Detection of pulmonary calcification in haemodialised patients by whole-body scintigraphy and the impact of the calcification to parameters of spirometry

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Abstract

The early diagnosis of metastatic pulmonary calcification is beneficial, as some patients may develop restrictive changes in respiratory function or in some cases lethal acute respiratory distress. The aim of the study was to evaluate whether scanning with ^{99m}Tc DPD might be useful in early diagnosis of pulmonary calcification in setting of chronic renal failure and hemodialysis and if presence of pulmonary calcification is associated with an abnormality in respiratory parameters. Forty-two patients with end-stage renal disease, who were treated by regular haemodialysis, were investigated. Twenty five (59.5%) out of forty two patients had increased lung uptake of ^{99m}Tc DPD at whole body scintigraphy-grade 2 group. These patients were on dialysis 149±26 months compared with 57±16 months in 17 patients with a normal lung uptake of ^{99m}Tc DPD at whole body scintigraphy- grade 1 group ($p<0.01$). In grade 2 group 22 patients (88%) had significantly lower ($p<0.01$) parameters of spirometry (FEF25-75, FEF75 FEF50, FEF25) compared to predicted values while in grade 1 group the parameters were significantly lower in only six patients (35.3%). There was statistically insignificant difference between these two groups regarding parathyroid hormone level ($p>0.05$). These observations confirm previous findings that scintigraphy with ^{99m}Tc DPD may be efficious in early diagnosis of pulmonary calcification in hemodialised patients as well as the fact that spirometry is useful in patients with confirmed pulmonary calcifications.

KEY WORDS: pulmonary calcification, hemodialysis, bone scintigraphy

Introduction

Metastatic pulmonary calcification occurs in setting of chronic renal failure and hemodialysis. Calcifications are detected at autopsy in 60–80% of patients receiving regular hemodialysis. In the lungs, calcium deposits have been found in the interstitium of the alveolar septum, bronchiole walls, in the large airways and even in the walls of pulmonary vessels. Many of these patients are asymptomatic and diagnosis of pulmonary calcification is set either clinically or by chest X–ray [1, 2]. The early diagnosis of metastatic pulmonary calcification is important, as some patients may develop deterioration in respiratory function or in some cases lethal acute respiratory distress. Also, calcium deposit in the lungs may increase pulmonary artery pressure and consequently affect right heart function [3, 4, 5, 6, 7, 8]. Previous studies have demonstrated the ability of ^{99m}Tc diphosphonate (DPD) used for bone scan to detect pulmonary calcification. One study reported that 61% of patients receiving long term hemodialysis therapy with normal chest X–ray demonstrated abnormal uptake of ^{99m}Tc DPD by the lungs, indicating the presence of pulmonary calcification [9]. The aim of the study was to evaluate whether scanning with ^{99m}Tc DPD might be useful in early diagnosis of pulmonary calcification in setting of chronic renal failure and hemodialysis and if presence of pulmonary calcification is associated with an abnormality in respiratory parameters.

Materials and Methods

Patients

The study population consisted of 42 patients, 26 males and 16 females with chronic renal failure. The mean age of the patients was 48±7 years (range 29-71 years). Patients were treated by regular hemodialysis through arterio-venous fistula three times per week in 4 hourly sessions. Dialysis solution contained 1,75 mmol/L Ca. Patients with history of cardiac, pulmonary and other systemic diseases were excluded from the study. Three patients refused to participate in the study. All patients which were included in this trial are patients with

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Submitted 2 May 2010 / Accepted 19 October 2010

interdialysis liquid gain <5%. Our local institutional clinical research ethics review board approved the research protocol.

