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Rates of hypercalcemia and hyperparathyroidism among patients with porcelain gallbladder

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ABSTRACT

Background: Porcelain gallbladder is characterized by calcification of the gallbladder wall, possibly associated chronic inflammation from cholelithiasis. It is unknown whether porcelain gallbladder is associated with higher rates of hypercalcemia and/or hyperparathyroidism compared to cholelithiasis without porcelain gallbladder.

Methods: We searched our patient database for patients with porcelain gallbladder on imaging and patients with cholelithiasis without porcelain gallbladder. We collected data on patient age, gender, calcium levels, parathyroid hormone (PTH) levels, and medications/comorbidities known to cause hypercalcemia.

Results: 1000 patients within our database had porcelain gallbladder on imaging. Of these, 661 (245 male) had at least one serum calcium value for analysis. These patients were matched by age and gender with 6610 patients with cholelithiasis who had at least one serum calcium value. Rates of recurrent/persistent hypercalcemia were higher among patients with porcelain gallbladder at 16.8% versus 11.1% ($p < 0.01$). Rates of hyperparathyroidism were also higher among porcelain gallbladder patients at 12% versus 7.5% ($p < 0.01$).

Conclusion: Patients with porcelain gallbladder show higher rates of hypercalcemia and hyperparathyroidism than patients with cholelithiasis alone.

Introduction

Porcelain gallbladder refers to partial or complete calcification of the gallbladder wall. It is a rare entity that is estimated to occur in 0.06%–1.1% of gallbladder specimens.[1,2] While rare, it is a pathological finding that most general surgeons will encounter during their career. The pathogenesis of porcelain gallbladder remains poorly understood and there are a few different theories as to why this occurs. One such theory is that chronic inflammation leads to deterioration of tissues into hyaline, which subsequently becomes calcified.[3] Another theory is that stagnant bile leads to calcium precipitation within the gallbladder mucosa.[1] It has been previously shown in animal models that biliary calcium levels are positively associated with serum calcium levels.[4–6] This led us to question whether elevated serum calcium may be associated with the development of porcelain gallbladder. The objectives of this retrospective case-control study were to assess rates and underlying causes of hypercalcemia among patients with porcelain gallbladder and compare these with a control group of patients with cholelithiasis alone (without calcification of the gallbladder wall).

Methods

This study was approved by the Institutional Review Board of the Mayo Clinic. Our institution maintains a data repository of patient information extracted from the electronic medical record including patient demographics, diagnoses, laboratory and radiology data, clinical notes, and pathology reports with the ability to search via text-based queries. Using this data repository, we identified patients with radiographic evidence of porcelain gallbladder. Among these patients, we selected those with at least one serum calcium value for analysis. Imaging studies that showed a porcelain gallbladder had been obtained between October 1994 and October 2018 and included X-ray, MRI, CT, and ultrasound. Next, we

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identified a control group of individuals with radiographic evidence of cholelithiasis without gallbladder wall calcification as well as at least one serum calcium value for analysis. Ten controls per porcelain gallbladder patient were randomly selected and matched based on patient age (at the time of their imaging study) and sex. After patients were identified, additional chart review was performed to extract and verify clinical characteristics.

Hypercalcemia was defined as serum calcium above the reference range for its particular assay. Due to variation in assays throughout the years, the upper limit of normal total serum calcium values ranged from 10.0 to 10.5 mg/dl. Hypercalcemia can be a transient phenomenon in patients presenting with acute hypovolemia, so we subdivided these hypercalcemic patients into two groups: transient hypercalcemia with only 1 value above reference range and recurrent/persistent hypercalcemia with multiple values above reference range. Hyperparathyroidism was similarly defined as serum parathyroid hormone above the reference range for its particular assay. Due to variation in assays throughout the years, the upper limit of normal parathyroid hormone values ranged from 50 to 80 pg/ml. Results that were reported in mmol/L were converted to pg/ml using a conversion factor of 9.4. Gallbladder malignancy was identified based on diagnosis codes for primary malignant neoplasm of gallbladder.

