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Analysis of circulating bone-glucose profile and exerkine irisin across parathormone quartiles in patients with primary hyperparathyroidism

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Abstract

Background: Parathyroid tumors, mostly single or multiple adenomas, cause a hormonal imbalance *via* parathormone (PTH) excess, that further increases serum calcium (primary hyperparathyroidism) with both PTH- and calcium-related multi-organ consequences. Testing the bone turnover markers (BTM) profile might capture the essence of associated bone turnover anomalies with practical applications in the clinical setting. *Objective*: Our objective was to compare the BTM across mineral metabolism panel, glucose profile, as well as circulating irisin levels in patients with primary hyperparathyroidism *vs.* (tumor-free) controls by refining the analysis based on PTH values quartiles. *Patients, Materials and Methods*: A prospective study with a single-center design in menopausal adults, who were enrolled between December 2024 and May 2026. *Results*: 148 enrolled across four PTH quartiles (mean age 63.39 years and menopause length 16.55 years): 27.09±5.56 pg/mL (Q1), 38.33±2.58 pg/mL (Q2), 46.34±2.93 pg/mL (Q3) and 65.78±16.51 pg/mL in Q4 (p<0.001 for each). Glycated hemoglobin (HbA1c) was lower (statistically significantly): Q4 of 5.74±0.32% compared to non-Q4 of 5.98±0.67% (p=0.006), as well as triglycerides of 103.39±36.34 *vs.* 124.41±66.26 mg/dL (p=0.017). Fasting insulin was also different among PTH quartiles, with the highest median value in Q4 of 8.35 (6.47, 11.49) µIU/mL (p=0.027). Median homeostatic model assessment for insulin resistance (HOMA-IR) was higher in Q2 *vs.* Q1 (p=0.034), Q3 *vs.* Q1 (p=0.016) and Q4 *vs.* Q1 (p=0.005). Osteocalcin was statistically significantly different among quartiles (p=0.036). Receiver operating characteristic (ROC) curve analysis of osteocalcin to predict primary hyperparathyroidism revealed area under the curve (AUC) 0.645 (p=0.006). The cut-off osteocalcin with the highest Youden index was for the value of 21.26 ng/mL (sensitivity 63.90%; specificity 63.10%). In Q4, irisin associated a statistically significant and positive correlation with the value of calculated body mass index (BMI) (r=0.361, p=0.042). *Conclusions*: In this PTH-based quartiles analysis of menopausal females with/without primary hyperparathyroidism, we found a distinct interpretation of the glucose profile and BTM depending on quartiles, while irisin positive corelated with BMI in cased with parathyroid tumors.

Keywords: parathyroid tumor, osteoporosis, bone, parathormone, calcium, irisin.

Introduction

Parathyroid tumors, mostly single or multiple adenomas, cause a hormonal imbalance *via* parathormone (PTH) excess, that further increases serum calcium (primary hyperparathyroidism) with both PTH- and calcium-related multi-organ consequences [1–3]. While the parathyroid tumor size usually is not directly corelated with the degree and the number of organ/system complications, the bone remains a traditional target, especially in populations at high fracture risk (*e.g.*, menopausal women) [4–6].

Parathyroid tumor-associated PTH release induces a higher bone remodeling and a consequent increased bone resorption. Thus, bone mass [bone mineral density (BMD) at dual-energy X-ray absorptiometry (DXA) evaluation] and bone quality [trabecular bone score (TBS)] decreases, which causes a higher incidence of fragility fractures [7–9]. In very severe cases, a massive bone resorption might cause brown tumors and/or *osteitis fibrosis cystica*, which represent PTH-induced skeleton complications that are extremely rare nowadays. While osteoporosis remains a standalone standard complication in primary hyperparathyroidism, this type of bone consequences is regarded as exceptional due to the fact that early detection allowed a mildly symptomatic (if any symptomatic at all) presentation of these parathyroid tumors across the contemporary medical era [10–13].

The pivotal role of chronic exposure to high endogenous PTH causes increased bone turnover, especially resorption and, hence, the profile of blood/urinary bone turnover markers (BTM) might capture the essence of this anomaly, even in patients who are accidentally detected with primary hyperparathyroidism, for instance, during routine calcium

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screening protocols, and even in cases diagnosed with normocalcemic variant of the endocrine condition in relationship with a parathyroid adenoma [14–17].

Aim

Our objective was to compare the BTM across mineral metabolism panel, glucose profile as well as circulating irisin levels in patients with primary hyperparathyroidism *vs.* (tumor-free) controls by refining the analysis based on PTH values quartiles.

Patients, Materials and Methods

Study population

Prospective, single-center study, between December 2024 and May 2026 was conducted in patients who were diagnosed with active primary hyperthyroidism *vs.* controls (females without a parathyroid tumor).

Inclusion criteria: menopause confirmation in active females, aged between 50 and 80 years; signed informed consent by each patient according to the study protocol; primary hyperparathyroidism confirmation according to the endocrine evaluation (study group) in a single tertiary center of endocrinology.

Exclusion criteria: lack of criteria for primary hyperparathyroidism (control group), secretor endocrine neoplasia, any type of suspected/confirmed oncological, bone, renal or metabolic bone disease, type 1 diabetes, history of bariatric surgery, therapy with glucocorticoids, insulin, anti-obesity and oral anti-diabetes medication, and anti-osteoporotic agents, as well as calcium lowering agents (*e.g.*, Cinacalcet), acute or renal failure, *osteogenesis imperfecta*, *osteitis fibrosa cystica*, brown tumors, secondary and/or tertiary hyperparathyroidism, a 25-hydroxyvitamin D <15 ng/mL. Of important note, subjects who were confirmed with primary hyperparathyroidism were included only in the absence of parathyroidectomy for the originating parathyroid tumor (regardless they further on became surgery candidates).

Study protocol

The eligible patients who underwent screening for this study were either enrolled in the group with parathyroid tumors, either in control group. Demographic parameters were collected.

Hormonal evaluation for the mineral metabolism profile confirmed primary hyperparathyroidism based on high total serum calcium and PTH. All enrolled patients were tested in the morning (fasting status).

Hormonal panel also included 25-hydroxyvitamin D and exerkine (myokine) irisin (a muscle-originating hormone), while biochemically, serum phosphorus was assessed, as well. Circulating BTM were of formation [procollagen type 1 *N*-terminal propeptide (P1NP), total alkaline phosphatase (ALP), osteocalcin] and of resorption (CrossLaps).

Glucose profile analysis included testing fasting glycated hemoglobin (HbA1c), insulin, glycemia [with homeostatic model assessment for insulin resistance (HOMA-IR) calculation]. Lipids profile involved triglycerides (TG) and cholesterol assays. Also, fasting uric acid (UA), urea and creatinine were tested.