Methods

All patients underwent full clinical evaluation with chest X–ray. Laboratory investigations included parathyreoid hormone (PTH, reference range: 8–76 pg/mL) hemoglobin hematocrit, blood urea nitrogen (BUN), creatinin, serum calcium, serum phosphorous, alkaline phosphatase. One hour after completion of hemodialysis all patients were examined by whole body scintigraphy in Department of Nuclear Medicine, Clinical Center Banja Luka. ^{99m}Tc DPD whole body scintigraphy and static scan of the chest was performed using one-had gamma camera equipment with a high resolution collimator. The energy pick was centred at 140 KeV with the 10% window. Scintigraphy was performed three hours after intravenous injection of 555 MBq of ^{99m}Tc DPD. The degree of lung uptake was determined by two independent nuclear medicine specialists. The uptake was graded as: no uptake or lung uptake intensity less than bone uptake =1, lung uptake intensity similar or greater than bone uptake=2. Grade 1 was considered as normal. Grade 2 was considered as elevated. All patients had pulmonary function testing (spirometry) immediately after scintigraphic examination. On the day of the examination, patients' medical history was taken as well. We recorded flow–volume loops, forced vital capacity (FVC), forced expiratory volume in one second (FEV1), forced expiratory flow at 75, 50, 25 % of remaining VC (FEF75, 50, 25) one hour before and one hour after completion of haemodialysis according to standard protocol. Lung function reference values corrected for sex, age, and height were used. For these measurements, we used a portable spiromethar "mikrolab" Micro Medical Ltd. At least three reproducible tests were carried out for each measurement and the best one was recorded.

Statistical analysis

We analyzed data that we obtained from our study using SPSS statistical package, version 17. The Student t test was used for analysis of continuous data; p<0,05 was considered to be statistically significant. Data are presented as mean ±SD.

Results

Twenty five (59.5%) out of forty two patients had grade 2 uptake in the lungs which represents increased lungs uptake of ^{99m}Tc DPD on whole body scintigraphy. Figure 1 shows one of these scans with increase lungs uptake of ^{99m}Tc DPD. Grade 1 uptake in the lungs was seen in 17 patients. These patients had normal lung uptake of DPD. Pulmonary calcification was not diagnosed by chest X ray in all patients. Mean PTH values in patients with grad 1 and grad 2 ^{99m}Tc DPD uptakes in lungs are presented in Table 1. There was no significant difference between these two groups regarding parathyroid hormone level (p>0.05). Laboratory findings in patients with grade 1 and grade 2 ^{99m}Tc DPD uptakes in the lungs are presented in Table 2.

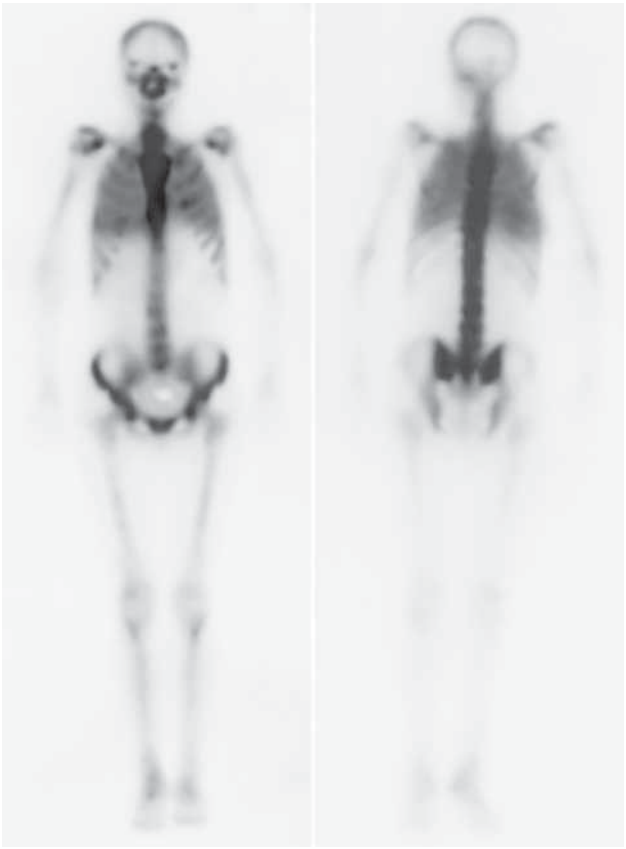

FIGURE 1. Whole body scintigraphy with ^{99m}Tc DPD (anterior and posterior) – increase uptake in the lungs

TABLE 1. Mean PTH levels in patients with grade 1 and grade 2 ^{99m}Tc DPD lungs uptake

	Grade 1	Grade 2	*p* value
PTH (mean value)	48.8 ± 14.8 pg/mL	50.2 pg/mL	NS

Grade 1 - no uptake or lung uptake intensity less than bone uptake; Grade 2 - lung uptake intensity similar or greater than bone uptake

