

# Should Symptoms Be Considered an Indication for Parathyroidectomy in Primary Hyperparathyroidism?

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**ABSTRACT:** Asymptomatic primary hyperparathyroidism is a very common endocrine condition, yet management of this disease process remains controversial. Primary hyperparathyroidism can lead to a myriad of symptoms which not only decreases the quality of life of patients but also increases the risk of cardiovascular disease, osteoporosis, and kidney stones. Parathyroidectomy is the only known cure for the disease. This review explores the definition of asymptomatic primary hyperparathyroidism, the burden of disease, and the overwhelming benefits of parathyroidectomy.

**KEYWORDS:** Hyperparathyroidism, parathyroidectomy, asymptomatic hyperparathyroidism, primary hyperparathyroidism, quality of life, benefits

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## Introduction

Primary hyperparathyroidism is a clinical condition caused by over production of parathyroid hormone from the parathyroid glands. It is diagnosed by the presence of hypercalcemia with an inappropriately normal or elevated parathyroid hormone level. This clinical entity is now the most common cause of hypercalcemia in the outpatient setting. Prior to routine automated serum calcium measurements in the mid-1960s, primary hyperparathyroidism was a rare diagnosis only discovered when patients presented with severe sequelae of the disease including osteitis fibrosa cystica or nephrolithiasis.<sup>1,2</sup> The incidence increased significantly in the 1970s on introduction of automated serum calcium measurements.<sup>1,2</sup> The incidence of hyperparathyroidism increases with age and is 2 to 3 times higher in women compared with men.<sup>3,4</sup> Yeh et al<sup>5</sup> reported the prevalence to be 233 per 100000 women and 85 per 100000 men. The prevalence has been estimated to be as high as 1% of the general adult population and 2% to 3.4% in postmenopausal women.<sup>1,3,5–7</sup> The true prevalence is not known as only approximately one-third of patients with hypercalcemia undergo further evaluation with a parathyroid hormone level, which suggests the prevalence is likely vastly underestimated.<sup>8</sup> Thus, despite its commonality, primary hyperparathyroidism remains very underdiagnosed and undertreated. It is agreed that all patients with biochemically confirmed primary hyperparathyroidism who have specific complications of the disease should undergo parathyroidectomy.<sup>9</sup> However, management of this disease process in more “asymptomatic” patients is still highly debated.

The National Institutes of Health (NIH) and the National Institute of Diabetes and Digestive Kidney Diseases compiled guidelines for parathyroidectomy in patients with primary hyperparathyroidism.<sup>9–11</sup> The criteria included a markedly elevated serum calcium, history of an episode of life-threatening hypercalcemia, reduced creatinine clearance, markedly elevated 24-hour urine calcium with increased renal stone formation

**Table 1.** National Institutes of Health consensus guidelines for parathyroidectomy.

|   |
|---|
| 1. Serum calcium > 1 mg/dL above upper limit of normal  |
| 2. Bone density T score < –2.5  |
| 3. Vertebral fracture by imaging  |
| 4. Creatinine clearance < 60 mL/min   |
| 5. 24-hour urine calcium > 400 mg/d and increased stone risk by biochemical stone risk analysis |
| 6. Presence of kidney stones  |
| 7. Age < 50   |

risk, nephrolithiasis, age less than 50, and substantially reduced bone mass (Table 1).<sup>9–11</sup>

