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ORIGINAL ARTICLE

Treatment of osteoporosis with recombinant parathyroid hormone, utilisation of total body DXA to observe treatment effects on total body composition and factors determining response to therapy

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Abstract

Purpose Recombinant parathyroid hormone (rPTH) increases bone mineral density (BMD). However, certain other potential effects of rPTH remain to be studied. The aim of this study is to identify whether bone turnover markers, relevant biochemical parameters or total body fat and muscle composition affect the response to rPTH and to establish if these parameters in particular change during treatment.

Methods One hundred seventy-two participants were treated with rPTH, and 128 subjects who fully complied with the therapy and completed their investigations including biochemical bone markers and total body composition at baseline, 6 months and 1 year of the treatment were divided into responder and non-responder groups. A total body dual-energy X-ray absorptiometry (DXA) scanner was used to assess the body muscle, fat and bone composition.

Results rPTH significantly increased BMD spine at 1 year ($p = 0.000$). Twenty-four-hour urinary calcium was significantly increased at 6 months in the responder group ($p = 0.00$). There was a trend to an increase in the fat and muscle mass ($p = 0.52$ and 0.45, respectively), and it was not negatively affected by rPTH. Bone turnover markers (P1NP and OC) did not show statistically significant difference over time between responders and non-responders ($p = 0.74$ and $p = 0.19$, respectively).

Conclusions Hypercalciuria which is a frequent feature in osteoporotic population may predict non-responders at 6 months of rPTH, and it may help to optimise individual patient's treatment. Unlike endogenous PTH in pathological conditions, rPTH is anabolic to bone and has no detrimental effects on the body fat and muscle composition.

Keywords Bone mineral density (BMD) · DXA · Osteoporosis · Recombinant parathyroid hormone (rPTH) · Total body composition · Treatment non-response · Treatment response

Introduction

Intermittent administration of recombinant parathyroid hormone (rPTH) has exhibited significant anabolic effects on human skeleton in terms of bone mineral density (BMD) gain at both spine and hip regions of patients as shown on their dual-energy X-ray absorptiometry (DXA) scans [1–3]. Besides the BMD effect of rPTH, there are certain other potential effects which remain to be studied. These include total body muscle and fat composition and total body BMD. In addition, other factors which might affect treatment response need to be considered such as previous drug or fracture history or other medical comorbidities.

It is well-recognised that excess endogenous parathyroid hormone has been associated with a risk of sarcopenia [4]. However, no information is available on the effects of low-dose exogenous rPTH and its effects on total body muscle and fat composition measured by total body DXA scan. There is also a lack of evidence in relation to total BMD gain on a DXA scan after the use of rPTH in osteoporosis.

Likewise, it is recognised that a certain number of patients fail to respond to rPTH treatment [5]. Currently, BMD gain shown on the DXA scan at the completion of treatment is used to identify the response to rPTH treatment. As bone markers correlate well with BMD, they might also be used to identify an adequate or an inadequate response to treatment at an early stage in the treatment.

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Aims

The objectives of this investigation were (1) to determine if markers of bone turnover and relevant biochemical parameters can potentially identify non-responders to rPTH, (2) to identify what percentage of patients will respond inadequately to rPTH treatment, (3) to identify whether total body fat and muscle composition at baseline are different in responders and non-responders to to rPTH and (4) to identify whether body composition changes during rPTH treatment.

Materials and methods

Study population

Ethics permission was sought from the combined ethics committee for Tallaght and St. James's Hospitals prior to treatment of the patients with rPTH. All the patients included in the study were attending the Osteoporosis Services of St. James's Hospital (SJH). The bone health clinic in SJH is a specialised service for treating osteoporosis; it accepts patients from local and tertiary centres, and over 3000 new patients attend per year. It maintains a database on all patients attending for treatment of their osteoporosis. The referral sources of the patients included in the study were as follows: general practitioners (GP) and hospital-based consultants; respiratory clinic for patients with steroid-induced osteoporosis; gastroenterology clinics including coeliac and inflammatory bowel clinics; orthogeriatric team referrals for elderly in-patients with fractures; clinical nurse specialist-led osteoporosis preassessment clinics; and patients attending the bone health service who had failed to respond to previous therapy for osteoporosis.

Inclusion criteria

Patients with established osteoporosis including those with non-vertebral and vertebral fractures were considered suitable unless they had one or more of the exclusion criteria. Osteoporosis was confirmed according to the WHO classification for diagnosis of osteoporosis using BMD measurements. According to this classification, osteoporosis is defined as BMD more than 2.5 standard deviations below peak adult and osteopenia as BMD between 1 and 2.5 standard deviations below peak adult. Severe osteoporosis is associated with one or more fragility fractures.

Exclusion criteria

Patients were excluded if they had hypersensitivity to rPTH or any of its excipients, pre-existing hypocalcaemia, severe renal impairment or a glomerular filtration rate less than 30 ml/min, metabolic bone diseases other than primary osteoporosis (including hyperparathyroidism and Paget's disease of the bone), unexplained elevations of alkaline phosphatase, prior external beam or implant radiation therapy to the skeleton, skeletal malignancies or bone metastases, renal stones in the last 5 years, alcohol abuse, unfused epiphyses or if they were pregnant. Additional exclusion criteria for the purpose of this study included elevated endogenous PTH levels, significant hepatic impairment, cognitive impairment, and history of significant non-vertebral fracture (hip fracture) within the previous 6 months.

