

Frequency of Parathyroid Hormone Assessment in the Evaluation of Hypercalcemia. A Comparison Between Patients With and Without a History of Malignancy in a 20-year Dataset of 20,954 Patients

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Michael T Sheehan¹ , Ya-Huei Li², Suhail A Doi³
and Adedayo A Onitilo⁴

¹Department of Endocrinology, Marshfield Clinic Health System, Weston, WI, USA. ²Cancer Care and Research Center, Marshfield Clinic Research Institute, Marshfield, WI, USA. ³Department of Population Medicine, College of Medicine, Doha, Qatar. ⁴Department of Oncology, Marshfield Clinic Health System, Weston, WI, USA.

ABSTRACT

BACKGROUND: The purpose of this study was to evaluate whether a prior diagnosis of malignancy affected the assessment of parathyroid hormone (PTH) in hypercalcemic patients and whether the rate of this assessment changed over time.

METHODS: A retrospective cohort study was designed that included adult patients with hypercalcemia with and without a history of malignancy between January 1, 2000 and December 31, 2019 in the Marshfield Clinic Health System (MCHS). The overall and annual rates of PTH assessment in each group was determined. In patients with a PTH assessment, duration of time and number of elevated serum calcium levels between the first documentation of hypercalcemia and the assessment of PTH were recorded, as was the degree of hypercalcemia.

RESULTS: Approximately a quarter (23%) of the patients in each group had a PTH assessment. The rate of PTH assessment initially increased over time but later declined significantly. Although a more severe degree of hypercalcemia predicted a greater probability of PTH assessment, the rate of assessment declined with all degrees of hypercalcemia in the last 5 years. While most patients who had a PTH assessed did so within a few months of the first documentation of hypercalcemia, less than half (40%) had a delay of more than 2 years before a PTH level was drawn.

CONCLUSION: This lack of appropriate and timely assessment may have significant health consequences in both groups of patients. Better education of providers about the appropriate and timely assessment of PTH in the evaluation of hypercalcemia is urgently needed.

KEYWORDS: Parathyroid hormone, PTH, hypercalcemia, malignancy

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CORRESPONDING AUTHOR: Michael T Sheehan, Department of Endocrinology, Marshfield Medical Center, Weston, 3400 Ministry Pkwy, Weston, WI 54476, USA. Email: sheehan.michael@marshfieldclinic.org

Introduction

Hypercalcemia is a frequent finding on routine laboratory testing. The prevalence appears to range between 0.17 and 2.92% in hospitalized patients and 1.0% to 3.9% in outpatients,¹ with the highest frequencies seen in women over the age of 60 years.² There are many reviews on the various etiologies of hypercalcemia, with primary hyperparathyroidism making up the vast majority of cases, especially in the outpatient arena.^{3–5} In this setting, primary hyperparathyroidism accounts for approximately 80% to 85% of all cases of hypercalcemia. However, in the hospital, malignancy makes up nearly 50% of all cases of hypercalcemia.^{6,7} The first step in the evaluation of hypercalcemia is to repeat the calcium level, often with a simultaneous assessment of parathyroid hormone (PTH). This allows for simultaneous confirmation of hypercalcemia and determination of whether it is PTH-dependent or PTH-independent, the latter indicated by a suppressed PTH.^{4,5} Although there may be discussion on what cutoff point should be utilized to

determine a suppressed PTH, most of the literature suggests a PTH value equal to or below 20 pg/mL or 2.12 pmol/L.^{4,8–10}

Primary hyperparathyroidism is fairly common. It has a female to male predominance of approximately 3 to 4:1, and its incidence increases with age,^{8,9,11} with a higher incidence in African Americans. The lowest incidence is similar between genders and races under 50 years-of-age, with a rate of 12.1 to 24.4 per 100 000 person-years and highest in African American women aged 70 to 79 at a rate of 921.5 per 100 000.¹¹ Although classic complications at the presentation of primary hyperparathyroidism are the exception rather than the rule in the United States with increased routine laboratory testing, it does still carry a significantly increased risk of both skeletal and renal complications.^{8,10} An accurate and timely diagnosis of primary hyperparathyroidism is necessary for the proper screening and monitoring for these complications. Despite a simple means with which to diagnose primary hyperparathyroidism, for various reasons, this is a diagnosis that is often overlooked by lack