TABLE 2. Laboratory findings in patients with grade 1 and grade 2 ^{99m}Tc DPD lung uptake

Laboratory findings	Grade 1	Grade 2	*p* value
Hemoglobin (g/dL)	9.8 ± 1.8	10.2 ± 1.5	NS
Hematocrit (%)	33.3 ± 4.8	34.1 ± 6.1	NS
BUN (mg/dL)	66 ± 17	68 ± 18	NS
Creatinin (mg/dL)	9.1 ± 1.9	9.7 ± 2	NS
Serum calcium (mmol/L)	2.5 ± 0.2	2.7 ± 0.3	NS
Serum phosphorus (mmol/L)	1.4 ± 0.2	1.6 ± 0.3	NS
Alkaline phosphatase (U/L)	72.37 ± 17	78.2 ± 13.3	NS

Grade 1 - no uptake or lung uptake intensity less than bone uptake; Grade 2 - lung uptake intensity similar or greater than bone uptake

There were no significant differences between these two groups regarding hematocrit, hemoglobin, serum calcium, phosphorous, bicarbonate, magnesium, urea, creatinin and alkaline phosphatase.

TABLE 3. Duration of hemodialysis in patients with grade 1 and grade 2 ^{99m}Tc DPD lungs uptake

	Grade 1	Grade 2	*p* value
Duration of hemodyalisis	57 ±16 months	149 ± 26 months	p<0.01

Grade 1 - no uptake or lung uptake intensity less than bone uptake; Grade 2 - lung uptake intensity similar or greater than bone uptake

Table 3 shows statistically significant difference between duration of hemodialysis in patients with grade 1 compared to grade 2 ^{99m}Tc DPD uptake in lungs (p<0.05).

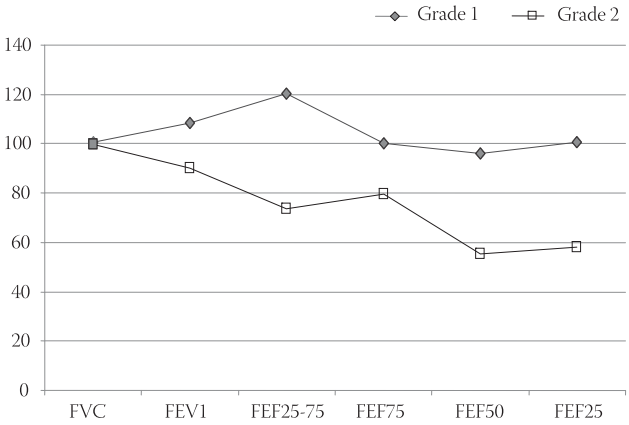

FIGURE 2. Results of pulmonary function tests in patients with grade 1 and grade 2 ^{99m}Tc DPD lung uptake

Figure 2 shows comparison of percentages of predicted values of pulmonary function tests between patients with grade 1 ^{99m}Tc DPD uptake (blue line) and patients with grade 2 ^{99m}Tc DPD uptake (red line). Results of the pulmonary function testing (spirometry) show that patients with grade 2 ^{99m}Tc DPD lungs uptake had statistically significant less measured values compared to patients with grade 1 ^{99m}Tc DPD lungs uptake.

