Revista Información Científica

ISSN 1028-9933
Universidad de Ciencias Médicas de Guantánamo

June 2025 Volume 104 e4948
DOI:https://doi.org/10.5281/zenodo.14850662

CASE REPORT

Severe renal and skeletal presentation of primary hyperparathyroidism in a young adult: a report of two cases

Presentación renal y esquelética grave del hiperparatiroidismo primario en adulto joven: a propósito de dos casos

Apresentação renal e esquelética grave de hiperparatireoidismo primário em um adulto jovem: relato de dois casos

Adalberto Luis Infante Amorós[I], Sergio Enrique Zayas Puig[I]*

[I]Universidad de Ciencias Médicas de La Habana. Hospital Clínico Quirúrgico "Hermanos Ameijeiras". La Habana, Cuba.

***Corresponding author:** sergiozayaspuig@gmail.com

Received: 09-02-2025 **Accepted:** 09-06-2025 **Published:** 19-06-2025

ABSTRACT

Primary hyperparathyroidism is a rare endocrine disease characterized by excessive secretion of parathyroid hormone, which generally produces hypercalcemia and a range of variable clinical manifestations. A study was conducted to describe the severe renal and skeletal manifestations of primary hyperparathyroidism found in two cases of young adults seen in the Endocrinology Department of the Hospital Clínico Quirúrgico "Hermanos Ameijeiras", Havana, Cuba. The first case: a 22-year-old female patient with generalized osteoporosis, a salt-and-pepper lytic pattern in the frontoparietal region of the skull, subperiosteal resorption at the distal ends of the tibias and phalanges, brown tumors at the level of the right scapula and left glenoid and metacarpals, and a pathological fracture of the right femur. The second: a 22-year-old male patient with a deformity at the right hip, a shortened and externally rotated right lower limb, with functional inability to stand and walk, and multiple brown tumors in the bony pelvis. In both cases, surgical treatment was performed, and a pathological diagnosis of parathyroid adenoma was confirmed, with favorable outcomes. Severe renal and skeletal presentations of primary hyperparathyroidism are rare in young adults. Timely diagnosis and treatment improve the quality of life of those affected and prevent potentially fatal complications.

Keywords: primary hyperparathyroidism; hypercalcemia; osteitis fibrosa cystica; nephrolithiasis; pathological fractures

RESUMEN

El hiperparatiroidismo primario es una enfermedad endocrina poco frecuente, caracterizada por una secreción excesiva de hormona paratiroidea que produce generalmente hipercalcemia y un conjunto de manifestaciones clínicas variables. Se realizó una investigación para describir las manifestaciones renales y esqueléticas graves del hiperparatiroidismo primario encontradas en dos casos de adultos jóvenes atendidos en el servicio de Endocrinología del Hospital Clínico Quirúrgico "Hermanos Ameijeiras", La Habana, Cuba. El primer caso: paciente femenina de 22 años con osteoporosis generalizada, patrón lítico en sal y pimienta en la región frontoparietal del cráneo, resorción subperióstica en los extremos distales de las tibias y falanges, tumores pardos a nivel de escápula derecha y glenoide izquierda y metacarpos, y fractura patológica del fémur derecho. El segundo: paciente masculino de 22 años con deformidad a nivel de la cadera derecha, miembro inferior derecho acortado y en rotación externa, con impotencia funcional a la bipedestación y deambulación, con múltiples tumores pardos en pelvis ósea. En ambos casos se realizó tratamiento quirúrgico y se confirmó diagnóstico anatomopatológico de adenoma paratiroideo, con evolución favorable. Las formas de presentación renal y esquelética grave del hiperparatiroidismo primario son poco frecuentes en adultos jóvenes. Su diagnóstico y tratamiento oportuno mejora la calidad de vida de quienes lo padecen y evita la aparición de complicaciones potencialmente fatales.

