Denosumab for Osteoporosis in Patients With Primary Hyperparathyroidism and Renal Insufficiency

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Research Article

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Abstract

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia. The only curative treatment is parathyroidectomy. However, patients are often ineligible or decline surgery. Denosumab (Dmab) is an antiresorptive pharmaceutical alternative. The effects of exposure to Dmab in subjects with chronic kidney disease (CKD) and PHPT are unknown.

Purpose: We aimed to assess the efficacy and safety of denosumab in postmenopausal women with PHPT- related osteoporosis and CKD.

Methods: Women over 50 years of age with PHPT or postmenopausal osteoporosis (PMO) were retrospectively recruited into this longitudinal study. These PHPT and PMO groups were further categorized into four subgroups based on the presence of CKD (Glomerular filtration rate (GFR) <60 mL/min/1.73mBI): patients with PHPT with and without CKD and patients with PMO with and without CKD. All patients were given denosumab over 24 months due to verified osteoporosis. The primary outcomes were changes in bone mineral density (BMD) and serum calcium levels.

Results: 145 postmenopausal women median age 69 [63;77] were recruited and assigned to one of the subgroups. Denosumab treatment significantly increased BMD (median ΔT-score: L1-L4 +0.65 ($p<0.001$), femur neck +0.3 ($p=0.012$); radius 33% +0.2 ($p<0.05$)) in PHPT-related osteoporosis and CKD at 24 months. Changes in BMD were similar in all study groups compared to baseline. A marked decline in calcium was noted in the primary study group of PHPT with CKD (median ΔCa = -0.24 mmol/L $p<0.001$), compared to PHPT without CKD (median ΔCa = -0.08 mmol/L $p<0.001$) and PMO with or without CKD. Denosumab treatment was well-tolerated with no serious adverse events.

Conclusion: Denosumab treatment was similarly effective at increasing BMD in patients with PHPT and PMO with and without renal insufficiency. The calcium lowering effects of denosumab were most significant in patients with PHPT and CKD. The safety of denosumab did not differ among participants with and without CKD.

Introduction

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia and elevated or inappropriately normal parathyroid hormone (PTH) levels [1, 2]. PHPT affects between 0.3–0.9% of the general population, with increased prevalence in postmenopausal women 2–5% [2–4]. The cause of PHPT is solitary parathyroid adenoma in 80% of cases or multiple-gland hyperplasia in 10–15% of cases [5, 6]. The only curative treatment for PHPT is parathyroidectomy [7]. However, patients with advanced age or comorbidities are often ineligible or decline surgery. Continuous exposure to high levels of PTH in PHPT leads to increased bone remodeling, accelerated bone loss, hypercalcemia and hypercalciuria further resulting in osteoporosis, reduced kidney function and kidney stones [5, 8]. Additionally, ageing is associated with osteoporosis and a gradual decline in kidney function which are deteriorated by PHPT. Consequently, pharmaceutical alternatives to prevent future complications are desirable. Cinacalcet

lowers and maintains serum calcium levels, but does not prevent bone mineral density (BMD) loss, whereas bisphosphonates (BP) improve BMD and decrease calcium levels but with reduced effects over time [9]. In vivo studies show that PTH, delivered either intermittently or continuously leads to increased expression of the receptor activator of nuclear factor kappa-B ligand (*RANKL)*, while osteoprotegerin (*OPG)* expression decreases or remains unchanged [10–14]. Similarly, bone biopsies from patients with PHPT show an increase in RANKL and a decrease in OPG gene expression, which is reversed after parathyroidectomy [14]. Denosumab (Dmab) is an antiresorptive agent which blocks the PTH-mediated activation of the RANK/RANKL pathway and therefore could prove an effective treatment for osteoporosis associated with PHPT [15]. Dmab decreases bone resorption, increases BMD and has proven efficacy at preventing fragility fractures in postmenopausal osteoporosis (PMO) [16, 17]. As Dmab does not accumulate in bone tissue, discontinuation results in a rapid decline in BMD leading to increased fracture risk [18–20]. Nevertheless, Dmab is more effective at increasing BMD in PMO compared to alendronate or any other BP [21–24]. In a randomized control prospective trial Dmab was effective at increasing BMD without decreasing serum calcium levels in 15 patients with PHPT versus placebo control over 2 years of treatment [25]. However, the effects of exposure to Dmab in subjects with renal insufficiency and PHPT are unknown. In contrast to BP, Dmab is not renally excreted and showed similar efficacy and safety among subjects with and without renal impairment [24, 26, 27]. Consequently, Dmab may be favorable in elderly patients with PHPT and compromised kidney function. The aim of this study is to evaluate the efficacy and safety of Dmab in postmenopausal women with PHPT related osteoporosis and mild-to-moderate chronic kidney disease (CKD) (glomerular filtration rate (GFR) 30–60 ml/min/1.73 m^2).

Materials And Methods

Study design and participants

In this retrospective longitudinal study, we evaluated the medical records (n = 352) of patients who received Dmab between September 2013 and September 2019. All patients were referred to and under observation in the Endocrinology Research Centre, Russia. One hundred and forty-five (n = 145) women over 50 years of age with verified osteoporosis based on BMD T-score ≤ -2.5 SD or at least one low-trauma fracture were eligible for enrolment. Patient records were grouped according to the presence or absence of PHPT. These two PHPT (n = 60) and PMO (n = 85) groups were further categorized into four subgroups based on the presence of CKD (Glomerular filtration rate (GFR) < 60 mL/min/1.73m^2). Patients with PHPT and GFR 30–60 ml/min/1.73 m^2 (n = 22) were enrolled in the primary investigation group. Other patients were enrolled as control groups with PHPT and GFR > 60 ml/min/1.73 m^2 (n = 38), PMO and GFR 30–60 ml/min/1.73 m^2 (n = 17) and PMO and GFR > 60 ml/min/1.73 m^2 (n = 68). Patients received Dmab 60 mg subcutaneously (SC) every 6 months for 24 months. All patients were invited for evaluation at the end of treatment just before or after the final injection of Dmab. Exclusion criteria were other diseases or medications affecting bone metabolism (premenopausal age, thyrotoxicosis, gastrointestinal disorders known to cause malabsorption, terminal renal or hepatic failure, severe

