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**Case Report**

# Normocalcemic Primary Hyperparathyroidism. A Case Report and Literature Review

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**Abstract:** Normocalcemic primary hyperparathyroidism (PHP) has been proposed to be a new phenotype of the disease. It is characterized by persistently high levels of parathyroid hormone (PTH) and normal calcium levels. Since there are no known causes of secondary hyperparathyroidism or PTH elevation, the exact biological mechanism is not known. It could be the first stage of the disease or a unique situation marked by resistance of the kidneys and bones to the effects of PTH. This is a disease that is getting more and more common. It is often found when evaluating perimenopausal women with low bone mass or when evaluating or following up on patients with osteoporosis. Normocalcemic PHP has a diverse and varied phenotype that ranges from cases with no usual PHP symptoms to cases with symptoms and specific complications. The method to diagnosing secondary hyperparathyroidism should focus on ruling out all possible causes, especially vitamin D deficiency (25-OH vitamin D levels less than 30ng/mL) and kidney function impairment (glomerular filtration rate less than 60 mL/min, as measured by CKD- EPI). Not much is known about its past in the wild. Some people get hypercalcemia, but more than 75% of them don't. There don't seem to be any ways to predict who will get hypercalcemia, so measuring total and adjusted calcium levels once a year is recommended. Even though measuring ionic calcium is a part of what it means to have Normocalcemic PHP and is recommended by some writers during follow-up, there are a number of real problems with it that should be kept in mind.

**Keywords:** Hyperparathyroidism, Normocalcemic primary hyperparathyroidism, parathyroid surgery, calcium, parathyroid hormone.

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## INTRODUCTION

Primary hyperparathyroidism (PHPT) is a frequent condition. The prevalence of primary hyperparathyroidism (PHPT) in the United States was estimated to be 233 per 100,000 in women and 85 per 100,000 in men. Additionally, it is observed that PHPT is more frequently observed in women once they reach menopause. In the United States, the nature of the illness has undergone a shift from a symptomatic state, commonly associated with the presence of "stones, bones, and psychic moans" in the pre-multichannel laboratory test period, to a less symptomatic one. The classification of individuals with primary hyperparathyroidism (PHPT) was proposed at the 5th international workshop on the assessment and therapy of this condition. The workshop recommended categorizing patients into three distinct groups: symptomatic PHPT, asymptomatic PHPT, and Normocalcemic PHPT (NPHPT). From a biochemical standpoint, primary hyperparathyroidism (PHPT) is often distinguished by the presence of hypercalcemia, accompanied by increased or abnormally normal levels of parathyroid hormone (PTH), and normal to raised levels of urine calcium. Elevated ionized calcium levels are observed in certain individuals, while others experience sporadic episodes of hypercalcemia. The significance of the diagnosis lies in the potential correlation between mild primary hyperparathyroidism (PHPT) and several health implications, including

reduced bone mineral density (BMD), alterations in bone microarchitecture, heightened susceptibility to vertebral and other fractures, as well as an elevated occurrence of kidney stones. A correlation has been observed between neuropsychiatric symptoms and cardiovascular disease. The measurement of parathyroid hormone (PTH) involves many physiological concerns. In particular, whereas blood calcium levels remain generally consistent over adulthood, the release of parathyroid hormone (PTH) increases as individuals age. It is anticipated that around 20% of women who are 80 years old may experience increased PTH levels, mostly due to age-related declines in renal function.

