A Retrospective Study of Incidental Primary Hyperparathyroidism in an Acute Hospital Population and Review of the Literature

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ABSTRACT

Background: Hypercalcemia and associated primary hyperparathyroidism (pHPT) are relatively common but are likely to be under-recognized and undertreated. This study aimed to assess the prevalence of incidental hypercalcemia, investigation, and follow-up with definitive care for an acute surgical Australian metropolitan population. This was complemented by a systematic review of the literature.

Materials and methods: A retrospective cohort study was conducted in a metropolitan, 172-bed general hospital within the Metro South Health service district of South-East Queensland, Australia. The electronic medical records of all acute general surgical admissions over a 6-month period (February–July 2019 inclusive) were reviewed and analyzed. This was supplemented by a systematic literature review of incidental hypercalcemia and hyperparathyroidism.

Results: Of 486 eligible patients requiring acute surgical admission, two were identified to possess incidental hypercalcemia, equating to an incidence of 0.41%. Within this context, the systematic review revealed a reported hypercalcemia prevalence of between 0.1 and 3.3% and a pHPT prevalence of between 1.3 and 3.5%. The incidence of new pHPT was between 6 and 50 per 1,00,000.

Discussion: This study is the first to investigate the incidence of incidental hypercalcemia and related hyperparathyroidism in an acute general surgical admission setting. Whilst the outcomes of this study have not shown expectedly high rates of hypercalcemia and hyperparathyroidism, this provides a platform for future clinical education, awareness, local protocol development, and improved patient care.

Clinical significance: The first study to investigate the incidence of incidental hypercalcemia and hyperparathyroidism in an acute general surgical admission setting. Lower than expected rates of hypercalcemia and hyperparathyroidism (2 out of 486 eligible patients) based on literature review which sets the platform for future research directions.

Keywords: Hypercalcemia, Hyperparathyroidism, Parathyroidectomy.

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INTRODUCTION

Primary hyperparathyroidism is the third most common endocrine disorder after diabetes and thyroid disease. Dramatic changes in pHPT epidemiology have recently been observed due to the increasing availability of biochemistry and osteoporosis screening tools. However, pHPT is still underdiagnosed and thus undertreated in the community particularly given the increasing burden of milder, asymptomatic disease. The most common causes for delayed diagnosis include failure to identify hypercalcemia, inadequate investigation following diagnosis of hypercalcemia, and not contemplating a diagnosis of pHPT.

Untreated pHPT can cause several significant long-term multisystem problems including an increased risk of cardiovascular diseases (hypertension, stroke, coronary heart disease), renal disease, neurocognitive and fracture risk, and nephrolithiasis. Given far-reaching consequences, the true burden of disease is difficult to estimate, impacting patient outcomes, healthcare resources, and associated budgets.

Hypercalcemia is the classical hallmark of pHPT and should always prompt further investigation with the diagnosis of pHPT generally being made by primary care physicians. This does, however, require a high index of suspicion as the symptoms of pHPT are typically non-specific. The unifying biochemical pattern between serum calcium level and unsuppressed parathyroid hormone (PTH) is the foundation for diagnosis.

Parathyroidectomy is the only definitive treatment for pHPT and cure rates remain over 95% with minimal morbidity in experienced centers. Despite proving to be more cost-effective than observation or medical treatment, the surgical referral rate still remains low.

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The aim of this study was to (1) identify the true incidence of incidental hypercalcemia in an acute metropolitan hospital population, and (2) ascertain the extent to which such cases are appropriately investigated and managed following identification. This will be analyzed within the context of the existing body of literature and employed to develop local guidelines for pHPT recognition, investigation, and treatment. Ultimately, this aims to minimize the long-term morbidity of an under-recognized disease with significant resource and monetary cost savings.

Materials and Methods
Ethical approval was obtained from the Metro South Human Research Ethics Committee (HREC/2020/QMS/63523). The project was deemed low/negligible risk.

Retrospective Case Notes Review
This study involved a single-centered review of cases presenting acutely to the Redland Hospital, a General Metropolitan Hospital with 172 beds located in Brisbane, Queensland, Australia. A retrospective review of electronic medical record case notes was performed on all acute general surgery admissions within a defined 6-month study period (February–July 2019 inclusive). Data was collated by two independent data collectors/study co-authors (AC and AL). To ensure data collation homogeneity, the two reviewers analyzed the first ten charts together. Data conflict was resolved by the senior author (JG).