To investigate potential etiologies of hypercalcemia (other than hyperparathyroidism), we performed both text-based queries of patient charts and searched diagnosis codes for the following characteristics: thiazide diuretic use, lithium use, diagnosis of sarcoidosis, hypercalcemia of malignancy, elevated parathyroid-related peptide levels, hypervitaminosis D, hypervitaminosis A, and familial hypercalcemia.

Descriptive statistics were used to provide a summary of the data. Categorical data were reported as absolute frequencies (percentages). Continuous data were presented as mean and standard deviation. Tests of association included the 2-tailed Fisher's exact test or Pearson's chi-squared test. P values < 0.05 were considered statistically significant. All statistical analyses were conducted using JMP version 14.1.0 (SAS Institute, Cary, NC).

Results

There were 1000 patients with porcelain gallbladder identified, of which 661 had at least one serum calcium value. The age- and gender-matched control group of patients with cholelithiasis alone included 6610 patients (Table 1). The average age of these patients was 68.9 ± 13.3 years (mean $\pm$ SD, range 22–96 years). 62.9% (416/661) of patients were female. These values were identical in the cholelithiasis group because we had matched these patients based on age and gender.

A calcium level above the reference range was found in 24.4% (161/661) of patients with porcelain gallbladder compared with 20.6% (1359/6610) of patients with cholelithiasis alone ($p = 0.02$, Table 1). Recurrent/persistent hypercalcemia occurred in 111/661 (16.8%) of the patients with porcelain gallbladder and 734/6610 (11.1%) of the patients with cholelithiasis alone ($p < 0.01$, Table 1). Of all patients with hypercalcemia and porcelain gallbladder, 68.9% (111/161) had recurrent/persistent hypercalcemia compared to 53.9% (734/1361) with cholelithiasis alone ($p < 0.01$). Average high calcium levels were slightly different between groups as well, with the porcelain gallbladder group averaging 9.90 ± 0.75 mg/dl (mean $\pm$ SD, 95% CI 9.84–9.96) and the cholelithiasis alone group averaging 9.80 ± 0.62 mg/dl (mean $\pm$ SD, 95% CI 9.78–9.81, $p < 0.01$).

With the exception of elevated PTH, there were not significant differences in rates of the various potential risk factors for hypercalcemia (Table 1). There was a high proportion of patients in both groups on thiazide diuretics at 23.3% (154/661) for the porcelain gallbladder patients and 22.1% (1462/6610) for the cholelithiasis patients (Table 1, $p = 0.49$). Of the patients on thiazide diuretics, 19.9% (322/1616) displayed recurrent/persistent hypercalcemia.

Elevated parathyroid hormone levels occurred at a higher rate in the porcelain gallbladder group at 12.0% (79/661) vs. 7.5% (499/6610) in the cholelithiasis group ($p < 0.01$, Table 1). When subdivided into primary, secondary, or tertiary hyperparathyroidism, most of this difference arose from a higher proportion of secondary hyperparathyroidism in the porcelain gallbladder group (7.6% vs. 4.3%, $p < 0.01$, Table 1). Table 2 demonstrates the distribution of hyperparathyroidism types among the 79 porcelain gallbladder and 499 cholelithiasis patients with elevated PTH levels. Again, we see that the porcelain gallbladder group has a higher percentage of hyperparathyroid patients with secondary hyperparathyroidism than the group with cholelithiasis alone at 63.3% vs 56.7%. However, when analyzing just the subgroups of just patients with elevated PTH, the populations are no longer powered enough show a significant difference in these rates ($p = 0.27$). The mean PTH level was higher among patients hyperparathyroid patients with porcelain gallbladder as opposed to cholelithiasis alone at 223.1 ± 255.6 pg/ml (95% CI 180.15–265.97) vs. 161.9 ± 181.1 pg/ml (95% CI 144.74–179.05)($p < 0.01$, Table 2). Of note, only 58.5% (495/845) of the patients with recurrent/persistent hypercalcemia ever had their parathyroid hormone levels checked during the time period studied (October 1994–October 2018). Therefore, there may have been additional patients with undiagnosed hyperparathyroidism who were not accounted for in these percentages.