Discussion

Metastatic pulmonary calcification is a complication of chronic renal failure which may lead to significant pulmonary dysfunction. The diagnosis of metastatic pulmonary calcification is rarely set antemortem [10]. The early diagnosis of metastatic pulmonary calcification is important, as some patients may develop lethal acute respiratory distress. Several studies reported reduced lung vital capacity with poor inhalation distribution and impaired gas diffusing capacity in patients with end-stage renal disease (ESRD) [11, 12, 13, 14]. Metastatic pulmonary calcification is assigned to have an important role in the genesis of functional derangements in pulmonary function in ESRD patients. Functional abnormalities, including reductions in vital capacity, carbon monoxide diffusion capacity and arterial oxygen level correlated closely with the degree of calcification [1, 9]. Similarly to these findings, our study showed significantly lower pulmonary function tests (FEF25-75, FEF75, FEF50 and FEF25) in grade 2 ^{99m}Tc DPD lung uptake. Pulmonary calcification associated with chronic renal failure is potentially reversible after adequate treatment [1]. A non-invasive method for the diagnosis of pulmonary calcification has not, as yet, been firmly established. The calcification is so fine and diffuses that chest X–ray is relatively insensitive. Usually, chest X-ray does not show the infiltrates or they cannot be distinguished from other parenchymal processes. One study has reported abnormal chest X-ray in only 1 out of 15 hemodialised patients with pulmonary microcalcification. High resolution computed tomography (CT) of the chest with or without densitometry measurements provides better results. Electron beam CT and spiral CT are highly sensitive techniques for detecting pulmonary calcification [15]. Magnetic resonance imaging (MRI) is relatively insensitive for detecting pulmonary calcification [16]. Increased radionuclide uptake in the lungs of the patients is well documented with ^{99m}Tc DPD and MDP and ^{67}Galium [17, 18]. ^{67}Gallium is not available in every nuclear medicine department; it is expensive so it is not routinely recommended for detection of pulmonary calcification. Several reports have documented depositions of ^{99m}Tc DPD or MDP in lungs in absence of radiographic findings. These results suggest that metastatic pulmonary calcification can be detected non-invasively by scintigraphy with ^{99m}Tc MDP or DPD [17, 19, 20]. Radionuclide uptake in the lungs is usually bilateral, and its grade is usually similar or greater than bone uptake. Study which included 23 hemodialised patients showed that although all patients had normal chest X-ray, 14 of them (61%) had ^{99m}Tc MDP lung uptake [9]. Similar study reported 40% prevalence of ^{99m}Tc MDP lung uptake without corresponding findings in X-ray or CT of the chest [21]. The present study shows similar data, increase ^{99m}Tc DPD lung uptake in 25 (59.5%) of patients. This result can be explained by the structure of the calcium salt in the lung. ^{99m}Tc DPD or MDP is well taken up by amorphous whitlockite type mineral ($[CaMg]_3[PO_4]_2$). In heamodialysed patients predominant calcium salt in lungs is hydroxyapatite crystals ($Ca_{10}[PO_4]_6[OH]_2$), which result in lower uptake of ^{99m}Tc MDP or DPD [22]. The advantage of scintigraphy lays in the fact that the other organs can be concurrently evaluated for metastatic calcification or ossification. A common complication of chronic kidney disease is the development of secondary hyperparathyroidism (SHPT). SHPT develops as a consequence of mineral metabolism disturbances and is characterized by elevated parathyroid hormone (PTH) and parathyroid hyperplasia [23]. In both groups of our patients, grade 1 and grade 2, serum calcium, phosphorous or PTH were not elevated. Hence, we can exclude SHPT as a reason for pulmonary calcification. The only distinguishing clinical feature in group with the positive scan was a longer mean duration of hemodialysis (149±26 months) compared

to group with the negative scan (57±16 months). One possible explanation for metastatic pulmonary calcification in this study could be the high concentration of Ca in dialysis solution. In this study dialysis solution contained 1.75 mmol/l Ca. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI™) guidelines and international Dialysis Outcome Practice Patterns Study (DOPPS) recommend differential protocols for haemodialysis. High concentration of Ca in dialysis solution can be the reason for Ca precipitation in tissues and development of SHPT. The longer patient is on haemodialysis the probability for Ca precipitation in tissues is greater which was also shown in this study. Metastatic calcification was seen in patients with longer dialyses period. The available evidence from both COSMOS and DOPPS demonstrate the need for new strategies and the development of new treatments for the management of bone and mineral disorders. Until that, it is necessary to make the modification of current therapeutic options by avoiding high-dose vitamin D, high-dose oral calcium, high-calcium dialysate and by using dialysis solution with low calcium concentration (1.25–1.50 mmol/L Ca) [24, 25, 26, 27, 28].

Conclusion

These observations suggest that scintigraphy with ^{99m}Tc DPD may be efficious in establishing an early diagnosis of pulmonary calcification in hemodialised patients. Pulmonary function is often reduced in patients with pulmonary calcification associated with chronic renal failure. Hence, in long term haemodialised patients we suggest performing scintigraphy with ^{99m} Tc DPD as well as testing of pulmonary function.

Declaration of Interest

We did not receive any financial support for this work and there is no conflict of interest.

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