All patients admitted acutely under general surgery with baseline blood tests (with serum calcium levels) were eligible for study inclusion. Exclusion criteria involved patients with known, or risk factors for, secondary/tertiary HPT (e.g., chronic renal failure; defined as eGFR < 60 mL/min/1.73 m²) or those not undergoing blood tests.

Hypercalcemia on admission was defined as a corrected calcium level of > 2.60 mmol/L. Following identification, case notes were critically reviewed to ascertain if hypercalcemia was: (1) recognized by the treating team, and (2) subsequently investigated. Demographic details, medical/surgical history, and medication history were also recorded.

Data analysis was completed with SPSS version 25.0 and a p-value of < 0.05 was deemed significant. Data are presented with descriptive statistics and quantitatively with regard to hypercalcemia.

Systematic Literature Review
PRISMA guidelines were employed for a systematic review of the literature regarding the incidence of hypercalcemia and/or pHPT. A comprehensive database (Medline Complete and Cumulative Index of Nursing and Allied Health Literature; CINAHL) search was undertaken and confined to the last 10 years (2010–2021). Only human studies written in the English language were included. The medical subject headings search terms used in the search included: incidence; prevalence; general surgery; hypercalcemia; hyperparathyroidism; “acute surgery”/txt; surgery operative. The reference lists of identified studies were also reviewed to include all relevant publications. Any study identifying the incidence or prevalence of pHPT, the incidence of hypercalcemia, and/or management of incidental hypercalcemia was included. Case reports, abstracts, and editorial studies were excluded. Publications identified for inclusion were reviewed by two authors (AC and AL) with conflict being resolved by the senior author (JG).

The incidence of incidental hypercalcemia was defined as the number of new cases of hypercalcemia identified incidentally from the blood tests/number of total candidates who had blood tests for the same year and presented to the Redland Hospital within the setting of this study. The incidence of primary hyperparathyroidism was defined as the number of new pHPT cases per year/number of study candidates for the same year. Prevalence was defined as the number of pHPT cases at a specific time point.

Results
Redland Hospital Cohort
Five hundred forty-four acute surgical admissions were identified throughout the study period. Thirty were found to be re-admissions, leaving a total of 514 patients. Only four did not have serum calcium tested and were thus excluded. In addition, we identified 24 patients with biochemical evidence of chronic kidney disease with an eGFR < 60 mL/min/1.73 m² and they were also excluded from this study. In total, 486 patients with 516 encounters were included in this study. Flowchart 1 demonstrated the process of patient selection, and Table 1 summarized the characteristics of patients with incidental hypercalcemia.

The median (± standard error) age of the study cohort was 49.3 ± 0.8 years. Fifty-eight percent were women and 42% were men. The median (± standard error) length of stay in the hospital was 2.0 ± 0.1 days. Four patients were found to have incidental hypercalcemia. On review of case notes one patient was identified to have known pHPT and another patient with incidental hypercalcemia had chronic kidney disease. Hence, the incidence rate of incidental hypercalcemia was 0.41% (2 out of 486) in our study group.

Systematic Review
A systematic review according to PRISMA guidelines identified a total of 84 studies. Following the application of inclusion and exclusion criteria, this was reduced to 10 papers. After full-text review, three papers were removed, leaving a total of seven papers for final study review (Flowchart 2). The year of publication...
Retrospective Study of Incidental pHPT in an Acute Hospital Population