Patient training and education

All patients were given instructions by trained nursing staff on the administration of rPTH via a pen device, its side effects and the details for contacting clinical nursing staff. Their GPs were informed about their treatment, and any other osteoporosis treatment was discontinued before commencing rPTH for at least 6 months. All the individuals were given the 1000 mg of calcium and 800 IU of cholecalciferol on commencement of rPTH treatment. The patients were regularly followed up for assessment and monitoring of treatment compliance.

Total body DXA assessment

The total body DXA scanner used in this study was the Lunar Prodigy (GE Healthcare) which is a fan beam system, and the phantom calibration was performed on a daily basis. GE Lunar Prodigy DXA equipment utilise the enCore graphical interface software to control all aspects of scanning and analysis. This is a Microsoft Windows-based application. The software version was 10.51 which works using the Windows XP Professional platform. The precision error by default was $\leq 1\%$. All scans were performed while the subjects were wearing light indoor clothing and no metal accessories. Participants were placed in the supine position on the scanning table. The body was aligned with the central horizontal axis, arms were positioned parallel to the body with forearms pronated and hands were flat on the bed. Height and weight were measured using standardised equipment. In this study, the total body DXA scan was performed at baseline and after 1 year of rPTH treatment.

The parameters that were measured included total body bone mineral density (BMD), bone mineral content (BMC) and total body fat and muscle composition. At specific regions of interest, lean tissue mass, body fat and bone mineral content were measured and BMD was measured at the spine and hip. The parameters examined in this analysis with the relevant values are expressed as follows: android fat percentage (%); gynoid fat percentage (%); total body fat percentage (%); total body tissue mass (gm); total body fat mass (gm); lean body mass (gm); fat free mass (gm); BMC (gm); and BMD (gm/cm^2).

Radiological definition of a non-responder

A non-responder was defined based on failure of BMD at the lumbar spine to increase by 3% in the first year of treatment. BMD gain of 3% at the lumbar spine is accepted internationally as the definition of a response and is used in osteoporosis research [6]; it corresponds to the least significant change (LSC) necessary to ensure that the measured change in BMD for an individual patient is a true biologic change and not simply a reflection of the inherent imprecision of the DXA scanner [7].

Study design

One hundred seventy-two patients were selected to prospectively participate in this study between 2009 and 2011. Patients were divided into two main groups at 1 year of the treatment: responders and non-responders. The changes in BMD were expressed as the percentage change from baseline after 1 year of the treatment.

Biochemical measurements

Blood sample measurements taken at baseline and at 6 months and 1 year of treatment were used in the analysis, and these samples were taken during attendance at a morning-scheduled clinic. The biochemical variables assessed in the study were serum markers of bone turnover (osteocalcin—OC, procollagen type 1N-terminal propeptides—PINP, serum type 1 collagen C-terminal telopeptide breakdown products—CTX); serum parathyroid hormone—PTH; 25-hydroxy vitamin D (25OHD); serum-corrected calcium—Ca; serum phosphate—PO4; and 24-h urinary calcium—24hUrCa. In this study, hypercalciuria was defined according to the international standards which suggest a 24-h urinary calcium > 7.5 mmol for males and > 6.25 mmol for females.

The blood samples for the biochemical bone markers were spun and separated immediately, with the serum being frozen within 1 h at − 70 °C. Biochemistry and immunoassays were performed on the Roche Modular Cobasc system which is a biochemical and immunoassay-automated analyser in a single integrated system. 25OHD was analysed using a chemiluminescence immunoassay (Applied bio system API 4000), and bone markers including CTx, P1NP, OC and PTH were analysed by the Roche Modular Cobasc system using chemiluminescence enzyme immunoassay utilising commercial kits.

Statistical analysis

All statistical procedures were performed using IBM SPSS statistics version 19.0 software for Windows. A one-sample Kolmogorov-Smirnov (KS) test was applied to assess normality of the different parameters. After testing for normality, parametric or non-parametric tests were used accordingly. Changes that passed the tests for normality were expressed as the mean and SD and evaluated using the paired Student *t* test. The Mann-Whitney *U* test was used for non-parametric measures. Spearman's correlation coefficient was used for testing correlations of non-normally distributed data, and Pearson's was used for normally distributed data. A p value of ≤ 0.05 was considered statistically significant.

Baseline characteristics of the study population were expressed as the mean and standard deviation (SD). The difference between the total body, hip and spine BMD, fat composition and muscle mass at baseline and after 12 months of PTH treatment was calculated. Changes in BMD were expressed as the percentage change from baseline after1 year of treatment.

The effects of past medical history, drug history and fracture history on the two groups, responders and non-responders, were separately analysed by using descriptive cross tabulations; the chi-square test was used for this method. Two-sample Student's *t* test and repeated measures ANOVA with Greenhouse-Geisser corrections were performed to determine statistical differences between means. Logistic regression and step-wise multiple regression analyses were used to evaluate the relationships between the variables.

Results

Regardless of excellent team-work, the dropout rate was 16% at 1 year on treatment. However, despite some minor side effects experienced by the patients, in general, the majority of patients tolerated the drug very well. Overall, the patients in the study were satisfied and content with the level of care provided and with the drug itself.