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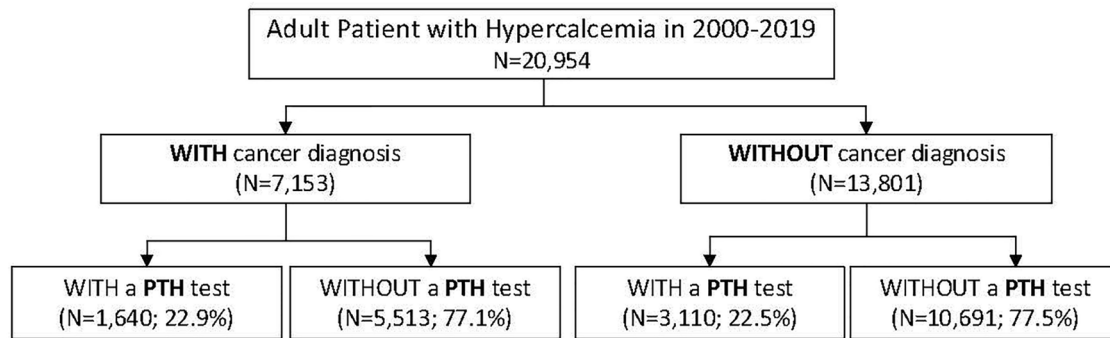


Figure 1. Subgroups of patients with hypercalcemia.

of and/or incorrect interpretation of biochemical testing.¹²⁻¹⁷ Multiple studies have shown that only approximately 30% of patients with documented hypercalcemia have ever had a PTH level assessed.¹²⁻¹⁷ However, the frequency range at different facilities described in a single study varied widely from as low as 4% to as high as 57%.¹⁶

Hypercalcemia of malignancy (HCM) is an important complication of malignancy, most often seen in advanced stages of the clinical course of a patient. Estimates of its frequency appear to be decreasing, recent studies suggesting a prevalence on the order of 0.67% to 2.0%,^{18,19} while older studies suggest a higher prevalence of between 20% and 30%.^{4,20} Parathyroid hormone levels in HCM will be suppressed to ≤ 20 pg/mL (2.12 pmol/L) outside the rare case of PTH-mediated HCM seen in parathyroid carcinoma or extremely rare cases of ectopic production of PTH.^{4,20} The first step in identifying HCM is to assess a PTH level to confirm PTH suppression indicating PTH-independent hypercalcemia, after which further biochemical and radiographic analysis should be performed to determine the underlying cause. This assessment of PTH is also important in those patients with a history of malignancy, as a significant portion may actually have primary hyperparathyroidism and not HCM.^{21,22}

We conducted a retrospective analysis of a 20-year dataset of patients presenting with hypercalcemia in the Marshfield Clinic Health System (MCHS) between January 1, 2000 and December 31, 2019. Unique to other studies in this regard, we separated hypercalcemic patients into 2 groups: those with and without a pre-existing history of malignancy. We sought to determine whether a history of malignancy affected a provider's decision to order a PTH level in the assessment of hypercalcemia. The dataset was also analyzed to determine if there was any temporal trend in the likelihood of PTH assessment in hypercalcemic patients throughout the 20-year study period. Both the duration of time and the number of elevated calcium levels between the initial documentation of hypercalcemia and the eventual assessment of PTH were assessed. Lastly, potential factors that influenced a provider's decision to assess a PTH and, in those patients who did have a PTH level assessed, factors affecting the likelihood of PTH-independent hypercalcemia were documented.

Methods

We used a retrospective study design to identify patients with hypercalcemia over a 20-year period from January 1, 2000, to December 31, 2019. Prior to commencement, the study was reviewed and approved by the MCHS Institutional Review Board with waiver of informed consent. An electronic algorithm was used to query laboratory data to identify cases of hypercalcemia. ICD-9 and ICD 10 codes were used to identify the subgroup of these hypercalcemic patients who had a history of malignancy at any time before or within 1 month after the first identification of hypercalcemia. Patients with leukemia or simple skin cancers and those under the age of 18 years were excluded. In each of the 2 subgroups, whether or not a PTH level was drawn within 1 month before or after the elevated calcium was documented was then captured. In those patients with a PTH level assessed, age, gender, and drug flag of medications that might elevate serum calcium (thiazide diuretics and lithium) at the time of hypercalcemia were recorded. Furthermore, the dates of the first elevated calcium and eventual PTH assessment as well as the number and highest serum calcium level drawn prior to that eventual assessment of PTH were captured. The timespan between the first elevated calcium and the eventual assessment of PTH was calculated. Hypercalcemia was defined as any serum total calcium > 10.3 mg/dL (2.6 mmol/L). Ionized calcium and albumin were not captured and, thus, corrected calcium was not recorded. Parathyroid hormone-independent hypercalcemia was defined as a PTH ≤ 20 pg/mL (2.12 pmol/L) and PTH-dependent hypercalcemia was defined as a PTH above this threshold.

