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Research Article

# Perturbation Patterns of Bone Metabolism Secondary to COVID-19 Among Nigerian Healthcare Workers

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## Abstract

*Background*: Severe acute respiratory coronavirus-2 (SARS-CoV-2), the etiologic agent of coronavirus disease of 2019 (COVID-19) is known to affect several organ systems. However, the disease's influence on bone metabolism is poorly characterized especially among native Nigerians. Consequently, the current study explored the effect of the disease on bone metabolism among Nigerian healthcare workers (HCWs). *Methods:* This was a prospective longitudinal study conducted in the Department of Chemical Pathology of the Rivers State University Teaching Hospital among unvaccinated HCWs in Rivers State, Southern Nigeria. Eligible HCWs (n=96) were followed up from when they unwittingly had contact with SARS-CoV-2 infected/COVID-19 patients until they developed symptomatic RT-PCR-confirmed COVID-19. Demographic, anthropometric, clinical, and laboratory data were obtained before and at diagnosis/confirmation of COVID-19 among the eligible HCWs. Statistical analysis was done using descriptive/inferential statistics at a p-value of <0.05. *Results*: At COVID-19 diagnosis, the HCWs had increased levels of inflammatory markers (procalcitonin, C-reactive protein, and D-dimer), raised bone resorption marker (s-CTX), but reduced bone formation marker (s-PINP) compared to the pre-COVID-19 parameters (p<0.001). These cardinal biochemical findings were more prominent among those with severe disease variant than those with non-severe disease variant (p<0.001). In addition, a negative correlation pattern was observed between these inflammatory markers and the bone formation marker, however, a positive correlation was observed between the inflammatory markers and the bone resorption marker (p<0.001). *Conclusion:* The current finding indicates perturbation of bone metabolism, associated with increased bone resorption pattern, secondary to COVID-19 among the studied population. Hence, it is highly recommended that the evaluation of bone metabolism status be incorporated into the management protocols for COVID-19.

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## Keywords

SARS-CoV-2, COVID-19, Bone Markers, PINP, CTX

## 1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, which was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has a place in history as one of the worst pandemics to have hit mankind [1]. Though the devastations induced by the pandemic are gradually fading, various research findings continue to emerge on the consequences of the disease on the various organ systems [2]. At its very inception, the disease was thought to be solely a respiratory one [2]. However, due to the enriched presence of the SARS-CoV-2 receptor, widely believed to be the angiotensin-converting enzyme-2 (ACE2) in humans, COVID-19 has been found to influence other extra-pulmonary organ systems [2-4].

In humans, ACE2 is widely known to be highly expressed within the skeletal system [5, 6]. Virtually all cellular structures within the skeletal system, including the osteoclast, osteoblast, and osteocytes, are known to express the biological receptor of SARS-CoV-2 [5-7]. Consequently, COVID-19 has been widely documented and reported to negatively influence skeletal metabolism through several pathophysiologic mechanisms [7].

Due to the rapid spread of COVID-19 and increased mortality risk associated with the disease, especially the severe disease variants, determination of its effects on diverse metabolism and discovering reliable laboratory markers are required to elucidate the disease's impact on various organ systems [5-7]. As the disease's influence on metabolism is yet to be deciphered, there is an urgent need for studies geared towards the impact of the disease on various human organs and tissues, such as bone [5-7].

However, most of the previous reports relating to the influence of COVID-19 on the metabolic status of the skeletal system have been documented in the Western population. To date, no data has been documented on this subject among Nigerians. Hence, the current study explored the influence of COVID-19 on bone metabolism among healthcare workers (HCWs) in Rivers State, Southern Nigeria.

## 2. Materials and Methods

### 2.1. Study Design, Site, and Setting

The study was designed as a prospective longitudinal study. It was conducted in the Department of Chemical Pathology of one of the tertiary healthcare facilities [Rivers State University Teaching Hospital (RSUTH)] in Rivers State, Southern Nigeria. The hospital has a designated unit for isolating suspected cases of COVID-19 and also a molecular laboratory where detailed molecular tests including the reverse transcriptase polymerase chain reaction (RT-PCR) test are conducted to confirm COVID-19 among the suspected cases. The Department of Chemical Pathology of the hospital is well-equipped with several biochemical analyzers for routine/complex biochemical investigations including vastly experienced analysts.

### 2.2. Ethical Considerations

Approval for the study was granted by the Rivers State Health Research Ethics Committee of the Rivers State Hospital Management Board. All study populations agreed to participate and provided written/signed informed consent. The study was conducted with strict adherence to the recommended guidelines and the principles embodied and laid down in the Helsinki Declarations of 1964, and as revised in 2013.

