Review



# Post COVID-19 Syndromes -Some New Data on the Changes of Phosphocalcium Metabolism

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*Review*

# Post COVID-19 Syndromes -Some New Data on the Changes of Phosphocalcium Metabolism

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**Abstract:** Phosphocalcium metabolism disorders have emerged as potential complications in individuals recovering from COVID-19. This abstract provides a concise summary of the current understanding of phosphocalcium metabolism disturbances post-COVID, their prevalence, clinical manifestations, and underlying mechanisms. The impact of COVID-19 on phosphorus, calcium, and parathyroid hormone levels is discussed, highlighting the importance of regular monitoring and appropriate management strategies. The abstract emphasizes the need for further research to enhance our understanding of these disorders and improve post-COVID patient care.

**Keywords:** COVID-19; phospho-calcium; parathyroid hormone; post-COVID complications; hypocalcemia; hypophosphatemia

## 1. Introduction

The COVID-19 pandemic has had significant global health implications, affecting millions of individuals worldwide. While the acute respiratory symptoms of COVID-19 have been extensively studied, emerging evidence suggests that the disease can have systemic effects, including disturbances in phosphocalcium metabolism [1]. This manuscript review aims to summarize and critically analyze the current research on phosphocalcium metabolism disorders post-COVID, providing insights into the potential mechanisms and clinical implications [2–4].

Phosphocalcium metabolism plays a crucial role in maintaining the balance of phosphorus and calcium in the body, which is essential for various physiological processes, including bone health, muscle function, nerve transmission, and cellular signaling [5]. Any disturbances in this delicate equilibrium can lead to a spectrum of metabolic disorders, with significant implications for an individual's overall well-being.

This manuscript review aims to provide a comprehensive analysis of the current state of research on phosphocalcium metabolism disorders post-COVID. It will delve into the existing literature to explore the impact of COVID-19 on phosphorus, calcium, and parathyroid hormone levels, along with the prevalence and clinical manifestations of these disturbances in recovering individuals [6].

Understanding the consequences of COVID-19 on phosphocalcium metabolism is of paramount importance for healthcare professionals managing post-COVID patients. By identifying and

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addressing these metabolic disturbances, healthcare providers can potentially mitigate long-term complications and improve patient outcomes. Furthermore, this review will highlight potential avenues for future research to enhance our understanding of the pathophysiological mechanisms involved and develop effective strategies for managing phosphocalcium metabolism disorders in the aftermath of COVID-19.

In the following sections, this manuscript review will present a comprehensive overview of the research findings, providing valuable insights into the clinical implications and potential interventions for individuals experiencing phosphocalcium metabolism disorders after recovering from COVID-19.

## 2. Physiology

### *2.1. Phosphocalcium metabolism*

The minerals calcium and phosphorus are essential components in the process of bone mineralization. Both minerals are found in bones and can be dissolved in serum or found intracellularly in soft tissues. Calcium and phosphorus are stored within the bone structure in the form of a crystalline compound known as hydroxyapatite. This compound not only acts as a storage site for these minerals but also serves as the fundamental building block of the bone, providing the necessary strength and support to bear the weight of the body. Calcium and phosphorus in serum exist in three forms: ionized, bound to albumin, or present in other ion complexes [2]. Calcium is involved in various physiological processes, including muscle contraction, hormone, and neurotransmitter release, as well as enzyme activation and coagulation pathways [3]. The presence of soluble calcium and phosphorus in serum is crucial for maintaining homeostasis and facilitating the proper functioning of various systems, including the nervous and muscular systems. Consequently, these levels are tightly regulated by hormones through processes such as intestinal absorption, bone resorption, renal excretion, and reabsorption [7].

The regulation and monitoring of calcium levels in the bloodstream are closely managed through the utilization of calcium-sensing receptors (CaSR) [8]. The calcium-sensing receptors (CaSRs) are a type of G-protein coupled receptors that are predominantly located in the kidneys and parathyroid glands. When calcium levels are high, an excessive amount of calcium binds to calcium-sensing receptors (CaSRs), leading to a decrease in the synthesis and secretion of parathyroid hormone. Additionally, it causes a reduction in the reabsorption of calcium by the kidneys [8].

