„CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY

BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

Clinical and Biological Correlations in Primary Hyperparathyroidism

ABSTRACT OF DOCTORAL THESIS

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CONTENT

The Fundamental Problem

Primary hyperparathyroidism (PHPT) is a chronic condition that involves autonomous secretion of parathyroid hormone (PTH) and consequently, inadequate increase in calcium. Today, it is considered the thrid most common endocrine disease, with an incidence of 0.4-82 cases/100 000 inhabitants, with a great geographic variability (Griebeler ML, 2015), (Darba J, 2020).

The clinical presentation of PHPT is predominantly defined by complications determined either by chronic, direct exposure to PTH of target organs and tissues, or indirectly, mediated by hypercalcemia (Bilezikian JP, 2022).

Prior to the 1980s, cystic fibrous osteitis was the primary skeletal damage in PHPT. Other severe extraskeletal complications, included nepholitiasis, nephrocalcinosis, renal failure, gastric ulcer and neuro-psychiatric phenomena (Ohe MN, 2005), (Heath H 3rd, 1980). PHPT underwent a paradigm shift with the increased accessibility of calcium measurement and the introduction of it as a screening test; this changed increased the rate of diagnosis, which in turn increased the incidence of the disease and facilitated the diagnsis of patients with asymptomatic or paucisymtomatic forms of disease (Ohe MN, 2005). As a result, in addition to the extraordinary rise in prevalence, there was also a noticeable change in the clinical picture, moving from the traditional form of the disease, marked by severe complications, to a modern form, much more clinically discrete, frequently found by chance in patients who were asymptomatic (Eufrazino C, 2013). The pace and geographic uniformity, however, varied depending on the level of development in various towns or regions. As a result, recorded data on the prevalence or seriousness of this condition's complications still vary depending on the period of time and place where they are gathered (Yadav SK, 2020).

In the last 10 years, the increased availability of plasma iPTH dosing has led to the emergence of a new disease phenotype, normocalcemic primary hyperparathyroidism, considered by the experts in the field to be an early form of the disease, whose subclinical complications, or, possible evolution to hypercalcemic PHPT, are still being studied (Bollerslev J, 2022).

The aim of management and research in the contemporary, paucisymptomatic phenotypes of PHPT is the early detection of subclinical complications related to PHPT and the selection of a treatment aimed at delaying the onset of a symptomatic form of the disease,

reducing the risk of developing severe complications.

We can summarize that the classic form of HPTP represents a challenge from the point of view of management for the clinician, through the heterogeneity and severity of complications, while the asymptomatic or normocalcemic forms represent a challenge for medical research.

Hypotheses

We hypothesize that the clinical picture of HPTP patients in Romania, even in the modern or asymptomatic forms of the disease, associates subclinical complications that can influence the long-term prognosis, and these HPTP comorbidities vary depending on the severity of the hyperparathyroid status, characterized by the maximum values of calcium and parathormone. Being a systemic, chronic disease, patients with moderate or severe forms of the disease associate both skeletal and extraskeletal complications. part of them, with varying degrees of reversibility after parathyroidectomy. The benefit of curative parathyroidectomy on bone mass has been very well documented and leaves no room for doubt, which is why international protocols recommend surgical treatment for patients with HPTP and osteoporosis or fragility fracture. However, there are few data at hand regarding the improvement of metabolic complications following surgical treatment, this representing an area of current scientific interest, with an interdisciplinary focus. In Romania, very few publications address the problem of changing HPTP dressings, the epidemiological data not satisfactorily covering the ever-changing spectrum of complications and highlighting the need for therapeutic protocols adapted to this condition in the Romanian area.

Objectives

By evaluating patients with HPTP in a tertiary endocrinology center, the study of this theme proposes the following general objectives:

- characterization of HPTP patients;
- the study of the prevalence of comorbidities associated with HPTP and the exploration of their etiopathogenesis;

- the severity of the complications of this condition and the relationship between them with iPTH and calcemia, as the main indicators of the hyperparathyroid status;
- the study of non-classical complications in relation to the severity of the disease;
- evaluation of densitometry parameters, their relationship with fracture risk and integration into the clinical profile of patients;
- identification of determining factors for the clinical prognosis of patients;
- comparative evaluation between etiopathogenic forms of the disease;
- potential benefits of parathyroidectomy and comparison with medical management.

Research Methodology

Inclusion criteria: positive diagnosis of HPTP (increased iPTH accompanied by inappropriately elevated calcemias).

Exclusion criteria:

- calciuria and hereditary collateral history suggestive of familial hypocalciuric hypercalcemia (FHH);
- paraclinical determinations suggestive of secondary hyperparathyroidism;
- the presence of other bone metabolic diseases except osteoporosis;
- patients with osteolytic lesions secondary to malignant neoplasms;
- other PTH-independent hypercalcemias;
- insufficient data;
- lack of informed consent of the patients to participate in the study.

The study was conducted in the Emergency University Hospital "Elias" in the Department of Endocrinology, during the period 2012-2021. The collection of materials was retrospective for the data obtained in the period 2012-2017 and cross-sectional or prospective for those obtained in the period 2017-2021. Of the 344 consecutive presentations proposed for evaluation, 186 patients did not meet the inclusion criteria or presented exclusion criteria. The 158 patients with a positive diagnosis of HPTP, taken into the department's records, formed the body of Study 1. Of these, 8 subjects were suspected or confirmed with MEN1 endocrine neoplasia and another 4 represent postoperative evaluations, leaving 146 patients with active hyperparathyroidism disease isolated. Of these, 62 subjects were lost to follow-up, leaving 84 with longitudinal assessments; 35 of them benefited from curative parathyroidectomy and 46

were treated medically or had no surgical resolution, representing the object of Study 3. For a subgroup of 49 postmenopausal women from Study 1, within the limits of availability of scans performed on the same osteodensitometer and of the criteria for calculating the trabecular bone score (TBS), a control group was created, matched for age and body mass index (BMI), by the nearest-neighbor method, within the variability range of ± 1 year and ± 1 kg /m2, comprising 132 subjects. These two subgroups formed the body of Study 2.

For the patients included in the study, clinical data were collected, such as: age, height, weight, ventricular allure and blood pressure (BP) in two distinct measurements; anamnestic data about the personal medical history of osteoporosis, fragility fractures, chronic kidney disease (CKD), nephrolithiasis, hyperuricemia, diabetes type 2 (DM), dyslipidemia, ischemic heart disease (ICD), hypertension (HTN), treatments followed, etc. . The biological evaluation included complete blood count, erythrocyte sedimentation rate (ESR), fibrinogen, biochemistry, ionogram, blood glucose, glycosylated hemoglobin (HbA1c), urea, creatinine (for calculating the estimated glomerular filtration rate - eRFG using the MDRD and CDK-formulas EPI), serum uric acid (AUS), lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), Magnesium (Mg) iPTH, total serum calcium, ionic calcium, 25(OH)-vitamin D, calciuria/ urine collected in 24 hours, alkaline phosphatase. From an imaging point of view, we used anterior cervical ultrasound, abdominal-pelvic ultrasound, scintigraphy with Technetium99-Sestamibi, and from 2018 the skeletal evaluation was performed using the GE Lunar iDXA osteodensitometer, to obtain bone mineral density (BMD), T score and score Z for lumbar spine (LS), hip and radius. MedImaps iNsight 1.8 software was used to calculate TBS and 10-year fracture risk (FRAX) for major osteoporotic fracture (FRAX MOF) and TBS-adjusted hip fracture; geometry and bone morphometry parameters were extracted using the Advanced Hip Analysis (AHA) program of the GE Lunar iDXA osteodensitometer from the patients' hip scan, recording values for Hip Axis Length (HAL), Neck Shaft Angle (NSA), Strength Index (SI), Buckling Ratio (BR), Section Modulus (SM), Cross-Sectional Moment of Inertia (CSMI), Cross-Sectional Area (CSA), Cortical Width Neck (CWN), Cortical Ratio Neck (CCN), Cortical Width Calcar (CWC), Cortical Ratio Calcar (CRC), Cortical Width Shaft (CWS) and Cortical Ratio Shaft (CRS).