rheumatic or hematological disease, uncontrolled diabetes mellitus, hypercortisolism, or the following medications: cinacalcet, glucocorticoids, lithium, bisphosphonate or teriparatide treatment at the time of enrollment), genetic causes of PHPT, parathyroid cancer, substance abuse (alcohol, drugs). Bone biopsies were not performed in patients with CKD as there were no patients with CKD 5 and only 2 patients with CKD 4. Although a recent review stated that bone histomorphometry is the gold standard to evaluate bone abnormalities of CKD-MBD starting from stage 3, there is no solid recommendation to perform bone biopsies in routine practice in CKD stage 3–5 [28]. The evidence-based review for the 2017 KDIGO CKD-MBD stated that dual-energy X-ray absorptiometry (DXA) BMD measurements predicted fractures across the spectrum from CKD G3a to G5DT [29]. Based on this data we focused on BMD measurements as surrogate markers of Dmab efficacy. Patients with PHPT were of postmenopausal age and therefore BMD loss could be related to both PHPT and PMO. Our study is not powered to assess fracture risk. Nevertheless, we reported the available fracture incidence. PHPT was diagnosed based on the presence of hypercalcemia and high or inappropriately normal PTH levels [2, 8]. Patients with PHPT were enrolled in the study due to parathyroidectomy being declined for various reasons. Among the primary investigation group with PHPT and CKD, surgery was declined in 9 cases due to an assessment of high risk by surgeons or anesthesiologists (cardiovascular diseases, oncology ect.) and in 13 cases surgery was declined by patients. Among the group with PHPT without CKD, 10 patients had contraindication and 28 refused surgery.

All subjects were prescribed vitamin D (cholecalciferol supplement 800–2000 IU daily) over the study duration and those with 25(OH)D less than 30 ng/mL received additional cholecalciferol supplementation. Dairy products were recommended to all subjects without restriction. Calcium supplements (500–1000 mg daily) were recommended to patients with PMO. Patients with PMO and CKD with hypocalcemia/hyperphosphatemia or severe hyperparathyroidism additionally received alfacalcidol at a dose of 0.5-1 mcg daily. Informed consent was obtained from all individual participants included in the study.

The study was formally approved by The Local Ethics Committee of the Federal State Institution "NMIC of Endocrinology", which is an autonomous, independent expert body guided in its activities by the current legislative normative legal acts of the Russian Federation and the basic principles of conducting clinical trials. All subjects signed informed consent approving the use of their data for research purposes.

Outcome measures

The primary outcome was change in BMD measured by DXA, which was analyzed and presented as T-score. The median change in BMD T-score at lumbar spine, femur neck, and radius 33% (for patients with PHPT only) was determined. BMD measurements were taken at baseline and 24 months from the start of Dmab therapy using machine model GE Lunar iDXA (with coefficients of variations Neck 1.4%, Total Hip 0.7%, Spine L1-L4 1.1%) or GE Lunar Prodigy. BMD was measured at anteroposterior lumbar spine (L1-L4) and femur neck positions according to standard protocol. Individual patients used the same DXA machine throughout the study. For patients with PHPT we additionally performed radius 33% BMD

measurements. Quality control procedures were carried out in accordance with the manufacturers' recommendations.

The secondary outcomes were changes in serum calcium levels and other routine biochemical parameters. Blood samples (fasting, 8 a.m. – 9 a.m.) were taken at the beginning and after 24 months of Dmab treatment. PTH (reference 15–65 pg/mL) and C-terminal telopeptide of type 1 collagen (CTx) (reference range 0.01–0.69 ng/mL) were measured by ECLIA on automatic analyzer Roche Cobas e 601. Calcium (reference range 2.15–2.55 mmol/L), phosphate (reference range 0.74–1.52 mmol/L), albumin (reference range 35–50 g/L), total alkaline phosphatase (ALP) (reference range 50–150 U/L) and creatinine (reference range 50–98 mcmol/L) in serum along with calcium in 24-hour urine (reference range 2.5-8 mmol/24h) were measured using standard colorimetric techniques. Albumin adjusted calcium was calculated using the following equation (adjusted [Ca](mmol/L) = total [Ca](mmol/L) + 0.02 (40 - [albumin] (g/L)). A CKD-EPI study equation was used for Glomerular Filtration Rate (GFR) calculations. Kidney function was estimated as follows: CKD stage 3a = GFR 45–59 mL/min/1.73 m^2; CKD stage 3b = GFR 30–44 mL/min/1.73 m^2; CKD stage 4 = GFR 15–29 mL/min/1.73 m2 (31). In this study we focused on CKD with GFR below 60 mL/min/1.73 m^2 as this stage of declined kidney function is associated with bone tissue involvement [29]. Hypocalcemia was registered if blood calcium levels were less than or equal to 2 mmol/L. We considered hypocalcemia to be mild when albumin adjusted calcium levels were 1.9-2.0 mmol/L.

