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Vascular calcification in continuous ambulatory peritoneal dialysis patients

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Abstract

Vascular calcifications represent a severe complication of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) stage 5. The factors influencing the development of this complication are in close relation with the pathology of chronic dialysis premorbid condition, and with therapy as well. The present article highlights the association between several factors and the development or the aggravation of vascular calcifications in continuous ambulatory peritoneal dialysis (CAPD) patients. The results are not always in accordance with similar literature data, but there is a lack of researches regarding mineral metabolism in peritoneal dialysis patients *versus* those on chronic hemodialysis.

Keywords: vascular calcifications, valvular calcifications, CAPD.

Introduction

Vascular calcifications represent a severe complication of chronic kidney disease (CKD), especially in late stages. Although, in the last decades, there have been a notable improvement in the knowledge of secondary hyperparathyroidism pathogenesis (Table 1), prevention and therapy is still a challenge for physicians [1–5].

Table 1 – ***Factors involved in development of vascular calcifications in CKD (modified after [1–5])***

Vitamin D (native and/or activated) deficiency	Decreased VDRs (vitamin D receptors)
Hypocalcemia/hypercalcemia	Calcium set-point
Hyperphosphatemia	Fetuin A deficiency
Increased iPTH (intact parathormone)	Klotho deficiency
CaR (calcium sensing-receptor)	Decreased osteocalcin
Increased FGF23 (fibroblast growth factor 23)	–

Over the years, several trials have been reported various target values to achieve the suitable biological profile for markers of calcium and phosphorus metabolism and iPTH, as well [1, 5, 6]. In an attempt to unify these findings, in 2009 a new organization was formed – KDIGO (*Kidney Disease: Improving Global Outcome*) – which elaborated new guidelines and introduced the concept of *Chronic Kidney Disease-Mineral and Bone Disorder* (CKD-MBD), term which emphasized the magnitude of the phenomena from strictly bone to a systemic level [6].

In the last decades, although the number of peritoneal dialysis (PD) patients increased, most of the studies related to vascular calcifications development focused especially on hemodialysis (HD) population.

Therefore, the aim of the present article is to identify different factors related to the development of vascular and valvular calcifications in a group of continuous ambulatory peritoneal dialysis (CAPD) patients and, also, the influence of treatment upon these complications. The results, statistically analyzed, are compared with recent literature data.

Patients and Methods

During a prospective three-year study (between October 2009 and September 2012), conducted in our Department of Nephrology and Dialysis, "St. John" Emergency Clinical Hospital, Bucharest, Romania, 21 CAPD patients with secondary hyperparathyroidism were selected. At the moment of inclusion, the subjects had a history of at least three months of dialysis, were >18-year-old, signed Patient Informed Consent and the data were assessed according to our University Ethic and Research Committee. All individuals performed four exchanges/day, 19 patients with 2 liters/exchange and 2 with 1.5 liters/exchange. Median age was 57 years, with limits between 33–79 years. Male:female ratio was 15:6. Patients presenting primary hyperparathyroidism, sarcoidosis, myeloma, neoplastic diseases, renal transplantation/death during the study, diabetic nephropathy as primary renal disease, and transfer in other dialysis centers were excluded.

At the beginning of our research, the following information was collected from personal medical history or from hospital documents: age, gender, primary renal disease, years of dialysis, cardiovascular comorbidities. Additionally, all patients underwent a protocol of clinical laboratory tests (Table 2). Dialysis efficiency was tested with Kt/V and peritoneal equilibration test was performed at three and six months, respectively.

Table 2 – *Clinical laboratory tests used in the study*

Analysis	Time interval	Normal values
Calcium (Ca) Corrected Ca	monthly monthly	8.5–10.2 mg/dL
Phosphate (P)	monthly	2.5–4.5 mg/dL
Bicarbonate	monthly	22–30 mEq/L
Albumin	monthly	3.9–5 mg/dL
C-reactive protein (CRP)	at three months	≤6 mg/L
Alkaline phosphatase (ALP)	at three months	30–120 U/L
Ca×P	monthly	<55 mg^2/dL^2
iPTH	at six months	10.7–74.2 pg/mL

Abnormal levels were considered values outside the range of 8.5–10.2 mg/dL for calcium and 2.5–4.5 mg/dL for phosphate, respectively. Regarding iPTH levels, values between 150–300 pg/mL were considered suitable, according to KDIGO recommendations [6]. These biological limits had been followed when initiation or change of therapy were needed.

