

Hyperparathyroid pathology treated in three Costa Rican hospitals

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Abstract

Aim: To determine the frequency and characteristics of patients who received treatment for hyperparathyroid pathologies in the Mexico, San Juan de Dios and “Dr. Rafael Ángel Calderón Guardia” hospitals in a three-year period.

Methods: Analysis of records of high serum intact parathormone, medical records and bibliographical review. Descriptive study, whose sample was patients treated between January 2007 and December 2009. Determination of frequencies and proportions for the qualitative variables was made by means of the Chi-Square test. The quantitative variables were determined by the estimate of Student’s t-test.

Results: Out of 199 patients studied, 9 were excluded. Women prevailed (68.9 %), the most frequent age group was 60 years and over (33.1 %). Primary hyperparathyroidism was the most frequent disease (n=46, 24.2 %; 73.9 % women, 69.5% older than 50), then hypovitaminosis D and chronic renal failure. The majority lived in San José (59.4 %) and was assisted at the Mexico Hospital (65.8%). There is no clear concept among some doctors, thus normocalcemic hyperparathyroidism is underestimated. The majority do not request determinations of vitamin D in these patients.

Discussion: Patients with raised PTH by diverse reasons are exposed to many diseases that can compromise their survival and quality of life. Hypovitaminosis D would probably be more frequent if measurement was requested more often. The request for calciphediol must be emphasized in any parathyroid disease.

Keywords: Hyperparathyroidism, PTH, parathormone, vitamin D.

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México, San Juan de Dios and “Dr. R.A. Calderón Guardia” Hospitals, CCSS.

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Abbreviations: CCSS, Caja Costarricense de Seguro Social; USA, United States of America; HCG, “Dr. Rafael Ángel Calderón Guardia” Hospital; FHH, Familiar Hypocalciuric Hypercalcaemia; HM, México Hospital; HPT, hyperparathyroidism; HPTp, Primary Hyperparathyroidism; HSJD, San Juan de Dios Hospital; CKD, Chronic Kidney Disease; MEN-I, Multiple Endocrine Neoplasia Type I; PAHO, Pan American Health Organization; PTH, parathormone; PTHi, intact parathormone.

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Intact PTH (PTHi) serum measurement has increased through the years, mainly due to research and management of osteoporosis in public health. Thus, it is important clearing up if elevated PTHi reports obey to cases of primary hyperparathyroidism or of other causes, which is essential for the correct diagnosis and management. A way to clear up the diagnosis is through the serum measurement of calcifediol (an inactive metabolite of vitamin D, also known as 25OHVD and as cholecalciferol), used only recently in two hospitals in Costa Rica’s Social Security.

Hypercalcaemia is defined as the abnormally high concentration of calcium in the bloodstream. There are three known causal mechanisms: increased in bone resorption, increased gastrointestinal absorption and decreased renal excretion.^{1,2} The main defense of the organism against hypercalcaemia is decreasing the secretion of PTH. This, will decrease the bone resorption and the kidney production of the active metabolite of vitamin D (VD), with the consequent decrease of intestinal absorption and increase urinary loss of calcium.² To address schematically hypercalcaemic disorders, a practical way is to establish the dependency and independency to PTH (table 1).³

PTH and VD are the main regulatory hormones of calcium homeostasis, and both influence in each other synthesis. The first stimulate the kidney enzyme 1α -hydroxylase, and the second has a negative feedback over PTH.⁴

PTH is a lineal peptide of 84 amino acids, produced in the parathyroid gland. Is the regulatory hormone of calcium, phosphate and VD concentrations in serum and its classical biologic activities are mediated by PTH1R receptors in different tissues. The amino terminal region of the molecule possessed the sequence needed to activate this receptor. The metabolism is complex: it starts in the parathyroid secretory granules and ends in diverse tissues, primarily the liver and kidneys; a series of "PTH peptides" are presented in serum, in normal conditions and in diverse states if hyperparathyroidism.⁵

