ORIGINAL ARTICLE

The Changing Presentation of Hyperparathyroidism Over 3 Decades

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Objective: To analyze changes in the presentation of primary hyperparathyroidism over the last 3 decades.

Design: Retrospective review.

Setting: Tertiary referral center.

Patients: Three hundred patients undergoing parathyroidectomy for primary hyperparathyroidism, 100 each in the years 1985, 1995, and 2005.

Main Outcome Measures: Analysis was performed based on patient age, sex, preoperative calcium value, duration of hypercalcemia, symptoms at presentation, and reason for surgical referral.

Results: Patients from the years 1985, 1995, and 2005 were similar in age and sex. Mean (SEM) preoperative calcium values decreased from 11.8 (0.1) mg/dL in 1985 to 11.2 (0.1) mg/dL in 2005 ($P<.001$) (to convert milligrams per deciliter to millimoles per liter, multiply by 0.25). The proportion of patients with preoperative calcium values less than 11.0 mg/dL steadily rose from 10% in 1985 to 43% in 2005 ($P<.001$). The mean (SEM) time from diagnosis of hypercalcemia until surgical referral decreased from 2.5 (0.4) years in 1985 to 1.6 (0.2) years in 2005 ($P=.08$). The primary reason for referral has shifted toward osteoporosis (20% in 2005 vs 7% in 1985; $P=.03$). The percentage of patients diagnosed with osteoporosis or osteopenia preoperatively increased from 10% in 1985 to 44% in 2005 ($P<.001$), and the recognition of these conditions in men increased from 3% to 26% ($P=.10$).

Conclusions: Over the last 3 decades, increased awareness of hyperparathyroidism and its consequences as well as the institution of screening bone densitometry have changed the profile of patients who are referred for surgery. Patients are being referred sooner, with a lesser degree of hypercalcemia and greater recognition of osteoporosis.

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HYPERPARATHYROIDISM, RECognized as a clinical entity less than 100 years ago, has undergone a dramatic change of face since the introduction of the chemistry autoanalyzer in the early 1970s. Only then did we begin to routinely measure serum calcium values as part of an annual physical examination or an unrelated medical encounter, and these measurements uncovered a large cohort of previously unrecognized hypercalcemic patients. Immediately after the introduction of screening blood chemistries in 1 community, the incidence of primary hyperparathyroidism increased from 15 cases per 100 000 individuals to 112 cases per 100 000 individuals.[1] Recognition of a significantly higher disease prevalence based on screening laboratory results, not symptoms, quickly effected a change in the presentation of primary hyperparathyroidism. Many patients had disease discovered in the early stages of the disease process before the development of classical findings such as nephrolithiasis, brown tumors, bone cysts, and pathologic fractures.[2]

Prior to 1970, serum calcium measurement was ordered only on request in the course of a physician-guided investigation. Patients suspected of having hypercalcemia because they presented with nephrolithiasis, radiographically detected bone demineralization, gastrointestinal symptoms, or neurologic symptoms were appropriately tested. Now it is increasingly uncommon to find a patient who presents with classical findings and no prior documentation of hypercalcemia. More often, patients are first diagnosed as hypercalcemic and only secondarily diagnosed with symptoms attributable to their biochemical abnormality.[2] This reverse chronology—biochemical abnormality preceding symptoms—better known as screening, is preva-

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lent in many aspects of modern-day medicine, and in the case of hyperparathyroidism it is responsible for the welcome and significant decline in what were once common morbidities of this disease.

