Challenges and opportunities for osteoporosis care during the COVID-19 pandemic

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ABSTRACT

Purpose: The Coronavirus Disease 2019 (COVID-19) has both directly and indirectly affected osteoporosis diagnosis and treatment throughout the world.

Methods: This mini-review summarizes the available evidence regarding the effects of COVID-19, its treatment, and the consequences of the pandemic itself on bone health. Additionally, we review evidence and expert recommendations regarding putative effects of osteoporosis medications on COVID-19 outcomes and vaccine efficacy and summarize recommendations for continuation of osteoporosis treatment during the pandemic.

Results: The use of standard screening procedures to assess for osteoporosis and fracture risk declined dramatically early in the pandemic, while rates of fragility fractures were largely unchanged. COVID-19, its treatments, and public health measures to prevent viral spread are each likely to negatively affect bone health. Osteoporosis treatments are not known to increase risk of adverse events from COVID-19, and pre-clinical data suggests possible beneficial effects of some therapies. Vitamin D deficiency is clearly associated with adverse outcomes from COVID-19, but it remains unclear whether vitamin D supplementation may improve outcomes. Osteoporosis treatment should be continued whenever possible, and recommendations for substituting therapies, if required, are available.

Conclusion: The COVID-19 pandemic has decreased screening and disrupted treatment for osteoporosis. Osteoporosis medications are safe and effective during the pandemic and should be continued whenever possible. Further studies are needed to fully understand the impact of the COVID-19 pandemic on long-term bone health.

Keywords: osteoporosis, COVID-19, SARS-CoV2, anti-resorptive, vitamin D, vaccination

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has affected every aspect of medical care, from diagnosis and screening to acute and chronic disease management. In particular, ramifications of the pandemic on osteoporosis care have been widespread. Many primary care and specialty clinics temporarily closed, paused, or slowed schedules for screening dual-energy X-ray absorptiometry (DXA) scans, or scrambled to safely deliver needed clinic-administered medications. Numerous questions remain regarding the interaction of osteoporosis and COVID-19, as well as that of COVID-19 treatments, osteoporosis treatment delays, and physical distancing on long-term bone health. In this review, we discuss the myriad consequences of the pandemic on individual and population bone health, including effects on and recommendations for the screening, diagnosis, and treatment of osteoporosis.

SEARCH STRATEGIES

We performed a literature review using PubMed for English-language articles published between January 2020 and June 2021. Search terms included ("COVID-19" OR "SARS-CoV-2") AND ("osteoporosis" OR "fracture" OR "bone density" OR "DXA" OR "bisphosphonate" OR "denosumab" OR "PTH(rP) analog" OR "romosozumab" OR "vitamin D"). Pertinent data were abstracted and used to compile this review article.

IMPACT OF THE PANDEMIC ON OSTEOPOROSIS DIAGNOSIS AND COMPLICATIONS

The COVID-19 pandemic has disrupted routine care throughout the world, including dramatic decreases in routine screening for osteoporosis. Multiple studies have demonstrated a decrease in rates of DXA scans of greater than 50% during the early stages of the pandemic (1,2). In one Italian practice, DXA exams declined by greater than 80% in the first two months of the pandemic (3). In our academic medical center in Boston, Massachusetts, the Bone Density Center closed from mid-March to early June 2020 as physicians, nurses, and operations staff were redeployed to support the care of

inpatients during the first COVID-19 surge; after reopening in June 2020, rates of performed DXA scans increased slowly, reaching approximately 75% of pre-pandemic levels by the end of 2020 and not approaching pre-pandemic levels until March of 2021. In total, approximately 40% fewer DXA scans were performed in March 2020-2021 (n=6,048) as compared to March 2019-2020 (n=10,156), although no differences in age, gender, or race/ethnicity were seen among DXA scan recipients before and during the pandemic. Barriers to care cited by patients and providers included fears of exposure and difficulty scheduling DXA scans, related to clinic and imaging center closures or spaced scheduling as part of infection control measures instituted by most institutions (4). Similarly, global use of the Fracture Risk Assessment Tool (FRAX), used to estimate 10-year fracture risk and to determine eligibility for osteoporosis treatment, decreased by greater than 50% in the spring of 2020 (5), suggesting a significant decrease in new diagnoses and clinical appointments for osteoporosis. These declines are especially concerning considering the already very low rates of screening and treatment for osteoporosis (6–8).