Moreover, the production of parathyroid hormone (PTH) has dynamic characteristics, characterized by intermittent pulses occurring alongside a baseline level of secretion. Additionally, PTH secretion follows a circadian pattern. There are several other parameters that should be taken into consideration since they have the potential to impact measures of parathyroid hormone (PTH) and calcium levels. These factors include hemoconcentration, levels of albumin and protein, immobilization, and pH-dependent alterations in protein-bound calcium. The phenomenon of Normocalcemic primary hyperparathyroidism (NPHPT) was first documented some years ago. One of the primary challenges in diagnosis lies in distinguishing between primary hyperparathyroidism (NPHPT) and secondary hyperparathyroidism (SHPT). Classical hypercalcemic primary hyperparathyroidism (HPHPT) is distinguished by the presence of increased or normal (non-suppressed) levels of parathyroid hormone (PTH) alongside hypercalcemia. This condition arises from the independent functioning of one or more parathyroid glands. Intermittent hypercalcemia may manifest, with increased levels shown just during the measurement of ionized calcium. NPHPT is distinguished by the presence of high parathyroid hormone (PTH) levels, while maintaining consistently normal levels of albumin-corrected total calcium and ionized calcium over a duration of at least 3 to 6 months. In addition, it should be noted that individuals who remain untreated for Normocalcemic primary hyperparathyroidism (NPHPT) have the potential to revert to a normal state. On the other hand, individuals with less severe cases of primary hyperparathyroidism (PHPT) may have increased parathyroid hormone (PTH) levels that mirror NPHPT, although having normal calcium levels. Secondary hyperparathyroidism is a medical condition that is distinguished by increased levels of parathyroid hormone (PTH) in conjunction with consistently normal (or low) levels of albumin-corrected total calcium and ionized calcium. This condition is not generated by independent parathyroid function, but rather by a physiological stimulus that triggers the production of PTH. Based on the above definitions, it becomes evident that distinguishing between NPHPT and SHPT might provide challenges in some instances.

## CASE REPORT

The patient in question is a 53-year-old female with a familial background that includes instances of prostate cancer, kidney cancer, and ovarian cancer in her sister. The patient has a prolonged history of Diabetes Mellitus type 2, which has been treated with Insulin NPH. They also have a long-standing history of systolic arterial hypertension, which has been managed with Losartan. Recently, the patient has been diagnosed with chronic kidney disease classified as KDIGO IV. Additionally, they have a medical history of Reno ureteral lithiasis and complicated emphysematous pyelonephritis, which required surgical intervention in the form of open nephrectomy. The patient also has a history of other surgical procedures. Laparoscopic procedures, also known as minimally invasive surgeries, involve the use of the area of endocrinology conducts an assessment of the patient to monitor and manage their metabolic functions. As part of this evaluation, control laboratories are utilized to get relevant data. The obtained laboratory results are as follows: Thyroid-stimulating hormone (TSH) level is 3.23, parathyroid hormone (PTH) level is 104.4, calcium (Ca) level is 9.4, phosphorus (P) level is 4.4, and fasting glucose (FA) level is 153. As a result of alterations in PTH and hypercalcemia levels, the decision has been made to conduct a thyroid ultrasound examination, which revealed the identification of two nodules with a TIRADS score of 4. Additionally, an oval nodule with greater than broad dimensions, irregular borders, and the absence of calcifications was observed in the left parathyroid gland. A fine needle aspiration biopsy was conducted, yielding a final diagnosis of benign follicular lesion pathology according to the Bethesda classification system (Bethesda II). Additional laboratory tests were conducted, yielding the following results: parathyroid hormone (PTH) level of 148, vitamin D3 level of 19.9, albumin (Alb) level of 4.0, calcium ion (Ca++) level of 9.6, phosphorus (P) level of 4.4, and urinary calcium (CaU) level of 2.0. Consequently, a thyroid gamma grama procedure was decided upon, involving focal capture in the lower pole of the left thyroid lobe and capture in the upper pole of the right thyroid lobe. A parathyroidectomy has been arranged by the Department of Endocrine Surgery. A 1 x 0.2 x 0.1 cm ovoid fragment with pathology, including the presence of parathyroid tissue and adipose infiltration, was received in the lower left region.

