Mini Review

Hyperparathyroidism: Cancer and Mortality

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ABSTRACT

Hyperparathyroidism is a commoner endocrinopathy today with a large number of asymptomatic patients in contrast to the scenario five decades ago. Surgery is indicated for patients fulfilling the NIH criteria who are mostly symptomatic while individuals with mild disease are managed conservatively. Several studies indicate increased risk of malignancy involving several sites and related mortality in primary hyperparathyroidism (PHPT) with the risk persisting for several years after surgery. PHPT is associated with structural & functional cardiac abnormalities and premature death from increased cardiovascular disease with risk normalising only several years after surgery. Mortality risk is associated with pre-operative serum calcium & parathormone and parathyroid adenoma weight. However, the issue of existence of similar risk and surgical benefit in mild PHPT is mired in controversy although some studies have shown an association and beneficial trends with surgery. With current evidence, it would be prudent to follow up PHPT patients for malignancy and cardiovascular disease and possibly adopt a more liberal attitude towards surgery.

Key Words: Hyperparathyroidism, cancer, mortality

The parathyroid glands were discovered by Sir Richard Owen, the curator of the Natural History Museum, in 1852 when he was dissecting a dead rhinoceros from the London Zoo. It was only fifty years later in 1903 that Askanazy made the association between bone disease and parathyroid tumor during an autopsy while Mandl was the first to remove a parathyroid tumor in 1925 with subsequent disease improvement.[1]

Interestingly, the clinical profile of primary hyperparathyroidism (PHPT) has undergone a sea change over the last fifty years or so. From being an uncommon disease of "bones, stones and groans", it is presently a commoner endocrinopathy with a preponderance of elderly patients with asymptomatic disease following introduction of routine serum calcium measurements using biochemistry auto-analyzers. The incidence of primary hyperparathyroidism is approximately 28 per 1,00,000 population, with a female to male ratio of 2:1 with the prevalence in postmenopausal women being as high as 3%-4% and an adenoma in one or more glands being the aetiology in 85% of patients.[2]

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The strategy for the management of primary hyperparathyroidism has evolved in parallel with its changing presentation. While we have an enviable armamentarium of drugs to battle hypercalcemia, surgery constitutes the only available definitive treatment but is usually only offered to patients fulfilling the NIH criteria. In spite of achieving disease remission in almost all patients following parathyroidectomy, the risk of premature mortality from cardiovascular disease and malignancy persists for some time and several studies have looked into possible preoperative prognostic markers for the same. However, the vast majority of patients have asymptomatic and milder disease without complications and are managed conservatively.

The natural history of mild PHPT remains incompletely understood with available studies suggesting limited risk of disease progression, although the duration of follow-up and patients' compliance has not been uniform. However, some studies have suggested an increased risk of premature death from cardiovascular disease and malignancy in patients with mild to moderate hypercalcemia who did not undergo surgery. The optimal treatment in this predominant

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subgroup of patients is mired in controversy with available studies throwing up conflicting results.

Hyperparathyroidism and Cancer

There is increasing evidence suggesting a link between PHPT and risk of malignancy outside a hereditary pathway (multiple endocrine neoplasia syndrome). The establishment of this association is important in deciding on the management of patients as regards screening for malignancy in PHPT and the decision to opt for surgery. Several studies indicate an increased risk of malignancy in PHPT compared to the normal population which is a contributor to the risk of premature death. However, the tumor sites are different in different studies implying that the relationship between PHPT and cancer is more general in character than specific.

A retrospective study from the Swedish Cancer Registry in 1988 involving 4,163 operated patients followed up for 22 years showed a significantly increased relative risk of developing gastrointestinal cancers, endocrine tumors (involving adrenals, thymus, pituitary and pancreas), kidney carcinoma and mammary carcinoma.[3] Another retrospective study from Sweden in 1990 involving 896 operated patients followed up for about 13 years showed the presence of 24 different tumor locations among the 72 patients who died from malignancy with a significant association only with pancreatic adenocarcinoma.[4] In 2002, a record-linkage study among 2,425 patients of hyperparathyroidism using the Danish National Cancer Registry showed a 25% increased risk of cancer with the risk being higher in women. Hematopoietic malignancies (particularly multiple myeloma) were significantly more in PHPT while patients with unspecified hyperparathyroidism had significantly increased carcinoma of the urinary tract and thyroid gland. Patients with secondary hyperparathyroidism had an insignificant overall cancer risk suggesting that malignancies were not due to parathyroid hormone (PTH) itself.[5] A retrospective Danish study in 2004 involving 1,578 PHPT patients found a total of 77 cases of death from malignancy with significantly increased mortality from oral and oesophageal cancer, as well as hematological malignancy in men and colonic cancer in women.[6] In a Swedish prospective cohort study in 2006 involving 7,847 women, serum calcium levels showed inverse association with breast cancer risk in premenopausal women in a dose-response manner but a positive association in overweight peri/post-menopausal women.[7] In 2007, a retrospective cohort study using the Swedish cancer registry including 9,782 operated patients showed an increased overall risk of cancers in both genders with risk persisting beyond 15 years after parathyroidectomy. Breast cancer accounted for a quarter of cancer incidence in women and an increased risk of kidney, colonic and squamous cell cancer was found in both genders. The risk of endocrine and pancreas cancer was increased in the small subgroup who were operated before 40 years of age.[8] A recent record linkage study from Scotland involving 3,039 PHPT patients showed increased incidence and mortality from cancers in both surgically and conservatively managed patients with the commonest cancers being those of the skin (non-melanoma), breast, colon and lung. Surgery was found to delay but not reduce the occurrence of cancers.[9] However, it is pertinent to note that as the absolute number of organ-specific tumors in all the above mentioned studies is small, organ-specific malignancy data need to be interpreted with caution.