### 2.3. Study Tools and Population

The study population consists of eligible HCWs who were followed up from when they unwittingly had contact with SARS-CoV-2 infected/COVID-19 patients until they had symptomatic RT-PCR-confirmed COVID-19. Demographic, anthropometric, clinical, and laboratory data were obtained before and at diagnosis/confirmation of SARS-CoV-2 infection/COVID-19 among the eligible HCWs.

### 2.4. Sample Size Determination

The calculated minimum sample size required for this study is 96. The sample size was determined using a mathematical formula for cross-sectional studies for defined characteristics in a population >10,000 using a 0.015% prevalence of COVID-19 in Nigeria as documented by Nas and colleagues [8, 9]. Though the result from the sample size calculation was 0.230, to improve the power of the study, we enrolled 400% of this value; that is 92 (0.230 x 400% = 92) inclusive of a projected 10% non-compliance rate. However, we enrolled 96 due to the availability of eligible study populations.

## 2.5. Eligibility Criteria

Criteria for inclusion are HCWs with positive COVID-19 contact/exposure, adult (aged ≥18 but ≤44 years), normal health status before SARS-CoV-2 infection/COVID-19 diagnosis, and RT-PCR-confirmed symptomatic COVID-19 status on follow up. The criteria for exclusion are age <18/>44 years, COVID-19 vaccination status, post-menopausal, hypogonadism, hypopituitarism, thyroid disorders, pregnancy, COVID-19 re-infection, past/pre-existing comorbidities (cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, human immune-deficiency virus/acquired immune deficiency disease (HIV/AIDS), diabetes, cancer, obesity, acute/chronic kidney disease, chronic liver disease, previous/current cigarette smoker, organ transplant recipient, and receiving immunosuppressive therapy) before SARS-CoV-2 infection/COVID-19 diagnosis, and on current medications known to influence sex hormones or bone metabolism such as steroids, androgens, oral contraceptive pills, bisphosphonates, glucocorticoids, calcitonin, vitamin D, calcium, etc.

## 2.6. Data Collection

The study populations were recruited upon referral to the Department of Chemical Pathology for biochemical investigations from the COVID-19 isolation unit following exposure/contact with RT-PCR-confirmed COVID-19 individuals. Upon presentation and after the acquisition of informed consent, a semi-structured questionnaire was used to obtain baseline demographic, anthropometric, and clinical data, and to determine eligibility status followed by baseline specimen acquisition to determine baseline laboratory parameters. Following confirmation of positive COVID-19 status, a follow-up specimen was again acquired within 24 hours of symptom onset to determine follow-up laboratory parameters. Acquired data included baseline pre-COVID-19 demographics (age, sex), vaccination status, oxygen saturation ($SpO_2$), plasma urea, creatinine, glucose, albumin, pro-calcitonin (PCT), C-reactive protein (CRP), D-dimer levels, intact PTH, vitamin D, calcium, phosphate, magnesium, and metabolic bone markers including the bone formation marker (serum total N-terminal pro-peptide of type 1 procollagen [s-PINP]) and the bone resorption marker (serum total cross-linked C-terminal telopeptide of type 1 collagen [s-CTX]).

## 2.7. Specimen Acquisition, Processing, and Laboratory Analysis

Fasting whole blood acquisition into heparin/plain specimen tubes and laboratory analysis were done following standardized procedures. The heparinized plasma was analyzed for plasma sodium, potassium, bicarbonate, and chloride on an ion-selective electrode chemistry analyzer (SFRI 6000, SFRI Diagnostics, France) and the analyses for urea, creatinine, albumin, calcium, phosphate, magnesium, alkaline phosphatase, and CRP were done on an automated chemistry analyzer (BS200, Mindray, China). Plain-tube processed serum was analyzed for pro-calcitonin and D-dimer on an automated immunoassay analyzer (Mini Vidas, Biomerieux, France) while serum intact parathyroid hormone (PTH), vitamin D [25(OH)D], and the bone markers (s-PINP/s-CTX) were determined with enzyme-linked immunoassay (ELISA) method using standard reagents kits (Elabscience, Texas, USA).

## 2.8. Infection Prevention and Control Measures

Adequate infection prevention and control measures, as recommended by the Nigeria Center for Disease Control, were strictly adhered to during the data acquisition, specimen collection, and laboratory analysis [10].

