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Original Article

AGE-RELATED CHARACTERISTICS OF MINERAL AND BONE METABOLISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE 5D ON HEMODIALYSIS

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Summary

Abnormalities in mineral and bone metabolism are a risk factor for increased cardiovascular and all-cause mortality and bone fractures in patients with chronic kidney disease stage 5D (CKD 5D). This single-center study aimed to investigate the age-related features of mineral and bone disorders in patients with CKD 5D on haemodialysis treatment and analyse the therapy provided. The biochemical parameters of mineral and bone metabolism and the ongoing therapy were studied in 90 patients undergoing hemodialysis treatment, of whom 44 (48.9%) were aged <65 years and 46 (51.1%) were aged ≥65 years. Serum phosphate, 25(OH) vit.D, parathyroid hormone, and serum albumin were significantly lower in patients aged ≥65 years compared with patients aged <65 years. There was a significant negative correlation between these parameters and age. We found no significant differences in therapy between the two age groups. A significant proportion of the patients aged ≥65 years had serum calcium and parathyroid hormone values below the lower desirable limit, while most of those aged <65 years had hyperphosphatemia and parathyroid hormone ≥600 pg/ml. Mineral and bone metabolism in CKD stage 5D patients on hemodialysis showed age-dependent patterns. Knowing them is crucial for optimal treatment.

Keywords: chronic kidney disease, chronic kidney disease mineral and bone disorder, hemodialysis

Introduction

Disorders of mineral and bone metabolism (CKD-MBD) are among the most common complications of chronic kidney disease (CKD) and are nearly "universal" in stages 5 and 5D. They are a risk factor for cardiovascular disease and mortality in dialysis patients. [1]. Worldwide, the number of adults with end stage chronic kidney disease (ESRD) increases [2]. Age over 65 years is associated with functional and cognitive impairment, limited exercise capacity, malnutrition, and increased incidence of falls and bone fractures [3]. These disorders are further modifying factors of CKD-MBD. They are part of the reasons for the different

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CKD-MBD profiles of elderly CKD 5D patients on hemodialysis treatment compared to young and middle-aged patients. Age-related differences in the clinical spectrum of CKD-MBD determine subsequent differences in the therapy administered in different age groups [4-6].

The present single-center study aimed to analyze the age-associated features of CKD-MBD in CKD 5D patients undergoing hemodialysis treatment and to evaluate differences in therapy according to the age group of patients.

Material and methods

We analyzed biochemical parameters of CKD-MBD according to age <65 years and ≥65 years and the ongoing therapy in 90 CKD 5D patients on hemodialysis treatment enrolled in an observational, cross-sectional study of vit. D levels in patients with CKD stage 3b-5D. The study was approved by the Ethics Committee of the Medical University - Pleven and was conducted at the Clinic of Nephrology and Dialysis of the Dr. Georgi Stranski University Hospital. The patients signed informed consent for participation. The duration of hemodialysis treatment of all studied patients was longer than three months. Demographic data, data on comorbidities, dialysis prescription, laboratory tests, and ongoing therapy for CKD-MBD were collected. Information on this has already been presented in a previous publication [7]. Two of the patients aged <65 years and two aged ≥65 years had undergone parathyroidectomy more than five years previously.

Statistical analysis

Qualitative variables are presented as absolute frequencies and relative proportions, and continuous quantitative variables as median with 1-3 quartiles or minimum-maximum value (asymmetric distribution) and mean±standard deviation (normally distributed variables). Demographic, clinical, laboratory, and ongoing therapy data were compared using the Mann-Whitney test, Student t-test, and Chi-Square test. Pearson or Spearman correlation analysis was performed between age and study parameters. Conclusions were based on a two-tailed test. A $p<0.05$ value was accepted as statistically significant. Statistical analysis was performed using IBM Statistics SPSS v. 25 software.