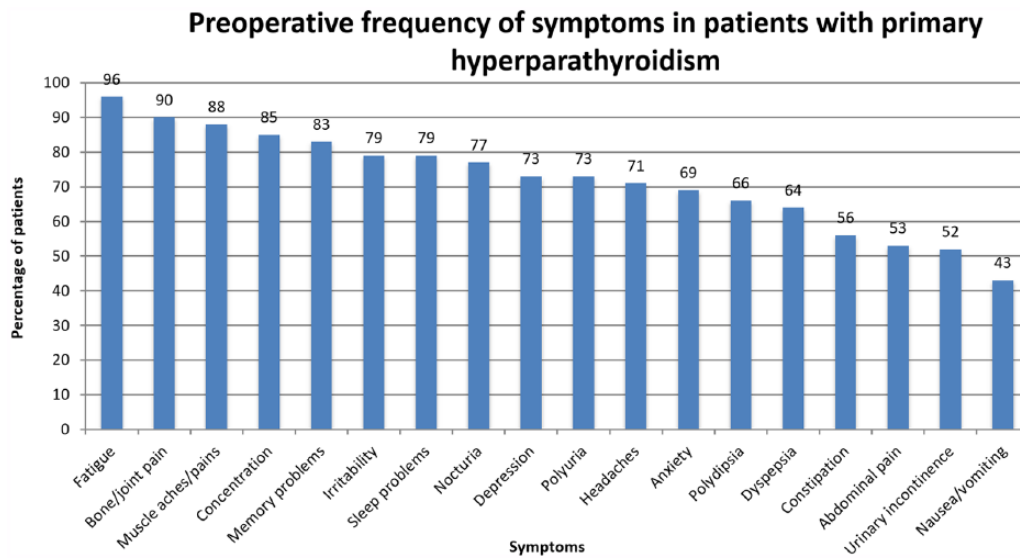
These guidelines were met with much criticism as they are based only on criteria that can be easily measured and do not take into account patients with more subjective symptoms, elderly patients, and patients with milder disease.<sup>12</sup> The guidelines have patients wait until problematic sequelae from hyperparathyroidism develop and exclude many more subjective symptoms commonly associated with this disease.<sup>11</sup> The NIH Guidelines do not clearly define “asymptomatic” primary hyperparathyroidism.<sup>11</sup> Furthermore, more recently, there has been ample data in the literature detailing the benefits of parathyroidectomy in all patients with hyperparathyroidism.

In this chapter, we will explore the definition of asymptomatic primary hyperparathyroidism, the burden of disease, and the overwhelming benefits of parathyroidectomy.

## Definition of Asymptomatic Primary Hyperparathyroidism

Patients with “asymptomatic” primary hyperparathyroidism, by definition, lack symptoms classically associated with the





**Figure 1.** Frequency of symptoms with primary hyperparathyroidism. Reprinted with permission from Murray et al.<sup>14</sup> 2018 Elsevier.

**Table 2.** Parathyroidectomy Assessment of Symptoms.

|  |
|--|
| Pain in the bones                        |
| Feeling tired easily                     |
| Mood swings                              |
| Feeling “blue” or depressed              |
| Pain in the abdomen                      |
| Feeling weak                             |
| Feeling irritable                        |
| Pain in the joints                       |
| Being forgetful                          |
| Difficulty getting out of a chair or car |
| Headaches                                |
| Itchy skin                               |
| Being thirsty                            |

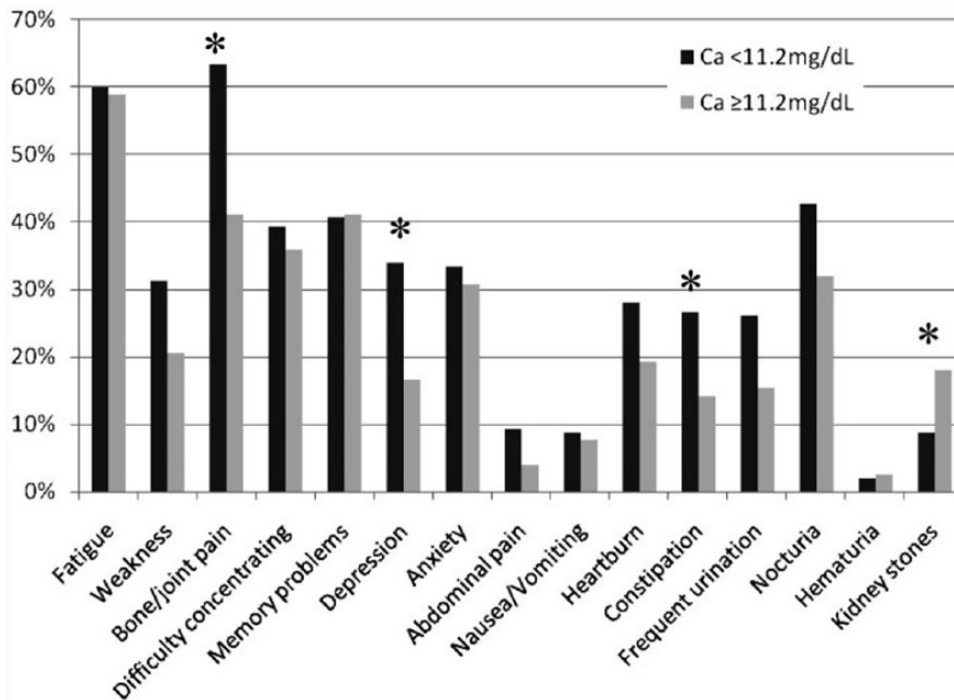
disorder, including history of renal calculi, fragility fractures, osteoporosis, severe bone and joint pain, and significant neuropsychiatric impairment.<sup>13</sup> However, greater than 90% of patients labeled as “asymptomatic” have significant symptoms likely related to hyperparathyroidism, as many symptoms are nonspecific and difficult to quantify.<sup>14,15</sup> Based on a growing body of evidence in the literature, hyperparathyroidism affects one’s general well-being and cardiovascular health. Multiple sources give evidence to the fact that primary hyperparathyroidism is rarely, if ever, truly asymptomatic.<sup>11,13</sup> Moreover, patients classified as “asymptomatic” have a 23% to 62% risk of developing complications of hyperparathyroidism by 10 years if just observed.<sup>3</sup>