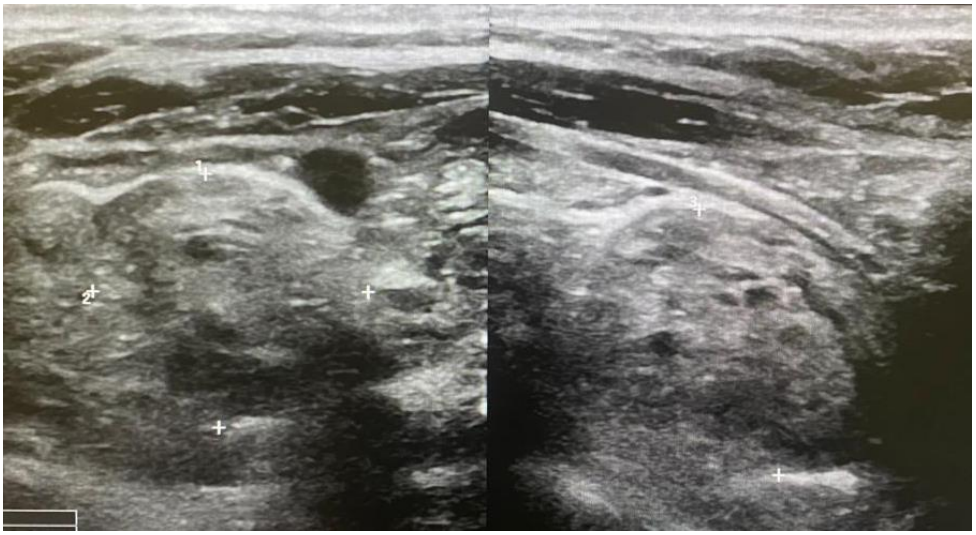

**Figure 1: Thyroid Ultrasound**

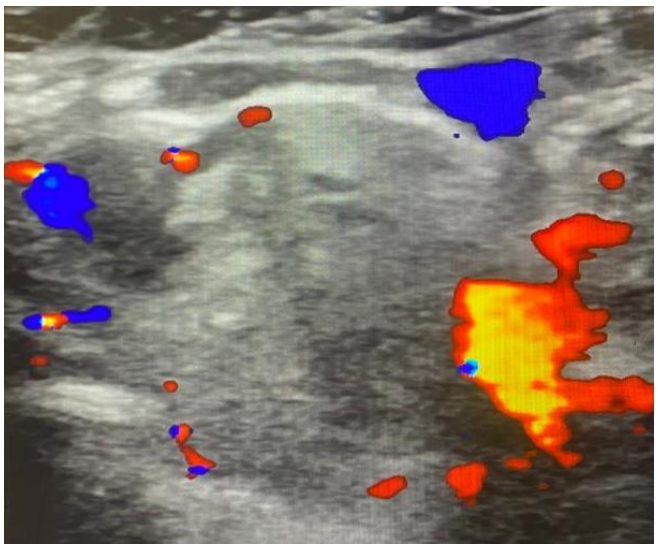

**Figure 2: Doppler Thyroid Ultrasound**

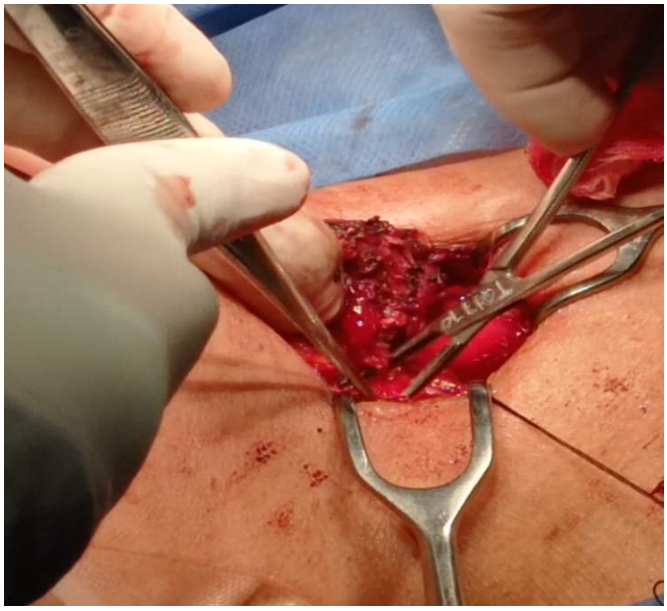

**Figure 3: Cervical Frontal Approach, Surgical Time**

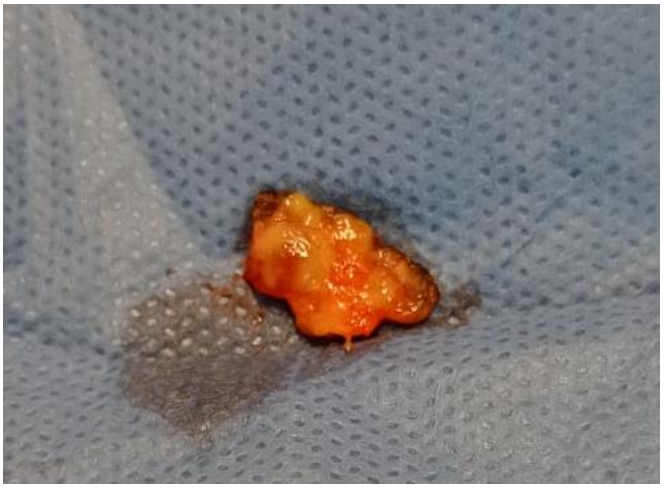

