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Commentary

Management of Primary Hyperparathyroidism With Severe Hypercalcemia During the COVID-19 Pandemic

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ABSTRACT

Purpose: In patients with primary hyperparathyroidism (PHPT) and severe hypercalcemia, parathyroidectomy remains the only curative therapy. During the coronavirus disease 2019 (COVID-19) pandemic, when many hospital visits are suspended and surgeries cannot be performed, the management of these patients represents a challenging clinical situation. This article presents a literature review and discussion of the pharmacologic management of PHPT and severe hypercalcemia, which can be used as a temporary measure during the COVID-19 pandemic until parathyroidectomy can be performed safely.

Methods: This narrative review was conducted by searching literature on the PubMed, Medline, and Google Scholar databases using the terms *primary hyperparathyroidism, hypercalcemia, cinacalcet, bisphosphonates, denosumab, vitamin D, raloxifene, hormone replacement therapy, coronavirus,* and *COVID-19*.

Findings: Appropriate monitoring and remote medical follow-up of these patients are essential until the resolution of the pandemic. Cinacalcet is the drug of choice for controlling hypercalcemia, whereas bisphosphonate or denosumab is the drug for improving bone mineral density. Combined therapy with cinacalcet and bisphosphonates or cinacalcet and denosumab should be considered when the effects on serum calcium and bone mineral density are simultaneously desired.

Implications: Medical management of PHPT and severe hypercalcemia presents a reasonable alternative for parathyroid surgery during the COVID-19 outbreak and should be instituted until the pandemic ends and surgery can be performed safely. (*Clin Ther.* 2021;43:711–719.) © 2021 Elsevier Inc.

Keywords: COVID-19 pandemic, primary hyperparathyroidism, severe hypercalcemia.

INTRODUCTION

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, health care systems have been placed under extraordinary obligations. Elective hospital admissions, outpatient visits, and nonurgent surgeries have been postponed to cope with acute care and limit the spread of the infection. In addition, several statements, advice, and recommendations were issued to guide the management of different medical diseases, including endocrine disorders, during the lockdown and social distancing.[1–3] In patients with primary hyperparathyroidism (PHPT) complicated by significant hypercalcemia, parathyroidectomy remains the only curative therapy.[4] Therefore, the management of these patients during the COVID-19 pandemic represents a challenging clinical situation. To avoid poor outcomes, endocrinologists should be apprised of the available treatment options that can be used as a temporary therapeutic bridge until surgery is possible after the resolution of the COVID-19 pandemic.

In the present review, we discuss the pharmacologic management of PHPT and severe hypercalcemia that can be used as temporary therapeutic measures during the COVID-19.

MATERIALS AND METHODS

This narrative review was conducted by searching literature on the PubMed, Medline, and Google Scholar databases using the terms *primary hyperparathyroidism, hypercalcemia, cinacalcet, bisphosphonates, denosumab, vitamin D, raloxifene, hormone replacement therapy, coronavirus,* and *COVID-19*.

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RESULTS

PHPT and COVID-19

Theoretically, patients with PHPT and concurrent infection with COVID-19 may have symptomatic forms of infection because both hypercalcemia and COVID-19 could cause gastrointestinal symptoms, renal impairment, arrhythmias, and cognitive impairment.[5] However, there is no evidence to suggest that patients with PHPT or hypercalcemia are at increased risk from COVID-19.[1–3] Conversely, hypocalcemia was reported to be a distinctive biochemical feature of COVID-19 that increases disease severity.[6]

Hypertension is linked to cardiovascular and kidney diseases. PHPT may cause hypertension, and if not controlled, it may be associated with a higher risk for adverse outcomes of COVID-19.[7] In addition, due to angiotensin-converting enzyme 2 down-regulation by severe acute respiratory syndrome coronavirus (SARS-CoV)-2, the renin-angiotensin-aldosterone system is activated, with increased levels of angiotensin II and aldosterone. Therefore, concurrent infection with COVID-19, hypothetically, could worsen hypertension in patients with PHPT.