### The Burden of Disease

Studies have shown that patients diagnosed with primary hyperparathyroidism report a vast number of symptoms. Murray et al<sup>14</sup> explored the frequency of symptoms that patients experienced. They queried 18 symptoms, including fatigue, bone/joint pain, memory and concentration problems, irritability, depression, anxiety, sleep problems, and so on.<sup>14</sup> No patient in the cohort was truly asymptomatic with the lowest reported number of symptoms of 3.<sup>14</sup> What is more, 17 symptoms were present in greater than 50% of the patients (Figure 1).<sup>14</sup>

Pasiaka et al<sup>16</sup> developed and validated a disease-specific surgical outcome tool to measure the frequency of symptoms in patients with hyperparathyroidism (Table 2). This instrument investigated not only the presence of symptoms but also the severity to which each patient experienced the symptom in question allowing for quantitative measurement of symptoms specific to hyperparathyroidism and for calculation of the Parathyroidectomy Assessment of Symptoms (PAS) score.<sup>16</sup> When compared with patients with nontoxic thyroid undergoing thyroidectomy, patients with hyperparathyroidism had significantly higher preoperative PAS scores.<sup>16</sup>

Bargren et al<sup>15</sup> found the most common symptoms reported by patients to be fatigue, bone pain and joint pain, occurring in greater than 50%, with memory problems and difficulty concentrating occurring in approximately 40%. Interestingly, symptom severity could not be predicted by the degree of the biochemical abnormalities.<sup>15,16</sup> Patients with a calcium > 1 mg/dL above the upper limit of normal did report more renal calculi.<sup>15</sup> However, bone pain, joint pain, depression, and constipation were actually significantly more common in patients with only mild hypercalcemia (Figure 2).<sup>15</sup> In addition, there was no correlation between degree of parathyroid hormone elevation or vitamin D deficiency and symptomatology.<sup>15</sup>



**Figure 2.** Symptoms of hyperparathyroidism based on degree of hypercalcemia. Reprinted with permission from Bargren et al.<sup>15</sup> 2018 Elsevier.

### Symptomatic Improvement Following Parathyroidectomy

The literature clearly illuminates the frequency of symptom occurrence in patients with hyperparathyroidism. However, is there evidence demonstrating improvement of these symptoms after surgical treatment of hyperparathyroidism? Murray et al<sup>14</sup> evaluated symptom improvement over time following parathyroidectomy. They discovered that all symptoms were reported less frequently after surgical intervention.<sup>14</sup> Fatigue, bone pain, and joint pain were found to improve as quickly as 1 week postoperatively.<sup>14</sup> By 6 weeks postoperatively, most symptoms improved in greater than 50% of patients.<sup>14</sup> Neurocognitive symptoms including difficulty concentrating, irritability, memory problems, anxiety, and depression demonstrated peak improvement at 6 weeks postoperatively with a slight decrease in improvement at 6 months postoperatively.<sup>14</sup>