The most common reasons for drop out were as follows in a descending order of frequency: flu-like symptoms including headache and dizziness-—4%; nausea and dyspepsia—4%; compliance issues—3%; pre-existing diagnosis of malignancy not disclosed by the subjects before recruitment—2%; hypocalcaemia—< 1%; hot flushes/skin rash—<1%; and treatment refusal for non-specific reasons—< 1%.

Out of the total of one hundred seventy-two patients, only those who had been compliant with rPTH for 1 year and who also had complete sets of biochemical bone markers and total body DXA scans were included in the analysis. The total number of individuals included was therefore one hundred twenty-eight female patients. Of these, 40 were non-responders and 88 were responders to rPTH according to use.

Results on past medical and drug history

Coexisting medical conditions and previous medication use including bone medications were not statistically different between the responder and non-responder groups. The

frequencies of different comorbidities and previous medication use are expressed in (Table 1).

Biochemistry and biochemical bone marker results

The serum biochemistry and serum biochemical bone markers of the whole cohort at baseline, 6 months and 1 year of rPTH treatment with means and standard deviations are shown in Table 2. The differences between the two groups over time in serum biochemical measurements including bone formation markers (OC, P1NP) at baseline, 6 and 12 months are shown in Table 3.

The 24-h urinary calcium was increased significantly in the whole cohort over the duration of study ($p = 0.001$, Fig. 1a).

Table 1 Past medical history and medication use in responders and non-responders at baseline

Past history	Responders ($N = 88$)	Non-responders ($N = 40$)
Past medical history		
COPD	11.4% ($N = 10$)	6.3% ($N = 2$)
Hypothyroid	11.4% ($N = 10$)	6.3% ($N = 2$)
Hyperthyroid	5.7% ($N = 5$)	0% ($N = 0$)
Diabetes mellitus	8.6% ($N = 7$)	6.3% ($N = 2$)
Arthritis	2.9% ($N = 2$)	0% ($N = 0$)
CRF	0% ($N = 0$)	0% ($N = 0$)
Malabsorption	11.4% ($N = 10$)	6.3% ($N = 2$)
Smoking status		
Current smoker	8.6% ($N = 7$)	0% ($N = 0$)
Ex smoker	11.4% ($N = 10$)	31.3% ($N = 12$)
Relevant med use		
Steroid inhalers	8.6% ($N = 7$)	12.5% ($N = 5$)
Steroid oral	2.9% ($N = 2$)	0% ($N = 0$)
Eltroxin	8.6% ($N = 7$)	6.3% ($N = 2$)
Diabetic meds	5.7% ($N = 5$)	6.3% ($N = 2$)
Loop diuretics	2.9% ($N = 2$)	12.5% ($N = 5$)
Thiazide diuretics	2.9% ($N = 2$)	6.3% ($N = 2$)
Statins	14.3% ($N = 12$)	12.5% ($N = 5$)
Antidepressants	2.9% ($N = 2$)	31.3% ($N = 12$)
Neuroleptics	2.9% ($N = 2$)	26.7% ($N = 10$)
Bone medications		
rPTH	0% ($N = 0$)	0% ($N = 0$)
Denosumab	0% ($N = 0$)	0% ($N = 0$)
Vit D or analogues	2.9% ($N = 2$)	0% ($N = 0$)
HRT or related meds	0% ($N = 0$)	0% ($N = 0$)
Strontium ranelate	8.6% ($N = 7$)	12.5% ($N = 5$)
Ibandronate	2.9% ($N = 2$)	12.5% ($N = 5$)
IV bisphosphonates	2.9% ($N = 2$)	0% ($N = 0$)
Risedronate	31.4% ($N = 27$)	31.3% ($N = 12$)
Alendronate	22.9% ($N = 20$)	31.3% ($N = 12$)
Ca/Vit D supplements	74.3% ($N = 65$)	93.8% ($N = 37$)

Chi-squared comparison of proportions $p = 0.05$

There was no significant difference at baseline in 24-hr urinary calcium between the two groups. The mean 24-h urinary calcium was significantly increased at 6 months in the responder group ($p = 0.0005$, Fig. 1b). Serum-corrected calcium increased over time, particularly at 6 months in the whole cohort ($p = 0.001$, Fig. 2a). Although, there was a trend towards increasing serum calcium over time in both groups, it did not reach a statistically significant value ($p = 0.24$). Serum phosphate was higher at baseline but due to a large standard deviation, the value did not differ over time (Table 2). Other biochemical measures including serum magnesium and 25OHD in the whole cohort remained at stable levels over time (Table 2) and also failed to show any significant difference when compared between the two groups (Table 3).

Due to increased variability of bone formation markers among individuals, percent change was considered to observe the difference between these values. P1NP and OC were positively correlated at baseline ($p = 0.001$). There was a significant increase with time in OC and P1NP among the whole cohort, and this increase was at its highest at 6 months of treatment ($p = 0.001$, Table 2). However, these measures did not show a statistically significant difference between responder and non-responder groups at 6 months and 1 year ($p = 0.74$, 0.19, respectively; Table 3).