## 2.9. Variable Definitions

COVID-19 severity was classified based on the Nigerian Centre for Disease Control National (NCDC) case management guidelines as non-severe and severe [10]. The disease severity was defined as the presence of fever >38˚C or suspected respiratory infection, plus one of respiratory rate >30 breaths/min; severe respiratory distress; oxygen saturation ($SpO_2$) of ≤ 93% on room air and the presence of co-morbid conditions such as diabetes, asthma, hypertension in adults and cough or difficulty in breathing and at least one of the following central cyanosis or $SpO_2$ <92%; severe respiratory distress e.g. grunting breathing, very severe chest in-drawing and signs of pneumonia in children.

## 2.10. Data Management/Statistical Analyses

Data management and analyses were done using SPSS software for Windows version 25. The continuous data were initially evaluated for conformity to a normal distribution pattern using the Shapiro-Wilk tests. Any continuous data violating the normal distribution patterns were log-transformed before analysis, expressed using means ± standard deviations, and compared by independent student t-test. Categorical data were reported as counts/percentages and compared with the Chi-square or Fisher's exact tests, as appropriate. Pearson's correlation was used to evaluate associations between continuous variables. A p-value <0.05 was deemed statistically significa.

***Table 1.*** *Demographic and clinical parameters of the studied population before and at COVID-19 diagnosis.*

| Variables | Before COVID-19 n = 96<br>Mean ± SD/n | At COVID-19 Diagnosis n = 96<br>Mean ± SD/n | p-value |
|---|---|---|---|
| Age, mean, years | 36.41 ± 4.11 | ----- | NA |
| Gender: males versus females | 54/42 | ----- | <0.001* |
| BM1, kg/m$^2$ | 28.36 ± 3.85 | ----- | NA |
| Clinical course: non-severe versus severe | ----- | 76/20 | <0.001* |
| Oxygen saturation ($SpO_2$), % | 98.23 ± 5.44 | 97.02 ± 5.07 | 0.260 |

*Statistically significant; BMI: body mass index; SD: Standard deviation; NA: Not applicable

***Table 2.*** *Distribution of laboratory parameters of studied population before and at COVID-19 diagnosis.*

| Variables | Before COVID-19 n = 96<br>Mean ± SD/n | At COVID-19 Diagnosis n = 96<br>Mean ± SD/n | p-value |
|---|---|---|---|
| Urea, mmo/L | 4.23 ± 1.24 | 4.44 ± 1.33 | 0.215 |
| Creatinine, µmol/L | 79.44 ± 6.21 | 81.05 ± 6.06 | 0.210 |
| Adjusted total calcium, mmol/L | 2.22 ± 0.51 | 2.30 ± 0.66 | 0.622 |
| Phosphate, mmol/L | 1.10 ± 0.39 | 1.11 ± 0.44 | 0.400 |
| Magnesium, mmol/L | 0.85 ± 0.15 | 0.87 ± 0.16 | 0.533 |
| Intact parathyroid hormone, ng/L | 39.64 ± 4.20 | 40.17 ± 4.28 | 0.376 |
| Vitamin D, nmol/L | 45.66 ± 6.50 | 43.88 ± 6.53 | 0.433 |
| Albumin, g/L | 34.66 ± 4.56 | 33.45 ± 4.33 | 0.172 |
| Pro-calcitonin, µg/L | 1.66 ± 0.83 | 4.19 ± 1.43 | <0.001* |
| C-reactive protein, nmol/L | 122.37 ± 5.23 | 241.31 ± 11.66 | <0.001* |
| D-dimer, µg/L | 224.11 ± 17.35 | 984 ± 24.76 | <0.001* |
| PINP, pg/mL | 289.77 ± 15.81 | 118.62 ± 8.54 | <0.001* |
| CTX, pg/mL | 2.23 ± 1.02 | 7.04 ± 1.23 | <0.001* |

*Statistically significant; BMI: body mass index; SD: Standard deviation; PINP: Procollagen type I N-pro-peptide; CTX: C-terminal telopeptide of type 1 collagen