Phosphorus serves as a structural constituent of bone in the form of hydroxyapatite. Phosphorus primarily serves the crucial role of facilitating cellular energy production and supporting metabolic processes by acting as a constituent of adenosine triphosphate (ATP). The maintenance of serum phosphorus homeostasis is achieved through the ongoing processes of bone mineralization and resorption, which are regulated by a delicate equilibrium between osteoblasts, the cells responsible for bone formation, and osteoclasts, the cells involved in bone reabsorption [2,4].

The regulation of calcium and phosphorus in the body is primarily controlled by three hormones: vitamin D 25(OH), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) [3].

### *2.2. Regulation by Vitamin D*

Various forms of vitamin D suffer biochemical conversion to an active form known as vitamin D1,25(OH)2 or calcitriol (Figure 1). The synthesis of vitamin D3 (cholecalciferol) in the skin of animals begins with the conversion of 7-dehydrocholesterol through exposure to UVB radiation and heat. Vitamin D2, also known as ergocalciferol, is derived from plant and fungal sources [2]. Additional sources of vitamin D include fish liver, oily fish, and its supplementation in milk and orange juice. Within the hepatic system, the hydroxylation process takes place, wherein D2 and D3 undergo conversion into calcidiol, also known as vitamin D25(OH) [2]. The primary role of this intermediate metabolite is to serve as the reservoir for vitamin D. Within the renal system, calcidiol undergoes additional hydroxylation through the enzymatic action of 1$\alpha$-hydroxylase, leading to the production

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of calcitriol, an active form of vitamin D. This process ultimately enhances the absorption of calcium and phosphorus in the intestines [1,2,4].

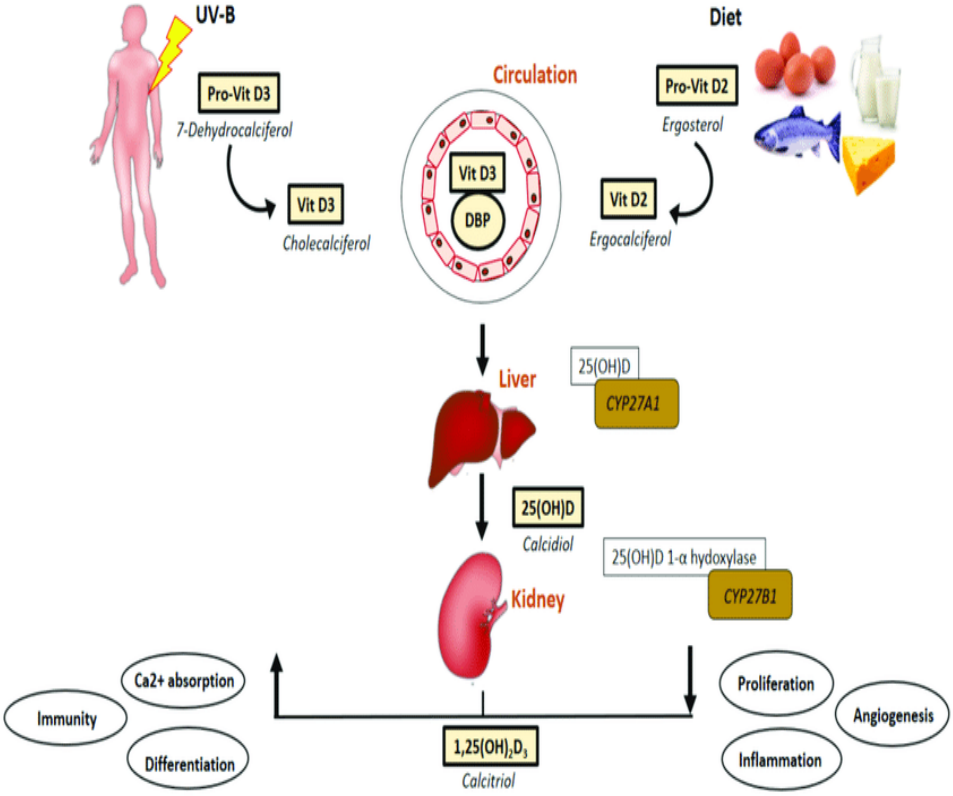


**Figure 1.** Schematic illustration of vitamin D synthesis pathway and signaling mechanisms relevant to PAD formation. The primary variants of vitamin D found in the natural environment encompass vitamin D3 (cholecalciferol), which is biosynthesized in the epidermis of animals and humans upon exposure to sunlight, as well as acquired through dietary sources.

