




Pros and Cons of Skeletal Medications in the COVID-19 Era

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Abstract

Purpose of Review This review provides an overview regarding osteoporosis therapies during the COVID-19 pandemic.

Recent Findings The COVID-19 pandemic has disrupted treatments for osteoporosis and resulted in decreased adherence particularly for parenteral regimens. Osteoporosis medications are safe and effective during the pandemic and should be continued whenever possible. Bisphosphonates have long-lasting effects on bone turnover such that delays in their administration are unlikely to be harmful to skeletal health. In contrast, interruption of denosumab treatment is strongly discouraged because of rapid loss of bone mass and an associated increased risk for rebound vertebral fractures. When osteoanabolic treatments cannot be continued during the pandemic, change to an oral bisphosphonate is advised. Preclinical data suggest possible beneficial effects of some therapies against COVID-19, but require validation in clinical studies. Vitamin D deficiency is associated with a more severe COVID-19 clinical course but data supporting improvements in outcomes with vitamin D supplementation are lacking.

Summary The impact of the COVID-19 pandemic on long-term bone health remains unknown but focused interventions to ensure osteoporosis treatment initiation/maintenance should

be implemented. Future studies are needed to determine whether osteoporosis medications have an impact on SARS-CoV-2 pathophysiology and COVID-19 clinical outcomes.

Introduction

At the time of this writing, SARS-CoV-2, the causative virus for the COVID-19 pandemic, has infected more than 554 million people and resulted in over 6.3 million deaths worldwide [1]. The COVID-19 pandemic has disrupted routine medical care globally, with the reallocation of personnel and infrastructure for the acute management of patients suffering from COVID-19 having taken its toll on the treatment of many chronic conditions including musculoskeletal diseases. In addition, social distancing and isolation have led to reduced physical activity and increased sedentary lifestyles, both of which are associated with sarcopenia, osteoporosis, and an increased incidence of fragility fractures [2, 3]. In view of the impact of the pandemic on musculoskeletal health, both professional societies and bone specialists have issued recommendations for the optimization of osteoporosis treatment in this era [4•, 5•, 6•, 7•]. In this review, we examine the current literature on pharmacologic and non-pharmacologic regimens for patients suffering from osteoporosis in the COVID-19 era and discuss putative “pros” and “cons” of such agents and approaches in this setting.

Vitamin D and calcium supplementation

The importance of vitamin D for the regulation of calcium and phosphate homeostasis is well established. Vitamin D insufficiency leads to impaired calcium absorption, secondary hyperparathyroidism, osteoporosis, and fragility fractures [8], while daily supplementation of 800–2000 IU cholecalciferol co-administered with calcium reduces hip fracture rates by 15–30% and other non-vertebral fractures by 20% [9]. Whether the beneficial effects of vitamin D extend beyond musculoskeletal health has been the subject of research from the earliest stages of the pandemic. Theoretically, additional non-musculoskeletal benefits seemed possible, since vitamin D is known to modulate both innate and adaptive immunity, is involved in inflammatory processes, and may decrease the risk of infection [10, 11]. Numerous observational studies have investigated the association of circulating vitamin D levels with a number of

outcomes including the severity of COVID-19 disease, need for hospitalization, duration of hospital stay, intensive care unit (ICU) admission and duration of stay, time to symptomatic recovery and time to seronegative conversion, risk of complications, and mortality rate following COVID-19 infection. Two recent narrative reviews [6, 12], as well as a systematic review and meta-analysis [13•], have presented these findings. To summarize the evidence, observational studies have shown that serum 25(OH)D concentrations <20 ng/mL are linked to a higher probability of SARS-CoV-2 infection and are associated with increased risk for ICU admission, mechanical ventilation, and COVID-19 mortality [6, 12, 13•]. It is noteworthy, however, that observational studies have a high risk of bias and are limited by confounding, i.e., the relationship between vitamin D status and other comorbidities also linked to adverse outcomes following COVID-19 infection such as diabetes mellitus, obesity, cardiovascular and respiratory diseases, and malignancy [14]. In addition, since vitamin D is an inverse acute phase reactant with lower levels during times of increased physiologic stress [15], observational studies in this setting are potentially prone to reverse causation [12].

