ARTICLE ORIGINAL / ORIGINAL ARTICLE

# PREVALENCE OF PERIPHERAL VASCULAR CALCIFICATIONS IN PATIENTS ON CHRONIC HEMODIALYSIS AT A TERTIARY CARE CENTER IN BEIRUT
## A Pilot Study

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Al-Rifai R, Arabi A, Masrouji R, Daouk M. Prevalence of peripheral vascular calcifications in patients on chronic hemodialysis at a tertiary care center in Beirut: A pilot study. J Med Liban 2011 ; 59 (3) : 117-121.

**ABSTRACT • BACKGROUND : Vascular calcifications are highly prevalent in patients maintained on chronic hemodialysis. They have been linked to numerous risk factors and have been associated with an increased risk of cardiovascular morbidity and mortality. The purpose of this pilot study is to assess the prevalence of vascular calcifications among dialysis patients in our tertiary care center and to identify the associated risk factors.**

**METHODS : In the current study, we reviewed the charts of 43 patients undergoing hemodialysis at our center. We estimated the prevalence of vascular calcifications among dialysis patients using plain X-ray of the hand as the screening tool. We compared patient's characteristics and tried to identify possible risk factors, with a special emphasis on the subgroup of patients with diabetes.**

**RESULTS : Vascular calcifications were prevalent among half of the patients on hemodialysis. Duration of dialysis ($p = 0.02$), diabetes ($p < 0.001$), and hypertension ($p = 0.01$) were highly associated with vascular calcifications. No association was found between vascular calcifications and age, gender, calcium-based phosphate binders, vitamin D supplementation, smoking, and lipid control. In multivariate analyses, diabetes and duration of dialysis were the only independent predictors of vascular calcifications and diabetics developed vascular calcifications earlier than non-diabetics (31 months vs 69 months].**

**CONCLUSION : Vascular calcifications are moderately prevalent among patients undergoing hemodialysis at our center, and were found to be strongly correlated with diabetes and duration of dialysis. A larger, multicenter, prospective study should be conducted at national level, in order to confirm the findings of this study and to identify further modifiable risk factors, to decrease the incidence of vascular calcifications and the incurring cardiovascular morbidity and mortality in our population.**

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Al-Rifai R, Arabi A, Masrouji R, Daouk M. La prévalence des calcifications vasculaires chez les patients sous hémodialyse chronique : Une étude pilote. J Med Liban 2011 ; 59 (3) : 117-121.

**RÉSUMÉ • Les calcifications vasculaires (CVs) sont très répandues chez les patients maintenus sous hémodialyse chronique. Ces calcifications ont été associées à un risque accru de morbidité et mortalité cardiovasculaires. Le but de cette étude était d'évaluer la prévalence de CVs chez les patients maintenus sous hémodialyse au Liban et d'identifier les facteurs de risque.**

**MÉTHODES : Nous avons examiné les dossiers de 43 patients maintenus sous hémodialyse au centre médical de l'Université américaine de Beyrouth. Une radiographie de la main a été utilisée pour dépister la présence de CVs chez ces patients et nous avons étudié les caractéristiques cliniques et biochimiques des patients afin d'identifier les facteurs de risque.**

**RÉSULTATS : Les CVs ont été détectées chez la moitié des patients. La durée de dialyse ($p = 0,02$), le diabète ($p < 0,001$), et l'hypertension ($p = 0,01$) étaient fortement associés aux CVs. Aucune association n'a été trouvée avec d'autres facteurs de risque tel que l'âge, le sexe, l'utilisation de chélateurs de phosphate à base de calcium, la supplémentation en vitamine D, le tabagisme ou les taux de lipides. Après ajustement pour les autres facteurs de risque, le diabète et la durée de la dialyse ont été les seuls prédicteurs indépendants de CVs. En plus, les diabétiques ont développé des CVs plus tôt que les non-diabétiques (Médiane 31 mois après le début d'hémodialyse chez les diabétiques contre 69 mois chez les non-diabétiques).**