As in many other outpatient clinics across the U.S., our clinical center moved to 100% virtual care for several months. Even as the pandemic surges have eased and our clinic has reopened, our experience has been that we are continuing to have a balance of in-person and virtual appointments. Although the rapid increase in availability of telehealth has improved access to appointments for some, barriers remain for many patients. In particular, racial and ethnic minorities, individuals with limited English proficiency, and older adults may have less access to telemedicine (9–11). These disparities may further exacerbate pre-existing racial disparities in osteoporosis screening and treatment (12–17) and result in failure to reach older individuals who are at greatest risk for osteoporosis and fracture. Further, the improvement in access brought about by telemedicine only applies to services that can be performed virtually, notably excluding DXA scans, laboratory monitoring, and administration of parenteral medications. In light of potential limitations on in-person care during pandemic surges, a joint statement from the American Society for Bone and Mineral Research (ASBMR) along with the Endocrine Society and other international osteoporosis groups recommended prioritizing testing which is necessary to osteoporosis care (e.g., checking appropriate

safety labs prior to first administration of denosumab or zoledronic acid, or prior to subsequent administrations of these agents specifically among patients with higher risk of hypocalcemia) (18). At the same time, this statement recognized that some monitoring for osteoporosis, including DXA scans, is elective and can often be delayed based on prevailing public health guidance or patient preference to avoid in-person exposures.

While care for osteoporosis has declined during the pandemic, complications of osteoporosis have unfortunately not slowed. Although overall rates of fracture decreased significantly after the pandemic began (19–22), several studies suggested that this was driven entirely by a decline in traumatic fractures, with the rates of osteoporotic hip fractures either unchanged (19,21) or potentially increased (23) from prior years. In our academic center, the annual rate of hip fracture was unchanged to slightly increased between March 2020-2021 (n=700), as compared to March 2019-2020 (n=612); furthermore there were no obvious differences in the age nor gender of hip fracture patients during the two time periods, with the majority of fractures occurring among women and among adults aged ≥ 70 years old. A multi-center study in China examined characteristics of 2,489 patients with fracture and found that fractures after the pandemic were more likely to occur in older adults, occur in the home, and be classified as osteoporotic fractures (24). While long-term rates of follow-up and clinical outcomes after osteoporotic fracture during the COVID-19 pandemic have yet to be reported, one study did demonstrate the feasibility of a virtual fracture liaison service via telehealth: among 110 patients with fracture invited to a virtual visit, 79% attended their appointment, and 98% of those who completed a survey about the experience would recommend the service to others (25).

Fragility fractures may also be a marker associated with adverse outcomes related to COVID-19. Among 114 hospitalized older adults in Italy with COVID-19, the prevalence of pre-existing vertebral fracture was 36%, and patients with vertebral fractures had higher rates of non-invasive mechanical ventilation and mortality (26). Similarly, among 209 patients admitted with COVID-19 in Turkey, lower vertebral bone density, as assessed by computed tomography, was associated with increased mortality risk in multivariate analyses (27). A risk prediction algorithm developed in a large U.K. cohort found that history of osteoporotic fracture was independently associated with mortality

among those testing positive for SARS-CoV-2 (hazard ratio (HR) 1.12 (1.00-1.26) for women, HR 1.41 (1.24-1.61) for men), even after adjusting for age, sex, race/ethnicity, socioeconomic deprivation, body mass index, and numerous comorbidities (28). Although it is possible that severe vertebral fractures may impair respiratory mechanics (29), it is more likely that prevalent fractures are a marker of frailty and comorbidities that presage worse outcomes with COVID-19. In turn, COVID-19 infection co-occurrence at the time of hip fracture is associated with higher mortality rates than hip fracture alone (23,30–32), as well as longer length of stay and higher rates of non-surgical treatment (20).

These studies support both the ongoing importance of treating osteoporosis and the role osteoporosis may play as a marker of fragility and predictor of worse COVID-19 outcomes.