Body composition results on total body DXA

Table 4 shows total body composition parameters in the whole cohort, and measurements are expressed as mean ± standard deviation (SD) and standard error of means (SEM). The difference in total body composition between the two groups is either expressed as mean ± SD and SEM (Table 5) or mean rank (Table 6) as required. The percentage change from baseline at 1 year in the total body composition in responders and non-responders is shown in (Table 7) expressed as mean ± SD and SEM and (Table 8) expressed as mean rank. The percentage changes in lean mass, fat free mass and BMC were significantly lower in the non-responder group (Table 8). From baseline to 1 year, rPTH made no significant difference to the fat and muscle of the subjects.

We observed a significant increase in BMD spine at 1 year (from a mean ± SD of 0.78 ± 0.1 at baseline to 0.85 ± 0.1 at 1 year, $p = 0.000$), while BMD at the hip and the total body BMD showed a trend to increase which was not statistically significant at 1 year ($p = 0.46$, 0.33, respectively; Table 4). However, when the cohort was divided into responder and non-responder groups, the BMD percentage gain at the hip in the responder group was significantly higher (mean 1.4 ± 4.2) compared to the non-responder group (mean − 1.7 ± 3.1, $p = 0.01$, Table 7). BMD, BMC, fat parameters and muscle parameters did not show a statistically significant difference among the two groups at baseline (Tables 5 and 6). In terms of percentage change in body composition of the two groups, no

Table 2 Biochemical changes over time in the whole cohort

	Units	Baseline Mean ± SD*	6 months	1 year
24-h urinary calcium	(mmol/24 h)	3.4 ± 2.4	5.4 ± 2.5	4.9 ± 2.3
Serum calcium	(mmol/l)	2.26 ± 0.1	2.46 ± 0.2	2.44 ± 0.2
Serum vitamin D	(nmol/l)	75 ± 28.8	71 ± 17.1	70 ± 17.1
Serum PTH	(pg/ml)	36.75 ± 19.4	74.7 ± 120.0	43.07 ± 68.7
Serum phosphate	(mmol/l)	1.73 ± 4.4	1.01 ± 0.1	1.07 ± 0.1
Serum magnesium	(mmol/l)	0.8 ± 0.08	0.74 ± 0.1	0.74 ± 0.08
Serum osteocalcin percentage change	(%)		321.39 ± 314.9	278.24 ± 221.3
Serum P1NP percentage change	(%)		656.23 ± 863.0	470.07 ± 613.8

*t test $p = 0.001$

significant differences in any parameters were observed over time in either group (Tables 7 and 8).

Discussion

This study was performed to determine potential predictors of inadequate response to rPTH, which in general is a very potent and useful anabolic drug to treat osteoporosis. It has been established in the past that both compliance and sufficient calcium and vitamin D supplementation are the primary requirements to attain a response to the osteoporosis treatment along with a treatment period of at least 1 year to allow sufficient time for the treatment to be fully effective [5]. Both of these requirements were fulfilled by the patients in our study as only those participants who were fully compliant with rPTH at 1 year were included in the analyses. Despite this, not all patients treated with rPTH in our study cohort achieved optimal skeletal benefit despite being compliant to the treatment.

Table 3 Biochemical changes over time between responders vs non-responders

	Reference values	*N*	Baseline	6 months	1 year	*p* value*
24-h urinary calcium (mmol/24 h)	2.5–7.5					
Non-responders		40	4.6 ± 2.7	5.3 ± 1.5	5.2 ± 1.9	0.03
Responders		88	2.87 ± 2.07	5.5 ± 2.8	4.8 ± 2.4	
Serum calcium (mmol/l)	2.2–2.7					
Non-responders		40	2.26 ± 0.1	2.5 ± 0.2	2.5 ± 0.3	0.24
Responders		88	2.26 ± 0.1	2.4 ± 0.1	2.4 ± .1	
Serum vitamin D (nmol/l)	50–80					
Non-responders		40	71.5 ± 21.0	72.4 ± 18.8	70.8 ± 14.7	0.54
Responders		88	77.8 ± 31.8	71.2 ± 16.6	69.9 ± 18.3	
Serum PTH (pg/ml)	10–65					
Non-responders		40	32.3 ± 9.2	50.4 ± 63.3	60.0 ± 110.3	0.20
Responders		88	38.7 ± 22.4	85.8 ± 137.9	35.3 ± 37.08	
Serum phosphate (mmol/l)	0.8–1.4					
Non-responders		40	0.97 ± 0.2	1.02 ± 0.4	0.98 ± 0.2	0.43
Responders		88	2.08 ± 5.3	1.01 ± 0.1	1.05 ± 0.1	
Serum magnesium (mmol/l)	0.7–1.0					
Non-responders		40	0.80 ± 0.08	0.79 ± 0.08	0.75 ± 0.1	0.20
Responders		88	0.81 ± 0.08	0.71 ± 0.09	0.74 ± 0.06	
Serum osteocalcin percent change (%)	NA					
Non-responders		40		317.49 ± 291.2	263.3 ± 192.3	0.74
Responders		88		354.6 ± 315.6	285.0 ± 235.7	
Serum P1NP percent change (%)	NA					
Non-responders		40		490.2 ± 324.9	303.1 ± 275.9	0.19
Responders		88		732.4 ± 857.0	546.3 ± 708.1	