Quantification of vascular calcifications was performed with Kauppila score [7, 8] calculated on lateral abdominal radiographs: K1 represented the values of Kauppila score at the beginning of the trial, and K2 at the end. Presence or absence of valvular calcifications (aortic and mitral) was noted performing echocardiogram at the beginning and end of the study.

Development and evolution of vascular and valvular calcifications in correlation with biological and/or epidemiological parameters were the aims of the present study; comparison of the results with other literature researches was discussed, as well.

Statistical analysis

The statistical analysis included descriptive methods (mean and standard deviation for the normal distribution parameters), Student's *t*-test and *Z*-test in order to compare results ($p<0.05$). All data were analyzed using Excel and SPSS 12.0 software.

Results

For all 21 CAPD patients, there was noticed a positive correlation between aortic calcification scores K1 and K2 and time on dialysis (Figure 1), but no statistical association between these scores and patient's age (Figure 2).

In the beginning, the presence of vascular calcifications (K1≥1) was noted in 18 (85.71%) patients; median K1 value was 8.55, with limits between 1 and 18. After three years, 20 (95.24%) patients had vascular calcifications (K2≥1); median K2 value was 10.2, with limits between 2 and 20 (Figure 3). The median increase of Kauppila score was 2.5, ranging between 1 and 4 (Figure 3, Table 3).

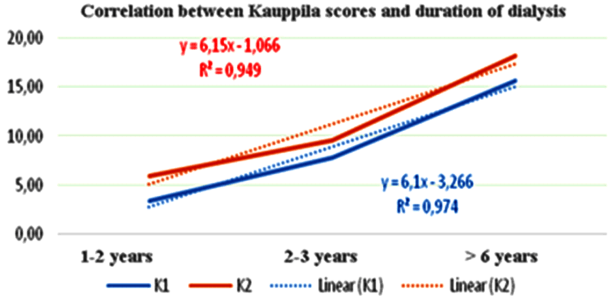

Figure 1 – *Positive correlation between Kauppila scores and duration of dialysis.*

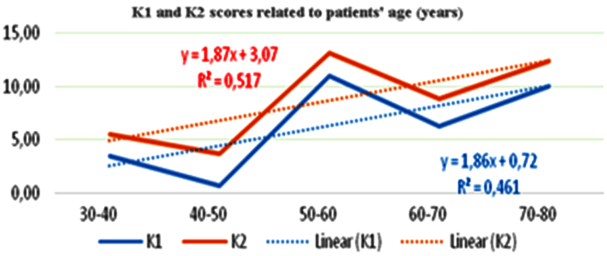

Figure 2 – *Lack of correlation between Kauppila scores and patient's age.*

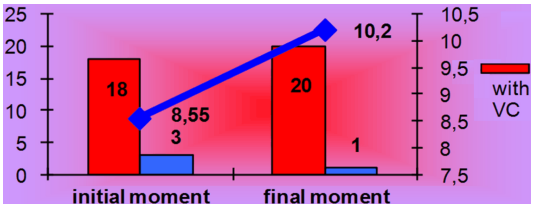

Figure 3 – *Increased presence of vascular calcification (VC) during the study in CAPD patients.*

Table 3 – *Increased severity of Kauppila score during the study in CAPD patients*

Kauppila score	1–5	6–10	11–15	>15
K1 (18 pts.)	5 (27.78%)	7 (38.89%)	4 (22.22%)	2 (11.1%)
K2 (20 pts.)	5 (25%)	6 (30%)	4 (20%)	5 (25%)

Our findings suggested a greater frequency of new vascular calcifications development in men compared with women (from 83.33% to 100% in men *versus* 86.66% to 93.33% in women). In addition, the presence of vascular calcifications was more frequent in tubulointerstitial diseases compared with other primary renal diseases (Figure 4).