At the time of enrollment and 24 months later, all participants were questioned regarding any recent low traumatic fractures, back pain and height changes. Height was measured by stadiometer and body mass index (BMI) was calculated as kilograms per meter squared. In addition to this, patients underwent standard spinal radiographs in anterior-posterior and lateral positions of the vertebrae Th4-L4 (Axiom Icons R200 ‘Siemens'). A deformity was considered a fracture if a visual inspection perceived a reduction in vertebral height (anterior, posterior or middle) of 20% or more. Lateral vertebral X-rays were taken at baseline and 24 months from the start of Dmab therapy in order to estimate the presence of new vertebral fractures during treatment. Two or more incidents of fragility fracture over 24 months of treatment resulted in a participant being classified as non-responsive to treatment. Safety was evaluated on the basis of adverse event (AE) incidence.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Base (SPSS, USA). Continuous values are presented as medians, 1st and 3rd quartiles. The difference is presented in absolute values. Categorical variables are presented as percentages. Comparison of continuous variables between independent groups was performed using the Mann-Whitney U-test. The Kruskal-Wallis test was used to compare differences within the study groups. The Wilcoxon criteria were used to find the difference between dependent groups. In order to account for baseline parameters that were different between groups, analysis of covariance (ANCOVA) was used with the corresponding baseline parameter being a covariate. In order to account for the baseline differences between groups (namely, differences in age when

treatment started with denosumab and number of fractures before treatment started with denosumab), a generalized linear model (GLM) was applied with the following parameters: delta of corresponding T-score as dependent variable, baseline age, number of previous fractures and baseline T-score as independent covariates, and group as fixed factor. P-values were calculated for the entire sample as two-sided and p-values < 0.05 were considered statistically significant.

Results

Subject characteristics

One hundred and forty-five postmenopausal women aged 69 [63;77] were enrolled into the study based on eligibility and were assigned to either the PHPT or postmenopausal osteoporosis (PMO) without PHPT groups. The characteristics of subjects with PHPT-related osteoporosis were as follows: [n = 60; calcium – 2.60[2.50;2.73] mmol/L ; GFR – 72[51;82] ml/min/1.73 m^2]. Among the PHPT group there were patients with CKD n = 22, including CKD 3a (n = 13), CKD 3b (n = 7) and CKD 4 (n = 2).

The characteristics of subjects with PMO-related osteoporosis were as follows: [n = 85; calcium – 2.4[2.3;2.47] mmol/L; GFR – 76[60;84] ml/min/1.73 m2]. Among patients with PMO and CKD n = 17, there was CKD 3a n = 13 and CKD 3b n = 4. As we focused on the efficacy of denosumab in patients with PHPT and CKD, both groups (PHPT and PMO) were subdivided based on GFR (< 60 ml/min/1.73 m2 CKD 3–4 and > 60 ml/min/1.73 m2 (without CKD)). Full Biochemical and clinical characteristics of all enrolled patients at baseline are provided in Table 1.

Table 1
General patient characteristics at baseline

	PHPT and CKD	PHPT	PMO and CKD	PMO	p-value
Patient number, n	22	38	17	68	
Age (years)	73 [61;82]	67 [63;72]	78 [69;81]	68[62;76]	0.009
Prior use of osteoporosis medications, n (%)					
Without treatment	11 (50)	22 (57.9)	8 (47)	24 (38)	0.184
Bisphosphonate (oral)	9 (41)	14 (36.8)	8 (47)	39 (60)	
Other (Teriparatide, Calcitriol, Hormone replacement therapy, Estrogens, calcitonin)	2 (9)	2 (5.3)	1 (6)	1 (2)	
Patients with previous fractures, n (%)	14 (64%)	13 (34%)	15 (88%)	47 (73%)	< 0.001
Vertebral fractures, n	6	3	6	22	
Vertebral and non-vertebral fractures, n	4	8	8	18	
Non-vertebral fractures, n	4	2	1	7	
Locations in non-vertebral fractures, n	Radius (n = 6), femur (n = 3), tibia (n = 1), ankle (n = 2).	Radius (n = 6), femur (n = 1), tibia (n = 1), ankle (n = 1) ischiatic bone (n = 1).	Radius (n = 6), femur (n = 1), humerus (n = 3), kneecap (n = 1).	Radius (n = 15), femur (n = 6), humerus (n = 4), kneecap (n = 1), ankle (n = 4), radius (n = 2), pelvis (n = 2), fibula (n = 2), rib (n = 5), clavicle (n = 1), sternum (n = 1).	
BMD Lumbar spine T-score*	-2.0[-3.0;-1.1]	-2.95[-3.63;-2.1]	-3.4[-3.8;-2.45]	-3.1[-3.7;-2.1]	0.026
BMD Femoral neck T-score*	-2.4[-2.8;-1.9]	-2.3[-2.73;-1.78]	-2[-2.35;-1.58]	-2.25[-2.6;-1.73]	0.537

	PHPT and CKD	PHPT	PMO and CKD	PMO	p-value
BMD Radius 33% T-score*	-3.2[-3.9;-2.8]	-3.3[-3.8;-2.65]			
Corrected calcium, mmol/L* **(reference 2.15–2.55)**	2.64[2.55;2.7]	2.6[2.5;2.75]	2.36[2.27;2.47]	2.42[2.3;2.47]	< 0.001
C-terminal telopeptide of type 1 collagen, ng/ml* **(reference 0.01–0.69)**	0.6[0.32;1.05]	0.49[0.37;0.9]	0.47[0.2;0.5]	0.45[0.25;0.67]	0.501
Phosphate serum, mmol/L* **(reference 0.74–1.52)**	1.19[0.93;1.3]	0.94[0.88;1.06]	1.15[1.1;1.34]	1.14[1.08;1.3]	< 0.001
ALP, U/L* **(reference 50–150)**	79[74;90]	85.5[70;129]	105[82;137]	78[64;87]	0.437
PTH, pg/ml* **(reference 15–65)**	106[82;171]	94[68;146]	38[17;42]	40[28;59]	< 0.001
Creatinine serum, mcmol/L* **(reference 50–98)**	103[93;131]	66[63;73]	96[93;102]	68[63;73]	< 0.001
GFR, *	47[34;52]	80[72;85]	50[46;54]	79[72;87]	< 0.001
Calcium 24Urine, mmol/24h* **(reference 2.5-8)**	4.25[1.98;7.05]	7.37[4.83;9.86]	5.25[2.85;7.3]	3.56[2.22;7.16]	0.03

* Median [1st and 3rd quartiles]

† Normal renal function = glomerular filtration rate (GFR) ≥ 90 mL/min/1.73 m2; CKD stage 2 = GFR 60 - 89 mL/min/1.73 m2; CKD stage 3a = GFR 45 - 59 mL/min/1.73 m2; CKD stage 3b = GFR 30 - 44

mL/min/1.73 m2; CKD stage 4 = GFR 15 - 29 mL/min/1.73 m2.