*ANOVA with repeated measures with a Greenhouse-Geisser correction

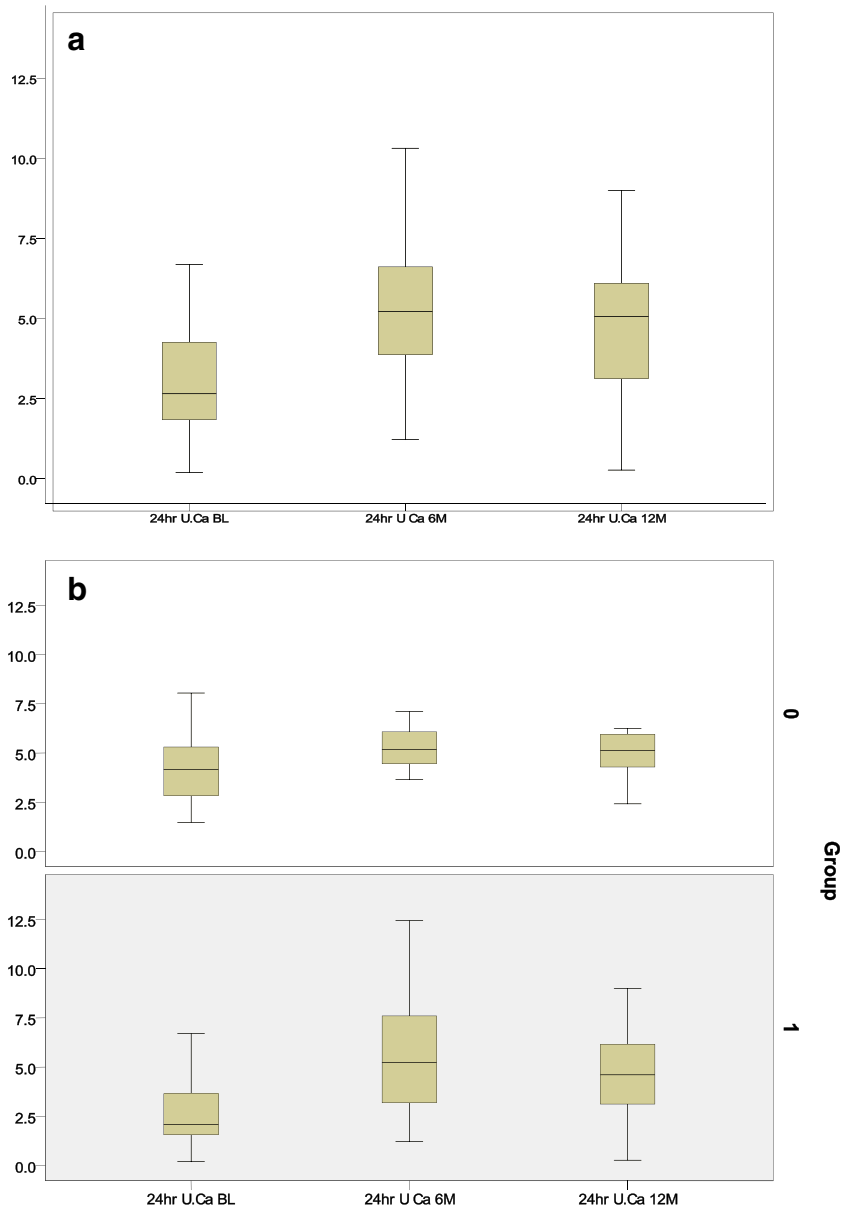

Fig. 1 **a** 24-h urinary calcium at baseline, 6 months and 12 months of rPTH. *t* test 0.001. 24hUrCa BL 24-h urinary calcium at baseline. 24hUrCa 6 M 24-h urinary calcium at 6 months. 24hUrCa 12 M 24-h urinary calcium at 12 months. 24-h urinary calcium values are expressed in millimoles per 24 h. **b** 24-h urinary calcium in responders (1) and non-responders (0) at baseline, 6 months and 12 months of rPTH. ANOVA with repeated measures with a Greenhouse-Geisser correction $p = 0.0005$

Our study cohort had a similar background with severe osteoporosis and failure on multiple treatments before being considered for treatment with rPTH; therefore, coexisting medical conditions, use of bisphosphonates or other medications for osteoporosis did not have any further detrimental bone effects in this population, and there was a general trend to increase in BMD at 1 year of treatment. This outcome was consistent with previous studies which had shown that exogenous PTH induced positive effects on BMD and bone formation markers in postmenopausal women with established osteoporosis, regardless of previously long-term exposure to anti-resorptive therapies [3]. Therefore, past medical and drug history may not be markers that predict a poor response to the treatment.

Serum biochemical markers of bone turnover (P1NP and OC) were included in the analysis due to their significance in clinical practice. Some researchers have also used these markers to predict individuals at fracture risk with accelerated bone loss, to identify appropriate treatment options for these individuals, to assess relative efficacy of treatment and to promote treatment compliance [8, 9]. However, their use has not been established in guidelines for monitoring anti-osteoporotic therapy in the general population [8]. Considering our study results, no bone turnover marker significantly differed enough between the responders and non-responders to predict the treatment outcomes at 1 year, which demonstrates that changes in biochemical bone markers are not always indicators of the degree of response to rPTH treatment. Thus, while the increase or decrease in these markers during the course of treatment could be suggestive of drug compliance, they may not indicate if a particular individual was responding to rPTH therapy. Consequently, attention should be given to other biochemical parameters to help identify a treatment response or non-response.