Given such caveats associated with association studies, randomized-controlled studies (RCTs) of vitamin D supplementation in the context of COVID-19 infection are more likely to provide evidence of potential benefits [16]. Two RCTs which used single-bolus high-dose vitamin D versus placebo (540,000 IU and 200,000 IU respectively), however, reported no survival benefit or differences in secondary outcomes related to hospitalization [17, 18], findings which were confirmed in a meta-analysis of RCTs [19•]. Moreover, a Mendelian randomization study based on participants from eight distinct genome-wide association studies (GWAS) showed no effect of alleles associated with 25(OH)D levels on COVID-19 susceptibility, indicating no genetic evidence to support vitamin D supplementation [20]. In conclusion, since existing data do not support a clear

and strong cause-effect relationship between vitamin D status and COVID-19 outcomes, no recommendations for supraphysiologic doses of vitamin D supplementation to treat or prevent COVID-19-related complications can be issued. In fact, supplementation with high-dose bolus vitamin D may even have a negative impact on fall and fracture outcomes [21, 22]. It is notable that there are currently >40 RCTs in ClinicalTrials.gov examining the role of vitamin D in COVID-19. However, until more information becomes available, it seems reasonable to tailor vitamin D supplementation according to osteological society recommendations, i.e., daily supplementation with 800–2000 IU to maintain 25(OH) D concentrations ≥ 30 mg/mL [23]. Finally, patients infected with COVID-19 commonly present with hypocalcemia. Although hypocalcemia

has been shown to correlate with higher rates of adverse outcomes [24, 25], it is unclear whether low serum calcium levels constitute a COVID-19-specific effect or rather serve as a general marker of severe illness. No RCTs on the effects of supplementation with calcium alone on the course of COVID-19 have been published to date, although a retrospective cross-sectional study of 490 patients treated with calcium supplements for osteoporosis revealed a decreased risk of COVID-19 infection (RR=0.64, 95% CI 0.37, 1.12) in this population [26]. A phase I/II study to investigate the tolerability and safety of calcium carbonate versus placebo concomitant with the best available treatment (BAT) is currently in the recruitment phase (NCT04900337).

Pharmacological treatment of osteoporosis

There is a well-recognized gap in the treatment of osteoporosis that extends worldwide, with just one-fifth of patients provided with treatment after a hip fracture, the time when patients are most at risk for another fracture [27]. The discrepancy between a diagnosis of osteoporosis and the provision of optimal care has been further exacerbated during the COVID-19 pandemic, with the treatment of osteoporosis appearing to rank comparatively lower when compared to other competing clinical priorities. As evidence of this, a number of national and international surveys have documented considerable delays and poor adherence to treatment, especially with regard to parenteral osteoporosis treatments, both as a result of reallocation of personnel to acute services, and because affected patients have been unwilling or unable to attend care facilities for scheduled treatments [28–31]. Importantly, osteoporosis treatments are not known to increase the risk for adverse events from COVID-19, and preclinical data suggest that some therapies may have favorable effects. Below, we discuss what is known regarding commonly used medications for the treatment of osteoporosis with respect to COVID-19 susceptibility, pathogenesis, and clinical course as well as the impact of the COVID-19 pandemic on individual osteoporosis therapeutic regimens.

Estrogen and selective estrogen receptor modulators (SERMs)