***Table 3.*** *Distribution of demographic, clinical, and laboratory parameters at COVID-19 diagnosis by disease severity.*

| Parameters | Non-Severe COVID-19 n = 76<br>Mean ± SD/n | Severe COVID-19 n = 20<br>Mean ± SD/n | p-value |
|---|---|---|---|
| Age, mean, years | 34.55 ± 4.17 | 33.67 ± 4.17 | 0.176 |
| Gender: males versus females | 53/23 | 6/14 | 0.060 |
| BM1, kg/m$^2$ | 26.77 ± 3.22 | 27.06 ± 3.03 | 0.0204 |

| Parameters | Non-Severe COVID-19 n = 76<br>Mean ± SD/n | Severe COVID-19 n = 20<br>Mean ± SD/n | p-value |
|---|---|---|---|
| Pro-calcitonin, µg/L | 1.44 ± 0.68 | 5.27 ± 1.67 | <0.001* |
| C-reactive protein, nmol/L | 117.24 ± 5.02 | 266.31 ± 12.82 | <0.001* |
| D-dimer, µg/L | 210.10 ± 15.22 | 1,241 ± 25.89 | <0.001* |
| PINP, pg/Ml | 277.65 ± 14.61 | 105.44 ± 7.56 | <0.001* |
| CTX, pg/Ml | 2.17 ± 0.93 | 8.11 ± 1.55 | <0.001* |

*Statistically significant; SD: Standard deviation; BMI: Body mass index; PINP: Procollagen type I N-propeptide; CTX: C-terminal telopeptide of type 1 collagen

***Table 4.*** *Correlation between bone and inflammatory markers by COVID-19 severity.*

| | Non-Severe COVID-19 Cases | | Severe COVID-19 Cases | |
|---|---|---|---|---|
| | s-PINP | s-CTX | s-PINP | s-CTX |
| Inflammatory Markers | r; p-value | r; p-value | r; p-value | r; p-value |
| Pro-calcitonin, µg/L | -0.123; 0.134 | 0.176; 0.149 | -0.656; <0.001* | 0.577; <0.001* |
| C-reactive protein, nmol/L | -0.164; 0.223 | 0.141; 0.123 | -0.567; <0.001* | 0.619; <0.001* |
| D-dimer, µg/L | -0.104; 0.156 | 0.182; 0.181 | -0.744; <0.001* | 0.661; <0.001* |

*Statistically significant; r: correlation coefficient; PINP: Procollagen type I N-propeptide; CTX: C-terminal telopeptide of type 1 collagen

## 3. Results

During the studied period (2020-2023), 118 HCWs with positive contact/exposure to individuals with RT-PCR-confirmed COVID-19 presented in the department through the COVID-19 isolation unit of the hospital (RSUTH). Among these 118, 96 were eligible to be enrolled in the study.

As depicted in Table 1, most of the studied HCWs were males (n=54) compared to the females (n=42) (p<0.001). In terms of clinical severity of the disease, most patients had the non-severe disease (n=76) compared to those with the severe disease (n=20) variant (Table 1; p<0.001).

At the diagnosis of COVID-19, as shown in Table 2, the HCWs who developed COVID-19 during quarantine had significantly increased inflammatory markers (pro-calcitonin, CRP, D-dimers) and raised bone resorption marker (s-CTX) but reduced bone formation marker (s-PINP) compared to the pre-COVID-19 parameters (p<0.001).

As shown in Table 3, the increased levels of the inflammatory markers, the raised bone resorption marker, and the reduced bone formation marker were more pronounced among those with severe disease variant than those with non-severe disease variant (p<0.001).

As shown in Table 4, there was a negative correlation between the inflammatory markers and the bone formation marker (s-PINP) (p<0.001). However, there was a positive correlation between the inflammatory markers and the bone resorption marker (s-CTX) (p<0.001).

## 4. Discussion

### 4.1. Major Findings

The current study demonstrated that HCWs with COVID-19 had increased levels of inflammatory markers (procalcitonin, C-reactive protein, and D-dimer), raised bone resorption marker (s-CTX), but reduced bone formation marker (s-PINP) compared to the pre-COVID-19 parameters before the disease. These findings were more prominent among those with severe disease variants compared to those with non-severe disease variants. Moreover, a negative correlation pattern was observed between the inflammatory markers and the bone formation marker, however, a positive correlation was noted between the inflammatory markers and the bone resorption marker. These findings strongly suggest perturbation of bone metabolism associated with increased bone resorption pattern secondary to

COVID-19 among the studied population.

### 4.2. Relationship with Previous Studies

Though data on this subject remain very limited, our findings seem to conform with similar studies in the literature [11-15]. A similar study conducted among Chinese COVID-19 patients, by Li and colleagues, during the early phase of the COVID-19 pandemic found s-PINP and other bone formation markers (osteocalcin) decreased among COVID-19 patients compared to healthy controls. However, the study by Li and colleagues was conducted only among non-severe COVID-19 patients which contrasts with the current study [11].