The diagnosis of osteoporosis and osteopenia was standardized according to WHO criteria (Camacho PM, 2020). Depending on the trabecular score, the batch was divided into three categories, according to the manufacturer's recommendations: preserved microarchitecture with TBS ≥ 1300, partially degraded microarchitecture with TBS between 1200-1300 and degraded microarchitecture with TBS ≤ 1200 (Med-Imaps). The cardiovascular

risk of atherosclerotic events (ASCVD) at 10 years, optimal or lifetime, was calculated using the prediction tool recommended by the American College of Cardiology, integrating sex, age, systolic and diastolic blood pressure values, the presence or treatment of diabetes, dyslipidemia and HTN and lipid profile values (Arnett DK, 2019). The obtained score was divided into four subcategories: low ASCVD risk (< 5%), borderline (5-7.4%), intermediate (7.4-19.9%) and high (> 20%). Patients were stratified according to the severity of hypercalcemia into: mild hypercalcemia (< 12.2 mg/dl), moderate (12.2-14 mg/dl) and severe (> 14 mg/dl) (Walsh J, 2016). Vitamin D deficiency was established by a value of 25(OH)-vitamin D below 30 ng/ml (Pludowski P, 2022). A diagnosis of hyperuricemia was considered at AUS values > 5.7 mg/dl for women and > 7 mg/dl for men.

Microsoft Office Excel was utilized to collect the data, and IBM SPSS version 26 was used to conduct the statistical analysis. The Shapiro-Wilk test was used to confirm the normality of the data distribution. Utilizing the chi-square test, categorical variables were compared. Means or medians were used to express continuous variables. The association between the variables was assessed by the Spearman correlation test, and the Wilcoxon test was used to determine the median difference between the continuous non-parametric variables. Depending on the distribution of the data, comparisons between groups were carried out using the t-student, ANOVA, or Mann-Whitney tests. The Kruskal-Wallis test was used to analyze paired data collected at various time points. Linear or logistic regression models were used to identify independent predictors among the covariates associated with the dependent variable. $p \leq .05$ was considered statistically significant.

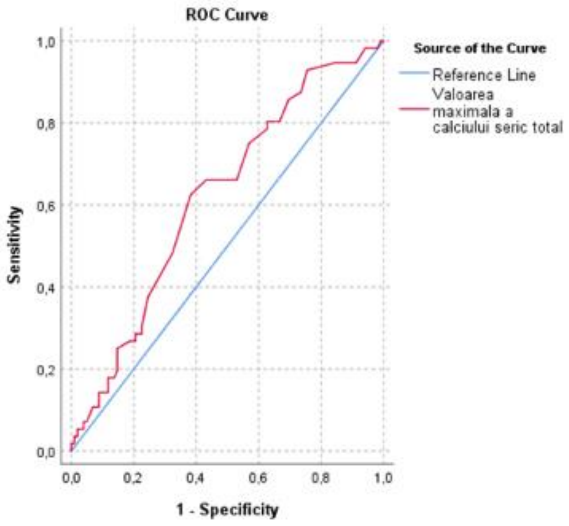
Results

The general description of the group revealed a median age at diagnosis of 60.7 [51.99; 67.82] years and a B:F sex ratio of 1:7 for the 158 patients included in Study 1. 12/158 cases (7.6%) had normocalcemic HPTP and 8 patients (7.6%) were suspected or diagnosed with MEN1 syndrome. The median value of iPTH was 163.3 [108;273.9] pg/ml and of total calcium 11.5 [10.87; 12.2], showing significant differences between men and women 12 [11.1; 12.57] vs. 11.4 [10.8; 12] mg/dl, **p =.048**. By dividing the study group according to the severity of hypercalcemia, 119/158 (75.3%) were classified as mild hypercalcemia, 30/158 (19%) moderate, and 9/158 (5.7%) were classified as severe hypercalcemia. 80.4% of the patients had a residence in the urban environment. 141/158 patients (89.2%) had an indication for curative

parathyroidectomy. The most prevalent comorbidities were: arterial hypertension (HT) in various degrees (75.3%), osteoporosis (50%), dyslipidemia (47.5%), obesity (36.1%), nephrolithiasis (35.4%) and hyperuricemia (29.7%). Chronic kidney disease (CKD) defined by an eRFG value lower than 60 ml/min/1.73 m2 was represented in 19% of cases and 14.5% of patients had a prevalent fragility fracture.

The 1st Study aimed to evaluate the prevalence of renal, metabolic and cardio-vascular complications associated with HPTP, the comparative assessment of the severity of the presentation of HPTP in relation to these complications and the study of hyperparathyroid status on risk factors and cardiovascular risk of atherosclerotic events.

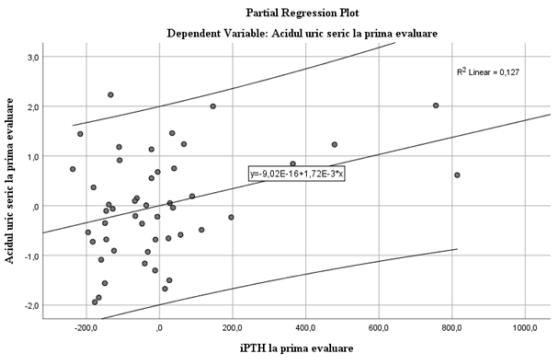
Patients with HPTP and nephrolithiasis had significantly higher maximum total calcium values compared to patients without renal lithiasis: 11.7 [11.1; 12.28] vs. 11.35 [10.7; 11.97] mg/dl, **p =.010**, but there were no significant differences in calcium between the two subgroups. The presence of nephrolithiasis was positively associated with the maximum value of iPTH (p =.001, r =.253), of total calcium (p =.012, r =.199) and with the presence of vitamin D deficiency (p =.025, r =.022). According to the model generated by the 95% ROC curve and AUROC, the total calcium value of 12.2 mg/dl as the threshold of moderate hypercalcemia had a specificity of 80% for the prediction of nephrolithiasis, at an AUC (Area Under Curve) of .640, **p =. 008**.