Hormone replacement therapy (HRT) improves bone mineral density (BMD) and reduces fracture risk in women with osteoporosis. Low-dose transdermal HRT is less likely to cause breast cancer, endometrial hyperplasia, coronary artery disease (CAD), and venous thromboembolism (VTE), which have been

linked to standard-dose oral HRT regimens [32]. HRT is therefore used for the primary prevention and treatment of osteoporosis in appropriate candidates [32]. Interestingly, males are more susceptible than females to SARS-CoV-2 infection, and older men with comorbidities have a greater risk of developing severe COVID-19 disease [33]. Although environmental factors are undoubtedly important, it is possible that such differences may be at least partially attributable to sex-specific genetic and hormonal factors [34]. Innate and adaptive immune responses to many viral infections differ between males and females, with evidence pointing to the more favorable clearance of viral pathogens in women [35], as well as reduced expression of ACE2, a receptor facilitating the entry of SARS-CoV-2 into target cells [36], and negative correlations between estradiol and IL-6, IL-2R, and interferon γ -inducible protein 10 [37]. In this vein, it is noteworthy that there are currently two RCTs (NCT04539626, NCT04865029) underway designed to investigate the effects of a short course of systemic treatment with estradiol and progesterone in addition to BAT on COVID-19 symptoms in patients with mild/moderate disease.

Selective estrogen receptor modulators (SERMs) are characterized by mixed agonism/antagonism effects at the estrogen receptor (ER) of specific tissues, with beneficial estrogenic effects in some organs and avoidance of adverse or off-target effects in other tissues. Raloxifene, a widely used SERM, has been approved for the prevention and treatment of osteoporosis in postmenopausal women, as well as to reduce the risk of invasive breast cancer in postmenopausal women [38, 39]. The most common adverse effects associated with raloxifene therapy are hot flashes, nausea, and vomiting, while the most significant adverse effects are venous thromboembolic events [40]. Although raloxifene is not approved for use in men, existing data demonstrate tolerability as well as efficacy in men in terms of bone turnover markers and lipid metabolism [41]. Of note, an older study in humans had shown that raloxifene decreases levels of both IL-6 and tumor necrosis factor α (TNF- α), thus highlighting its anti-inflammatory effects [42]. In addition, *in vitro* studies have confirmed inhibition of viral replication and/or infection against HCV [43], HBV [44], and the Zika virus [45], while the addition of raloxifene to BAT of interferon 2α /ribavirin proved beneficial for the treatment of chronic hepatitis C infection in humans [46].

Recently, raloxifene was identified *in silico* among 400,000 candidate molecules and was preselected to proceed with *in vitro* testing among 7000 molecules via the supercomputing platform 'ExaScale smart pLatform Against paThogEns' (EnsEXSCALATE) as a promising molecule with antiviral activity to treat oligosymptomatic COVID-19 disease [47••]. According to data generated via this platform, raloxifene was predicted to bind to relevant SARS-CoV-2 proteins, while also having a higher pulmonary distribution relative to other SERMs. Notably, the relatively low pharmacologic concentrations in the lung have been a major limitation of currently used antiviral medications used to treat COVID-19 respiratory complications [47]. It is also noteworthy that no clinically relevant interactions have been described between raloxifene and frequently co-administered drugs [47••]. A multicenter placebo-controlled phase 2 study to investigate the efficacy and safety of two different

doses of oral raloxifene in patients with early diagnosis of pauci-symptomatic COVID-19 was recently completed, with the results pending (NCT05172050).

In conclusion, both HRT and raloxifene have pleiotropic effects which may affect COVID-19 severity, including modulating ACE2 expression which might impact both infection risk and clinical course, and via inhibition of IL-6 signaling which could potentially mitigate cytokine storm [48]. However, as both HRT and raloxifene are associated with a modest increase in thrombotic risk, the results of ongoing RCTs investigating their efficacy and safety in the setting of COVID-19 will be particularly important. It will also be of interest to ascertain whether the effects of HRT and raloxifene differ between males and females.

Bisphosphonates

Bisphosphonates are the most commonly used medications for the treatment of primary and secondary osteoporosis in both women and men. After bisphosphonate discontinuation, bone turnover markers which had been suppressed eventually revert to baseline levels, and bone mineral density (BMD) remains stable or gradually diminishes over years [49, 50]. Bisphosphonates' antiresorptive effects last after treatment is discontinued as a result of the strong affinity of bisphosphonates for binding to hydroxyapatite. This property holds especially true for the aminobisphosphonates alendronate and zoledronate. There is also some evidence for long-term antifracture effects following bisphosphonate cessation, although these findings are less well supported [51, 52].