Palabras clave: hiperparatiroidismo primario; hipercalcemia; osteítis fibrosa quística; nefrolitiasis; fracturas patológicas

RESUMO

O hiperparatireoidismo primário é uma doença endócrina rara, caracterizada pela secreção excessiva de hormônio da paratireoide, que geralmente produz hipercalcemia e uma gama de manifestações clínicas variáveis. Um estudo foi realizado para descrever as manifestações renais e esqueléticas graves do hiperparatireoidismo primário encontradas em dois casos de adultos jovens atendidos no Departamento de Endocrinologia do Hospital Clínico Quirúrgico "Hermanos Ameijeiras", em Havana, Cuba. O primeiro caso: uma paciente de 22 anos com osteoporose generalizada, padrão lítico sal-e-pimenta na região frontoparietal do crânio, reabsorção subperiosteal nas extremidades distais das tíbias e falanges, tumores castanhos ao nível da escápula direita e glenoide e metacarpos esquerdos, e fratura patológica do fêmur direito. O segundo caso: um paciente do sexo masculino, de 22 anos, com deformidade no quadril direito, membro inferior direito encurtado e rotacionado externamente, com incapacidade funcional para ficar em pé e caminhar, e múltiplos tumores marrons na pelve óssea. Em ambos os casos, foi realizado tratamento cirúrgico, confirmando-se o diagnóstico patológico de adenoma de paratireoide, com desfechos favoráveis. Apresentações renais e esqueléticas graves de hiperparatireoidismo primário são raras em adultos jovens. O diagnóstico e o tratamento oportunos melhoram a qualidade de vida dos afetados e previnem complicações potencialmente fatais.

Palavras-chave: hiperparatireoidismo primário; hipercalcemia; osteíte fibrosa cística; nefrolitíase; fraturas patológicas

How to cite this article:
Infante Amorós AL, Zayas Puig SE. Severe renal and skeletal presentation of primary hyperparathyroidism in a young adult: a report of two cases. Rev Inf Cient [Internet]. 2025 [cited Access date]; 104:e4948. Available at: http://www.revinfcientifica.sld.cu/index.php/ric/article/view/4948

NTRODUCTION

Primary hyperparathyroidism (PHPT) is a rare endocrine disorder characterized by excessive secretion of parathyroid hormone (PTH), which generally causes hypercalcemia and a range of variable clinical manifestations.[1]

Its prevalence ranges from 1/1,000 to 21/1,000 according to various published studies. The incidence of PHPT has changed in recent decades and is currently estimated at 10-15 cases per 100,000 per year. Women are affected more than men in a 3:1 ratio, and the peak incidence is in the 50s or 60s.[2,3] In 85% of cases, the cause is a single parathyroid adenoma, in 15% of cases there is multiple glandular involvement (diffuse hyperplasia or multiple adenomas), and in less than 1%, it is a parathyroid carcinoma.[4]

Nowadays, it is much more common to find people with elevated blood calcium levels and an elevated or inappropriately normal parathyroid hormone level, but without any clinical manifestations[5]. Since the most prevalent form is asymptomatic, its discovery is often incidental, for example, during a routine calcium measurement for some nonspecific symptomatology or within the study of a bone metabolic disorder; It is rarely used in the workup of urolithiasis[6]. The most severe specific manifestations are nephrolithiasis/nephrocalcinosis and osteitis fibrosa cystica[1], which characterize the clinical phenotype of the cases presented.

The classic biochemical diagnosis of primary hyperparathyroidism is characterized by elevated parathyroid hormone (PTH) levels, high serum calcium and low phosphorus levels, elevated 1,25-dihydroxyvitamin D levels, and hypercalciuria.[6]

The objective of this study is to describe the severe renal and skeletal manifestations of primary hyperparathyroidism found in two cases of young adults seen in the Endocrinology Department of the "Hermanos Ameijeiras" Clinical and Surgical Hospital in Havana, Cuba.

CASE PRESENTATION 1

A 22-year-old female patient with white skin and no medical history was referred from Granma province because in December 2022 she presented to the Orthopedics and Traumatology Service of the aforementioned province with severe, fixed pain in her right thigh following a minor trauma. This pain worsened with movement and changes in position of the right lower limb, and was not relieved with analgesics.

Physical examination revealed increased volume, deformity, shortening, and internal rotation of the right lower limb, absolute functional incapacity, pain on palpation, and bone crepitus. A pathological fracture of the proximal third of the right femur was diagnosed, and she was referred to the "Frank País García" International Orthopedic Scientific Complex in Havana, where she underwent surgery.

After a favorable postoperative period, the patient presented with severe pain in the right knee and edema throughout the leg, distal coldness, and tenderness upon palpation of the muscle masses. An X-ray of the right knee and Doppler ultrasound revealed evidence of a second pathological fracture site (a non-displaced fracture of the medial condyle of the right knee) and deep vein thrombosis in the saphenofemoral area. The decision was made to treat the fracture conservatively with rest, and the patient was transferred to the Intensive Care Unit (ICU) for treatment and monitoring of the deep vein thrombosis.