Central DXA (GE Lunar Prodigy) provided BMD and T-score, and provided standard osteoporosis criteria, as well as TBS [18–20].

After checking for the inclusion/exclusion criteria, the patients underwent fasting blood testing (mineral metabolism, glucose profile and irisin) according to this study protocol.

Patients were then categorized into four quartile-based groups (Q1–Q4) according to the following PTH cut-off values for subsequent analyses:

- Q1 (PTH ≥13.75; ≤34.1 pg/mL);
- Q2 (PTH ≥34.2; ≤42.27 pg/mL);
- Q3 (PTH ≥42.28; ≤51.91 pg/mL);
- Q4 (PTH ≥52.92; ≤119.5 pg/mL).

Of important note, all patients who were prospectively included in this study had a prior endocrine assessment of their serum total calcium and PTH levels according to standard guideline criteria for this endocrine ailment within previous one week to three months (double testing) [21–23]. Within Q1, Q2 and Q3 quartiles, we included only the patients to whom primary hyperparathyroidism was ruled out (tumor-free controls), while within Q4 quartile only those females who were prior confirmed with primary hyperparathyroidism were included (higher PTH and total serum calcium above upper normal limit). Notably, PTH levels might suffer variations across a timeline perspective of testing its circulating levels, and even in cases with high-normal PTH at the moment of study enrollment, the diagnosis of primary hyperparathyroidism stands on previous (recent) double PTH/calcium assays, as mentioned.

Statistical analysis

Quartile cut-off values (25th, 50th, and 75th percentiles) were estimated using the Weighted Average method in IBM Statistical Package for the Social Sciences (SPSS) Statistics.

Ethical aspects

The study received hospital and university approval as shown below.

Results

PTH-based quartiles in patients with primary hyperparathyroidism (Q4) *vs.* tumor-free controls (Q1, Q2, Q3)

One hundred and forty-eight patients were divided into four groups corresponding to PTH quartiles: PTH was statistically significantly different in every between-group comparison, with a mean value of 27.09±5.56 pg/mL in Q1 group, 38.33±2.58 pg/mL in Q2 group, 46.34±2.93 pg/mL in Q3 group and 65.78±16.51 pg/mL in Q4 group (p<0.001 for each).

Age (63.39±8.88 years) was statistically significantly different among groups. HbA1c was lower in Q4 group (5.74±0.32%) compared to non-Q4 group of 5.98±0.67% (p=0.006), as well as TG of 103.39±36.34 mg/dL *vs.* 124.41 ±66.26 mg/dL (p=0.017) (Table 1).

Fasting insulin was also different among PTH quartiles, with the highest median value in Q4 group of 8.35 (6.47, 11.49) μIU/mL (p=0.027) (Figure 1).

HOMA-IR showed statistically significant different median values among all groups, with the highest value of 2.14 (1.57, 2.92) in Q4 group (p=0.015) (Figure 2).

Table 1 – ***Entire group and groups divided by PTH quartiles: demographic features***

Parameter	Entire group (*N*=148, 100%)	Q1 (*N*=39, 26.40%)	Q2 (*N*=37, 25.00%)	Q3 (*N*=36, 24.30%)	Q4 (*N*=36, 24.30%)	Non-Q4 (*N*=109, 73.60%)	*p*-value among all quartiles	*p*-value between Q4 and non-Q4	Normal range
Age [years], mean ± SD	**63.39±8.88**	**60.67±8.89**	**66.03±8.05**	**62.03±9.62**	**64.97±8.13**	62.88±9.08	**0.029**	0.219	
Years since menopause, mean ± SD	16.55±10.19	13.72±8.49	17.97±10.42	16.66±11.93	17.91±9.47	16.09±10.42	0.254	0.361	
BMI [kg/m^2], mean ± SD	30.16±5.71	29.03±5.59	30.37±6.62	30.88±5.29	30.43±5.26	30.08±5.86	0.547	0.761	
SC [mg/dL], mean ± SD	0.75±0.17	0.74±0.17	0.77±0.16	0.74±0.14	0.74±0.20	0.75±0.15	0.780	0.690	0.7–1.2
SU [mg/dL], mean ± SD	38.18±11.27	38.55±10.89	39.18±9.27	37.51±9.16	37.40±15.18	38.43±9.76	0.892	0.706	22–43
UA [mg/dL], mean ± SD	4.94±1.17	4.78±1.25	5.36±0.94	4.99±1.18	4.64±1.20	5.04±1.15	0.052	0.081	2.4–5.7
Fasting glycemia [mg/dL], mean ± SD	104.35±16.39	102.36±15.74	107.16±23.53	106.64±12.22	101.36±11.32	105.31±17.66	0.357	0.230	80–115
Fasting insulin [μIU/mL], median (Q1, Q3)	**7.12 (4.78, 11.15)**	**4.94 (3.58, 8.45)**	**6.82 (5.43, 11.57)**	**8.13 (4.94, 14.02)**	**8.35 (6.47, 11.49)**	6.45 (4.66, 11.10)	**0.027**	0.157	1.9–23
HOMA-IR, median (Q1, Q3)	**1.77 (1.17, 2.99)**	**1.22 (0.73, 1.96)**	**1.75 (1.21, 3.07)**	**2.10 (1.24, 3.98)**	**2.14 (1.57, 2.92)**	1.65 (1.08, 2.99)	**0.015**	0.183	0.7–2
HbA1c [%], mean ± SD	5.92±0.62	5.92±0.59	6.04±0.86	5.97 ±0.59	**5.74±0.32**	**5.98±0.67**	0.214	**0.006**	4.8–5.9
TC [mg/dL], mean ± SD	198.67±48.13	184.67±40.62	205.96±50.10	207.08±52.83	197.94±47.08	198.91±48.67	0.154	0.917	0–200
TG [mg/dL], mean ± SD	119.30±60.92	122.49±79.71	132.24±63.24	118.44±52.97	**103.39±36.34**	**124.41±66.26**	0.238	**0.017**	0–150

Blue font: Primary hyperparathyroidism. BMI: Body mass index; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment for insulin resistance; *N*: No. of patients; PTH: Parathormone; SC: Serum creatinine; SD: Standard deviation; SU: Serum urea; TC: Total cholesterol; TG: Triglycerides; UA: Uric acid.