The suspected underlying etiology of persistent/recurrent hypercalcemia among both patient groups is presented in Table 3. As previously mentioned, more patients had persistent/recurrent hypercalcemia in the porcelain gallbladder group than the cholelithiasis group (16.8% vs 11.1%, $p < 0.01$), yet the causes of hypercalcemia were quite similar between groups. The most common etiology was thiazide diuretics which were used in 42.3% (47/111) of patients with porcelain gallbladder and 37.6% (275/734) of the patients with cholelithiasis alone ($p = 0.32$). PTH-mediated hypercalcemia (primary and tertiary hyperparathyroidism) was the underlying cause among 25.8% of the hypercalemic patients with no difference between groups (25.2% vs. 26.0%, $p = 0.88$).

Hypervitaminosis D (Total 25-hydroxyvitamin D levels >80 ng/ml) occurred rarely among all patients at rates of 0.8% vs. 0.6% (5/661 vs. 39/6610, $p = 0.59$, Table 1). Of these 44 patients with hypervitaminosis D,16 (36.4%) had recurrent/persistent hypercalcemia as a result with no difference between groups. This accounted for 1.9% of the patients with hypercalcemia (Table 3). In addition to these patients, who were typically taking supraphysiologic doses of non-prescription vitamin D, 22 patients who were in renal failure became hypercalcemic while taking paricalcitol (vitamin D analog frequently prescribed to patients on dialysis), which accounted for 1.9% of patients with hypercalcemia (Table 3).

Sarcoidosis, hypercalcemia of malignancy, familial hypercalcemia, lithium use, and hypervitminosis A were all relatively rare and occurred at similar rates between groups (Table 1, Table 3). A large number of hypercalcemic patients (329/845, 38.9%) did not undergo a thorough workup and a cause was unable to be determined (Table 3).

Gallbladder malignancy was discovered in 3.0% (20/661) of patients with porcelain gallbladder, which is a 6-fold increase over those patients with cholelithiasis alone, who had a malignancy rate of 0.5% (31/6610, $p < 0.01$, Table 1).

Discussion

Cholelithiasis is a fairly common phenomenon with a

Table 1
All patients: Demographics, laboratory results, and comorbidities. SD = Standard Deviation, CI = Confidence Interval of the mean, PTH = Parathyroid Hormone. *p-Value <0.05. †Not all patients had a parathyroid hormone level drawn, please see "n" under each column.

	Porcelain Gallbladder (n = 661)	Cholelithiasis Alone (n = 6610)	p-Value
Age in years (mean ± SD)	68.9 ± 13.3	68.9 ± 13.3	1.00
Gender (% Female)	62.9%	62.9%	1.00
*Hypercalcemia	161/661 (24.4%)	1359/6610 (20.6%)	0.02
*Recurrent/Persistent Hypercalcemia	111/661 (16.8%)	734/661 (11.1%)	<0.01
*Maximum Total Calcium (mg/dl, mean ± SD (95% CI))	9.90 ± 0.75 (9.84–9.96)	9.80 ± 0.62 (9.78–9.81)	<0.01
*Elevated PTH	79/661 (12.0%)	499 (7.5%)	<0.01
Primary Hyperparathyroidism	27/661 (4.1%)	204/6610 (3.1%)	0.87
*Secondary Hyperparathyroidism	50/661 (7.6%)	283/6610 (4.3%)	<0.01
Tertiary Hyperparathyroidism	2/661 (0.3%)	12/6610 (0.2%)	0.37
*PTH† (pg/ml, mean ± SD (95% CI))	153.57 ± 221.88 (114.13–193.01) n = 124	97.98 ± 142.68 (89.06–106.9) N = 985	<0.01
Thiazide Diuretics	154/661 (23.3%)	1462/6610 (22.1%)	0.49
Hypervitaminosis D (>80 ng/ml)	5/661 (0.8%)	39/6610 (0.6%)	0.59
Sarcoidosis	7/661 (1.1%)	62/6610 (0.9%)	0.76
Hypercalcemia of Malignancy	0/661 (0%)	7/6610 (0.1%)	0.40
Familial Hypercalcemia	0/661 (0%)	3/6610 (0.1%)	0.78
Lithium	5/661 (0.8%)	42/6610 (0.6%)	0.61
Hypervitaminosis A	3/661 (0.5%)	21/6610 (0.3%)	0.48
*Gallbladder Malignancy	20/661 (3.0%)	31/6610 (0.5%)	<0.01