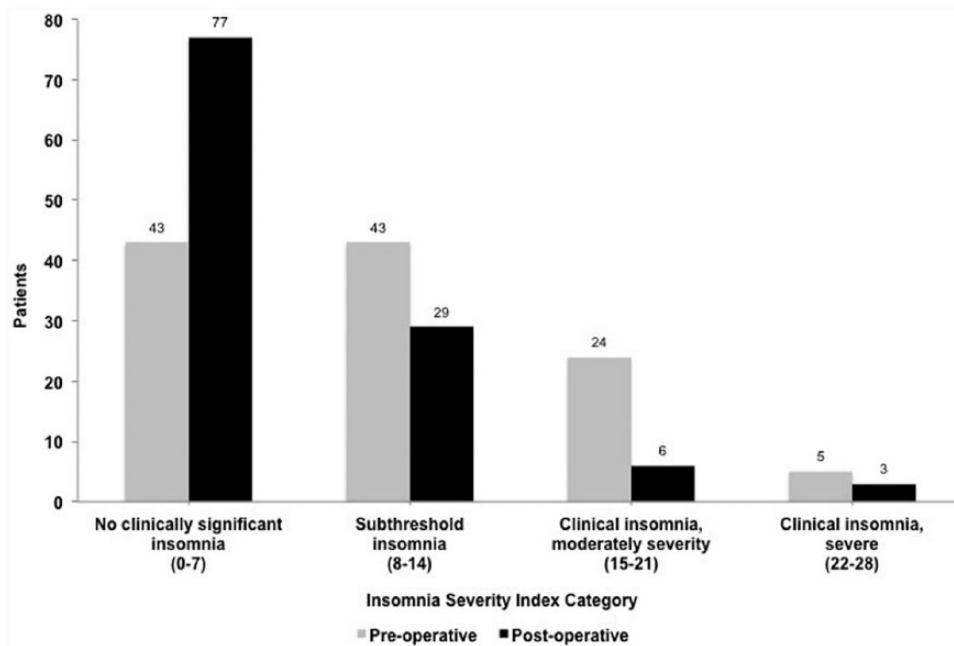
Pasieka et al<sup>16</sup> demonstrated similar results. Preoperative and postoperative PAS scores were calculated and compared for patients with primary hyperparathyroidism in an international study of patients in the United States, Canada, and Australia.<sup>16</sup> Remarkably, the total PAS scores and individual symptom scores significantly decreased indicating significant improvement in patient symptomatology following parathyroidectomy.<sup>16</sup> Patients continued to experience improvement in symptoms even 10 years postoperatively.<sup>17</sup>

Regarding symptomatology, there has been no difference shown between patients diagnosed with primary hyperparathyroidism fulfilling the NIH criteria and patients not meeting these criteria. Eigelberger et al<sup>11</sup> revealed symptoms occur

with equal frequency between the 2 groups and that symptomatic improvement in patients not fulfilling the NIH guidelines is just as great as those who do. Several studies have also investigated whether the symptomatic improvement seen in patients following parathyroidectomy is potentially just a placebo effect of surgery by comparing symptom improvement in patients undergoing thyroidectomy with those undergoing parathyroidectomy.<sup>11,16</sup> Patients with primary hyperparathyroidism report significantly more symptoms preoperatively than patients with thyroid disease.<sup>11,16</sup> Postoperatively, there is no change in symptoms in the thyroid patients, yet there is a significant decrease in reported symptoms following parathyroidectomy.<sup>11,16</sup> Thus, this improvement in symptoms is unlikely to be merely a placebo effect from surgery itself or to be present only in those with markedly elevated calcium levels.<sup>11,16</sup>

Blanchard et al<sup>18</sup> developed a preoperative clinical scoring system to predict which patients would most benefit from parathyroidectomy. The clinical score is calculated based on the patient's age, presence or absence of preoperative weight loss, abdominal pain, abdominal distention, fatigue, and depressive symptoms.<sup>18</sup> Patients with a high predictive score were found to most likely show symptomatic improvement following surgery.<sup>18</sup> However, patients who score less than or equal to 3 on the preoperative clinical scoring system were unlikely to show symptomatic improvement following parathyroidectomy.<sup>18</sup>

From here, we will discuss the value of parathyroidectomy on specific symptoms relating to hyperparathyroidism.



**Figure 3.** Preoperative versus postoperative total insomnia severity index scores. Reprinted with permission from Murray et al.<sup>21</sup> 2018 Springer Nature.