### Table 1: Baseline characteristics of patients with incidental hypercalcemia

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Serum calcium/corrected calcium level (mmol/L)</th>
<th>Diagnosis of surgical admission</th>
<th>eGFR</th>
<th>Past medical/surgery history</th>
<th>Medication</th>
<th>Include/exclude</th>
</tr>
</thead>
<tbody>
<tr>
<td>60/Female</td>
<td>2.45/2.65</td>
<td>Retrocaval collection requiring percutaneous drainage</td>
<td>&gt;90</td>
<td>Grave disease, HTN</td>
<td>Thyroxine, perindopril</td>
<td>Include</td>
</tr>
<tr>
<td>64/Female</td>
<td>2.66/2.62</td>
<td>D2 Post-elective parathyroidectomy while the patient is on caltrate</td>
<td>&gt;52</td>
<td>GORD, dyslipidemia, diverticulardisease, fatty liver disease</td>
<td>Aspirin, ezetimibe, denosumab</td>
<td>Excluded as the patient was on a calcium tablet</td>
</tr>
<tr>
<td>71/Female</td>
<td>2.51/2.62</td>
<td>Surgical site fascial dehiscence from incisional hernia repair</td>
<td>&gt;90</td>
<td>Anxiety/depression, HTN, GORD, recurrent UTI</td>
<td>Candesartan, mirtazapine, candesartan, lerca-nidipine, omeprazole, hydralazine</td>
<td>Include</td>
</tr>
<tr>
<td>83/Female</td>
<td>2.45/2.60</td>
<td>Post-surgical site infection</td>
<td>42–48</td>
<td>AF, dyslipidemia, HTN, T2DM, vertigo, previous breast ca</td>
<td>Anastrozole, atorvastatin, digoxin, apixaban, vildagliptin, hydralazine, furosemide, fenofibrate, metoprolol, insulin</td>
<td>Excluded due to CKD</td>
</tr>
</tbody>
</table>

Flowchart 2: Flowchart of systematic literature review for incidence/prevalence of hypercalcemia and/or pHPT

- 84 of records identified through database searching
- 84 of records screened
- 74 of records excluded
- 10 of full-text articles assessed for eligibility
- 3 of full-text articles excluded with reasons
- 7 of studies included in qualitative synthesis

showed a general increase in the number of studies published over the 10-year review period.

### Incidence and Prevalence of Incidental Hypercalcemia

Balentine et al.\(^2\) reviewed a total of 68,2704 patients from a single tertiary center over a 4-year period and identified 10,432 patients with hypercalcemia (1.5%). Among those patients with hypercalcemia, only 28% had a documented diagnosis of hypercalcemia, only 31% of this group were tested for parathyroid hormone and only 22% of diagnosed patients were referred for a surgical opinion.

In addition, Asban et al.\(^3\) have shown that up to 10% of pHPT was unrecognized, even amongst patients with clear complications of pHPT. Of this cohort, surgical treatment was not employed in up to 20%.

### Incidence and Prevalence of Hyperparathyroidism

The incidence and prevalence of pHPT remain quite variable among different studies. Abood et al.\(^4\) examined 33 years worth of national data in Denmark and revealed a continuing increased incidence of pHPT in both genders during the 2000–2010 period. The incidence of pHPT was 16 per 1,00,000 per year in 2010, which compares to 21.6 per 1,00,000 per year in the US.\(^1\)

One of the largest studies conducted by Yeh et al. in the United State showed that the incidence of pHPT fluctuated between 36.3 and 120.2 in women and 13.4 and 35.6 in men, with an average incidence of 65.5 and 24.7, respectively.\(^15\) The prevalence of pHPT was also found to be increased by a factor of 3.05 in women and 2.80 in men over the study period. The highest rates occurred in black races, and older black women in particular Table 2 summarized systematic review data.

### Discussion

The most common etiology for hypercalcemia is pHPT, with roughly 1,00,000 new cases per year in the United States.\(^16\) Despite previous studies, the true numbers of pHPT cases are still difficult to define. The current study attempted to examine this issue within a local Southeast Queensland, metropolitan hospital setting. Acute surgical admissions were identified given the relative ease of case identification and data capture. Whilst skewed toward acute surgical pathology, this group served as a cross-section of all hospital admissions and the community in general. It could be argued that this then selects out a group of patients for whom fluid balance and electrolyte disturbances may make it difficult to truly define hypercalcemia and thus, pHPT. Whilst theoretically true, this did not appear to be an issue in practice as reflected by the very low numbers of patients identified as being hypercalcemic.