A few crucial therapeutic implications could complicate the management of hypercalcemia in patients with PHPT and concurrent COVID-19. There is a risk for acute respiratory distress syndrome in patients with COVID-19, which may be worsened by profuse IV hydration. Hence, careful fluid monitoring and replacement are warranted during hypercalcemia management in patients with COVID-19. Small doses of IV furosemide should be considered after rehydration.[1,2] Second, due to the activation renin-angiotensin-aldosterone system, hypercalcemia management with IV fluids and furosemide could enhance hypokalemia. So, careful monitoring and replacement of potassium are required. Finally, flu-like symptoms in the days following IV bisphosphonate administration is a common side effect, and the symptoms may be confused with COVID-19 symptoms.[1,2]

Management Strategies

Pharmacologic management of PHPT presents a reasonable alternative to parathyroid surgery during the COVID-19 outbreak and should be instituted until the pandemic ends and surgery can be performed safely.[1] Preventive measures include avoiding factors that provoke hypercalcemia and encouraging physical activity, adequate fluid intake, adequate dietary calcium intake, and vitamin D supplementation to achieve serum 25-hydroxy (OH) vitamin D levels of at least ≥20 ng/mL. Pharmacologic therapies effective in controlling hypercalcemia include calcimimetic agents and potentially denosumab.[1,2] Oral bisphosphonates, denosumab, or raloxifene effectively controls skeletal complications. Combination therapy with a calcimimetic agent and bisphosphonates or a calcimimetic agent and denosumab should be considered when effects on serum calcium and bone mineral density (BMD) are simultaneously desired.[8] The Table summarizes the modalities used for managing PHPT and severe hypercalcemia during the COVID-19 pandemic.

Appropriate monitoring and remote medical follow-up of these patients by phone or video consultations are essential. Serum calcium should be measured regularly for the detection of any significant changes that may necessitate hospital admission and/or surgery. The optimal frequency of calcium measurement in these patients is not well defined, but it depends on the severity and symptoms of hypercalcemia. Blood testing should be done away from the acute hospital setting. Educating patients regarding their diseases and engaging them in the management plan will empower them to take care of themselves during the pandemic.[1] Patients should be instructed to self-monitor for the symptoms of hypercalcemia, such as anorexia, nausea, vomiting, bone and abdominal pain, polyuria and polydipsia, and cognitive changes. They should be advised to seek emergency care if they develop symptoms suggestive of hypercalcemic crisis, such as oliguria, anuria, somnolence and/or coma, or if their calcium has reached a critical level (>3.5 mmol/L). Patients with hyperparathyroid crisis should be admitted to the hospital and treated with urgent parathyroidectomy, the only cure for hypercalcemic crisis caused by PHPT.[9,10] Controlling hypercalcemia before surgery is essential and can be achieved by rehydration, calciuresis, and bisphosphonate therapy. Treatment with calcitonin may also be helpful during the first 24 or 48 hours. Hemodialysis should be considered in patients with cardiac and renal comorbidities and/or if calcium level has not improved using medical therapy.[9,10]

Preventive Measures

Patients should avoid factors that can provoke hypercalcemia, such as volume depletion, long periods of immobility, and high calcium intake (>1000 mg/d).

Table. Approaches to managing primary hyperparathyroidism and severe hypercalcemia during the COVID-19 pandemic.

Measures	Effect
Encourage physical activity	Reduces bone resorption
Adequate fluid intake	Reduces the risk for kidney stones
Adequate dietary calcium intake	Inhibits further increases in serum PTH levels
Vitamin D supplementation (400–800 IU/d) to achieve serum 25-OH vitamin D level of ≥20 ng/mL	Reduces PTH levels and bone turnover
Cinacalcet	Reduces serum calcium
Oral bisphosphonates	Improves BMD
Denosumab	Improves BMD and reduces serum calcium
Combination of cinacalcet + alendronate	Reduces serum calcium and improves BMD
Combination of cinacalcet + denosumab	Reduces serum calcium and improves BMD

BMD = bone mineral density; PTH = parathyroid hormone.