**Figure 4: Left Parathyroid Gland**

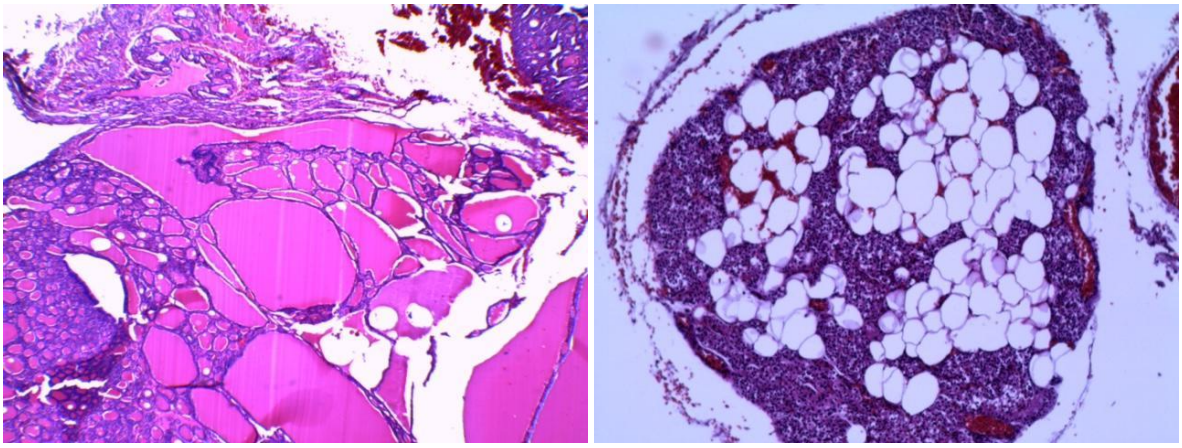

**Figure 5: Normal adult parathyroid glands contain a mixture of parenchymal and adipose cells**

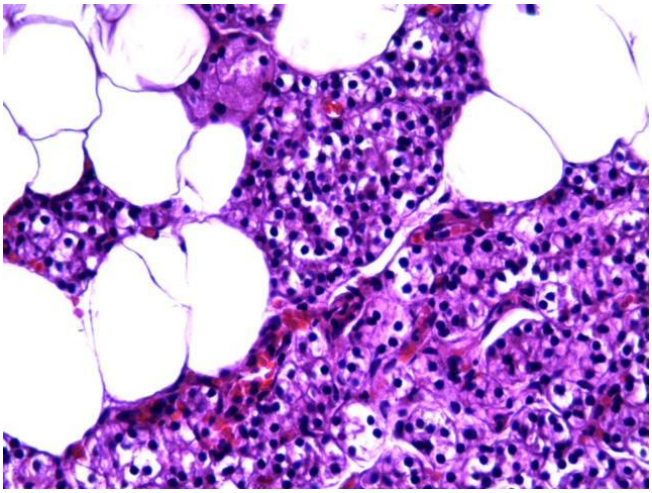

**Figure 6: Parathyroid hyperplasia: trabecular and organoid arrangement of the lesional cells. Transitional oxyphilic nature of the cells**