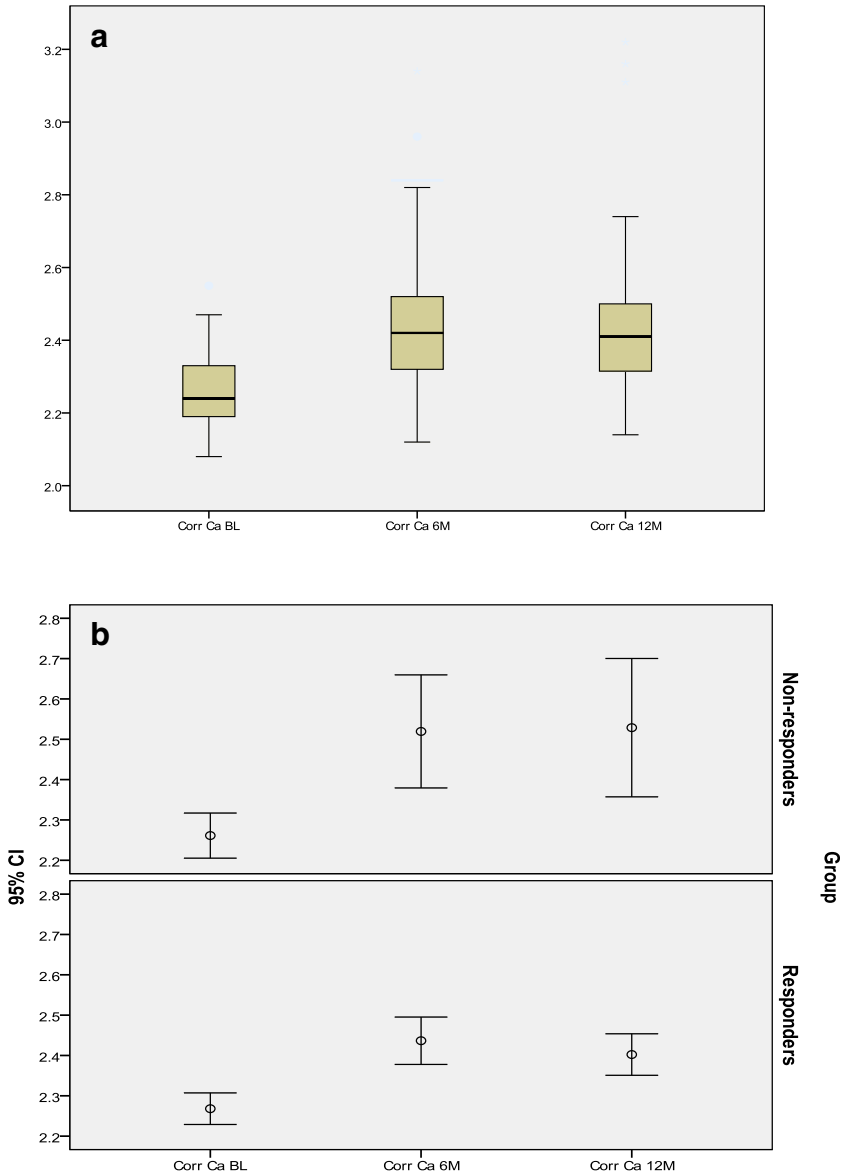

Fig. 2 **a** Serum-corrected calcium changes in the whole cohort over time. Values expressed in millimoles per litre $p = 0.001$ (t test). Corr Ca BL serum-corrected calcium at baseline. Corr Ca 6 M serum-corrected calcium at 6 months. Corr Ca 12 M serum-corrected calcium at 12 months. **b** Serum-corrected calcium changes in both groups considering means with 95% confidence interval. Values expressed in millimoles per litre $p = 0.24$ (ANOVA). Corr Ca BL serum-corrected calcium at baseline. Corr Ca 6 M serum-corrected calcium at 6 months. Corr Ca 12 M serum-corrected calcium at 12 months

While 24-h urinary calcium (24hUrCa) excretion is considered by some as a valuable tool either in identifying osteoporosis or in determining response to treatment, no clear-cut indications for measuring 24hUrCa as a primary or first-line diagnostic tool in osteoporosis are currently available. The effect of rPTH treatment on 24hUrCa excretion has not been widely studied. Some studies show that 24hUrCa is increased over time on rPTH treatment [10]; however, the beneficial or detrimental aspects of this increase are still not well-understood. Some studies have shown rPTH effects on calcium metabolism in a pattern consistent with the known actions of endogenous PTH [11] and demonstrated the pharmacologic effect of rPTH following once-daily subcutaneous administration causing a transient and modest increase in serum calcium, which returns to pre-dose levels prior to administration of the next dose. However, 24hUrCa has not been measured in these studies [11].