AUC	Std Err	p	95% CI
.640	.046	.008	[.531; .710]
Value	**Sensitivity**		**1-Specificity**
11.03	.804		.667
11.08	.804		.627
12.22	.286		.206
12.27	.268		.186

The prevalence of CKD according to the degree of renal insufficiency was: 17.7% for stage 3 and 0.6% for grade 4, respectively for grade 5. Representation of CKD (**χ2 =.001**) and estimated rates of glomerular filtration (**p =.006**) were significantly different according to the severity of hypercalcemia, respectively 11.8% in the subgroup with mild hypercalcemia

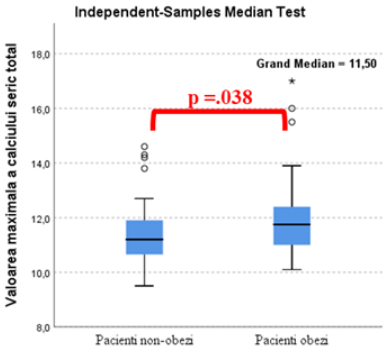
(median eRFG 80.7 [68.77; 91.82] ml/min/1.73m2), 33.3% for the subgroup with moderate hypercalcemia (median eRFG 70.45 [56.17; 88.55] ml/min/1.73m2) and 66.7% for the severe hypercalcemia group (median eRFG 57.95 [42.9; 81.45] ml/min/1.73m2). The value of iPTH proved to be an independent predictor for creatinine values. Patients with HPTP and CKD had higher prevalences of fragility fractures (9/30 – 30% vs. 14/128 – 10.9%, **χ2 =.017**), registering statistically significantly higher values for the age at diagnosis (67.8 [60.4; 70.1] vs. 58 [49.5; 65.5] years, **p =.004**) and serum levels of iPTH (335.2 [214; 868.9] vs. 144 [105.6; 209] pg/ml, **p =.001**), total calcium (12.25 [11.15; 13.82] vs. 11.4 [10.8; 11.9] mg/dl, **p =.002**) and of AUS (7.4 [5.7; 8.3] vs. 5.1 [4.2; 6.47] mg/dl, **p =.001**). Creatinine value correlated positively with age at assessment (p =.001, r =.277), total calcium (p =.001, r =.274), iPTH (p =.026, r =.189), AUS (p <.001, r =.529) and negatively with Mg (p =.001, r =-.322). A linear regression model that predicted 47.5% of the variability in creatinine value identified iPTH (**p =.039**), urea (**p =.001**) and Mg (**p =.027**) as independent predictors.

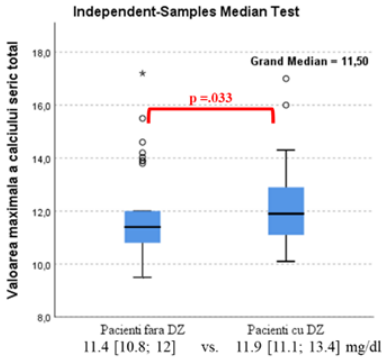


Depending on the severity of hypercalcemia, significant differences in the prevalence of hyperuricemia were noted: 30/87 (34.5%) in mild hypercalcemia, 15/22 (68.2%) in moderate and 2/5 (40%) in severe hypercalcemia, **χ2 = .016**. Intermediate and increased 10-year ASCVD risk was more prevalent (**χ2 =.009**) in the subgroup of patients with hyperuricemia - 20/30 (66.7%) having a median risk of 12 [5.02; 26.5]%, compared to 15/45 (34.9%) in the group of normouricemic patients who presented a median ASCVD risk at 10 years of 5.8 [2.5; 10.05], **p =.006**. We noted a significantly higher magnesium value among patients without hyperuricemia (2.12 [2; 2.2] vs. 1.98 [1.87; 2.1] mg/dl, **p =.009**). The AUS value correlated with age (p =.014, r =.279), eRFG, CDK-EPI (p <.001, r =-.429), calcium value (p <.001, r =.426), iPTH (p =.032, r =.247), blood glucose (p =.022, r =.261), triglycerides (p =.001, r =.491), GGT (p =.005, r = .349) and magnesium (p =.001, r =-.433). The linear regression model that explained 62.8% of AUS variability identified iPTH (**p =.019**), eRFG CDK-EPPI (**p =.002**) and magnesium (**p =.005**) as independent predictors.

The median value of the body mass index of the patients of Study 1 was 28.18 [25.13; 32.43] kg/m2, with the following distribution: 4 patients (3.75%) underweight, 20 patients

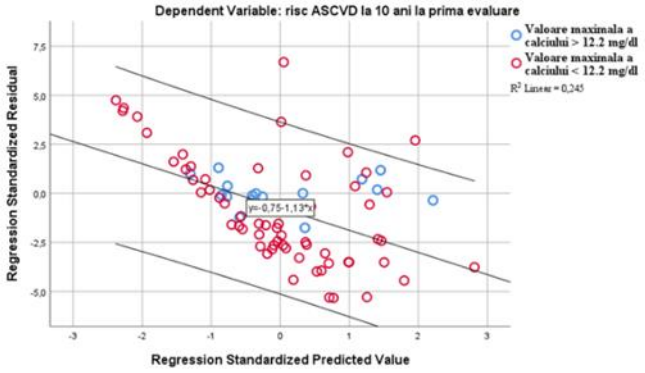
(18.9%), 39 (36.45%) overweight, 26 (24.3%) obesity grade 1, 9 (8.41%) obesity grade 2 and 9 (8.41%) morbid obesity. Obese patients recorded significantly higher maximum total calcium values (11.75 [11; 12.4] vs. 11.2 [10.6; 11.9] mg/dl, **p =.038).** Depending on the severity of hypercalcemia, different prevalences of diabetes were recorded: 11.8% in mild hypercalcemia, 16.7% in moderate and 44.4% in severe, **χ2 =.029**. Median total calcium values were significantly higher among the 23 diabetic patients: 11.9 [11.1; 13.4] vs. 11.4 [10.8; 12] mg/dl, **p =.033**. Although in the entire study group we did not notice associations with specific HPTP parameters, after excluding normocalcemic patients, the blood glucose value correlated with the iPTH value (p =.042, r =.188). There were no differences in prevalence or lipid parameters in relation to the biological determinants of HPTP.





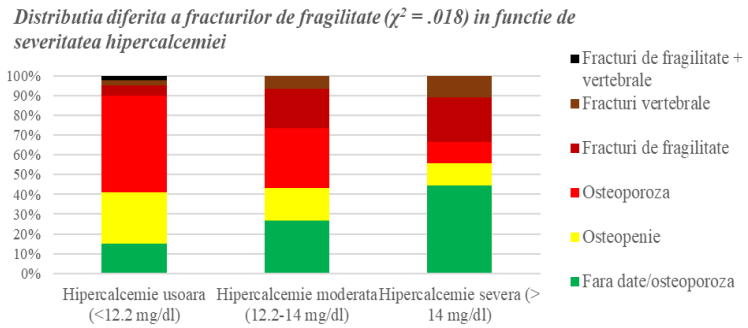
Patients with a confirmed diagnosis of ischemic heart disease (ICD) had more frequent fragility fractures (6/18 – 33% vs. 17/140 – 12.1%, **χ2 =.028**) and a significantly higher maximum calcium value (12.15 [11.2; 14.6] vs. 11.4 [10.82; 12] mg/dl, **p =.041**) suggesting the clinical picture of a classical form of HPTP.