From the time that Felix Mandel operated on his first patient and proved that the ravages of hyperparathyroidism could be reversed, the surgical community embraced parathyroidectomy as the only effective means of curing these symptomatic patients. From the 1920s through the 1960s, it remained primarily these symptomatic patients who came to medical attention. When the serum chemistry autoanalyzer changed the demographics of hyperparathyroidism, questions arose as to the criteria for surgical intervention, and despite 2 National Institutes of Health (NIH) Consensus Conferences on just this topic, the debate continues.[2,3]

The well-known NIH criteria for operating on patients with hyperparathyroidism were established in 1990 and updated in 2002 (**Table 1**). These criteria mention the less-concrete symptoms associated with the disease—neuromuscular, neuropsychiatric, and gastrointestinal—but do not include them as operative indications. Despite these omissions, increasing numbers of patients with modestly elevated serum calcium values undergo parathyroidectomies and experience significant improvement from a multitude of measurable symptoms.[4,5] There is also increased recognition of a subgroup of patients with hyperparathyroidism whose serum calcium values are normal. These patients report similar frequencies of preoperative symptoms and postoperative improvement.[6]

In this study, we reviewed the evolution in presentation, evaluation, and treatment of patients with primary hyperparathyroidism at a single tertiary care institution.

Table 1. National Institutes of Health Criteria for Parathyroidectomy[a]

Criteria
Serum calcium value > 1 mg/dL higher than normal
Age < 50 y
Nephrolithiasis
Substantially reduced bone density, T score < –2.5
Markedly elevated 24-h urinary calcium level, > 400 mg
Creatinine clearance reduced by 30%
Osteitis fibrosa cystica
Classic neuromuscular disease

SI conversion factor: To convert serum calcium values to millimoles per liter, multiply by 0.25.

[a] Criteria established by the National Institutes of Health as indications for surgical treatment of primary hyperparathyroidism.

METHODS

The study population comprised 300 patients with primary hyperparathyroidism undergoing first-time parathyroidectomy. One hundred patients who underwent parathyroidectomy for the diagnosis of primary hyperparathyroidism in each of the years 1985, 1995, and 2005 were chosen for review. This selection was made to provide a snapshot of patient characteristics for each period. Patients with the diagnoses of secondary, tertiary, persistent, or recurrent hyperparathyroidism were excluded from analysis.

Each group comprised the first 100 patients taken to surgery in that calendar year. In 1985 and 1995, fewer than 100 patients with primary hyperparathyroidism were treated surgically (40 and 57 patients, respectively), so the remainder of the 100 came from the next calendar year. All of the patients in 1985 and 1995 were treated by a single surgeon (C.E.), and the patients from 2005 were treated by 2 surgeons (M.M. and A.E.S.). At surgery, all of the 300 patients had a standard 4-gland exploration, and the operating surgeon determined the pathologic state based on gland appearance. Data for patients who underwent operations in 1985 and 1995 were obtained from record reviews. Beginning in 2000, records of all of the patients undergoing parathyroid surgery at the Cleveland Clinic were entered into a prospective database, which was used to obtain the 2005 data. The study proposal was institutional review board approved.

Each patient record was systematically reviewed to establish the primary reason for surgical referral. Judgments were based on the available, often extensive documentation by the referring physicians, resident surgeons, and operating surgeons with the goal of identifying the symptom, laboratory, or radiographic finding that ultimately prompted surgical referral and treatment. In addition, a comprehensive list of all of the symptoms elicited from the patient at the time of surgical referral was compiled.

As a rule, the documentation of symptoms and signs of hyperparathyroidism as well as recording of the surgical indication were exceptionally and consistently thorough. This allowed for complete and accurate determination of all of the findings pertinent to the diagnosis of hyperparathyroidism at the time of referral. Although it is true that many patients had more than 1 symptom or indication for surgery, the primary reason was determined to be that which developed most proximate to the time of surgery. For instance, if a patient carried the diagnosis of hypercalcemia for years and was only referred when he or she developed nephrolithiasis, nephrolithiasis was chosen as the primary reason for surgical referral.

