.16	162.6 \pm 17.21	0.181
Range	122 – 211	131 – 189	
CRP level (mg/dl)			
Mean \pm SD	3.1 \pm 1.19	3.5 \pm 3.91	0.192
Range	1 – 5	2 – 5	

Regarding ECHO parameters, groups 1 had significantly higher LVMI with p value <0.01, higher EDD p (value <0.01). While EF was significantly higher in group 2 with normal vitamin D level p value <0.01.

Diastolic dysfunction was more frequent in group 1 with low vitamin D levels with p value <0.01, also valvular calcification was higher in group 1 with p value <0.01 (**Table 6**).

Table (6): Comparison between the two groups as regard echocardiographic data

Parameters \ Groups	Group 1		Group 2		P value	
LVMI (g/m2)						
Mean \pm SD	149.3 \pm 11.85		64.1 \pm 7.27		< 0.01	
Range	128 – 167		55 – 76			
EDD (Cm)						
Mean \pm SD	6.3 \pm 0.79		4.2 \pm 0.75		< 0.01	
Range	5 – 8		3 – 5			
EF %						
Mean \pm SD	37.7 \pm 4.62		53.8 \pm 1.89		< 0.01	
Range	31– 49		51 – 56			
Diastolic dysfunction		No	%	No	%	< 0.01
	No	1	2.6	7	63.6%	
	Grade 1	7	17.9%	4	36.4%	
	Grade 2	6	15.4%	0	0%	
	Grade 3	25	64.1%	0	0%	
Valvular calcification		10	25.6	9	81.8	< 0.01

Using a linear regression model for multivariate analysis, serum vitamin D level was significantly correlated to MBP with p value <0.01, negative correlation indicted that with vitamin D increase MBP drops. Blood urea was significantly correlated to vitamin D level; positive correlation was found between high levels of vitamin D and blood urea level p value 0.015.

Regarding cardiac functions, LVMI was significantly correlated to vitamin D

level with p value <0.01, there was a strong negative correlation between vitamin D level and LVMI R= -0.95. As well as EDD which also reveal a strong positive correlations with serum vitamin D level with p value <0.01.

Finally, left ventricular function (EF) was significantly correlated to serum vitamin D level with p value <0.01, it demonstrate a strongly positive correlations R=0.93 (Table 7).

Table (7): Linear regression model showing correlation between vitamin D level with demographics and clinical data

Clinical data		Serum VIT D level (IU/dl)
Age (years)	R	0.016
	p-value	0.914
BMI (Kg/M2)	R	-0.025
	p-value	0.865
MBP (mmHg)	R	-0.409**
	p-value	< 0.01
Hemodialysis duration (months)	R	0.228
	p-value	0.112
Serum VIT D level (IU/dl)	R	
	p-value	
TLC (106/L)	R	-0.051
	p-value	0.727
Serum creatinine (mg/dl)	R	0.070
	p-value	0.628
Blood urea (mg/dl)	R	0.341*
	p-value	0.015
Fasting blood sugar (mg/dl)	R	-0.087
	p-value	0.550
Serum Cholesterol (mg/dl)	R	-0.139
	p-value	0.334
Serum Triglycerides (mg/dl)	R	0.113
	p-value	0.434
CRP level (mg/dl)	R	0.276
	p-value	0.052
HB% (g/dl)	R	0.279
	p-value	0.050
LVMI (g/m2)	R	-0.958**
	p-value	< 0.01
EDD (Cm)	R	-0.809**
	p-value	< 0.01
EF %	R	0.931**
	p-value	< 0.01

DISCUSSION

In patients suffering from chronic kidney disease (CKD), the prevalence of cardiovascular disease is much more common than in the general population (*Toussaint et al., 2017*).

Their high morbidity and mortality cannot be explained by traditional cardiovascular risk factors, such as advanced age, the presence of diabetes, hypertension, hypertriglyceridemia and low levels of high-density lipoprotein (HDL) cholesterol.

According to studies, also abnormalities of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) are associated with the occurrence of cardiovascular disease (*Fanari et al., 2015*).

Some of them also indicate a relationship between vitamin D deficiency and hypertension, insulin resistance, diabetes, and dyslipidaemia (*Zheng et al., 2013*).

Vitamin D deficiency has been associated with numerous events and conditions in the general population such as falls, fractures, diabetes, autoimmune diseases, cardiovascular and renal diseases, tuberculosis, depression, neurodegenerative diseases, and cancer (*Holick, 2007*).

Vitamin D deficiency is present even in the early stages of chronic kidney disease. Numerous observational studies have confirmed low levels of both total 25-hydroxyvitamin D 25(OH)D which enables the assessment of the adequacy of vitamin D stores) and 1,25-dihydroxyvitamin D (1,25(OH)₂D—biologically active form of vitamin D), in

patients with CKD and end-stage renal disease (ESRD) (*Wang et al., 2014*).

Clinical studies among patients with CKD have largely shown that a poor vitamin D status is an independent risk factor for prevalent and incident heart disease, including coronary vascular calcification, heart failure, and CV mortality (*Toussaint et al., 2017*).

The role of vitamin D deficiency had been underestimated until a significant association was found between vitamin D therapy and survival benefit in haemodialysis patients. Theoretically age may be a risk factor for atherosclerosis and cardiac dysfunction, however in our study there was no significant difference between the two groups. This result is in an agreement with *Beaulieu et al. (2017)* who found no significant effect of age on cardiac function in hemodialysis patients.

