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Does Osteoporosis Treatment Choice Change the Prevalence or Course of COVID-19 in Older Adults?

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Abstract

Objective: This study aimed to investigate whether the prevalence or course of Coronavirus disease-2019 (COVID-19) changes according to osteoporosis treatment choice and to discuss the necessity of changing osteoporosis treatment during the pandemic especially in older adults.

Materials and Methods: We used the data of 828 subjects that we followed up with the diagnosis of osteoporosis in our outpatient clinic in the last two years. Patients were divided into four groups according to the osteoporosis treatment they received (alendronate, denosumab, teriparatide, intravenous zoledronic acid). Treatments for osteoporosis, treatment durations, and COVID-19 evaluations were obtained from electronic file records retrospectively. Symptomatology, diagnostic methods, polymerase chain reaction (PCR) results, and radiological findings of computerized tomography scans, treatments of the patients who had COVID-19 were noted.

Results: Fifty-two (6.2%) patients had been diagnosed with COVID-19. Between osteoporosis treatment groups, there were no significant differences in terms of COVID-19 prevalence, symptomatology, PCR results, radiological findings, treatments, and outcomes.

Conclusion: To the best of our knowledge, there is no clear evidence that osteoporosis treatment affects the course of COVID-19. In our study, we could not find a relationship between the actual treatments used for osteoporosis, and the prevalence or course of COVID-19. So during the COVID-19 outbreak, it is more crucial to emphasize the importance of the treatment continuity than changing modality for osteoporosis. Considering the burden of osteoporosis in the older population, the continuation of osteoporosis treatment needs to be prioritized during the COVID-19 pandemic.

Keywords: Osteoporosis, COVID-19, aged, immunosenescence

Introduction

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) caused the worldwide pandemic Coronavirus disease-2019 (COVID-19) started in late 2019 and is ongoing. The virus is known to reveal a wide range of symptoms, from acute respiratory infections to severe multi-organ insufficiency resulting in death. The mortality rates are higher above the age of 80, which may be due to the presence of comorbidities and changes in immunity. Also, the course of COVID-19 can be different in older adults (1).

Osteoporosis is a public health problem characterized by reduced bone mineral density and increased fracture risk. During the COVID-19 pandemic, factors predisposing bone and muscle loss, such as inflammation, immobilization, hospitalization, and home isolation, are increased, especially in the elderly, leading to fragility and hip fractures. The one-year mortality rate due to osteoporotic hip fractures in the geriatric population was 20%, but this rate has increased to 36% with the COVID-19 pandemic (2).

Osteoporosis treatment regimens may cause immune system dysregulation, which may lead to reconsidering treatment options in the elderly during the COVID-19 pandemic. Bisphosphonates, specifically alendronate, one of the most commonly used agents in osteoporosis treatment, can cause monocyte/macrophage migration inhibition in addition to

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suppressing antigen presentation and inhibiting the production of a variety of bone-resorbing cytokines including tumor necrosis factor-α (TNFα), IL-1β, and IL-6 (3). Zoledronic acid can act as an immunostimulant which could increase gamma/delta (γδ) T-cell expansion or a dendritic cell modulator which possibly can change the immune regulation. As a result, the number of natural killers increases, explaining why approximately 50% of patients under zoledronic acid treatment experience an acute phase reaction (4). Furthermore, denosumab, a human monoclonal antibody with a high affinity to RANKL (receptor activator of nuclear factor K-β ligand), can act as an immune system modulator. The RANKL/RANK system takes place in lymph-node development, lymphocyte differentiation, dendritic cell survival, and T-cell activation. So denosumab treatment may modulate the immune response to viral infections (5). Teriparatide (recombinant human parathyroid hormone 1-34) is an anabolic agent for osteoporosis treatment, leading to the expansion of regulatory T-cells. It is also known that teriparatide treatment can increase peripheral hematopoietic stem cells in post-menopausal women (6).

