

## SARS-COV-2 Long and Short Term Effects on the Bones Health: Systematic Literature Review

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### Abstract

This review is aiming to discuss the Non pharmacological pain management, the presented review was conducted by searching in Medline, Embase, Web of Science, Science Direct, BMJ journal, and Google Scholar for, researches, review articles, and reports, published over the past years. Were searched up to December 2021 for published and unpublished studies and without language restrictions, if several studies had similar findings, we randomly selected one or two to avoid repetitive results. Early report from the studies on the first Severe acute respiratory syndrome (SARS) epidemic of 2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012 show significant association between the SARS and MERS and bone health Sequelae in from of many clinical presentation and diseases like sarcopenia and osteoporosis. Which lead to the assumption that SARS-COV-2 will result in the similar problems as it from the same viral family of SARS and MER or maybe worth.

Recent review show that SARS-COV-2 have many effect on the bone health as it can cause Reactive Arthritis, decrease Vitamin D the the activation of some inflammatory pathways. On the other hand it can affect the quality of the patients life through some manifestation life like the Arthralgias, Myalgias, and Fatigue; which result in impair of some patients motor function; thus the quality of life. More studies needed to have sold evidences about the effect of COIVD-19 or it's treatment on bone health putting in mind the some factors like ethnic groups, environmental factors, patients occupation, and life style; which also can contribute directly or indirectly to the skeletal presentation.

**Keywords:** COVID-19; SARS-Cov-2; Osteoporosis; Arthralgias; Myalgias; Renin; Angiotensin; ACE2; Vitamin D; Musculoskeletal System

### Abbreviations

SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; ACE2: Angiotensin-Converting Enzyme 2; NICE: National Institute For Health And Care Excellence; SIGN: Scottish Intercollegiate Guidelines Network; RCGP: Royal College Of General Practitioners; BMD: Bone Mineral Density

### Introduction

As result of he worldwide pandemic of the novel coronavirus according to the information reported in the World Health Organization website by 26 November 2021, there have been 259,502,031 confirmed cases of COVID-19, including 5,183,003 deaths.

COVID-19 is considered respiratory disease mainly caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) but researches and evidence show that COVID-19 can have short and long term effect on other organs and body parties [1]. Most of the survivors for the first Severe acute respiratory syndrome (SARS) epidemic of 2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012, Show significant long-term clinical problems need rehabilitation and specific healthcare services [2,3]. As COVID-19 is members of the same virus family as SARS and MERS; Alongside acute challenges, we also have to consider the long and the short sequelae of this disease.

Caring after the patient after recovering from the acute phases of the illness is important factor for maintaining the quality of life of the patients as they will take time to recover from the physical, mental, and social sequelae of the COVID-19 in addition it will help to plan for the healthcare system needs like the workforce with will require multidisciplinary team to cover the patient health needs and evidence based practice based on clear research priorities [4].

Based on the reviewed researches and literature it classify the symptoms and abnormalities present and not attributable to alternative diagnoses beyond the acute phase of COVID-19 into two categories: (1) Sub-acute or ongoing symptomatic (short term) which range from 4 to 12; weeks and (2) chronic or post-COVID-19 syndrome (long term) ) which continue for more than 12 weeks and are not explained by an alternative diagnosis [5,6].

COVID-19 it is not exclusive respiratory disease it has multi organ effect and one of it’s direct and indirect Sequelae affecting the skeletal system with various mechanism summarized by Dr. K. Zheng, et and his colleague from the department of Orthopedics, Hospital of Soochow University, Suzhou, China; in four mechanism 1) Angiotensin-converting enzyme 2 (ACE2) which induce the bone resorption, 2) marked release of the inflammatory cytokines like IL-1 $\beta$ , IL-6, TNF- $\alpha$ , G-CSF, IP-10, MCP-1, MIP-1 in patients infected with COVID-19 contribute in bone loss, 3) the immunosuppression effect produced by the IL-17 with released from Th17 cells (end result of the T cells differentiation); which accelerate the osteoclast differentiation that degraded the bone matrix, 4) the effect of the hypoxaemia which in activate the osteoclastogenic effect and inhibit the osteoprotegerin (OPG) which lead to bone destruction [7,8,10,11].

Understanding the impact of the COVID-19 on the Skeletal system is highly important because; the main age group affected by COVID-19 are the elderly people who already suffering from the aging affect of the bone [12]. thus will give the chance to work on the prevention and the treatment of the expected Sequelae, on the other hand to study the effect of the current management intervention and it’s effectiveness; So we are aiming through this review to discuss the long and the short effect of COVID-19 on the bone and the Skeletal system in general.

**Materials and Methods**

The present review was conducted in November 2021 in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) declaration standards for systematic reviews. We reviewed all the topics on SARS-CO-2 long and short term effects on the bones health, such as myalgias, arthralgias, neuropathies, myopathies, joint pain, fatigue, followed by back pain, low back pain, and neck pain. To achieve this goal, we searched Medline, Embase, Web of Science, Science Direct, and Google Scholar for, researches, review articles and reports, published over the past 5 years.

