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Vitamin D Deficiency and Diastolic Dysfunction in Chronic Hemodialysis

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Abstract

Introduction: Vitamin D deficiency is common and may contribute to increased cardiovascular risk. Cardiovascular complications are the main cause of mortality and morbidity in chronic haemodialysis patients. The aim of this study was to determine the frequency of vitamin D deficiency and its association with left ventricular diastolic dysfunction in chronic haemodialysis patients. **Material and Methods:** This was a descriptive cross-sectional study conducted over a 3-month period from 15 November 2021 to 14 February 2022 in the Donka National Haemodialysis Centre. **Results:** Out of a total of 247 haemodialysis patients, cardiac Doppler ultrasonography was performed in 100 patients, with only 21 (8.50%) patients presenting with diastolic dysfunction associated with vitamin D deficiency. The mean age was 43.40 ± 13 years, with extremes of 18 and 68 years. Males predominated in 16 cases (53%). The main cardiovascular risk factors were hypertension and sedentary lifestyle, with proportions of 73.3% and 33.3% respectively. The majority of patients were in group 1 with a deficiency of between (8 - 29 ng/ml), and there was a statistically significant relationship (p = 0.065) between the stage of diastolic dysfunction and vitamin D deficiency. **Conclusion:** Cardiovascular complications are the main cause of mortality and morbidity in chronic haemodialysis patients. 25-hydroxy-vit D (25OHvit D) deficiency is common in dialysis patients. This deficiency is implicated not only in mineral-bone disorders but also in the worsening of diastolic dysfunction. Only 21 (8.50%) patients had diastolic dysfunction associated with vitamin D deficiency. Studies including large sample size and potential confounding factors such as diet, duration of dialysis and seasonal variations in vitamin D synthesis could provide the most accurate possible answer to this question of cardiovascular morbidity and mortality in chronic haemodialysis patients.

Keywords

Vitamin D Deficiency, Diastolic Dysfunction, Chronic Haemodialysis Patients

1. Introduction

Cardiomyocytes, smooth muscle cells and vascular endothelial cells, in particular fibroblasts, express VDR and 1α-hydroxylase, an enzyme that enables the production of the active form of vitamin D, calcitriol or 1,25(OH)2-vitamin D from 25(OH)D. In myocardial hypertrophy, VDR is overexpressed [1]. There are many studies in favour of the involvement of vitamin D in the pathophysiology of cardiovascular events. There are also numerous studies of the association between low vitamin D and cardiovascular events and/or mortality. Intervention studies on the intermediate parameters that explain cardiovascular events. However, there are contradictory studies and studies that show an abrupt increase in the number of cardiovascular events for low concentrations of 25(OH)D (<20 ng/ml) [2].

Vitamin D deficiency is common and may contribute to increased cardiovascular risk [3]. Cardiovascular complications are the main cause of mortality and morbidity in chronic haemodialysis patients [4]. Annual mortality from cardiovascular disease in dialysis patients is substantially higher than in the general population. They are responsible for around 50% of deaths and 30% of hospitalisations in dialysis patients [4]. This disparity is present at all ages but is most marked in the youngest age group (25 to 34), where cardiovascular mortality is 500 times higher in patients with ESRD than in controls of the same age with normal kidney function [5]. For example, 40% of patients who have started dialysis show signs of coronary heart disease, and 85% of these patients have abnormal left ventricular structure and function [5]. Vitamin D plays a key role in bone health, but its role in the prevention of a number of diseases could become increasingly important, particularly in the cardiovascular field [2]. 25-hydroxy-vit D (25OHvit D) deficiency is common in dialysis patients. This deficiency is implicated not only in mineral-bone disorders but also in the worsening of diastolic dysfunction (DD), left ventricular hypertrophy (LVH) and vascular calcifications [6]. In a review (Pilz *et al*., 2011), Grandi's meta-analysis found an 83% increase in risk for serum 25(OH)D concentrations of between 10 and 20 ng/ml; more cardiovascular events were observed for low 25(OH)D concentrations, but also for high 25(OH)D concentrations [2]. Two other studies, one assessing the risk of acute coronary events and coronary mortality (Dror *et al*., 2013) and the other cardiovascular mortality (Durup *et al*., 2012) show an increase in events for concentrations below 20 ng/ml and a modest increase in the number of events above 36 to 40 ng/ml [2].

