https://doi.org/10.31871/WJRR.16.2.3
World Journal of Research and Review (WJRR)
ISSN: 2455-3956, Volume-16, Issue-2, February 2023 Pages 09-12

Primary Hyperparathyroidism and Increased Cardiovascular Risk—A Review Article

Dr. Khalid Farooqui, Dr. Farooq Haider, Dr. Hadil Alfar, Dr. Maen Mhd Baroudi, Dr.Khaled ferih, Dr.Farah Farooqui, Dr. Abdul Naser Elsouki

***Abstract*— Primary hyperparathyroidism (pHPT) is a common endocrine disease of the parathyroid gland tissues which leads to inappropriate overproduction of the Parathyroid Hormone (PTH). The symptoms of pHPT vary and they include renal stones, osteoporosis, constipation, and weakness secondary to hypercalcemia and hypophosphatemia. Moreover, it has been reported that patients with pHPT are at increased risk of death due to cardiovascular disease. Many research papers have shown that there is an increased mortality rate in patients with pHPT due to the effect of PTH on the heart. This review article is discussing the effect of pHPT on the cardiovascular system as it is a common cause of mortality.**

***Index Terms*— Primary hyperparathyroidism, cardiovascular disease ,heart disease, hypercalcemia, parathyroid hormone.**

I. Introduction

Primary hyperparathyroidism (pHPT) is a disease of the parathyroid glands which leads to the overproduction of the Parathyroid Hormone (PTH) in the blood. pHPT is characterized by hypercalcemia and hypophosphatemia which lead to the symptoms of the disease. The symptoms include loss of cortical bone due to diffuse bone resorption, renal stones, weakness, and constipation. Many of the cases are asymptomatic and are detected incidentally. pHPT is usually detected after the age of 60 and it has female preponderance (1). pHPT complications have been mainly attributed to cortical bone loss which results in fragility and pathological bone fractures which ultimately lead to greater morbidity and mortality. It has also been associated with other neuroendocrine tumors like multiple endocrine neoplasia type 1 (MEN1), type 2 (MEN2), and hyper parathyroid jaw tumor syndrome (2). Several studies have suggested that there is an increased cardiovascular risk and mortality in patients with pHPT due to the direct action of parathyroid hormone on the cardiovascular system and long-standing hypercalcemia with hypertension, impaired glucose tolerance, hyperuricemia, and dyslipidemia that act as contributory factors to the elevated risk of cardiovascular disease in pHPT. (3) (4) This evidence-based review article aims to indicate the cardiovascular risk associated with primary hyperparathyroidism which is one of the common causes of mortality.

Dr.Khalid Farooqui[a], Dr.Farooq Haider[b], Dr. Hadil Alfar[a], Dr.Maen Mhd Baroudi[a], Dr.Khaled ferih, Dr.Farah Farooqui[d], Dr. Abdul Naser Elsouki[a,c]

a- internal medicine department, Hamad medical corporation, Doha Qatar
b- Cardiology department, Hamad medical corporation, Doha Qatar
c- College of Medicine, Qatar University, Doha Qatar
d- Aster DM Medical Center, Doha Qatar

II. Embryology of Parathyroid Glands

The parathyroid glands originate from the 3rd and 4th pharyngeal pouches. Superior parathyroid glands develop from the dorsal wing of the 4th pharyngeal pouch. In the seventh week of gestation, the gland separates from the pharyngeal wall and gets attached to the posterior surface of the thyroid gland. The ventral wing differentiates to an ultimo brachial body which fuses with the posterior surface of the thyroid gland to give rise to the parafollicular C cells of the thyroid gland. Inferior Parathyroid glands develop from the dorsal wing of the 3rd pharyngeal pouch. In the seventh week of gestation, the inferior parathyroid glands separate from the posterior pharyngeal wall, then they follow the path of the isthmus and finally they get attached to the posterior surface of the thyroid gland.