Considering the effects of hypercalciuria, it is generally believed to be detrimental to bone health in the non-rPTH-treated population and it has been suggested as a pathological factor responsible for low bone mass in populations with osteopenia or osteoporosis [12]. However, it is crucial to determine the type of hypercalciuria in a particular individual before considering it responsible for osteoporosis. The three commonly described types of hypercalciuria are renal, absorptive and fasting or resorptive hypercalciuria. It has mostly been proposed that resorptive hypercalciuria, but not the other types, is linked with bone loss. Having said that, some researchers also believe that hypercalciuria of intestinal origin may be associated with bone loss or osteoporosis. An example of this is a retrospective analysis of a cohort of 319 patients with postmenopausal osteoporosis or osteopenia. It described low spinal BMD among patients with absorptive hypercalciuria exhibiting intestinal

Table 4 Total body composition at baseline and 1 year for the whole cohort

	Baseline Mean ± SD (SEM)	1 Year	*p* value*	
Android fat (gm)	38.74 ± 10.6 (1.4)	37.91 ± 12.1 (1.7)	0.29	
Gynoid fat (gm)	42.62 ± 8.4 (1.1)	39.94 ± 10.4 (1.4)	0.07	Age: 71.1 ± 11.5
Total body fat percentage (%)	36.31 ± 8.6 (1.2)	36.13 ± 9.1 (1.2)	0.65	
Regional fat percentage (%)	34.83 ± 8.6 (1.2)	35.52 ± 9.3 (1.3)	0.40	
Tissue mass (gm)	55,644.6 ± 12,739.2 (1783.8)	56,366.96 ± 13,756.7 (1926.3)	0.66	
Total body fat mass (gm)	21,222.14 ± 7684.0 (1075.9)	21,433.57 ± 8646.6 (1210.7)	0.52	
Lean body mass (gm)	35,651.76 ± 6274.5 (878.6)	35,082.54 ± 7613.5 (1066.1)	0.45	
Fat-free mass (gm)	37,573.94 ± 6399.3 (896.0)	37,605.75 ± 5921.3 (829.1)	0.91	
Bone mineral content (gm)	2243.0 ± 2739.4 (387.4)	1840.72 ± 392.8 (55.5)	0.29	
BMD hip (gm/cm^2)	0.756 ± 0.10 (0.0)	0.759 ± 0.11 (0.0)	0.46	
BMD total body (gm/cm^2)	0.967 ± 0.07 (0.0)	0.961 ± 0.08 (0.0)	0.33	
BMD spine (gm/cm^2)	0.789 ± 0.1 (0.0)	0.853 ± 0.1 (0.0)	0.000	

Means ± standard deviation and standard error of mean

*Paired samples *t* test

hyperabsorption of calcium and kidney stones, and thus, they linked intestinal calcium hyperabsorption to postmenopausal low bone mineral density [13]. In contrast, other research groups have proposed that in the absence of any PTH pathology, the absorptive type of hypercalciuria is not a compensatory phenomenon, but probably the marker of disturbed cell calcium transport, involving both intestinal and bone tissues. In fact, patients with absorptive hypercalciuria less frequently show bone disease and a consequential reduction in their dietary calcium greatly increases the probability of bone loss in these subjects [14]. Considering the mechanism of absorptive hypercalciuria, a study involving histomorphometric analysis of the bone has shown that the bone loss in absorptive hypercalciuria is due to reduced bone formation rather than increased bone resorption as seen in resorptive hypercalciuria [15].

Considering the above discussion and referring to our study, it is well-established that rPTH increases bone formation and bone turnover, which has also been reflected by the significant BMD spine gain in our responder group. Therefore, the bone loss linked to absorptive hypercalciuria is not applicable in this case. In fact, better calcium absorption reflected by increased urinary calcium secretion in the responder group reflects the better action of rPTH in this particular group which has subsequently shown significant positive bone effects. Hence, hypercalciuria observed in individuals on rPTH treatment in the absence of any renal or PTH impairment is an indicator of a good

Table 5 Total body composition of responders vs non-responders at baseline

	Group	N	Mean ± SD	SEM	*p* value*
BMD spine (gm/cm^2)	Non-responders	40	0.83 ± 0.08	0.02	
	Responders	88	0.76 ± 0.11	0.01	0.03
BMD hip (gm/cm^2)	Non-responders	40	0.78 ± 0.12	0.03	
	Responders	88	0.74 ± 0.10	0.01	0.23
BMD total body (gm/cm^2)	Non-responders	40	1.00 ± 0.09	0.02	
	Responders	88	0.95 ± 0.06	0.01	0.03
Total body fat percentage (%)	Non-responders	40	37.35 ± 9.01	2.25	
	Responders	88	35.83 ± 8.51	1.43	0.56
Regional fat percentage (%)	Non-responders	40	36.38 ± 8.91	2.22	
	Responders	88	34.12 ± 8.51	1.43	0.57
Tissue mass (gm)	Non-responders	40	61,342.38 ± 13,144.55	3286.14	
	Responders	88	53,040.00 ± 11,839.51	2001.24	0.02
Total body fat mass (gm)	Non-responders	40	23,227.94 ± 7963.05	1990.76	
	Responders	88	20,305.20 ± 7489.71	1265.99	0.21

Mean ± standard deviation and standard error of mean among groups

*Independent samples *t* test

Table 6 Total body composition of responders vs non-responders at baseline

	Group	N	Mean rank	Sum of ranks	*p* value*
Lean body mass (gm)	Non-responders	40	29.75	476.00	
	Responders	88	24.29	850.00	0.2
Bone mineral content (gm)	Non-responders	40	31.22	499.50	
	Responders	88	23.61	826.50	0.09
Fat-free mass (gm)	Non-responders	40	28.13	450.00	
	Responders	88	23.48	775.00	0.2

*Mann-Whitney *U* test

response to the treatment and is absorptive in nature. However, in practice, a clear demarcation between absorptive and resorptive (renal leak) hypercalciuria can be very difficult or subtle and a meticulous understanding is required to clearly distinguish between these types. Studies using radioisotope calcium measurement would allow a better understanding of the mechanism of hypercalciuria in different clinical scenarios.