Symptoms at presentation and reasons for referral included the following: (1) hypercalcemia only (reference range, 8.5-10.5 mg/dL [to convert milligrams per deciliter to millimoles per liter, multiply by 0.25]); (2) nephrolithiasis; (3) osteoporosis or osteopenia; (4) gastrointestinal manifestations, which included gastroesophageal reflux, peptic ulcer disease, dyspepsia, and pancreatitis; (5) neuromuscular symptoms, which included fatigue, lethargy, muscle aches, and bone aches; (6) neuropsychiatric symptoms, which included insomnia, memory loss, depression, and mood disturbance; (7) hypertension; and (8) polyuria.

The last preoperative serum calcium value was used to make all of the comparative analyses. Serum parathyroid hormone (PTH) values were available for most but not all patients, especially not for those from 1985. The values from 1985 often were not intact PTH measurements but rather C-terminal or midmolecule assays. As the assays have targeted multiple regions of the PTH molecule and have varying reference ranges, we reported the ratio of PTH to the upper limit of the reference range in the comparison. An additional data point included the number of years between recognition of hypercalcemia and time to surgical referral.

The data were analyzed for statistical significance using χ^2 and t tests and are presented as mean (standard error of the mean). $P \leq .05$ was used to denote statistical significance.

RESULTS

The demographic features of the 3 patient groups are summarized in **Table 2**. During the period from 1985 to 2005, the patient sex distribution did not significantly change.

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Table 2. Epidemiologic Data of Patients Referred for Surgical Treatment of Primary Hyperparathyroidism During 3 Decades

Characteristic	1985	1995	2005	*P* Value
Age, mean, y	55	61	59	.34
Age <50 y, %	40	23	17	≤.001
Sex, F/M, %	70/30	79/21	73/27	.34
Serum calcium value, mean, mg/dL	11.8	11.4	11.2	<.001
Followed up with hypercalcemia, y	2.4	2.0	1.7	.08

SI conversion factor: To convert serum calcium values to millimoles per liter, multiply by 0.25.

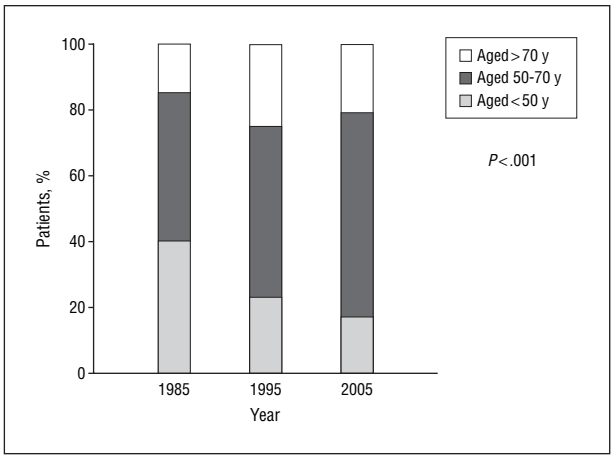

Figure 1. Ages of patients referred to surgery for a diagnosis of primary hyperparathyroidism in 1985, 1995, and 2005.

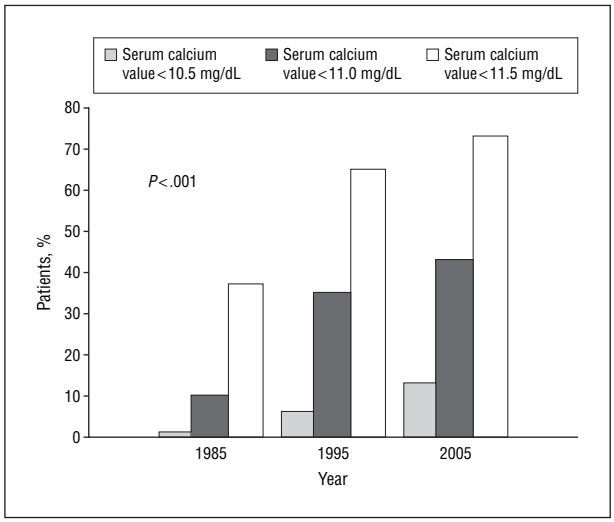

Figure 2. Percentages of patients whose serum calcium measured less than 11.5 mg/dL, less than 11.0 mg/dL, and less than 10.5 mg/dL in 1985, 1995, and 2005 (to convert serum calcium values to millimoles per liter, multiply by 0.25).