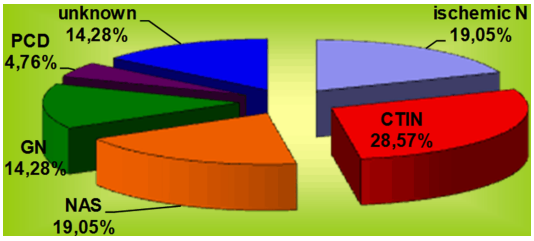

Figure 4 – *Percentage of patients with vascular calcifications (K1≥1) depending on the primary renal disease, at the beginning of the study.*

Furthermore, quantification of vascular calcifications with Kauppila score revealed that in chronic tubulointerstitial nephropathies both scores K1 and K2 presented increased values compared with other etiologies (Student's *t*-test) (Figure 5).

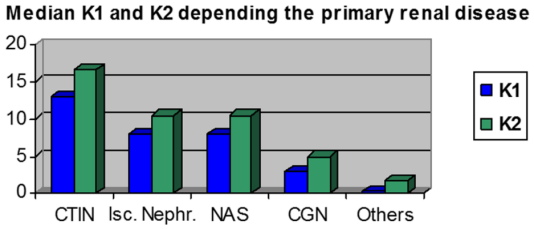

Figure 5 – *Aortic calcifications scores depending on the primary renal disease.*

Presence of valvular calcifications (mitral/aortic or both) in echocardiography was closely correlated with the preexistence of aortic calcifications on the lateral abdominal radiographs (*Z*-test). 77.77% of all patients with K1≥1 had mitral calcifications, 66.66% aortic valves

calcifications and in 55.55% both valvular calcifications were present, respectively (Figure 6).

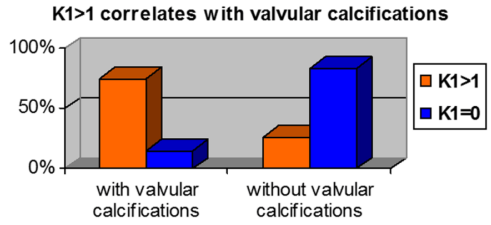

Figure 6 – ***K1 score ≥1 is associated with valvular calcifications.***

Cardiovascular comorbidities were present in 88.88% of all subjects with K1≥1. During the three-year period, we recorded 14 death and 71.42% were due to cardiovascular causes.

There was a direct correlation between iPTH levels and the presence of vascular calcifications at the end of the research (K2≥1) (Figure 7). Additionally, we noticed a statistically relevant association between the degree of hyperphosphatemia and the presence of vascular calcifications at the end of the study (K2≥1) (Figure 8).

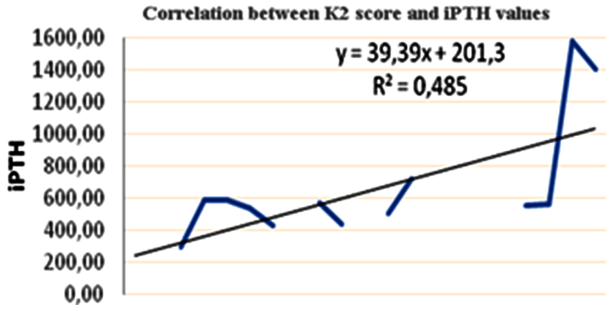

Figure 7 – ***Correlation between K2 score and iPTH values.***

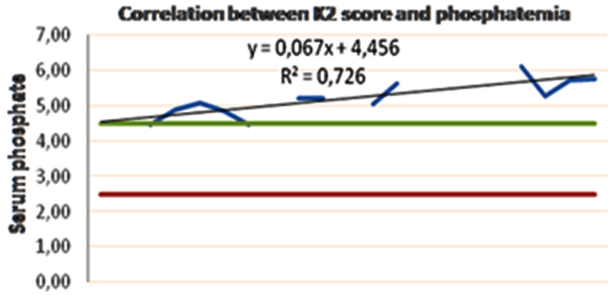

Figure 8 – ***Correlation between K2 score and phosphatemia.***

No relationship between K2 scores and calcium, calcium×phosphorus (Ca×P) product, serum albumin or bicarbonate was established. Instead, there was a direct link between C-reactive protein values and K2 scores (Figure 9) and between alkaline phosphatase (ALP) and K2, as well (Figure 10).