### Impact of Parathyroidectomy on Heartburn

Hyperparathyroidism instigates upper and lower gastrointestinal smooth muscle atony leading to multiple symptoms including heartburn and nausea.<sup>19</sup> Reiher et al<sup>20</sup> studied the impact of parathyroidectomy on symptoms of gastroesophageal reflux disease and need for anti-reflux medications. Following surgical intervention, patients related a significant improvement in the presence of heartburn, impact on diet, dysphagia, and odynophagia.<sup>20</sup> While controlling for body mass index, 67% of patients evidenced greater than 50% improvement on a gastroesophageal reflux disease health-related quality of life (GERD-HRQOL) questionnaire.<sup>20</sup> In addition, there was a significantly decreased use of anti-reflux medications 6 months postoperatively in those who reported improvement compared with those who did not.<sup>20</sup> While certainly primary hyperparathyroidism is not the only cause of GERD, it is an issue that should be considered when weighing the risks and benefits of surgical intervention. Correcting the hypercalcemia may treat the origin of the patient's GERD and decrease the need for other medical or surgical therapies.

### Impact of Parathyroidectomy on Sleep

Sleep impairment and insomnia, which have a significant detriment on patient quality of life, have been associated with hyperparathyroidism.<sup>21</sup> The prevalence of sleep impairment in patients with primary hyperparathyroidism is between 44% and 62% with 25% meeting the criteria for clinical insomnia.<sup>21,22</sup> The incidence of patients with clinical insomnia in the setting of underlying hyperparathyroidism is over 4-fold that of the general population (6%).<sup>21</sup> Following parathyroidectomy, patients report significant reduction in sleep disturbances with

a resolution of insomnia in 70% of patients (Figure 3).<sup>21</sup> In addition, those with clinical insomnia sleep a significantly increased number of hours each night following surgical cure of hyperparathyroidism.<sup>21</sup> When compared with patients with thyroid disorders, patients with hyperparathyroidism have significantly worse sleep quality.<sup>23</sup> Following parathyroidectomy, patients' sleep quality and sleep efficiency improves with a decrease in time to fall asleep and a greater number of hours slept.<sup>23</sup> On the contrary, patients undergoing thyroidectomy have no improvement in sleep quality.<sup>23</sup>

### Impact of Parathyroidectomy on Quality of Life

Not only does parathyroidectomy decrease symptoms of gastroesophageal reflux disease and insomnia, it also affects patients' overall quality of life in a beneficial way. Multiple studies have assessed quality of life, many using a well-recognized and validated survey instrument known as the 36-Item Short Form Health Survey (SF-36).<sup>12,24-27</sup> Two prospective randomized clinical trials evaluating patients with mild asymptomatic primary hyperparathyroidism assigned patients into 2 groups: parathyroidectomy or no-surgery.<sup>24,27</sup> Compared with patients observed without surgical intervention, Ambrogini et al<sup>24</sup> revealed that those who underwent parathyroidectomy evidenced significant improvement in quality of life particularly regarding bodily pain, general health, vitality, and mental health. Patients have also revealed improvements in physical functioning as well as role limitations due to physical health, emotional problems, and social functioning.<sup>26</sup> These effects on health-related quality of life show durability at 1 year.<sup>26</sup> Rao et al<sup>27</sup> also demonstrated a significant benefit in social and emotional function following parathyroidectomy even at 3 years postoperatively.

Caillard et al<sup>12</sup> performed a prospective multicentric study evaluating the effect of parathyroidectomy on patients' nonspecific symptoms and quality of life. Results were compared between patients who fulfilled the NIH guidelines for parathyroidectomy and those who did not.<sup>12</sup> This study evidenced a significant improvement in nonspecific symptoms and quality of life following parathyroidectomy in both groups, regardless of whether patients met the NIH criteria.<sup>12</sup> Symptom and quality of life improvements have even been demonstrated in patients with normocalcemic hyperparathyroidism following surgical intervention.<sup>28</sup>