The current availability of second generation bioassays allows a negative feedback, produced by the ionized calcium (iCa) and not by the total calcium; detected by calcium sensing receptors in the extracellular space. PTH is the major regulator of calcaemia, especially when changing from hypocalcaemia to normocalcaemia; however, some in vitro studies had proposed that this is not the only mechanism to maintain the serum calcium.^{7,8}

The activity and the control of PTH is regulated through an intricate system, in which serum ionized calcium (main parathyroid calcium regulator), phosphor, calcitriol and derivatives participate with other less studied factors, acting on the parathyroid gland and influencing in its synthesis and secretion (aluminium, estrogen, magnesium, corticosteroids, cytokines and fibroblastic growth factor).²³ Several receptors, such as the calcium, the vitamin D and the fibroblastic growth factor receptors, mediate this system. There are other indirect actions on calcium and vitamin D receptors, with correlation dependence between calcium, calcitriol and phosphor. The serum ionized calcium in the parathyroid gland produces sigmoidal responses in PTH secretion: small calcium changes provoke great variations in PTH. An example can be seen when analyzing the independent variables.³ It is considered that in vivo, PTH different regulatory factors possessed interrelations that difficult the interpretation of each role separately.⁹

Normal levels of PTH and calcium in serum, does not necessarily means healthy parathyroid glands, in autopsy reports large parathyroid glands in patients were found without the presence of hyperparathyroidism.¹⁰ There are also reports of parathyroid carcinomas with normal serum levels of calcium. This cancer is an uncommon cause of hyperparathyroidism, and presents more frequently in severe hypercalcaemia and high levels of PTHi.¹¹

Elevated serum PTH with normal calcaemia is an independent predictor of long term survival prognosis in certain population groups. Calcium and vitamin D (is the

main cause of PTH elevation), are not significant long term survival prognosis indicators, especially in the elderly.¹²

Hyperparathyroidism is the increase secretion of PTH with or without clinical manifestations. The following are causes of elevated PTH, that can be related to different levels of calcaemia: primary hyperparathyroidism (most common), hypovitaminosis D, hypomagnesemia, milk-alkali syndrome, granulomatose diseases or neoplasias, prolonged immobilization, hyperthyroidism, adrenal insufficiency, familial hypocalciuric hypercalcaemia, kidney disease (with creatinine clearance below 50cc/min), liver disease, hypercalciuria, malabsorption syndromes, medications (litium, anticonvulsivants, loop diuretics, esteroids, biphosphonates), Paget's disease and other bone pathologies.¹³

This research provides a novelty to Costa Rica's medical bibliography, as the first record of individuals with hyperparathyroid pathologies, and the relevance that possessed the serum measurement of vitamin D to define the diagnosis, and in other pathologies where the measurement of this hormone is essential.

Materials and Methodology

This is a descriptive study. The blood samples were taken from patients with age ≥ 18 years old, attended in Mexico, San Juan de Dios and "Dr. Rafael Ángel Calderón Guardia" Hospitals in a three year period (January 2007 to December 2009).

The record of different hyperparathyroidism in Costa Rica's hospitals, is based in the file: "Clasificación estadística interna de enfermedades y problemas relacionados con la salud" (CIE-10) (Internal Statistic Classification of Diseases and Health-related problems), a work from PAHO (Pan American Health Organization).¹⁴

The classification above is used to record only hospitalized patients, thus it was necessary to appeal to another strategy with the purpose of finding the samples collected from outpatients. From the database of Hormone and Clinical laboratories of Mexico and "Dr. Rafael Ángel Calderón Guardia" Hospitals, a list of patients with elevated serum measurement of PTHi was selected. From the database of Hormone laboratory of San Juan de Dios Hospital, the list of patients with calcifediol serum determinations were from samples from the three hospitals mention above. The next step was to analyze the clinical files. The research forms were executed in the Excel software. A chronogram was elaborated from visits to hospitals, in pursuit of data from different hospital sections: File, Laboratory (Hormone and Clinical), and Biostatistics and from Outpatient Departments.