The patient continued to progress favorably and was on anticoagulant therapy with warfarin (2 mg) or 8 mg/day. The patient was transferred to the Endocrinology Department of the "Hermanos Ameijeiras" Clinical-Surgical Hospital for further evaluation and treatment due to clinical suspicion of primary hyperparathyroidism.

At this institution, laboratory tests confirmed elevated serum calcium (3.49 mmol/L), ionic calcium (1.85 mmol/L), alkaline phosphatase (1245 mmol/L), and parathyroid hormone (580 pg/ml); in addition, decreased serum phosphate (0.46 mmol/L).

Regarding imaging studies, a right femur X-ray revealed a bone rupture at the proximal third of the shaft, with multiple osteolytic images of varying sizes.

The bone survey study (Figures 1 and 2) showed severe generalized osteoporosis, salt and pepper lytic pattern in the frontoparietal region of the skull, subperiosteal resorption in the medial and distal ends of the tibias and phalanges, brown tumors at the level of the right scapula and left glenoid and metacarpals, and pathological fracture of the right femur.

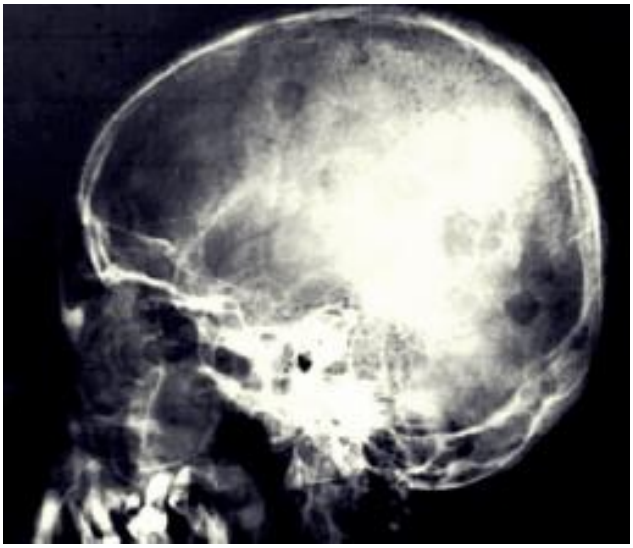

Fig. 1: Bone survey showing moth-eaten skull with salt and pepper lithic pattern

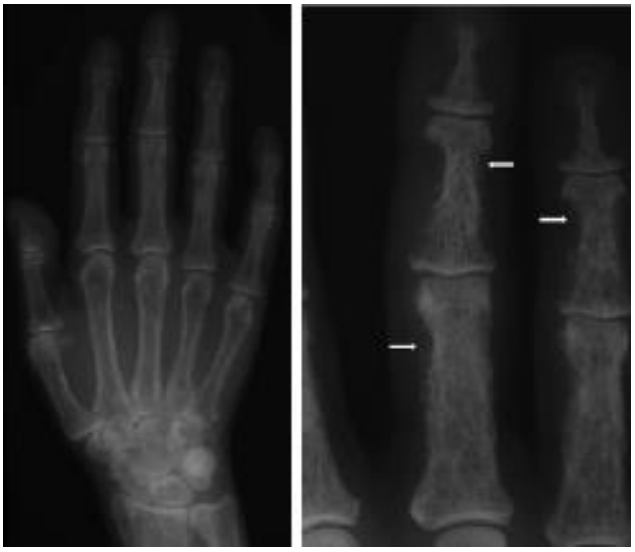

Figure 2: Bone survey showing osteitis fibrosa cystica and subperiosteal resorption of the medial aspect of the middle and distal phalanges of the hand

Computed tomography (CT) scan of the chest and neck revealed a hyperdense image below the left lower lobe of the thyroid with densities of 40 to 56 HU and a coronal measurement of 2.9 x 1.9 cm, corresponding to a parathyroid gland (Figure 3).