Results

The mean age of the 90 patients studied was a median of 65 (Q1-3:56-72) years, and 56.6% of the patients were male. The most represented age groups were 50-59 (n=18, 20%), 60-69

Table 1. Demographic and clinical characteristics

	Total	< 65 years	≥ 65 years
Patients, n (%)	90 (100.0%)	44 (48.9%)	46 (51.1%)
Age (years)	65 (56-72)	56 (46-60)	72(68-76)
Sex, male, n (%)	51 (56.6%)	27 (61.4%)	24 (52.2%)
Body mass index (kg/m2)	24 (21-28)	24 (21-26)	25 (22-29)
Cause of ESRD, n (%)			
Diabetic nephropathy	14 (15.6%)	6 (13.6%)	8 (17.4%)
Hypertensive nephropathy	24 (26.7%)	9 (20.5%)	15 (32.6%)
Chronic glomerulonephritis	23 (25.6%)	17 (38.6%)	6 (13.0%) *
Chronic interstitial nephritis	15 (16.7%)	4 (9.1%)	11 (23.9%)
Polycystic kidney disease	9 (10.0%)	4 (9.1%)	5 (10.9%)
Other	5 (5.6%)	4 (9.1%)	1 (2.2%)
Coexisting disease, n (%)			
Diabetes Mellitus	24 (26.7%)	7 (15.9%)	17 (37.0%) *
Ischemic heart disease	35 (38.9%)	16 (36.4%)	19 (41.3%)
Peripheral vascular disease	8 (8.9%)	6 (13.6%)	2 (4.3%)
Cerebrovascular disease	11 (12.2%)	5 (11.4%)	6 (13.0%)

Data are presented as mean ± standard deviation or median (1-3 quartile). *p<0,05 between two age groups.

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Table 2. Biochemical characteristics

	All patients	< 65 years	≥ 65 years
Serum alb-corr. Ca (mmol/L)	2.18±0.195	2.18±0.2	2.18±0.2
Serum phosphorus (mmol/L)	1.97 (1.5-2.3)	2.14 (1.75-2.5)	1.78 (1.43-2.17) *
Calcium-phosphate product (mmol2/L2)	4.3 (3.3-5.1)	4.5 (3.5-5.9)	4.0 (3.3-4.4) *
Serum albumin (g/L)	40.80±2.9	41.6±3.0	40.0±2.5*
Total alkaline phosphatase (IU/L)	96 (74-135)	109 (80-156)	90 (74-127)
i PTH (pg/ml)	307 (137-561)	435 (240-772)	199 (96-421) **
25(OH)D (ng/ml)	26 (18-38)	30 (20-53)	23 (15-34) ***
Dialysis vintage (mths)	42 (19-79)	50 (23-76)	32 (16-88)
URR %	67±8	66±7	67±9
Serum creatinine before HD (mcmol/L)	106 (683-961)	870 (725-1022)	717 (654-832) *

Serum alb-corr. Ca, serum albumin and URR % are presented as mean ± standard deviation. Serum phosphorus, calcium-phosphate product, total alkaline phosphatase, i PTH, 25(OH)D, dialysis vintage and serum creatinine as median (1-3 quartile). Alb-corr. Ca: albumin-corrected Ca, i PTH: intact parathyroid hormone, URR% - urea reduction ratio, HD - hemodialysis. * p <0.01, ** p <0.001 and *** p <0.05 between two study groups.

Table 3. Patients distribution by serum levels of calcium, phosphates and PTH, n (%)

Serum alb-corr. Ca (mmol/L)	Total, n=90	< 65 years, n=44	≥ 65 years, n=46
<2.15	35 (38.9%)	15 (34.1%)	20 (43.5%)
2.15-2.55	54 (60.0%)	29 (65.9%)	25 (54.3%)
>2.55	1 (1.1%)	0 (0.0%)	1 (2.2%)
Serum phosphorus (mmol/L)			
<0.85	1 (1.1%)	0 (0.0%)	1 (2.2%)
0.85-1.8	35 (38.9%)	12 (27.3%)	23 (50.0%)
>1.8	54 (60.0%)	32 (72.7%)	22 (47.8%)
i PTH (pg/ml)			
< 150	24 (26.7%)	5 (11.4%)	19 (41.3%)*
150-300	21 (23.3%)	9 (20.5%)	12 (26.1%)
300-600	26 (28.9%)	16 (36.4%)	10 (21.7%)
> 600	19 (21.1%)	14 (31.8%)	5 (10.9%)*
25(OH)D (ng/ml)			
< 30	50 (55.6%)	23 (52.3%)	27 (58.7%)
> 30	40 (44.4%)	21 (47.7%)	19 (41.3%)
> 50	13 (14.4%)	12 (27.3%)	1 (2.2%)*

Alb-corr. – albumin corrected, *p<0.05 between two study groups

(n=31, 34.4%) and 70-79 (n=23, 25.6%) years. Forty-four (48.9%) of the patients were aged <65 years and 46 (51.1%) were aged ≥65 years. Table 1 presents the demographic and clinical characteristics of the patient groups studied.