In the years 1985, 1995, and 2005, the percentages of female patients were 70%, 79%, and 73%, respectively. The mean (range) patient ages were 55 (13-83), 61 (25-88), and 59 (13-87) years, respectively ($P=.34$). However, the percentage of patients younger than 50 years steadily dropped from 40% to 23% to 17%, respectively ($P\leq.001$) (**Figure 1**). Simultaneously, the 50- to 70-year-old cohort grew from 45% of patients in 1985 to 52% in 1995 to 62% in 2005 ($P=.05$). The percentage of patients older than 70 years did not significantly change over 3 decades ($P=.21$).

The average serum calcium values are shown in Table 2. There has been a gradual but significant decrease over time from 11.8 (0.1) mg/dL in 1985 to 11.4 (0.1) mg/dL in 1995 to 11.2 (0.1) mg/dL in 2005 ($P<.001$). More striking is the highly significant increase in the number of referred patients who have serum calcium values lower than 11.0 mg/dL (**Figure 2**). These patients composed 10% of the total in 1985, 35% in 1995, and 43% in 2005 ($P<.001$). Those patients referred with calcium values lower than 11.5 mg/dL composed 37% of the total in 1985, 65% in 1995, and 73% in 2005 ($P<.001$). Also notable was the substantial increase in the number of patients referred for surgery who had normal serum calcium values (<10.5 mg/dL) and elevated PTH values, or so-called normocalcemic patients with hyperparathyroidism. There was 1 such patient in 1985 vs 6 such patients in 1995 and 13 such patients in 2005 ($P=.003$).

Analysis of the patients from 2005 revealed no significant differences in vitamin D levels in patients who had normal serum calcium values vs those with serum calcium values higher than 10.5 mg/dL. Thirty-one percent of patients with normal serum calcium values had vitamin D levels that were deficient or insufficient (<20 ng/mL [to convert nanograms per milliliter to nanomoles per liter, multiply by 2.496]). For patients with serum calcium values higher than 10.5 mg/dL, 43% had deficient or insufficient levels of vitamin D ($P=.11$). Vitamin D measurements were not available for patients in the 1985 and 1995 cohorts.

Table 3 shows the diagnosis that prompted surgical referral for each individual. The most significant change has been the increased percentage of patients referred for osteoporosis and osteopenia, accounting for 7% in 1985, 13% in 1995, and 20% in 2005 ($P=.03$). Simultaneously, the diagnosis of nephrolithiasis as the reason for referral has decreased from 24% to 14%. The frequency with which hypercalcemia was specified as the primary reason for surgical referral did not change during the study period, responsible for 46% of referrals in 1985 and 51% in both 1995 and 2005.

The prevalence of gastrointestinal manifestations of hypercalcemia as the primary reason for surgical referral has decreased from 9% to 2%. Whereas pancreatitis prompted referral in 9 of 100 patients in 1985, there were only 2 such patients in 1995 and 1 such patient in 2005. Other gastrointestinal symptoms included peptic ulcer disease, dyspepsia, and nausea in a few patients from each group.

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Table 3. Surgical Indications[a]

Reason for Referral	Patients, % 1985	1995	2005	*P* Value
Hypercalcemia only	46	51	51	.71
Nephrolithiasis	24	13	14	.07
Bone disease	7	13	20	.03
Gastrointestinal	9	3	2	.07
Neuromuscular	8	8	7	.96
Neuropsychiatric	3	10	6	.12
Hypertension	3	0	0	.04
Polyuria	0	2	0	.33

[a] Primary reason patients were referred for surgical treatment of their hyperparathyroidism, as determined by thorough record review, for 100 patients in each of the years 1985, 1995, and 2005.