For group comparison, a chi-square test was performed for categorical information. A *t*-test was performed for numerical variables. The cutoff for statistical significance was set to 0.05. All analyzes were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

The total sample of adult patients with hypercalcemia was 20954, of which 7153 (34.1%) had a previous or concurrent diagnosis of malignancy, and 13801 (65.9%) had no prior history of malignancy. There were no differences between the 2 groups in terms of the frequency of hypercalcemic patients who had a PTH level assessed (Figure 1 and Table 1). Overall,

Table 1. Comparison of hypercalcemic patients: with (N = 7153; 34.14%) versus without a history of malignancy (N = 13801; 65.86%).

VARIABLES		WITH CANCER	WITHOUT CANCER	P-VALUE
		N (%)	N (%)	
Gender	Female	4822 (67.41)	9250 (67.02)	0.571
	Male	2331 (32.59)	4551 (32.98)	
Drug-flag*	No	5113 (71.48)	9828 (71.21)	0.684
	Yes	2040 (28.52)	3973 (28.79)	
PTH test	No	5513 (77.07)	10691 (77.47)	0.520
	Yes	1640 (22.93)	3110 (22.53)	
Age of the first high serum calcium (years); Mean \pm SE		62.36 \pm 0.16	59.20 \pm 0.14	<.001
Number of high serum calcium (>10.3 mg/dL); Mean \pm SE		2.94 \pm 0.04	1.79 \pm 0.02	<.001
The maximum serum calcium level (mg/dL); Mean \pm SE		11.02 \pm 0.01	10.78 \pm 0.01	<.001

Divide serum calcium in mg/dL by 4 to convert to mmol/L.

*thiazide diuretics or lithium.

throughout the entire 20-year timeframe, less than a quarter of patients in each group had a PTH level assessed in the evaluation of their hypercalcemia. Also shown in Table 1, neither patient gender nor the presence of a medication that could potentially affect calcium levels differed between the groups. However, patients with a history of malignancy were significantly older at the time of their first documentation of hypercalcemia and had a significantly higher number of elevated serum calcium levels. Furthermore, the maximum serum calcium level was higher in patients with a prior history of malignancy than in those without.

The variables found to affect the likelihood of a PTH assessment are listed in Table 2. Female gender, age older than 60 years, use of medications known to possibly affect serum calcium levels, and degree of hypercalcemia were associated with an increased likelihood of PTH assessment. Figure 2 shows the frequency of PTH assessment throughout the 20-year timeframe. There was an increase in the frequency of assessment of PTH in both groups between 2000 and 2006, followed by relative stability in the assessment until 2012, and thereafter the rate of PTH assessment declined, eventually to a frequency lower than at the beginning of the 20-year time frame. Furthermore, while there were a couple of instances of a significant difference in the likelihood of PTH assessment between the 2 groups, the frequency of PTH assessment, for the most part, showed no difference between the groups over time. The change in assessment of PTH over time for different degrees of hypercalcemia is depicted in Figure 3. These data show while patients with more severe hypercalcemia were more likely to have a PTH assessed, the decline in frequency of this assessment in the latter quartile of the 20-year period occurred regardless of the degree of hypercalcemia.

Table 2. Variables associated with PTH testing in hypercalcemic patients.

VARIABLE	OR (95% CI)	P-VALUE
Female gender	1.58 (1.47–1.70)	<.001
>60 years of age	1.12 (1.05–1.19)	.001
Thiazide diuretic or lithium use	1.17 (1.09–1.25)	<.001
Cancer diagnosis	1.02 (0.96–1.09)	.520
Serum calcium level		<.001
≤10.4 mg/dL	1.00 [reference]	
10.5 mg/dL	1.45 (1.28–1.64)	
10.6 mg/dL	1.80 (1.59–2.05)	
10.7 mg/dL	2.60 (2.28–2.97)	
10.8 mg/dL	2.72 (2.35–3.15)	
10.9 mg/dL	2.96 (2.53–3.46)	
11.0–11.4 mg/dL	4.26 (3.79–4.79)	
11.5–12.4 mg/dL	4.34 (3.78–4.99)	
≥12.5 mg/dL	6.14 (5.23–7.21)	

OR (95% CI): odds ratio (95% confidence interval).

Divide calcium in mg/dL by 4 to convert to mmol/L.