Exercise for reducing bone resorption should be encouraged, and adequate fluid intake is recommended (≥2 L/d of water). Thiazide diuretics and lithium should be avoided if possible because they can exacerbate hypercalcemia.[11]

Calcium Supplementation

Adequate dietary calcium intake should be recommended in patients with PHPT, as a lower intake may further increase serum parathyroid hormone (PTH) levels and could worsen the bone disease.[12] Calcium intake of 1000 mg/d is recommended, but a lower intake (eg, <800 mg/d) is advised if the concentration of serum vitamin D is high to prevent exacerbation of hypercalcemia or hypercalciuria.[13]

Vitamin D Supplementation

Vitamin D deficiency is common among patients with PHPT and is associated with higher PTH levels and lower BMD.[14] Thus, the serum 25-OH vitamin D level should be maintained at ≥20 ng/mL in patients with PHPT. To achieve this level, a moderate intake of vitamin D (400–800 IU/d) is suggested.[15] Low levels of vitamin D have been shown to influence patients with COVID-19 adversely.[16] Hence, adequate vitamin D supplementation during the pandemic is recommended.[16]

Antiresorptives for Skeletal Protection

PHPT is characterized by excessive bone resorption. Patients with PHPT and osteoporosis (T-score of <–2.5), fragility fractures, or a high fracture risk as determined by the fracture risk–assessment tool should be managed with antiresorptive therapy, such as bisphosphonates, denosumab, or raloxifene.

Bisphosphonates. Oral Bisphosphonates.

Oral bisphosphonates significantly increase BMD at the lumbar spine and femur in association with reductions in vertebral, nonvertebral, and hip fractures. A meta-analysis of data from studies of bisphosphonate therapy versus parathyroidectomy in PHPT showed comparable increases in BMD at the spine and femoral neck after 1 year in the two treatment groups.[17] However, oral bisphosphonates have shown no noticeable effects on lowering serum calcium.[18] Alendronate is the most extensively examined pharmacologic therapy for patients with PHPT and osteoporosis. Alendronate is considered the first-line drug in most cases, given its efficacy, low cost, and long-term tolerability data. Alendronate treatment has been associated with a significant increase in BMD at the lumbar spine, total hip, and femoral neck in PHPT, with significant bone-turnover reductions.[19,20] However, no significant changes were noted in the distal radius BMD or in serum calcium, PTH, or urine calcium levels.[19,20] Lumbar spine, but not femoral neck, BMD was improved with 2-year treatment with risedronate in postmenopausal women with PHPT.[21]

IV Bisphosphonates

IV zoledronic acid is more potent than oral bisphosphonates and has been approved for use in the treatment of hypercalcemia and osteoporosis. Treatment with zoledronic acid effectively reduces serum calcium in PHPT complicated by severe hypercalcemia; however, no data are available on its skeletal effects.[22] Zoledronic acid administration requires a hospital visit or admission and is commonly associated with flu-like symptoms following its administration, which could be confused with the symptoms of COVID-19. Hence, the use of zoledronic acid during the COVID-19 pandemic is not a reasonable option, except in cases of severe hypercalcemia that require admission.

Denosumab

Denosumab is a monoclonal antibody against the receptor activator of nuclear factor-κB ligand. Denosumab suppresses osteoclast activity and inhibits bone resorption; thus, it increases BMD significantly at the lumbar spine and femur and reduces vertebral, nonvertebral, and hip fractures. Denosumab is indicated in patients with osteoporosis at high risk for fracture, such as those with a history of osteoporotic fracture, multiple risk factors for fracture, or unresponsiveness or intolerance to other available anti-osteoporosis therapies.[12] Denosumab is not excreted by the kidney; therefore, it can be used in patients with chronic kidney disease, particularly if the estimated glomerular filtration rate is <30 and other treatment options, such as bisphosphonates, are contraindicated. In a recent retrospective study, treatment with denosumab for 24 months results in a greater increase in the BMD of the lumbar spine and total hip among postmenopausal women with PHPT than in postmenopausal women with primary osteoporosis.[23]

Denosumab reduces serum calcium levels by inhibiting bone resorption and has been approved for use in the treatment of hypercalcemia of malignancy, but at higher doses than that required for treating osteoporosis, that is, 120 mg q4wk, with 2 additional 120-mg doses during the first month of therapy. Case reports have described the use of denosumab in the treatment of severe hypercalcemia in patients with PHPT or parathyroid carcinoma.[24,25]

Because denosumab improves BMD and can reduce serum calcium levels, it could be a potential monotherapy for use in improving both hypercalcemia and skeletal complications of PHPT as a bridge to surgery. However, given that the reduction in serum calcium induced by denosumab is often short-lived, frequent and higher doses may be required. Future studies examining this potential indication and the doses required for controlling hypercalcemia are needed. Appropriate measures used for supporting the self-injection of denosumab or domiciliary administration during the COVID-19 pandemic should be explored. There are currently no data to suggest an increased risk for viral infection when denosumab is used for the treatment of osteoporosis.[26]

One crucial issue after denosumab discontinuation is a rapid increase in bone-turnover markers and a reduction to baseline in BMD, with a possible increase in the risk for multiple vertebral fractures. Therefore, sequential therapy with bisphosphonates after denosumab discontinuation is advised to prevent bone loss and maintain the benefits achieved with denosumab.[27–29] Given the mode of administration, cost, and the observed bone loss following denosumab discontinuation, it may be considered as an alternative to bisphosphonates.

