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.

\section*{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.

\section*{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

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Time interval</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (Ca)</td>
<td>monthly</td>
<td>8.5–10.2 mg/dL</td>
</tr>
<tr>
<td>Corrected Ca</td>
<td>monthly</td>
<td>2.5–4.5 mg/dL</td>
</tr>
<tr>
<td>Phosphate (P)</td>
<td>monthly</td>
<td>22–30 mEq/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>monthly</td>
<td>3.9–5 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>monthly</td>
<td>8.5–10.2 mg/dL</td>
</tr>
<tr>
<td>C-reactive protein (CRP)</td>
<td>at three months</td>
<td>≤6 mg/L</td>
</tr>
<tr>
<td>Alkaline phosphatase (ALP)</td>
<td>at three months</td>
<td>30–120 U/L</td>
</tr>
<tr>
<td>Ca×P</td>
<td>monthly</td>
<td>&lt;55 mg/dL²</td>
</tr>
<tr>
<td>iPTH</td>
<td>at six months</td>
<td>10.7–74.2 pg/mL</td>
</tr>
</tbody>
</table>

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).

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).

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).

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...
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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.

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 trial 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-

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

Figure 10 – Correlation between K2 score and alkaline phosphatase values.
with VC in our CAPD patients. No association between of iPTH, high C-reactive protein, chronic tubulointerstitial diseases in these particular primary renal diseases and explained by the prolonged duration of chronic kidney 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 positively 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.

References


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Received: February 12, 2015
Accepted: August 18, 2015