## DISCUSSION

In modern medical practice, hypercalcemic primary hyperparathyroidism (PHPT) is increasingly recognized as a condition that often manifests without obvious symptoms. However, if screening measures are implemented in accordance with established criteria, the prevalence of kidney stones or vertebral fractures tends to be higher among affected individuals. In contrast, people with normocalcemic illness cohorts often have symptoms. The observed phenomenon can be attributed to selection bias, as individuals with normal blood calcium levels are typically only evaluated for parathyroid illness when they present with a fracture or nephrolithiasis. Although severe traditional primary

hyperparathyroidism (PHPT) with notable increases in serum calcium levels can lead to symptoms affecting various organ systems, research on the nonclassical manifestations of mild, asymptomatic hypercalcemic PHPT has produced inconsistent findings regarding potential complications such as hypertension, left ventricular hypertrophy, glucose intolerance, and quality of life. The normocalcemic phenotype has also been the subject of investigation in patients with nonclassical symptoms. Limited research has been conducted on the natural history of normocalcemic primary hyperparathyroidism (PHPT). Existing data primarily arise from studies with small cohorts, which indicate that a significant proportion of individuals with normocalcemic PHPT may not have hypercalcemia. There is a lack of population-based studies that examine the prevalence of normocalcemic primary hyperparathyroidism (PHPT) in patients who are in good health.

This is mostly due to the infrequent ordering of parathyroid hormone (PTH) values in the absence of hypercalcemia or symptoms. Therefore, characterizing the epidemiology within a group of individuals in good health is a challenging task. Furthermore, a limited number of studies have assessed the levels of ionized calcium, and there are notable variations in the literature on the exclusion of secondary factors contributing to hyperparathyroidism, particularly in the thresholds for 25-hydroxyvitamin D and estimated glomerular filtration rate (eGFR). The frequency of the condition seems to be rather low, as indicated by many investigations that have employed defined criteria, with reported rates ranging from 0.1% to 0.7%. The Fourth International Workshop on Management of Asymptomatic Primary Hyperparathyroidism (PHPT) proposed the use of parathyroidectomy (PTX) as a treatment option for Normocalcemic PHPT patients who exhibit disease progression, such as deteriorating bone mineral density (BMD), or have new symptoms, such as fractures or kidney stones. This recommendation aligns with the approach used for hypercalcemic patients. In the existing body of literature, it has been observed that cohorts diagnosed with Normocalcemic primary hyperparathyroidism exhibit elevated incidences of nephrolithiasis, osteoporosis, and fracture. This finding is to be expected, as many patients with normal serum calcium levels who undergo parathyroid hormone (PTH) testing are typically being evaluated for these specific conditions. It is important to note that the observed high prevalence of symptomatic forms of the disease may be attributed to selection bias in the study population.

While traditional hypercalcemic primary hyperparathyroidism is typically identified as an incidental finding during routine blood tests, Normocalcemic primary hyperparathyroidism is predominantly diagnosed when there is an abnormality in the target organ. In certain cases, the reported cohorts indicate a higher prevalence of symptomatic disease for Normocalcemic primary hyperparathyroidism compared to hypercalcemic disease. The present study aimed to investigate the correlation between the detection of parathyroid lesions and the manifestation of hypercalcemia or normocalcemia in individuals. The findings of the study revealed that 4D-CT had a greater sensitivity in the detection of these lesions when compared to ultrasound and gammagraphy. In particular, the percentage of positive among Normocalcemic individuals was found to be 56% when utilizing 4D-CT imaging technique. In contrast, ultrasonography yielded a positivity rate of 22%, while gammagraphy had the lowest rate of positivity at 11%. In contrast, the positive rate for hypercalcemic individuals was found to be 75% when using 4D-CT, 58% when using ultrasonography, and 75% when using gammagraphy. The primary objective of this research endeavor is to examine the physiological and biochemical impacts of a certain pharmaceutical compound on the human organism. In the event that the patient's whereabouts cannot be determined, a bilateral neck scan is performed. The incorporation of intraoperative parathyroid hormone (IOPTH) readings in the context of surgical operations.