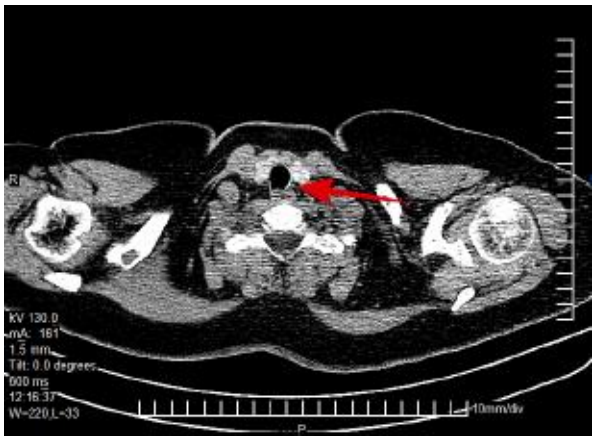

Figure 3: Computed axial tomography (CT) scan of the chest and neck, showing a hyperdense image, measuring 2.9 x 1.9 cm in coronal view, corresponding to a parathyroid gland

From the pathological standpoint, biopsies were performed from the fracture sites, which revealed brown tumors of hyperparathyroidism. Surgical treatment was decided upon based on a diagnosis of primary hyperparathyroidism, with clinical suspicion of a parathyroid adenoma.

CASE PRESENTATION 2

A 22-year-old male patient from Holguín province reported that three months ago he had experienced severe pain of sudden onset, located at the level of the right hip, which made it impossible to walk; for which reason he was evaluated at the "Lucía Iñiguez Landín" Clinical and Surgical Hospital in Holguín. The physical examination revealed elevated blood pressure, a deformity at the right hip, a shortened and externally rotated right lower limb, and functional inability to stand and walk.

A pathological fracture of the right hip was diagnosed, and the patient was transferred to the "Frank País García" International Orthopedic Scientific Complex, where he was admitted for two months. Laboratory studies revealed elevated serum calcium and a CT scan of the pelvis, which revealed multiple brown tumors of hyperparathyroidism in the pelvis, and a bone tumor in the right iliac bone. Primary hyperparathyroidism was suspected, and a transfer to the Endocrinology Department of the "Hermanos Ameijeiras" Clinical and Surgical Hospital was arranged to begin a workup program.

Laboratory tests confirmed elevated serum calcium (3.8 mmol/L), elevated ionic calcium (2.078 mmol/L), elevated alkaline phosphatase (395 U/L), elevated creatinine (150.9 µmol/L), elevated parathyroid hormone (1034 pg/ml), normal alpha-fetoprotein (3.01 IU/ml), normal carcinoembryonic antigen (1.49 ng/ml), and normal human chorionic gonadotropin (0.1 mU/ml).

Regarding imaging studies, abdominal ultrasound revealed numerous microcalculi occupying all calyceal groups in both kidneys. A chest CT scan (Figure 4) revealed multiple lytic lesions with calcified areas within them, resembling soap bubbles scattered across multiple ribs.

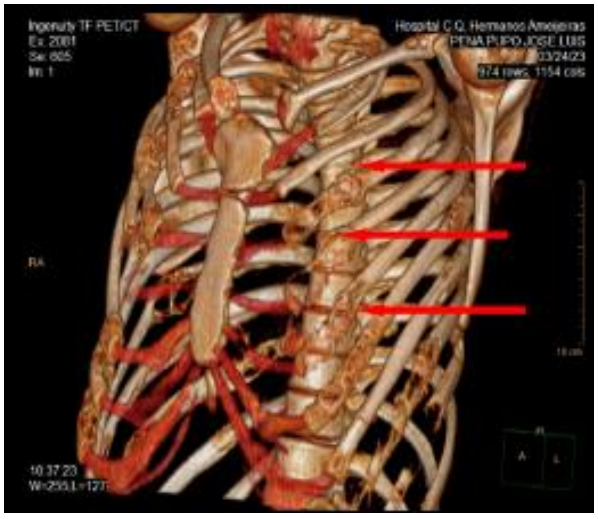

Figure 4: Chest CT scan showing multiple lytic lesions with calcified areas within them, resembling soap bubbles scattered across multiple ribs.

A neck ultrasound revealed a complex mass measuring 4 mm x 36 mm, projected at the lower pole of the right thyroid lobe, and a solid hypoechoic lesion measuring 1.3 cm x 1.4 cm was found at the posteromedial aspect of the left lobe.

A CT scan of the abdomen and pelvis (Figure 5) revealed multiple calcifications at the level of the kidneys, possibly related to nephrocalcinosis, and a bone tumor in the right wing of the iliac bone, measuring approximately 9 cm x 9 cm, involving the acetabular rim. A pathological subtrochanteric fracture of the right femur was noted.