**CONCLUSION : La prévalence de CVs est élevée chez les patients sous hémodialyse au Liban. Une forte corrélation avec le diabète et la durée de dialyse a été constatée. En outre, une étude plus large devrait être menée au niveau national, en collaboration avec les autres centres de dialyse au Liban, pour confirmer les résultats de cette étude et/ou identifier d'autres facteurs de risque modifiables, afin de diminuer l'incidence des calcifications vasculaires et par conséquent la morbidité et la mortalité cardiovasculaires dans cette population.**

## INTRODUCTION

Vascular calcifications (VCs) are highly prevalent among chronic kidney disease (CKD) and hemodialysis patients [1-5]. Russo et al. reported that 40% of all CKD patients had VCs as compared to 13% in a matched controlled population. Hemodialysis patients have VCs even more frequently.

Over the last decade, VCs have emerged as a potential cause of increased morbidity and cardiovascular mortality in CKD and HD patients [1-2, 8].

Vascular calcification may occur at any site. They may promote arterial stiffness, left ventricular hypertrophy (LVH), cardiovascular events, and mortality depending upon the two distinct types of VCs: intimal and medial wall calcifications. A recent report showed that the presence of any vascular calcification in hemodialysis patients was associated with reduced survival although intimal lesions promote worse prognosis compared to medial ones [6].

Several observational studies in dialysis patients have shown that abnormal mineral metabolism, a consequence of chronic kidney disease, is a main predictor for increased cardiovascular and overall mortality [1, 5-6]. This has led the Kidney Disease Improving Global Outcomes (KDIGO) to recommend a new classification for chronic kidney disease mineral and bone disorder (CKD-MBD) that includes the presence of VC.

Several risk factors have been associated with VC among which are the classic: aging, hypertension, diabetes, dyslipidemia, and smoking. Other risk factors are more specific to CKD such as abnormal mineral metabolism.

Diabetes has been associated with a higher incidence of vascular calcification, and it has been shown to be one of the most significant predictors for the presence of VCs [3]. The most significant predictor in diabetic patients being poor glycemic control, whereas older age and longer duration of dialysis were the most important factors in non-diabetics [3].

Often the patient has no, or nonspecific symptoms. Several imaging techniques have been described in the literature as possible screening tools for vascular calcifications ranging from the more sophisticated EBCT or multislice CT of coronaries, to ultrasonography of the large arteries or echocardiography to assess for the presence of valvular calcifications, to a simple plain X-ray [1, 4]. Although EBCT of coronaries is considered the gold standard for quantitative evaluation of vascular calcification, it is very expensive, not widely available, and is nonspecific in dialysis patients. It does not distinguish between intimal and medial wall calcification. Thus, using any of the plain X-ray methods is inexpensive, easy to interpret, and useful in terms of cardiovascular risk stratification as well as therapeutic guidance [1, 6]. Different X-ray methods can be used to identify VC in dialysis patients: plain X-ray of hand and pelvis, the abdominal aorta, or the vascular access [1].

The prevalence and severity of VC vary according to the population studied and to the vascular bed assessed [2]. To our knowledge the prevalence of VC in Lebanese patients undergoing hemodialysis has not been previously studied. Thus, we aimed in this pilot study at estimating the prevalence of VC among patients undergoing hemodialysis at a tertiary care center (American University of Beirut), using plain X-ray of the hand as the screening tool.

## METHODS

### Subjects

Medical records of 43 patients undergoing hemodialysis at the American University of Beirut Medical Center were reviewed. The clinical practice at our hemodialysis center is to measure serum calcium, phosphorus on monthly basis by standard calorimetric methods, using the Hitachi 912 analyzer (Mannheim, Germany) and serum PTH is measured every 6 months by ELSA-PTH immunoradiometric assay (CisBio International, Gif-sur-Yvette, Cedex, France). A plain X-ray of the hands is done once yearly.