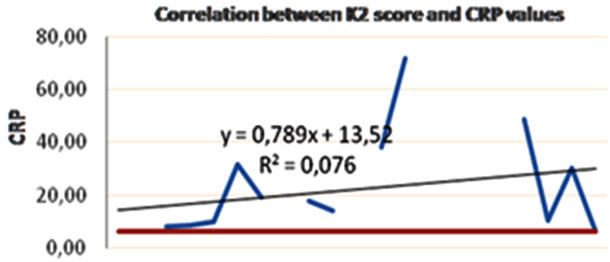

Figure 9 – ***Correlation between K2 score and C-reactive protein values.***

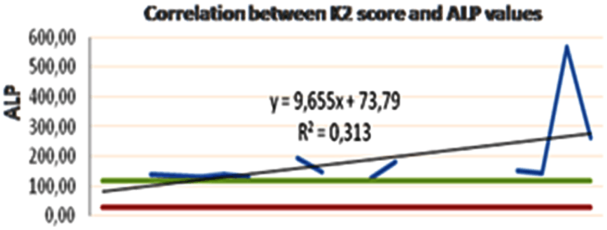

Figure 10 – ***Correlation between K2 score and alkaline phosphatase values.***

Discussion

Comparing our findings with literature data was difficult to assess because of a lack of researches performed only on chronic peritoneal dialysis patients. Most of the studies classified the patients as hemodialysis patients or CKD stage 5 without detailing the form of chronic dialysis; neither the form of hemodialysis (low *versus* high-flux) is not always specified – the removal of phosphates or other solutes important for calcium-phosphorus metabolism is different during the two modalities. In case of PD technique, the morphological changes of the peritoneum (vessels, interstitial tissue, intercellular junction, mesothelium modifications – thickening, impairment of aquaporin activity, etc.), induced by long-term dialysis, play an important role in the removal of these solutes [9, 10].

According to various trials, we also observed a positive association between the development and/or aggravation of vascular calcifications (VC) and time on dialysis, iPTH values, hyperphosphatemia, alkaline phosphatase and the inflammatory state (C-reactive protein) [1–6]. During the three-year period, there was a progression of VC with a median increase of Kauppila score of 2.5. The presence of valvular calcifications was correlated with the preexistence of aortic calcifications – appreciated by Kauppila score on lateral abdominal radiograph, observation also in concordance with literature data [3, 5, 8, 11, 12].

Contrary to other researches [2, 5, 6, 13], in our study, patient's age was not a risk factor for VC development. An explanation of this finding may be a younger median age in our cohort of patients. Although in literature is stipulated that VC may occur in older patients in the absence of renal failure [3, 14], it is also emphasized that the patterns of the calcifications are different in these two situations [14, 15]. The methods used in our trail to reveal the degree of VC cannot make the difference between intimal and medial calcifications, but this was a limitation of other researches, too [16].

The observations regarding the correlation between serum calcium and/or Ca×P product and VC are controversial [1, 17, 18]. Most studies highlighted a positive connection between high serum calcium and/or high Ca×P product and the development of VC [2, 5, 6]. In our study, we did not find a positive association: the development or aggravation of VC was positive correlated only with high phosphorus, but not with low phosphorus, high/low corrected serum calcium or high Ca×P product. These findings may be explained by the coexistence of additional factors specific for peritoneal dialysis, which contribute to the development of VC: hyperlipidemia, peritoneal calcifications, and high-glucose solution abuse. Another explanation can be the more liberal diet in peri-

toneal patients, because of a significant residual renal function.

In contrast with other studies [19, 20], no correlation between serum albumin and development of VC was noted.

A last observation, which could not been compared with literature data, consists in the presence of a significantly higher frequency of VC in patients with interstitial nephropathies *versus* other primary renal diseases. Additionally, the severity of the calcifications, measured by Kauppila score, was significantly increased in the same group of primary renal diseases. Both findings may be explained by the prolonged duration of chronic kidney diseases in these particular primary renal diseases and the prolonged acidosis state in predialysis stages.

Conclusions

Time on dialysis, high serum phosphorus, high values of iPTH, high C-reactive protein, chronic tubulointerstitial nephropathies were the main factors positive correlated with VC in our CAPD patients. No association between VC and Ca×P product, serum calcium, albumin or bicarbonate was found. Further researches are needed in order to identify factors influencing development of VC in peritoneal dialysis population.

Conflict of interests

The authors declare that they have no conflict of interests.

Contribution note

All the authors contributed equally to this paper.

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