Encapsulating peritoneal sclerosis and other aspects of long-term peritoneal dialysis
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Citation for published version (APA):
Vlijm, A. (2010). Encapsulating peritoneal sclerosis and other aspects of long-term peritoneal dialysis
Chapter 5

ARE PERITONEAL CALCIFICATIONS IN LONG-TERM PERITONEAL DIALYSIS RELATED TO AORTIC CALCIFICATIONS AND DISTURBANCES IN MINERAL METABOLISM?

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Nephrol Dial Transplant 2010; in press
Background Peritoneal calcifications are associated with long-term peritoneal dialysis (PD). Case reports have suggested a relation with disturbances in mineral metabolism such as the presence of severe hyperparathyroidism. Our aim was to investigate whether relationships are present between peritoneal calcifications and aortic calcifications or disturbances in mineral metabolism in long-term PD patients.

Methods We included all long-term PD patients (PD ≥ 4 years) in our center from 1996-2008 who had undergone an abdominal computed tomographic (CT) scan. The scans were reviewed by 2 experienced radiologists in consensus. The presence or absence of peritoneal calcifications was scored and a severity scoring system for abdominal aortic calcifications was used: 1 = none, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe. For each patient laboratory data on plasma calcium corrected for albumin, phosphorus, and parathyroid hormone (PTH) levels were retrieved every 6 months up to 5 years prior to the CT scan. Individual mean values over 5 years were calculated.

Results We included 31 patients: 12 patients with peritoneal calcifications and 19 patients without. No difference was found in aortic calcification scores (median scores: 3 versus 3). Also median (range) calcium, 10.7 (9.6-11.5) versus 10.3 (9.4-11.3) mg/dL, phosphorus, 5.2 (3.4-7.0) versus 4.9 (2.9-6.5) mg/dL, and PTH levels, 271 (101-910) versus 263 (40-1197) pg/mL were not different between patients with and without peritoneal calcifications.

Conclusion The presence of peritoneal calcifications in long-term PD patients could not be related to the presence of aortic calcifications or disturbances in mineral metabolism. Perhaps local peritoneal factors play a role in the formation of peritoneal calcifications.
Introduction

Causes for peritoneal calcifications are diverse \(^1\) but the association with long-term peritoneal dialysis (PD) is well established. Marichal \textit{et al.} were the first to describe what was then called calcifying peritonitis in PD patients \(^2\). Peritoneal calcifications have been associated with severe hyperparathyroidism in several case reports \(^3\)\textendash\(^5\). Also excessive administration of vitamin D has been postulated to cause a calcified peritoneum \(^6\). However, this type of ectopic calcification is also seen in the absence of parathyroid overactivity. Several other factors have been associated with this condition such as peritoneal contact with ferric ions, recurrent peritonitis episodes, and exposure to calcium containing dialysis solutions \(^7\)\textendash\(^12\). A study by Nakazato \textit{et al.}, in which peritoneal tissues of 18 PD patients, 5 hemodialysis (HD) patients, and 3 pre-PD patients were examined showed that calcium deposition and osteopontin precipitation were not exceptional in long-term PD \(^13\).

Disturbances in mineral metabolism are linked to an increased cardiovascular mortality risk in HD patients \(^14\), \(^15\). Noordzij \textit{et al.} showed that concentrations of phosphorus and calcium-phosphorus product greater than the Kidney Disease Outcomes Quality Initiative (K/DOQI) targets \(^16\) were associated with an increased all-cause mortality risk, both in HD and in PD patients \(^17\). High phosphorus and calcium product concentrations have also been associated with coronary artery calcifications in dialysis patients \(^18\). This type of vascular calcification is common in PD patients and progresses during time on dialysis \(^19\). Stompór \textit{et al.} showed that the vascular calcification score of coronary arteries increased significantly faster in PD patients with low serum parathyroid hormone (PTH) levels than in those with higher PTH levels \(^20\). These findings suggest that in a state of adynamic bone disease, substrate for the development of vascular calcifications is present in these patients \(^21\).

Peritoneal calcification is a common feature detected by computed tomography (CT) in patients with encapsulating peritoneal sclerosis (EPS) \(^22\), \(^23\). However, progressive calcifying peritonitis and EPS are considered to be separate entities \(^6\), \(^24\), \(^25\). Current knowledge on the possible origin of peritoneal calcifications in PD is mainly based on case reports and small case series. In our previous study on CT findings characteristic for EPS, we studied 15 EPS patients and 16 long-term PD control patients. Peritoneal calcifications were more often seen in EPS but were also present in long-term PD patients without EPS \(^23\).