The distribution of estimated cardiovascular risk of atherosclerotic events (ASCVD) at 10 years in the entire Study 1 cohort was 35/95 (36.8%) low risk, 13/95 (13.7%) borderline risk, 28/95 (29.5%)) intermediate and 19/95 (20%) high risk, registering differences in prevalence depending on the severity of hypercalcemia (**χ2 =.033**). Patients with moderate and severe hypercalcemia had a significantly higher median 10-year ASCVD risk compared to those with mild hypercalcemia (10.45 [7; 14.95] and 6.1 [2.5; 14.3]%, respectively, **p =.029**). Similarly, patients with osteoporosis (10.05 [6.02; 21], respectively 3.2 [1.72; 6.22]%, **p =.001**) had a higher 10-year ASCVD risk than those without bone damage. The absolute values of ASCVD risk at 10 years were correlated with: age at assessment (p <.001, r =.831), male gender (p =.001, r =.347), osteoporosis (p <.001, r =.444), DM (p <.001, r =.417), dyslipidemia (p =/036, r =.215), CKD (p =.004, r =.292) and with prevalent fracture (p =.010, r =.264). The linear regression model that explained 93.3% of the variability of ASCVD risk at 10 years in the group of patients with maximum total calcium values over 12.2 mg/dl identified the

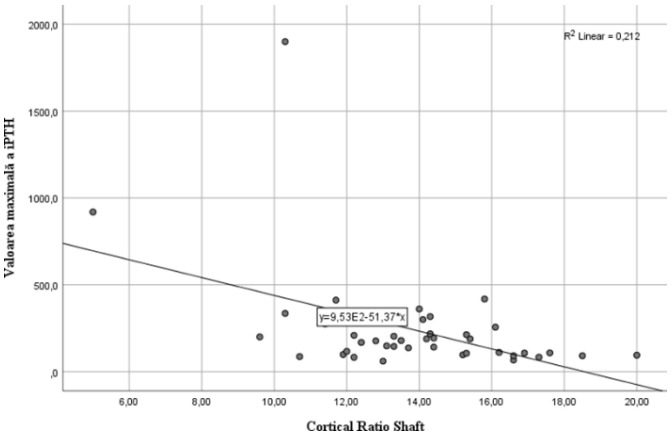


presence of osteoporosis (**p =.030**), diabetes (**p =.007**), chronic kidney disease (**p =.008**) and age (**p <.001**) as independent predictors. The value of calcium was positively associated with the difference between the ASCVD risk estimated at 10 years and the optimal one (p =.001, r =.359). These results highlight the multifaceted clinical picture of HPTP patients and the need for an appropriate interdisciplinary management.

The 2nd Study aimed to evaluate the bone mineral density (BMD) obtained by osteodensitometry (DXA), the prevalence of fragility fractures stratified according to the severity of hypercalcemia and the relationship between them and other cofactors. BMD, parameters of bone geometry and quantitative morphometry, trabecular bone score (TBS) and its importance in fracture risk assessment between HPTP patients and the control group were comparatively evaluated.



Despite percentages without significant differences in the prevalence of osteoporosis in group 1 divided according to the severity of hypercalcemia (59/101 – 58.4% in mild hypercalcemia, 16/22 – 72.7% in moderate and 4/5 – 80% in severe, $\chi 2 = .316$), the prevalence of fragility fractures was different between these groups (**$\chi 2$ = .018**), as follows: 12/119 (10.1%) in mild hypercalcemia, 8/30 (26.6%) in moderate and 3 /9 (33.3%) in severe hypercalcemia, signaling an important limit of BMD determination for fracture risk assessment. Patients with fragility fracture had a significantly higher median age at diagnosis 69.4 [66.61; 74.4] vs. 58.34 [50.7; 64.91] years, **p =.001**, significantly lower BMD values, T and Z scores in all scan areas and a significantly lower TBS (1.207 ± 0.144 and 1.313 ± 0.116 respectively, **p =.023**) than patients without fracture of fragility. There were no differences between the mean/median values of geometry and bone morphometry parameters according to the presence of fragility fracture.



The thickness of the cortex of the proximal femur, expressed by Cortical Ratio Shaft (CRS), and Cortical Width Calcar, was negatively associated with the iPTH value (p =.026, r =-.288), respectively with the ion calcium value (p =.009 , r =-.649), highlighting subcortical osteoresorption determined by chronic exposure to PTH. Renal function impairment was associated with a lower bone resistance to bending forces: Strength Index (p =.006, r =.356), Section Modulus (p =.043, r =.264) and Cross-Sectional Area (p <.001, r =.485). The cumulative impact of HPTP and chronic kidney disease (CKD) on bone metabolism is a future research challenge.

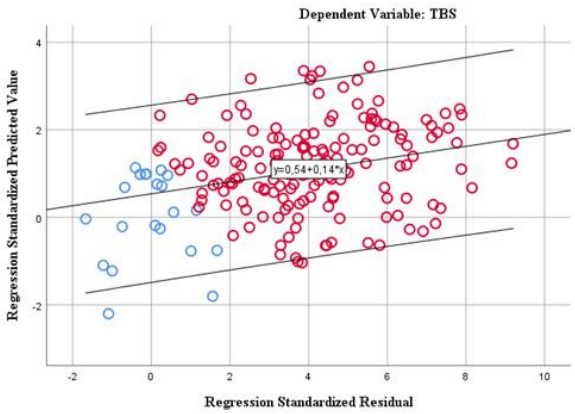
Analyzing exclusively postmenopausal women in group 1, we observed significantly higher parathyroid hormone values (171.2 [116.9; 300] vs. 1114.85 [97.2; 299.4] pg/ml, **p =.050**) for the 67 patients diagnosed with osteoporosis compared to the 28 patients without osteoporosis.

From the comparison with the 132 controls, the 49 postmenopausal women with HPTP had significantly lower BMD values in all areas of interest. Thus, the prevalence of osteoporosis and severe osteoporosis demonstrated a significantly more frequent bone damage among hyperparathyroid patients (55.1%) compared to the control group (33.3%), **$\chi 2$ = .010**. The mean value of TBS was significantly lower in the HPTP group (1.287 ± 0.117 vs. 1.331 ± 0.091, **p =.008**). The distribution of the categories of microarchitectural damage, as well as the median values of TBS for the respective categories between the two subgroups of the Study 2.2 batch can be found below

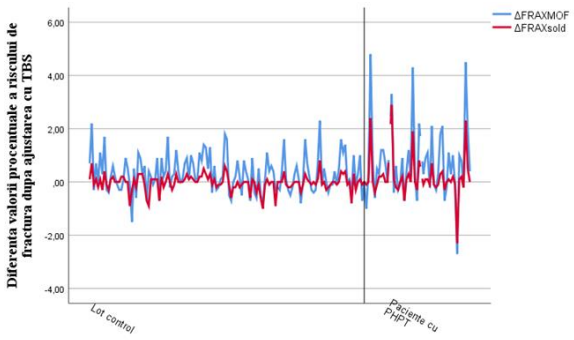
Prevalences of different degrees of microarchitectural damage and related mean TBS values between the two subgroups of the Study 2.2 cohort

		PHPT subgroup (N=49)	**Control subgroup (N=132)**	*Sig.*
Preserved microarchitecture (TBS>1.3)		22 (44.9%)	85 (64.4%)	NS
		16 (32.7%)	37 (28%)	NS
Degraded microarchitecture (TBS<1.2)		11 (22.4%)	10 (7.6%)	**.008**
	Mean TBS	1.144 ± 0.016	1.174 ± 0.008	**.043**
Abnormal microarchitecture (TBS< 1.3)		27 (55.1%)	47 (35.6%)	**.026**

TBS values showed statistically significant positive correlations with BMI (p <.001, r =.279), LS BMD (p <.001, r =.659), hip BMD (p <.001, r =.439) and negative with age (p <.001, r =-.332) and with the presence of HPTP (p =.023, r =-.332). Applying a linear regression model in the subgroup with degraded microarchitecture (TBS<1.2) with TBS variation as the dependent variable, we identified HPTP (**p =.031**), in addition to BMD CL (**p =.040**) as independent predictors.