Table 4. Symptoms at Presentation[a]

Symptoms	Patients, % 1985	1995	2005	*P* Value
Hypercalcemia only	16	28	20	.12
Nephrolithiasis	33	21	29	.15
Osteoporosis	10	24	44	<.001
Gastrointestinal	28	12	4	<.001
Neuromuscular	31	27	33	.64
Neuropsychiatric	15	13	15	.90
Hypertension	27	13	6	<.001
Polyuria	0	6	0	.004

[a] All of the symptoms reported and discovered at the time of surgical evaluation in 100 patients in each of the years 1985, 1995, and 2005.

The percentage of patients referred for neuromuscular symptoms remained constant at 8% in both 1985 and 1995 and 7% in 2005. There was a small but insignificant increase in the percentage of patients referred because of neuropsychiatric symptoms, from 3% in 1985 to 10% in 1995 and 6% in 2005 ($P=.12$).

Hypertension accounted for 3% of referrals in 1985 but none in the latter groups, and polyuria was cited as the reason for referral in 2 patients in 1995 but not at all in the other 2 groups.

The 3 groups of patients were also analyzed with regard to all of the symptoms recorded at the time of preoperative presentation (**Table 4**). The first noteworthy finding was that most patients who underwent operations in these 3 groups had findings attributable to hyperparathyroidism other than just hypercalcemia, and this finding did not significantly diminish over the years. In 1985, 84% of patients had additional symptoms, and the percentage remained high at 72% in 1995 and 80% in 2005 ($P=.11$).

Figure 3 shows changes in the percentage of asymptomatic patients taken to surgery. There was a significant increase in the percentage of patients with calcium values lower than 11.5 mg/dL who had no findings other than hypercalcemia. In 1985, only 14% of patients with calcium values lower than 11.5 mg/dL had no other documented symptoms. By 1995, this percentage was 31%; in 2005, it was 19% ($P=.009$). By contrast, the percentage of asymptomatic patients with serum calcium values of 11.5 mg/dL or higher did not significantly change: 18% in 1985, 23% in 1995, and 22% in 2005 ($P=.59$).

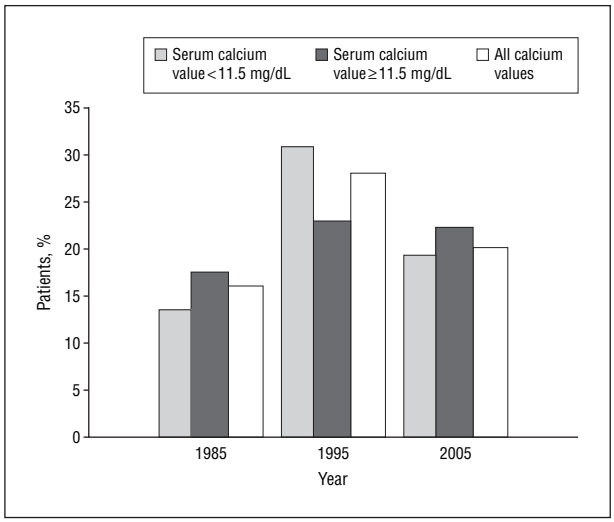

Figure 3. Percentages of asymptomatic patients analyzed by degree of hypercalcemia in each of the years 1985, 1995, and 2005 (to convert serum calcium values to millimoles per liter, multiply by 0.25).