As regard sex, there was no significant difference between the two groups. This result is in disagreement with *Masengu et al. (2016)* who found a significant effect of sex on cardiac function in hemodialysis patients as males are more susceptible than females.

In our study, there was no significant difference between the two groups as regard BMI. This result is in agreement with *Voorzaat et al (2017)* who found no significant effect of BMI on cardiac function in hemodialysis patients.

In our study, there was no significant difference between the two groups as regard DM. This result is in disagreement with *Yan et al. (2018)* who found a significant effect of DM on cardiac function in hemodialysis patients.

As regard HTN, there was no significant difference between the two groups. This result is in disagreement with *Bashar et al. (2015)* who found a significant effect of HTN on cardiac function in hemodialysis patients.

End stage renal disease patients are characterized by dyslipidaemia which contributes for inflammation and diffuse atherosclerosis.

In our study, there was no significant difference between the two groups as regard cholesterol and TG levels. This result is in agreement with *Siddiqui et al. (2018)* who found no significant effect of cholesterol and TG on cardiac function in hemodialysis patients. However, as regard LDL and HDL, there was a significant difference between the two groups. This result is in agreement with *Kirkpantur et al. (2008)* who found a significant effect of LDL and HDL on cardiac function in hemodialysis patients.

As regard fasting blood sugar, there was no significant difference between the two groups. This result is in an agreement with *Yan et al. (2018)* who found no significant effect of fasting blood sugar on cardiac function in hemodialysis patients.

In our patients, we discovered that there was a highly significant difference between the two groups as regard vit D deficiency and cardiac dysfunction in HD patients This result is in an agreement with *Gluba-Brzózka et al. (2018)* we found strong relation between Vitamin D deficiency with coronary heart disease, Ejection fraction (EF%), Left ventricular mass index (LVMI), End diastolic and End systolic diameters, Diastolic function and Valvular calcification in HD patients with 25-hydroxyvitamin D insufficiency.

CONCLUSION

Clinical studies among patients with CKD on HD have largely that a poor vitamin D status is an independent risk factor for prevalent and incident heart disease, including coronary vascular calcification, heart failure, and CV mortality.

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دراسة العلاقة بين مستوى فيتامين (د) وقصور وظائف القلب في مرضي الاستصفاة الدموي الكلوي

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خلفية البحث: مرض الكلى المزمن هو مشكلة صحية عامة و مهمة و لها نسبة انتشار مرتفعه، يعاني مرضى الكلى المزمن بشكل عام من نقص فيتامين(د) مقارنةً بعموم السكان بسبب التغيرات المحددة في التمثيل الغذائي للمعادن والعظام الموجودة في هؤلاء المرضى منذ المراحل المبكرة من المرض آثار حالة فيتامين (د) في مرض الكلى المزمن على اضطرابات المعادن والعظام، ومخاطر القلب والأوعية الدموية، واضطرابات التمثيل الغذائي، تم العثور على زيادة في مخاطر الإصابة بأمراض القلب والأوعية الدموية، في وجود نقص فيتامين د.

الهدف من البحث: قياس مدي الارتباط بين نسبة فيتامين د في الدم و وظائف القلب.

المرضى وطرق البحث: قمنا بجمع بيانات من 50 مريضاً متتاليًا تم تشخيص إصابتهم بالفشل الكلوي المزمن و يتلقون العلاج عن طريق غسيل الكلى المنتظم لمدة < 6 أشهر وقمنا بتقييم مستوى فيتامين د باستخدام اختبار ELISA. و عمل موجات فوق صوتيه علي القلب و عمل ارتباطات احصائية بين مستوى فيتامين د و وظائف القلب.

النتائج: أظهرت النتائج أن نموذج الانحدار الخطي للتحليل متعدد المتغيرات، كان مستوى فيتامين (د) في المصل مرتبطًا بشكل كبير بمتوسط ضغط الدم بقيمة، فيما يتعلق بوظائف القلب، ارتبط حجم البطين الايسر ارتباطًا وثيقًا بمستوى فيتامين (د) بقيمة $p < 0.01$ ، وكان هناك ارتباط سلبي قوي بين مستوى فيتامين (د) و $R = -0.95$. وكذلك حجم القلب عند الانبساط الذي يكشف أيضًا عن ارتباط إيجابي قوي بمستوى فيتامين (د) في الدم بقيمة $p < 0.01$. أخيرًا، ارتبطت وظيفة

البطين الأيسر بشكل كبير بمستوى فيتامين (د) في الدم بقيمة $p < 0.01$ ، فقد أظهرت ارتباطاً إيجابياً قوياً $R = 0.93$.

الاستنتاج: في النهاية افضت الدراسات إلى أن مستوى فيتامين (د) في الدم مرتبط بشكل كبير بوظيفة القلب ارتبط مستوى فيتامين د في الدم معنوياً بمؤشر كتلة البطين الأيسر. ارتبط مستوى فيتامين د في الدم بشكل كبير مع تكلس الصمامات. ارتبط مستوى فيتامين (د) في الدم بشكل كبير مع الخلل الانبساطي.

الكلمات الداله: نقص فيتامين د، الفشل الكلوي المزمن، اعتلال القلب.