prevalence of approximately 10–15% in developed countries.[7] In contrast, porcelain gallbladder is a relatively rare entity that has been found in approximately 0.06%–1.1% of gallbladder specimens.[1,2] Previous studies indicate that calcium is an important component of bile that plays a role in the formation and growth of several types of gallstones.[8,9] However, it is unknown whether calcium levels play a role in the pathogenesis of porcelain gallbladder and there have been no previous studies assessing calcium levels among these patients. In our study, we found that patients with a radiographic diagnosis of porcelain gallbladder had a high rate of recurrent/persistent hypercalcemia at 16.8%. Patients with cholelithiasis alone had a somewhat lower, but still substantial, hypercalcemia rate of 11.1% ($p < 0.01$).

Due to the high prevalence of recurrent/persistent hypercalcemia in both patient groups, screening for calcium-related disorders among patients with gallbladder disease may be prudent. Serum calcium levels can often be added-on to stored serum used for metabolic and hepatic function lab panels, making screening a non-invasive and low-cost event. If hypercalcemia is discovered, further workup for etiology should be pursued.

An association between hyperparathyroidism and cholelithiasis has been an area of debate. Some studies show higher-than-expected rates of cholelithiasis among patients with hyperparathyroidism compared with the general population.[10] However, other studies show no such correlation.[11] The prevalence of primary hyperparathyroidism has been estimated at 0.08–0.23% among women and 0.03–0.09% among men in a US population.[12] In our study, rates of primary hyperparathyroidism were much higher than this expected value at 4.1% for patients with porcelain gallbladder and 3.1% for patients with cholelithiasis alone. This would suggest that primary hyperparathyroidism may have an association with the development of cholelithiasis in select patients. Several patients with recurrent/persistent hypercalcemia did not undergo PTH testing (350/845, 41.4%), so the actual prevalence of primary hyperparathyroidism in these populations may, in fact, exceed these values. Additionally, we only classified patients as having primary hyperparathyroidism if they met strict criteria of both serum calcium and PTH above normal. It is well-known that hyperparathyroidism exists on a spectrum which includes hypercalcemia with inappropriately non-suppressed PTH and normocalcemic primary hyperparathyroidism. Including these milder phenotypes would only have increased the already higher-than-expected rates of hyperparathyroidism seen in our study.

In our study, there were higher rates of all types of hyperparathyroidism (PTH above reference range) among patients with porcelain gallbladder compared with patients with cholelithiasis alone 12.0% vs 7.5%, $p < 0.01$). However, further inquiry revealed that much of this difference was made up by patients with secondary hyperparathyroidism. Why secondary hyperparathyroidism would be associated with porcelain gallbladder remains unknown. Perhaps it results from medications commonly prescribed to patients with secondary hyperthyroidism. For instance, previous studies have shown an association between cinacalcet (a calcimimetic commonly prescribed to patients with secondary hyperparathyroidism) and gallstones with 47.8% of patients on the medication demonstrating cholelithiasis on ultrasound compared with 15.8% of patients with end stage renal failure but not on cinacalcet.[13] Perhaps the same milieu that increases risk of cholelithiasis among patients on such medications patients could also predispose these patients to porcelain gallbladder. Alternatively, porcelain gallbladder may be an example of metastatic calcification: calcification of soft tissues that occurs in renal failure patients with secondary hyperparathyroidism and elevated calcium-phosphorus ion product. It is not a rare phenomenon: Metastatic calcification has been found in 60%–80% of dialysis patients at autopsy or by bone scintigraphy.[14] Soft tissue calcification has been