### **Bone Improvements Following Parathyroidectomy**

Fractures and osteoporosis have long been known to be affected by hyperparathyroidism. However, many questioned the utility of surgery in patients without evidence of fractures or other overt symptoms. Over a 10-year time period, patients with hyperparathyroidism who underwent parathyroidectomy have a significant increase in bone mineral density of the lumbar spine and femoral neck.<sup>29</sup> Significant improvement is evidenced as early as 1 year following surgery and sustained or even better at 10 years.<sup>24,29</sup> This has been further verified on a skeletal microarchitectural level.<sup>30</sup> Using high-resolution peripheral quantitative computed tomography (HRpQCT), the improvement in cortical and trabecular volumetric bone density still exists.<sup>30</sup> Interestingly, patients with the lowest T scores displayed the greatest improvement in bone mineral density of the lumbar spine.<sup>24</sup> Those with the disease not undergoing surgery showed no improvement in bone mineral density.<sup>29</sup> Even worse, Silverberg et al<sup>29</sup> revealed that there can be progression of disease with a 10% decrease in bone mineral density in 27% of patients not undergoing parathyroidectomy by 10 years. These findings are supported by a recent prospective randomized trial of patients with mild primary hyperparathyroidism.<sup>31</sup> Lundstam et al<sup>31</sup> randomized patients with the disease to either parathyroidectomy or observation. Following a 5-year follow-up period, patients observed with primary hyperparathyroidism had a significant decrease in bone mineral density at the femoral neck, radius, ultradistal radius, and total body.<sup>31</sup> Patients treated with parathyroidectomy had a significant increase in bone mineral density of the lumbar spine with stable bone mineral density of the femoral neck, ultradistal radius, and total body as well as a significant decrease in biochemical markers of bone turnover.<sup>31</sup> Koumakis et al<sup>32</sup> revealed that even many patients with normocalcemic hyperparathyroidism benefit from parathyroidectomy with an increase in bone mineral density.

Elevation of parathyroid hormone leads to increased bone turnover, decreased bone mineral density, and increased risk of fracture.<sup>33</sup> This increased risk of fracture is seen even as great as 10 years prior to patients undergoing parathyroidectomy and is not associated with severity of preoperative serum calcium concentration.<sup>33</sup> Moreover, the increased risk of fracture

associated with hyperparathyroidism resolves in less than 1 year postoperatively.<sup>33</sup> The 10-year fracture-free survival is 73% in patients treated surgically compared with 59% in patients observed without surgical intervention.<sup>34</sup> In other words, 41% of patients observed with primary hyperparathyroidism suffered a fracture at 10 years, whereas only 27% of patients undergoing parathyroidectomy suffered a fracture.<sup>34</sup> When comparing parathyroidectomy versus observation, surgical intervention is less costly and more effective when fracture risk reduction is taken into account.<sup>35</sup> These data not only exemplify the benefit of parathyroidectomy but also highlight that lack of surgical intervention can have grave consequences especially for bone health.

Medical management has been shown to improve bone mineral density but not to the degree of surgical intervention.<sup>36</sup> Horiuchi et al<sup>36</sup> performed a randomized control trial evaluating the impact of surgery versus bisphosphonate therapy on bone mineral density. Whereas bisphosphonate treatment led to a 10% increase in bone mineral density, parathyroidectomy resulted in a 20% increase.<sup>36</sup> This study highlights that bisphosphonate therapy may be used as alternative treatment for patients who are not surgical candidates but that the degree of benefit is not as great and is not curative.<sup>34,36</sup> Thus, all patients with the biochemical diagnosis of primary hyperparathyroidism should be offered parathyroidectomy if medically able.<sup>34</sup>

### **Impact of Parathyroidectomy on Cardiovascular Health**

The effects of hyperparathyroidism on bone health is common knowledge; however, what is less known is the degree to which hypercalcemia and hyperparathyroidism also affects patients' cardiovascular health. Previous studies have evidenced a greater frequency of cardiac disease in patients with primary hyperparathyroidism compared with age-matched controls.<sup>37</sup> The effect of primary hyperparathyroidism on left ventricular hypertrophy, the strongest predictor of cardiovascular morbidity is controversial. Early studies performed by Piovesan et al<sup>37</sup> reported that left ventricular hypertrophy is present in 65% of patients with primary hyperparathyroidism. This finding is independent of hypertension.<sup>37</sup> In fact, when controlling for hypertension, the frequency and the degree of left ventricular hypertrophy continues to be significantly greater in hyperparathyroid patients compared with those without the disease.<sup>37</sup> Elevated parathyroid hormone levels correlate with increased left ventricular mass index.<sup>37</sup> Following normalization of parathyroid hormone levels, there is also a reduction of left ventricular mass index evidenced on echocardiogram.<sup>37</sup> This improvement is seen as early as 6 months following parathyroidectomy.<sup>37</sup>