INTERACTION OF SARS-CoV-2 AND COVID-19 THERAPIES WITH CALCIUM HOMEOSTASIS AND OSTEOPOROSIS

Beyond the new barriers to osteoporosis care, it is possible that COVID-19 itself may impact bone health. Although not yet reported for SARS-CoV-2, the SARS-CoV-1 virus in the early 2000s was associated with increased osteoclastogenesis *in vitro* (33). SARS-CoV-2 shares many characteristics of SARS-CoV-1, and the systemic inflammation and cytokine storm associated with SARS-CoV-2 may also be expected to adversely affect bone health (34,35). Indeed, the clinical presentation of COVID-19 may include an array of musculoskeletal symptoms, including myositis and exacerbation of inflammatory arthropathies (36).

Further, very high rates of hypocalcemia (up to 60-80%) have been reported in patients admitted with COVID-19 (37–42). Low calcium levels are associated with numerous predictors of poor outcomes, including older age, male sex, and higher levels of inflammatory markers (37,41), as well as with higher rates of adverse outcomes (37,39,41,42). This is similar to findings of SARS-CoV-1, for which hypocalcemia was also common, occurring in up to 70% of patients (43), and was associated with more severe disease (44). To date, it is unclear whether this hypocalcemia represents a

COVID-19-specific effect or a marker of severe illness, and the long-term effects of acute hypocalcemia on bone health are unknown.

In contrast, the association between phosphorus levels and COVID-19 severity is unclear. Hypophosphatemia is common among patients admitted with COVID-19 (45,46), and in a small study of 32 patients admitted with COVID-19 in China, phosphorus levels were lower in those who were critically ill as compared to those with less severe illness (46). However, in a sample of 280 patients with CKD admitted with COVID-19, lower phosphorus levels were associated with lower mortality (47). In another study, hypocalcemia and hypophosphatemia were specific, albeit not sensitive, for identifying severe COVID-19 (48). Phosphorus excursions during admission for COVID-19 may be a marker of critical illness, as in other pathologies such as sepsis and pancreatitis.

Finally, both hyper- and hypomagnesemia have been reported in patients admitted with COVID-19, and both have been associated with more severe illness (49,50). One observational study found that individuals admitted with COVID-19 who were supplemented with vitamin D, vitamin B12, and magnesium were less likely to require oxygen or ICU care as compared to historical controls (51); however, numerous differences in baseline comorbidities and changing standards of COVID care between groups may have confounded results. Some authors have suggested magnesium supplementation may be beneficial for patients with COVID-19 (52,53), but to our knowledge, no primary data exists to support this claim.

Current treatments for COVID-19 may also adversely affect bone health. High-dose glucocorticoids, now standard of care for hospitalized patients with COVID-19 (54), are well-known to decrease bone mineral density (BMD) and increase risk of fracture in a dose and duration-dependent manner (55). Indeed, treatment for patients during the SARS epidemic involved prolonged courses of very high doses of glucocorticoids that resulted in reduced bone mass and a 7-fold increased risk of avascular osteonecrosis of the hip (34,56–58). It is important to note, however, that dexamethasone regimens for COVID-19 are generally shorter (≤10 days) and involve lower cumulative dosing than the very high doses of glucocorticoids used in the original SARS epidemic, and therefore the long-term skeletal consequences of this treatment remain to be seen. Importantly,

glucocorticoid-induced osteoporosis can be at least partially prevented by several osteoporosis therapies, and should be considered for patients who may require long-term treatment (≥3 months) with glucocorticoids (59). To date, other COVID-19 therapies such as remdesivir and bamlanivimab are not known to affect BMD or fracture risk, although bamlanivimab has only briefly been available for study. Baricitinib, a Jak1/2 inhibitor, has shown some favorable effects on bone resorption, suppressing RANK ligand expression and inhibiting osteoclastogenesis *in vitro* (60), but is used infrequently for COVID-19 treatment (61). Protease inhibitors such as ritonavir have been associated with increased risk for osteoporosis (62), whereas hydroxychloroquine may have favorable effects on bone density (63); however, neither of these treatments are commonly used for COVID-19 any more.

