Blood Parathyrin and Mineral Metabolism Dynamics

A clinical analyze

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Circulating parathyrin (PTH or parthormon) is increased in primary hyperparathyroidism (PHP) in association with high total/ionic calcium (T/I Ca) and others mineral metabolism anomalies. This is a clinical cross-sectional and case-control study analyzing these changes after PHP surgical correction in menopausal women. Baseline parameters were: mean age at diagnosis (59.63±9.6 years), TCa of 10.9±0.7 mg/dL, PTH of 138.02±59.36 pg/mL. Longitudinal data showed: final TCa p<0.00001, ICa p<0.00001, phosphorus p<0.0001, magnesium p=0.9, 24-h urinary calcium p=0.4, 25-hydroxycholecalciferol p=0.01, PTH p<0.00001. High circulating parathyrin values due to PHP normalized after surgery in addition to statistical significant changes of TCa, ICa, P, lumbar Bone Mineral Density provided by Dual-Energy X-Ray Absorptiometry; Mg and 24-h Ca might not be a marker of general mineral metabolism improvement.

Keywords: parhytyrin, parathormone, bone, calcium

Parathyrin represents parthomorne (PTH) or parathyroid hormone, the product of parathyroid glands [1]. Many diseases of the bone like primary/secondary osteoporosis or osteomalacia induce changes of circulating parathyrin [2-4]. Even metabolic conditions like metabolic syndrome and/or each of its components are linked to anomalies of bone turnover markers (BTM) and bone hormones including 25-hydoxyvitamin D (25OHD) and PTH. [5-8] Moreover, endocrine tumours or dysfunction of different endocrine glands may lead to skeleton anomalies like increase bone resorption or hypovitaminosis D with potential secondary parathyrin raise, for instance, in endogenous or exogenous glucocorticoids excess or in hypogonadism [9-13]. However, the most important change of mineral metabolism regarding parathyrin is expected in primary hyperparathyroidism (PHP) which is a clinical condition caused by a PTH producing tumour, usually of benign type. [2,3] Surgical tumour removal is the best therapy which is typically followed by a normalisation of circulating parathyrin and serum calcium, as well as of serum phosphorus, and bone turnover markers, and a significant improvement of bone mineral density (BMD) [2,3].

Parathyrin is a biochemical product acting on bone metabolism: it activates the renal induction of 1,25-dyhydroxycholecalciferol, the active form of vitamin D (also named calcitriol), bone remodelling, and *via* its mechanisms PTH exerts a negative feedback with serum calcium: high blood calcium inhibits parathyroid cells while low calcemia stimulates it [1-3]. Chemical aspects of PTH include the primary secreted pro-hormone (a polypeptide

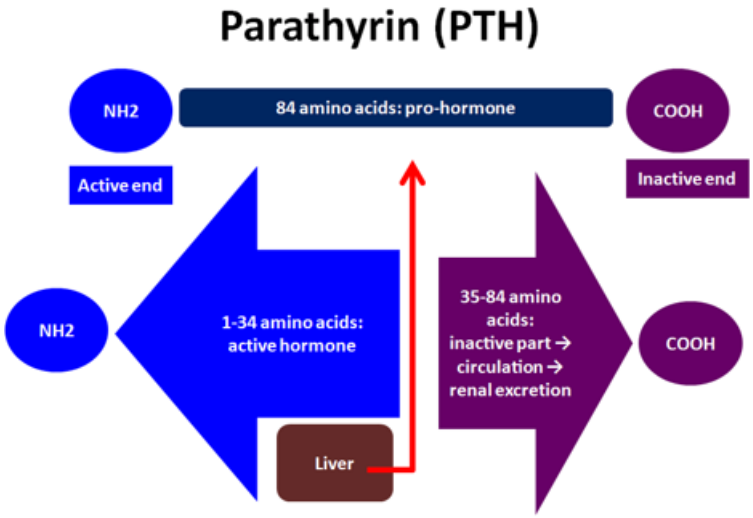

Fig. 1. Parathormone or parthyrin is a molecule of 84 amino acids, the active end is N-terminal and the active part which actually activates the specific receptors is represented by N-end -34 amino acids

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of 84 amino acids) and the active hormone (a section of 34 amino acids), responsible for the activation of type 1 and type 2 parathyroid receptors [1-3]. Parathyrin has a molecular mass of 9500 Da**.** Figure 1 illustrates the chemical aspects of the PTH as molecule into human body [1].

Experimental part

The aim of the study

Our purpose is to study the changes of PTH levels and others mineral metabolism elements in patients with primary hyperparathyroidism who suffered the parathyroid tumour removal (PTR).