Table 1. Causes of Hypercalcaemia

Parathyroid-dependent Hypercalcaemia
Primary Hyperparathyroidism
Terciary hyperparathyroidism
Familiar Hypocalciuric Hypercalcaemia
Litium associated Hypercalcaemia
Anti-Calcium Sensing Receptors Antibodies
Parathyroid-indepent Hypercalcaemia
Neoplasias: prPTH dependent, other humoral syndromes, Focal osteolysis disease (including metastasis)
prPTH excess(non neoplastic)
Vitamin D activity excess: Excessive ingestion of VD or analogues, topic vitamin D analogues, granulomatose disease, Williams' syndrome.
Tyrotoxicosis
Adrenal Insufficiency
Kidney failure: Acute renal failure, chronic renal failure with aplasic bone disease
Immobilization
Jansen's Disease
Medications
Source: table 27-2 adaptation of the literature quotation number 3.

From all variables, a distribution according to absolute and relative frequencies was made. A stratified analysis according to genre, age groups, and pathologies associated with hyperparathyroidism, home residence and hospital assistance was made. All analysis were developed through Epiinfo 3.4.1 (CDC-2007) statistical software, and was defined as statistically significant, a critical point of 0.05 ($\alpha \leq 0.05$).

This research was approved by the Medical Directors of the three hospitals, after the analysis the local committees of bioethics and research (CLOBI), endorsed from an ethical and methodological point of view, recommended to go through this research.

Results

A total of 199 patients were analyzed, in which 9 were excluded (they were incomplete). From 190 cases, most of them were females (68.9%), and the most common age group found were of ≥ 60 years old (33.1%), followed by the age group between 50 and 59 years old (28.9%; table 2).

Of the pathologies found with high PTHi, the primary hyperparathyroidism was the most common (24.2%; 73.9% women; 69.5% ≥ 50 years old), followed by hypovitaminosis D (21.6%; 87.5% women; 72.5% ≥ 50 years old), chronic kidney disease (20.5%; 66.6% men; 30.7% between ages 40 to 49 years old) and osteoporosis with treatment with alendronate (13.1%; 92% women; 76% ≥ 50 years old; table 2).

In relation to the place of residence, the majority lives in the province of San José (59.4%), followed by Alajuela (17.3%). The majority of cases with primary hyperparathyroidism were also from San José (16.8%; table 3). In relation to the attending hospital of individuals with high PTHi, the majority were found in Mexico Hospital (65.8%; table 4).

In relation to vitamin D measurement, physicians don't give enough relevance to asked for the test in different pathologies in which are required. For example of the above, the following situations have been found: a VD measurement in the majority of hyperparathyroid patients was not requested; some cases in where normocalcaemic hyperparathyroidism was diagnosed (essential aspect for diagnosis) the measure of VD was not found. The request of calcifediol were found only in 14 patients with primary hyperparathyroidism, with an average of 70.2nmol/L (limit 34.5 to 139nmol/L), in which nine (71.4%) were within limits of insufficiency and 2.17% were within limits of deficiency. Three patients diagnosed with PTH, didn't have a VD measurement.

Discussion

Individuals with elevated PTHi, as a consequences of diverse pathologies representing primary or secondary hyperparathyroidisms, are exposed to an elevated risk of cardiovascular morbidity and mortality, and are an example of many pathologies that compromises the patient's survival and quality of life.¹⁵⁻¹⁷

The majority of studies found in the international medical library about carriers of diverse pathologies related to elevated PTHi, there are works dedicated to each entity separately and the reports of women and elderly were the most common variables. There were no reports on the frequency of different hyperparathyroid pathologies analyzed jointly. Multiple references about the incidence and prevalence of each pathology are mentioned, but a comparative study between findings cannot be done.

The most common entity found in this study is primary hyperparathyroidism, followed by hypovitaminosis D, although this last one could have been more frequent if its measurement was done more frequently.

This research found that the most common pathologies (primary hyperparathyroidism, hypovitaminosis D and osteoporosis) are higher in frequency in women and elderly, while chronic kidney disease was more frequent in men and younger individuals.