Although it was not possible to accurately determine the number of patients meeting NIH criteria in each of the cohorts owing to a lack of data on bone density and urinary calcium values, that information was available for the 2005 group. Seventy-six percent of those pa-

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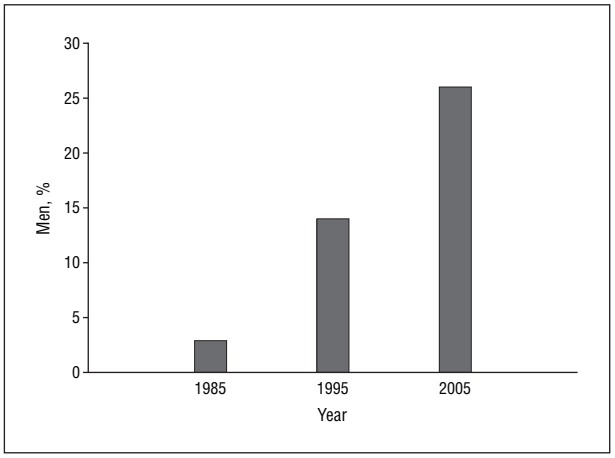

Figure 4. Percentages of men referred for surgery for primary hyperparathyroidism who were diagnosed with osteoporosis or osteopenia in 1985, 1995, and 2005.

tients met NIH criteria and 24% did not. In 1985, despite the lack of bone densitometry and 24-hour urinary calcium measurements, at least 89% of the group would have met today's NIH criteria because of their higher serum calcium values.

While the prevalence of some symptoms remained relatively constant over the decades, others significantly changed (Table 4). The constants included nephrolithiasis, which was present in 33%, 21%, and 29% of patients in 1985, 1995, and 2005, respectively. Neuromuscular and neuropsychiatric symptoms were stable over the years, being present in approximately 30% and 15%, respectively, in all of the 3 cohorts. The presenting symptoms that changed included osteoporosis and osteopenia, gastrointestinal symptoms, and hypertension. Diagnosis of bone disease more than quadrupled from 10% in 1985 to 44% in 2005 ($P<.001$), and recognition of this diagnosis in men increased from 3% in 1985 to 14% in 1995 to 26% in 2005 ($P=.10$) (**Figure 4**). The frequency of gastrointestinal symptoms decreased from 28% to 4% during the same period ($P<.001$). Hypertension decreased similarly from 27% to 6% ($P<.001$).

The duration between diagnosis of hypercalcemia and surgical referral trended downward but did not reach statistical significance ($P=.08$) (Table 2). In 1985, the average patient was followed for a mean (SEM) of 2.4 (0.4) years from the time of documented hypercalcemia to the time of referral. This interval fell to 2.0 (0.4) years in 1995 and further to 1.7 (0.2) years in 2005 ($P=.08$). The number of patients followed up for very long periods has also decreased. In 1985, 7% of patients with hypercalcemia were followed up for longer than 10 years. Such prolonged observation fell to 5% in 1995 and 1% in 2005 ($P=.09$).

The number of hypertrophied glands identified at surgery (**Table 5**) varied significantly during the 3 decades ($P=.02$) because of a decreased number of patients with hyperplasia and double adenomas in 1995. The change of operating surgeons in 2000 may account for a portion of these variations; however, the same surgeon operated on all of the patients in 1985 and 1995. There were no statistically significant differences between the distribution of enlarged single- vs multiple-gland disease between 1985 and 2005 ($P=.39$).

Table 5. Surgical Pathologic Findings[a]

Pathologic Finding	Patients, % 1985	1995	2005
Single adenoma	81	92	75
Double adenoma	7	4	14
4-Gland hyperplasia	12	4	11

[a] Identified at the time of 4-gland exploration.

Over the years, the assays used to measure serum PTH levels have become much more specific for intact PTH as well as more uniform. In the 1980s and into the 1990s, multiple assays recognized multiple different regions of the PTH molecule; therefore, the reference ranges differ greatly from assay to assay and year to year. To enable comparison of varying PTH assays, we calculated a PTH ratio by dividing the patient's measured preoperative PTH value by the upper limit of the reference range for the assay that was used. The mean (SEM) ratios for the years 1985, 1995, and 2005 were 2.95 (0.66), 2.09 (0.21), and 2.32 (0.12), respectively. None of these differences reached statistical significance ($P=.34$).