III. Physiology of Parathyroid Hormone

Parathyroid hormone (PTH) leads to increased serum calcium levels via multiple mechanisms. At the level of the kidneys, it leads to increased calcium absorption in the distal convoluted tubule, and it also increases phosphate excretion in the proximal convoluted tubule. Furthermore, it facilitates the activation of Vitamin D to its active form, calcitriol. In the bones, PTH stimulates RANKL which leads to osteoclast differentiation which in turn increases bone resorption. In the GI tract, PTHincreases the activity of vitamin D which results in increased calcium and phosphate absorption in the small intestine.

IV. pHPT effect on the heart

PTH and calcium ionsaffect the cardiovascular system in different ways. PTH causes hypertrophy of cardiac myocytes by activating protein kinase C (5). It increases the pacemaker current of the SA node and modulates blood flow and contractility of cardiac myocytes.

Normally, calcium enters cardiac myocytes by L-type calcium channels after the cytosolic efflux of calcium from the sarcoplasmic reticulum utilizing ryanodine receptor channels, which in turn resultsin the contraction of cardiac myocytes.Increased cytosolic calcium is removed by sodium-calcium exchanger during the diastolic phase of cardiac contraction.

Recent observation showed that increased cytosolic calcium leak during the action potential generation and abnormal

sodium-calcium exchanger activityis the basis of various supraventricular arrhythmias (6,7)

Parathyroid hormone relaxes vascular smooth muscles by limiting calcium ion entry into the cells secondary to blockage of L-type calcium channels and calcium increases the contraction of smooth muscles (8). PTH and calcium influence vascular smooth muscles in a complex and regulated manner, and it leads to the expression of various atherosclerotic and inflammatory mediators that lead to the development of receptor-advanced glycation end products and IL6(9). In this way, PTH induces the expression of mRNA of VEGF 165 and influences atherosclerosis and remodeling of vascular endothelium (10).

There is accumulating evidence that suggests the role of PTH in providing NO synthetase in vascular endothelium which plays an important role in vasodilatation. Moreover, calcium influences the permeability of various substances that promote positive influences on overall vascular endothelium and form the pathologic basis of disease if the equilibrium disturbs due to other factors (11).