In Algeria in 2023, in a series of 109 chronic haemodialysis patients with uraemia, vitamin D deficiency (<10 ng/mL) was predominant in 37.61% of patients, followed by deficiency (10 - 20 ng/mL) in 30.27% and insufficiency (20 - 30 ng/mL) in 18.34% [7]. It remains difficult to say whether vitamin D insufficiency is the cause or consequence of cardiovascular disease. Numerous observational and experimental studies provide arguments in favour of a protective role for vitamin D against cardiovascular disease [2]. In Guinea no studies have been carried

out on this subject, as the high mortality rate due to cardiovascular complications in chronic haemodialysis patients. The aim of this study is therefore to determine the frequency of vitamin D deficiency and its association with left ventricular diastolic dysfunction in chronic haemodialysis patients.

2. Materials and Methods

This is a descriptive cross-sectional study in the Donka National Haemodialysis Centre, located within the Donka University Hospital. This is a public dialysis centre that currently has 30 dialysis machines. It is also the only national centre for public dialysis, a reference centre for renal diseases and the treatment of chronic end-stage renal failure.

Chronic haemodialysis patients constituted the study material, the study media were the medical records of haemodialysis patients, dialysis diaries, reports of cardiac echo-Doppler and biochemical results of vitamin D3 and a survey form for data collection. This was a cross-sectional descriptive study conducted over a 3-month period from 15 November 2021 to 14 February 2022.

Chronic haemodialysis patients were targeted during the study period; the study population consisted of haemodialysis patients with vitamin D3 deficiency who had undergone cardiac Doppler echocardiography concluding in left ventricular diastolic dysfunction. Chronic haemodialysis patients with a clinical presentation of right, left or congestive heart failure despite regular haemodialysis were included in the study. These haemodialysis patients were selected on the basis of a blood vitamin D3 deficiency of less than or equal to 29 ng/ml and who had a cardiac echodoppler E/A ratio of less than 1, confirming left ventricular diastolic dysfunction.

All patients receiving chronic haemodialysis during the study period who met the inclusion criteria were recruited. A minimum sample of 21 patients was obtained, all of whom had vitamin D3 deficiency associated with left ventricular diastolic dysfunction. The haemodialysis centre was the study setting for the management of haemodialysis patients. It was far from the cardiology department, which is a referral service for cardiovascular diseases, and the low economic level was an obstacle to the performance of cardiac ultrasound. The data was collected on an individual survey form.

The variables were defined by epidemiological data (frequency, age, sex), clinical data (initial nephropathy, cardiovascular history, cardiovascular risk factors, cardiovascular physical signs), biological data (vitamin D3 blood test) and cardiac echodoppler data.

- Epidemiological data:
  - Frequency: the number of patients with vitamin D3 deficiency associated with diastolic dysfunction out of the number of haemodialysis patients during the study period expressed as a percentage.
  - Age: Divided into age groups of 10-year amplitude to determine the mean age.

- Sex: to determine the M/F sex ratio.