Although there is a wide variability in tumor site involvement, multiple studies have conclusively shown an increased risk of malignancy in PHPT which persisted even after surgery. The increased risk could be related to hypercalcemia or they could share common aetiologic factors, either genetic and/or environmental. Increased mitotic activity induced by hypercalcemia is a possible mechanism and experimental studies have also shown PTH to have anti-apoptotic and tumor promoting effects. Both, calcium and PTH have been found to potentiate the mitogenic activity in bone marrow and lymphocyte mitogenesis. However, the prolonged persistence of risk post surgery has diluted the possibility of biochemical derangements contributing to cancer risk and has shifted the focus to other possible mechanisms. Vitamin D induces apoptosis, cell-cycle arrest, and differentiation and inhibits invasiveness and angiogenesis, thereby producing an anti-tumor effect and vitamin D receptors (VDR) are expressed in several body cells. A genetic predisposition due to disturbances in VDR alleles may cause impaired regulation of parathyroid glands, as well as defective apoptosis and increased incidence of preneoplastic lesions.[3,8]

Hyperparathyroidism and Death

A number of studies have established an increased risk of mortality in PHPT from cardiovascular disease, malignancy and renal disease, with risk probably persisting for several years post surgery and factors like preoperative serum calcium and PTH level and post-operative parathyroid adenoma weight being able to predict the same.

A retrospective Swedish study involving 441 operated PHPT patients in 1987 showed an increased mortality risk predominantly due to cardiovascular disease which decreased only 5 to 8 years after surgery. Immediate post-operative mortality rate (within 1 month of surgery) was 1.8% and were among patients with hypercalcemic crisis

or among elderly persons (older than 70 years) with severe arteriosclerosis.[10] A similar finding was seen in another Swedish study published in 1990 in 896 operated patients in which malignancy and renal disease (uremia) were found to be additional contributors to increased mortality.[4] In 1995, another Swedish study in 713 patients operated for single parathyroid gland disease showed adenoma weight to be significantly related to mortality risk, as well as preoperative serum calcium although serum calcium did not have an independent predictive value.[11] Since, it is impossible to estimate the exact duration of hyperparathyroidism before diagnosis, the size of parathyroid adenoma could be reflective of the same and could further strengthen the concept of adopting a liberal attitude towards early surgery. However, a study from Mayo clinic published in 1997 involving 435 PHPT patients (of whom only 126 were operated) put forward certain contrary suggestions. Overall mortality or mortality due to cardiovascular disease or cancer was not increased in this cohort although there was a non-significant trend for decreased survival in patients treated conservatively, especially after 10 years following initial calcium elevation. Patients in the highest quartile of serum calcium had worse survival compared to the three lower quartiles, although this increased mortality risk showed a non-significant trend when compared to age and gender matched controls.[12] The contradictory findings in this North American study compared to those reported by Scandanavian authors is in all probability due to the presence of less advanced disease in this cohort. The earlier Swedish studies were corroborated by another study from the same country in 1998 involving 4461 operated patients which showed an increased mortality risk from cardiovascular disease even in mild or moderate PHPT with significant risk reduction following surgery.[13] A German study in 2000 involving 360 operated patients demonstrated an increased mortality from cardiovascular disease predominantly in women.[14] In an interesting Swedish study published in 2001, 172 patients with mild hypercalcemia (confirmed 2 years post initial diagnosis) who were followed up for 25 years showed an increased risk of dying from cardiovascular disease despite a significant decrease in serum calcium value with time and had little risk of developing clinically apparent renal damage.[15] An elaborate Danish study published in 2004, found a significantly increased risk of premature death from cardiovascular disease and cancer in 1,578 patients with a hospital diagnosis of PHPT. Women treated conservatively had significantly increased mortality from ischemic heart disease and cerebrovascular disease and there was a trend towards improved survival with surgery. Men had significantly increased mortality from cerebrovascular disease but not ischemic heart disease and this risk was not influenced by surgery.[6] It is today well-confirmed that symptomatic PHPT patients suffer from increased mortality before and after treatment with parathyroidectomy although, more definitive and conclusive evidence for the same in asymptomatic patients is warranted.