The aim of this study was to investigate whether relationships are present between peritoneal calcifications and aortic calcifications or disturbances in mineral metabolism in long-term PD patients. We used our previously studied patient group \(^23\) and designed a new
study in which the patients were divided according to the presence or absence of peritoneal calcifications.

**Subjects and methods**

*Patients*

The patient group consisted of all long-term PD patients in our center from 1996 until 2008 with a PD duration of at least 4 years who had undergone an abdominal CT scan, either for the suspicion of EPS or for other reasons such as suspicion of an abscess. The patients were divided into two groups: patients with peritoneal calcifications and those without based on their CT scan. Information on the presence of EPS, diabetes and hypertension, the use of vitamin D analogues for at least 6 months during the study period, possible parathyroidectomies before the CT scan, and the total amount of peritonitis episodes were collected for all patients. EPS was defined as a macroscopically confirmed condition of encapsulating sclerosis, or a clinically evident presentation with symptoms like repeated bowel obstruction, non-resolving peritonitis and ultrafiltration failure.

*Review of the CT scans*

The CT scans were reviewed in consensus by 2 experienced abdominal radiologists from our center with more than 10 years of clinical experience. The presence or absence of peritoneal calcifications was scored as yes or no. A severity scoring system for abdominal aortic calcifications was developed (Figure 1). In this scoring system a score of 1 represented no abdominal aortic calcifications, 2 was mild, 3 was moderate, 4 was severe, and 5 was very severe presence of abdominal aortic calcifications.

![Figure 1 – The calcification severity score applied by the 2 observers is shown in schematic cross-sections of the abdominal aortic wall.](image)
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Plasma and serum levels of mineral metabolism
To prevent variation in laboratory findings over time from influencing the results, we calculated individual mean values of a 5 year period. For each patient data on calcium, albumin, phosphorus, and PTH levels were retrieved every 6 months up to 5 years prior to the CT scan. These data collections led to a maximum of 11 measure points per patient. Plasma calcium levels were corrected for plasma albumin levels. Calcium, albumin, and phosphorus were determined by spectrophotometry. Serum PTH levels were determined by immunoassay. The number of measure points that exceeded or were below the K/DOQI threshold for corrected calcium, phosphorus, and PTH were counted in each patient.

Statistics
Data are presented as medians and ranges, unless stated otherwise. Differences between the two groups in age, PD duration, total amount of peritonitis episodes, laboratory values, and the number of measure points that exceeded or were below the K/DOQI threshold were tested non-parametrically with Mann-Whitney U tests, assuming an abnormal distribution due to the sample size. Differences in gender, the presence of EPS, diabetes and hypertension, the use of vitamin D analogues, and parathyroidectomies were analyzed with chi-square statistics or Fisher’s exact probability tests.

Results
Patients
We included 31 patients: 12 patients with peritoneal calcifications and 19 patients without. Patient characteristics are shown in Table 1. Patients with peritoneal calcifications were significantly younger and had a significantly longer PD duration than those without. No differences were present in gender and the presence of EPS. Both groups had a similar percentage of diabetic patients, use of vitamin D analogues and parathyroidectomies. Hypertension was more often seen in the patients without peritoneal calcifications, but these patients were also older. There was no difference in the total amount of peritonitis episodes. All patients were treated with a conventional dialysis solution, or had been treated with one for at least several years before it was replaced with a more biocompatible one. No patient was treated with biocompatible solutions alone.
Review of the CT scans

A total of 31 CT scans were reviewed. The indications for the CT scans varied: suspicions of abscesses or haematomas in 9, suspicion of EPS in 7, peritonitis in 5, ultrafiltration failure in 1, suspicion or follow-up of bowel perforation, leakage of peritoneal fluid, diverticulitis, abdominal aortic aneurysm, tumor, gastric malignancy, bowel ischemia, and liver ischemia in 1 each, and in 1 case the indication was not specified. Around the date of the CT scan, 22 patients were still on PD or had transferred to haemodialysis or had received a kidney transplant within weeks to a few months of this date. Four patients had transferred to HD 1 to 4 years prior to the CT scan and 5 patients had received a transplant 6 months to 3 years prior to the CT scan.

Almost all scans were spiral CT scans with a slice thickness of 5 – 5.5 mm. As mentioned previously, the 2 observers scored 12 patients with and 19 patients without peritoneal calcifications. The localization of the calcifications was sometimes parietal, sometimes visceral.
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surrounding the bowel loops, spleen or liver, and in some cases both parietal and visceral. No difference was present between patients with and without peritoneal calcifications in aortic calcification scores (Figure 2). The median score in both groups was 3 (range 1 – 5). In an additional analysis, we divided the patients by aortic calcification score: 1 and 2 (none and mild) versus 3, 4 and 5 (moderate to very severe), and compared their age. As expected, the patients with a more severe aortic calcification score were significantly older.