Raloxifene

Raloxifene is a selective estrogen receptor modulator that acts as an agonist in bone and an antagonist in breast and uterine tissues; hence, it is considered safer than hormone-replacement therapy (HRT). It improves lumbar spine BMD and reduces bone turnover. In postmenopausal women with osteoporosis and PHPT, raloxifene has been shown to be equally effective as alendronate in improving BMD at the lumbar area.[30] In a small-scale study, serum calcium and markers of bone turnover were reduced with raloxifene use in postmenopausal women with PHPT[31]; however, the effect on serum calcium was not demonstrated in another study.[30] Raloxifene may be appropriate as initial therapy in osteoporotic, postmenopausal women with PHPT requiring drugs with spine-specific efficacy if other antiresorptive agents, such as oral bisphosphonates or denosumab, cannot be administered for any reason.[32] Raloxifene has been demonstrated to have substantial direct antiviral activity against COVID-19 *in vitro*.[33] Hence, it could be an effective treatment for COVID-19 patients with mildly symptomatic infection. The advantages of raloxifene include its tolerability, and known side effects. The Italian Medicines Agency has authorized a clinical trial of raloxifene in COVID-19 patients with mild symptoms.[34]

Hormone-Replacement Therapy

HRT improves lumbar spine and hip BMD and reduces biochemical markers of bone turnover in women with PHPT.[35] However, HRT does not lower serum calcium, and data on its effect on fracture risk are lacking.[12] Due to the overall health risks associated with HRT, its use should be restricted to early-postmenopausal women with PHPT when other antiresorptive agents are contraindicated or not feasible.[32]

Interestingly, as men are more likely than women to develop severe COVID-19 infection, there is an assumption that estrogen might protect women. Whether HRT provides a promising therapeutic potential in postmenopausal women with COVID-19 is not known and requires further testing.[36]

Calcium-Lowering Medications

Calcimimetics

Cinacalcet is a calcimimetic drug that stimulates the calcium-sensing receptor in the parathyroid gland and subsequently inhibits PTH secretion and reduces calcium concentrations.[37] Cinacalcet often normalizes serum calcium and modestly decreases PTH levels in patients with PHPT.[38] However, cinacalcet has no positive effects on BMD and has an uncertain effect on quality of life.[39]

Cinacalcet is considered the drug of choice for the management of severe hypercalcemia in PHPT when parathyroidectomy is contraindicated or not feasible.[39] It has been shown to reduce hypercalcemia in patients with a spectrum of PHPT disease severity, including patients who failed parathyroidectomy, with symptomatic PHPT, and with mild asymptomatic PHPT.[40] Additionally, cinacalcet has been reported to provide effective short- and long-term control of hypercalcemia. In one study, the efficacy of cinacalcet was maintained for up to 4.5 years of follow-up.[40] Cinacalcet has been reported to be effective and well tolerated in controlling calcium and PTH levels in patients with type 1 multiple endocrine neoplasia syndrome.[41,42] Also, serum calcium level was effectively lowered with the use of cinacalcet in patients with parathyroid carcinoma and has been approved for use in the treatment of severe hypercalcemia in inoperable parathyroid cancer.[39] Moreover, numerous case reports have described cinacalcet use in the treatment of humoral hypercalcemia of malignancies mediated by PTH-related protein, such as metastatic renal cell carcinoma, metastatic breast cancer, and lung cancer.[43,44]

IV bisphosphonates and denosumab reduce serum calcium levels by inhibiting bone resorption. Cinacalcet has been reported to reduce calcium levels through its effects on calcium-sensing receptor in the parathyroid gland and inhibition of PTH secretion. In addition, cinacalcet may reduce calcium levels through its effects on calcium-sensing receptor in the distal nephron and enhancing renal calcium excretion.[44]

The tolerability and effectiveness of cinacalcet during pregnancy in patients with PHPT and hypercalcemia have been described in case reports.[45,46] Overall, cinacalcet is well tolerated, and nausea, vomiting, muscle spasms, and paresthesia are the most common adverse effects.[39] The typical cinacalcet dose is 30 mg BID (ranging from 30–180 mg/d). Cinacalcet is expensive, which may limit its use. In addition, whether cinacalcet reduces morbidity and mortality in patients with PHPT is unclear.