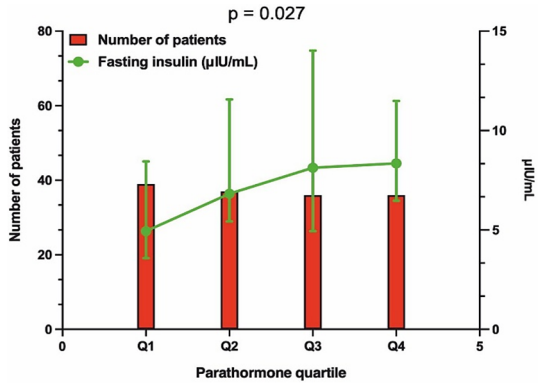

Figure 1 – ***Bar chart with error bars showing median fasting insulin in each group divided by PTH quartiles. PTH: Parathormone.***

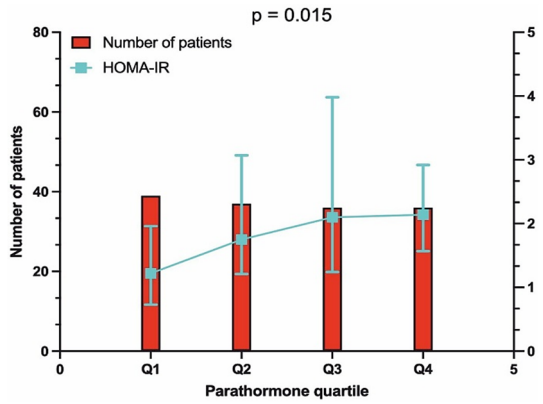

Figure 2 – ***Bar chart with error bars showing median HOMA-IR in each group divided by PTH quartiles. HOMA-IR: Homeostatic model assessment for insulin resistance.***

Between-groups analysis showed that age was higher in Q2 group in comparison to Q1 group (p=0.007) and in Q4 group *vs.* Q1 group (p=0.032) (Figure 3).

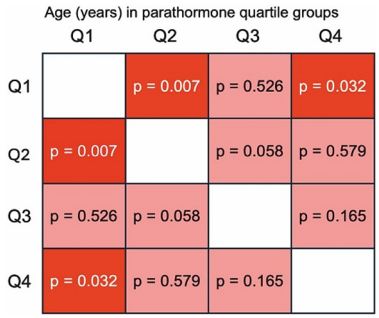

Figure 3 – ***Heatmap showing p-values of pairwise comparisons of age between PTH quartile groups.***

Fasting insulin level was higher in Q2, Q3 and Q4 groups when each *vs.* Q1 group (p=0.034, p=0.016, and p=0.005, respectively) (Figure 4).

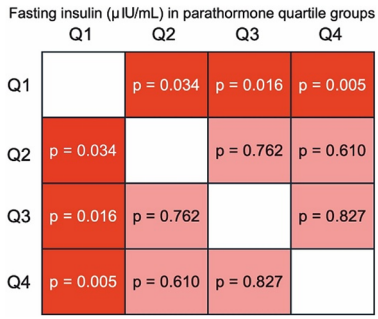

Figure 4 – ***Heatmap showing p-values of pairwise comparisons of fasting insulin between PTH quartile groups.***

Median HOMA-IR was higher in Q2 group *vs.* Q1 group (p=0.034), Q3 group *vs.* Q1 group (p=0.016) and Q4 group *vs.* Q1 group (p=0.005) (Figure 5).

Bone turnover markers sub-analysis

Osteocalcin was different among groups (p=0.036). BTM were higher in Q4 group compared to non-Q4 group: osteocalcin of 25.11±8.95 ng/mL *vs.* 20.83±7.16 ng/mL (p=0.004), ALP of 86.07±35.23 U/L *vs.* 74.71±21.86 U/L (p=0.023) and CrossLaps of 0.47±0.21 ng/mL *vs.* 0.39 ±1.17 ng/mL (p=0.021), respectively (Table 2).

Serum phosphorus was lower in Q3 group of 3.53 ±0.28 mg/dL and in Q4 group of 3.50±0.51 mg/dL compared to Q1 group of 3.86±0.66 mg/dL (p=0.006 and p=0.011, respectively) (Figure 6).

Mean osteocalcin was statistically significantly higher in Q4 group compared to Q1 group (p=0.022) and to Q3 group (p=0.016) (Figure 7).

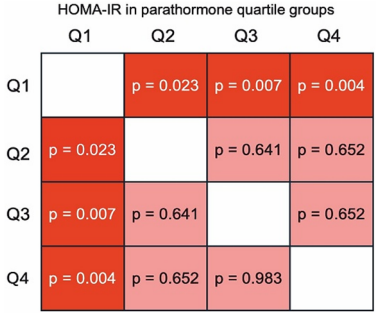

Figure 5 – ***Heatmap showing p-values of pairwise comparisons of HOMA-IR between PTH quartile groups.***

Table 2 – ***Circulating markers in the entire group and groups divided by PTH quartiles***

Variable	Entire group (*N*=148, 100%)	Q1 (*N*=39, 26.40%)	Q2 (*N*=37, 25.00%)	Q3 (*N*=36, 24.30%)	Q4 (*N*=36, 24.30%)	Non-Q4 (*N*=109, 73.60%)	*p*-value among all quartiles	*p*-value between Q4 and non-Q4	Normal range
Total serum calcium [mg/dL], mean ± SD	9.51±0.51	9.44±0.48	9.52±0.59	9.49±0.40	9.58±0.56	9.48±0.50	0.726	0.345	8.4–10.2
Ionized serum calcium [mg/dL], mean ± SD	4.08±0.27	4.05±0.24	4.07±0.33	4.04±0.22	4.16±0.28	4.05±0.26	0.453	0.111	3.9–4.9
Total proteins [g/dL], mean ± SD	7.44±0.51	7.40±0.57	7.46±0.48	7.50±0.49	7.40±0.51	7.45±0.51	0.792	0.582	6.5–8.7
Serum phosphorus [mg/dL], mean ± SD	**3.64±0.53**	**3.86±0.66**	**3.64±0.52**	**3.53±0.28**	**3.50±0.51**	3.68±0.53	**0.012**	0.077	2.3–4.7
25-hydroxyvitamin D [ng/mL], mean ± SD	30.84±9.17	32.21±9.56	28.49±9.69	31.05±9.00	31.58±8.23	30.61±9.47	0.315	0.583	30–100
PTH [pg/mL], mean ± SD	**44.34±16.65**	**27.09±5.56**	**38.33±2.58**	**46.34±2.93**	**65.78±16.51**	**37.26±8.79**	**<0.001**	**<0.001**	15–65
Osteocalcin [ng/mL], mean ± SD	**21.87±7.82**	**20.67±7.24**	**21.39 ±7.21**	**20.40±7.19**	**25.11±8.95**	**20.83±7.16**	**0.036**	**0.004**	15–46
ALP [U/L], mean ± SD	77.49±26.11	74.76±26.35	74.34±20.73	75.05±18.03	**86.07±35.23**	**74.71±21.86**	0.161	**0.023**	35–104
P1NP [ng/mL], mean ± SD	57.39±25.07	57.86±22.28	56.99±28.75	53.23±20.02	61.56±28.66	56.06±23.80	0.581	0.260	20.25–76.31
CrossLaps [ng/mL], mean ± SD	0.41±0.18	0.40±0.17	0.40±0.19	0.36±0.14	**0.47±0.21**	**0.39±0.17**	0.087	**0.021**	0.33–0.782
Circulating irisin [ng/mL], median (Q1, Q3)	73.39 (37.75, 123.64)	69.79 (21.73, 108.36)	73.40 (36.63, 151.87)	80.33 (40.35, 171.17)	79.54 (43.23, 113.71)	71.66 (34.43, 137.55)	0.570	0.883	

