Editorial Commentary

Is cardiovascular evaluation necessary for elderly patients with primary hyperparathyroidism?

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Primary hyperparathyroidism (PHPT) is an increasingly prevalent endocrine disorder, with an incidence ranging from 1.3 to 50 cases per 100,000 person-years according to previous reports (1-3). Characterized by the excessive secretion of parathyroid hormone and subsequent hypercalcemia, PHPT can show non-classical manifestation of cardiovascular and psychological systems as well as classical manifestation targeted the skeletal and renal systems (4-6).

There have been small studies about association between PHPT and cardiovascular disease, encompassing conditions like hypertension, left ventricular hypertrophy, and myocardial infarction (7,8). However, these observations lack a clear pathophysiological basis. Furthermore, the impact of parathyroidectomy on cardiovascular outcomes remains a topic of ongoing debate (6,9). Until now, cardiovascular evaluation in PHPT is not recommended and cardiovascular abnormalities, if present, should not be used as criteria for decision making for surgery (10). The recent study by Grant *et al.* encompassed a robust dataset comprising 108,869 PHPT patients, mostly hypercalcemic PHPT, identified within the Medicare database and a matched comparison group of 1,088,690 (11). There were modest statistical significances in the 5-year disease-free survival rates, major cerebrovascular events, and major cardiovascular events between patients with PHPT and the comparison group. Additionally, among patients who had parathyroidectomy, there was only reduction trend in the risk of major cerebrovascular and cardiovascular events compared to the comparison group. However, the authors pointed out an interesting trend: in cases where patients with hypertension underwent parathyroidectomy, there was a suggestion of reduced risk of major cerebrovascular events compared to the comparison subjects who did not undergo parathyroidectomy (hazard ratio of 0.87; 95% confidence interval: 0.75–1.01) (11). In conjunction with the study by Grant *et al.*, we recently reported that patients who had parathyroidectomy with complications, notably mood disorders, faced heightened risks of cardiovascular and cerebrovascular events, as well as mortality (3). While both studies draw from nationally representative datasets, it is important to note a crucial distinction in the racial composition of the patient populations that our study included only Asians and the study by Grant *et al.* included mostly Caucasians. This underscores the need for a comprehensive care of PHPT patients to optimize cardiovascular outcomes, considering the management of risk factors even after parathyroidectomy.

While parathyroidectomy can be considered as a potential intervention to mitigate cardiovascular and

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cerebrovascular risks in PHPT patients, it is paramount to recognize that hypertension often coexists with PHPT both before and after surgery (3,12). Although there has been studies that report the improvement of hypertension control after parathyroidectomy (13,14), several studies underscore that despite successful parathyroidectomy, hypertension may persist or even emerge *de novo* in a subset of patients (9,15). Despite an extensive evaluation of elderly PHPT patients, who are at a relatively elevated risk for cerebrovascular and cardiovascular incidents, the difference in the incidence of significant events between the surgery group and the control group was marginal. This observation underscores the complexity of PHPT's impact on cardiovascular health and the imperative for well-structured, long-term prospective studies. These studies may employ well-designed methodologies like propensity score matching or inverse probability of treatment weighting due to the inherent challenges of conducting randomized controlled trials within this disease setting.

However, it is essential to consider the factors contributing to the decision not to perform parathyroidectomy in some PHPT patients. The study does not provide detailed baseline characteristics of the surgical and non-surgical groups, making it challenging to ascertain whether patients who did not have surgery were not appropriate for the procedure due to advanced age, poor health conditions, or less severe forms of PHPT that are not indicated for surgery. This lack of baseline characteristics between patients who did and did not undergo parathyroidectomy makes it difficult to isolate the specific impact of parathyroidectomy. Furthermore, it is important to recognize that the study's retrospective nature may introduce biases and confounding variables that cannot be fully controlled for. The reliance on Medicare data, although comprehensive, may not capture all relevant clinical details and may lack information on certain confounding factors. Additionally, the absence of data on patient adherence to medical therapy and lifestyle modifications, which can significantly impact cardiovascular outcomes, is a notable limitation. Moreover, the study primarily focuses on major cardiovascular and cerebrovascular events as primary outcomes, and other clinically relevant endpoints, such as changes in bone health or quality of life, were not assessed.

Despite these limitations, the study's findings suggest a notable pattern in which PHPT patients with hypertension who underwent parathyroidectomy experienced a tendency of reduction in cardiovascular events compared to those who did not. This observation underscores the potential benefits of surgical intervention in certain PHPT cases and highlights the need for further research to better delineate the specific patient profiles that would benefit most from parathyroidectomy. The fact that even patients with milder forms of PHPT who did not undergo surgery may still experience cardiovascular events emphasizes the importance of careful evaluation and individualized management for all PHPT patients, especially those with hypertension.

In conclusion, Grant *et al.*'s study offers valuable insights into the potential advantages of parathyroidectomy in diminishing cardiovascular events among PHPT patients. Nonetheless, it also underscores the intricacies of result interpretation, acknowledging the possible influence of age-related factors and the presence of heterogeneity among those who underwent parathyroidectomy and those who did not. Additional research is needed to further clarify the beneficial effect of parathyroidectomy on cardiovascular and cerebrovascular health.

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