PHPT - primary hyperparathyroidism, CKD - chronic kidney disease, PMO - postmenopausal osteoporosis, BMD = bone mineral density, ALP - alkaline phosphatase, PTH - parathyroid hormone

Patients with PMO were approximately the same age 70[64;78] 95%CI 67–72 as PHPT 68[62;75] 95% CI 65–71 (p = 0.483) and had no significant differences in blood levels of creatinine (p = 0,109) or GFR (p = 0,114). As expected, patients with PHPT compared to PMO had higher levels of serum calcium 2.6 vs 2.4 mmol/L (p < 0,001), PTH 96 vs 39 pg/ml (p < 0,001) and urinary calcium 7.03 vs 3.56 mmol/24h (p < 0,05). The prevalence of kidney stones or nephrocalcinosis in patients with PHPT was 38.3% (23 out of 60) including 31.8% (7 out of 22) in patients with PHPT and CKD and 42.1% (16 out of 38) in patients with PHPT without CKD.

The prevalence of previous low traumatic fracture was 45% (27 out of 60) in patients with PHPT and 73% (62 out of 85) in patients with PMO. There were no significant differences in PHPT groups vs PMO groups in BMD Lumbar Spine T-score – 2.9[-3.3; -1.6] VS -3.1[-3.7;-2.1] (p = 0,055) and femoral neck – 2.3[-2.8; -1.8] VS -2.2[-2.6;-1.6] (p = 0,360). As expected, patients with PHPT had low BMD in distal radius – 3.25[-3.85;-2.7]. Around half of the patients received BP before the prescription of Dmab, specifically 55% of patients with PMO (including 47% of patients with PMO and CKD) and 38% of the PHPT group (including 41% of PHPT and CKD). The mean duration of previous BP therapy and the prevalence of inadequate responders to BP therapy did not differ between groups.

The most common comorbidities were arterial hypertension and dyslipidemia as registered. None of our patients received insulin or suffered from severe uncontrolled diabetes. The most common medications were statins and blood pressure lowering drugs.

Changes in BMD and fracture incidence

In patients with PHPT-related osteoporosis the median increase in BMD according to T-score was L1-L4 + 0.65[0.3;0.95] 95%CI 05-0.85 (p < 0.001), femur neck + 0.2[0.1;0.4] 95%CI 0.1–0.3 (p < 0.001), radius 33% +0.3[0.05;0.6] 95%CI 0.2–0.45 (p = 0.002). In patients with PMO, Dmab increased BMD according to T-score at L1-L4 + 0.6[0.30;0.80] 95%CI 0.4–0.6 (p < 0.001), femur neck + 0.2[0.001;0.4] 95%CI 0.1–0.3 (p = 0.004). There were no statistically significant differences in delta BMD L1-L4 (p = 0.244) and femur neck (p = 0.202) between PHPT and PMO patients. Specific analysis among the subgroups with and without CKD showed a stable increase in BMD in all patients from baseline to the end of 24-month Dmab treatment (Fig. 1). In patients with PHPT-related osteoporosis and CKD, the median increase in BMD according to T-score was L1-L4 + 0.65 (p < 0.001), femur neck + 0.3 (p = 0.012); radius 33% + 0.2 (p < 0.05). In patients with PHPT-related osteoporosis without CKD the median increase in BMD according to T-score was L1-L4 + 0.65 (p < 0.001), femur neck + 0.2 (p < 0.001); radius 33% +0.3 (p = 0.013). In patients with PMO and CKD, Dmab increased BMD at lumbar spine L1-L4 + 0.5 (p < 0.001), femur neck + 0.02 (p = 0.8). In subjects with PMO without CKD: the median increase in BMD according to T-score was L1-L4 + 0.6 (p < 0.001), femur neck + 0.2 (p < 0.001).

Analysis of L1-L4 T-score delta using GLM didn't confirm statistical significance of any covariates, group factor was also insignificant (p = 0.89). Analysis of femur neck T-score delta showed that baseline T-score was a significant co-variate, however, other covariates were insignificant, as was the group difference (p = 0.92). Analysis of radius 33% T-score delta didn't show significant input for any covariates. The incidence rate of new fracture was 0% for CKD groups (with PHPT or PMO), 8% for the PHPT group (2 vertebral fractures, 1 femur fracture) and 9% for the PMO group (4 vertebral fractures and 2 fractures of fibula and tibia).

Biochemical changes in response to Dmab treatment

At the end of 24-month Dmab treatment, serum calcium levels and bone turnover markers had decreased in all groups versus baseline evaluation. In patients with PHPT-related osteoporosis, the median decrease in calcium serum levels was − 0.11[-0.25;-.04] mmol/L 95% CI -0.41;-0.05 (p < 0.001). The highest decrease in calcium levels was observed in the PHPT-related osteoporosis and CKD subgroup − 0.24 mmol/L (p < 0.001) whereas the decrease in calcium levels was less marked in PHPT-related osteoporosis without CKD − 0.08 mmol/L (p < 0.001). In patients with PMO, the median decrease in calcium serum levels was − 0.04[-0.12;0.01] mmol/L 95%CI -0.10–0.08 (p = 0.002); in the subgroup of PMO and CKD − 0.04 mmol/L (p = 0.4); in subjects with PMO without CKD − 0.04 mmol/L (p = 0.02) (Fig. 2). After two years of Dmab treatment calcium levels were within the reference range in 17 out of 22 patients in the PHPT and CKD subgroup and 22 out of 38 patients in the PHPT without CKD subgroup.