Herein, we aimed to examine whether the prevalence or course of COVID-19 changes according to the preferred agent in the treatment of osteoporosis. Considering the effects of the agents used in the treatment of osteoporosis on the immune system, we aimed to answer the necessity of the treatment change during the pandemic, especially in older adults.

Materials and Methods

This cross-sectional study was approved by the institutional review board of Hacettepe University with the number of 2021/11-32 and was conducted in geriatric outpatient clinics of the Hacettepe University Medical Faculty Hospital, Ankara, Turkey.

A total of 828 individuals aged 65 years and older, who were admitted to geriatric outpatient clinics in the last two years (January 2019-December 2020) before the outbreak of the pandemic and receiving osteoporosis treatment were included in the study. Patients' age, gender, comorbidities, osteoporosis treatment, treatment durations, and COVID-19 evaluations were obtained from the hospital's electronic file records. Patients were divided into 4 groups according to the osteoporosis treatment they received (alendronate, denosumab, teriparatide, intravenous zoledronic acid). Symptomatology, diagnostic methods, polymerase chain reaction (PCR) findings, and radiological computed tomography (CT) scan findings of the patients who had COVID-19 were recorded. Individuals who had vitamin D deficiency, end-stage malignancy, or renal disease and take immune-suppressive treatment were excluded.

Statistics

The data collected were analyzed by using SPSS v. 23.0 (SPSS, Turkey). Categorical variables were presented as counts and percentages (n/%). Data distribution characteristics were evaluated with the Kolmogorov-Smirnov test. Abnormally distributed variables were presented as median [interquartile range (IQR)]. The chi-square test or Fisher's Exact tests were used for intergroup comparisons of categorical variables. Kruskal-Wallis test was used to compare numerical parameters with more than two categorical data. Post-hoc analysis was performed to determine the origin of the significance. Bonferroni correction was performed while calculating the p-value of the significant comparisons. A p-value of <0.05 was considered significant.

Results

A total of 828 patients were examined. One hundred fourty-one (17.1%) of the patients were male, and 687 (82.9%) were female. The median age of the sample was 78 (IQR: 10), while the median age was lower in the alendronate group ($p<0.001$). The prevalence of diabetes mellitus, dementia, and pulmonary diseases were higher in the zoledronic acid group. The prevalence of chronic kidney disease was higher in the denosumab group. Demographic features and the prevalence of comorbidities are presented in Table 1.

A total of 52 (6.2%) patients were diagnosed with COVID-19. When patients were divided into 4 groups according to their osteoporosis treatments, COVID-19 prevalences were similar. In the alendronate group, there were 8 patients diagnosed with COVID-19, in the denosumab group 14 patients, in the teriparatide group 3 patients, in the zoledronic acid group 27 patients. Fourty-six (5.5%) of the COVID-19 patients had positive PCR results, while 6 (0.7%) of the patients were negative but clinically accepted as COVID-19. CT was not performed in 14 (1.6%) patients, 11 (1.3%) of patients had no particular finding in thorax CT, while 2 (0.2%) of them had unilateral, 20 (2.4%) of them had bilateral involvement, and 5 (0.6%) of them had atypical CT findings. Also, there was no significant difference in radiological findings between groups. The patients were divided into three groups according to COVID-19 symptoms: Mild, moderate, and severe. There was no difference regarding the COVID-19 symptoms according to the osteoporosis treatment they received. Only 3 (0.3%) patients had severe symptoms. Patients were divided into five groups for COVID-19 evaluation. Most of the patients survived the disease at home. Only 1 (0.1%) patient died in the teriparatide group. There was no statistical difference between the groups regarding COVID-19 evaluation. The relationship between osteoporosis treatment and COVID-19 evaluation is shown in Table 2.