V. The Mortality Rate in pHPT-patients

Ithas been established and well-confirmed that symptomatic pHPT cases are having increased mortality before and after undergoing parathyroidectomy. Cardiovascular diseases such as myocardial infarction, cardiac hypertrophy, and heart failure are highly prevalent causes of death among pHPT-patients. (12)One of the largest studies that study the mortality rates included 4461 patients with pHPT who underwentparathyroidectomy between 1987 and 1994, and the study found that there is a highly significant increase in all-cause death, as well as cardiovascular death in pHPT patients. Moreover, thepercentage of female patients was higher than men (1.85% for females compared to1.71% for men). The study concluded that long-standing pHPT may still carry a risk of cardiovascular disease and mortality in patients with or without undergoing parathyroidectomy. Another study aimed at studying cardiovascular events during pre- and post-parathyroidectomy and mortality rates after surgery in pHPT patients. The study showed that the risk of acute MI is upto 10 times more before surgery andit drastically falls to normal after > 1 year post-surgery. Other risk factors like hypertension, diabetes, stroke and heart failure were observed in patients with pHPT. The study also showed that pre-operative cardiovascular disease was associated with an increased risk of death. (13) A study in 2012 by Elena osto et.al showed that pHPT patients have coronary microvascular dysfunction that is completely restored after parathyroidectomy. (14) Areview article by Thalassini Delistathi et.al which was published in 2015 discussed the cardiovascular complications in the setting of pHPT (15), and it included the first article that studied the relation between primary hyperparathyroidism and increased cardiovascular risk by Ronni-Sivula et al and they concluded that these patients have increased mortality from cardiovascular disorders (16).It also reviewed another study by Wermers MDA et al, who concluded that the level of PTH and calcium levels preoperatively and the weight of the adenoma of the parathyroid glands are independent factors associated with cardiovascular risk in patients with primary hyperparathyroidism who undergo parathyroidectomy (17).In another study where 19 patients were followed post-parathyroidectomy with persistent raised PTH and were found to have increased cardiovascular morbidity compared to controls. (18)Few prospective studies found that there is an increasedprevalence of hypertension in patients with pHPT, especially in blacks with a median follow-up of 6 years. There are a few theories that discuss the relationship between PTH, and hypertension and they include the PTH-induced vascular remodeling and activation of the RAAS system. However, the exact mechanism is still not clearly understood and further studies are needed to be carried out in this area particularly.(19) Hvarfner et al in 1989 highlighted the effect of increased calcium on blood systolic and diastolic pressure. (20)There was a randomized controlled clinical trial to assess the reduction of cardiovascular risk in patients with mild to moderate pHPT after parathyroidectomy compared to patients who did not undergo the surgery.The primary outcomes of the study were to check for office and 24 hours ambulatory BP, Pulse wave velocity, and fasting cholesterol levels. They concluded that parathyroidectomy may reduce the cardiovascular risk by decreasing the fasting cholesterol levels, and pulse wave velocity but ambulatory diastolic BP was higher post-surgery.(21)Heart failure is one of the most common complications of cardiovascular disease and the cause of mortality. One of the multiethnic atherosclerosis studies aimed to check the relationship between PTH levels, the incidence of Heart failure and left ventricular mass. The results of 4763 patients who were assessed for PTH and left ventricular mass by cardiac MRI were found to have 180 incidents of heart failure over a follow-up period of 8 years. Moreover, PTH > 65pg/ml was associated with a 50% greater risk of incident of heart failure and an increase in LV mass compared to the PTH group of <65 pg/ml patients. They concluded that high serum PTH levels are associated with an increased risk of left ventricular mass and an increased incidence of heart failure. (22) Patrik Andersson et al observed that LV systolic function does not seem to be affected in patients with pHPT, whereas any influence on LV diastolic performance needs further evaluation. (23)

hyperparathyroidism.

Name of the study	Author	Year	Conclusion
pHPT patients have coronary microvascular dysfunction that is completely restored after parathyroidectomy. (24)	Elena Osto et al	19. Jul 2012	PHPT patients have coronary microvascular dysfunction that is completely restored after parathyroidectomy. PTH independently correlates with coronary microvascular impairment, suggesting a crucial role of the hormone in explaining the increased cardiovascular risk in PHPT
Cardiac structural and functional abnormalities in primary hyperparathyroidism (25)	S.Purra et al	29. Jul 2021	valuation of PHPT patients should not only include traditional end organs like bones and kidneys but also the cardiovascular system in the form of echocardiography to detect subclinical cardiac dysfunction so that the cardiovascular health of such patients can be optimized.
Primary hyperparathyroidism and heart disease--a review (26)	Patrik Andersson et al	10. Jul 2004	LV systolic function does not seem to be affected in patients with pHPT, whereas any influence on LV diastolic performance needs further evaluation
Long-term effect of surgical treatment on the symptoms of primary hyperparathyroidism. (27)	Ronni-Sivula H	01. Jan 1085	increased mortality from cardiovascular disorders
Survival after the Diagnosis of Hyperparathyroidism: A Population-based Study (28)	Robert AWermersMDA et al	Feb 1998	The factors which independently are associated with cardiovascular risk in patients with primary hyperparathyroidism who undergo parathyroidectomy are the value of PTH pre-operatively, the levels of serum calcium pre-operatively, and the weight of the adenoma of the parathyroid gland
Interactions between indices of calcium metabolism and blood pressure during calcium infusion in humans. (29)	Hvarfner et al	Aug 1989	There is a substantial increase in blood pressure, both diastolic and systolic after the infusion of calcium in subjects with normal or near-normal blood pressure
The Hoorn study (30)	A. J. van Ballegooijen	April 2013	levels of PTH increased in both univariate and multivariate analyses the risk of death of general and cardiovascular causes