Our search was completed without language restrictions. Then we extracted data on study year, study design, and key outcome on SARS-CO-2 long and short term effects on the bones health. The selected studies were summarized and unreproducible studies were excluded. Selected data is shown in the table 1.

Clinic Definition	Duration
Acute COVID-19	Up to 4 weeks.
Ongoing symptomatic COVID-19 (short term effect)	From 4 to 12 weeks.
Post-COVID-19 syndrome (long term effect)	More than 12 weeks and are not explained by an alternative diagnosis.

**Table 1:** Show the different timeline and the clinic definitions of the COVID-19.

Studies has been rated as being high quality by an established evaluation process based on the DyunaMed criteria and it’s based on the level of evidence as following:

- **Level 1 (likely reliable) evidence:** Representing research results addressing clinical outcomes and meeting an extensive set of quality criteria which minimize bias. example: Randomized controlled trial/meta-analysis.
- **Level 2 (mid-level) evidence:** Representing results addressing clinical outcomes, and using some methods of scientific investigation but not meeting the quality criteria to achieve level 1 evidence labeling. Example: well-designed non-randomized clinical trials.
- **Level 3 (lacking direct) evidence:** Representing reports that are not based on scientific analysis of clinical outcomes. Examples include case series, case reports, expert opinion and conclusions extrapolated indirectly from scientific studies.

**Inclusion criteria**

Inclusion criteria were SARS-CoV-2, COVID-19, Bone complication, Musculoskeletal Sequelae.

**Exclusion criteria**

Irrelevant articles [not related to the aim of this review and articles that did not meet the inclusion criteria in this review.

**Data extraction and analysis**

Information relating to each of the systematic review question elements was extracted from the studies and collated in qualitative tables. Direct analysis of the studies of cleft palate.

**Results and Discussion**

In order to differentiate between long and short term effect of the COVID-19 on the bone; clinic definitions has been made based on the guideline developed by the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the Royal College of General Practitioners (RCGP) [13]. This guide is sign and symptoms based clinic definitions which meanly rely of the the duration of the sign and symptom as in table 2 show the different timeline and the clinic definitions of the COVID-19.

Author and year	Sample	Types of the effect	Outcome/s measured	Findings	Levels of evidence
Huang C, <i>et al.</i> 2021 [14].	1733 adult patients (48% women, 52% men; median age 57·0 years, IQR 47·0–65·0	Short term	Fatigue	the most frequently reported symptom was persistent fatigue or muscle weakness (63%, 1038 of 1655).14 which meanly affect the quality of patients life and the way range of motion	Level 2
Hønge BL, <i>et al.</i> 2021 [15].	5 cases report	Long term	Reactive Arthritis	5 cases showing the features of polyarthritis after being diagnosed with COVID-19; investigations show negative RA factor and anti-CCP,	Level 3

Harvey W. K, <i>et al.</i> 2020 [16].	191,779 patients	Long term	Vitamin D Deficiency	study show inverse relationship between circulating 25(OH)D levels and SARS-CoV-2 positivity; “Patients with the lowest circulating levels of 25(OH)D had approximately 5–7% higher absolute SARS-CoV-2 positivity across northern, central, and southern latitudes”.	Level 2
Carfi A., <i>et al.</i> 2020 [18].	143 patients were included	Short term	Arthralgias and Myalgias	High proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%)	Level 2

**Table 2:** Results from sequencing studies.

Wide range of bone related problem can appear as result of the COVID-19 Sequelae which mainly caused by four different mechanism which as mentioned earlier by Dr. K. Zheng, et and his colleague from the department of Orthopedics, Hospital of Soochow University, Suzhou, China; 1) Angiotensin-converting enzyme 2 (ACE2), 2) marked release of the inflammatory cytokines, 3) the immunosuppression effect, 4) the effect of the hypoxaemia. All of his listed causes result in different effect range from the simple joint pain to pathological fracture or autoimmune disorders; which mainly affect the quality of the quantity of the bone mass.

**Fatigue**

Chaolin Huang and his colleagues conduct cohort study following 1733 adult patients (48% women, 52% men; median age 57.0 years, IQR 47.0 – 65.0) diagnosed with COVID-19 and discharged from the hospital (Wuhan, China). 6 months after illness onset; the most frequently reported symptom was persistent fatigue or muscle weakness (63%, 1038 of 1655).14 which mainly affect the quality of patients life and the way range of motion.<sup>14</sup>

**Reactive arthritis**

As a COVID-19 considered to be an inflammatory disease, therefore it can affect other body parts; in case of bone it can cause inflammatory reactive arthritis resembling rheumatoid arthritis. Hønge BL and his colleagues reported 5 cases showing the features of polyarthritis after being diagnosed with COVID-19; investigations show negative RA factor and anti-CCP, inflammatory reactive arthritis come as the suggested diagnosis. The author proposed that COVID-19 activate the pro-inflammatory markers secondary to this event comes the inflammatory reactive arthritis [15].