Finally, intensive care itself, and the prolonged immobilization associated with critical illness, is known to negatively affect bone health (64,65), as well as skeletal muscle health which can impact fall and fracture risk (66). Prolonged intensive care can also affect vitamin D levels through limits on nutrition and sun exposure; in patients surveyed 8 weeks after discharge from the ICU for COVID-19, rates of vitamin D deficiency were higher than prior to admission, and vitamin D deficiency and PTH elevation were more common among those who had survived more severe COVID-19 (67).

Although limited data is available, it is likely that both COVID-19 and its treatments will adversely affect the bone health of those who become ill from SARS-CoV-2.

SECONDARY EFFECTS OF THE COVID-19 PANDEMIC ON LONG-TERM BONE HEALTH

In addition to the physiologic effects of COVID-19 and its treatment, the very measures used to prevent the spread of COVID-19 may contribute to bone loss in the general population by inhibiting healthy habits that promote bone health. For example, stay-at-home orders led to significant decreases in physical activity in both younger (68,69) and older adults (70). In older adults, physical activity levels recovered after these orders were lifted, but not in socially isolated individuals (71). Weight-bearing exercise, and particularly resistance training can improve physical performance and attenuate loss of BMD (72–75), so this decrease in physical activity during pandemic stay-at-home

orders may contribute both to decreased BMD related to immobilization and to increased frailty and fall risk (76). Unfortunately, the effects of quarantine on musculoskeletal health and body composition may be only partially attenuated by home-based exercise training, as demonstrated by a small randomized study of resistance training among elderly individuals confined to their homes (77).

Similarly, stay-at-home and quarantine orders, as well as safety concerns related to interacting with others, have driven many indoors. With decreased sun exposure for months on end, it is reasonable to believe that vitamin D levels will decline in adults who do not take daily supplements (76), raising the risk of vitamin D deficiency, secondary hyperparathyroidism, and fractures.

IMPACT OF THE PANDEMIC ON OSTEOPOROSIS TREATMENT REGIMENS

In addition to the many COVID-19 and pandemic-related factors impacting bone health and osteoporosis screening rates, many physicians and patients report struggling to continue medication regimens during the pandemic, especially parenteral therapies administered in the clinic (1,2). For example, one nationwide analysis revealed decreases of 18-49% in administration of denosumab and intravenous bisphosphonates in the first two months of the pandemic (78). Smaller, but still significant, declines in bone-directed therapies have been reported in patients with active malignancy at risk for pathologic fractures (79).

Moreover, many patients have unfortunately been confronted with loss of all healthcare access related to loss of employment and health insurance or significant financial strains of the pandemic (80). This has disproportionately affected racial and ethnic minorities (81,82) who are both more likely to experience COVID-19 infection (83) and were less likely to receive appropriate screening and treatment for osteoporosis before the pandemic (12–17).

Multiple expert opinions have offered recommendations for the safe initiation and continuation of osteoporosis therapy during the pandemic (18,84,85), and these are summarized in the Table. For patients with newly diagnosed osteoporosis, treatment initiation should not be delayed due to the pandemic, especially in patients with recent fracture. In these situations, it may be most

expedient to start oral therapy (e.g., alendronate) or self-administered parenteral therapy (e.g., teriparatide or abaloparatide) in conjunction with a telemedicine appointment; however, alternate therapies should not be discounted if they are the best option for the patient and are accessible.