The majority of hyperparathyroid individuals were from Mexico Hospital. If San Juan de Dios and "Dr. Rafael Ángel

Table 2. Patients with elevated PTHi, according to diagnosis, genre and age group (in years). México, San Juan de Dios and "Dr. Calderón Guardia" hospitals. January 2007 to December 2009. Absolute numbers

Diagnosis	Fem	Masc	10-19	20-29	30-39	40-49	50-59	≥ 60
Carcinomas*	7	1	0	1	1	0	1	5
Normocalcaemic Hyperparathyroidism	7	7	0	0	1	6	5	2
Primary Hyperparathyroidism	34	12	0	3	3	8	14	18
Hyperthyroidism	4	0	0	1	1	0	1	1
Hypoparathyroidism	1	1	0	1	0	0	0	1
Hypovitaminosis D (HypoVD)	35	5	1	2	5	3	13	16
HypoVD + chronic renal failure	1	0	0	0	0	0	0	1
Chronic renal failure	12	26	2	2	3	12	11	8
Multiple endocrine neoplasia - 1	3	2	0	0	4	0	1	0
Osteoporosis with treatment**	23	2	0	0	1	5	8	11
Others***	3	3	0	1	1	3	1	0
Pseudohypoparathyroidism	1	0	0	0	1	0	0	0
Total	131	59	3	11	21	37	55	63

Source: Files, Biostatistical, clinical and hormone laboratory sections. México, San Juan de Dios and "Dr. RA Calderón Guardia" Hospitals. * Including: leukemia, neuroendocrine, uterine, breast and indetermined metastatic. **All individuals treated with alendronate, calcium and VD. *** Including: Wilson's disease, hepatic cirrhosis, osteitis on study, S protein deficiency, multiple sclerosis and Klinefelter's syndrome.

Calderón Guardia" hospitals, could have an easiness to locate these pathologies, and all departments where these patients were evaluated (for example, Rheumatology, Urology, Internal Medicine, Endocrinology, Metabolic Diseases), had a database of the outpatients, the results would be different.

The record of diverse problems related to the parathyroid glands is scarce in the studied hospitals. Many physicians don't follow the requirements needed to approach these pathologies.

It draws attention, when discussing with physicians and analyzing the clinical files, that occasionally the concept is not clear, and the diagnosis of these pathologies are disdain (for examples normocalcaemic hyperparathyroidism).

The measurement of calcifediol in Costa Rica's social security hospitals, to the closure of the current study, is made only in one laboratory, located in San Juan de Dios hospital. The main cause is credited as it is an onerous reactive, but through the research course we found that many doctors don't give importance to the necessity of requesting it, for the diagnosis of different pathologies. The report of normal levels of hormone allows clearing up and guiding a series of pathologies in the clinical practice. The early identification of individuals with hypovitaminosis D, associated with various parathyroid and non parathyroid pathologies, is essential. It can mean favorable changes in the quality of life and the prognosis of different comorbidities in a large population group. Diagnosis of individuals with normocalcaemic hyperparathyroidism, without VD

determination, translates into an erroneous concept about this pathology. The request of levels of calcifediol should be emphasized when approaching any parathyroid pathology.

Study Limitations

The majority of individuals with hyperparathyroidism are overruled in these three hospital's outpatient departments. There is not enough information in the medical record offices, to structure a more complete research.

Another limitation parts from the difficulty to search for hyperparathyroid patients in the CCSS, associated with problems with its classification and the fact that medical record offices take into account hospitalized patients and not the ones in the outpatient departments. The CIE-10 section for hyperparathyroid pathologies is ambiguous; diverse cases of secondary hyperparathyroidism could be classify in item E21.5, and because the workers of Medical record offices are not medical professionals, they don't have clear and aren't indicate where to write down the diagnosis. Thus, the analysis of the provided lists was made from the hormone laboratory from the hospitals mentioned above.