Blue font: Primary hyperparathyroidism. ALP: Alkaline phosphatase; *N*: No. of patients; P1NP: Procollagen type 1 *N*-terminal propeptide; PTH: Parathormone; SD: Standard deviation.

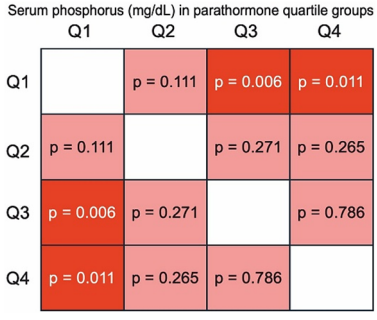

Figure 6 – ***Heatmap showing p-values of pairwise comparisons of serum phosphorus between PTH quartile groups.***

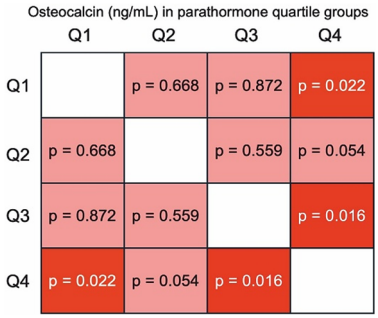

Figure 7 – ***Heatmap showing p-values of pairwise comparisons of osteocalcin between PTH quartile groups.***

DXA sub-analysis

Femoral neck BMD and T-score showed statistically significant different mean values among quartile groups (p=0.025 and p=0.020, respectively), and hip BMD and T-score (p=0.011 and p=0.009, respectively). Lumbar BMD was lower in Q4 group of 0.990±0.179 g/cm^2 compared to non-Q4 group of 1.073±0.163 g/cm^2 (p=0.044), as well as lumbar T-score of -1.46±1.36 standard deviation (SD) *vs.* -0.82±1.29 SD (p=0.048). There were statistically significantly more patients with prevalent fragility fractures in Q4 group (38.89%) in comparison to non-Q4 group (22.02%) (p=0.040) (Table 3).

Table 3 – ***DXA analysis***

Parameter	Entire group (*N*=148, 100%)	Q1 (*N*=39, 26.40%)	Q2 (*N*=37, 25.00%)	Q3 (*N*=36, 24.30%)	Q4 (*N*=36, 24.30%)	Non-Q4 (*N*=109, 73.60%)	*p*-value among all quartiles	*p*-value between Q4 and non-Q4	Normal range
Lumbar BMD	1.054±0.170	1.051±0.152	1.072±0.184	1.093±0.157	**0.990±0.179**	**1.073±0.163**	0.186	**0.044**	
Lumbar T-score	-0.97±1.32	-1.01±1.09	-0.65±1.47	-0.80±1.30	**-1.46±1.36**	**-0.82±1.29**	0.188	**0.048**	>-1
Femoral neck BMD	**0.870±0.119**	**0.859±0.115**	**0.878±0.113**	**0.920±0.127**	**0.817±0.101**	**0.887±0.120**	**0.025**	**0.015**	
Femoral neck T-score	**-0.92±0.95**	**-1.06±0.83**	**-0.81±0.97**	**-0.52±1.06**	**-1.35±0.76**	**-0.79±0.97**	**0.020**	**0.016**	>-1
Total hip BMD	**0.951±0.132**	**0.937±0.123**	**0.984±0.127**	**0.996±0.135**	**0.881±0.115**	**0.972±0.130**	**0.011**	**0.004**	
Total hip T-score	**-0.41±1.10**	**-0.54±1.03**	**-0.11±1.09**	**-0.04±1.12**	**-0.99±0.92**	**-0.23±1.09**	**0.009**	**0.004**	>-1
Third distal radius BMD	0.786±0.099	0.812±0.107	0.773±0.094	0.795±0.098	0.753±0.093	0.795±0.099	0.386	0.175	
Third distal radius T-score	-0.93±1.11	-0.64±1.18	-1.18±1.06	-0.85±1.18	-1.18±0.97	-0.87±1.14	0.464	0.187	>-1
Trabecular bone score, median (Q1, Q3)	1.342 (1.281, 1.412)	1.376 (1.291, 1.440)	1.320 (1.281, 1.404)	1.342 (1.258, 1.431)	1.335 (1.285, 1.394)	1.346 (1.278, 1.430)	0.782	0.712	>1.350
Osteoporosis, *N* (%)	21 (14.19)	5 (12.82)	3 (8.11)	5 (13.89)	8 (22.22)	13 (11.93)	0.380	0.168	
Osteopenia, *N* (%)	63 (42.57)	13 (33.33)	19 (51.35)	13 (36.11)	18 (50.00)	45 (41.28)	0.290	0.319	
Normal DXA, *N* (%)	49 (33.11)	14 (35.90)	11 (29.73)	14 (38.89)	10 (27.78)	39 (35.78)	0.430	0.187	
Prevalent fragility fractures, *N* (%)	38 (25.68)	11 (28.21)	7 (18.92)	6 (16.67)	**14 (38.89)**	**24 (22.02)**	0.132	**0.040**	

Blue font: Primary hyperparathyroidism. BMD: Bone mineral density; DXA: Dual-energy X-ray absorptiometry; *N*: No. of patients; PTH: Parathormone.

Between-groups comparison showed that femoral neck BMD was lower in Q4 group *vs.* Q3 group (p=0.004) (Figure 8).

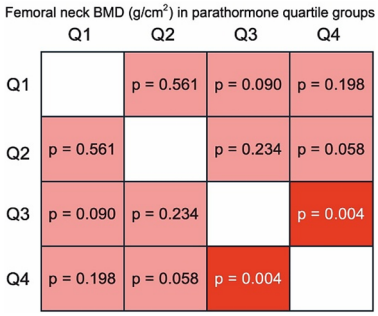

Figure 8 – ***Heatmap showing p-values of pairwise comparisons of femoral neck BMD between PTH quartile groups. BMD: Bone mineral density.***

Mean value of femoral neck T-score was lower in Q4 group compared to Q2 group (p=0.045) and in Q4 group in comparison to Q3 group (p=0.004) (Figure 9).