In patients already receiving osteoporosis therapy, whenever possible, it is recommended to continue the patient's current therapy (84). This is straightforward for oral medications (e.g., alendronate, raloxifene) but can present challenges for clinician-administered therapies if lockdown measures are in place. Strategies recommended to overcome these challenges include exploring alternative care delivery models including use of off-site clinics, drive-through administration, or in-home administration of intravenous and subcutaneous medications (e.g., denosumab and romosozumab) (18). Additionally, less frequent dosing regimens of zoledronic acid (86–88) or transition from parenteral therapies to oral bisphosphonates may be considered (84,89–92), especially if continuation of parenteral therapies cannot be accomplished without significant delays which may result in increased risk of rebound vertebral fractures from discontinuation of denosumab or loss of BMD gains from discontinuation of anabolic therapy (93,94). In our academic medical center in Spring 2020, approximately half of patients receiving denosumab were transitioned to bisphosphonate therapy, one quarter received denosumab with some delay, and the remaining received their scheduled medication through an alternate mechanism of care delivery such as off-site or in-home administration. Among patients receiving romosozumab, half continued treatment with some delay, and the other half were either transitioned to bisphosphonate therapy or received their injection at an off-site facility. Anecdotally, following the initial switch to bisphosphonates, some patients eventually transitioned back to their earlier therapy, while others have chosen to continue bisphosphonates.

INTERACTION OF OSTEOPOROSIS THERAPIES WITH COVID-19

It is worth considering the effects, if any, of osteoporosis medications on COVID-19 pathogenesis. Although limited primary data has been published regarding specific medications and the risk of COVID-19, data from observational studies support the ongoing use of osteoporosis medications. In an observational study of over 2000 patients in Spain, adults treated with osteoporosis medications did not appear to have an increased risk for COVID-19 infection compared to the general population (95). Denosumab warrants special consideration, as there has been concern regarding denosumab and the risk of infection based on numeric imbalances in infection rates in clinical trials and associations in meta-analyses and observational data (96–99). Denosumab is a monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), and both RANKL and its receptor are expressed on immune cells, including B and T lymphocytes and dendritic cells, and may play an important role in immune signaling and maturation of the adaptive immune system (100–103). However, this concern, especially in the setting of COVID-19, is tempered by a recent meta-analysis of randomized controlled trials demonstrating that denosumab did not increase the risk of upper respiratory infections, pneumonia, or infection-related mortality, although there was an increased risk of ENT and GI infection-related adverse events (104). Further, denosumab was not associated with risk of COVID-19 in small samples of patients receiving osteoporosis therapy in Italy (105) and Spain (95).

There are also pre-clinical and pre-COVID-19 data to suggest that certain osteoporosis therapies may have positive physiologic effects which might decrease risk of severe COVID-19. Bisphosphonates, the most commonly used medication for osteoporosis treatment, have been associated with decreased risk of pneumonia and pneumonia-related mortality in select patients (106,107). Selective estrogen receptor modulators (SERMs) like raloxifene and even estrogen itself may have pleotropic effects affecting COVID-19 severity (108–111), including modulating angiotensin converting enzyme 2 (ACE2) expression which may impact risk of infection (112), inhibiting IL-6 signaling which may moderate cytokine storm (113), and *in vitro* efficacy in treating

other respiratory infections such as influenza A (114). However, as estrogen and SERMs modestly increase thrombotic risk, it will be important to await the results of ongoing randomized trials examining the efficacy and safety of these treatments in the setting of COVID-19.

The relationship between vitamin D and COVID-19 remains controversial, despite many known interactions between vitamin D, immunity, and other common infections (115). Prior to the COVID-19 pandemic, extensive evidence highlighted the importance of activated vitamin D in the immune response to viral pathogens (116,117), with roles impacting viral entry and replication (118,119), and promotion of autophagy (120). Studies in the pre-COVID era demonstrated that low vitamin D levels are associated with higher rates of infection (121–123) and adverse outcomes from infection (124–127), and treatment with vitamin D is specifically linked to lower rates of viral infection (128–132), although this is not seen in all studies (133,134). These differences in treatment efficacy may arise from differences in patient selection (vitamin D deficient vs. sufficient) and vitamin D dosing frequency (daily or weekly vs. monthly). Indeed, one meta-analysis found that vitamin D prevention of acute respiratory infection was only present amongst patients with low baseline vitamin D levels (<10 ng/mL) and which involved supplementation with daily or weekly dosing of vitamin D (130).