Figure 2 – The aortic calcification score, 1 = none, 2 = mild, 3 = moderate, 4 = severe and 5 = very severe is given for the patients with (grey bars) and without (white bars) peritoneal calcifications.

Plasma and serum levels of mineral metabolism
Mean calcium corrected for albumin, phosphorus, and PTH levels over a 5 year period were not different between patients with and without peritoneal calcifications (Table 2). The number of measure points that exceeded or were below the K/DOQI threshold for corrected calcium, phosphorus, and PTH was not different (Table 3). In an additional analysis, we compared the number of PTH measure points that was < 100 pg/mL, indicating adynamic bone disease. Again, no difference was found between patients with and without peritoneal calcifications.
EPS patients are often malnourished and might therefore have lower plasma albumin levels. Therefore, we performed an additional analysis comparing calcium levels corrected for albumin, phosphorus levels, calcium phosphorus product, and PTH levels between patients with and without EPS. No differences were found between the groups.
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Discussion

Peritoneal calcifications could not be linked to abdominal aortic calcifications in this study using our severity scoring system. Sophisticated CT techniques such as electron beam CT and spiral CT have proven to be useful and reproducible in detecting aortic and coronary calcifications\textsuperscript{26-28}. Both plain CT and CT angiography can be used to assess abdominal aortic calcification\textsuperscript{29}. Another elegant CT method was developed to assess the fractional area of the aorta showing calcifications with the average density in the plaques\textsuperscript{30}. Due to the retrospective design of the present study and the use of CT scans which were done for clinical reasons in stead of for this study purpose, measurement of abdominal aortic calcifications could not be done in the previously described ways. However, the fact that most CT scans were spiral scans with a similar slice thickness judged by 2 experienced radiologists in consensus ensured the accuracy of the measurements of aortic calcifications used in this study.

The presence of peritoneal calcifications in long-term PD patients could not be related to high calcium, phosphorus or PTH levels. In addition, a state of adynamic bone disease, indicated by low PTH levels and after parathyroidectomy, was also not associated with the development of peritoneal calcifications. This is in contrary to the hypothesis for the development of vascular calcifications\textsuperscript{21}.

This study has several limitations. First, we cannot rule out a confounding effect of EPS in the present study due to a selection of patients. Moreover, all our patients had a clinical indication for a CT scan and are, therefore, a selection of long-term PD patients in our center rather than a cross-section of the PD population. Second, the design of this study did not take the used dosage and possible cumulative effects of vitamin D into account. Therefore the possible role of excessive vitamin D administration in causing a calcified peritoneum could not be ruled out\textsuperscript{6}. Third, the use of calcium containing phosphate binders was not taken into account. However, their effect lies in increasing plasma calcium levels, which were studied over a 5 year period in each patient. Fourth, due to the wide time span during which the patients were included, calculation of cumulative calcium exposure caused by the peritoneal dialysis fluids was impossible.

Causes for peritoneal calcification formation in long-term peritoneal dialysis patients remain unknown. A relationship between plasma magnesium levels and vascular and soft tissue calcifications has been described\textsuperscript{31}. Because plasma magnesium levels were not routinely measured in our study population, we were not able to analyze a possible association with peritoneal calcifications. Low plasma levels of fetuin-A, which is involved in the
development of vascular calcifications, are associated with morbidity and mortality in CKD patients. We could speculate that fetuin-A levels, which inhibits the formation of ectopic calcifications, were lower in patients with peritoneal calcifications than in those without. We could not find an explanation for the fact that patients with peritoneal calcifications were younger, but causality seems unlikely. PD duration on the other hand, which was significantly longer in the patients with peritoneal calcifications, is more likely to be in the causal pathway of the formation of peritoneal calcifications.

In conclusion, in our study population, which was relatively large in comparison to the case reports described previously, we could not confirm the theories that peritoneal calcifications are related to hyperparathyroidism or vitamin D use. Also vascular calcification did not seem to be related to a calcified peritoneum. Because we found a significantly longer PD duration in patients with peritoneal calcifications, we believe that local peritoneal factors are more likely to be involved. We did not find a difference in the total amount of peritonitis episodes and this is therefore unlikely to be a causative factor. All our patients were treated with a conventional dialysis solution alone, or had been treated with one for an extended period before it was replaced with a more biocompatible solution. Poor biocompatibility of PD solutions, to which our patients were chronically exposed, might have contributed to the development of peritoneal calcifications.
References


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