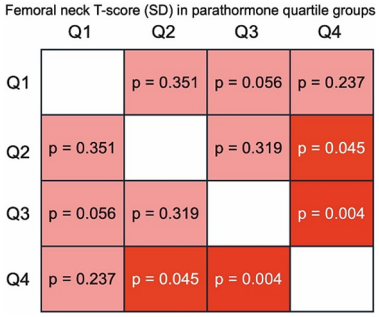

Figure 9 – ***Heatmap showing p-values of pairwise comparisons of femoral neck T-score between PTH quartile groups.***

Total hip BMD was statistically significantly lower in Q4 group of 0.881±0.115 g/cm^2 *vs.* Q2 group of 0.984±0.127 g/cm^2 (p=0.007) and *vs.* Q3 group of 0.996±0.135 g/cm^2 (p=0.003) (Figure 10).

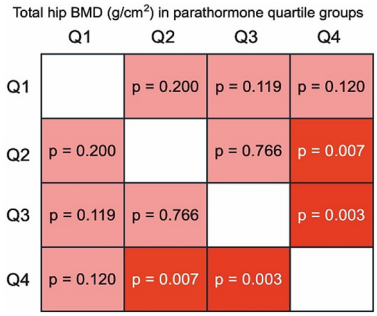

Figure 10 – ***Heatmap showing p-values of pairwise comparisons of total hip BMD between PTH quartile groups.***

Total hip T-score had a statistically significantly lower mean value in Q4 group of -0.99±0.92 SD compared to Q2 group of -0.11±1.09 SD (p=0.006) and compared to Q3 group of -0.04±1.12 SD (p=0.003) (Figure 11).

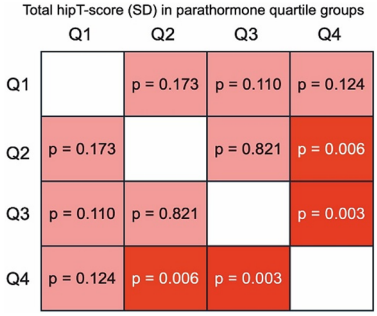

Figure 11 – ***Heatmap showing p-values of pairwise comparisons of total hip T-score between PTH quartile groups.***

PTH showed a positive correlation with fasting insulin (r=0.230, p=0.013) and HOMA-IR (r=0.245, p=0.008).

Irisin sub-analysis

Irisin was statistically significantly and positively correlated with body mass index (BMI) (r=0.391, p<0.001),

fasting insulin (r=0.366, p<0.001), HOMA-IR (r=0.338, p<0.001) and HbA1c (r=0.186, p=0.024). TBS showed a statistically significant negative correlation with age (r=-0.254, p=0.026) (Table 4).

Table 4 – *Correlations glucose–mineral metabolism (all)*

Parameter	Age [years]	Years since menopause	BMI [kg/m^2]	Fasting glycemia [mg/dL]	Fasting insulin [µIU/mL]	HOMA-IR	HbA1c [%]
Total serum calcium	*r*=0.001 *p*=0.999	*r*=0.019 *p*=0.823	***r*=-0.183** ***p*=0.030**	***r*=0.210** ***p*=0.014**	*r*=0.111 *p*=0.229	*r*=0.121 *p*=0.190	*r*=0.127 *p*=0.125
Ionized serum calcium	*r*=0.026 *p*=0.815	*r*=0.118 *p*=0.306	*r*=-0.151 *p*=0.180	*r*=0.197 *p*=0.082	*r*=0.154 *p*=0.214	*r*=0.130 *p*=0.289	*r*=0.127 *p*=0.257
25-hydroxyvitamin D	*r*=0.156 *p*=0.059	*r*=0.162 *p*=0.056	***r*=-0.360** ***p*<0.001**	***r*=-0.215** ***p*=0.012**	*r*=-0.152 *p*=0.100	*r*=-0.172 *p*=0.061	*r*=-0.138 *p*=0.095
PTH	*r*=0.141 *p*=0.091	*r*=0.140 *p*=0.099	*r*=0.093 *p*=0.278	*r*=-0.035 *p*=0.685	***r*=0.230** ***p*=0.013**	***r*=0.245** ***p*=0.008**	*r*=-0.091 *p*=0.279
Osteocalcin	*r*=-0.019 *p*=0.817	*r*=-0.104 *p*=0.221	*r*=-0.082 *p*=0.337	*r*=-0.103 *p*=0.233	*r*=-0.130 *p*=0.160	*r*=-0.125 *p*=0.176	*r*=-0.100 *p*=0.231
ALP	*r*=0.005 *p*=0.956	*r*=-0.054 *p*=0.524	***r*=0.172** ***p*=0.042**	*r*=0.151 *p*=0.080	*r*=0.098 *p*=0.292	*r*=0.102 *p*=0.274	*r*=0.112 *p*=0.179
P1NP	*r*=-0.128 *p*=0.125	***r*=-0.218** ***p*=0.010**	*r*=0.096 *p*=0.263	*r*=-0.080 *p*=0.360	*r*=-0.095 *p*=0.310	*r*=-0.084 *p*=0.367	*r*=-0.060 *p*=0.473
CrossLaps	*r*=-0.001 *p*=0.993	*r*=-0.060 *p*=0.485	*r*=-0.056 *p*=0.511	*r*=-0.015 *p*=0.861	*r*=-0.049 *p*=0.595	*r*=-0.046 *p*=0.617	*r*=-0.050 *p*=0.552
Irisin	*r*=0.062 *p*=0.452	*r*=0.087 *p*=0.306	***r*=0.391** ***p*<0.001**	*r*=0.067 *p*=0.436	***r*=0.366** ***p*<0.001**	***r*=0.338** ***p*<0.001**	***r*=0.186** ***p*=0.024**
Lumbar BMD	*r*=-0.007 *p*=0.943	*r*=0.020 *p*=0.850	***r*=0.205** ***p*=0.044**	***r*=0.234** ***p*=0.027**	***r*=0.251** ***p*=0.024**	***r*=0.258** ***p*=0.021**	*r*=0.115 *p*=0.265
Lumbar T-score	*r*=0.011 *p*=0.913	*r*=0.043 *p*=0.685	*r*=0.119 *p*=0.252	***r*=0.264** ***p*=0.013**	***r*=0.236** ***p*=0.037**	***r*=0.248** ***p*=0.028**	*r*=0.130 *p*=0.213
Femoral neck BMD	***r*=-0.287** ***p*=0.005**	***r*=-0.255** ***p*=0.014**	*r*=0.158 *p*=0.128	***r*=0.251** ***p*=0.020**	*r*=0.163 *p*=0.156	*r*=0.199 *p*=0.082	*r*=0.180 *p*=0.085
Femoral neck T-score	***r*=-0.293** ***p*=0.004**	***r*=-0.257** ***p*=0.013**	***r*=0.219** ***p*=0.034**	*r*=0.201 *p*=0.064	*r*=0.207 *p*=0.071	***r*=0.240** ***p*=0.036**	*r*=0.171 *p*=0.102
Total hip BMD	*r*=-0.164 *p*=0.115	*r*=-0.144 *p*=0.172	***r*=0.354** ***p*<0.001**	***r*=0.272** ***p*=0.011**	***r*=0.347** ***p*=0.002**	***r*=0.371** ***p*<0.001**	*r*=0.188 *p*=0.071
Total hip T-score	*r*=-0.164 *p*=0.115	*r*=-0.136 *p*=0.196	***r*=0.365** ***p*<0.001**	***r*=0.263** ***p*=0.014**	***r*=0.343** ***p*=0.002**	***r*=0.367** ***p*=0.001**	*r*=0.190 *p*=0.068
Third distal radius BMD	***r*=-0.418** ***p*<0.001**	***r*=-0.524** ***p*<0.001**	*r*=0.183 *p*=0.142	*r*=0.161 *p*=0.227	***r*=0.343** ***p*=0.002**	***r*=0.323** ***p*=0.016**	*r*=0.103 *p*=0.415
Third distal radius T-score	***r*=-0.479** ***p*<0.001**	***r*=-0.575** ***p*<0.001**	***r*=0.278** ***p*=0.024**	*r*=0.226 *p*=0.089	***r*=0.315** ***p*=0.019**	***r*=0.415** ***p*=0.002**	*r*=0.127 *p*=0.312
Trabecular bone score	***r*=-0.254** ***p*=0.026**	*r*=-0.217 *p*=0.060	*r*=0.105 *p*=0.364	*r*=0.090 *p*=0.463	*r*=-0.020 *p*=0.875	*r*=-0.003 *p*=0.984	*r*=0.136 *p*=0.240