The distribution of PTH levels is shown in Figure 4. A significantly greater number of patients with a history of malignancy had suppressed PTH. While just under 50% of the patients in each group had an elevated PTH, around one-third had a PTH level within the normal range. Table 3 analyzes the patients who had a PTH test, comparing those with

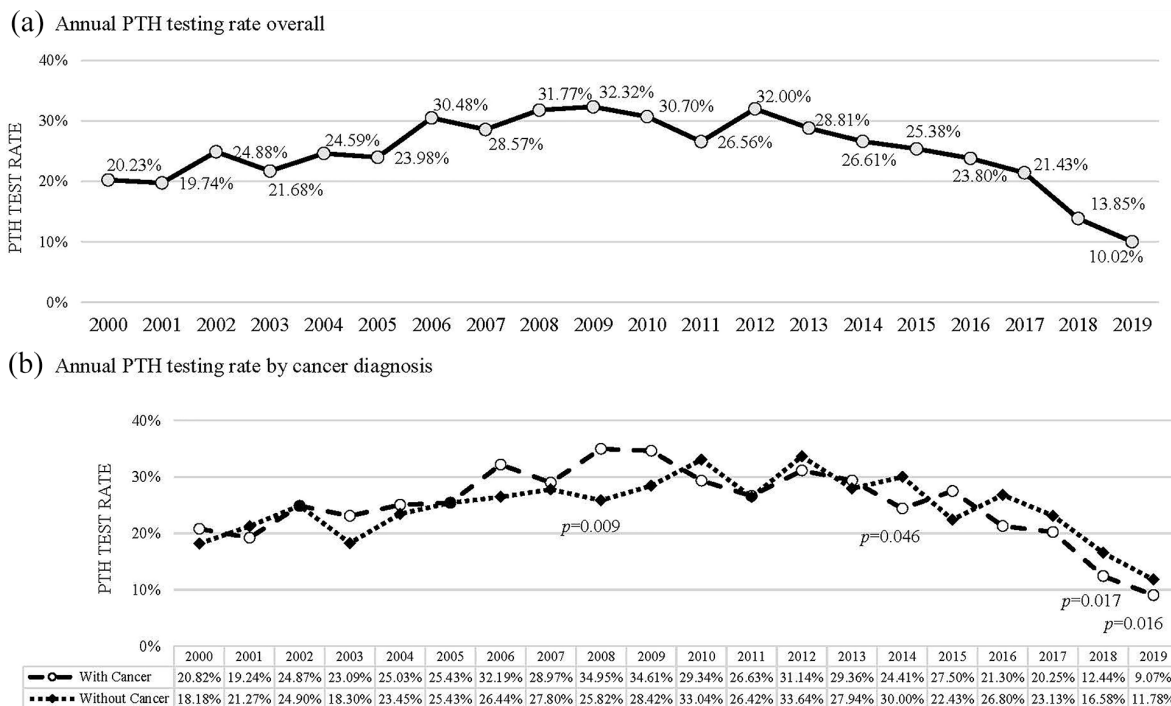


Figure 2. Annual PTH testing rates: (a) overall and (b) with/without history of malignancy.

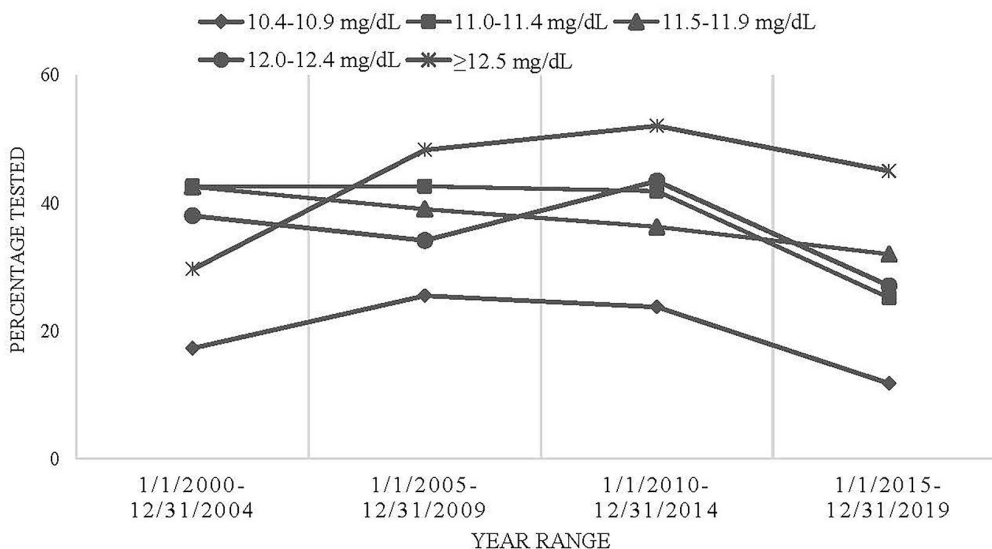


Figure 3. PTH testing rates by serum calcium level (all patients).