PTH levels did not change significantly in the PHPT group 3.9[-10.5;23] pg/mL (p = 0.335) or PMO group 2.0[-16.85;11.50] pg/mL (p = 0.29) (Fig. 3).

Shift in renal function from baseline

Most participants with baseline CKD remained at the same CKD stage throughout the study; less than 5% progressed to CKD stage 4 (n = 1 in the group with CKD and PHPT and n = 1 in the group with CKD and PMO). Among subjects with normal renal function at baseline, 75% with PHPT and 76% with PMO maintained normal renal function throughout the study until the last on-study visit, while 25% and 24% respectively progressed to CKD stage 2. Renal replacement therapy was not initiated in any subjects. No statistically significance decrease in renal function or changes in phosphate levels before or after treatment was found.

Incidence of hypocalcemia and other adverse events (AE)

There was no statistically significant difference in the rate of adverse events between the four groups. Two subjects in the PMO and CKD group developed hand dermatitis for a short period after each Dmab administration. Mild hypocalcemia as an AE occurred in one subject with PMO and CKD.

Discussion

This is the first study reporting the efficacy and safety of Dmab in postmenopausal women with PHPT-related osteoporosis complicated by CKD. Twenty-four months of Dmab treatment was similarly effective at BMD increase and bone resorption marker decrease in postmenopausal women with PHPT and CKD versus PHPT without CKD, PMO with CKD and non-complicated PMO. Serum calcium levels decreased in all patient groups, most significantly in patients with PHPT and CKD. As there were no severe cases of hypocalcemia, the decrease in calcium levels in PHPT patients was beneficial. Over 24 months of observation, we did not register significant changes in PTH levels including in patients with PHPT.

In randomized controlled trials Dmab remained effective and safe in PMO patients with CKD including GFR less than 30 ml/min [27, 31], which is a contraindication to BP or teriparatide prescription. Recently a randomized placebo-controlled trial proved the efficacy of Dmab in preventing bone loss at lumbar spine and total hip in patients with PHPT receiving either Dmab alone (n = 15) or a combination of Dmab and cinacalcet (n = 15) versus placebo (n = 15) [25]. Similarly, in retrospective observational studies Dmab 60mg every 6 months was effective at preventing BMD loss in patients with PHPT without renal impairment [32, 33]. In our study, the increase in BMD was compared within patient groups of PHPT or PMO with and without CKD showing that the efficacy of Dmab at increasing BMD is equal in patients with PHPT and PMO regardless of the presence of stage 3 CKD. In addition to lumbar spine and femur neck, we reported BMD gain at radius 33% in patients with PHPT. It is known that Dmab is the only drug that consistently improves BMD in the distal one-third radius [34, 35, 36]. The increase in BMD in one-third radius + 0.3[0.05;0.6] 95%CI 0.2–0.45 ($p < 0.005$) was less evident than in lumbar spine + 0.65[0.3;0.95] 95%CI 05-0.85 ($p < 0.001$), but significant. Previous data focusing on BP treatment in patients with PHPT demonstrated its efficacy at increasing BMD at lumbar spine, stabilization at femur neck and mild decrease in serum calcium levels [37]. In our study, 44.8% of patients were not treated for osteoporosis before the administration of Dmab while 48.3% previously received therapy with BP. Nevertheless, a significant increase in BMD at lumbar spine and femur neck was observed in all groups. Thus, the difference in antiresorptive effects of BP and Dmab on bone remodeling ensure a continuous increase in BMD and the maintenance of bone metabolism at a low level in the treatment of Dmab after BP [24].

The hypocalcemic effects of Dmab are expected to be beneficial for patients with PHPT. Our study demonstrated a significant decrease in calcium levels in PHPT patients from an elevated level to within the reference range, both in patients without CKD (from 2.6 to 2.54 mmol /l $p < 0.001$) and in patients with CKD (from 2.64 to 2.41 $p < 0.001$). These changes in calcium levels were more pronounced in the group with CKD $p = 0.008$. In a study by C Eller-Vainicher et al. [32] the authors found a small but significant decrease in serum calcium levels both in patients with PHPT and PMO. Similarly, a decrease in calcium levels was reported in a case series with PHPT [38], in a child with PHPT [39] and metastatic parathyroid carcinoma [40], but not in the randomized control trial of Dmab versus Dmab and cinacalcet or placebo [25]. Dmab was also effective for the treatment of BP resistant hypercalcemia in a hemodialysis patient [41]. However, withdrawal of Dmab 120 mg administered to treat hypercalcemia in a patient with parathyroid carcinoma was associated with severe hypercalcemia [42].

Dmab treatment was not associated with the progression of CKD in our study similarly to the results of other studies using Dmab in PHPT without moderate CKD [32, 33], whereas parathyroid surgery was associated with CKD progression [43].

In our study, only a mild case of hypocalcemia was recorded in a PMO and CKD patient. In the published literature, the incidence of hypocalcemia following Dmab administration to CKD patients was approximately 13% – 15% [43, 44]. Hypocalcemia is more common in patients with more advanced CKD and is usually observed after a first Dmab dose [45–49].

Dmab administration might cause a rapid increase in PTH levels. However, these levels gradually declined in Leere JS et al. [25] and in our study, returning to original levels.