ALP: Alkaline phosphatase; BMD: Bone mineral density; BMI: Body mass index; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment for insulin resistance; P1NP: Procollagen type 1 *N*-terminal propeptide; PTH: Parathormone.

Analysis of patients diagnosed with primary hyperparathyroidism (within Q4 quartile according to PTH-based quartiles)

Within the Q4 group, 25-hydroxyvitamin D was negatively correlated with BMI (r=-0.384, p=0.030) and fasting glycemia (r=-0.417, p=0.016). Irisin showed correlation with BMI (r=0.361, p=0.042). Lumbar BMD and T-score were correlated with BMI, as well as femoral neck T-score, total hip BMD and T-score and radius T-score. Total hip BMD and T-score also showed statistically significant correlations with fasting glycemia, fasting insulin and HOMA-IR (Table 5).

Table 5 – *Correlations glucose–mineral metabolism in Q4 group by PTH quartiles*

Parameter	Age [years]	Years since menopause	BMI [kg/m^2]	Fasting glycemia [mg/dL]	Fasting insulin [µIU/mL]	HOMA-IR	HbA1c [%]
Total serum calcium	*r*=0.190 *p*=0.268	*r*=0.199 *p*=0.251	*r*=-0.240 *p*=0.185	*r*=0.072 *p*=0.690	*r*=-0.131 *p*=0.484	*r*=-0.086 *p*=0.644	***r*=-0.519** ***p*=0.001**
Ionized serum calcium	***r*=0.658** ***p*=0.002**	***r*=0.686** ***p*<0.001**	*r*=-0.269 *p*=0.265	*r*=0.180 *p*=0.461	*r*=-0.050 *p*=0.845	*r*=-0.036 *p*=0.887	*r*=-0.345 *p*=0.137
25-hydroxyvitamin D	*r*=0.313 *p*=0.063	***r*=0.366** ***p*=0.031**	***r*=-0.384** ***p*=0.030**	***r*=-0.417** ***p*=0.016**	*r*=-0.146 *p*=0.433	*r*=-0.235 *p*=0.203	*r*=0.085 *p*=0.621
PTH	*r*=0.184 *p*=0.282	*r*=0.202 *p*=0.244	*r*=0.053 *p*=0.773	*r*=0.009 *p*=0.961	*r*=-0.228 *p*=0.218	*r*=-0.183 *p*=0.324	*r*=0.059 *p*=0.731
Osteocalcin	*r*=0.183 *p*=0.285	*r*=0.074 *p*=0.675	*r*=0.078 *p*=0.671	*r*=-0.028 *p*=0.878	*r*=-0.131 *p*=0.482	*r*=-0.140 *p*=0.452	*r*=0.017 *p*=0.923
ALP	*r*=-0.004 *p*=0.981	*r*=-0.138 *p*=0.431	*r*=0.110 *p*=0.548	*r*=0.195 *p*=0.277	*r*=0.157 *p*=0.400	*r*=0.199 *p*=0.284	*r*=-0.085 *p*=0.622
P1NP	*r*=-0.030 *p*=0.863	*r*=-0.076 *p*=0.669	*r*=0.147 *p*=0.430	*r*=0.045 *p*=0.808	*r*=-0.178 *p*=0.347	*r*=-0.159 *p*=0.402	*r*=-0.099 *p*=0.572
CrossLaps	*r*=0.170 *p*=0.322	*r*=0.158 *p*=0.365	*r*=-0.007 *p*=0.972	*r*=0.175 *p*=0.331	*r*=0.015 *p*=0.936	*r*=0.017 *p*=0.930	*r*=-0.064 *p*=0.713
Irisin	*r*=-0.174 *p*=0.309	*r*=0.011 *p*=0.950	***r*=0.361** ***p*=0.042**	*r*=0.168 *p*=0.351	*r*=0.191 *p*=0.304	*r*=0.210 *p*=0.257	*r*=0.255 *p*=0.134