Material and method

The study design includes a cross-sectional descriptive part which represents the baseline data of the patients and a longitudinal analyze in order to point out the changes between baseline (pre-operative) and post-surgery mineral parameters dynamics. The longitudinal study is case-control because each subject becomes his own control. The data were provided by two centres of endocrinology and the patients agreed for anonymously use of their medical data. Data collection (Excel) and statistical analysis (SPSS) included descriptive parameters like mean, standard deviation (SD), median, and functions as student ttest and linear regression. Statistical significance was for $p<0.05$.

Subjects

The inclusion criteria were:

1.Female subjects

2.Menopausal status

3.At least one year of secondary amenorrhea

4.Informed written consent

5.Confirmation of PHP by each patient' current physician

6.Available data of mineral metabolism pre- and post-operatory

7.Lumbar DXA scan at baseline

The exclusion criteria were:

1.Non-PTH -related causes of high serum calcium

2.Active cancers

3.Bone primary or secondary neoplasia

4.Others (non-PHP) bone metabolic conditions as Paget's disease, multiple myeloma

5.Prior or current exposure to specific drugs for osteoporosis like bisphosphonates, denosumab, teriparatide

6.Lack of confirmation of a benign parathyroid tumour after PTR based on pathological report

7.Chronic renal failure

8.Prior or current HRT (Hormone Replacement Therapy) for menopause

9.Persistent or recurrent PHP after a previous attempt of PTR.

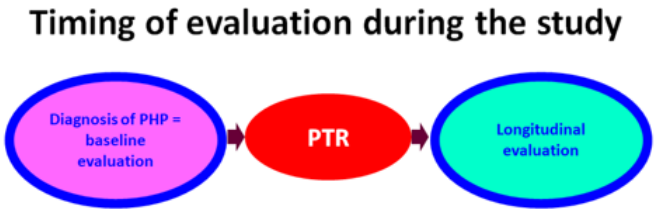

Fig. 2. Timing of assessment according to longitudinal clinical analyze

Evaluation

First (baseline) assessment is represented by the first diagnosis of PHP. The longitudinal analyze (the second assessment) was performed after PTR at one to 6 months, and it included the priory mentioned parameters 1 to 9. The same analyzer and method was used for each parameter before and after PTR (fig. 2).

The baseline parameters included:

1.Patient's age at diagnosis of PHP

2.The calculation of years since menopause (based on last menstruation)

3.Calculated BMI (Body Mass Index) using weight, and height (table 1).

4.Biochemical data: total serum calcium (TCa), ionic serum calcium (ICa), total proteins, serum phosphorus and magnesium, 24 h urinary calcium (24-h Ca).

5.Blood BTM meaning bone formation markers (alkaline phosphatase, and osteocalcin), respective bone resorption marker (CrossLaps).

6.Circulating hormones of bone metabolism: 25OHD and PTH.

The methods of detection for each parameter are introduced in table 2. The normal values of measured/ calculated parameters are introduced in table 3.

7.Lumbar central DXA (Dual-Energy X-Ray Absorptiometry) based on a General Electric Lunar Prodigy device. DXA provided lumbar BMD and device-derived T-score and Z-score.

Results and discussions

22 females of mean 59.63 years were evaluated at baseline and after PTR. They were all confirmed with PTH. The period of time between first diagnosis and post-operative assessment was 6-12 months. The baseline demographic parameters of menopausal population are included in table 4. The bone parameters analyzed in the study were included in table 5**.** Average values of TCa, ICa, PTH were outside the normal ranges, mean serum phosphorus had a low-normal value while magnesium was within normal limits, as well as BTM, and 24-h Ca (table 5). The values of PTH were all abnormally increased as part of primary diagnosis (table 5). Figure 3 introduced the circulating values of parathyrin at the moment of PHP confirmation. 25OHD showed prevalent low values (table 5). Lumbar BMD analyze provided a mean value of osteo-

Table 1

FORMULAS OF CALCULATION FOR BODY MASS INDEX, TOTAL CALCIUM AND IONIC CALCIUM

Formula	Abbreviation	Calculation	Units
Body Mass Index	BMI	weight (kg) / (height)^2 (sqm).	kg/sqm
Corrected serum total calcium	TCa	Measured TCa (mg/dL) + 0.8[4-measured serum albumin (g/dL)]	mg/dL
Ionic calcium	ICa	[6XTCa(mg/dL) – measured total proteins (g/dL)/3]:[total proteins(g/dL) + 6]	mg/dL