*2.3. Regulation by PTH*

Parathyroid hormone (PTH), which is secreted by the four parathyroid glands, plays a crucial role in regulating calcium and phosphorus levels in bone, the gastrointestinal tract, and the kidneys. The provided information is represented in Figure 2. Within the renal tubules, parathyroid hormone (PTH) has the effect of augmenting the reabsorption of calcium while simultaneously enhancing the excretion of phosphorus [2]. Within the gastrointestinal tract, parathyroid hormone (PTH) facilitates the process of reabsorption of calcium and phosphorus. This is achieved indirectly through the stimulation of 1$\alpha$-hydroxylase, as supported by previous studies [3]. Within the skeletal system, parathyroid hormone (PTH) serves as a stimulant for both osteoblasts and osteoclasts, leading to an elevation in bone turnover and ultimately resulting in bone resorption. The process of bone resorption leads to elevated levels of phosphorus and calcium. However, it is important to note that parathyroid hormone (PTH) also enhances the excretion of phosphorus in the kidneys [9]. Consequently, the overall outcome is an elevation in serum calcium levels and a reduction in serum phosphorus levels [2,3]. The impact of parathyroid hormone (PTH) on renal function is characterized by a rapid onset, manifesting within minutes.

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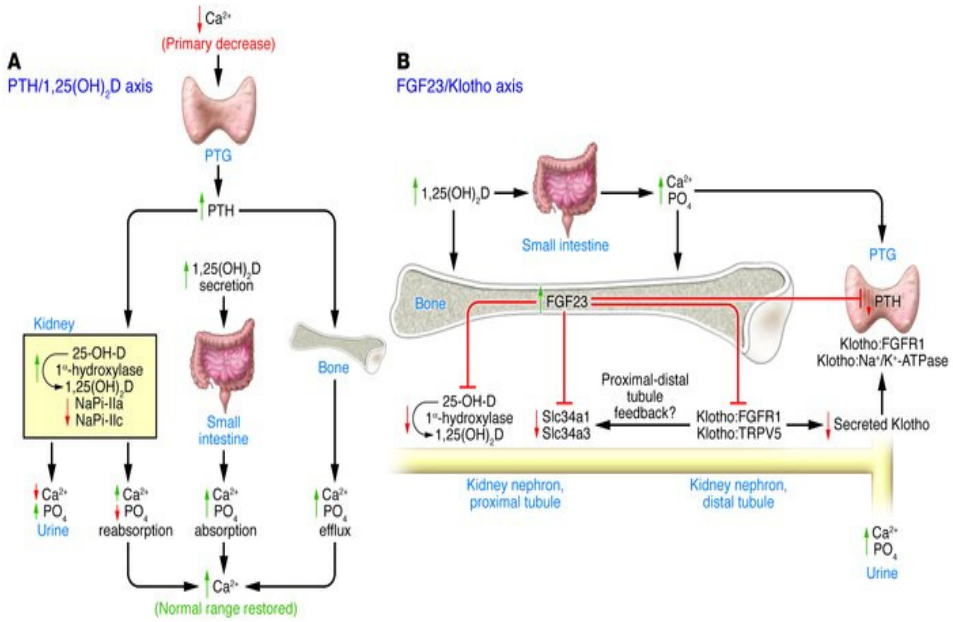


**Figure 2.** The maintenance of calcium-phosphate balance is controlled by the parathyroid glands, bone, kidneys, and intestinal tract.