Table 2
Distribution of hyperparathyroidism types and mean PTH values among patients with elevated PTH levels. PTH = Parathyroid Hormone.

	Hyperparathyroid Patients with Porcelain Gallbladder (n = 79)	Hyperparathyroid Patients with Cholelithiasis Alone (n = 499)	p-Value
Primary	27/79 (34.1%)	204/499 (40.9%)	0.26
Secondary	50/79 (63.3%)	283/499 (56.7%)	0.27
Tertiary	2/79 (2.5%)	12/499 (2.4%)	0.95
PTH (pg/ml, mean ± SD (95% CI))	223.1 ± 255.6 (180.15–265.97)	161.9 ± 181.1 (144.74–179.05)	<0.01

Table 3
Etiology of Persistent/Recurrent Hypercalcemia among patients with porcelain gallbladder and cholelithiasis alone. Percentages do not add up to 100% because some patients had multiple potential etiologies (i.e. Hyperparathyroidism + Thiazide use).

Suspected Etiology of Hypercalcemia	Hypercalcemic patients with Porcelain Gallbladder (n = 111)	Hypercalcemic patients with Cholelithiasis alone (n = 734)	p-Value
Thiazide	47/111 (42.3%)	275/734 (37.6%)	0.32
PTH-mediated (1° and 3°)	28/111 (25.2%)	190/734 (26.0%)	0.88
Vitamin D > 80 mg/ml	2/111 (1.8%)	14/734 (1.9%)	0.94
Supratherapeutic Paracalcitol[a]	2/111 (1.8%)	22/734 (3.0%)	0.48
Recurrent Hypovolemia	5/111 (4.5%)	15/734 (2.0%)	0.17
Hypercalcemia of Malignancy	0/111 (0%)	7/734 (9.5%)	0.60
Lithium	2/111 (1.8%)	6/734 (0.8%)	0.28
Sarcoidosis	3/111 (2.7%)	5/734 (0.7%)	0.08
Familial	0/111 (0%)	3/734 (0.4%)	1.0
Hypervitaminosis A	0/111 (0%)	5/734 (0.7%)	1.0
Unknown	39/111 (35.1%)	290/734 (39.5%)	0.38

[a] Vitamin D Analog

described in a variety of tissues including the lungs, skin and subcutaneous tissue, cornea and conjunctiva, muscle, breast parenchyma, and myocardium.[15–18] Conceivably, these patients could be at increased risk of gallbladder wall calcifications as well.

Of note, a substantial portion of patients in our study were found to be on thiazide diuretics (1616/7271, 22%). Thiazides have been shown to reduce mortality and cardiovascular events for patients with essential hypertension and are considered a first-line agent.[19] However, thiazides have the well-known side effect of hypercalcemia. In our study, recurrent/persistent hypercalcemia occurred among patients on thiazides at a rate of 20% (322/1616). Use of thiazide diuretics has also been linked to gallbladder disease: In a prospective study involving women taking thiazide diuretics, the relative risk of cholecystectomy increased 36% for past users and 57% for current users.[20] In our study, thiazides were used at equivalent rates between the two groups, which indicates that there is no increased risk of porcelain gallbladder exceeding that of cholelithiasis alone.