PTH-independent versus PTH-dependent hypercalcemia. Male gender, a prior history of malignancy diagnosis, and a higher degree of hypercalcemia were more likely to be associated with PTH-independent hypercalcemia. Patient age did not affect whether the PTH was suppressed or not. Parathyroid hormone-dependent hypercalcemia was more commonly associated with the use of medications that potentially raise serum calcium. Lastly, PTH-independent hypercalcemia was identified with a similar number of elevated calcium levels (mean 1.86 tests) when compared with PTH-dependent hypercalcemia (mean 2.37 tests). The median lead time till the PTH was assessed was 2 months earlier when PTH was suppressed versus

not suppressed (median 4.7 compared to 6.7 months, respectively), although this did not reach statistical significance.

As shown in Figure 5, while there was no difference in the duration of time at which a PTH was checked and documented to be suppressed or not suppressed, a substantial proportion of patients in each group had a delay of more than 2 years before the PTH was finally assessed (38.8% and 39.1%, respectively). Further characterization of this delay in PTH assessment is presented in Figure 6, showing the number of elevated serum calcium levels that were documented in the laboratory record within each temporal timeframe of delay. For example, when looking at the same group who had a longer than 2 year delay in

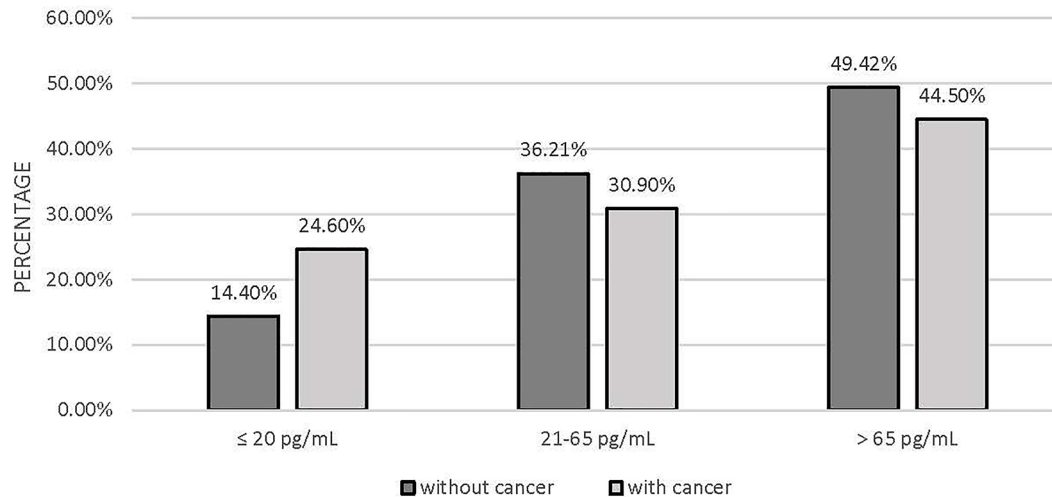


Figure 4. PTH level by history of malignancy among hypercalcemic patients in whom a PTH level was obtained.

Table 3. Comparison of hypercalcemic patients with PTH test obtained: suppressed (≤ 20 pg/mL) versus non-suppressed PTH level (> 20 pg/mL).

VARIABLES		SUPPRESSED PTH LEVEL	NON-SUPPRESSED PTH LEVEL	P-VALUE
		N (%)	N (%)	
Gender	Female	544 (15.34)	3000 (84.65)	<.001
	Male	307 (25.45)	899 (74.54)	
Drug-flag*	No	620 (18.97)	2648 (81.03)	.005
	Yes	231 (15.59)	1251 (84.41)	
Cancer diagnosis	No	447 (14.37)	2663 (85.63)	<.001
	Yes	404 (24.63)	1236 (75.37)	
Age of the first high serum Ca ²⁺ (years); Mean \pm SE		61.43 \pm 0.52	61.39 \pm 0.22	.946
Number of high serum Ca ²⁺ levels (> 10.3 mg/dL) prior to the PTH assessment; Mean \pm SE		1.86 \pm 0.08	2.37 \pm 0.05	<.001
The maximum serum Ca ²⁺ level (mg/dL) that did not prompt a PTH assessment; Mean \pm SE		11.82 \pm 0.05	10.97 \pm 0.01	<.001
Level of serum Ca ²⁺ (mg/dL) at PTH assessment; Mean \pm SE		11.76 \pm 0.05	10.89 \pm 0.01	<.001
Time difference between the first elevated Ca ²⁺ and the Ca ²⁺ level prompting the PTH test (months); Median (range)		4.73 (0–235)	6.70 (0–235)	.438

Ca²⁺: total calcium.

Sample size: suppressed-PTH level: N=851 (17.9%); non-suppressed PTH level: N=3899 (82.1%). Divide serum calcium levels in mg/dL by 4 to convert to mmol/L and multiply PTH in pg/mL by 0.1061 to convert to pmol/L. SE, standard error.

*Thiazide diuretics or lithium.

the assessment of PTH, while the majority had between 1 and 5 elevated calcium levels documented, ~20% had hypercalcemia documented ≥ 6 times; ~5%, ≥ 11 times, and ~1%, ≥ 20 times.