Demographic, clinical and biochemical data of the last year were retrieved. The mean values of serum PTH, calcium and phosphorus levels measured during the last year were calculated and used in the analyses. The last X-rays of the hands were assessed qualitatively for the presence or absence of vascular calcifications.

The study was approved by the institutional review board of the American University of Beirut.

### Statistical analysis

The prevalence of vascular cacifications among all patients was calculated. The relationship between vascular calcifications and potential risk factors was assessed in bivariate analyses and then in multivariate analyses. In bivariate analyses, t-test was used to assess the relationship with continuous variable such as age, mean calcium, phosphorus, PTH, lipid levels, and duration of dialysis. Chi-square assessed the relationship with categorical variables such as presence of diabetes, hypertension, smoking and gender. Multivariate analysis was then performed in order to determine the independent predictors of VC using binary logistic regression. The model was built with the presence or absence of VCs as an outcome and the variables showing a significant relationship with VCs in the bivariate analyses as independent variables.

**TABLE I**
CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION*

| Characteristics | Yes / *No* |
|---|---|
| Smoking | 7 (16.3%) / *36 (83.7%)* |
| Diabetes | 19 (44.2%) / *24 (55.8%)* |
| Hypertension | 38 (88.4%) / *5 (11.6%)* |
| Calcium based phosphate-binders | 39 (90.7%) / *4 (9.3%)* |
| Non-Calcium based phosphate-binders | 2 (4.7%) / *41 (95.3%)* |
| Calcium channel-blockers | 21 (48.8%) / *22 (51.2%)* |
| ACEI's | 6 (14.%) / *37 (86%)* |
| Alfacalcidiol | 31 (72.1%) / *12 (27.9%)* |
| Hypoglycemic agents | 14 (32.6%) / *29 (67.4%)* |
| Warfarin | 4 (9.3%) / *39 (90.7%)* |
| ß-blockers | 21 (48.8%) / *39 (90.7%)* |

* N = 43 [25 (65%) Males & 18 (35%) Females]. Values are: numbers (%).
**ACEI**: Angiotensin-converting enzyme inhibitors

## RESULTS

Clinical and demographic data of the study population are shown in Table I.

Data from medical records of 43 subjects undergoing dialyses [25 men (65%) and 18 women (35%)] were retrieved. Five patients did not yet have X-ray of hands done probably due to recent initiation of dialysis. The median age of the study population was 72 years [43-90] and a median duration of dialysis of 22 months [1 month-25 years]. The median height was 166.5 cm [144-180] and the median weight was 66.5 kg [36-97].

Nineteen subjects (44.2%) were diabetics, 38 (88.4%) were hypertensive, 7 (16.3%) were smokers. Among the 43 patients included in the study, 19 (44.2%) had vascular calcifications and 19 were disease-free. X-ray was not available for 5 patients (11.6%). Thirty-one subjects (72%) were on alfacacidiol, 39 (90.7%) were on Ca-based phosphate binders, and only 2 patients (4.7%) were on Sevalamer. Other medications used included ACEI's in 14%, ß-blockers in 48.8%, and warfarin in 9.3% of patients.

Subjects with VC had higher mean systolic blood pressure (140.2 ± 22.4 vs 124.7 ± 8.9, $p = 0.01$), lower serum HDL levels (38.7 ± 6.2 vs 59.5 ± 29, $p = 0.05$) and were on dialysis for a longer duration (44.8 ± 31.7 months vs 25.3 ± 26.6 months, $p = 0.02$) compared to those without VC (Table II).

Fourteen (74%) of the subgroup of patients with VC were diabetics as compared to 3 (16%) in those without VC ($p < 0.001$). All patients with vascular calcifications and 74% of subjects without vascular calcifications were hypertensive ($p = 0.01$ for difference between groups).

No association was found between VC and gender, smoking, serum calcium, phosphorus, iPTH levels, intake of calcium-containing phosphate binders and/or vitamin D analogues.

In multivariate analyses, only diabetes and duration of dialysis were independent predictors of vascular calcifications ($p = 0.09$ and 0.02 respectively). Moreover, diabetic subjects developed VC earlier than non-diabetics (median duration of 31 months vs 69 months, $p = 0.02$) [Figure 1].