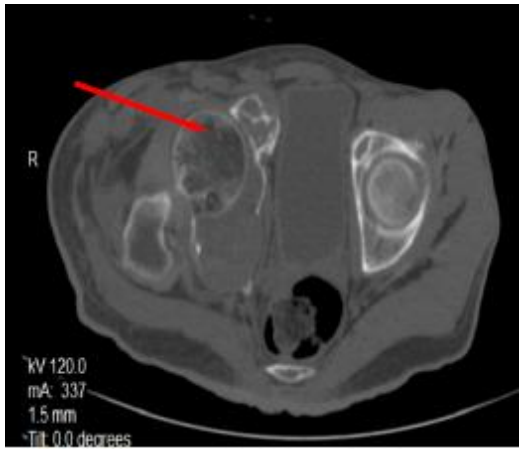

Figure 5: CT scan of the pelvis identifying a bone tumor in the right wing of the iliac bone, measuring approximately 9 cm x 9 cm.

The Pathology Department interpreted a bone mass biopsy in the right iliac bone and reported a bone tumor consisting of a proliferation of osteoclast-like giant cells, a conclusive histological finding of a brown tumor of hyperparathyroidism. Furthermore, the biopsy of the intrathyroid nodules revealed the presence of cells that appeared to be parathyroid cells when viewed in the left nodule, and a papillary formation was observed in the right nodule. Bethesda V was not conclusive regarding malignancy.

A multidisciplinary evaluation was conducted by the Endocrinology, Surgery, Orthopedics, Nephrology, and Oncology departments. based on the clinical, laboratory, and imaging findings, the patient was diagnosed with primary hyperparathyroidism complicated by osteitis fibrosa cystica, pathological subtrochanteric fracture of the right femur, recurrent calcium nephrolithiasis and nephrocalcinosis, stage 3A chronic kidney disease, and secondary arterial hypertension. Furthermore, neoplastic disease was ruled out. The therapeutic approach for primary hyperparathyroidism was to perform total thyroidectomy with parathyroidectomy and surgical treatment of the pathological subtrochanteric fracture of the right femur.

DISCUSSION

In the 1930s, Fuller Albright first described the hypercalcemic state caused by primary hyperparathyroidism as a disease of the bones and kidney stones.[7] In the clinical cases presented, the renal component and the skeletal system were the most affected. Nephrolithiasis is the most common clinical manifestation, occurring in 15%–20% of cases. Furthermore, PPH can be identified in 5% of patients with nephrolithiasis. Most stones are composed of calcium oxalate, sometimes calcium phosphate, and a determining factor is hypercalciuria, which is observed in 35%–40% of cases with PPH.[1]

Osteitis fibrosa cystica accounts for less than 2% of cases. Bone involvement is characterized by subperiosteal bone resorption and osteolysis of some bones, such as the distal third of the radius, tibia, and middle phalanges. This is only seen in cases of long-standing or highly active disease; A salt-and-pepper skull, bone cysts, and brown tumors are also observed.[8,9]

Brown tumors most frequently affect the mandible, skull, clavicle, ribs, femoral bone, and spine. The decrease in bone mineral density (BMD) is different from that of primary osteoporosis and most commonly affects cortical-rich bones, the distal third of the radius, and then the hip and vertebrae. Excess parathyroid hormone leads to increased osteoclastic activity, activation of the inflammatory cascade, resulting in macrophage infiltration and deposition of fibrovascular tissue in the bone.[9]

Therefore, biochemical assessment of calcium, PTH, and vitamin D is important to differentiate these entities. Since serum calcium and vitamin D levels have been routinely measured, these bone manifestations are rare in Western countries. However, cases of hyperparathyroidism with its classic form of bone involvement can still be seen.[8,9]

As a result, pathological fractures are common, especially vertebral and hip fractures, of which age and female sex are predictors. After surgery, BMD improves, especially in the first year in the spine and in the second year in the hip. It does not change in non-operated patients.[8,9]

PPH has an estimated prevalence of 0.86% in the general population. Diagnosis is often delayed, resulting in patients not being referred promptly to specialized care for evaluation and treatment.[10]