Parameter	Age [years]	Years since menopause	BMI [kg/m^2]	Fasting glycemia [mg/dL]	Fasting insulin [µIU/mL]	HOMA-IR	HbA1c [%]
Lumbar BMD	*r*=0.182 *p*=0.419	*r*=0.149 *p*=0.509	***r*=0.440** ***p*=0.040**	*r*=0.258 *p*=0.259	*r*=0.174 *p*=0.462	*r*=0.223 *p*=0.346	*r*=0.086 *p*=0.705
Lumbar T-score	*r*=0.236 *p*=0.291	*r*=0.195 *p*=0.384	***r*=0.496** ***p*=0.019**	*r*=0.325 *p*=0.150	*r*=0.231 *p*=0.327	*r*=0.279 *p*=0.233	*r*=0.091 *p*=0.686
Femoral neck BMD	*r*=-0.136 *p*=0.547	*r*=-0.077 *p*=0.734	*r*=0.387 *p*=0.075	*r*=0.373 *p*=0.096	*r*=0.268 *p*=0.254	*r*=0.337 *p*=0.146	*r*=0.288 *p*=0.193
Femoral neck T-score	*r*=-0.153 *p*=0.496	*r*=-0.100 *p*=0.659	***r*=0.432** ***p*=0.045**	***r*=0.449** ***p*=0.041**	*r*=0.333 *p*=0.151	*r*=0.417 *p*=0.067	*r*=0.314 *p*=0.154
Total hip BMD	*r*=-0.001 *p*=0.996	*r*=0.139 *p*=0.539	***r*=0.594** ***p*=0.004**	***r*=0.516** ***p*=0.017**	***r*=0.481** ***p*=0.032**	***r*=0.518** ***p*=0.019**	*r*=0.334 *p*=0.128
Total hip T-score	*r*=-0.023 *p*=0.919	*r*=0.153 *p*=0.496	***r*=0.605** ***p*=0.003**	***r*=0.523** ***p*=0.015**	***r*=0.451** ***p*=0.046**	***r*=0.492** ***p*=0.027**	*r*=0.331 *p*=0.132
Third distal radius BMD	*r*=-0.364 *p*=0.222	*r*=-0.415 *p*=0.159	*r*=0.404 *p*=0.171	*r*=0.407 *p*=0.189	*r*=0.146 *p*=0.669	*r*=0.178 *p*=0.601	*r*=0.211 *p*=0.489
Third distal radius T-score	*r*=-0.491 *p*=0.088	*r*=-0.421 *p*=0.152	***r*=0.551** ***p*=0.050**	*r*=0.461 *p*=0.131	*r*=0.406 *p*=0.215	*r*=0.338 *p*=0.309	*r*=0.216 *p*=0.479
Trabecular bone score	*r*=0.178 *p*=0.542	*r*=0.461 *p*=0.097	*r*=0.121 *p*=0.681	*r*=0.330 *p*=0.271	*r*=0.161 *p*=0.618	*r*=0.224 *p*=0.484	*r*=0.222 *p*=0.445

Blue font: Primary hyperparathyroidism. ALP: Alkaline phosphatase; BMD: Bone mineral density; BMI: Body mass index; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment for insulin resistance; P1NP: Procollagen type 1 *N*-terminal propeptide; PTH: Parathormone.

Receiver operating characteristic (ROC) curve analysis of the ability of osteocalcin to predict primary hyperparathyroidism revealed a statistically significant area under the curve (AUC) of 0.645 (p=0.006). The cut-off value of osteocalcin with the highest Youden index was 21.26 ng/mL, associating a sensitivity of 63.90% and specificity of 63.10% (Table 6; Figure 12).

A ROC curve plotted for multiple cut-off values of CrossLaps for predicting primary hyperparathyroidism; highest Youden index corresponded to 0.465 ng/mL, with 52.80% sensitivity and 73.0% specificity. AUC was 0.613 (p=0.050) (Table 7).

Table 6 – ***Sensitivity and specificity of 21.26 ng/mL cut-off value of osteocalcin for predicting primary hyperparathyroidism (Q4 group by PTH quartiles)***

Parameter	Cut-off value for predicting primary hyperparathyroidism [ng/mL]	AUC	*p*-value	Sensitivity [%]	Specificity [%]	Youden index
Osteocalcin	21.26	0.645	0.006	63.90	63.10	0.242

Blue font: Primary hyperparathyroidism. AUC: Area under the curve; PTH: Parathormone.

Table 7 – ***Sensitivity and specificity of 0.465 ng/mL cut-off value of CrossLaps for predicting primary hyperparathyroidism (Q4 group by PTH quartiles)***

Parameter	Cut-off value for predicting primary hyperparathyroidism [ng/mL]	AUC	*p*-value	Sensitivity [%]	Specificity [%]	Youden index
CrossLaps	0.465	0.613	0.050	52.8	73.0	0.258

Blue font: Primary hyperparathyroidism. AUC: Area under the curve; PTH: Parathormone.

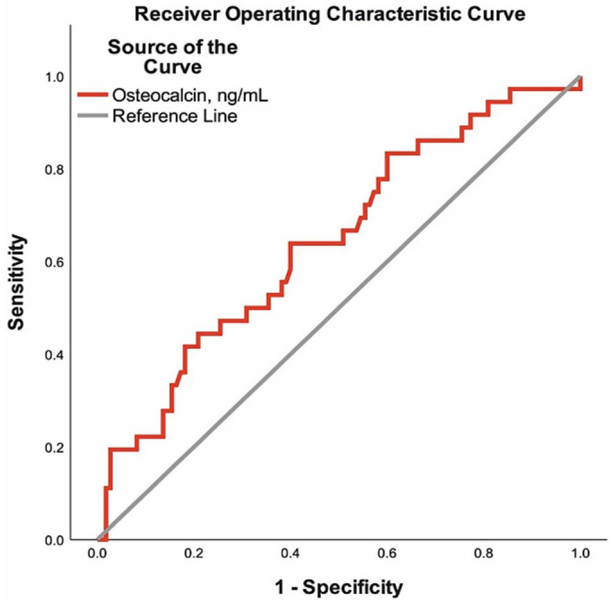

Figure 12 – ***ROC curve of osteocalcin for predicting hyperparathyroidism (Q4 group by PTH quartiles). ROC: Receiver operating characteristic.***

Discussions

In this study, we enrolled 148 adults (age: 63.39 years, menopause length: 16.55 years), who were then assessed based on PTH quartiles, noting that Q4 quartile (N=36) enrolled females who had a prior confirmation of primary hyperthyroidism without a parathyroid tumor removal at the moment of study enrollment and without medication that potentially interfere with the mineral metabolism such as calcium lower agents or drugs against osteoporosis in order to avoid an iatrogenic bias [24, 25]. In this specific instance, the biological phenotype showed mildly increased PTH levels, including forms with intermittent normocalcemic values. Nowadays, the face of primary hyperparathyroidism has changed into a less severe presentation, associated with an early detection that allows a prompt diagnosis and fewer complications during surveillance [26, 27].