The median age of the patients in this study was 68.9 years, which may also be partially accountable for the high rates of hypercalcemia in the two groups. Several of the factors that lead to hypercalcemia increase in incidence with age including hyperparathyroidism, thiazide diuretic use, and malignancy. Of note, the ages of the cholelithiasis alone control group were selected to match those of the porcelain gallbladder group and are likely older than the standard population of patients with cholelithiasis. While we showed an 11.1% hypercalcemia rate among the cholelithiasis group in our study, the general population of patients with cholelithiasis is likely younger and could display a lower rate of hypercalcemia.

An additional factor to consider is that serum calcium levels can become mildly increased with episodes of acute hypovolemia. By separating out patients who exhibited only one elevated calcium level, we aimed to limit the amount of patients with such a transient etiology for their hypercalcemia. However, patients with gallbladder disease could conceivably be presenting multiple times in states of hypovolemia due to associated vomiting, leading to their being diagnosed with recurrent hypercalcemia in our study. We identified 20 such patients (Table 3) by reviewing charts for the terms “hypovolemia/hypovolemic” and “dehydration/dehydrated” and analyzing the associated documentation. However, there may be more patients with transient, hypovolemia-related hypercalcemia who could not be so easily identified.

In our cohort of patients, the gallbladder malignancy rate was found to be 3% (20/661) for the porcelain gallbladder group versus 0.5% (31/6610) for the cholelithiasis group ($p < 0.01$). The association between gallbladder cancer and a calcified gallbladder wall was first described in the 1950s.[3,21] The incidence reported in the literature is highly variable, with older studies citing gallbladder carcinoma rates as high as 12.5–61.5% in patients with porcelain gallbladder.[1,3,22–24] The high rates reported in the early literature are likely due in part to the less sensitive imaging modalities that were available at the time. More recent studies from the past 25 years show much lower carcinoma rates of 0–7.7% among porcelain gallbladder patients.[2,25–27] A notable study by Stephen and Berger indicated that selective mucosal calcification was associated more strongly with gallbladder carcinoma than diffuse calcification of the wall.[25] In our study, we did not differentiate between selective mucosal calcification and diffuse intramural calcification, so we cannot comment on this finding in our particular cohort of patients.

Whether a 3% malignancy rate warrants prophylactic cholecystectomy in patients with porcelain gallbladder is a matter of controversy in the current literature. Some authors have proposed that the risk of malignancy in is low enough that asymptomatic patients may be safely observed[2,28] while other authors maintain that cholecystectomy should be performed even on asymptomatic patients because the outcomes of advanced gallbladder cancer are so poor.[29] We prefer to base the decision on individual patient factors, favoring cholecystectomy except when surgical comorbidities would preclude tolerance of a potentially open cholecystectomy.

Limitations

Many of the patients in our study had persistent or recurrent hypercalcemia that was never fully evaluated. This is likely reflective of a larger problem: the underdiagnosis and delayed diagnosis of patients with calcium metabolism disorders. Persistent hypercalcemia is never normal and should be appropriately evaluated. Additionally, primary hyperparathyroidism exists on a spectrum and, by using stringent criteria, we possibly overlooked patients on the mild end of the spectrum: namely those with inappropriately non-suppressed parathyroid hormone or normocalcemic hyperparathyroidism.

Given our methodology, we did not determine the temporal relationship between the patients’ hypercalcemia and the development of porcelain gallbladder. With both of these diagnoses often being chronic and commonly undiagnosed for long periods of time, efforts to determine the exact onset of these diagnoses would likely be fraught with error.

Conclusions

The prevalence of persistent/recurrent hypercalcemia is high in patients with porcelain gallbladder at 16.8%. Persistent/recurrent hypercalcemia is also seen to a lesser extent in patients with cholelithiasis at 11.1%. The underlying cause of these patients’ hypercalcemia is variable and includes thiazide use, hyperparathyroidism, or more rare causes. When patients with gallbladder disease, especially porcelain gallbladder, are encountered in clinical

practice, clinicians should consider evaluating for hypercalcemia. Recurrent/persistent hypercalcemia is never normal and should incite a thorough workup.

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Appendix A. Supplementary data

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