Discussion

Our study, over a 20-year period, documents a rate of PTH assessment in the setting of hypercalcemia of approximately 23%, which is slightly lower than previous reports.^{12–17} While many previous studies showed slightly higher rates of

assessment of ~25%–30%,^{12,13,15,17} 1 did document rates as low as 4% in 1 facility.¹⁶ Our approach was unique in that we sought to determine whether or not a history of malignancy affected the rate of PTH assessment. While we had hypothesized that patients with a prior history of malignancy might be more likely to have a timely and appropriate evaluation of their hypercalcemia, this was not the case, as there was no difference in the rate of assessment of PTH between the 2 groups. Similar to previous studies, we found female gender

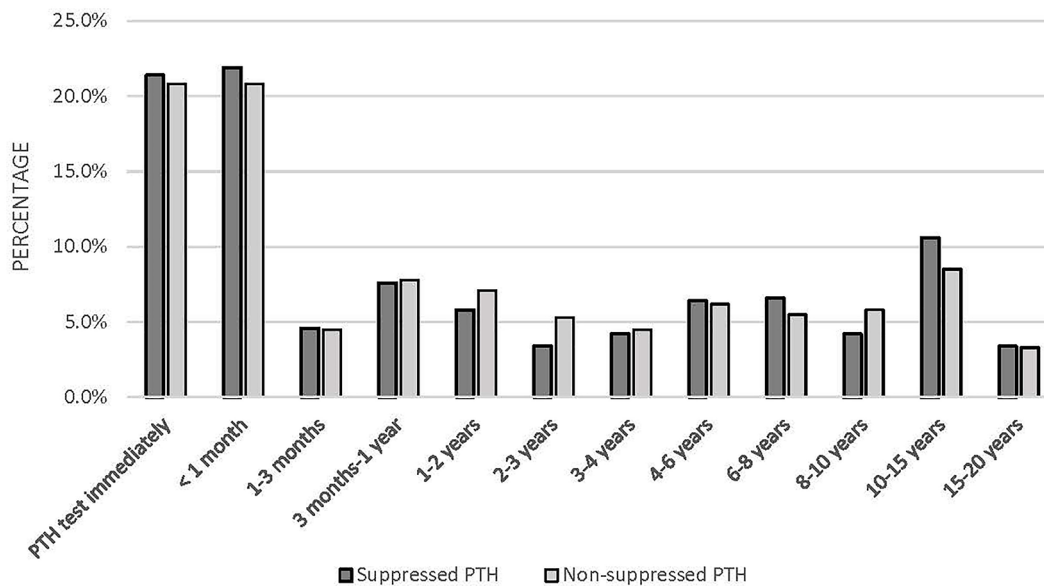


Figure 5. Time difference between the first elevated serum calcium and that which prompted assessment of PTH, grouped by suppressed versus non-suppressed PTH.

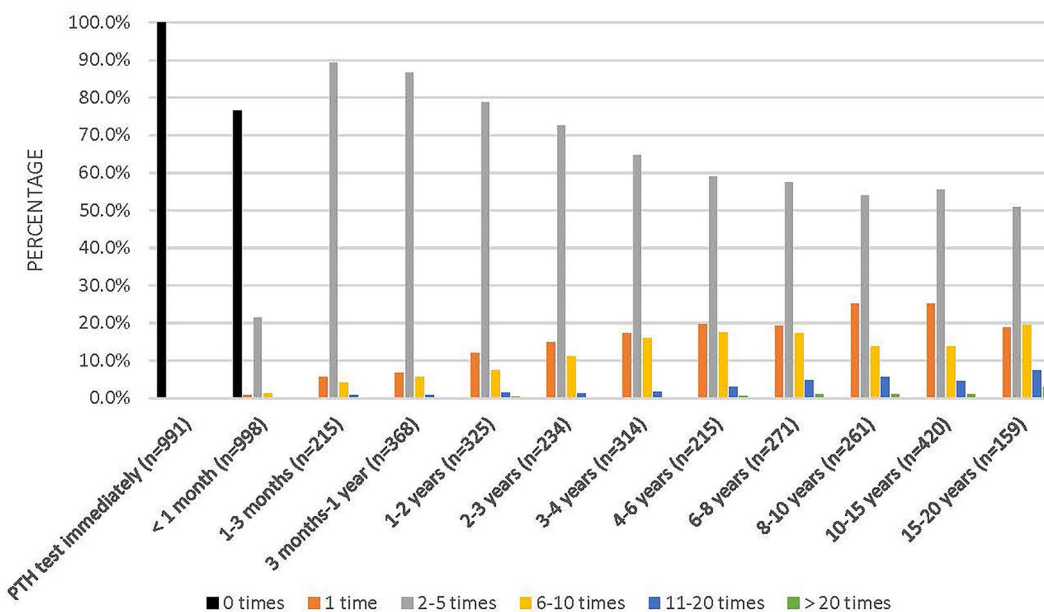


Figure 6. Time difference between the first elevated serum calcium and that which prompted assessment of PTH, sub-classified by the number of elevated serum calcium levels within that timeframe (both suppressed and non-suppressed PTH levels).