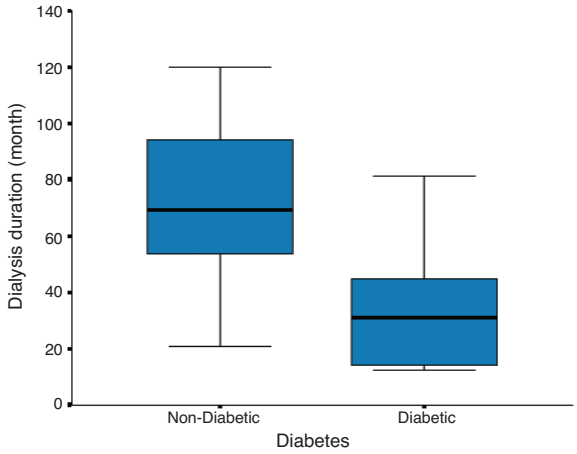


**FIGURE 1.** Box-plots showing the median, 25th & 75th percentiles of the duration on dialysis in diabetic and in nondiabetic patients having vascular calcifications. Diabetics developed vascular calcifications after a median duration of 31 months whereas non-diabetics developed vascular calcifications after a median duration of 69 months, $p = 0.02$ for difference between groups.

## DISCUSSION

This pilot study found that half of the population undergoing hemodialysis at our center developed peripheral vascular calcifications after a median duration of 22 months (mean 39 ± 50). Patients who developed VC were all hypertensive, had higher systolic blood pressure and lower HDL levels than those without VC. Dialysis duration and diabetes were independent predictors of VC and diabetic patients developed VC earlier than non-diabetics.

In 2004, Russo et al. reported that 40% of all CKD patients had VCs as compared to 13% in a matched con-

**TABLE II** BIOCHEMICAL CHARACTERISTICS OF PATIENTS WITH VASCULAR CALCIFICATIONS, WITHOUT VASCULAR CALCIFICATIONS AND IN THE WHOLE POPULATION*

| | Population | | | *p*-value** |
|---|---|---|---|---|
| | Overall | With vascular calcifications | Without vascular calcifications | |
| **Calcium** (mg/dl) | 9.1 ± 0.6 | 9.0 ± 0.7 | 9.2 ± 0.8 | *0.47* |
| **Phosphorus** (mg/dl) | 5.2 ± 1.0 | 5.5 ± 1.1 | 5.1 ± 1.0 | *0.28* |
| **PTH** (pg/ml) | 328 ± 299 | 424 ± 405 | 246 ± 227 | *0.23* |
| **Total cholesterol** | 166 ± 39 | 160 ± 37 | 175 ± 40 | *0.4* |
| **LDL** (mg/dl) | 86 ± 31 | 98 ± 53 | 83 ± 38 | *0.7* |
| **HDL** (mg/dl) | 45.6 ± 14.4 | 38 ± 6 | 59 ± 29 | *0.05* |
| **Triglycerides** (mg/dl) | 175.1 ± 99.4 | 239 ± 221 | 169 ± 45 | *0.4* |
| **Systolic BP** (mmHg) | 130.0 ± 16.6 | 140.2 ± 22.4 | 124.7 ± 10.9 | *0.01* |
| **Diastolic BP** (mmHg) | 73.3 ± 6.3 | 75.3 ± 6.1 | 72.8 ± 8.9 | *0.3* |
| **Duration of dialysis** (months) | 39.4 ± 50.4 | 44.8 ± 31.7 | 25.3 ± 26.6 | *0.02* |