A number of studies have investigated whether bisphosphonate use for the treatment of osteoporosis is associated with COVID-19 outcomes. A nationwide, multicenter, retrospective study from Turkey during the first wave of the COVID-19 pandemic compared patients diagnosed with COVID-19 who were treated with anti-osteoporosis medications with COVID-19 positive patients who did not receive bone active drugs. Of the 1997 women included, 89.5% were treated with bisphosphonates. This study revealed that hospitalization risk, ICU admissions, and mortality rates were not influenced by bisphosphonates or any other drug category [53]. In comparison, a separate study showed that treatment with zoledronate was associated with a 40% decreased risk of COVID-19 infection, whereas oral bisphosphonates had no effect on COVID-19 incidence [26•]. A third population-based retrospective observational cohort study comprising 9% of the Italian population also showed no benefit of oral bisphosphonate treatment with regard to the incidence of COVID-19 hospitalization, need for ICU care, and mortality rates [54•]. Although these findings need to be verified in further studies, the potent aminobisphosphonate zoledronate might differentially modulate aspects of COVID-19 susceptibility and clinical course.

It is notable that earlier studies not performed in patients with COVID-19 infection had reported lower mortality with zoledronate treatment, with postulated mechanisms including a reduction in cardiovascular risk and fracture prevention, but also enhanced regulation of the immune system and a lower incidence of pneumonia [55–57]. These immunomodulatory effects have

been ascribed to an increase in natural killer cells as well as a stimulatory effect on $\gamma\delta$ cells T cells in response to zoledronate [58, 59]. In this context, it is worth noting the distinct profile involving selective expansion of $\gamma\delta$ T cell populations was described in the aftermath of the 2003 SARS outbreak [60], while T-cells, including $\gamma\delta$ cells T cells, are depleted in patients suffering from severe COVID-19 [61••]. In this context, zoledronate could plausibly hinder endosomal homeostasis, a process which appears to be pivotal for SARS-CoV-2 survival [62•]. In terms of mechanism of action, zoledronate inhibits prenylation of small GTPases, proteins necessary for endosomal trafficking in osteoclasts [63]. Given that osteoclasts and dendritic cells arise from a common precursor and share a number of functions [64, 65], zoledronate may have similar effects on endosomal exocytosis of SARS-CoV-2 infected dendritic cells [62]. It remains to be seen whether clinical trials will be able to support these putative effects.

To summarize, while bisphosphonates (particularly zoledronate) are theoretically capable of ameliorating the immune host status to provide protection against SARS-CoV-2 infections, clinical studies to this effect are lacking. Current data do not support the hypothesis that oral bisphosphonates can prevent COVID-19 or mitigate its severity; however, oral bisphosphonates do not appear to increase infection risk. With regard to osteoporosis treatment, in patients in whom intravenous bisphosphonate treatment cannot be administered, delays of even several months are acceptable because of their long-lasting residence and maintenance of activity within the bone.

Denosumab

Denosumab, a monoclonal antibody against the receptor activator of nuclear factor B ligand (RANKL), is a potent antiresorptive agent that suppresses bone turnover markers (BTMs), increases BMD, and significantly lowers fracture risk, with evidence for a good safety profile when provided every 6 months for up to 10 years [66]. When denosumab is discontinued, however, its effects on BMD and BTMs are rapidly reversed. After 1–2 years after treatment discontinuation, BMD returns to pre-treatment baseline values, with BTMs exceeding baseline values within 3 months and thereafter remaining persistently elevated before slowly returning to baseline levels [67]. There is now good evidence that denosumab discontinuation may be associated with multiple vertebral fractures (Vfx), with current expert recommendations counseling against denosumab discontinuation unless an alternative treatment is subsequently initiated [68•]. Given these considerations, it is evident that disruption of the standard denosumab every 6-month dosing administration schedule, as has increasingly been documented during the pandemic [28–31], can have devastating skeletal effects. As an example, a retrospective analysis of 768 patients receiving denosumab at a large hospital in Singapore during the COVID-19-first wave period revealed that adherence to treatment decreased significantly compared to the pre-COVID-19 period, with the odds of adherence increased if the treating physician was an endocrinologist [69].