PHPT has been associated with hypertension, left ventricular hypertrophy (LVH), increased calcification of the valves and coronary arteries, abnormal endothelial vasodilatory response and increased arterial stiffness along with metabolic abnormalities like dyslipidemia, obesity and insulin resistance; all of which contribute to increased cardiovascular death and some of which regress following surgery. LVH is a strong and independent predictor of cardiovascular mortality while valvular sclerosis increases risk of cardiac events. Following surgery, reversal of LVH is seen, particularly in normotensive patients and no further deterioration occurs in sclerosis of the aortic and mitral valves. Some studies have demonstrated an impaired endothelium-dependent vasodilatation in PHPT while others have shown decreased vascular smooth muscle mediated vasodilatation to be responsible for vascular dysfunction. Stiffening of the arteries might cause an augmentation of the pressure in central arteries and thereby increasing afterload on the heart. PTH acts on adult cardiomyocytes by binding to the PTH/PTHrP receptor, thereby inducing a rise in the intracellular levels of calcium which activates protein kinase C and mediates hypertrophic, as well as metabolic effects on the cardiomyocyte. PTH also appears to have an effect on the energy utilization in heart cells with both *in vitro* and *in vivo* studies showing PTH to significantly lower the content of creatinine phosphate, ATP, ADP, AMP and decrease the mitochondrial oxygen consumption in the cardiomyocyte. LVH in PHPT develops irrespective of blood pressure, patients' biochemical profile and disease symptoms implying that even patients with mild and asymptomatic PHPT may have an increased risk of cardiovascular death.[16]

A reasonable and educated opinion is the fact that absolute serum calcium and PTH levels and duration of disease are all culprits in the harmful effects of PHPT. The contradictory results in clinical trials of PHPT could be due to the fact that the duration of disease is an unknown variable. A large multicentric prospective randomized controlled trial is needed to settle the issue of surgical intervention in asymptomatic patients who do not otherwise fulfil the present day NIH criteria. Parathyroid surgery in the present day is performed by specialists with an impeccable success rate and minimal complications which could justify and tilt the balance in favor of establishing a lower threshold for surgery. Even in patients otherwise managed conservatively, being vigilant about possible malignancy and

prompt management of cardiovascular aberrations as far as practicable could significantly contribute to increased survival in this disorder.

References

1. Albright F. A page out of the history of hyperparathyroidism. J Clin Endocrinol 1948;8:637-57.
2. Marx SJ. Hyperparathyroid and hypoparathyroid disorders. N Engl J Med. 2000;343:1863–1875.
3. Palmer M, Adami HO, Krusemo UB, Ljunghall S. Increased risk of malignant diseases after surgery for primary hyperparathyroidism – A Nationwide Cohort Study. Am J Epidemiol 1988;127:1031-40.
4. Hedback G, Tisell LE, Bengtsson BA, Hedman I, Oden A. Premature death in patients operated on for primary hyperperathyroidism. World J Surg 1990;14:829-36.
5. Pickard AL, Gridley G, Mellemkjae L, Johansen C, Kofoed-Enevoldsen A, Cantor KP, *et al*. Hyperparathyroidism and subsequent cancer risk in Denmark. Cancer 2002;95:1611-7.
6. Ogard CG, Engholm G, Almdal TP, Vestergaard H. Increased mortality in patients hospitalised with primary hyperparathyroidism during the period 1977-1993 in Denmark. World J Surg 2004;28:108-11.
7. Almquist M, Manjer J, Bondeson L, Bondeson AG. Serum calcium and breast cancer risk: Results from a prospective cohort study of 7847 women. Cancer Causes Control 2007;18:595-602.
8. Nilsson IL, Zedenius J, Yin L, Anders E. The association between primary hyperparathyroidism and malignancy: Nationwide cohort analysis on cancer incidence after parathyroidectomy. Endocr Relat Cancer 2007;14:135-40.
9. Ghosh S, Collier A, Clark D, Elhadd T, Malik I. Primary hyperparathyroidism (Nationwide cohort study): an increased risk of cancer and decreased survival. Paper presented at: European Congress of Endocrinology 2009; April 25-29; Istanbul, Turkey.
10. Palmer M, Adami HO, Bergstrom R, Akerstrom G, Ljunghall S. Mortality after surgery for primary hyperparathyroidism: A follow-up of 441 patients operated on from 1956 to 1979. Surgery 1987;102:1-7.
11. Hedback G, Oden A, Tisell LE. Parathyroid adenoma and the risk of death after treatment for primary hyperparathyroidism. Surgery 1995;117:134-9.
12. Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, Fallon MO, *et al*. Survival after the diagnosis of hyperparathyroidism: A population-based study. Am J Med 1998;104:115-22.
13. Hedback G, Oden A. Increased risk of death from primary hyperparathyroidism - an update. Eur J Clin Invest 1998;28:271-6.
14. Walgenbach S, Hommel G, Junginger T. Outcome after surgery for primary hyperparathyroidism: Ten-year prospective follow-up study. World J Surg 2000;24:564-70.
15. Lundgren E, Lind L, Palmer M, Jakobsson S, Ljunghall S, Rastad J. Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcaemia followed up for 25 years. Surgery 2001;130:978-85.
16. Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease – a review. Eur Heart J 2004;25:1776-87.

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