In San Juan de Dios hospital laboratory, the only way to analyzed the PTHi records were to print them all, implying a huge expense of stationery, which the hospital management wouldn't authorized. Also, of the departments that treat hyperparathyroid patients, only the Endocrinology

Table 3. Patients with elevated PTHi, according to province of residence. México, San Juan de Dios and “Dr. Calderón Guardia” Hospitals. January 2007 to December 2009. Absolute numbers

Diagnósticos	San José	Alajuela	Cartago	Heredia	Guanacaste	Puntarenas
Carcinomas	4	2	0	2	0	0
Normocalcaemic Hyperparathyroidism	10	1	0	3	0	0
Primary hyperparathyroidism	32	9	0	5	0	0
Hyperphthyroidism	1	1	0	1	0	1
Hypoparathyroidism	1	0	0	1	0	0
Hypovitaminosis D	27	5	0	5	0	1
Hypovitaminosis D + Chronic renal failure		1	0	0	0	0 0
Chronic renal failure	12	9	1	5	9	2
NEM-1	1	1	1	1	0	1
Osteoporosis with treatment	19	2	0	3	1	0
Others	3	2	0	1	0	0
Pseudohypoparathyroidism	0	1	0	0	0	0
Total	113	33	2	27	10	5

Source: Files, Biostatistical, clinical and hormone laboratory sections. México, San Juan de Dios and “Dr. RA Calderón Guardia” Hospitals. Patients living in Limón were not found.

department possessed a database of the movements of patients in the outpatient department. The above influence in the compiled samples, for it is expected, that the cases of hyperparathyroidism were much more than registered. The patients found in this hospital were only those found in the clinical files of the outpatient departments of Endocrinology for a three year period.

“Dr. Rafael Ángel Calderón Guardia” hospital’s hormone laboratory doesn’t possess a database of different hormones reports. A few months earlier to this research, the measure of PTHi in this hospital was only starting, thus, a printed list of this hormone measurement could be obtained.

San Juan de Dios and “Dr. Rafael Ángel Calderón Guardia” hospitals should have a database similar to the one in Mexico hospital that would facilitate the search of information directed to these pathologies.

The samples were compiled from the outpatient departments of endocrinology, internal medicine, urology and metabolic diseases of these three hospitals. Enough representation of patients with this diagnosis was not made, and is not a reflection on the incidence or prevalence of this pathology in a national level.

The compilation time period of samples was short, with hardships in the capture of more patients, due to the underrecords of the biostatistical and files offices, file location and clearing up of the diagnosis by some physicians.

Table 4. Patients with elevated PTHi, according to hospital. México, San Juan de Dios and “Dr. Calderón Guardia” hospitals. January 2007 to December 2009. Absolute numbers

Diagnósticos	HM	HSJD	HCG
Carcinomas	6	2	0
Normocalcaemic Hyperparathyroidism	6	2	6
Primary Hyperparathyroidism	31	10	5
Hyperthyroidism	3	0	1
Hypoparathyroidism	1	0	1
Hypovitaminosis D	20	15	5
Hypovitaminosis D + Chronic renal failure	0	1	0
Chronic renal failure	34	1	3
NEM-1	3	1	1
Osteoporosis with treatment	15	2	8
Others	5	1	0
Pseudohypoparathyroidism	1	0	0
Total	125	35	30

Source: Files, Biostatistical, clinical and hormone laboratory sections. México (HM), San Juan de Dios (HSJD) and “Dr. RA Calderón Guardia” (HCG).

The relevance of this work in Costa Rica’s medical practice is based on the first national level study that registered the different causes of hyperparathyroidism, also the variables of the record and diagnosis approach, essential aspects to take into consideration to plan better strategies for management and treatment. During the research process, a

series of institutional weaknesses obstruct the search of a greater number of samples. It is recommended that more related researches of the pathologies associated with hyperparathyroidism should be made, principally due to the increasing reports on a national level, about deleterious effects, primarily on bone and cardiovascular morbidity and mortality that as an independent variable, means that individuals present high levels of serum PTHi.

Conflict of interest: The author declares no conflict of interest.

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