and increasing severity of hypercalcemia did correlate with an assessment of PTH.^{12,13,16} However, our results differed in that age greater than 60 years and use of medications that might affect serum calcium levels also correlated with assessment of PTH. While it may make sense for women to be more likely to have a PTH assessment given their higher prevalence of primary hyperparathyroidism, it could be argued that it is more important for men to have a PTH assessment in the context of hypercalcemia due to their greater likelihood of having a PTH-independent hypercalcemia, most of which would be HCM. As such, our data indicate that men may be most at risk for long-term consequences of a lack of PTH

assessment in the setting of hypercalcemia (i.e., delay in the potential diagnosis of HCM).

Our analysis and findings with regard to the change in frequency of PTH assessment in hypercalcemic patients over the course of the 20-year time frame are also unique, as other studies have not reported this assessment longitudinally. Generally, an increase in the appropriate assessment of hypercalcemia would be expected over the course of time as medical knowledge and education improve. Therefore, the increase in frequency of PTH assessment between 2000 and 2006 is not surprising, as was the stability for the subsequent 6 years to 2012. However, after 2012, the steady and significant drop in the frequency to levels lower

than at the beginning of the study is surprising and remarkable. While it is uncertain what contributed to the decline in the frequency of PTH assessment in the last 8 years of the study, the rate declined in both patients with and without a prior history of malignancy, as shown in Figure 2B. Interestingly, it was not the absolute number of PTH levels assessed that appeared to decline; rather, there was an increase in the frequency of hypercalcemia documented in the laboratory data. This was only seen, however, in 2018 and 2019, with a 2.4-fold increase in the frequency of hypercalcemia in those final 2 years, which corresponds with the more significant drop in PTH assessment frequency (data not shown). Therefore, with a greater number of abnormally high calcium levels, providers were less likely to check a PTH, at least in 2018 to 2019. One could argue that, perhaps, provider stress or burnout in dealing with a greater number of abnormal laboratory values led to a lack of appropriate evaluation of documented hypercalcemia. There are data to suggest that physician burnout and stress does lead to increased medical errors.²³⁻²⁶ Furthermore, primary care providers may be continually overwhelmed by the broader scope of conditions they are expected to evaluate and manage.²⁷ Another possibility might be related to the increasing utilization of advanced practice providers (APP) in primary care over the last 10 years. One study showed a relatively stable percentage of APPs in primary care clinics between 2008 and 2010, followed by a slight increase between 2010 and 2014, and then a more significant increase between 2014 and 2018.²⁸ However, there is evidence that nurse practitioners may actually order a greater number of diagnostic tests, at least in the form of imaging studies, compared to physicians.²⁹ However, data on the possible differences in laboratory ordering practices between APPs and physicians are limited.^{30,31} Although we were unable to track which providers (physicians or APPs) ordered the calcium levels, within MCHS the number of APPs increased by 17% between 2018 and 2020 to 37% of all providers. The severity of hypercalcemia did not appear to affect the decline in testing frequency with all 5 groups showing a decline (albeit to different degrees) between the third and fourth date quartile as shown in Figure 3. This is also of concern since one would hope and expect that more severe hypercalcemia would not have a drop off in the rate of appropriate assessment of PTH levels over time.

In those patients who had a PTH assessed, PTH-independent hypercalcemia was more common in patients with a history of malignancy. Also, as expected, nearly 15% of patients without a history of malignancy who had a PTH assessed had PTH-independent hypercalcemia. Importantly, those patients with a history of malignancy who had a PTH assessed had a non-suppressed PTH 75% of the time, indicating their hypercalcemia was likely not related to their malignancy, but rather to primary hyperparathyroidism. Given the increased incidence of primary hyperparathyroidism in women, it is not surprising that men in our study were more likely to have a suppressed PTH. Furthermore, the greater likelihood of a suppressed PTH in the setting of a higher serum calcium is