The effects of endogenous PTH on human muscle were observed in a large prospective study of 1008 males and females aged 55–85 years. Measurement of appendicular skeletal muscle mass using DXA was one of the parameters in this study. High PTH levels (≥ 4.0 pmol/l) were associated with an increased risk of sarcopenia, compared with low PTH (< 3.0 pmol/l), odds ratio = 2.35 (1.05–5.28) based on muscle mass. A per unit increase in PTH led to a 3.52 (95% CI 1.43–8.67) increased risk of sarcopenia based on appendicular skeletal muscle mass [4]. Osteoporosis is also linked with sarcopenia. However, to date, no study has shown frail patients given rPTH treatment for osteoporosis develop further sarcopenia. The effects of rPTH on skeletal muscle have been observed in animal studies. For decades, both PTH 1-84 and PTH 1-34 had been linked with impaired energy production, energy transfer and energy utilisation in skeletal muscle of rats [16]. Studies also demonstrated that perfusion of the isolated rat liver with PTH-(1-84) induced the production of bioactive IL-6 and the IL-6sR which then increased the circulating levels of these cytokines in vivo [17]. This was found to be applicable in the elderly, when elevated levels of IL-6 were linked with smaller muscle area, less appendicular muscle mass and lower muscle strength in a well-functioning 70–79-year-old population [18]. Nevertheless, the effects of rPTH treatment directly on human skeletal muscle remain unexplored. The measurement of body composition by total body DXA in our study population, while on rPTH treatment, was an innovative step to further explore its effects on the human body rather than monitoring the bone effects alone. There was no significant difference in the muscle or fat parameters in the whole cohort after 1 year of rPTH treatment. When the percentage change in these values at 1 year was observed discretely among the two groups, the responders showed they had more muscle at 1 year post-rPTH treatment. Conclusively, it is reassuring to comprehend that in addition to its positive effect on bone formation unlike animal model studies, recombinant PTH does not have a detrimental effect on human muscle or on fat tissue.

Our study utilised a very comprehensive DXA imaging and follow-up imaging protocol including both hip and spine AP measurements, spinal lateral morphometry and total body composition. The main limitation of this study was that it consisted of relatively small numbers. Though the total

Table 7 Percentage change in body composition of two groups at 1 year

	Group	N	Mean ± SD	SEM	*p* value*
Total body fat percentage (%)	Non-responders	40	− 0.21 ± 7.2	1.8	
	Responders	88	− 0.72 ± 10.8	1.8	0.86
Regional fat percentage (%)	Non-responders	40	13.19 ± 20.3	5.0	
	Responders	88	6.98 ± 26.9	4.5	0.41
Total body fat mass (gm)	Non-responders	40	0.08 ± 9.2	2.3	
	Responders	88	− 0.03 ± 14.2	2.4	0.47
BMD hip	Non-responders	40	− 1.73 ± 3.1	0.7	
(gm/cm^2)	Responders	88	1.40 ± 4.2	0.7	0.01
BMD total body (gm/cm^2)	Non-responders	40	− 0.95 ± 6.3	1.5	
	Responders	88	− 0.30 ± 3.3	0.5	0.63

Mean ± standard deviation and standard error of mean among groups

*Independent samples *t* test

Table 8 Percentage change in body composition of two groups at 1 year

	Group	N	Mean rank	Sum of ranks	*p* value*
Android fat (gm)	Non-responders	40	28.13	450.00	
	Responders	88	25.03	876.00	0.2
Gynoid fat (gm)	Non-responders	40	30.34	485.50	
	Responders	88	24.01	840.50	0.07
Tissue mass (gm)	Non-responders	40	20.94	335.00	
	Responders	88	28.31	991.00	0.05
Lean body mass (gm)	Non-responders	40	19.25	308.00	
	Responders	88	29.09	1018.00	0.01
Bone mineral content (gm)	Non-responders	40	19.03	304.50	
	Responders	88	27.89	920.50	0.02
Fat-free mass (gm)	Non-responders	40	19.06	305.00	
	Responders	88	27.88	920.00	0.02

*Mann-Whitney *U* test

number of participants was 172, only 128 completed all the investigations within the tight time frame at every point in the study, which was 0, 6 and 12 months. They were thus included in this analysis. Despite this, the results did show statistical significance using a comprehensive collection of bone markers and both blood and urinary bone biochemistry.

Conclusion

The excursions in biochemical markers of bone turnover may be used to monitor drug compliance but they cannot be established as indicators of response to rPTH treatment. Hypercalciuria is a frequent feature in the osteoporotic population which is not necessarily detrimental to bones. Low urinary calcium levels at 6 months could predict non-responders, who might benefit from extended rPTH therapy or a switch to an alternate treatment. This may help to focus and optimise individual patient's treatment. Our study also reflects that unlike endogenous PTH in pathological conditions, where it is continuously elevated, a low-dose recombinant PTH treatment is not detrimental to body fat and muscle composition and, therefore, remains a safe and effective anabolic osteoporotic medication regardless of comorbidities and medication history.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This is not a case report, and all data was kept anonymous; therefore, individual patient consent was not required.

Conflict of interest The authors declare that they have no conflict of interest.

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