More specifically, only three patients were found to be hypercalcemic (after excluding chronic kidney disease), equating to 0.62% of the total cohort investigated. This is consistent with previous studies which have defined a range between 0.1 and 3.3%. Further to this, examination of case notes revealed an absence of recognition of hypercalcemia in all except one case with known pHPT. Not surprisingly then, none of these remaining two patients were then investigated or followed up within the context of potential pHPT. Not surprisingly then, none of these remaining two patients were then investigated or followed up within the context of potential pHPT. Therefore, the true extent of pHPT within this cohort is unable to be quantified. The only firm conclusions regarding this cohort relate to the under-recognition of hypercalcemia in general and also within the context of potential pHPT, which should be acknowledged.

Given the low case numbers of hypercalcemia/pHPT, the authors undertook a systematic review of the literature to define the true extent of the problem worldwide. The prevalence of incidental hypercalcemia was found to vary between 0.1\(^17\) and 4%.\(^18\) Following on from this, the prevalence of pHPT is estimated to be 0.1–0.86%.\(^4\)
Table 2: Summary of relevant studies from the literature search

<table>
<thead>
<tr>
<th>Author, years, and paper type</th>
<th>The setting, duration of the study, location, and age of participants if available</th>
<th>Inclusion, exclusion criteria, and statistical method</th>
<th>The main results include incidence/prevalence of hypercalciemia and/or hyperparathyroidism</th>
<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abood et al. 2013, retrospective study</td>
<td>National Hospital Discharge Register (Sundhedsstyrelsens Landspatientregister) in Denmark between 1977 and 2010.</td>
<td>Inclusion: diagnosis of pHPT based on the ICD 8 (between 1977 and 1993) and ICD 10 codes (1994 and 2010). Exclusion: not mentioned. Stats: t-tests for the two groups.</td>
<td>A higher percentage of incidence rates of pHPT among women compared to men, 24 per 1,00,000 compared to six in men in 2010. The average age of patients with pHPT also increased, from 49.4 in 1977 to 63.7 in 2010.</td>
<td>No mention of exclusion criteria or study population.</td>
</tr>
<tr>
<td>2. Griebeler et al. 2014, retrospective study</td>
<td>Medical records-linkage system (the Rochester Epidemiology Project) including all Rochester residents first diagnosed with pHPT between 2002 and 2010. The paper also included previous data from an existing epidemiology project from 1965 in the United State.</td>
<td>Inclusion: all patients with serum calcium &gt;2.52 mmol/L at least twice between 2002 and 2010. Exclusion: familial benign hypocalciuric hypercalciemia. Stats: Pearson Chi-square and Mann–Whitney tests.</td>
<td>The epidemiology of pHPT has significant changes over the last 5 decades, which appears to largely reflect alterations in medical practice. Overall pHPT incidence of 50.4 per 1,00,000 person-years from 1998 to 2010.</td>
<td>The population of Rochester is primarily white. Unable to capture BMD testing prior to 1998. No clear explanation for the decline in pHPT incidence in the last 2 years of the study. Ascertainment bias due to osteoporosis-related testing being performed on the patients most likely to have pHPT.</td>
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<tr>
<td>3. Lindner et al. 2013, retrospective cross-sectional descriptive cohort study</td>
<td>All Emergency presentations at the University Hospital Bern between 2008 and 2011 in Switzerland.</td>
<td>Inclusion: all blood tests with serum calcium &gt;2.55 mmol/L after correction for serum albumin. Exclusion: under 15 years of age. Stats: Mann–Whitney U test and X² tests.</td>
<td>0.1% of all patients had hypercalciemia. The median corrected calcium was 2.9 mmol/L. 8% had primary hyperparathyroidism and 12% had secondary hyperparathyroidism.</td>
<td>Lack of single management protocol. Nonstandardized documentation. Serum calcium was only measured in 19% of the participants. No follow-up assessment as it is a cross-sectional study.</td>
</tr>
<tr>
<td>4. Press et al. 2013, retrospective cohort study</td>
<td>Electronic medical records (EMR) in a single large tertiary referral center (Cleveland Clinic Foundation), including nine hospitals and 13 outpatient settings, in the United State from 2008–2009.</td>
<td>Inclusion: ≥ 2 elevated serum calcium over a 2 year period. Exclusion: serum creatinine ≥ 2 mg/dL or with end-stage renal disease. Stats: univariate analysis - fisher's exact test and contingency tables.</td>
<td>Out of a total of 7,269 patients. 1.3% had pHPT and 16 underwent parathyroidectomy. 2% of the healthcare system's patients had hypercalcemia.</td>
<td>The study is based on EMR–information contained in the EMR depends on the construction of the EMR and the accuracy of documentation. If a diagnosis of pHPT was not entered into the patient’s list of medical problems, it will not be included in the search. No review of bias in this study. Did not clarify who were the examiners.</td>
</tr>
<tr>
<td>5. Royer et al. 2014, retrospective cohort study</td>
<td>Medical records at the University of Tennessee College of Medicine Chattanooga (United States) from 2012–2013.</td>
<td>Inclusion: ≥ 2 elevated serum calcium and/or hyperparathyroidism. Exclusion: documented hypercalcemia but no online medical record available. Stats: Chi-square and Fisher's exact test. Age was analyzed with the Wilcoxon rank-sum test.</td>
<td>The total prevalence of hypercalcemia was 1% (168/17,150) and 101/168 were women with a mean age of 57y. 3.5% (6/168) had hyperparathyroidism. 24% of patients with mild hypercalcemia were discharged with no follow-up.</td>
<td>(Contd...)</td>
</tr>
</tbody>
</table>
This is the case. These include:

- Inappropriate risk bias: Physicians may overestimate the potential risk and/or benefits of treatment. Reassurance therapy for the patient may be preferred rather than pharmacologic intervention.
- Difficult diagnosis of pHPT: Normohormonal and normocalcemic pHPT are difficult to recognize. Patients with elevated calcium levels had undiagnosed or unrecognized pHPT with an estimated overall prevalence of 0.86% in his study. This is approximately eight times higher than the previously reported prevalence of 0.1%, indicative not only of the heterogeneity observed between series but also of the extent to which this underlying problem remains undiagnosed until identified incidentally.

Yeh et al. for instance estimated that the incidence of pHPT is 120.2 cases per 1,00,000 woman-years and 13.4–35.6 in 1,00,000 man-years. In this series, the mean age at pHPT diagnosis was 52 years for women and 56 years for men, with a female: male ratio of 3:4.

Press et al. also revealed that 43% of patients with elevated calcium levels had undiagnosed or unrecognized pHPT with an estimated overall prevalence of 0.86% in his study. This is approximately eight times higher than the previously reported prevalence of 0.1%, indicative not only of the heterogeneity observed between series but also of the extent to which this underlying problem remains undiagnosed until identified incidentally.

Table 2: Inclusion, exclusion criteria, and statistical method

<table>
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<th>Author, years, and paper type</th>
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<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Yeh et al. 2013, retrospective epidemiologic study</td>
<td>The population enrolled in Kaiser Permanente Southern California (KPSC) in the United States between 1995 and 2010, with participants over the age of 29.</td>
<td>Inclusion: at least one elevated serum calcium. Exclusion: age &lt;20 years of age, membership &lt;6 months, secondary hyperparathyroidism, and possible tertiary HPT. Only one elevated serum calcium level. Participants with a history of cancer or on thiazide, Stats: confidence intervals were estimated by applying correction factors.</td>
<td>53.8% were female and 63.3% were nonwhite. 40,857 eligible for inclusion, the incidence of pHPT was consistently higher among women than men. Mean incidence was 2.7 per 1,00,000.</td>
<td>Different diagnostic methods compared to previous epidemiologic studies using biochemical, histopathologic, radiologic, and clinical data sources. Ascertainment bias by using histopathologic data as it yields a higher detection rate. Not excluded are those with familial hypercalcemic hypercalcemia or other potential causes of non-pHPT hypercalcemia. Data from patients covered by private insurance. A single institution's data may have follow-up appointments at other institutions.</td>
</tr>
<tr>
<td>7. Balentine et al. 2017, retrospective study</td>
<td>Administrative data at the University of Alabama at Birmingham, from 2011–2015.</td>
<td>Inclusion: all patients seen at the UAB during the study period. Exclusion: no exclusion criteria. Stats: 2-tailed t-tests and Chi-square tests.</td>
<td>3.3% of the 3,15,300 participants had hypercalcemia. 71% of patients with clear HPT were not referred to a surgeon.</td>
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A review of the literature not only helped to identify various issues of pHPT identification and management but also highlighted an increasing trend in the disease incidence over time, which can be attributed to numerous factors: (1) routine calcium and biochemical testing since the 1970s, (2) a relatively low rate of exit through surgical treatment (e.g., in one study only 28% patients with recognized pHPT underwent surgery).