consistent with the fact that patients with HCM tend to have a more severe degree of hypercalcemia than patients with primary hyperparathyroidism.^{4,10} That fewer elevated calcium levels were documented before the discovery of a suppressed PTH than a non-suppressed PTH is consistent with this earlier assessment of PTH with a greater degree of hypercalcemia. Interestingly, however, there was still a median delay of approximately 5 (suppressed PTH group) and 7 (non-suppressed PTH group) months between the first discovery of hypercalcemia and the eventual assessment of PTH levels in those patients who finally had a PTH assessed. Certainly, this delay in proper evaluation of hypercalcemia is of clinical importance to the majority of patients in this setting who have primary hyperparathyroidism as, while many patients with primary hyperparathyroidism follow an indolent course over many years, there are some patients in whom this condition is a significant contributor to adverse bone and/or renal outcomes.⁸⁻¹⁰ Previous studies have mainly focused on this delay in the appropriate assessment of PTH in relation to the delay in the diagnosis and proper management of primary hyperparathyroidism.¹²⁻¹⁷ However, this delay is of greater concern in regards to patients found to have a suppressed PTH who most likely have HCM, given the extremely poor prognosis of such patients. This raises the possibility that, perhaps, HCM in many cases may not have such a rapid or dire clinical course as typically reported in the literature.^{4,20,32} Rather, a delay in appropriate evaluation and diagnosis may lead to these patients eventually presenting with more severe hypercalcemia and an advanced stage of their malignancy. Indeed, as shown in Figure 5, in those patients who eventually did have a PTH assessed and were found to be suppressed, nearly 40% had a delay of more than 2 years since the first documentation of hypercalcemia, and in 14% it was more than 10 years. Furthermore, a substantial portion of these patients had documented hypercalcemia on more than 6 occasions (Figure 6) and with a mean level of hypercalcemia not prompting a PTH assessment of 11.82 mg/dL or 2.96 mmol/L (Table 3). Presumably, a hypercalcemic patient documented to have a suppressed PTH has always had a suppressed PTH and, thus, has had PTH-independent hypercalcemia likely since the first documentation of hypercalcemia, when the calcium may have been more mildly elevated. It is likely, therefore, that these findings are of greater importance regarding the delay in the diagnosis and management of HCM.

Our study does have limitations. The main limitation is related to the longitudinal analysis wherein we attempted to track the number of elevated calcium levels between the initial documentation of hypercalcemia and the eventual, when it did occur, assessment of PTH. Due to the large dataset of more than 20000 patients with hypercalcemia, it was not feasible to perform any meaningful chart reviews toward this end. As such, we did not have the ability to discern what may have been a completely valid reason to avoid or delay the assessment of PTH. This is

particularly important in those instances where it may have been many months, if not years, between the initial documentation of hypercalcemia and the eventual assessment of PTH. The data on such delays are nonetheless intriguing and have not been previously noted in the literature, thus warranting further investigation at other centers. Additionally, we did not assess the dataset for any follow-up evaluation, treatment, or outcomes in these patients. That is, we did not attempt to determine which patients with PTH-mediated hypercalcemia eventually had surgical referral and/or parathyroidectomy. We also did not assess the eventual diagnosis (malignant or non-malignant) and any possible management of those patients who had PTH-independent hypercalcemia. However, our main purpose was simply to document the limited assessment and/or delay in the assessment of the first step in the fairly simple evaluation of hypercalcemia—the ordering of a PTH level. We did not evaluate the later stages of confirmation nor conduct an etiology evaluation. Lastly, this dataset is from medical records of a predominantly rural white/Caucasian population, so our findings may not be generalizable to more diverse populations. However, since many of our patients primarily receive care at MCHS facilities, the strength of our dataset lies in the long-term monitoring of these patients, which not only decreases the number of patients lost to follow-up, but also allows for a comprehensive analysis of changes in clinical practice over time.

Conclusion

While the initial evaluation of hypercalcemia is quite straightforward, only ~23% of our patients ever had a PTH level drawn and a previous diagnosis of malignancy did not make the assessment of a PTH level any more or less likely. This limited evaluation of hypercalcemia has gotten worse in the last 5 years. Furthermore, while many patients who did eventually have a PTH assessed did so within the first several months after initial documentation of hypercalcemia, a substantial portion did not have a PTH assessment for more than 2 years. Also, during this delay it was not uncommon for patients to have more than 6 documented elevated calcium levels before the PTH level was finally assessed. The potential increased burden of delaying the diagnosis of both primary hyperparathyroidism and HCM as well as other non-PTH mediated causes of hypercalcemia is significant. Better education of providers toward the appropriate and timely assessment of PTH in the evaluation of hypercalcemia is urgently needed.

Author Contributions


All authors have accepted responsibility for the entire content of this manuscript and approved its submission

Informed Consent/Ethical approval

Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as revised in 2013).

The study was reviewed and approved by the Marshfield Clinic Health System's Institutional Review Board with waiver of informed consent.

ORCID iD

Michael T Sheehan  <https://orcid.org/0000-0001-8512-7980>

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