Our study has several limitations. This research implies all limitations related to the retrospective observational design of a registry study and consequent absence of some clinical data as is frequently the case in real clinical practice analysis. We also enrolled patients with mild-to-moderate CKD (stage 3a-b) with only 2 at CKD stage 4 and none at CKD stage 5. The 3-year FREEDOM analysis reported by Jamal et al. included a larger number of subjects with PMO and CKD stage 4 (N = 73) and demonstrated that treatment efficacy and safety did not differ by renal function [31]. We did not perform bone biopsies before patient enrollment. However, there is no solid recommendation to do so for all patients with CKD stage 3 according to 2017 KDIGO guidelines [29]. Our study showed the efficacy and safety of Dmab over 24 months of treatment, though in patients with end stage CKD, Dmab should be considered a long term or even life-long treatment. The therapeutic effects of Dmab are fully reversible as are many other medications to treat other chronic diseases (hypertension, diabetes etc). The main concern about Dmab safety is related to the occurrence of multiple vertebral fractures after drug discontinuation [19, 20]. As there is no data proving that Dmab treatment beyond 10 years is harmful, we may continue treatment for a longer period of time. Bisphosphonates are currently used to mitigate BMD loss and the incidence of fractures after Denosumab withdrawal [20], however they cannot be used in CKD-G4 and G5. Moreover, if kidney function declines from CKD-G4 to the stage G5 and the patient receives dialysis, BP treatment may be suggested. Although the maintenance of BP in bone tissue gives us the opportunity and even necessity to provide a drug holiday due to loss of effectiveness and increase risk of adverse events (for example atypical fractures), a drug holiday if longer than 2 years is associated with an increased risk of fracture [50, 51]. As all enrolled subjects were postmenopausal women, we believe that continuous treatment with Dmab may be prescribed for as long a period of time as needed with further monitoring. However, new studies to evaluate the Dmab’s effectiveness and safety for a long time period are needed.

Conclusion

Denosumab treatment was effective at increasing BMD and decreasing bone turnover markers in postmenopausal women with PHPT and mild to moderate CKD, similarly to PHPT without CKD or PMO with and without CKD over two years of observation. The calcium lowering effects of denosumab were most significant in patients with PHPT and CKD.

Declarations

Declaration of interest

The authors Gronskaya Sofya, Belaya Zhanna, Rozhinskaya Liudmila, Mamedova Elizaveta, Vorontsova Maria, Solodovnikov Alexander, Golounina Olga and Melnichenko Galina declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The authors declare that they have no conflict of interest.

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Author Contributions

Gronskaya Sofya - the design of the study, data collection, data analysis, draft writing, substantial contributions to conception and design; drafting the article; approval of the version to be published.

Belaya Zhanna - the design of the study, conducting research, data analysis, article editing, substantial contributions to conception and design; drafting the article; approval of the version to be published.

Rozhinskaya Liudmila Y- the original concept of the study, conducting research, substantial contributions to conception and design; drafting the article; approval of the version to be published.

Mamedova Elizaveta - draft writing, conducting research, article editing, substantial contributions to conception and design; drafting the article; approval of the version to be published.

Vorontsova Maria - research design, article editing, substantial contributions to conception and design; drafting the article; approval of the version to be published.

Solodovnikov Alexander - data analysis , substantial contributions to conception and design; drafting the article; approval of the version to be published.

Golounina Olga – data collection, article editing, substantial contributions to conception and design; drafting the article; approval of the version to be published.

Melnichenko Galina A- organization of the research, article editing, substantial contributions to conception and design; drafting the article; approval of the version to be published.