The gender and BMI distributions were similar in the two age groups. Chronic glomerulonephritis was the leading cause of ESRD in the younger age group (n=17, 38.6%, p=0.022), followed by hypertensive (n=9, 20.5%) and diabetic (n=6, 13.6%) nephropathies. Hypertensive nephropathy (n=15, 32.6%), chronic interstitial nephritis (n=11, 23.9%) and diabetic nephropathy (n=8, 17.4%), were the three most common chronic nephropathies in the older patients (p=NS). We found no significant difference in the prevalence of diabetic nephropathy as the main

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renal disease, but diabetes mellitus was more common comorbidity in the patients aged ≥65 years (p=0.041). Ischemic heart disease and cerebrovascular disease were more common in elderly patients (p=NS).

The biochemical profile of patients was age dependent (Table 2).

Serum phosphate, calcium-phosphate product, and serum albumin were significantly lower in patients in the ≥65 years of age group compared with patients aged <65 years (1. 78 vs. 2.14 mmol/L, p=0.008, 4.0 vs. 4.5 mmol2/L2, p=0.006, and 40.0 vs. 41.6 g/L, respectively; p=0.009). The older patients had lower parathyroid hormone (PTH) levels, 199 (Q1-3: 96-421) vs. 435 (Q1-3: 240-772) at p=0. 000, 25(OH)vit D - 23 (Q1-3: 15-34) vs. 30 (Q1-3: 20-51) at p=0.012 and serum creatinine measured at the beginning of the hemodialysis session - 717 (Q1-3: 654-832) vs. 870(Q1-3: 725-1022) at p=0.002. Serum calcium levels (corrected according to serum albumin levels) were comparable in the two groups. According to age, there was no difference in the hemodialysis treatment duration and URR%. All patients underwent hemodialysis at a 1.5 mmol/L dialysate calcium concentration. Thirty-five (38.9%) of all the patients studied had serum calcium values below 2.15 mmol/L, of which 15 (34.1%) were in the <65 years age group and 20 (43.5%) were aged ≥65 years (p=NS) (Table 3).

Approximately 66% of the patients in the younger age group and 54.3% of the older patients had serum calcium in the desired range of 2.15-2.55 mmol/L (p=NS). Hypercalcemia was recorded in only one elderly patient. While 50% of patients aged ≥65 years had serum phosphate in the target range of 0.85-1.8 mmol/L, only 27.3% of younger patients had a phosphate level in the desirable range (p=NS). A large proportion of patients in both age groups had inadequate serum phosphate control and a level above 1.8 mmol/L. Total alkaline phosphatase was comparable in the two groups of patients (data not shown). PTH values below 150 pg/mL were more frequent in patients aged ≥65 years, 19 (41.3%), compared with patients aged <65 years, 5 patients (11.4%), p=0.004. Levels above 600 pg/ml were more common in patients aged <65 years, 14 (31.8%), compared to those aged ≥65 years, 5 (10.9%), p=0.039, respectively. Twenty-five (56.9%) of patients aged <65 years and 22 (47.8%) of older patients had PTH within the KDIGO recommended range of 150-600 pg/ml [8]. A 25(OH)vit. D level above 50 ng/ml was present in 12 (27.3%) of the younger patients and only one of the older patients (p=0.02). Regarding 25(OH) vit. D levels <30 and ≥30 ng/ml showed no significant difference between the two study groups. Target values of two parameters simultaneously, serum calcium (2.15-2.55 mmol/L) and PTH (150-600 pg/ml), were achieved in 15 (34.1%) patients aged <65 years and 8 (17.4%) patients aged ≥65 years, (p=NS). Optimal values of three parameters simultaneously - calcium, phosphate, and PTH were present in a small number of patients in both age groups.

Table 4. CKD-MBD therapy

	Total, n=90	< 65 years, n=44	≥ 65 years, n=46
Active vitamin D, n (%) (Calcitriol+Paricalcitol)	48 (53.3%)	20 (45.5%)	28 (60.9%)
Equivalent dose of active vitamin D (μg/wk)	1.25 (0.75-1.75)	1.5 (0.75-1.75)	0.875 (0.75-1.75)
Calcium carbonate, n (%)	83 (92.2%)	43 (97.7%)	40 (87.0%)
Calcium carbonate, (mg/day)	1200 (600-1800)	1200 (600-1800)	1200 (600-1800)
Sevelamer, n (%)	27 (30.0%)	16 (36.4%)	11 (23.9%)
Sevelamer, (mg/day)	1600 (800-3200)	1600 (800-2400)	1600 (800-3200)
Cinacalcet, n (%)	18 (20.0%)	12 (27.3%)	6 (13.0%)
Cinacalcet, (mg/day)	28.8±11.8	24.7±9.4	37.5±12.5