Subsequent studies have shown little difference in left ventricular hypertrophy. Whereas Farahnak et al<sup>6</sup> discovered no difference in global systolic or diastolic function or cardiac morphology compared with healthy-matched controls, patients with primary hyperparathyroidism did show a significant

decrease in blood pressure and regional peak systolic myocardial velocities following parathyroidectomy. Moreover, Walker et al<sup>38</sup> evidenced no linear association between mildly elevated serum calcium and parathyroid hormone levels with left ventricular mass index. However, higher serum calcium and parathyroid hormone levels were associated with diastolic dysfunction.<sup>38</sup> In addition, there is a correlation between decreased vitamin D levels and increased left ventricular mass index.<sup>38</sup> Thus, they concluded that left ventricular hypertrophy is related to the severity of calcium and parathyroid hormone elevation.<sup>38</sup>

Chronic hypercalcemia also leads to accelerated deposition of calcium in the coronary arteries and cardiac valves, thereby increasing the rate of atherosclerosis.<sup>39–40</sup> Moreover, patients with hypercalcemia due to hyperparathyroidism have a higher carotid intima-media thickness and greater arterial stiffness than patients without the disease.<sup>38,40</sup> One study even denoted that patients with hyperparathyroidism have an increased risk of acute myocardial infarction.<sup>41</sup> This increased risk of myocardial infarction exists 10 years before parathyroidectomy.<sup>41</sup> Following parathyroidectomy, studies have shown significant reduction of arterial stiffness 6 months postoperatively in patients with hypercalcemic primary hyperparathyroidism.<sup>29,42</sup> This improvement is maintained at 2 years postoperatively.<sup>42</sup> The impact of parathyroidectomy on carotid intima-media thickness has been only modest.<sup>40,42</sup> More importantly, the increased risk of myocardial infarction returns to normal level 1 year following parathyroidectomy.<sup>41</sup> Farahnak et al<sup>6</sup> recommend early parathyroidectomy before irreparable cardiovascular sequelae can occur in patients with mild primary hyperparathyroidism.

### Increased Risk of Mortality in Primary Hyperparathyroidism

The risk of premature death from ischemic heart disease, cerebrovascular disease, and cancer is significantly increased in patients with primary hyperparathyroidism.<sup>43</sup> Compared with the general population, the standard mortality ratio is elevated in women at 1.7 (95% CI, 1.5–1.9) and men at 1.6 (1.3–2.0) with primary hyperparathyroidism.<sup>43</sup> This risk is reduced in women undergoing parathyroidectomy.<sup>43</sup> When stratifying patients with hyperparathyroidism based on age, elderly patients experience significant improvements of symptoms following parathyroidectomy and tolerated surgery with no increase in mortality.<sup>44</sup>

### Overall Benefit of Parathyroidectomy

Not only are there many known benefits to parathyroidectomy, it is also the only known cure for this chronic disease.<sup>45</sup> Advances in surgical care have made parathyroidectomy a safe outpatient surgery with a low risk of complications. Furthermore, the success rate of hyperparathyroidism following parathyroidectomy is 95% to 98% when performed by an experienced surgeon.<sup>44–45</sup> Cost-effectiveness is paramount to

the success of our current health care system, and parathyroidectomy is less expensive than observation and a more efficient use of health care dollars.<sup>35,45</sup>

### Limitations

While this review summarizes much of the current literature on “asymptomatic” primary hyperparathyroidism, the authors acknowledge some important contributions to the literature may not be included. Unfortunately, there is an overall lack of large, randomized controlled trials regarding this important topic in the literature. Therefore, many of the studies cited herein are small observational cohorts, which may limit the ability to make concrete conclusions. The 4th International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism implores clinicians and scientists to continue to explore many of the unknowns.

### Conclusions

In summary, asymptomatic hyperparathyroidism is a very common endocrine malady affecting 0.2% to 3.4% of elderly women. Hyperparathyroidism can lead to a myriad of symptoms which not only decreases the quality of life of patients but also increases their risk of cardiovascular disease, osteoporosis, and kidney stones. Parathyroidectomy is the only known cure for the disease at this time. We must strive to increase awareness of this common disease by educating providers on the symptoms associated with this condition and the numerous benefits of surgical treatment. All patients with a diagnosis of primary hyperparathyroidism should be referred to an experienced endocrine surgeon to discuss the risks and benefits of parathyroidectomy.

### Author Contributions

All authors have made a substantial contribution to this work as detailed below.

ADM: manuscript preparation and critical revision; RSS: manuscript conception and critical revision.

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