Regardless of the number of patients presenting with the known or occult disease, one obvious issue involves the recognition and investigation of hypercalcemia which may prevent the diagnosis of pHPT from being made. There are many potential reasons why this is the case. These include:

- Fluctuations in serum calcium: Calcium levels can vary more than 1 mg/dL from day to day and often elevated serum calcium is deemed of lesser importance and is hence ignored.
- Inadequate investigation of hypercalcemia: Primary health practitioners often repeat serum calcium without PTH and/or vitamin D levels despite hypercalcemia previously being recognized.
- Lacking continuity of care: A new physician may fail to recognize prior episodes of hypercalcemia and no further investigation is organized.
- Difficult diagnosis of pHPT: Normohormonal and normocalcemic hyperparathyroidism are difficult to recognize.
- Inappropriate risk bias: Physicians may overestimate the potential risks and underestimate the benefits of parathyroidectomy. This risk bias results in a large number of patients who prefer medical management with calcium-reducing agents or observation.

Given these issues, it is reasonable to conclude that the primary reasons for delayed diagnoses and poor surgical referral rates are not patient-related characteristics.

To resolve the missed or delayed diagnosis of hypercalcemia, the utilization of automated programs in electronic medical records and pathology results systems can and should be employed to prompt clinicians to further evaluate hypercalcemia. Beyond this, engaging with primary healthcare providers through education programs should be facilitated to raise awareness of the importance of the diagnosis and the gravity of related pHPT complications. In parallel, an up-to-date understanding of modern surgical strategy, techniques, and outcomes is required. Local guidelines for the management of pHPT are presently being prepared and will go some way toward assisting in this regard.

Yeh et al. for instance estimated that the incidence of pHPT is 120.2 cases per 1,00,000 woman-years and 13.4–35.6 in 1,00,000 man-years. In this series, the mean age at pHPT diagnosis was 52 years for women and 56 years for men, with a female: male ratio of 3:4.1
A common misconception is that pHPT has a low impact on overall health; a mindset that has been raised in multiple papers. Symptons of pHPT are often quite nonspecific and may not involve the "classic" pentad of kidney stones, painful bones, abdominal groans, psychic moans, and fatigue overtones. Dombrowsky et al. for example, have demonstrated that untreated pHPT can have a larger impact on older patients (>75 years) with up to a 75% increase in fracture rate, a 2.5-fold increase in cardiovascular disease, 5-fold increase in kidney stones, 14-fold increase in renal failure, and 40% increase in mortality. The evidence would suggest that this is not entirely rational and represents a missed opportunity.

Despite parathyroidectomy being the only definitive treatment for primary HPT, not all patients with pHPT will proceed to surgery. Reluctance to refer for a surgical opinion may stem from a perception of surgical morbidity. The incidence of significant complications following parathyroidectomy remains low in experienced centers, with permanent hypoparathyroidism and recurrent nerve injury encountered in <1% of all cases. Hence, surgical morbidity is no justification in the modern era to withhold referral for a surgical opinion in the absence of efficacious and definitive medical therapy for this problem.

**CONCLUSION**

The current literature suggests that primary hyperparathyroidism continues to be a problem in the community and conveys a significant public health burden. Associated knock-on clinical consequences and related healthcare costs represent a clear opportunity for clinical intervention to mitigate this risk. This study represents one of the first series examining this issue in an acute surgical patient cohort. Whilst the low incidence of hypercalcemia (and potential pHPT) did not reflect the global literature, what is clear is that this issue is still not well recognized. This can be addressed with improved awareness and education articulating the importance of recognition. Beyond this, clear guidelines suggesting surgical referral should be implemented to ensure that patients are appropriately counseled, and intervention is offered where the evidence would suggest that there is a clear clinical benefit.

**REFERENCES**