VI. Conclusion

Primary hyperparathyroidism is one the most common endocrine pathologiesthat we come across in our daily clinical practice, where the focus has been always on the complications that affect the bones and kidneys due to high PTH levels and its action on the target organs. In this review article,we have highlighted the most important cardiovascular system complications involved and their relationship with pHPT. Several studies including experimental animal model studies have shown that PTH exerts its action on cardiomyocytes, the vascular endothelium of the cardiovascular system which leads to vasodilatory effect, vascular remodeling, positive inotropy, and chronotropic effect.Many observational studies, randomized controlled studies, and case reports haveshown a strong relationship between pHPT and increased cardiovascular risk, and its increasing association with hypertension, diabetes, and dyslipidemia. Some of the retrospective and prospective studies also showed the effect of parathyroidectomy on the reduction of cardiovascular risk. Many theories and explanations are not fully understood, therefore there is a potential area of research for the further association of increased cardiovascular risk in primary

References

[1] Williams text book of endocrinology 14th edition, chapter 29, section VII; Page:1221-1223

[2] Pausova Z, Soliman E, Amizuka N, et al. Role of the RET proto-oncogene in sporadic hyperparathyroidism and hyperparathyroidism of multiple endocrine neoplasia type 2. *J Clin Endocrinol Metab*. 1996;81(7):2711–2718.

[3] tournis S, Makris K, Cavalier E, Trovas G. Cardiovascular Risk in Patients with Primary Hyperparathyroidism. Curr Pharm Des. 2020;26(43):5628-5636. doi: 10.2174/1381612824999201105165642. PMID: 33155899.

[4] Stefenelli T, Abela C, Frank H, et al. Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. *J Clin Endocrinol Metab*. 1997;82(1):106–112.

[5] Schluter KD & Piper HM. Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide. *Cardiovascular Research* 1998 37 34–41

[6] El-Sherif N & Turitto G. Electrolyte disorders and arrhythmogenesis. *Cardiology Journal* 2011 18 233–2345.

[7] Voigt N, Li N, Wang Q, Wang W, Trafford AW, Abu-Taha I, Sun Q, Wieland T, Ravens U & Nattel S et al.Enhanced sarcoplasmic reticulum Ca2+ leak and increased Na+- Ca2+ exchanger function underlie delayed afterdepolarizations in patients with chronic atrial fibrillation. *Circulation* 2012 125 2059–2070.

[8] Pang PKT, Wang R, Shan J, Karpinski E & Benishin CG. Specific inhibition of long-lasting, L-type calcium channels by synthetic parathyroid hormone. *PNAS* 1990 87 623–627.

[9] Rashid G, Bernheim J, Green J & Benchetrit S. Parathyroid hormone stimulates endothelial expression of atherosclerotic parameters through protein kinase pathways. *American Journal of Physiology: Renal Physiology*2007 292 F1215–F1218.

[10] Rashid G, Bernheim J, Green J & Benchetrit S. Parathyroid hormone stimulates the endothelial expression of vascular endothelial growth factor. *European Journal of Clinical Investigation* 2008 38 798–803.
[11] Lum H & Malik AB. Regulation of vascular endothelial barrier function. *American Journal of Physiology* 1994267 223–241.

[12] LundgrenE, Lind L, Palmer M, et al. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years *Surgery* 2001;130:978 985.
[13] Vestergaard P, Mollerup CL, Frøkjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L. Cardiovascular events before and after surgery for primary hyperparathyroidism. World J Surg. 2003 Feb;27(2):216-22. doi: 10.1007/s00268-002-6541-z. PMID: 12616440.
[14] Osto E, Fallo F, Pelizzo MR, Maddalozzo A, Sorgato N, Corbetti F, Montisci R, Famoso G, Bellu R, Lüscher TF, Iliceto S. Coronary microvascular dysfunction induced by primary hyperparathyroidism is restored after parathyroidectomy. Circulation. 2012 Aug 28;126(9):1031-9.
[15] Delistathi T, Markogiannakis H, Tsamis D, Manouras A, Giotakis I, Zografos G. Primary hyperparathyroidism, and cardiovascular risk. Is there a connection? Nova. 2015;4(2):1-5.
[16] Ronni-Sivula H, Sivula A. Long-term effect of surgical treatment on the symptoms of primary hyperparathyroidism. Annals of clinical research. 1985 Jan 1;17(4):141-7.
[17] Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, Melton III LJ. Survival after the diagnosis of hyperparathyroidism: a population-based study. The American journal of medicine. 1998 Feb 1;104(2):115-22