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Figures

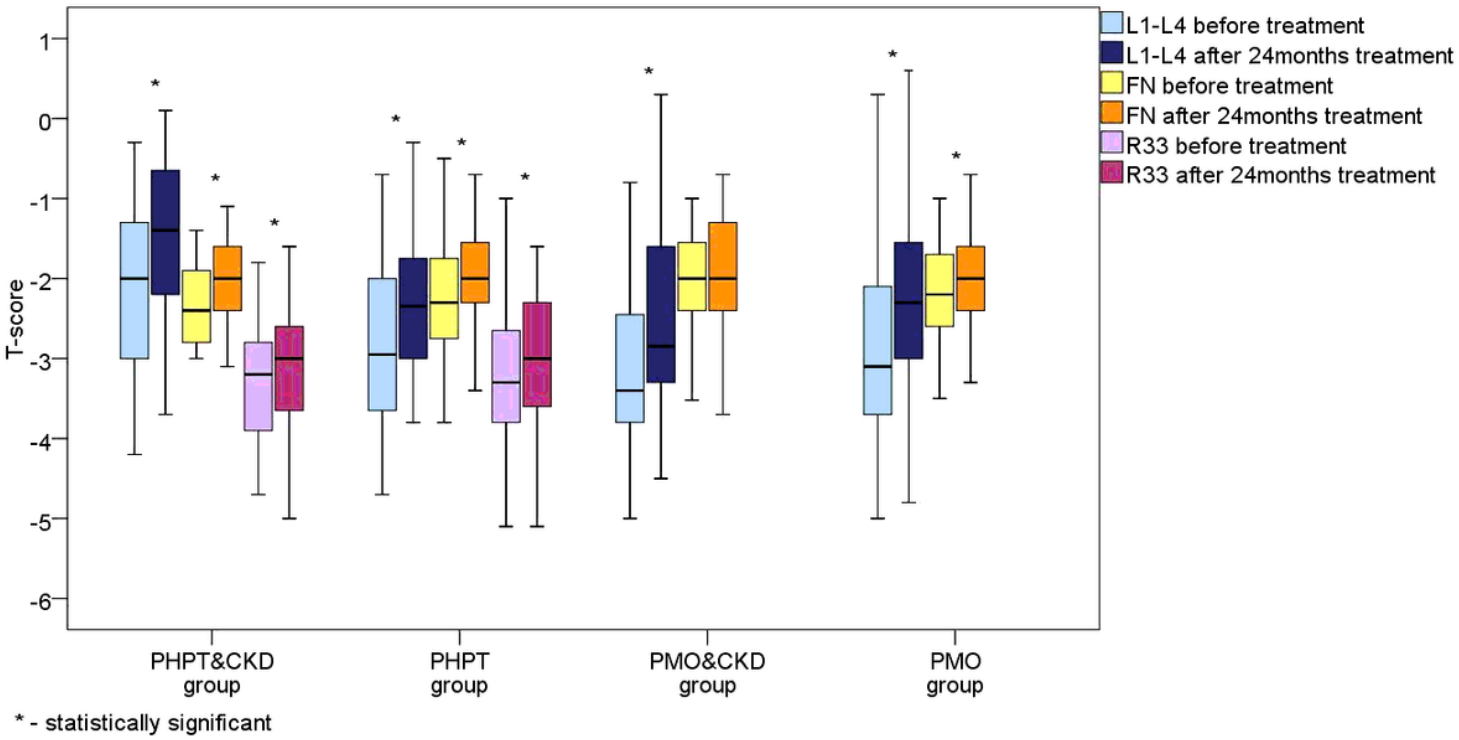

Figure 1

A. Changes in bone mineral density (BMD) at lumbar spine (L1L4), femoral neck (FN), distal 33% radius (R33) before and after 24 months of denosumab administration.

PHPT - primary hyperparathyroidism, CKD - chronic kidney disease, PMO - postmenopausal osteoporosis.

Over 24 months of treatment the median increase in BMD according to T-score at lumbar spine (L1-L4) was 0.65 ($p<0.001$) in patients with PHPT-related osteoporosis and CKD; 0.65 ($p<0.001$) in PHPT-related osteoporosis without CKD; 0.5 ($p<0.001$) in patients with PMO and CKD; 0.6 ($p<0.001$) in subjects with PMO without CKD. No statistically significant difference was found between the groups.

Over 24 months of treatment the median increase in BMD according to T-score in femoral neck was 0.3 ($p=0.012$) in PHPT-related osteoporosis and CKD; 0.2 ($p<0.001$) in PHPT without CKD; 0.02 ($p=0.8$) in PMO with CKD; and 0.2 ($p<0.001$) in subjects with PMO without CKD. No statistically significant difference was found between the groups.

Over 24 months of treatment the median increase in BMD according to T-score in radius 33% was 0.2 ($p<0.05$) in PHPT-related osteoporosis and CKD; 0.3 ($p=0.013$) in PHPT without CKD;

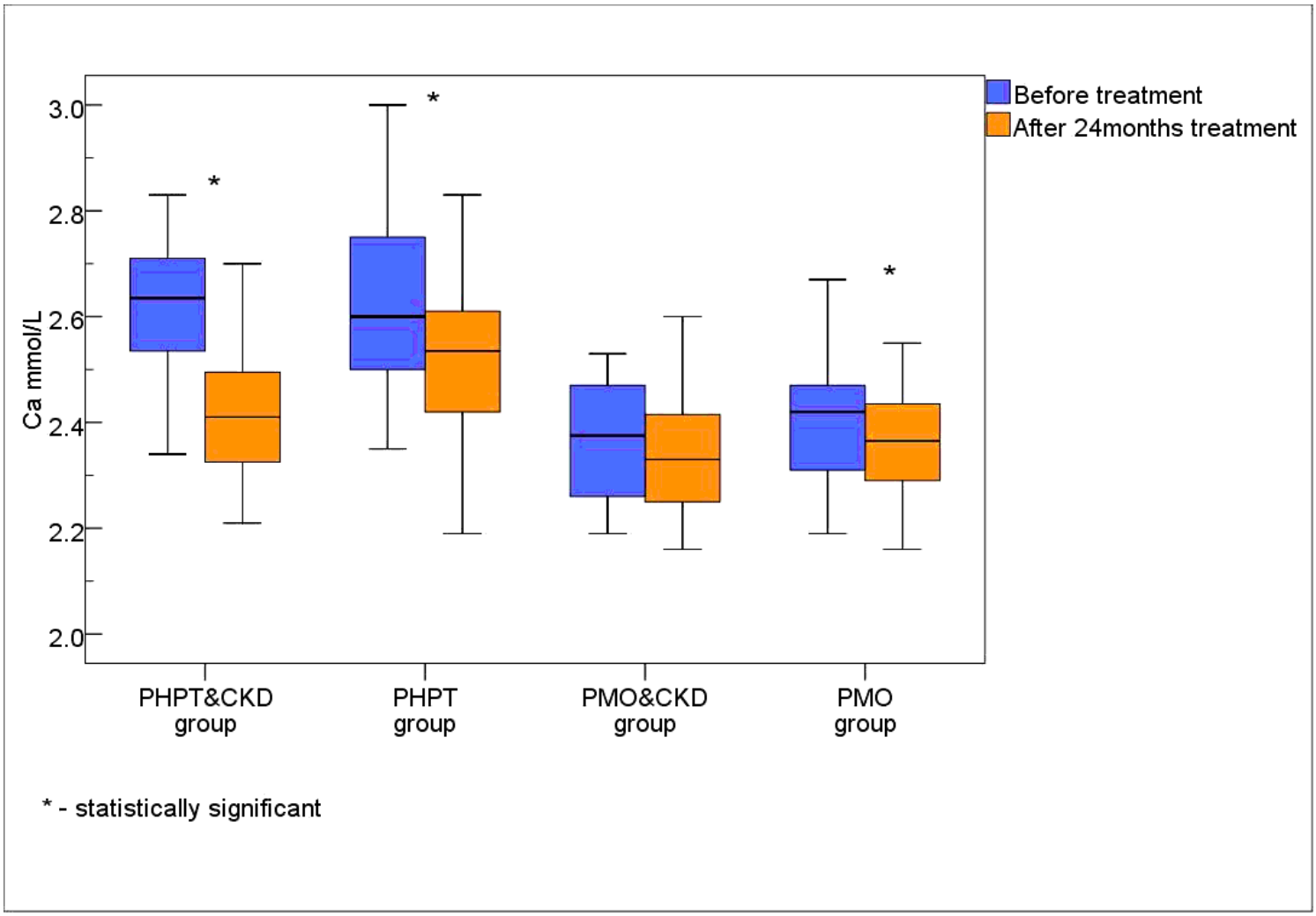

Figure 2

Changes in calcium serum levels, mmol/l (2.15-2.55) before and after 24 months of denosumab administration.