The median treatment duration for alendronate was 15 (IQR: 10) months, while it was 14 (IQR: 12) months for denosumab,

Table 1. Distribution of groups in terms of age, gender and comorbidity

		Alendronate	Denosumab	Teriparatide	Zoledronic acid	p-value
Age [median (IQR)] (year)		76 (10)	78 (10)	78 (11)	79 (10)	**p<0.001**
Sex (n) (%)	Female	167 (20.1%)	152 (18.3%)	78 (9.4%)	290 (35%)	**p<0.001**
	Male	34 (4.1%)	3 (0.3%)	4 (0.4%)	100 (12%)	
Comorbidities (n) (%)	DM	70 (8.4%)	37 (4.4%)	16 (1.9%)	101 (12.1%)	**p=0.024**
	HT	150 (18.1%)	110 (13.2%)	54 (6.5%)	267 (32.2%)	p=0.353
	HL	28 (3.3%)	21 (2.5%)	5 (0.6%)	63 (7.6%)	p=0.083
	Dementia	12 (1.4%)	37 (4.4%)	11 (1.3%)	75 (9%)	**p<0.001**
	Malignancy	8 (0.9%)	17 (2%)	4 (0.4%)	25 (3%)	p=0.069
	CKD	1 (0.1%)	26 (3.1%)	-	4 (0.4%)	**p<0.001**
	Pulmonary diseases	20 (2.4%)	2 (0.2%)	7 (0.8%)	51 (6.1%)	**p<0.001**
	CAD	33 (3.9%)	16 (1.9%)	10 (1.2%)	63 (7.6%)	p=0.248
	Rheumatologic diseaese	6 (0.7%)	10 (1.2%)	5 (0.6%)	17 (2%)	p=0.412

DM: Diabetes mellitus, HT: Hypertension, HL: Hiperlipidemia, CKD: Chronic kidney disease, CAD: Coronary artery disease, IQR: Interquartile range

Table 2. The relationship between osteoporosis treatment and COVID-19 evaluation

		Alendronate	Denosumab	Teriparatide	Zoledronic acid	Total
COVID-19 symptomatology [n (%)]	Not have disease Mild symptoms Moderate symptoms Severe symptoms	193 (23.3%) 6 (0.7%) 0 2 (0.2%)	141 (17%) 9 (1%) 5 (0.6%) 0	79 (9.5%) 1 (0.1%) 1 (0.1%) 1 (0.1%)	363 (43.8%) 20 (2.4%) 7 (0.8%) 0	776 (93.6%) 36 (4.2%) 13 (1.5%) 3 (0.3%)
p-value		0.701	0.639	0.165	0.432	
COVID-19 treatment [n (%)]	No treatment Home treatment Hospitalized NIV ICU Death	193 (23.3%) 6 (0.7%) 0 0 2 (0.2%) 0	141 (17%) 10 (1.2%) 4 (0.4%) 0 0 0	79 (9.5%) 1 (0.1%) 1 (0.1%) 0 0 1 (0.1%)	363 (43.8%) 19 (2.2%) 7 (0.8%) 1 (0.1%) 0 0	776 (93.6%) 36 (4.2%) 12 (1.3%) 1 (0.1%) 2 (0.2%) 1 (0.1%)
p-value		0.701	0.835	0.165	0.853	
PCR findings [n (%)]	Not evaluate Positive Negative	193 (23.3%) 8 (0.9%) 0	141 (17%) 12 (1.4%) 2 (0.2%)	79 (9.5%) 3 (0.3%) 0	363 (43.8%) 23 (2.7%) 4 (0.4%)	776 (93.6%) 46 (5.3%) 6 (0.6%)
p-value		0.267	0.707	0.519	0.442	
Radiological signs [n (%)]	Not have radiology Not have pathologic signs Unilateral pathologic signs Bilateral pathologic signs Atypical signs	5 (0.6%) 2 (0.2%) 0 1 (0.1%) 0	3 (0.3%) 3 (0.3%) 1 (0.1%) 4 (0.4%) 3 (0.3%)	1 (0.1%) 1 (0.1%) 0 1 (0.1%) 0	5 (0.6%) 5 (0.6%) 1 (0.1%) 14 (1.6%) 2 (0.2%)	14 (1.6%) 11 (1.2%) 2 (0.2%) 20 (2.2%) 5 (0.5%)
p-value		0.092	0.322	0.971	0.313	
COVID-19 diagnosis [n (%)]	Diagnosed Not diagnosed	8 (0.9%) 193 (23.3%)	14 (1.6%) 141 (17%)	3 (0.3%) 79 (9.5%)	27 (3.2%) 363 (43.8%)	52 (6.4%) 776 (93.6%)
p-value		0.205	0.250	0.383	0.476	