Data are presented as absolute number and relative frequencies (%). The weekly dose of Paricalcitol is equivalent to the weekly dose of Calcitriol (1 μg Paricalcitol = 0.25 μg Calcitriol). Doses of active vit. D, Calcium carbonate and Sevelamer are presented in median (min-max), Cinacalcet dose as mean ± standard deviation.

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We found no significant difference in the frequency of treatment with oral active Vit. D (Calcitriol and Paricalcitol) between the two groups of patients, but the equivalent weekly dose was higher in younger patients - 1.5 mcg/week compared to 0.875 mcg/week in older patients (Table 4).

Calcium carbonate treatment was given to a significant proportion of patients regardless of age. However, in older adults, the drug was used more frequently to correct hypocalcemia and provide additional daily calcium intake. Treatment with Sevelamer in the two groups, <65 years and ≥65 years, was 16 (36.4%) and 11 (23.9%), respectively, and with Cinacalcet 12 (27.3%) and 6 (13%), respectively.

We found a significant negative correlation between age and serum phosphate levels (ρ=0.345, p=0. 001), total alkaline phosphatase (ρ=-0.25, p=0.019), PTH (ρ=0.47, p=0.000), 25(OH)D (ρ=-0.30, p=0.004), albumin (ρ=-0.33, p=0.001), and creatinine before hemodialysis (ρ=-0.39, p=0.000).

Discussion

This single-center cross-sectional study analyzes age-related characteristics of CKD-MBD and ongoing therapy in a cohort of 90 patients on hemodialysis treatment. The age characteristics of the patient group we studied are consistent with global trends in the age structure of the dialysis population. As of February 2021, according to the Dialysis Outcomes and Practice Patterns Study (DOPPS), 51.2% of patients on hemodialysis in the United States were aged 55-74 years, and 22.0% were aged ≥75 years. The median age was 63.3 years [9]. In our study population, 52 (57.7%) of the patients were aged 55-74, and 19 (21.1%) were aged >75 years. Our data are also similar to data from a large national study in Hungary. The mean age of a dialysis population of 5008 patients was 63.4±14.2 years, and the relative proportion of those ≥65 years was 51.8% [5]. The median age in our study dialysis group was 65 years, and the proportion of patients aged ≥65 years was 51.1%. The leading causes of chronic renal failure in the two groups studied, and the higher prevalence of diabetes mellitus as comorbidity in elderly patients are consistent with the results of I. Kiss et al. [5]. In a study comprising 9169 patients undergoing haemodialysis treatment, S. Pelletier et al. found a lower BMI in patients aged ≥ 75 years [4]. We found no significant difference in sex and BMI in the two age groups. The biochemical profile of CKD stage 5D patients on haemodialysis treatment was age-dependent. Similar to the results of other authors, we found that elderly patients had significantly lower levels of serum phosphate, calcium-phosphate product, PTH, 25(OH) vit. D, serum albumin, and creatinine at the beginning of the dialysis session compared to the parameters in younger patients [4, 5, 6]. The lower serum phosphate level in the elderly patients was most likely due to reduced dietary phosphate intake and low bone turnover. A smaller proportion of them received phosphate-binding medications than the younger age group. Calcium carbonate was taken by 87% of the older and 97.7% of the younger group, and Sevelamer carbonate by 23.9% and 36.4%, respectively. Corrected serum calcium levels in the two age groups of our patient cohort were without significant differences. Since the diet of the elderly is lower in calcium [10], calcium carbonate was more frequently used in them for correction and maintenance of calcium homeostasis. However, 20 (43.5%) of the elderly patients had serum calcium below 2.15 mmol/L, and in 25 (54.3%), it was within the normal range of 2.15-2.55 mmol/L. Only one patient in the age group ≥65 years in the entire study population had hypercalcemia above 2.55 mmol/L.