A preliminary analysis of the same study showed that fractures on follow-up occurred less frequently in patients adherent to a 6-month treatment dosing interval [69]. Moreover, a retrospective analysis of 638 patients in China demonstrated that postponing denosumab treatment for 3 months (i.e., administration 9 months after the most recent previous dose) resulted in significant BMD decreases at the lumbar spine [70].

Regarding a possible influence of denosumab treatment on COVID-19 incidence, the study of Blanch-Rubió et al. [26•] showed a 40% decreased risk of COVID-19 infection in patients treated with denosumab, a similar finding to that found with zoledronate. Immune responses involving the RANK/RANKL system include lymph node formation, lymphocyte differentiation, dendritic cell survival, and T-cell activation [71]. Furthermore, RANKL inhibition modifies immune cell profiles and decreases the release of pro-inflammatory cytokines [72]. This attenuated inflammatory response may be beneficial during viral infections, as has previously been shown for osteoprotegerin, a decoy receptor for RANKL [73]. On the other hand, a recent meta-analysis demonstrated an increased risk for ear, nose, and throat and gastrointestinal infections in patients treated with denosumab, albeit without a higher overall risk for any infection or for mortality [74•]. Moreover, survey studies have not identified an association between denosumab therapy and increased risk of COVID-19 infection [53•, 75].

In summary, patients should be strongly dissuaded from stopping denosumab due to concerns related to rapid loss of bone mass and increased risk for multiple vertebral compression fractures. When denosumab treatment continuation cannot be guaranteed within 7 months of the most recent prior injection, a temporary transition to an oral bisphosphonate should be recommended [4]. Although data with regard to COVID-19 infection in patients treated with denosumab are scarce, it seems unlikely that denosumab therapy will aggravate the clinical course of COVID-19.

Romosozumab

Romosozumab is a humanized monoclonal antibody directed against sclerostin. It has a dual mode of action, i.e., enhancement of bone formation with simultaneous suppression of bone resorption, and proven efficacy with regard to BMD increase and fracture reduction [76]. However, like other bone anabolic agents, romosozumab discontinuation is associated with rapid bone loss within 1 year, with BTMs rising as early as 3 months from the time of the most recent previous dose if subsequent antiresorptive therapy is not provided [77]. However, transitioning from romosozumab to alendronate results in sustained BMD gains [78]. Thus, if romosozumab is discontinued in the setting of the pandemic, it is prudent to transition to an oral bisphosphonate [4, 30]. To date, no studies have investigated the putative effects of treatment with romosozumab on SARS-CoV-2 infection. Nevertheless, recent evidence has shown that upregulation of the canonical Wnt/ β -catenin pathway is associated with inflammation and cytokine storm in patients infected

with COVID-19 [79]. In these patients, the Wnt/ β -catenin pathway is stimulated via transforming growth factor- β (TGF- β) and can cause pulmonary fibrosis and pulmonary infarctions [80]. The impact of sclerostin, one of the major inhibitors of the Wnt/ β -catenin pathway, on SARS-CoV-2 infections is unknown. Accordingly, it is currently difficult to predict whether romosozumab may influence the clinical course of COVID-19 infection.

Teriparatide/abaloparatide

Teriparatide and the parathyroid hormone-related protein (PTHrP) analogue abaloparatide are osteoanabolic treatments with significant antifracture benefits. Teriparatide cessation is associated with progressive BMD loss over the course of 1 year [81], with the antiresorptive treatment required following teriparatide discontinuation to avoid loss of the osteoanabolic effect [82, 83]. Given that abaloparatide shares a similar biological profile to teriparatide, sequential treatment is equally applicable, with beneficial skeletal effects having been demonstrated for abaloparatide followed by alendronate [84]. Based on the above evidence, temporary transition to an oral bisphosphonate should be offered when either of these treatments must be discontinued during the pandemic [4, 30]. Although PTH receptors are located on various immune cells (neutrophils, B and T cells), clinical studies of the immunological effects of teriparatide have been limited by different PTH formulations (rat, bovine, and human) and have primarily been conducted in patients with renal impairment [85]. To date, there are insufficient data to predict whether teriparatide and abaloparatide may have an impact on SARS-CoV-2 infections.