The findings from a recent pilot study suggest that cinacalcet is effective in patients with PHPT complicated by nephrolithiasis.[47] The number and size of kidney stones were reduced with cinacalcet use in patients with PHPT.[47] In contrast, urine biochemistries did not improve, and the risk for recurrent calcium stone disease was not reduced with the use of cinacalcet in another recent study.[48]

Calcitonin

Calcitonin decreases serum calcium levels by inhibiting bone resorption and, to a lesser degree, by enhancing urinary calcium excretion. Calcitonin has a time-limited and transient effect on calcium level, with tachyphylaxis occurring ~3 days after administration.[49] Thus, calcitonin is not a suitable therapeutic option for protracted hypercalcemia in patients with PHPT during the COVID-19 pandemic.

Combined Therapy

In patients with PHPT seeking treatment during the COVID-19 pandemic, combination therapy with cinacalcet and an oral bisphosphonate should be considered when effects on serum calcium and bone density are simultaneously desired. In one report, in patients with PHPT, a combination of cinacalcet and alendronate normalized serum calcium and improved BMD.[50] in another study, serum calcium was normalized, and lumbar spine and total hip BMD were significantly increased after 12 months of therapy with a combination of cinacalcet and denosumab.[51] The

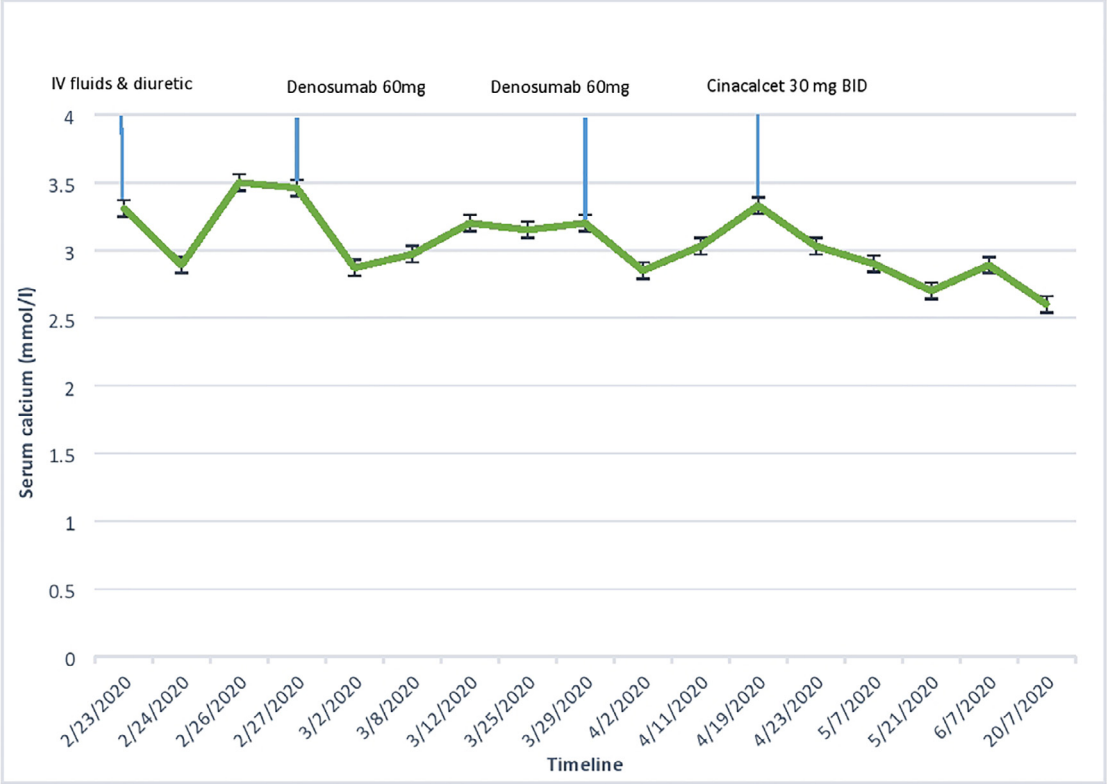

Figure. Patient's serum calcium levels over the treatment course of primary hyperparathyroidism and severe hypercalcemia during the COVID-19 pandemic.

latter combination may reduce serum calcium more effectively than the combination of cinacalcet and an oral bisphosphonate and could represent an option for use in the treatment of patients with PHPT and severe hypercalcemia who have not responded to cinacalcet alone.