Early diagnosis of patients with PPH reduces the recurrence of nephrolithiasis. A delay in surgery to treat PPH also increases the risk of associated bone and kidney morbidities, as demonstrated by follow-up studies in non-surgical patients, with bone mineral loss becoming evident at eight years of follow-up and becoming more severe after 10 to 15 years. In contrast, surgical reversal of PPH offers very early benefits, as demonstrated by biochemical parameters of bone remodeling and densitometric findings.[10]

In a multiple regression analysis, serum calcium clearance, PTH, and creatinine were the serum markers after curative surgery. Vitamin D deficiency is also frequently observed in HPP and can exacerbate its severity.[11]

A genetic basis for HPP occurs in approximately 10% of all patients; it can present as part of complex syndromes (multiple endocrine neoplasia (MEN) types 1, 2A, and 4; and mandibular tumor hyperparathyroidism syndrome; or an isolated nonsyndromic endocrinopathy such as isolated familial HPP, severe neonatal hyperparathyroidism, or familial hypocalciuric hypercalcemia)[11]. There is a close bidirectional association between primary hyperparathyroidism and parathyroid gland neoplasms; in most cases, primary hyperparathyroidism is caused by parathyroid tumors.

The most common cause of primary hyperparathyroidism was parathyroid adenoma, comprising 80–85% of cases, followed by primary parathyroid hyperplasia, which is found in 10–15% of patients. In the few cases of parathyroid carcinoma, they account for less than 1% of cases of primary hyperparathyroidism.[12]

Parathyroid adenoma is diagnosed if it is a single, noninvasive, encapsulated or circumscribed parathyroid neoplasm, without intralesional adipose tissue. Parathyroid hyperplasia presents as a multiglandular pathology showing a mixture of parenchymal and fat cells with an increased parenchymal-to-fat ratio. Unequivocal invasive growth and/or the presence of metastases justify a diagnosis of parathyroid carcinoma.[12,13]

Increased cell proliferation by the Ki-67 fraction has been demonstrated in parathyroid tumors and hyperplasia in contrast to unaltered glands. The average proliferation fraction reported in carcinoma ranges from 6.1% to 13.9%. In adenomas, the mean proliferation index is 1.9%–4.3%, significantly exceeding Ki-67 levels in residual parathyroid tissues.[12,14]

The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism has published an updated version of the Clinical Practice Guidelines for the treatment of asymptomatic HPP. The main message of these guidelines is that further evaluation of bone and renal involvement in these patients is necessary, as many cases show significant deterioration that may go unnoticed.

For this reason, determining the degree of bone fragility using vertebral radiology to identify asymptomatic fractures, or using more sophisticated techniques to assess bone structure is proposed. Bone densitometry plays a fundamental role in the assessment of these patients, who should undergo surgery if T-score values in the lumbar spine, femoral neck, or distal radius reach values below −2.5 SD, as well as imaging techniques for the identification of subclinical nephrolithiasis. Serum calcium values above 1 mg/dL of the upper limit of normal are also a criterion for surgical treatment.[12,15]

The following presentations of PPH are recommended: minor trauma fracture, kidney stones, a significant reduction in BMD to a T-score ≤-2.5 at any site, and a significant reduction in creatinine clearance.[12,15]

These were the clinical criteria of severity that led the medical community to decide that the appropriate management for both cases was surgical intervention by expert personnel. The fact that both patients are young and present with pathological fractures, lytic bone lesions, hypercalcemia, and nephrocalcinosis gives these cases relevance. They represent classic but aggressive presentations of primary hyperparathyroidism, which can lead to serious complications and fatal outcomes.

FINAL CONSIDERATIONS

Severe renal and skeletal presentations of primary hyperparathyroidism are rare in young adults. Timely diagnosis and treatment improve the quality of life of those who suffer from it and prevent the development of potentially fatal complications.