According to the Miami criterion, the surgical procedure should be discontinued if there is a decrease of more than 50% in intraoperative parathyroid hormone (PTH) levels within 10 minutes of initiating parathyroidectomy, when compared to the baseline PTH levels measured the day before surgery. The user's material is already written in an academic style and does not require any more rewriting. In a similar vein, the guidelines put forward by the American Association of Endocrine Surgeons advocate for surgical intervention in individuals exhibiting symptoms, without making a distinction between hypercalcemic primary hyperparathyroidism (PHPT) and Normocalcemic PHPT. According to a recent expert consensus from the European Society of Endocrinology, it is recommended that surgical intervention be contemplated solely subsequent to a thorough evaluation by an experienced endocrinologist. In such instances, surgical intervention should be pursued exclusively if there exist strong grounds and a well defined surgical objective. In our perspective, it is essential to consider the unique nature of discussions around surgery and thoroughly examine patient expectations prior to the surgical procedure. Surgery may be deemed appropriate for individuals with Normocalcemic primary hyperparathyroidism (PHPT) if the diagnosis has been definitively confirmed by a prolonged history of increased parathyroid hormone (PTH) levels, presence of symptoms, and identification of a distinct target using localization investigations and/or consultation with a proficient surgeon. The utilization of preoperative localization studies has significant importance in the surgical therapy of primary hyperparathyroidism (PHPT). Accurate

preoperative localization has the potential to facilitate minimally invasive surgical procedures, resulting in reduced operational duration and lower morbidity in the postoperative period. Neck ultrasonography and 99 mTc-sestamibi scintigraphy are commonly employed as the initial imaging modalities for the localization of hyperfunctioning glands.

## CONCLUSION

Despite the growing number of individuals diagnosed with Normocalcemic primary hyperparathyroidism, not much is known about the disorder. The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism stipulates that repeated measurements of total or ionized serum calcium must be normal for NHPT to be diagnosed. Serum calcium corrected with albumin has occasionally been used as a substitute; however, the majority of studies have included patients with few measurements of these biochemical factors; therefore, it is highly probable that NHPT will be misclassified as a milder form of classical HPTP.