Specifically regarding COVID-19, *in vitro* studies suggest that activated vitamin D may significantly decrease SARS-CoV-2 replication (135). Current evidence also strongly supports the association between vitamin D deficiency and adverse outcomes related to COVID-19, although causality remains to be proven. Observational studies suggest that vitamin D deficiency is highly prevalent among hospitalized patients with COVID-19 (136–141) and is associated with higher risk of infection (138,141–148), disease severity, and death (137,139–141,145,146,149–157). Use of vitamin D supplement use has also been associated with decreased rates of infection (144,158,159) and decreased disease severity (51,160–162) in observational studies, although these studies are limited by the inability to adjust for confounders which may explain differences in habitual dietary supplement use. Finally, several large-scale Mendelian randomization studies have harnessed genetic epidemiologic techniques to reduce confounding and found no evidence to support increasing serum

25-hydroxyvitamin D levels as a method to reduce COVID-19 susceptibility or severity in the general population, although it remains unclear whether these results apply to individuals with vitamin D deficiency (163–166).

There are fewer data currently available from randomized interventional vitamin D trials of patients with COVID-19. Two small randomized pilot studies suggested that vitamin D supplementation improved time to viral clearance in vitamin D deficient individuals with mild COVID-19 (167) and decreased COVID-19 disease severity (168). An additional small randomized study comparing two doses of daily vitamin D found that COVID-19 symptom resolution was shorter among those receiving 5000 IU/day as opposed to 1000 IU/day (169); however imbalances in baseline age and BMI may confound these results. In a randomized study of 130 vitamin D-deficient individuals admitted with COVID-19, daily high-dose vitamin D therapy resulted in a significant reduction in inflammatory markers which was not seen in the control group, although no differences were seen in rates of discharge or death (170). However, a larger placebo-controlled trial of single, high-dose vitamin D supplementation in 240 patients with and without baseline vitamin D deficiency found no difference in COVID-19 outcomes, including no improvement in mortality, ICU admission, or mechanical ventilation requirement (171). Thus, although some authors argue for the widespread or targeted supplementation of vitamin D at a population level (85,172), further research is needed to determine if vitamin D may have a causal role in COVID-19 disease severity. This is an active area of investigation with >45 randomized trials registered at ClinicalTrials.gov.

INTERACTION OF OSTEOPOROSIS THERAPIES WITH COVID-19 VACCINES

Finally, it is important to consider any relationship between osteoporosis and osteoporosis therapies with COVID-19 vaccines. To date, osteoporosis itself, independent of age and associated comorbidities, is not recognized as a risk factor for infection with SARS-CoV-2 or adverse outcomes from COVID-19, and experts do not recommend prioritizing patients with osteoporosis for vaccination (173,174), independent of other known risk factors.

To our knowledge, no data exists to suggest that any osteoporosis therapy would attenuate vaccine efficacy. In fact, estrogen may augment the effect of other vaccines (113), and vitamin D has critical interactions with the innate immune system (115,116,175), as discussed above. However, it may be reasonable to briefly delay certain therapies based on their associated side effects (Table), as noted in a recently published joint statement from the ASBMR, the Endocrine Society, and other osteoporosis groups (173). For example, infusion of either IV bisphosphonates or COVID-19 vaccines can induce a transient flu-like reaction (176–180); hence IV bisphosphonates may be delayed by approximately one week in order to not coincide with vaccine administration. This may avoid confusion, anxiety, and unnecessary testing in the event of fever, chills, or myalgias which might be caused by the infusion, the vaccine, or COVID-19 itself.

LIMITATIONS AND DIRECTIONS FOR FUTURE RESEARCH

To date, most studies of bone health related to COVID-19 are observational or include interventions on only a small number of individuals. Most osteoporosis therapies have not been directly studied in individuals with COVID-19. For this reason, expected associations between COVID-19 and bone health or osteoporosis medications and disease or vaccine outcomes are often extrapolated from data involving other infectious processes. As there are increasing expectations that COVID-19 will become endemic, there are many lines of research that are of interest to clarify the impact of COVID-19 on bone health. Of top clinical priority are rigorous randomized placebo-controlled trials evaluating whether vitamin D supplementation plays any therapeutic role in either the prevention or treatment of COVID-19 disease. Several such randomized trials are ongoing (160,181), and their results will be critical to provide guidance to clinicians and patients alike. Additional ongoing pilot trials of hormonal therapies in the treatment of COVID-19 will also shed light upon whether other bone-active treatments may impact the course of COVID-19. Primary data, particularly in the form of prospective cohorts, are urgently needed to help understand the immediate and potential long-term osseous effects of high-dose glucocorticoids used in COVID-19 treatment, as well as acute hypocalcemia associated with critical illness. Larger studies examining the association between