Although there were no statistically significant differences between FRAX MOF BMD and FRAX hip BMD between the HPTP and control groups, or between TBS-adjusted FRAX, for both MOF and hip fracture, we identified a statistically significant difference for FRAX MOF before and after TBS adjustment, both for the control group (4.5 ± 0.24 vs. 4.7 ± 0.26%, **p >.001**) and for HPTP patients (4.35 ± 0.6 vs. 5.25 ± 0.73%, **p <.001**), but not for hip FRAX. In addition, there was a statistically significant difference between how the risk of major osteoporotic fracture changes 10 years after TBS adjustment in the HPTP group (0.4 ± 0.2%) vs. control (0.2 ± 0.06%), **p =.044**, expressed as FRAX MOF Diff. The same difference was maintained when we highlighted the change in fracture risk as a percentage of baseline FRAX (FRAX MOF % Diff): the risk for MOF increases 1.1-fold in the HPTP group and 1.04-fold in the control group after TBS adjustment, **p=.034**.



Thus, when applying a linear regression model on the variation between FRAX MOF with BMD and after adjustment with TBS as the dependent variable and age, BMI, BMD CL and HPTP as covariates, we identified PHPT (**p =.043**), along with age (**p =.048**), BMI (**p =.024**) and BMD CL (**p <.001**) as independent predictors.

Linear regression model for the variation in the risk of major osteoporotic fracture after adjustment with TBS					
Variable	B	95% CI	β	t	p
Age at scan*	.012	[.000; .023]	.129	1.990	**.048**
BMI*	-.025	[-.047; -.003]	-.153	-2.280	**.024**
LS BMD*	-.2638	[-3.434; -1.842]	-.455	-6.544	**<.001**
PHPT*	.273	[.008; .538]	.127	2.035	**.043**

Note: R^2_{adj} = 0.337 (N = 179, p =.012). CI = confidence interval for B

Regarding bone geometry indices, in the group with HPTP, compared to the control group, we observed significantly lower median values of CSMI (8832 [7795.5; 10714.5], respectively 9766 [8122.25; 11074.75], **p =.005**), Cortical Width Calcar (2.9 [2.55; 3.4], respectively 3.4 [2.97; 4.1], **p =.012**) and Cortical Ratio Calcar (5.5 [4.95; 6.2], respectively 6.3 [5.5; 7.52], **p =.001**). Bone geometry parameters correlated with anthropometric or hyperparathyroid status-specific indices as follows: age at assessment correlated with CSA (p =.005, r =-.439), BMI correlated with Strength Index (p <.001 , r =-.551) and the maximum PTH value correlated with Cortical Ratio Shaft (p =.008, r =-.407).

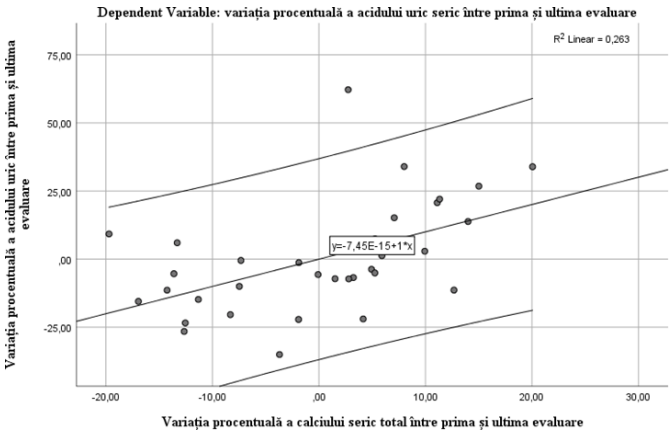
The 3rd Study proposed the longitudinal, comparative, medium-term follow-up of 36 patients with HPTP who benefited from curative parathyroidectomy versus 45 subjects with an indication for surgery who were treated medically. The objective was to identify potential differences regarding lipid and carbohydrate metabolism, cardiovascular risk, but also other parameters, such as uric acid or magnesium.

The average age at the first evaluation of the patients was 59.41 ± 10.89 years for the 36 patients cured after parathyroidectomy and 62.84 ± 11.36 years for the 45 patients treated with medication, without significant differences. Median follow-up periods were significantly different between the two subgroups: 0.55 [0.3; 1.07] years for surgically treated patients and 2 [0.9; 3] years for those with conservative therapy (**p =.002**).

Starting from significantly different median values of total serum calcium between the group of parathyroidectomized patients and those treated with medication (**p =.013**), the evolution of this parameter between the first and last presentation showed statistically significant differences only for the subgroup of surgically cured patients (11.7 [11.02; 12.25] vs 9.2 [8.52; 9.57] mg/dl, **p <.001**), and not for those with conservative therapy (11.05 [10.42; 11.5] vs 10.8 [10.5; 11.2] mg/dl, p =. 187). Not surprisingly, median iPTH values showed statistically significant differences preoperatively (168.75 [135.55; 410.02] pg/ml) versus

postoperatively (37.23 [29.02; 50.18] pg/ml), **p < .001**. Drug-treated patients apparently maintained their median iPTH values. We observed significant increases in median 25(OH)-vitamin D levels in both surgically cured patients (15.8 [10.31; 30.1] vs. 28.1 [23.5; 36.18] ng/ml, **p =.001**) and those treated with medication (18.42 [7.47; 27.25] vs. 29.75 [19.87; 38.67] ng/ml, **p =.010**).

It is worth mentioning the different dynamics depending on the therapeutic protocol followed of the median values of uric acid, although its initial values were not statistically significantly different between the two subgroups: 5.9 [4.94; 7.3] mg/dl at the first assessment and 5.1 [3.75; 6.55] mg/dl at the last evaluation, **p =.011**, among surgically cured patients, unlike the drug treatment subgroup, where AUS values at the first evaluation were 4.9 [4.53; 6.17] mg/dl and 5.7 [5.05; 6.57] mg/dl at the last evaluation, p =.820



The variation of serum uric acid between the first and last presentation was correlated with the variations of: total serum calcium (p <.001, r =.617), creatinine (p =.001, r =.487) and GGT (p =.040, r =.359). Entering these variables into a dynamic regression model with the variation of serum uric acid values as the dependent variable, we highlighted as independent predictors the variation of creatinine (**p =.003**) and total serum calcium (**p =.003**).