BIBLIOGRAPHIC REFERENCES

1. Muñoz-Torres M, García-Martín A. Hiperparatiroidismo primario. Med Clin [Internet]. 2018 [cited 1 Ago 2024]; 150(6):226-232. DOI:https://doi.org/10.1016/j.medcli.2017.07.020
2. Silverberg SJ, Walker MD,Bilezikian JP. Asymptomatic primary hyperparathyroidism. J Clin Densitom [Internet]. 2013 [cited 1 Ago 2024]; 16(1):14-21. DOI: https://doi.org/10.1016/j.jocd.2012.11.005
3. Nilsson IL, Yin L, Lundgren E, Rastad J, Ekbom A. Clinical presentation of primary hyperparathyroidism in Europe: Nationwide cohort analysis on mortality from nonmalignant causes. J Bone Miner Res [Internet]. 2002 [cited 1 Ago 2024]; 17(Supl 2):N68-74. DOI:https://pubmed.ncbi.nlm.nih.gov/12412780/
4. Syed H, Khan A. Primary hyperparathyroidism: diagnosis and management in 2017. Pol Arch Inter Med [Internet]. 2017 [cited 1 Ago 2024]; 127(6):438-441. DOI:https://doi.org/10.20452/pamw.4029
5. Builes-Montaño CE.Primary Hyperparathyroidism. Med & Lab [Internet]. 2017[cited 1 Ago 2024]; 23(1-2). Available at: https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=94783
6. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. Lancet [Internet]. 2018 [cited 1 Ago 2024];391(10116): 168–78. DOI:https://doi.org/10.1016/s0140-6736(17)31430-7
7. Minisola S, Gianotti L, Bhadada S, Silverberg SJ. Classical complications of primary hyperparathyroidism. Best Pract Res Clin Endocrinol Metab [Internet]. 2018[cited 1 Ago 2024];32(6):791-803. DOI:https://doi.org/10.1016/j.beem.2018.09.001
8. Misiorowski W, Czajka-Oraniec I, Kochman M, Zgliczyński W, Bilezikian JP. Osteitis fibrosa cystica-a forgotten radiological feature of primary hyperparathyroidism. Endocrine [Internet]. 2017 [cited 1 Ago 2024];58(2):380-385. DOI:https://doi.org/10.1007/s12020-017-1414-2
9. Paja-Fano M, Martínez-Martínez AL, Monzón-Mendiolea A. Retraso diagnóstico y terapéutico en el hiperparatiroidismo primario. Un problema no resuelto. Endocrinol Diabetes Nutr [Internet]. 2020 [cited 1 Ago 2024];67(6):357-363. DOI: https://10.1016/j.endinu.2019.11.002

10. Minisola S, Arnold A, Belaya Z, Brandi ML, Clarke BL, Hannan FM, et al. Epidemiología, fisiopatología y genética del hiperparatiroidismo primario. J Bone Miner Res [Internet]. 2022 [cited 1 Ago 2024]; 37(11):2315-2329. DOI: https://doi.org/10.1002/jbmr.4665
11. Uljanovs R, Sinkarevs S, Strumfs B, Vidusa L, Merkurjeva K, Strumfa I. Immunohistochemical profile of parathyroid tumors: a comprehensive review. Int J Mol Sci [Internet]. 2022[cited 1 Ago 2024];23(13):6981. DOI: https://doi.org/10.3390/ijms23136981
12. Bilezikian JP, Silverberg SJ, Bandeira F, Cetani F, Chandran M, Cusano NE, et al. Management of primary hyperparathyroidism. J Bone Miner Res [Internet]. 2022[cited 1 Ago 2024];37(11):2391–2403. DOI:https://doi.org/10.1002/jbmr.4682
13. Islam AK. Advances in the diagnosis and management of primary hyperparathyroidism. Ther Adv Chronic Dis [Internet]. 2021 [cited 1 Ago 2024];108(7):1643-1651. DOI:https://doi.org/10.1177/20406223211015965
14. Pimentel L, Portela S, Loureiro A, Bandeira F. Normocalcemic primary hyperparathyroidism: a long-term follow-up associated with multiple adenomas. Arq Bras Endocrinol Metab [Internet]. 2014[cited 1 Ago 2024]; 58(5). DOI: https://doi.org/10.1590/0004-2730000003367
15. Ng CH, Chin YH, Tan MHQ, Ng JX, Yang SP, Kiew JJ, et al. Cinacalcet and primary hyperparathyroidism: systematic review and meta regression. Endocr Connect [Internet]. 2020 [cited 1 Ago 2024]; 9(7):724-735. DOI: https://doi.org/10.1530/EC-20-0221

Conflicts of Interest:
The authors declare no conflicts of interest.

Author Contributions:
Adalberto Luis Infante Amorós: conceptualization, research, methodology, resources, writing-original draft, writing-review, and editing. Sergio Enrique Zayas Puig: research, formal analysis, methodology, resources, supervision, writing-original draft, writing-review, and editing.

Financing:
No funding was received for the development of this article.