*2.4. Regulation by FGF23*

FGF23 is a significant hormone involved in the regulation of phosphorus levels. It functions as a phosphatonin, playing a crucial role in promoting the excretion of phosphorus in urine [3] (Figure 3). The hormone in question is presumed to activate its effects on the proximal renal tubule by binding to its receptor FGFR1, in conjunction with the co-receptor klotho [3]. FGF23 functions as an inhibitor of 1$\alpha$-hydroxylase and reduces the concentrations of calcitriol (vitamin D1,25(OH)2) in association with this receptor [3,5]. High levels of phosphate in the bloodstream trigger the skeletal system to produce fibroblast growth factor 23 (FGF23), which subsequently inhibits the reabsorption of phosphate in the renal tubules and the synthesis of calcitriol. FGF23 also promotes the production of 24$\alpha$-hydroxylase, an enzyme responsible for the conversion of vitamin D25(OH) to vitamin D24,25(OH)2, which is an inactive metabolite.

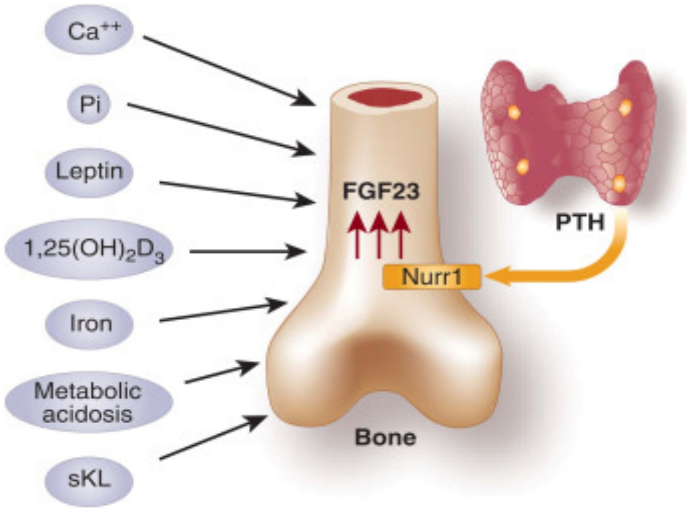


**Figure 3.** A schematic illustration of the several factors that have been identified as FGF23 production inducers. Calcium (Ca++), phosphate (Pi), leptin, secreted Klotho (sKL), iron, and metabolic acidosis.

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## 3. Materials and methods

### *3.1. Literature Search Strategy:*

A comprehensive search strategy was developed to identify relevant articles from an electronic database such as PubMed which were searched using keywords including "calcium metabolism disorders in COVID-19," "phosphocalcium metabolism," "hypophosphatemia in COVID-19," "hypoparathyroidism in COVID-19, " "hypocalcemia in COVID-19" and "post-COVID complications". The search was limited to articles from the last 4 years to ensure the inclusion of recent research.

### *3.2. Inclusion and Exclusion Criteria:*

Inclusion criteria:

- Research articles investigating phosphocalcium metabolism disorders in patients who have recovered from COVID-19.
- Studies with a clear study design and defined outcome measures related to phosphocalcium parameters.

Exclusion criteria:

- Articles focusing solely on acute COVID-19 cases or pre-existing phosphocalcium metabolism disorders.
- Review articles, editorials, and conference abstracts.

### *3.3. Data Extraction:*

- Two independent reviewers conducted the initial screening of the retrieved articles based on titles and abstracts.
- Full-text screening was performed for potentially eligible articles, and discrepancies were resolved through discussion.
- Data were extracted from the selected articles, including study characteristics (e.g., study design, sample size), patient demographics, COVID-19 severity, phosphocalcium-related parameters (calcium, phosphorus, PTH), and key findings related to phosphocalcium metabolism disorders.

### *3.4. Quality Assessment:*

Studies with low methodological quality were carefully considered during data synthesis.

### *3.5. Data Synthesis:*

The extracted data were synthesized to provide a descriptive overview of the selected studies' characteristics, findings, and implications.

### *3.6. Limitations:*

Potential limitations of this article review were acknowledged, such as the possibility of publication bias and the exclusion of non-English language articles.