Also important is the significant decrease in the median levels of magnesium in surgically cured patients (2.1 [1.9; 2.2] at the first assessment compared to 1.95 [1.8; 2.02] at the last assessment, **p =.002**) vs patients treated with medication (2.01 [1.81; 2.17] at baseline compared to 1.99 [1.79; 2.11] at the end of the follow-up period, p =.808). The percent change between baseline and end-of-follow-up median levels of serum magnesium correlated positively with percent changes in iPTH (p =.021, r =.40) and hemoglobin (p =.024, r =. 352) and negative with those of ESR (p =.041, r =-.358) and blood glucose (p =.031, r =-.342). A linear regression model that included the variation of magnesium values between the first and last assessment of the patients in the Study 3 group as a dependent variable, having as covariates the age at the first assessment and the initial values of total calcemia, blood glucose and serum urea, identified the initial calcemia (**p =.002**) as an independent predictor for 29.2% of the magnesium variation.

Linear regression model for variation in magnesium for patients at follow-up					
Variable	**B**	**95% CI**	**B**	**t**	**p**
Initial age	-.002	[-.008; .004]	-.116	-.703	.486
Initial Total Serum Calcium Level*	-.158	[-.255; -.061]	-.454	-3.308	**.002**
Initial Glucose Level	-.003	[-.006; .001]	-.227	-1.410	.167
Initial Urea Level	-.001	[-.005; .003]	-.061	-.430	.669
Note: R^2_{adj} = 0.292 (N = 41, p =.002). CI = confidence interval for B					

Median values of creatinine (0.76 [0.67; 0.88], respectively 0.8 [0.69; 0.93], p =.026) and glomerular filtration rates calculated using the MDRD formula (78.6 [67.72; 87.77], respectively 73.6 [60.35; 85.95] , **p =.010**), as well as with the help of the CDK-EPI formula (86 [77; 100], respectively 85 [63.5; 97], **p =.018**) showed significantly different values between the first and last evaluation of the patients treated with medication , probably through the longer duration of the follow-up period. However, in the entire group of Study 3, regardless of the treatment received, the percentages by which the initial values of serum creatinine varied from those at the last assessment were positively correlated with the variability of total serum calcium (p =.030, r =.265) and hemoglobin (p =.001, r =.405).

In the group of Study 3, there were no significant differences in the dynamics of the lipid profile parameters between the first and last evaluation of the subjects, between the subgroups divided according to the treatment received, although the initial values of HDL-cholesterol were significantly lower in patients treated surgically compared with those of patients treated with medication (48.03 ± 14.56 vs 59.26 ± 16.56, **p =.009**). However, calculating the cardiovascular risk score of atherosclerotic events at 10 years, we observed an apparent maintenance of its median values (7.6 [2.42; 16.72] at the first evaluation vs. 6.3 [2.2; 16.92], p =.796) among surgically treated patients compared to the values of subjects with conservative treatment (7.7 [4.3; 20.5] vs. 10.1 [3.8; 17.6], **p =.022**).

The present study also includes a series of nine histologically proven cases of HPTP through parathyroid tumor of uncertain malignant significance (atypical parathyroid adenoma). From their comparison with the entire group of HPTP patients, significantly higher iPTH median values were noted (411.7 [258.85; 803.15] pg/ml) compared to the rest of the HPTP patients included in the study (198 [138.3; 491.75] pg/ml), **p =.027**.

Characteristics of atypical parathyroid adenoma			
	Atypical parathyroid adenoma	**1st Study Group**	***Sig.***
Age at diagnosis	59.87 [50.04; 64.1]	61.06 [50.55; 67.7]	NS
Maximum value of iPTH levels (pg/ml)	**411.7 [258.85; 803.15]**	**198 [138.3; 491.75]**	**.027**
Maximum value of total serum calcium (mg/dl)	12 [12; 13.75]	11.7 [11.2; 12.35]	.835
% Osteoporosis	5/8 (62.5%)	74/120 (61.7%)	NS
% Fragility fractures	2/9 (22.2 %)	21/149 (14.1%)	.620
% Chronic Kidney Disease	4/9 (44.4%)	26/149 (17.4%)	.067
% Nephrolithiasis	4/9 (44.44%)	52/149 (34.9%)	.722

We did not notice significant differences in the forms of presentation, prevalence and severity of metabolic, renal and cardiovascular complications, these being similar to the entire group of patients. Also, the impact on bone metabolism does not seem to have been significantly influenced, not noticing different prevalences of osteoporosis or fragility fractures. However, compared with patients who had isolated parathyroid adenoma histopathologically, the median peak total calcium values were significantly different: 12 [12; 13.75] mg/dl for atypical adenoma, respectively 11.7 [11.1; 12.25] mg/dl, **p =.013**. Noting these aspects mentioned above, at an average age of 58.65 ± 10.28 years, this etiological form of HPTP seems to be more rapidly evolving than the isolated adenoma, with patients seeking medical services probably for symptoms directly associated with hypercalcemia and not because of chronic complications , such as fragility fracture or nephrolithiasis. We note that from all nine HPTP cases with a histopathological result of a parathyroid tumor of uncertain malignant significance, in our study group no recurrences or persistent forms of the disease were noted during the follow-up period, which had a median of 0.7 years.

Conclusions

1. Patients with nephrolithiasis or nephrocalcinosis associate significantly higher values of calcemia and iPTH and more frequently present vitamin D deficiency.

2. Patients with moderate or severe hypercalcemia more frequently associate chronic kidney disease, the glomerular filtration rate assessed by both MDRD and CDK-EPI being significantly lower in patients with severe hypercalcemia. Increased creatinine is positively associated with iPTH value and the presence of fragility fracture. The iPTH value was noted as an independent, significant predictor of increased creatinine in patients with

primary hyperparathyroidism.

3. The prevalence of hyperuricemia in the study group increases concomitantly with the severity of primary hyperparathyroidism, and the iPTH value was found to be an independent predictor for serum uric acid.

4. Prevalences of type 2 diabetes mellitus increase with the severity of hypercalcemia, with patients with this condition also having significantly higher median calcemia.

5. Patients with ischemic heart disease associated significantly higher values of calcium and a higher prevalence of fragility fractures, delineating a clinical picture of a classic form of primary hyperparathyroidism.

6. The risk of atherosclerotic cardiovascular events assessed at 10 years was significantly higher in patients with moderate or severe hypercalcemia compared to normocalcemic hyperparathyroidism or patients with mild hypercalcemia. The difference between the predicted 10-year risk of cardiovascular events of the patients and the risk considered optimal is positively associated with the value of calcemia and the presence of osteoporosis. Densitometric osteoporosis, an indirect indicator of the severity of primary hyperparathyroidism, was an independent predictive factor for the prediction of cardiovascular risk.

7. The prevalence of fragility fractures was insignificantly different between patients with normocalcemic hyperparathyroidism and patients with hypercalcemia, which highlights the possibility of complications of primary hyperparathyroidism even in the absence of hypercalcemia. These results argue for the determination of iPTH together with the value of calcium as screening tests.

8. Fragility fractures were more prevalent among patients with moderate or severe hypercalcemia compared to the group of patients with moderate hypercalcemia, with the prevalence of densitometric osteoporosis remaining similar between these groups. This aspect highlights an important limitation of the exclusive determination of bone mineral density in the assessment of fracture risk in patients with primary hyperparathyroidism.

