Editorial Commentary

Hypercalcemia from primary hyperparathyroidism

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It's all about serum calcium levels. Primary hyperparathyroidism (pHPT) has widespread impact on calcium trafficking and physiology which, when left undiagnosed or untreated, can adversely impair quality of life, contribute to co-morbidities, limit life expectancy, and increase health-related expenditures. pHPT is the leading cause of hypercalcemia among ambulatory population. Extreme and/or prolonged hypercalcemia can result in end organ damage (kidneys, bones, vasculature, etc.) which results in the morbidity and/or mortality of pHPT. The principal driver of atherosclerosis and thromboembolic events is calcification of lipid laden endothelial plaques (1).

Logic follows that as the periods of hypercalcemia are more pronounced or prolonged, so is the risk of calcified plaques. These vascular lesions are the drivers of vaso-occlusive events and infarctions. Hypercalcemia is also nephrotoxic resulting in diminished glomerular function and a resulting upward physiologic pressure on parathyroid hormone (PTH) production. Chronic kidney disease (CKD) is yet another independent risk factor for atherosclerotic vascular and end organ disease and those patients were excluded from this study in cases of end stage renal disease (ESRD) (2).

PHPT has been increasing for decades since the advent of adding calcium measurement to routine metabolic panel testing (3-5). PHPT goes largely unrecognized and untreated in contemporary practice which complicates the measurement of its impact upon vasculopathy (6-8). To make matters worse, the incidence of atypical or borderline pHPT is increasing which complicates pHPT diagnosis and decisions regarding subsequent intervention (9,10). This circumstance creates a situation where machine learning (ML)/artificial intelligence (AI) might be impactful (11).

AI implementation into the clinical work flows of hypercalcemia detection as well as the management of pHPT could take shape in radiology image assessments as well as laboratory value analysis from within the electronic medical record. The authors' primary interest and focus is upon the latter at present. The challenge, after identifying the known populations of hypercalcemics in the Electronic Medical Record (EMR) that are never evaluated further (6-8), is to match elevated calcium values to other laboratory studies and/or validated elements within a data phenotype to risk stratify individuals for the diagnosis of pHPT and notify their physicians to make appropriate referrals.

Grant *et al.* (12) set about, through a medical informatics approach, to establish the impact of pHPT upon the resultant mortalities of cerebral and coronary vascular disease and describe the impact successful parathyroid surgery could have upon the same. Cerebral vascular accident (CVA) and myocardial infarction (MI) are the tragic end results of atherosclerosis that have progressed from a stenotic lesion(s) to thromboembolism and starvation for circulation. Such studies can inform the surgeon as to population and patient level benefits of parathyroid surgery but also add support for refinement of data phenotypes

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of pHPT which can be used by AI to detect undiagnosed pHPT patients or to be a sentinel for known pHPT patients lacking adequate treatment (13). Furthermore, such an approach might identify specific risk factors for a parathyroid endocrinopathy which might be mitigated overtime, reducing the risk for prolonged hypercalcemia. Successful AI implementation will be constrained by limitations of past and present electronic medical records which are designed for clinical care, not research (11).

The authors examined a database of over 88 million Medicare recipients for pHPT and over 108K met their inclusion criteria. These were matched to 1 million non-pHPT Medicare recipients (a 1:10 match). There were no surprises in the pHPT group demographics (mostly female and Caucasian) but noteworthy, and consistent with other recent reports, was that only 37.2% underwent surgery (12), 8.6% were prescribed Cinacalcet, leaving over half of the population untreated. Unknown was whether the above treatments were ultimately successful in correcting hypercalcemia.

After accounting for known co-morbidities (hypertension, hyperlipidemia, or diabetes) which increase CVA and/or MI, disease-free survival (DFS) for any outcome, CVA, or MI were all highly significant. The respective increase in risk was 11%, 14%, and 6%, all more severe for males (12). The co-morbidities listed above all conferred a greater risk for stroke or MI than pHPT alone. Patients not operated upon but prescribed Cinacalcet had higher risks than the control group of developing a major vaso-oclusive event (12). A subgroup of hypertensive pHPT patients benefited from parathyroidectomy with a subsequent suggested decrease CVA risk and this subgroup may experience the most benefit from parathyroid surgery (12).

The authors report "This is the largest nationally representative study to evaluate risk of major cerebrovascular and major cardiovascular events in elderly patients with primary hyperparathyroidism and the effect of parathyroidectomy on those outcomes." (12). This data further highlights the risk of pHPT for increased cerebrovascular disease, which is novel, and cardiovascular disease which is confirmatory and marginal in its impact. These risks returned to the risk level for the control group upon (presumed successful) parathyroid surgery.

The risks of parathyroid surgery, though often reported as low, should not be disregarded. Parathyroid surgery should be assessed by its ability to restore normocalcemia (97–99%) but also by its potential for complications (14). These complications include recurrent laryngeal nerve injury, whether temporary or permanent, the need for revision parathyroid surgery, and if revision is required, the risk of hypoparathyroidism (15). Complications are often under reported in clinical series but appear more significant in registry studies (16).

Future studies might be directed towards other databases containing laboratory data and heart computed tomography (CT) results with calcium scores. Pre-, post-, and long-term CT calcium scores of the heart and carotid arteries might provide more definitive data regarding pHPT and risks for MI and stroke respectively.

Conclusions

Older patients, especially hypertensive males, are at increased risk for vascular end organ complications with untreated pHPT. Successful parathyroid surgery, one that corrects serum hypercalcemia, returns the risk for these vascular complications to the lower level of the comparison group without pHPT.

Improvements should be made to diagnose and treat patients with pHPT and AI/ML may be leveraged to do so. AI may identify modifiable risks for the development of pHPT and this may inform patient education and public health initiatives.

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Medical and Surgical Treatment of Parathyroid Diseases: *An evidence-based approach*. Brendan C. Stack, Jr., MD, FACS, FACE and Donald L. Bodenner, MD, PhD, editors. Cham Switzerland: Springer International Publishing; 2017. ISBN 978-3-319-26794-4. B.C.S. Jr is also the Chair of Endocrine Section in American Head and Neck Society. The author has no other conflicts of interest to declare.

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