COVID-19: Coronavirus disease-2019, NIV: Non-invasive ventilation, ICU: Intensive care unit, PCR: Polymerase chain reaction

15 (IQR: 7.25) months for teriparatide, and 17 (IQR: 11) months for zoledronic acid. In the zoledronic acid group, a significant difference was found between treatment durations and COVID-19 evaluation, as shown in Table 3 (p=0.024).

Discussion

The COVID-19 outbreak caused impairment in both the treatment and follow-up of many chronic diseases, especially in geriatric population. Physicians may consider treatment modification of chronic diseases such as osteoporosis since COVID-19 has various effects on the immune system. There are a few studies focusing on COVID-19 outcomes who were receiving anti-osteoporosis drugs. In this study, we considered the older population.

During the early stages of SARS-CoV-2 infection, lymphopenia, neutrophil count increase, depletion of both CD4+ and CD8+ T-cells, reducing T-cell receptor repertoires occurs as the virus enters the cell. Tissue-resident dendritic cells (DC), especially in the respiratory tract, get infected. Infection of DC causes a massive immune reaction response in COVID-19. An acute increase of serum levels of inflammatory mediators, such as IL-6, C-reactive protein, interferon-γ (IFN-γ), IFN-γ induced protein 10 (IP-10, or CXCL-10), TNF-α, IL-1β, IL-8, monocyte chemotactic protein (MCP)-1 (CCL2 chemokine ligand 2), and MCP-3 can be seen during the course known as the cytokine storm (7). Also, IFN- γ release from infected cells causes expansion of gamma/delta (γδ) T-cells. γδ T-cell expansion is associated with higher anti-SARS-CoV IgG titers. Toll-like receptors (TLR) play a crucial role in recognizing the strategic parts of the viruses by the antigen-presenting cells. In older individuals, both the TLR expression and downstream signaling are impaired, higher levels of proinflammatory cytokines IL-6, IFN-γ, and TNF-α, and lower T-cell counts (CD8+ and CD4+ T lymphocytes) are seen in the peripheral blood named as inflammaging, and due to immunosenescence, decreasing number of circulating competent B-cells, increasing terminally differentiated and senescent memory CD27 B-cells can be seen. They are the reasons for the severe course of COVID-19 in older population (8,9).

When the relationship of zoledronic acid with the immune system is examined, it was seen that it might inhibit the prenylation of small GTPases, which can cause endosomal exocytosis blockage in the DC. Thus it may lead to a T-cell expansion and increased natural killer cell activity (4,10,11). Some studies showed a decrease in serum levels of IL-2, IL-7, IL-12, and IL-15 following zoledronic acid treatment. These cytokines are responsible for T-cell activation, differentiation, and proliferation. As a result, T-cell reduction was observed in the bone marrow. In rat model studies, changes in the proportion of CD3+ T-cells and ϒδ T-cells in peripheral blood have been shown after zoledronic acid treatment (12). It was shown that preexisting use of zoledronic acid was associated with a reduced incidence of COVID-19 compared to oral bisphosphonate or denosumab regardless of treatment duration. The authors attributed this result to the protective effect of zoledronic acid on DC. And they emphasized that this protective effect prevents the progression of COVID-19 because it causes immune stimulation of T-cell expansion and enhanced activity of natural killer cells (13). In our study, the duration of zoledronic acid use was longer in patients who did not have COVID-19, thus, the protective effect of zoledronic acid treatment against COVID-19 can be mentioned.

Another bisphosphonate used in the treatment of osteoporosis is alendronate. It can cause increased neutrophil counts by reducing serum TNFα, IL-1β, and IL-6 and can inhibit monocyte-macrophage migration and suppress antigen presentation. Alendronate was found beneficial for patients with chronic idiopathic neutropenia associated with osteopenia-osteoporosis (14). In our study, we did not find a difference in the course of COVID-19 between individuals that were under bisphosphonates treatment and other treatment regimens.