**Vitamin D deficiency**

Retrospective cohort study in United States used observational analysis of deidentified tests performed at a national clinical laboratory to Test the correlation between 25(OH)D values and SARS-CoV-2 positivity, results from 218,372 patient included after excluding patients with missing residential zip code data (n = 26,387) or inconclusive SARS-CoV-2 NAAT results (n = 206), results from 191,779 (87.8%) patients remained for analysis. The results of this study show inverse relationship between circulating 25 (OH)D levels and SARS-CoV-2

positivity; “Patients with the lowest circulating levels of 25(OH)D had approximately 5 - 7% higher absolute SARS-CoV-2 positivity across northern, central, and southern latitudes”. “Although 25(OH)D levels appeared to play a role for all race/ethnicities, patients from predominantly black non-Hispanic zip codes had higher SARS-CoV-2 positivity than those from predominantly white non-Hispanic zip codes at every 25(OH)D level” [16].

This results show the inverse relationship between Vitamin D3 and SARS-CoV-2 Since the discovery of the Vitamin D3 beginning of the 19<sup>th</sup> century and it’s important role in the building of bone and the skeletal system health in general [17].

### Arthralgias and myalgias

Study in Italy From April 21 to May 29, 2020, 179 patients were potentially eligible for the follow-up post-acute care assessment; 14 individuals (8%) refused to participate and 22 had a positive test result. Thus, 143 patients were included. Patients were assessed a mean of 60.3 (SD, 13.6) days after onset of the first COVID-19 symptom; at the time of the evaluation, only 18 (12.6%) were completely free of any COVID-19-related symptom, while 32% had 1 or 2 symptoms and 55% had 3 or more. None of the patients had fever or any signs or symptoms of acute illness. Worsened quality of life was observed among 44.1% of patients. High proportion of individuals still reported fatigue (53.1%), dyspnea (43.4%), joint pain, (27.3%) and chest pain (21.7%) [18].

On the other hand reporting of the Arthralgias and Myalgias oftenly have been used interchangeably or wrongly in literature; however they are having the same effect on the musculoskeletal system and the body movement [19].

### Discussion

As COVID-19 is considered primary a respiratory disease, many studies show that SARS-COV-2 have extra-pulmonary manifestations which affect many organs other than the lung; and within this the skeletal system come on the to of the extra-pulmonary manifestations as with its role in supporting the body and facilitate the movement [20]. Although the important of this system there’s no many evidence or studies take about the long and short term effects on the skeletal system or bone, many studies with based it’s evidence on the first Severe acute respiratory syndrome (SARS) epidemic of 2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012 and the manifestations experienced by the survivors. And this can be related to several reasons as that we can suggest here like the research priorities are heading towards the vaccination and how to prevent this pandemic, on the other hand, it take long time to notice the impact of the COVID-19 on the people health, and the healthcare system in general.

Many studies we reviewed centre it’s hypothesis on four main mechanisms on how COVID-19 affect the bone or skeletal system as mentioned by Dr. K. Zheng, et and his colleague from the department of Orthopedics, Hospital of Soochow University, Suzhou, China; 1) Angiotensin-converting enzyme 2 (ACE2), 2) marked release of the inflammatory cytokines, 3) the immunosuppression effect, 4) the effect of the hypoxaemia. This mechanisms lead varies of sequences in the bone health as it can lead to in it final results to decrease the quality and the quantity of the bone mass as well as reduced bone mineral density (BMD). although many reports relate the decrease of the BMD to many acute critical illnesses and also can result from the side effect of the treatments which mainly the from the corticosteroids However, decreased BMD has also been reported in other acute critical illnesses and may occur independently of treatment with corticosteroids [21].

Studing post COVID-19 Sequelae is surrounded with many challenges Patients with community-acquired pneumonia can also have persistent sign and symptom which can easily misdiagnosed with COVID-19 presentation; so restricted follow up is needed to the patient and close mentoring for the patient in case of any hidden presentations show up [22].

Additionally Many other factor showed be considered like the ethnic groups, environmental factors, patients occupation, and life style; which also can contribute directly or indirectly to the skeletal presentation.

### Conclusion

Early report from the studies on the first Severe acute respiratory syndrome (SARS) epidemic of 2003 and the Middle East respiratory syndrome (MERS) outbreak of 2012 show significant association between the SARS and MERS and bone health Sequelae in from of many clinical presentation and diseases like sarcopenia and osteoporosis. Which lead to the assumption that SARS-COV-2 will result in the similar problems as it from the same viral family of SARS and MER or maybe worth.

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### Conflict of Interest

The authors of this article hasn't receive and support for this work and it was completely self-funded.

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