* Values are mean SD. ** *p*-values for difference between subjects with vascular calcifications and those without vascular calcifications using t-test.
**PTH:** Parathormone **LDL**: Low density lipids **HDL**: High density lipids **BP:** Blood pressure

trolled population. HD patients have VCs even more frequently; for instance 77.9% of HD patients had abdominal aortic calcifications and 57.4% had diffuse severe calcifications as compared to 37.5% and 17% in the general population respectively [2]. We expected vascular calcifications to be highly prevalent in our patients, even higher than those reported in the literature because of the high prevalence of diabetes and the high use of calcemic containing phosphate binders. Some studies in dialysis patients have demonstrated that vascular calcifications may progress or remain stable depending on the control of mineral metabolism alterations and that phosphate binder choice may have an impact on mortality [9]. London et al. showed an association between vascular calcifications and low bone turnover and found a significant interaction between calcium-containing phosphate binders and aortic calcifications and stiffness in the presence of adynamic bone disease [9-10]. However, only peripheral vascular calcifications were assessed in the current study using a plain X-ray film, which obviously has lower sensitivity than other methods in detecting VC. Moreover, the small sample size may have falsely lowered the prevalence in the current study.

Diabetes has been emphasized to be a strong risk factor for atherosclerotic cardiovascular disease, cardiac calcification, and peripheral vascular disease in chronic hemodialysis patients [5]. This is in consistence with our findings, where diabetes seems to be a strong predictor for the development of peripheral vascular calcifications ($p < 0.001$). This effect was independent of other risk factors. Indeed, only diabetes and duration of dialysis were independent predictors of the development of VCs in multivariate analyses. Patients with VCs were maintained on dialysis for a longer duration than those who did not have VC. Interestingly, diabetic subjects developed VC at almost half duration compared to non-diabetics. This is similar to results of many studies which have demonstrated a strong association between diabetes and the development of VCs with more than four-fold increased risk. Diabetes-related VCs are known to occur long before the initiation of dialysis. This could be attributed to the fact that diabetes is involved in both types of VCs but mainly medial calcifications which tend to be rapidly progressive [4]. Furthermore, duration of dialysis has been persistently described as an independent risk factor for the development of VCs in several studies [2-5].

We aimed to assess the glycemic control and check whether higher values of HbA1c are associated with higher risk of vascular calcification. Unfortunately, available data were insufficient to look at this aspect.

Hypertension was also strongly associated with the development of VCs. Indeed, all patients who developed VC were hypertensive and systolic blood pressure was higher in subjects with VC compared to the other group. In fact, hypertension has been shown to be an independent predictor of severe VCs [2].

The disturbed bone mineral metabolism in end-stage renal disease has been emphasized as a strong predictor of vascular calcifications [2]. In this respect, the main risk factors described include hyperphosphatemia, secondary hyperparathyroidism, and use of calcium-based phosphate binders. Our study failed to establish any statistically significant association between VCs and any of these variables. Although the level of serum phosphorus and serum PTH were higher among the group with vascular calcifications, the difference did not reach statistical significance.

It is noteworthy that some of the classic risk factors for cardiovascular disease among hemodialysis patients such as dyslipidemia, smoking, gender were not strong predictors of the outcome in our study.

Our study has several limitations. The small sample size, the lack of information about diabetes control and, the retrospective, cross-sectional nature of our study which would not allow the identification of all factors contributing to VC progression and survival. The assessment of the calcifications in the hand may be considered a limitation because the hand arteries are not important territories as the aorta or the coronary arteries. However, X-ray of the hands is done as part of the routine management of these patients at our center; moreover, it is a widely available and inexpensive method. Upper arm arteries and small hand arteries are almost always free of atherosclerosis and plaques and calcifications are almost always mediacalcosis type and not intimal. It would be interesting to do a study comparing these calcifications to the abdominal aorta, which are more of atherosclerosis-intimal type, and to compare differences in procalcifying factors between these two territories.

To our knowledge, no previous study described the prevalence and risk factors for having VCs in patients on chronic hemodialysis in our population. Further larger, multicenter, prospective study should be performed at a national level, in collaboration with other centers, in order to confirm the findings of the current study and to propose a plan to correct modifiable risk factors, in order to decrease the incidence of vascular calcifications and the incurring cardiovascular morbidity and mortality in our population.

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