COMMENT

EPIDEMIOLOGY

The number of parathyroidectomies performed at the Cleveland Clinic has steadily increased since 1985, and patient demographics have undergone significant change. Although the average patient age did not statistically differ, there was a marked and significant decrease in the percentage of patients younger than 50 years, decreasing from 40% in 1985 to 17% in 2005. This decrease was driven by the increased referral of older patients even when these patients lacked other classic features of hyperparathyroidism such as nephrolithiasis or osteoporosis.

CALCIUM VALUES

There was a significant decrease in the average serum calcium measurement over time from 11.8 mg/dL in 1985 to 11.2 mg/dL in 2005, and there was a dramatic increase in the percentage of patients with modestly elevated calcium values.

These significant trends illustrate increased willingness on the part of physicians and surgeons to refer and treat patients with hyperparathyroidism who are older and/or have modestly elevated serum calcium values. This may be owing to the medical community's growing awareness of the subtle symptoms and sequelae present in these patients as well as their potential for improvement.

When we analyzed the primary indication for which each patient was referred to surgery, we expected to find a steadily increasing rate of referral because of hypercalcemia. Instead, the percentage of patients referred be-

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cause of hypercalcemia or a worsening serum calcium level remained steady: 46% in 1985 and 51% in both 1995 and 2005. Although there was a significant increase in the percentage of patients with modest hypercalcemia, their rates of symptomatic disease were similar to those in patients with serum calcium values greater than 11.5 mg/dL.

Some investigators have suggested that most patients with hyperparathyroidism are asymptomatic, up to 80%.[2] Others have emphasized the importance of recognizing nontraditional symptoms characterized by fatigue, lethargy, weakness, depression, musculoskeletal symptoms, nausea, polyuria, memory loss, and insomnia.[4,5] They state that as few as 2% to 5% of patients with hyperparathyroidism are truly asymptomatic.[4,7] We found that in 2005, 80% of Cleveland Clinic patients remained symptomatic, and this held true for patients with calcium values lower or higher than the 11.5-mg/dL threshold (Figure 3).

Patients in a surgical series would be expected to have higher symptom prevalence than a group seen in a primary care or endocrinology setting. Using narrow definitions of *symptomatic*, it has been said that two-thirds of surgical candidates are asymptomatic, meaning they do not have nephrolithiasis, pathologic fractures, or overt neuromuscular symptoms.[2] In this study, a broader definition of *symptomatic* was used, and it has been validated by previous studies[4,5,8] showing measurable improvement of the symptom parameters assessed in these patients.

REASON FOR REFERRAL

Osteoporosis

One of the most significant changes over time was the increased recognition of osteoporosis and osteopenia in this patient population and its growing importance as a reason for surgical referral. This reflects the increasing efforts of primary care physicians to screen postmenopausal women for bone loss, but it also reflects efforts to identify bone demineralization in patients initially identified as having hyperparathyroidism. This phenomenon was well illustrated by the detection of bone disease in 3% of the male subjects in 1985, 14% in 1995, and 26% in 2005. In 2005, similar findings were echoed in a population of Australian patients where the prevalence of osteoporosis in patients undergoing parathyroidectomy increased from 4% in the period of 1962 to 1980 to 34% in the period of 1991 to 2001.[9]

Generally, it has been the practice at the Cleveland Clinic to surgically treat all of the patients with osteoporosis and osteopenia. Prospective data have shown that bone mineral density will decrease in 21% of patients followed up without surgery over at least 10 years.[10] These patients tended to have higher baseline serum calcium concentrations and were more likely to become menopausal during the follow-up period. The surgically treated patients had prompt and sustained increases in bone mineral density at the lumbar spine and femoral neck. Another randomized study[3] has shown significant differences in femoral neck and total hip bone mineral density after just 2 years between a group of patients treated surgically and a group followed up medically.