Illustrative Case

A 52-year-old woman was found to have severe hypercalcemia on routine blood testing, with a serum calcium level of 3.31 mmol/L (normal value, 2.2–2.6 mmol/L). Serum PTH was elevated, at 374 ng/L (normal, 15–65), confirming the diagnosis of PHPT. The patient was asymptotic, with no reports of polyuria, polydipsia, nausea, vomiting, or constipation and no history of kidney stones. She had no complications of PHPT apart from severe osteoporosis. Her T-scores were –3 at the lumbar spine and –2 at the femur neck. She had a history of a fracture of the right ankle several months prior to presentation. Her medical history was notable for type 2 diabetes and hypertension for 10 years. Her physical examination was unremarkable. Other laboratory results included a phosphorus level of 0.72 mmol/L (normal, 0.8–1.4), alkaline phosphatase of 173 U/L (normal, 46–122), creatinine of 46 μmol/L (normal, 46–96), 25-OH vitamin D of 18 ng/mL, and 24-hour urine calcium of 7.53 mmol/24 h (normal, 1.8–8).

The patient was managed in the emergency department using IV fluids and diuretics. Her serum calcium level was reduced to 2.89 nmol/L. IV bisphosphonates were not administered because the drugs were not available at that time. The patient was discharged, scheduled for localization imaging, and referred to the surgery clinic. However, with the lockdown during the COVID-19 pandemic, all procedures, including surgeries, were canceled. Subsequently, her calcium level increased to 3.5 mmol/L. Given the unavailability of cinacalcet, denosumab 60 mg SC was administered by a domiciliary nurse as the initial therapy to

lower calcium and improve her BMD. After 5 days, her serum calcium was reduced to 2.87 mmol/L; however, a rapid rebound of hypercalcemia occurred within 10 days after administration. By day 12, her calcium level reached 3.2 mmol/L. A second dose of denosumab 60 mg was administered 1 month after the first dose, which decreased the calcium level to 2.85 mmol/L at 8 days after administration. However, hypercalcemia reoccurred 2 weeks after the second dose, with a calcium level of 3.33 mmol/L. Given this persistently difficult-to-control hypercalcemia, cinacalcet was requested from the nephrology unit, and the patient was started on cinacalcet 30 mg BID. Her calcium level started to improve after 5 days and reached 2.7 mmol/L 1 month after the start of cinacalcet treatment; however, the PTH level did not decrease and remained high, at 394 ng/L. Vitamin D 1000 U/d was given when the patient's calcium reached 2.7 mmol/L but was subsequently discontinued as her serum calcium level increased to 2.89 mmol/L. Another reason for the latter increase in serum calcium may have been the poor compliance with cinacalcet treatment because of nausea. The patient was educated regarding the importance of drug compliance. In addition, alendronate 70 mg once weekly was started for the treatment of osteoporosis. For approximately 2 months, the calcium level remained normal to slightly high. The Figure presents the patient's serum calcium level over the course of treatment. At the end of quarantine, further work-up revealed an enlarged right inferior parathyroid gland, and she was scheduled for a parathyroidectomy.

CONCLUSIONS

The management of PHPT complicated by severe hypercalcemia during the COVID-19 pandemic, when surgery cannot be performed and hospital visits are restricted, represents a challenging clinical situation. Endocrinologists should be apprised of the treatment options available during this crucial time. Remote follow-up and appropriate monitoring of these patients are essential until the resolution of the pandemic, when surgery can be performed safely. Cinacalcet is the drug of choice for managing hypercalcemia, whereas bisphosphonates or denosumab improves BMD. Combined therapy with cinacalcet and a bisphosphonate or cinacalcet and denosumab should be considered if the effects on serum calcium and BMD are simultaneously desired.

DECLARATION OF COMPETING INTEREST

The author has indicated no conflicts of interest with regard to the content of this article.

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