Conclusion

The COVID-19 pandemic has created many challenges for patients with musculoskeletal diseases and the long-lasting impact of SARS-CoV-2 on bone health remains unknown. The disruption of access to healthcare and medications is expected to result in poor disease control and an increase in fracture risk and fracture outcomes. Osteoporosis drugs are safe and effective and should be continued during the pandemic. Although limited preclinical data exist for the beneficial effects of raloxifene and zoledronate in COVID-19 infection, any salutary effects must be confirmed in robust clinical studies. While osteoporosis drugs have not been proven to prevent SARS-CoV-2 infections or alleviate COVID-19 severity, they do not appear to increase any risks associated with COVID-19 infection (Table 1).

Table 1 Pros and cons of skeletal medications in the COVID-19 era

	Osteoporosis medication Advantages	Disadvantages
Vitamin D	Theoretical non-musculoskeletal benefits as modulator of innate and adaptive immunity Association of deficiency with more worsened COVID-19 clinical outcomes (observational studies) Supplementation as advised by osteological societies for musculoskeletal health	No clear evidence of COVID-19 course improvement through supplementation (RCTs) Negative impact of high-dose bolus on both falls and fracture risk
HRT/raloxifene	Potential beneficial effects on infection risk and COVID-19 clinical course (experimental & observational data) Raloxifene identified in drug repurposing program as an eligible candidate against oligosymptomatic COVID-19	RCT results confirming COVID-19 course improvement pending Associated with modest increase in thrombotic risk
Bisphosphonates	Long-lasting effects on suppression of bone turnover such that interruption during the COVID-19 pandemic is unlikely to be harmful Zoledronate theoretically capable of modulating the immune host status to protect against SARS-CoV-2 infections (experimental and observational data)	Acute phase reaction following zoledronate infusion may resemble flu-like symptoms of COVID-19 Logistical difficulties of providing zoledronate infusion during the COVID-19 pandemic
Denosumab	Theoretical benefit of attenuation of inflammatory response to SARS-CoV-2 infections (experimental and observational data) No increased risk of COVID-19 illness in patients treated with denosumab	Discontinuation causes rapid bone loss and an overshoot in bone turnover in all patients and multiple vertebral fractures in some patients Logistical difficulties in providing denosumab during the COVID-19 pandemic
Romosozumab	Self-administration logistically beneficial for skeletal health during the COVID-19 pandemic	Upregulation of the Wnt/ β -catenin pathway associated with cytokine storm; impact of sclerostin on SARS-CoV-2 infections unknown
Teriparatide/abaloparatide	Self-administration logistically beneficial for skeletal health during the COVID-19 pandemic	PTH receptor expression on immune cells, but insufficient data regarding effects on SARS-CoV-2 infections

Abbreviations: HRT, hormone replacement therapy; RCT, randomized-controlled trial

Key points

- Although vitamin D deficiency is associated with more severe clinical outcomes in patients infected by COVID-19, clear evidence to support the improvement of clinical outcomes through vitamin D supplementation is lacking.
 - HRT and raloxifene may have potential positive effects on infection risk and the clinical course of COVID-19 infection, but confirmatory studies are pending.
 - Zoledronate is theoretically capable of modulating the immune host status and thereby protecting against SARS-CoV-2 infections.
 - Denosumab discontinuation should be strongly discouraged, with a temporary transition to oral bisphosphonate therapy recommended when denosumab cannot continue to be provided per standard clinical dosing guidelines

Declarations

Conflict of Interest

ET has received research funding from MSD, honoraria for lectures from Amgen, UCB, Shire, Kyowa Kirin, and educational grants from Shire and UCB. Matthew T. Drake declares that he has no conflict of interest.

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