Denosumab, a human monoclonal antibody, inhibits the RANKL. RANKL inhibition can lead to decreased activity of pro-inflammatory cytokines. Osteoprotegerin (OPG) is a receptor for RANKL and OPG/RANKL/RANK systems and was demonstrated in lymphoid tissue. It has a role in the development of T and B lymphocytes. In addition, denosumab is known to increase serious adverse events of infections, mainly of the ear, nose, throat, and gastrointestinal origin (5). Kyrgidis et al. (15) showed that denosumab administration could increase peripheral blood monocyte CD14 + in female patients, which is one of the causes of immunity changes with denosumab treatment (15). Although there are initial suspicions against denosumab

Table 3. The relationship between treatment durations and COVID-19 evaluation

	Alendronate Treatment duration (month)	Denosumab Treatment duration (month)	Teriparatide Treatment duration (month)	Zoledronic acid Treatment duration (month)
COVID-19 diagnosis (+)	15 (9.75)	14 (12)	15 (8)	17 (11)
COVID-19 diagnosis (-)	14.5 (12.25)	14 (10.25)	14 (-)	20 (13)
p-value	0.948	0.872	0.770	**0.024**

COVID-19: Coronavirus disease-2019

therapy, in the short report by Formenti et al. (16), it was reported that denosumab treatment did not pose any risk factors for COVID-19. Also, Atmaca et al. (17) showed that using anti-osteoporotic drugs in women did not alter the course of COVID-19 or the risk of mortality, and authors mentioned that anti-osteoporosis drugs are safe during the COVID-19 era. In the study in which the relationship of zoledronic acid with reduced risk of COVID-19 was shown, the same effect was shown with denosumab (13). In our research, most of the denosumab using patients suffered from mild COVID-19, and there was no significant difference with other therapies in the prevelance of COVID-19.

Teriparatide, a parathormon (PTH) analog, causes an increase in the number of regulatory T-cells in human peripheral blood (18). PTH receptor presence was previously shown in human mononuclear cells (19). Also, in rat model studies, teriparatide treatment was proven to cause YΔ T-cells to increase in the peripheral blood (12). In addition, exogenous PTH administration was shown to cause an increase in the numbers of circulating lymphocytes and neutrophils in rat models (20). However, the exact effect on the immune system in the chronic use of teriparatide is unknown. In our research, three of the patients that received teriparatide had suffered from COVID-19, one of them died, and the deceased patient had a previously diagnosed pulmonary disease. There was no increased risk compared to other treatments.

Study Limitations

We should also mention the limitations of the study; the retrospective design and the relatively low number of patients with COVID-19 can be defined as the limitations. In addition, other drugs, comorbidities, socio-economic status and social backgrounds of participants should be considered. Random selection of participants may have hindered significant results. Further studies with more specific groups are needed.

Conclusion

To the best of our knowledge, there is no clear evidence that osteoporosis treatment affects the course of COVID-19. Our study could not find a relationship between the current treatments used for osteoporosis and the prevalence or course of COVID-19. Therefore, during the COVID-19 outbreak, it is crucial to emphasize the importance of treatment continuity than changing the treatment modality for bone metabolism. Considering the burden of osteoporosis in older adults, the management of osteoporosis needs to be prioritized during the COVID-19 pandemic.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the institutional review board of Hacettepe University with the number of 2021/11-32 and was conducted in geriatric outpatient clinics of the Hacettepe University Medical Faculty Hospital, Ankara, Turkey.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.H., Concept: M.H., M.G.H., Design: M.H., M.G.H., Data Collection or Processing: A.O.B., Z.Ş., Analysis or Interpretation: A.O.B., Ç.Ç., B.B.D., M.C., M.G.H., Literature Search: Z.Ş., Ç.Ç., Writing: M.H., B.B.D., M.C., M.G.H.

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