[18] HedbÃ¤ck G, OdÃ©n A. Persistent disease after surgery for primary hyperparathyroidism: the long-term outcome *Eur J Endocrinol*2004;150:19-25.
[19] Parathyroid hormone and the risk of incident hypertension: the Atherosclerosis Risk in Communities study.*Yao L, Folsom AR, Pankow JS, Selvin E, Michos ED, Alonso A, Tang W, Lutsey PL J Hypertens. 2016 Feb; 34(2):196-203.*

[20] Hvarfner A, Mörlin C, Wide L, Ljunghall S. Interactions between indices of calcium metabolism and blood pressure during calcium infusion in humans. Journal of human hypertension. 1989 Aug 1;3(4):211-20.

[21] Ejlsmark-Svensson H, Rolighed L, Rejnmark L. Effect of Parathyroidectomy on Cardiovascular Risk Factors in Primary Hyperparathyroidism: A Randomized Clinical Trial. J Clin Endocrinol Metab. 2019 Aug 1;104(8):3223-3232. doi: 10.1210/jc.2018-02456. PMID: 30860588

[22] Bansal N, Zelnick L, Robinson-Cohen C, Hoofnagle AN, Ix JH, Lima JA, Shoben AB, Peralta CA, Siscovick DS, Kestenbaum B, de Boer IH. Serum parathyroid hormone and 25-hydroxyvitamin D concentrations and risk of incident heart failure: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc. 2014 Dec 2;3(6):e001278. doi: 10.1161/JAHA.114.001278. PMID: 25468653; PMCID: PMC4338718.

[23] Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease—a review. European heart journal. 2004 Oct 1;25(20):1776-87.

[24] Osto E, Fallo F, Pelizzo MR, Maddalozzo A, Sorgato N, Corbetti F, Montisci R, Famoso G, Bellu R, Lüscher TF, Iliceto S. Coronary microvascular dysfunction induced by primary hyperparathyroidism is restored after parathyroidectomy. Circulation. 2012 Aug 28;126(9):1031-9

[25] Purra S, Lone AA, Bhat MH, Misgar RA, Wani AI, Bashir MI, Masoodi SR, Purra W. Cardiac structural and functional abnormalities in primary hyperparathyroidism. Journal of endocrinological investigation. 2022 Feb;45(2):327-35.

[26] Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease—a review. European heart journal. 2004 Oct 1;25(20):1776-87.

[27] Ronni-Sivula H, Sivula A. Long-term effect of surgical treatment on the symptoms of primary hyperparathyroidism. Annals of Clinical Research. 1985 Jan 1;17(4):141-7.

[28] Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, Melton III LJ. Survival after the diagnosis of hyperparathyroidism: a population-based study. The American journal of medicine. 1998 Feb 1;104(2):115-22.

[29] Hvarfner A, Mörlin C, Wide L, Ljunghall S. Interactions between indices of calcium metabolism and blood pressure during calcium infusion in humans. Journal of Human Hypertension. 1989 Aug 1;3(4):211-20.

[30] Van Ballegooijen AJ, Reinders I, Visser M, Dekker JM, Nijpels G, Stehouwer CD, Pilz S, Brouwer IA. Serum parathyroid hormone in relation to all-cause and cardiovascular mortality: the Hoorn study. The Journal of Clinical Endocrinology & Metabolism. 2013 Apr 1;98(4):E638-45.