Age was statistically significant different between the four quartiles (p=0.029). Patients within Q4 quartile had a mean age of 64.97±8.13 years, which was statistically significantly higher than the lowest tumor-free Q1 quartile (60.67±8.89 years, p=0.032). In the modern medical era, primary hyperparathyroidism affects more common

middle-aged women (in non-genetic forms of primary hyperparathyroidism), and post-menopausal detection is frequently described, for example, during routine (blood) biochemistry tests or during assessments for fracture risk, *e.g.*, after performing central DXA scan [27, 28].

Other parameters were found similar between quartiles, e.g., BMI, renal function, UA, suggesting that might not make a difference in women with parathyroid tumors *vs.* tumor-free subjects, according to this analysis on point.

However, glucose and lipids profile pointed out statistically significant differences between Q4 and non-Q4 groups, with respect to HbA1c (p=0.006) and TG (p=0.017), respectively, between all quartiles with respect to fasting insulin (p=0.027) and HOMA-IR (p=0.015). Lowest PTH quartile (Q1 group) showed a statistically significant lower insulin (median of 4.94 μIU/mL) *vs.* Q2 group (median of 6.82 μIU/mL, p=0.034), *vs.* Q3 group (median of 8.13 μIU/mL, p=0.016), and *vs.* Q4 group (median of 8.35 μIU/mL, p=0.005), respectively. HOMA-IR in Q1 group was the lowest (median of 1.22) *vs.* upper PTH quartiles such as Q3 group (median of 2.1, p=0.006) and Q4 group (median of 2.14, p=0.011).

Of note, patients with primary hyperparathyroidism showed a median HOMA-IR suggestive for insulin resistance (a value >2), which had been prior reported as a non-classical complication of tumor-related PTH excess. Currently, it does not represent an indication of parathyroidectomy (as, for instance, the confirmation of osteoporosis/osteoporotic fractures) [27–30]. However, the levels of HbA1c were found lower in Q4 group (5.74±0.32%) *vs.* controls (Q1–Q3 groups or non-Q4 group, of 5.98±0.67%, p=0.006), but with intra-normal average values (normal: 4.8% to 5.9%). As mentioned, we ruled adults who were prior diagnosed with type 1 diabetes and even cases with type 2 diabetes that received specific medication (*e.g.*, oral anti-diabetics and/or insulin).

Among the panel of BTM, osteocalcin showed statistically significant differences between Q4 and non-Q4 groups (p=0.004), respectively, Q4 group *vs.* Q1 group (p=0.022), and Q3 group (p=0.016) and a borderline significance for Q4 group *vs.* Q2 group (p=0.054). These biomarkers stand at the crossways between glucose and bone metabolism, being influenced by the presence of a PTH-induced abnormal bone metabolism or the co-presence of diabetes [31]. In addition, within Q4 group, ROC curve identified osteocalcin level to predict primary hyperparathyroidism based on AUC of 0.645 (p=0.006). The cut-off value of osteocalcin with the highest Youden index was 21.26 ng/mL, associating a sensitivity of 63.90% and specificity of 63.10%. ROC analysis for the other blood BTM did not show statistically significant results, except for a borderline significance for CrossLaps.

Serum phosphorus was not similar (as opposite to serum calcium, despite being a diagnosis criteria) between quartiles (p=0.012) and presented the lowest value in patients with primary hyperparathyroidism, but with mean levels within intra-normal ranges. This might explain PTH effects to some extent, yet the relatively mild phenotype of the endocrine disease is associated with minimal or intermittent phosphorus anomalies [28–35].

Central DXA revealed a statistically significant lower femoral neck BMD in Q4 group *vs.* highest quartile of controls (p=0.004), respectively for T-score (-1.35) *vs.* Q3 group (-0.52, p=0.003), and *vs.* Q2 group (-0.81, p=0.017). Additionally, total hip T-score in primary hyperparathyroidism (Q4 group) was lower (-0.99) *vs.* Q3 group (-0.04, p=0.003), respectively, Q2 group (-0.11, p=0.006). Paradoxically, for the comparison with Q1 group, the results did not reach a statistical significance, and a bias might come for concomitant factors to contribute to bone mass, such as age, BMI or diabetes. Moreover, the third distal radius site at DXA is particularly affected in patients with PTH producing tumors, and, yet we did not find this impact across our DXA analysis. Most probably, this is related to the fact that we enrolled less severe cases with a recent diagnosis in less symptomatic cases [36–38].

In this study, an analysis of the circulating myokine irisin was provided across each group, but with similar results. At this point, only a limited number of studies analyzed its profile in relationship with parathyroid tumors, noting that preclinical data are lacking human studies. According to our best knowledge, only a single study specifically addressed irisin in patients with primary hyperparathyroidism, showing an increase of its levels in cases with vitamin D supplementation [39–42]. Irisin was similar between quartiles regardless the parathyroid condition, but positively corelated with BMI, fasting glucose and insulin, HOMA-IR and HbA1c while specifically in the Q4 quartile, only the correlation with BMI was confirmed (r=0.361, p=0.042), which shows the need of a distinct interpretation in cases with primary hyperparathyroidism.

Limits and further research

Noting this was an exploratory analysis from the perspective of testing irisin, we are aware of some limitations such as the need of a larger sample size and more diverse population (including males and children). Longitudinal data are required in cases with surgery candidates *vs.* those who were conservatively managed. We did not analyze the post-operatory outcome, neither the potential correlations with the imaging aspects of the parathyroid tumors such as computed tomography, anterior neck ultrasound and ^{99m}Technetium parathyroid scintigram. A more complex analysis in primary hyperparathyroidism should take into consideration other potential complications such as the cardiovascular panel (arterial hypertension, arrythmia) and kidney stones [42–44]. The analysis of the glucose profile amid oral glucose tolerance test might improve these data. We assessed total ALP and not the bone-specific sequence, which may influence the results of BTM profile.

Conclusions

In this PTH-based quartiles analysis of menopausal females with/without primary hyperparathyroidism, we found a distinct interpretation of the glucose profile and BTM depending on quartiles, while irisin positive corelated with BMI in cased with parathyroid tumors.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board Statement

Ethical approval of the PhD research: C.I. Parhon National Institute of Endocrinology, Bucharest, Romania

(Approval No. 35 from 22 September 2025) and Carol Davila University of Medicine and Pharmacy, Bucharest, Romania (Approval No. 869 from 16 January 2026; PhD research). The research was conducted in accordance with the Declaration of Helsinki. The prospective study was approved by the Ethical Board of C.I. Parhon National Institute of Endocrinology, Bucharest, Romania (Approval No. 32 from 30 September 2024) for the project PN-IV-P8-8.3-ROMD-2023-0262.

Informed Consent Statement

Each patient signed the informed consent in order to be enrolled in the study.

Data Availability Statement

No other data are available.

Acknowledgments

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