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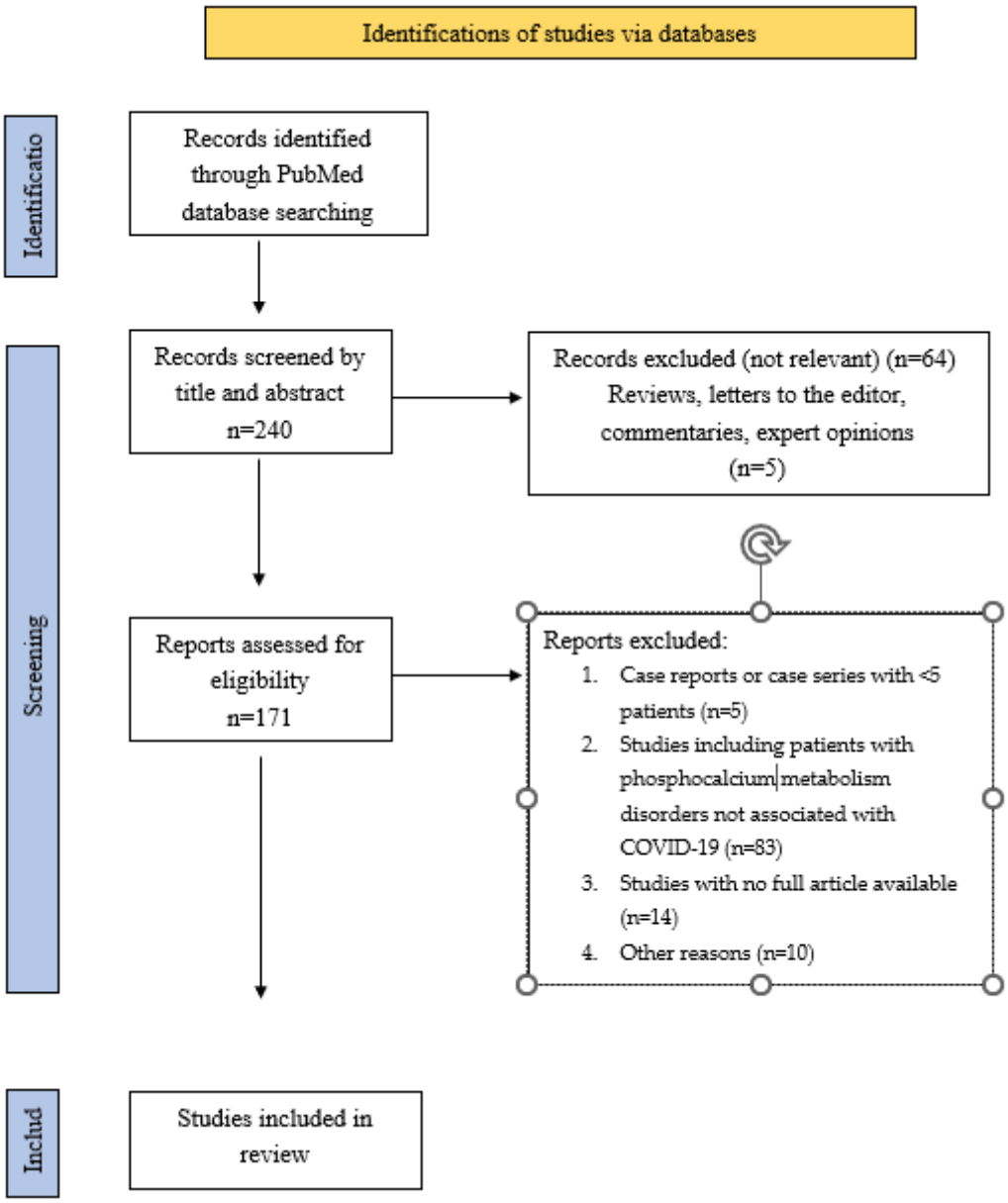


**Figure 4.** PRISMA Flowchart of published studies related to COVID-19-associated phosphocalcium metabolism disorders.

## 4. Results

### *4.1. Hypocalcemia*

Low calcium levels were a common biochemical result during the first pandemic outbreak in Europe. Beginning with the seminal observation of a case of severe acute hypocalcemia in a patient previously thyroidectomized with infection with SARS-CoV-2 [10], several studies taken worldwide to evaluate the possible causal or causal relationship between COVID-19 and hypocalcemia revealed an unexpectedly high prevalence of low calcium levels, ranging from 62.6 to 87.2% of patients, depending on the hypocalcemia definition used [5,11,12].