- Clinical data
- Initial nephropathies:
  - Vascular nephropathy: characterised by a history of arterial hypertension, low proteinuria of less than 1 g/24h, left ventricular hypertrophy and retinopathy of variable stage;
  - Diabetic nephropathy: history of diabetes associated with microalbuminuria or proteinuria and diabetic retinopathy.
  - Glomerular nephropathy: this is defined as glomerular proteinuria greater than 1.5 g/L, with or without microscopic haematuria, often associated with hypertension.
  - Chronic tubulo-interstitial nephropathy: this was suggested by the combination of a history of chronic pyelonephritis, malformative uropathy, humped kidneys, tubular proteinuria (less than or equal to 0.5 g/L), isolated leucocyturia, without oedema, and without hypertension ;
  - Undetermined nephropathy: this corresponded to cases not classified because of an incomplete paraclinical work-up.
- Cardiovascular antecedents: these were acute, chronic pathologies already treated and prior to the current pathology (hypertension, diabetes, HIV, stroke, heart disease, pulmonary tuberculosis).
- Modifiable cardiovascular risk factors:
  - HTA: PAS ≥ 140 mmHg, and/or PAD ≥ 90 mmHg, confirmed by three successive consultations
  - Smoking: active smoker or smoker who has stopped smoking for less than three years, expressed in packs/year was sought in patients.
  - Dyslipidaemia: increase in LDL cholesterol, decrease in HDL cholesterol
  - Obesity: body mass index (BMI) ≥ 30 kg/m^2
  - Diabetes: hyperglycaemia ≥1.26 g/L (7 mmol/L)
  - Sedentary lifestyle: absence of regular physical activity.
- Cardiovascular physical signs: irregular BDC, IMO, crackling rales, heart murmur, pericardial friction, ascites.
- Biological data: vitamin D3 blood assay: patients were divided into 3 groups according to values of results obtained: group1: 8 - 29 ng/ml, group2: 30 - 45 ng/ml, group3: 46 - 49 ng/ml. These values can be used to look for cases of diastolic dysfunction without vitamin D deficiency, in order to find a correlation between vitamin D and dystocic dysfunction.
- Cardiac echo-doppler data: the device used was SONOSITE M-TURBO, connected to a 5 MHZ ultrasound probe in the cardiology department of the Ignace Deen University Hospital, the device was used to look for diastolic dysfunction in chronic haemodialysis patients, who were selected at the Donka national haemodialysis centre. The patient lies on an examination table, naked on their left side in a dark room, to make it easier to read the images. The practitioner then applies a skin gel to the thorax to promote good ultrasound

transmission. The ultrasound echoes are recorded by a computer, which converts them into an image that can be seen on a screen. Once the examination is complete, the doctor interprets the results.

The study of diastolic dysfunction was possible thanks to the assessment of three parameters; E/A ratio <1, E/E' ratio ≥15 and LVEF ≥ 50% according to the Redfield classification.

Diastolic dysfunction:

- Mild: E/A < 0.75 and E/E' < 10
- Moderate: E/A < 0.75 - 1.5 and E/E' ≤ 10 - 15
- Severe: E/A > 1.5 and E/E' ≥ 15.

Type of diastolic dysfunction: the stage of severity of the dysfunction is divided into: mild stage, moderate stage, severe stage, diastolic dysfunction associated with systolic dysfunction, isolated diastolic dysfunction.

LV filling pressure: LV filling pressures are high when E/E' ≥ 15 LV filling pressures are intermittent when E/E' ≤ 10 - 15

Systolic dysfunction: Impaired ejection fraction: defined as LVEF < 40% moderate to impaired ejection fraction: defined as LVEF = 40% - 50% Preserved ejection fraction: defined as LVEF > 50%.

The data were collected on a survey form, the data were checked by manual tabulation, then entered into the 2016 office pack (Word, Excel).

The data were analyzed and processed using Epi info 7.4.0 software, the Chi-square test was used to determine a correlation between the associated variables, any P-value less than 0.05 was considered statistically significant.

3. Results

- Epidemiological data
  - Frequency: out of a total of 247 haemodialysis patients, cardiac Doppler ultrasound was performed in 100 patients only 21 (8.50%) patients had diastolic dysfunction associated with vitamin D deficiency (Figure 1).

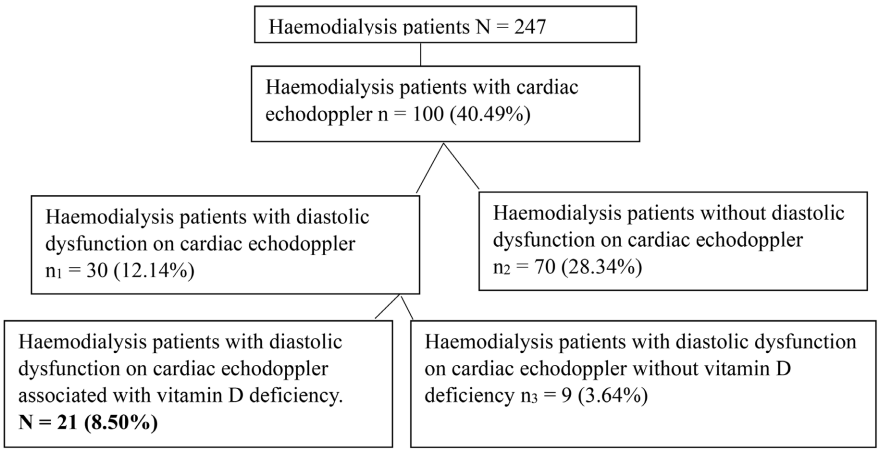

Figure 1. Frequency of patients with vitamin D3 deficiency associated with diastolic dysfunction.