Patients aged <65 years had significantly higher PTH values, with a median of 435 (Q1-3:240-772) pg/ml compared with 199 (Q1-3:96-421) pg/ml in older patients. Patients aged ≥65 years had more frequent serum PTH levels below 150 pg/ml (41.3 vs. 11.4%), and a level above 600 pg/ml was a more common result in younger patients (31.8 vs. 10.9%). Similar data were reported by I. Kiss et al. [5]. Because in the present study, active vit. D and calcium carbonate were used in the elderly patients in low doses to control calcium balance, and Cinacalcet treatment was less frequently administered to them, we assumed that the low PTH levels reflected the trend of higher incidence of adynamic bone disease in this age group. We found no significant difference between the characteristics of patients in the two groups who achieved target PTH levels of 150-600 pg/ml (data not shown). In contrast to

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other studies, we found a significant difference in vit. D levels (>50 ng/ml) concerning age and a negative correlation age-serum vit. D level [11].

We found no significant differences between the two age groups in terms of achieving the target values of one, two, or three parameters, serum calcium, phosphate, and PTH, in contrast to other authors [4, 5]. In our study population, most older patients remained with serum calcium and PTH values below the lower desirable limit, and patients <65 years of age - with hyperphosphatemia and high PTH ≥600 pg/ml.

A higher proportion of the patients aged <65 years were treated with higher doses of active Vit. D, compared with patients ≥65 years of age. The latter had less frequent therapy with phosphate binders and Cinacalcet. Similar results have been reported by S. Pelletier et al. and I. Kiss et al. [4, 5]. In the age group ≥65 years, efforts should be directed to control hypocalcemia, substitution with native Vit. D, and correction of low PTH levels with currently available options - avoiding iatrogenic effects, dialysis with lower calcium concentrations, improving patients' nutritional and inflammatory status. In the group aged <65 years, the goal should be to better correct hyperphosphatemia and secondary hyperparathyroidism.

The limitations of our study are its single-moment nature, the inability to follow long-term trends in CKD-MBD parameters, and their variations, which made assessing the effect of prior therapy and patient collaboration impossible.

Conclusions

The present study confirms the presence of age-related features of CKD-MBD in the population of CKD 5D patients on hemodialysis treatment. Patient age correlated negatively with serum phosphate, cholecalciferol, intact parathyroid hormone, and albumin levels. Older patients are less likely to require treatment with phosphate binders, Cinacalcet, and high doses of active vitamin D. Patients in the younger age groups require therapy more frequently for secondary hyperparathyroidism and/or hyperphosphatemia. Understanding the age-dependent features of CKD-MBD is essential in determining the appropriate therapeutic management to achieve optimal outcomes.

References

1. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004;15(8):2208-18.
2. End Stage Renal Disease: Chapter 1: Incidence, Prevalence, Patient Characteristics, and Treatment Modalities. (USRDS) United States Renal Data System, Annual Data Report (2020). Available at: www.usrds.org.
3. Kuhlmann MK. Management of CKD-MBD. In: Misra M editor. Dialysis in the older adult. New York: Springer Science Business Media; 2016. p.109-21.
4. Pelletier S, Roth H, Bouchet JL, Drueke T, London G, Fouque D, et al. Mineral and bone disease pattern in elderly haemodialysis patients. Nephrol Dial Transplant. 2010;25(9):3062-70.
5. Kiss I, Kiss Z, Ambrus C, Szabo A, Szegedi J, Balla J et al. Age-dependent parathormone levels and different CKD-MBD treatment practices of dialysis patients in Hungary - results from a nationwide clinical audit. BMC Nephrol. 2013;14:155.
6. Wang J, Bieber BA, Hou F-F, Port FK, Anand S. Mineral and bone disorder and management in the China Dialysis Outcomes and Practice Patterns Study. Chin Med J (Engl). 2019;132(23):2775-82.
7. Yankova M, Todorov V, Ruseva A, Todorova G, Gencheva I. [Vitamin D status and risk factors for 25(OH)D deficiency in patients with chronic kidney disease]. Nephrol Dial Transplant. 2021;27(2):26-31. Bulgarian
8. Kidney Disease: Improving Global Outcomes, (KDIGO) clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int. 2009;76 Suppl 113:S1-S130.
9. US-DOPPS Practis Monitor – Hemodialysis, May 2021; Available at: http://www.dopps.org/DMP.
10. Boyanov M. [Calcium-phosphorus metabolism in advanced and old age]. Nauka endocrinologia. 2021;15(2):69-76. Bulgarian
11. Guillaume J, Charra B, Chazot C. Vitamin D deficiency and associated factors in hemodialysis patients. J Ren Nutr. 2008;18(5),395-99.

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