Parameter	Method of detection
serum calcium	colorimetric
total proteins	colorimetric
serum phosphorus	colorimetric
magnesium	colorimetric
24-hours urinary calcium	spectophotometry
alkaline phosphatase	colorimetric (VITROS)
osteocalcin	electro- chemiluminescence
CrossLaps	electro- chemiluminescence
25-hydroxyvitamin D or (*6R*)-6-[(*1R,3aR,4E,7aR*)-4-[(*2Z*)-2-[(*5S*)-5-Hydroxy-2-methylidene-cyclohexylidene]ethylidene]-7a-methyl-2,3,3a,5,6,7-hexahydro-*1H*-inden-1-yl]-2-methyl-heptan-2-ol)	chemiluminescence
Parathyrin (PTH)	electro-chemiluminescence

Table 2
METHOD OF ASSAY FOR BONE BIOCHEMISTRY, BONE TURNOVER MARKERS AND BONE HORMONES

Parameter	Normal value
total serum calcium	8.5 – 10.2 mg/dL
ionic serum calcium	3.9 – 4.9 mg/dL
total proteins*	6.5 – 8.7 mg/dL
serum phosphorus	2.5 – 4.5 mg/dL
magnesium	1.6 – 2.55 mg/dL
24-hours urinary calcium	0.1 -0.4 g/24-hours
alkaline phosphatase	38 – 105 U/L
osteocalcin	15 – 46 ng/mL
CrossLaps	0.33 – 0.782 ng/mL
25-hydroxyvitamin D (25OHD)	30 – 100 ng/mL
Parathyrin (PTH)	

**not a bone parameter but a necessary tool to calculate corrected total calcium and ionic calcium*

Table 3
NORMAL VALUES OF MEASURED/CALCULATED PARAMETERS

	Age at diagnosis	Age at menopause	Years since menopause	BMI
Mean	59.63636364	51	8.045454545	27.69227273
SD	9.609248792	3.925778205	7.060805787	4.335153023
Median	60	52.5	5.5	27.465
Min	43	43	1	18.33
Max	74	58	20	37.7

Where: BMI = Body Mass Index (kg/sqm); age at diagnosis, age at menopause are expressed in years

Table 4
THE BASELINE DEMOGRAPHIC PARAMETERS OF STUDIED POPULATION (N=22)

Where: BMI = Body Mass Index (kg/sqm); age at diagnosis, age at menopause are expressed in years

Table 5
THE BONE PARAMETERS ANALYSED IN MENOPAUSAL POPULATION CONFIRMED WITH PHP

Parameter	Tca	Ica	TP	P	MG	24-h Ca	AP	CL	OC	25OH D	PTH
Mean	10.90409	4.691875	7.394211	2.649047	2.063158	0.241111	85.06	0.434667	28.41385	15.92056	131.0281
SD	0.736385	0.480131	0.480131	0.493841	0.191951	0.088663	24.23778	0.240088	10.09379	8.621718	59.36524
Median	10.8	4.7	7.28	2.7	2	0.23	0.455	0.455	32.19	14.595	111.5
Min	9.02	3.6	6.52	1.41	1.74	0.14	0.05	0.05	14.15	6.04	41.05
Max	12.6	5.73	8.2	3.55	2.5	0.38	0.75	0.75	46.72	36.31	253.2

Where: TCa = total calcium (mg/dL), ICa = ionic calcium (mg/dL), TP = total protein (g/dL), P = phosphorus (mg/dL), Mg = magnesium (mg/dL), 24-h Ca = 24-h urinary calcium (g/24-h), AP=alkaline phosphatase (U/L), CL = CrossLaps (ng/mL), OC = osteocalcin (ng/mL), 25OHD = 25-hydroxyvitamin D (ng/mL), PTH = parathormone (pg/mL)

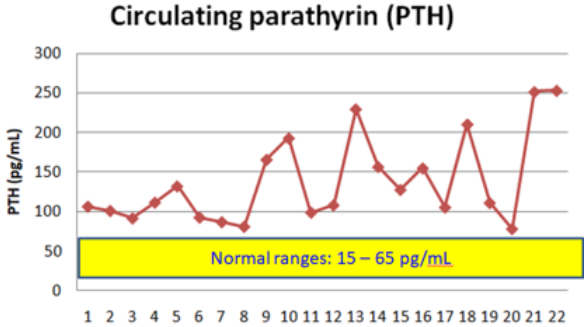

Fig. 3. The values of circulating parathyrin in each of the menopausal women confirmed with PHP