9. Patients who sustained a fragility fracture had an older median age and more prevalent chronic kidney disease. Also, the TBS value was significantly lower in this group. Each of these variables is recognized as a fracture risk factor independent of bone mineral density.

10. The thickness of the cortex of the proximal femur was negatively associated with the value of iPTH and ionic calcium, an aspect that highlights the subcortical osteoresorption

determined by the chronic exposure of the bone to PTH

11. Impaired renal function, a cardinal complication of primary hyperparathyroidism, has been associated with poorer bone resistance to bending forces. The cumulative effect of primary hyperparathyroidism and renal injury on the quantity, quality, and intrinsic distribution of bone mass is a very interesting area for further research.

12. Patients with primary hyperparathyroidism had significantly lower values of both bone mineral density in all regions of interest and TBS compared to the control group. These results highlight a holistic both quantitative and qualitative effect of primary hyperparathyroidism on bone. For patients with degraded bone microarchitecture, active parathyroid disease and bone mineral density were independent predictors of trabecular score.

13. FRAX-TBS adjustment significantly increased the 10-year estimate of major osteoporotic fracture in the group of patients with primary hyperparathyroidism compared to FRAX calculated with bone mineral density, resulting in a significant difference in the 10-year estimate of major fracture risk between the group with primary hyperparathyroidism and the control group. HPTP was identified as an independent predictor for the different trajectory of TBS-adjusted FRAX between the two study groups. Although a subtle influence, the manner in which primary hyperparathyroidism alters FRAX dynamics by TBS is significant, perhaps a small step forward in refining the prediction of 10-year fracture risk for these patients.

14. Patients with primary hyperparathyroidism had a significantly lower cortical bone thickness and structural stiffness (CSMI) of the femur compared to the control group, suggesting a structural reorganization of the bone mass associated with this condition.

15. During the follow-up period with a median of 2 years of medically treated patients, no significant increase of calcemia or iPTH was noted, which suggests either the slowly evolving character of this condition, or the good efficiency of medical treatment.

16. Curative parathyroidectomy was followed by a significant decrease in uric acid values, with preoperative calcemia variation being a significant predictor for uricemia variation. These results are of particular importance in highlighting the reversibility of hyperuricemia, highlighting one of the less studied benefits of parathyroidectomy. Considering these results and the relationship between uric acid and PTH identified in the first part of this thesis, the recommendation to determine serum uric acid in patients with primary hyperparathyroidism seems reasonable. In our study group, there were no significant benefits of parathyroidectomy compared to medical treatment on lipid or glycemic metabolism.

17. Surgical cure of primary hyperparathyroidism was followed by a significant decrease in magnesium. Preoperative calcemia was a significant predictor of serum magnesium

variation. This aspect seems surprising considering the negative association between magnesium and creatinine, serum uric acid, dyslipidemia and ischemic heart disease highlighted in Study 1. We recommend the determination of magnesium in patients proposed for parathyroidectomy and the supplementation of magnesium deficiency to prevent a postoperative sympathetic hypomagnesemia.

18. Patients with parathyroid tumor of uncertain malignant significance showed higher values of calcemia and iPTH, but the prevalence and severity of complications did not have statistically significant differences. During the post-operative follow-up period, there were no disease recurrences in these patients. However, the average follow-up period does not eliminate the risk of long-term recurrence and the need to monitor these patients.

Strengths, Limitations, and Future Research Directions

Strengths

• holistic approach to the forms of presentation and complications associated with primary hyperparathyroidism, paying particular attention to metabolic parameters and cardiovascular risk;

• highlights the relationships between the severity of primary hyperparathyroidism and metabolic risk factors, facilitating their integration in the prediction of cardiovascular atherosclerotic events;

• the follow-up over an average period of a native population with primary hyperparathyroidism with the evaluation of the consequences of curative parathyroidectomy by comparison with pharmacological treatment, in a native population;

• very well-matched age- and sex-matched control group for postmenopausal women with primary hyperparathyroidism, comparative analysis between the two subgroups of the Study 2.2 group

• evaluating the relationship between HPPT-TBS-FRAX in this way, thus identifying how the trabecular score changes the fracture risk of patients with primary hyperparathyroidism by comparison with the control group

• the first study that includes Romanian patients and highlights the different dynamics of uric acid and magnesium depending on the therapeutic approach, emphasizing a less studied benefit of parathyroidectomy with potential clinical consequences;

• characterization at diagnosis and follow-up of the series of 9 cases of parathyroid tumor with uncertain malignant significance, which provides results of both clinical and research interest.

• the obtained results suggest recommendations with direct clinical impact and interdisciplinary character for an optimal management of patients with primary hyperparathyroidism.

Limits

• heterogeneous population and relatively short follow-up period;

• overlapping of metabolic and cardiovascular risk factors - the mutual influence of these conditions makes it difficult to rigorously analyze the contribution of primary hyperparathyroidism in cardiovascular risk;

• the cardiovascular risk calculation tool was limited by the extreme values of age and lipid profile parameters, narrowing the analyzed group;

• data obtained retrospectively or cross-sectionally for Studies 1 and 2;

• the difficulty of standardizing the treatments of conditions associated with the metabolic syndrome, as well as the actual adherence vs. that reported by patients;

• the lack of usual data useful in the assessment of cardiovascular risk,

• lack of clear evidence of morphometric vertebral fractures,

• the small number of patients with normocalcemic primary hyperparathyroidism;

• the control group comes from a tertiary osteoporosis center, suggesting the presence of other fracture risk factors and thus reducing the representativeness of the group;

• insufficient or incomplete data on medication use (allopurinol, diuretic agents, antiresorptive medication, use of vitamin D supplements or food supplements with unproven or non-standardized biological response);

• lack of availability of bone turnover markers in the follow-up and osteodensitometric data in the group of cured patients;

Future research directions

• Recruiting more patients with normocalcemic primary hyperparathyroidism for the rigorous characterization of the possible complications associated with this condition compared to the hypercalcemic forms of the disease, but also with a control group.

• Assessment of insulin resistance by HOMA or OGTT index in patients with primary hyperparathyroidism without diagnosis confirmed by type 2 diabetes and the association of

cardiovascular risk prediction with indices of myocardial remodeling and cardiovascular stiffness.

• Assessment of markers of bone remodeling and indicators of bone geometry and their relationship to primary hyperparathyroidism and fracture risk. Long-term follow-up of patients to assess the actual 10-year incidence of fragility fractures and comparison with initial FRAX prediction.

• Larger prospective studies - the comparative evolution of metabolic parameters depending on the therapeutic approach of the patients; active re-evaluation of operated patients (bone turnover markers, TBS variation, integration of 25(OH)-vitamin D in the parathormone-uric acid feed-back loop, as well as a better understanding of the relationship between parathormone, calcium and magnesium, in order to include AUS and magnesium dosing in therapeutic decisions.

• Long-term evaluation of patients with a histological diagnosis of atypical parathyroid adenoma to highlight the risk of recurrence and the need for follow-up in clinical practice.