osteoporosis and COVID-19 outcomes, with adequate controls for age, frailty, and other confounders associated with increased risk from COVID-19, are also warranted. Other areas of research importance include prospective, longitudinal data examining the potential clinical consequences of decreased and delayed osteoporosis diagnosis and treatment during the pandemic, and cessation of exercise during stay-at-home orders. Importantly, now that "long-haul COVID" has been identified as a potentially important and long-term clinical syndrome, additional research will be required to delineate the musculoskeletal involvement of "long-haul COVID" symptoms and to evaluate whether common pathophysiologic pathways such as chronic inflammation may further negatively impact skeletal health. As COVID-19 therapies and vaccine availability are rapidly evolving, prospective follow-up of recipients of vaccines and novel therapies for COVID-19 should also be prioritized in order to examine the association between these therapies and musculoskeletal outcomes. As an osteoporosis community, we should also leverage recent pandemic-driven innovations to study the use of telemedicine to expand outreach for fracture liaison services and the development of rigorous home-based exercise programs.

SUMMARY AND CONCLUSION

The COVID-19 pandemic – including the disease itself, its treatments, and the public health measures employed to slow its spread – has significantly impacted bone health and osteoporosis diagnosis and treatment, both at an individual and a population level. At this time, we have no evidence to suggest that osteoporosis treatment may carry increased risk related to COVID-19 or impair vaccine efficacy, and in fact, pre-clinical evidence suggests possible positive effects related to certain therapies. Further, treatment of osteoporosis resulting in fracture prevention will help to decrease hospitalization-related COVID-19 exposures and unburden the strained hospital infrastructure throughout the world. Given the already profound rates of undertreatment of osteoporosis and the potential adverse effects of failing to recognize and treat osteoporosis, it is critical to find innovative ways to ensure patients at risk for osteoporosis and fracture continue to receive care during the pandemic.

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Table. Recommendations for osteoporosis therapy initiation and continuation during potential COVID-19-related resource restrictions and with concurrent COVID-19 vaccine administration.

	Initiating therapy in treatment-naïve patients	Continuing or transitioning therapy	Concurrent therapy administration with COVID-19 vaccine
Oral bisphosphonates	Initiate as usual, telemedicine appointment acceptable for counseling	Continue therapy	Continue therapy
IV bisphosphonates	Consider initiating oral bisphosphonate instead if no significant concerns for dysphagia, esophageal pathology, or malabsorption	Continue therapy if possible Alternatively, treatment delay or transition to oral bisphosphonate is acceptable	Separate by 1 week, if possible
Denosumab	Consider initiating alternate therapy if patient not able to reliably receive clinic-based administration If advanced kidney disease, may consider reduced-dose oral bisphosphonate	Strong recommendation to continue therapy if possible; consider off-site or self-administration If therapy must be delayed or discontinued, transition to oral bisphosphonate at the time that next administration is due	Separate by 4-7 days, if possible, and/or use alternate subcutaneous injection sites Ensure subsequent denosumab dose is administered within 7 months of last dose
PTH(rP) analogs	Initiate as usual May require in-person nursing visit to teach self-injection technique	Continue therapy if possible Brief treatment delay (e.g., 2-3 months) is acceptable Transition to oral bisphosphonate if longer delay expected	Continue therapy
Romosozumab	Consider initiating alternate therapy if patient not able to reliably receive clinic-based administration	Continue therapy if possible; consider off-site administration Brief treatment delay (e.g., 2-3 months) is acceptable Transition to oral bisphosphonate if longer delay expected.	Separate by 4-7 days, if possible, and/or use alternate subcutaneous injection sites
Raloxifene, estrogen	Initiate as usual, telemedicine appointment acceptable for counseling	Continue therapy	Continue therapy

PTH(rP) = parathyroid hormone (PTH) or PTH-related peptide