Renal Stones

While the diagnosis of nephrolithiasis as a primary reason for surgical referral has decreased by nearly half, from 24% in 1985 to 14% in 2005, its prevalence in the patient population undergoing parathyroidectomy is essentially unchanged: 33% in 1985 and 29% in 2005. This is potentially explained by the fact that a number of patients in each of the 3 groups had been previously treated for kidney stones and either were being followed up medically for mild hypercalcemia or were not recognized as hypercalcemic. It was not until these patients developed worsening hypercalcemia or significant osteoporosis that they were referred for surgery. This treatment delay in some patients with kidney stones in all of the 3 periods is noteworthy in that it illustrates an ongoing gap in our diagnostic and management strategies. There is extensive evidence that surgical cure of hyperparathyroidism in patients with nephrolithiasis minimizes further episodes, whereas nonsurgical management frequently leads to recurrences,[10] so even today practitioners need to be more diligent in assessing the role of hyperparathyroidism in patients with nephrolithiasis and ensuring timely surgical cure.

Gastrointestinal Symptoms

Presentations with peptic ulcer disease, pancreatitis, dyspepsia, gastroesophageal reflux, constipation, and nausea decreased both in overall prevalence and as a primary reason for referral. The reasons for this are not entirely clear but are likely multifactorial, including the increasingly common use of proton-pump inhibitors and histamine 2 blockers. It is also likely that these symptoms are not sought out by caregivers as assiduously as they had been in earlier decades.

Neuromuscular and Neuropsychiatric Symptoms

The prevalence of neuromuscular and neuropsychiatric symptoms remained steady at 30% and 15%, respectively, and there remains a minority of patients who are referred to surgery because of such symptoms. Although such symptoms are not listed by the NIH Consensus Conference of 2002 as worthy of surgical treatment for otherwise asymptomatic modest hypercalcemia, other investigators have demonstrated significant decreases in symptoms such as bone and joint pain, weakness, fatigue, and depression after surgical cure.[4] The Parathyroidectomy Assessment of Symptoms is a questionnaire specifically designed to monitor these patients preoperatively and postoperatively and has shown clear improvements in multiple symptoms after parathyroidectomy.[8] One study[11] has also documented an objective increase in grip strength after parathyroidectomy. It is not infrequent that a patient with hyperparathyroidism who denies such symptoms preoperatively will return for the 2-week postoperative visit and report that he or she feels much better because of an increased energy level and decreased aches and pains.[4]

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DURATION OF MEDICAL OBSERVATION

Analysis of the time elapsed between initial documentation of hypercalcemia and surgical referral revealed that patients are spending shorter periods with known hypercalcemia prior to surgery, which is consistent with an overall trend to more aggressively treat disease. This shift was significant in the older group of patients. In patients aged 60 years or older, the average period of observation was 3.8 years in 1985; this decreased to 1.7 years in 2005 ($P = .004$). Only being older than 60 years was significantly associated with a difference in the duration of observation over the decades.

CONCLUSIONS

In summary, this series analyzing data from 1985, 1995, and 2005 on 300 patients with primary hyperparathyroidism has clearly demonstrated a number of key epidemiologic trends. Most patients referred for surgery now have serum calcium values lower than 11.5 mg/dL, and bone disease is increasingly recognized as a reason for surgical referral, in men as well as women. The series also demonstrates symptom presence in 80% of patients up through the present decade. Finally, it is clear that primary care physicians and endocrinologists are referring all patients earlier in their disease course as well as referring more elderly patients who were followed up medically in the past.

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Author Contributions: Dr Mazzaglia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Milas and Siperstein. *Acquisition of data:* Mazzaglia, Berber, Kovach, Milas, Esselstyn, and Siperstein. *Analysis and interpretation of data:* Mazzaglia, Berber, Milas, and Siperstein. *Drafting of the manuscript:* Mazzaglia and Kovach. *Critical revision of the manuscript for important intellectual content:* Berber, Milas, Esselstyn, and Siperstein. *Statistical analysis:* Mazzaglia and Berber. *Study supervision:* Milas and Siperstein.
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