BMD	T-score	Z-score
0.890667	-2.35714	-1.03333
0.134371	0.957178	0.933095
0.877	-2.4	-0.8
0.734	-3.7	-2.5
1.078	-0.8	0.1

Where: BMD = Bone Mineral Density

Table 6
GE LUNAR PRODIGY DXA RESULTS AT LUMBAR SITE

Table 7
THE PARATHYRIN AND MINERAL METABOLISM DATA AFTER PTR IN MENOPAUSAL SUBJECTS

parameter	Tca	Ica	TP	P	MG	24-h Ca	AP	CL	OC	25OHD	PTH
Mean	9.185	4.045	7.42	3.498571	1.954167	0.185	71.41667	0.1425	12.6625	24.31	55.8194118
SD	0.941062529	0.233360	0.393319209	0.494755	0.127169	0.007071	15.88286	0.043493	4.355972	11.21466	34.0488336
Median	9.4	3.955	7.5	3.35	1.97	0.185	73	0.135	11.81	22.16	53.35
Min	6.5	3.8	6.75	3	1.67	0.18	48	0.1	8.38	7.99	251
Max	10.6	4.52	7.9	4.5	2.14	0.19	96	0.2	18.65	44.89	127.1

Where: TCa = total calcium (mg/dL), ICa = ionic calcium (mg/dL), TP = total protein (g/dL), P = phosphorus (mg/dL), Mg = magnesium (mg/dL), 24-h Ca = 24-hours urinary calcium (g/24-h), AP=alkaline phosphatase (U/L), CL = CrossLaps (ng/mL), OC = osteocalcin (ng/mL), 25OHD = 25-hydroxyvitamin D (ng/mL), PTH = parathormone (pg/mL)

penia according to T-score (table 6). Longitudinal data showed that bone parameters normalized according to mean values (table 7). None of the patients had persistent PHP during the mentioned period of time (table 7). The values of 25OHD improved after PTR (table 7). DXA results after PTR showed a mean T-score of -1.2+/-0.09 SD with a median of -1.267 SD (ranges between -1.3 and -1.2 SD). The baseline correlation between TCa/ICa and PTH did not reach the statistical significance. Student ttest between baseline and follow-up bone values showed the following results for:

1.TCa: $p<0.00001$
2.ICa: $p<0.00001$
3.P: $p<0.0001$
4.Mg: $p=0.9$
5.24-h Ca: $p=0.4$
6.AP: $p=0.09$
7.CL: $p=0.03$
8.OC: $p=0.09$
9.25OHD: $p=0.01$
10.PTH: $p<0.00001$
11.BMD: $p<0.00001$

The strengths of the study are the fact that is based on *real life medicine* which provided biochemical and endocrine data; the longitudinal observations are introduced using a case-control study, each subject represents his own control. Also, the numerous statistical significant results confirmed the literature regarding the mineral metabolism improvement once the circulating parahyrin is corrected after PTR. We achieved statistical significant data for TCa, ICa, PTH, P, CL, 25OHD, lumbar BMD, and a tendency for AP, respective OC.

The weak aspects of the study are the sample size of the cohort; the relative low period of time for surveillance; the changes of 25OHD are also due to the iatrogenic intervention once the diagnosis of vitamin D deficit was established by the same time with PHP confirmation; a very small number of patients had a high value of total calcium after PTR but with normal PTH, probably due to the introduction of calcium supplements immediately after PTR; also one patient had the maximum value of PTH after PTR of 127.1 pg/mL which was considered a component of secondary hyperparathyroidism due to low 25OHD levels and after vitamin D supplementation parathyrin normalized (the case was not considered a persistent PHP which are not included in the current study).

Generally the results for 25OHD showed hypovitaminosis D which partially corrected after PTR.

Conclusions

High circulating parathyrin values due to PHP normalized after PTR in addition to statistical significant changes of TCa, ICa, P, lumbar BMD-DXA; Mg and 24-h Ca might not be a marker of general mineral metabolism improvement.

Abbreviations

AP = Alkaline Phosphatase
BMI = Body Mass Index
BTM = Bone Turnover Markers
BMD = Bone Mineral Density
CL = CrossLaps
24-h Ca = 24-hours urinary calcium
25OHD = 25-hydroxyvitamin D
HRT = Hormone Replacement Therapy
ICa = ionic serum calcium
Mg = magnesium
OC = osteocalcin
PTH = parathormone, parathyrin
PHP = primary hyperparathyroidism
PTR = parathyroid tumour removal
P = Phosphorus
SD = standard deviation
TCa = total serum calcium
TP = total proteins

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