Hyperphosphatemia Appears Infrequently in Balkan Endemic Nephropathy Patients on Maintenance Hemodialysis

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Introduction

Balkan endemic nephropathy (BEN) is chronic kidney disease endemic to restricted areas of the Balkan Peninsula. It is classified as a non-destructive and non-inflammatory tubulointerstitial disease with slow progression towards end-stage renal failure (ESRD) (1).

Despite numerous investigations in the last five decades, BEN still presents challenging disease due to many unsolved problems. Prolonged life of BEN patients in ESRD by maintenance hemodialysis (HD) enabled manifestation of some insufficiently recognized disorders and also contributed to their better understanding. Our clinical experience indicated that HD patients with BEN suffer severe bone pain but have no sign of secondary hyperparathyroidism and their serum phosphorus levels are usually normal, even without the use of phosphate binders. In order to prove this empiric impression present study was undertaken to compare calcium and phosphorus balance disorder in HD patients with BEN and those with other renal diseases.

Patients and methods

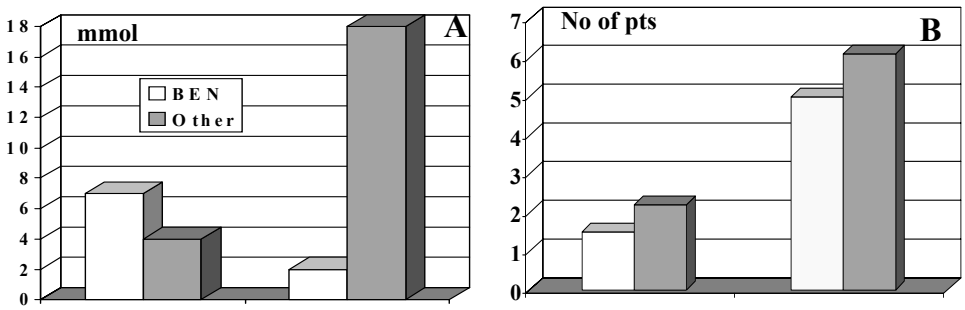
The study included two groups of patients on regular HD for more than five years: *BEN group* consisted of 21 patients (13 males, aged 63 ± 8 years) dialyzed 8.1 ± 2.9 years and *other renal diseases group* of 20 patients (14 males, aged 48 ± 13 years) on HD 7.5 ± 2.3 years. All patients were dialyzed three times weekly for 4 hours.

Retrospective analysis of medical records of all examined patients for the period 1998-2002 comprised following parameters measured every month before the mid-week HD: hematocrit, hemoglobin, serum levels of phosphorus, calcium, alkaline phosphatase, albumin. Additionally, number of blood transfusions per year and therapy with phosphate binders and vitamin D were also registered. At the time of study diuresis, urinary excretion of calcium and phosphorus and creatinine clearance were measured. Since it was impossible to measure PTH levels regularly, only PTH values (immunochemiluminometric assay) measured at the time of study are presented. Statistical analyses utilized Student's t test for parametric paired and unpaired data.

Results

Retrospective analysis of medical records of all examined patients revealed that only two BEN patients used phosphate binders but only occasionally when serum phosphate level exceeded 1.8 mmol/l. On the contrary, 18/20 patients with renal disease other than BEN used phosphate binders (Figure 1). Unfortunately, the patients had sometimes to discontinue use of phosphate binders and more often vitamin D due to drugs shortage in our country in the last decade.

Figure 1. Number of patients with BEN and other renal diseases with diuresis > 200 ml and those using phosphate binders (A); mean serum phosphorus levels and urinary phosphorus excretion in BEN patients and patients with other renal diseases (B).



Results of the laboratory analyses performed during the studied five-years period are presented in Table 1. Mean