Selective bibliography

Arnett, Donna K et al. "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." *Circulation* vol. 140,11 (2019): e596-e646. doi:10.1161/CIR.0000000000000678

Bilezikian, John P et al. "Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop." *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* vol. 37,11 (2022): 2293-2314. doi:10.1002/jbmr.4677

Bollerslev, Jens et al. "Effect of surgery on cardiovascular risk factors in mild primary hyperparathyroidism." *The Journal of clinical endocrinology and metabolism* vol. 94,7 (2009): 2255-61. doi:10.1210/jc.2008-2742

Camacho, Pauline M et al. "AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS-2020 UPDATE." *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* vol. 26,Suppl 1 (2020): 1-46. doi:10.4158/GL-2020-0524SUPPL

Darbà, Josep, and Alicia Marsà. "Epidemiology and management of parathyroid gland disorders in Spain over 15 years: A retrospective multicentre analysis." *PloS one* vol. 15,3 e0230130. 10 Mar. 2020, doi:10.1371/journal.pone.0230130

Eufrazino, Cátia et al. "Epidemiology of Primary Hyperparathyroidism and its Non-classical Manifestations in the City of Recife, Brazil." *Clinical medicine insights. Endocrinology*

and diabetes vol. 6 69-74. 4 Dec. 2013, doi:10.4137/CMED.S13147
Griebeler, Marcio L et al. "Secular trends in the incidence of primary hyperparathyroidism over five decades (1965-2010)." *Bone* vol. 73 (2015): 1-7. doi:10.1016/j.bone.2014.12.003
Heath, H 3rd et al. "Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community." *The New England journal of medicine* vol. 302,4 (1980): 189-93. doi:10.1056/NEJM198001243020402
Med-Imaps, T. i. *Advanced DXA Using TBS iNsight A New Bone Structure Assessment Technique Enhances Identification of Fracture Risk*. Preluat de pe https://www.vertec.co.uk/content/uploaded/WP1-HOLOGIC-eng.pdf
Ohe, M N et al. "Changes in clinical and laboratory findings at the time of diagnosis of primary hyperparathyroidism in a University Hospital in São Paulo from 1985 to 2002." *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas* vol. 38,9 (2005): 1383-7. doi:10.1590/s0100-879x2005000900013
Pludowski, Pawel et al. "Clinical Practice in the Prevention, Diagnosis and Treatment of Vitamin D Deficiency: A Central and Eastern European Expert Consensus Statement." *Nutrients* vol. 14,7 1483. 2 Apr. 2022, doi:10.3390/nu14071483
Walsh, Jennifer et al. "SOCIETY FOR ENDOCRINOLOGY ENDOCRINE EMERGENCY GUIDANCE: Emergency management of acute hypercalcaemia in adult patients." *Endocrine connections* vol. 5,5 (2016): G9-G11. doi:10.1530/EC-16-0055
Yadav, Sanjay Kumar et al. "Primary hyperparathyroidism in developing world: a systematic review on the changing clinical profile of the disease." *Archives of endocrinology and metabolism* vol. 64,2 (2020): 105-110. doi:10.20945/2359-3997000000211

List of published scientific papers

Oprea TE, Barbu CG, Martin SC, Sarbu AE, Duta SG, Nistor IM, Fica S. "Degraded Bone Microarchitecture in Women with PHPT-Significant Predictor of Fracture Probability." *Clinical medicine insights. Endocrinology and diabetes* vol. 16 11795514221145840. 20 Jan. 2023, doi:10.1177/11795514221145840

Oprea TE, Barbu CG, Martin SC, Sarbu AE, Calapod RI, Nistor IM, Fica SV. "Uric Acid in Primary Hyperparathyroidism: Assessment of Surgical versus Conservative Approach." *Chirurgia (Bucharest, Romania : 1990)* vol. 118,2 (2023): 146-152. doi:10.21614/chirurgia.2821

Oral presentations

- Carmen Gabriela Barbu, Theodor Eugen Oprea, Amalia Arhire, Alice Albu, Sorina Martin, Anca Sîrbu, Simona Fica, DO HIP AXIS LENGTH AND NECK SHAFT ANGLE MEASUREMENT LEAD TO A BETTER HIP FRACTURE RISK EVALUATION IN CLINICAL PRACTICE?, Congresul Naţional de Endocrinologie, ediţia XXVII, 19-22 Iunie 2019, Bucureşti, România.

- Theodor Eugen Oprea, Carmen Barbu, Anca Sîrbu, Sorina Martin, Alice Albu, Simona Fica. PTH – JUCĂTOR IMPORTANT ÎN ECHILIBRUL METABOLIC, Forumul Tinerilor Endocrinologi, 11-12 Decembrie 2020.
- Theodor Eugen Oprea, Carmen Barbu, Anca Sîrbu, Sorina Martin, Calapod Ruxandra Ioana, Nistor Irina Manuela, Simona Fica. Uric Acid in PHPT – Assesment of medical vs surgical Approach, Forumul Tinerilor Endocrinologi, 8-10 Decembrie 2022, Bucureşti.

Posters

- Theodor Eugen Oprea, Sorina Martin, Anca Elena Sîrbu, Alice Albu, Carmen Barbu, THE IMPORTANCE OF DISTAL FOREARM DXA IN PHPT: A RETROSPECTIVE STUDY OF 33 PATIENTS, P275,45th European Calcified Tissue Society Congress, 26-29 Mai 2018, Valencia, Spania. P275
- Theodor Eugen Oprea, Daniela Frunza, Amalia Arhire, Carmen Gabriela Barbu, ATYPICAL PARATHYROID ADENOMA, Congresul European de Endocrinologie, Editia XX, 19-22 Mai 2018, Barcelona, Spania. Edocrine Abstracts EP32
- Theodor Eugen Oprea, Carmen Gabriela Barbu, Simona Fica, ATYPICAL FEMORAL FRACTURE: THE PRICE FOR LONG TERM BIPHOSPHONATES ADHERENCE? P1131, WCO-IOF-ESCEO 4-7 Aprilie 2019, Paris, Franța.
- Carmen Gabriela Barbu, Anca Sîrbu, Alice Albu, Sorina Martin, Suzana Florea, Mădălina Cristina Pavel, Theodor Eugen Oprea, Hasan Cheaito, Amalia Arhire, Simona Fica, INCREASED BMI IN OSTEOPOROTIC
- PATIENTS, ENOUGH VITAMIN D STORED? OC.1.30, Congresul Național de Endocrinologie, Editia XXIV, 22-25 Iunie 2016, Brașov, România.
- Carmen Gabriela Barbu, Anca Sîrbu, Alice Albu, Sorina Martin, Suzana Florea, Mădălina Cristina Pavel,Theodor Eugen Oprea, Hasan Cheaito, Amalia Arhire, Simona Fica, CORRELATION BETWEEN SEXSTEROIDS AND RISK OF FALLS IN MEN WITH OSTEOPOROSIS, Congresul Național de Endocrinologie, Editia XXIV, 22-25 Iunie 2016, Brașov, România.
- Theodor Eugen Oprea, Gabriela Carmen Barbu, Amalia Arhire, Anca Sîrbu, Sorina Martin, Alice Albu, Simona Fica, METABOLIC OUTCOME OF SURGERY IN PHPT PATIENTS IN CLINICAL PRACTICE, Congresul Național de Endocrinologie, Editia XXVII, 19-22 Iunie 2019, București, România.