- Age: Of 21 patients presenting with diastolic dysfunction, 6 cases (29%) were in the 38 - 47 age group, with an average age of 43.40 ± 13 years and extremes of 18 and 68 years. Males predominated in 11 cases (52.38%) (Table 1).

Table 1. Age distribution of patients with diastolic dysfunction.

Age	Workforce (N = 21)	Percentage
18 - 27	2	9.52
28 - 37	4	19.04
38 - 47	**6**	**29**
48 - 57	5	23.80
≥58	4	19.05
Gender		
Male	**11**	**52.38**
Female	10	47.62

- Clinical data:
  - Initial nephropathies: of 21 patients with diastolic dysfunction the main nephropathy responsible for the initiation of chronic haemodialysis was dominated by glomerular nephropathy 8 cases or 38.09% (Table 2).

Table 2. Distribution of patients with diastolic dysfunction according to initial kidney disease.

Initial kidney disease	Workforce (N = 21)	Percentage
Glomerular nephropathy	8	38.09
Nephropathy undetermined	7	33.3
Vascular nephropathy	4	20
Diabetic nephropathy	1	3.4
Chronic tubulointerstitial nephropathy	1	3.4

In the population studied, the main cardiovascular risk factors were hypertension and sedentary lifestyle, with proportions of 71.42% and 33.33% respectively (Table 3).

The physical signs observed were dominated by oedema of the lower limbs (30%), followed by irregular BDC (36.3%) (Table 4).

Haemodialysis patients presenting with diastolic dysfunction associated with vitamin D deficiency, the majority of patients were in group 1 with a deficiency of between (8 - 29 ng/ml), there was a statistically significant relationship (p = 0.065)

between the stage of diastolic dysfunction and vitamin D deficiency (Table 5). There was also a significant correlation between the type of diastolic dysfunction and the vitamin D deficiency groups (Table 6).

Table 3. Breakdown of patients according to cardiovascular risk factors.

Cardiovascular risk factors	Workforce (N = 21)	Percentage
HTA	15	71.42
Sedentary lifestyle	7	33.33
Age	6	28.6
Smoking	4	19.05
Menopause	3	14.29
Diabetes	1	6.6
Gender	1	6.6

Table 4. Distribution of patients with diastolic dysfunction by physical signs observed.

Physical sign	Workforce	Percentage
Irregular BDC	8	38.09
Oedema of the lower limbs	6	28.57
Crackling rales	5	23.81
Heart murmur	4	19.04
Pericardial friction	1	3.3
Ascite	3	14.28

Table 5. Distribution of patients according to stage of diastolic dysfunction by vitamin D deficiency group.

Stadium	Vitamin D			P-Value
	8 - 29	30 - 45	46 - 49	
Slight				0.3952
Yes	8	1	0	
No	13	6	2	
Moderate				0.0658
Yes	6	5	1	
No	15	2	1	
Severe				0.5096
Yes	7	1	0	
No	14	6	2	

Table 6. Distribution of patients according to type of diastolic dysfunction by vitamin D deficiency group.

Type of diastolic dysfunction	Vitamin D			P-Value
	8 - 29	30 - 45	46 - 49	
Isolated diastolic dysfunction				0.3952
Yes	8	1	0	
No	13	6	2	
Isolated diastolic dysfunction				0.0658
Yes	6	5	1	
No	15	2	1	
Severe				0.5096
Yes	7	1	0	
No	14	6	2	

4. Discussion

In this study there were 247 haemodialysis patients, Doppler ultrasound was performed in 100 patients and only 21 patients (8.50%) had diastolic dysfunction associated with vitamin D deficiency. The mean age of the patients was 43.40 ± 13 years, and 11 cases (52.38%) were predominantly male. The basic nephropathy responsible for end-stage renal disease was dominated by glomerular nephropathy in 8 cases (38.09%). The main cardiovascular risk factors were arterial hypertension and a sedentary lifestyle. The combination of end-stage renal disease, chronic haemodialysis and cardiovascular risk factors had an impact on both diastolic dysfunction and vitamin D deficiency in the majority of patients, with a statistically significant relationship between diastolic dysfunction and vitamin D deficiency ($p = 0.065$). This association exposes haemodialysis patients to cardiovascular risk, a result similar to some data in the current literature.