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serum phosphorus levels were maintained within normal range in BEN patients group throughout the whole period. At the same time these values were significantly lower as compared with patients with other renal diseases who had increased phosphorus levels despite to phosphate binders therapy. Mean total serum calcium levels were similar in both groups. Alkaline phosphatase values were higher in 1998 than five years later, especially in BEN patients. No significant difference in alkaline phosphatase values was found between the groups (Table 1). PTH plasma level, measured at the time of analysis, was significantly lower in BEN patients than in patients with other renal diseases (294±128 vs. 510±488 pg/ml). Anemia is well known characteristic of BEN patients that is also demonstrated in the present study with significantly lower hemoglobin values in BEN patients than in non-BEN patients throughout the whole period. There was no opportunity for rHuEpo therapy and anemia was corrected only with blood transfusions. BEN patients received significantly more blood transfusions per year than patients with other renal disease (4.3±0.7 vs. 2.8±1.3). Aong BEN patients 7 had diuresis between 400 and 1500 ml and excreted 2.38 –11.93 mmol phosphorus and 0.72 –4.95 mmol calcium daily. In the group of patients with other renal diseases four had diuresis between 500 and 1500 ml and their daily excretion of phosphorus ranged between 1.83 and 6.64 mmol and calcium between 0.97 and 4.38 mmol (Figure 1). Xray of hands and pelvis revealed incipient signs of hyperparathyroidism in several patients with renal diseases other than BEN but in none patient with BEN.

Table 1. Mean (± SD) values of serum phosphate, calcium, alkaline phosphatase, albumin levels and hemoglobin calculated from the values measured monthly in five-years period in patients with Balkan endemic nephropathy (BEN) and those with other renal diseases maintained with hemodialysis.

		1998	1999	2000	2001	2002
s-$P0_4$, mmol/L	BEN	1.54±0.35✶	1.37±0.25✶	1.50±0.37✶	1.46±0.35✶	1.49±0.39✶
	Others	2.31±0.64	2.08±0.50	1.96±0.39	2.15±0.59	2.16±0.45
s-Ca, mmol/L	BEN	2.32±0.07	2.32±0.10	2.32±0.13	2.24±0.09	2.27±0.11
	Others	2.23±0.08	2.28±0.14	2.3±0.10	2.29±0.12	2.26±0.17
Alk.phosphatase,U/L	BEN	238±122	194±177	144±98	117±63	133±77
	Others	215±120	231±96	182±91	151±86	188±115
s-albumin, g/L	BEN	41±3.9	41±3.5	42±3.7	38±7.3	39±4.2
	Others	42±3.9	42±3.7	41±2.2	39±2.5	39±2.7
Hemoglobin, g/L	BEN	78±24#	73±11✶	73±10✶	76±13✶	78±16✶
	Others	93±14	89±15	91±18	88±13	98±20

- $p<0.05$; ✶ - $p< 0.01$

Discussion

Calcium and phosphorus homeostasis, regulated by complex interactions of vitamin D and PTH, is seriously disrupted in ESRD. Among several consequences of this disruption hyperphosphatemia presents one of the most common. It is well recognized as a key factor in the pathogenesis of secondary hyperparathyroidism, but recently it has been recognized as a cause of extraosseous calcification of both vascular and nonvascular tissues (2,3). Therefore, treatment of hyperphosphatemia is crucial in prevention of secondary hyperparthyroidism and extraosseous calcification.

Normal and low phosphate level is uncommon in patients on conventional HD. It can be caused by chronic tubular disorders and increased phosphate excretion (4,5) but also by malapsorption of phosphorus (6) or phosphate binders over dosage (7). Recently, normal or even low phosphorus levels were described in patients on quotidian HD (8).

Present study proved our empiric impression that hyperphosphatemia appeared very rarely in BEN patients on HD. During five-year period BEN patients maintained normal serum phosphorus levels without phosphate binders. Their serum phosphorus levels were significantly lower than in patients with renal disease other than BEN who used phosphate binders and had the similar HD regimen. Although BEN patients maintained diuresis more frequently than the patients with other renal diseases urinary excretion of phosphorus cannot completely explain absence of hyperphosphatemia in these patients.

A low plasma phosphorus levels may be the cause of low bone turnover. Osteomalacia was described in different patients groups with CRF and low phosphate levels and may be aggravated by metabolic acidosis and parathyreoidectomy (5-7, 9, 10). Aluminum-related osteomalacia is much less common than previously due to rare use of aluminum as a phosphate binder. Patients with BEN maintained with HD complain of severe and frequent bone pain. It might be proposed that these patients with normal phosphorus levels are at a higher risk for the development of low turnover bone disease, especially osteomalacia.

In conclusion, BEN patients on maintenance HD have normal phosphate levels and treatment with phosphate binder should be used only occasionally. It can be proposed that this feature of BEN has significant influence on the type of bone disease, but also on development of cardiovascular calcifications.

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