**Conflicts of Interests:** The researchers have disclosed no conflicts of interest.

## REFERENCES


- Anagnostis, P., Vaitsi, K., Veneti, S., Potoupni, V., Kenanidis, E., Tsiridis, E., Papavramidis, T. S., & Goulis, D. G. (2021). Efficacy of parathyroidectomy compared with active surveillance in patients with mild asymptomatic primary hyperparathyroidism: a systematic review and meta-analysis of randomized-controlled studies. *Journal of Endocrinological Investigation*, *44*(6), 1127–1137. https://doi.org/10.1007/s40618-020-01447-7
- Bilezikian, J. P., Khan, A. A., Silverberg, S. J., Fuleihan, G. E.-H., Marcocci, C., Minisola, S., Perrier, N., Sitges-Serra, A., Thakker, R. V., Guyatt, G., Mannstadt, M., Potts, J. T., Clarke, B. L., Brandi, M. L., & the International Workshop on Primary Hyperparathyroidism. (2022). 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*, *37*(11), 2293–2314. https://doi.org/10.1002/jbmr.4677
- Choi, H. R., Choi, S. H., Hong, N., Rhee, Y., Kim, J. K., Lee, C. R., Kang, S.-W., Lee, J., Jeong, J. J., Nam, K.-H., & Chung, W. Y. (2022). Comparisons between normocalcemic primary hyperparathyroidism and typical primary hyperparathyroidism. *Journal of Korean Medical Science*, *37*(13). https://doi.org/10.3346/jkms.2022.37.e99
- Corbetta, S. (2019). Normocalcemic Hyperparathyroidism. In *Parathyroid Disorders* (pp. 23–39). S. Karger AG.
- Cusano, N. E. (2021). Evaluation and management of elevated parathyroid hormone levels in normocalcemic patients. *The Medical Clinics of North America*, *105*(6), 1135–1150. https://doi.org/10.1016/j.mcna.2021.05.017
- Cusano, N. E., & Cetani, F. (2022). Normocalcemic primary hyperparathyroidism. *Archives of Endocrinology and Metabolism*, *66*(5), 666–677. https://doi.org/10.20945/2359-3997000000556
- Cusano, N. E., Silverberg, S. J., & Bilezikian, J. P. (2013). Normocalcemic primary hyperparathyroidism. *Journal of Clinical Densitometry: The Official Journal of the International Society for Clinical Densitometry*, *16*(1), 33–39. https://doi.org/10.1016/j.jocd.2012.12.001
- Eastell, R., Arnold, A., Brandi, M. L., Brown, E. M., D'Amour, P., Hanley, D. A., Rao, D. S., Rubin, M. R., Goltzman, D., Silverberg, S. J., Marx, S. J., Peacock, M., Mosekilde, L., Bouillon, R., & Lewiecki, E. M. (2009). Diagnosis of asymptomatic primary hyperparathyroidism: Proceedings of the third international workshop. *The Journal of Clinical Endocrinology and Metabolism*, *94*(2), 340–350. https://doi.org/10.1210/jc.2008-1758
- Eastell, Richard, Brandi, M. L., Costa, A. G., D'Amour, P., Shoback, D. M., & Thakker, R. V. (2014). Diagnosis of asymptomatic primary hyperparathyroidism: Proceedings of the fourth international workshop. *The Journal of Clinical Endocrinology and Metabolism*, *99*(10), 3570–3579. https://doi.org/10.1210/jc.2014-1414
- Hollowoa, B. R., Spencer, H. J., III, & Stack, B. C., Jr. (2021). Normocalcemic and normohormonal primary hyperparathyroidism: Laboratory values and end-organ effects. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *165*(3), 387–397. https://doi.org/10.1177/0194599820983728
- Horowitz, G., Leshno, M., Izkhakov, E., Halpern, D., Muhanna, N., Greenman, Y., Ungar, O. J., Carmel-Neidermann, N. N., Kampel, L., & Warshavsky, A. (2023). Revisiting age criterion for surgery in asymptomatic primary hyperparathyroidism. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *169*(2), 309–316. https://doi.org/10.1002/ohn.298
- Lowe, H., McMahon, D. J., Rubin, M. R., Bilezikian, J. P., & Silverberg, S. J. (2007). Normocalcemic primary hyperparathyroidism: Further characterization of a new clinical phenotype. *The Journal of Clinical Endocrinology and Metabolism*, *92*(8), 3001–3005. https://doi.org/10.1210/jc.2006-2802
- Martínez Díaz-Guerra, G., Jódar Gimeno, E., Reyes García, R., Gómez Sáez, J. M., Muñoz-Torres, M., & Grupo de Trabajo de Metabolismo Mineral y Óseo de la Sociedad Española de Endocrinología y Nutrición. (2013). Normocalcemic primary hyperparathyroidism: recommendations for management and follow-up. *Endocrinologia y nutricion: organo de la Sociedad Espanola de Endocrinologia y Nutricion*, *60*(8), 456.e1-6. https://doi.org/10.1016/j.endonu.2013.01.015
- Shaker, J. L., & Wermers, R. A. (2023). The eucalcemic patient with elevated parathyroid hormone levels. *Journal of the Endocrine Society*, *7*(4). https://doi.org/10.1210/jendso/bvad013
- Wilhelm, S. M., Wang, T. S., Ruan, D. T., Lee, J. A., Asa, S. L., Duh, Q.-Y., Doherty, G. M., Herrera, M. F., Pasieka, J. L., Perrier, N. D., Silverberg, S. J., Solórzano, C. C., Sturgeon, C., Tublin, M. E., Udelsman, R., & Carty, S. E. (2016). The American association of endocrine surgeons guidelines for definitive management of primary hyperparathyroidism. *JAMA Surgery*, *151*(10), 959. https://doi.org/10.1001/jamasurg.2016.2310
- Zavatta, G., & Clarke, B. L. (2021). Normocalcemic primary hyperparathyroidism: Need for a standardized clinical approach. *Endocrinology and Metabolism (Seoul, Korea)*. https://doi.org/10.3803/enm.2021.106