Marie courbebaisse *et al.* Reported in Paris in 2013 that vitamin D deficiency affects around 50% of the worlds population. In addition to these classic effects on mineral metabolism, vitamin D has numerous effects outside the bones, including effects on the cardiovascular system [2].

Zini *et al.* in 2020, in Tunisia at the Sfax University Hospital, found a deficiency in 86.7% of patients, 52.9% of whom had a vit D deficiency (15 - 30 ng/mL) and 33.8% a deficit (vit D < 15 ng/mL). Diastolic dysfunction was noted in 71% of patients. Of these 49 patients, 26 had minimal diastolic dysfunction, 19 moderate diastolic dysfunction and 4 severe diastolic dysfunction. The mean age was 52 years [24 - 91 years] with a sex ratio of 1.8. Initial kidney disease was chronic glomerular, chronic interstitial, vascular and undetermined in 31%, 24%, 11% and

34% of patients respectively [6].

Pr Laidouni *et al.* in 2023 in Algeria reported on 109 chronic haemodialysis uraemic patients who were included in the present study. The mean age of the patients was 54.85 ± 15.42 years. Vitamin D status was low, with a mean of 16.74 ± 12.97 ng/mL. Vitamin D deficiency (<10 ng/mL) was predominant in 37.61% of patients, followed by deficiency (10 - 20 ng/mL) in 30.27% and insufficiency (20 - 30 ng/mL) in 18.34% [7].

Busuioc et al in 2014 reported our experience of 57 patients (28 female, 29 male) with a mean age of 71 (45 - 92). Left ventricular mass index, left atrial diameter, isovolumic relaxation time and E/A ratio were significantly higher in patients with lower 25 (OH) D levels. Serum 25 (OH) D levels were separated into three groups: low (<20 ng/mL), moderate (20 - 45 ng/mL) and high (>45 ng/mL). 70% of patients had diastolic dysfunction and 30% had normal diastolic function [3].

The limitations of the study in comparison with the literature are to be found in the methodology, essentially retrospective in some studies and cross-sectional in others, but also in the study durations. However, the study populations are the same, which are made up of chronic haemodialysis patients, in this population there are still factors influencing vitamin D deficiency associated with diastolic dysfunction. These factors were not taken into account in this study, such as diet, haemodialysis lifespan and seasonal variations, which may be limitations of this study to be taken into account, impacting on the internal validity of the results. These different studies produced the same results, which are superimposable. These observations give external validity to this study. The comparison gives a generalisable character to the results obtained in relation to certain data in the current literature.

Ethical considerations: In the field, the informed consent of the participants was obtained before submitting them to the questionnaire and strict confidentiality was respected.

Limitations of the study: During the course of the study, our difficulties were a lack of financial resources and a reluctance to carry out vitamin D tests and cardiac ultrasound because of the cost.

5. Conclusion

Cardiovascular complications are the main cause of mortality and morbidity in chronic haemodialysis patients. 25-hydroxy-vit D (25OHvit D) deficiency is common in dialysis patients. This deficiency is implicated not only in mineral-bone disorders but also in the worsening of diastolic dysfunction, left ventricular hypertrophy and vascular calcifications. In this study, cardiac Doppler ultrasound was performed on 100 patients, with only 21 patients (8.50%) showing diastolic dysfunction associated with vitamin D deficiency. The majority of patients were in group 1 with a deficiency of between (8 - 29 ng/ml), and there was a statistically significant relationship ($p = 0.065$) between the stage of diastolic dysfunction and vitamin D deficiency. Studies including a large sample and potential confounding

factors such as diet, duration of dialysis and seasonal variations in vitamin D synthesis will be able to provide more precise answers to the question of cardiovascular morbidity and mortality in chronic haemodialysis patients.

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Conflicts of Interest

This manuscript is not the subject of any conflict between the authors and is not submitted to any other journal.

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