PHPT - primary hyperparathyroidism, CKD - chronic kidney disease, PMO - postmenopausal osteoporosis.

Over 24 months of treatment the median decrease in calcium serum were -0.24 mmol/L ($p<0.001$) in PHPT-related osteoporosis and CKD; -0.08 mmol/L ($p<0.001$) in PHPT-related osteoporosis without CKD; -0.04 mmol/L ($p=0.4$) in PMO with CKD; -0.04 mmol/L ($p=0.02$) in PMO without CKD.

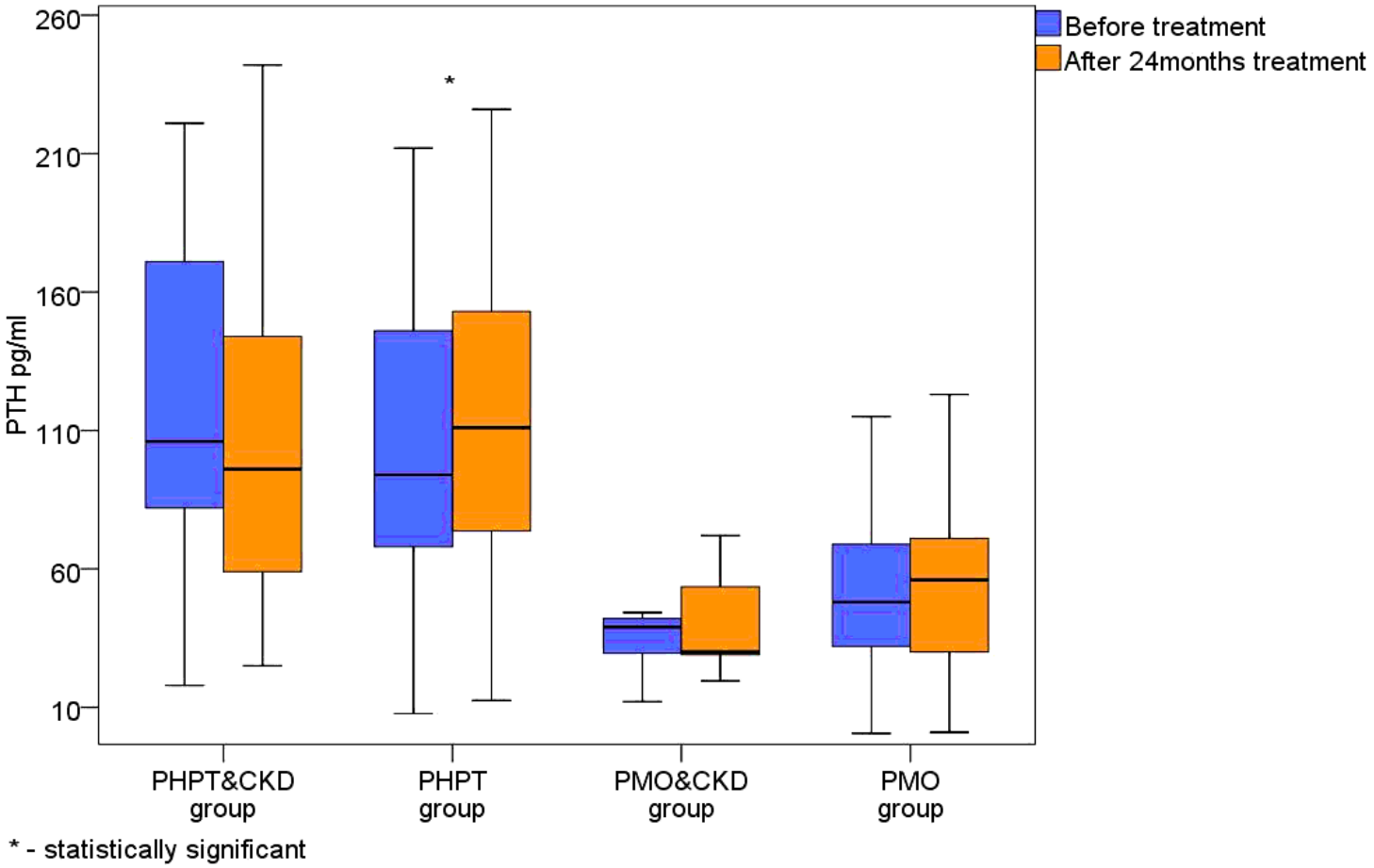

Figure 3

Changes in PTH levels, pg/ml (15-65) in four groups of patients before and after 24 months of denosumab administration.

PHPT - primary hyperparathyroidism, CKD - chronic kidney disease, PMO - postmenopausal osteoporosis.

Over 24 months of treatment the median changes in PTH were: 8 pg/mL (p=0.53) in PHPT-related osteoporosis and CKD; -12 pg/mL (p=0.04) in PHPT-related osteoporosis without CKD; 8 pg/mL (p=0.86) in PMO with CKD; -6 pg/mL (p=0.167) in PMO without CKD.