In addition, Gul and colleagues had recently observed that s-CTX levels were significantly higher in Turkish COVID-19 patients than in the control group with a positive weak relationship detected between CRP and s-CTX [15]. Gul and colleagues concluded that the increased s-CTX levels in COVID-19 patients were clear evidence of COVID-19-driven bone degradation. As observed by Gul and colleagues, the serum levels of s-CTX did not differ according to the disease severity which contrasts with the current study [15]. Findings from these previous studies, in addition to the current findings, strongly suggest increased COVID-19-induced osteoclastic bone degradation as suggested by Gul and colleagues [15].

### 4.3. Mechanistic Considerations

Although several pathophysiologic bases have been ascribed to the increased osteoclastic bone degradation in COVID-19, there is consensus that the exaggerated COVID-19-induced inflammatory cascade is the basis for the increased osteoclastic activity in COVID-19 [7, 14]. Several mediators of inflammation, such as tumor necrosis fact alpha (TNFα) stimulate receptor-activated nuclear factor kappa beta ligand (RANKL) production by lymphocytic and endothelial cells, and interleukin 1 and interleukin 6 induces prostaglandin E2 production by osteoblastic cells. These two mechanisms have been demonstrated recently to indirectly induce osteoclastogenesis with resultant pathologic bone resorption [16, 17]. This was corroborated in the current study where we found a positive correlation between the inflammatory markers and the bone resorption marker (s-CTX). Moreover, diverse research evidence suggests that SARS-CoV-2 infects various organs of the body via ACE2 receptors including bone-forming cells (osteoblasts) and a recent study documented a method by which SARS-CoV-2 reduces the osteogenic potential of osteoblast by increasing the expression of microRNA-4485 via targeting TLR4 (found to hinder effective fracture healing) in COVID-19 disease patients [18, 19].

### 4.4. Relevance to Clinicians and Future Studies

The findings here highlight the need to screen for COVID-19-associated metabolic bone perturbations during COVID-19 management. The genetic basis of COVID-19-induced metabolic bone perturbations should be an area of intense research.

### 4.5. Strength and Limitations

The study was strongly strengthened by the recruitment/analysis of only those COVID-19 patients with confirmed positive RT-PCR tests without any pre-existing confounding comorbidities. Yet, the study was limited by some factors which are potential areas for improvement in future studies. The study sample was small which may or may not have impacted the study conclusions. The study was a single-center study, so, its findings may not reflect the larger population within the studied region.

## 5. Conclusion

At COVID-19 diagnosis, the studied population had increased levels of inflammatory marker and raised bone resorption marker, but reduced bone formation marker (s-PINP) compared to the pre-COVID-19 parameters. These cardinal biochemical findings were more prominent among those with severe disease variants compared to those with non-severe disease variants. Additionally, a negative correlation pattern was observed between the inflammatory markers and the bone formation marker, however, a positive correlation was observed between the inflammatory markers and the bone resorption marker. The current finding indicates perturbation of bone metabolism, associated with increased bone resorption pattern, secondary to severe COVID-19 among the studied population. The impact on bone metabolism could be addressed via severe disease prevention and reduction through management protocols. Hence, it is highly recommended that the evaluation of bone metabolism status be incorporated into the management protocols for COVID-19.

## Abbreviations

| | |
|---|---|
| COVID-19 | Coronavirus Disease 2019 |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus-2 |
| ACE2 | Angiotensin Converting Enzyme-2 |
| RSUTH | Rivers State University Teaching Hospital |
| HCWs | Healthcare Worker(s) |
| RT-PCR | Reverse Transcriptase Polymerase Chain Reaction |
| HIV/AIDS | Human Immune-Deficiency Virus/ Acquired Immune Deficiency Disease |
| BMI | Body Mass Index |
| SpO2 | Oxygen Saturation |
| PCT | Pro-calcitonin |
| CRP | C-reactive Protein |
| PTH | Parathyroid Hormone |

| | |
|---|---|
| PINP | N-terminal Propeptide of Type 1 Procollagen |
| CTX | Cross-Linked C-terminal Telopeptide of Type 1 Collagen |
| RANKL | Receptor-Activator of Nuclear Factor Kappa Beta Ligand |
| TNFα | Tumour Necrosis Factor Alpha |

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## Author Contributions

**Friday Enwumelu Aaron:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

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## Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (CA) upon reasonable request.

## Conflicts of Interest

The authors declare no conflicts of interest.

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