In a recent study, researchers examined the relationship between calcium levels and various parameters related to inflammation, coagulopathy, and organ injury in individuals with COVID-19 [13]. The findings revealed a negative association between calcium levels and these parameters, suggesting that higher calcium levels were linked to better outcomes. Additionally, the study identified hypocalcemia, or low calcium levels, as an independent risk factor for adverse effects in COVID-19 patients [14]. This highlights the importance of calcium as a reliable and easily measurable

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biomarker for assessing disease severity in COVID-19. The results of this study provide valuable insights into the potential role of calcium in predicting and managing COVID-19 outcomes [15]. The findings of this research were supported by subsequent systematic reviews and meta-analyses, which also concluded that there is a significant correlation between hypocalcemia and various indicators of disease severity (Table 1) [16,17]. These indicators include hospitalization rates, length of hospital stay, admission to the intensive care unit, and the risk of mortality [18,19].

In their study, Cappellini et al. conducted a comprehensive analysis of calcium levels in a sample of 420 patients diagnosed with COVID-19, comparing them to a control group of 165 individuals without COVID-19. The researchers made a noteworthy discovery, as they observed a significant decrease in both serum total calcium and whole blood actual ionized calcium among the COVID-19 patients when compared to those without the virus. This finding shed light on the potential impact of COVID-19 on calcium homeostasis and highlights the importance of further investigation in this area [1].

### *4.2. Hypophosphatemia*

There is a suggested association between disturbances in phosphate metabolism and the impact of COVID-19 on the homeostasis of vitamin D, calcium, and phosphorus. The prevalence of vitamin D deficiency is high among individuals with severe COVID-19 infection [20]. Povaliaeva et al. recently conducted a study that established a correlation between abnormal kidney function, abnormal vitamin D metabolism, and hypophosphatemia (Table 2) [21]. According to the authors, individuals with severe COVID-19 manifested atypical vitamin D metabolism, increased serum creatinine levels, and decreased serum phosphate levels [21].

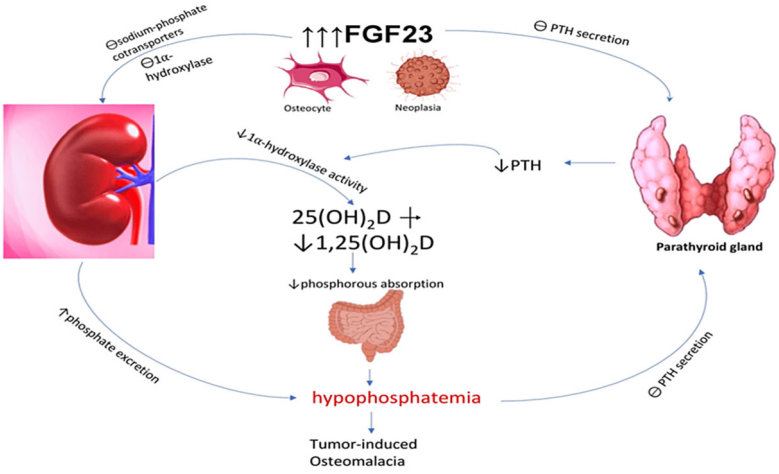


**Figure 5.** Correlation between serum phosphate levels and Vitamin D, PTH, and calcium.

### *4.3. Hypovitaminosis D*

The hypothesis of a strong correlation between VD and COVID-19 emerged during the initial stages of the pandemic, as VD has been widely recognized for its role in modulating both innate and adaptive immune responses [22]. Vitamin D (VD) has been recognized for its antimicrobial properties and ability to inhibit viral activity. It also plays a role in regulating the adaptive immune response by promoting a transition from a pro-inflammatory state to a tolerogenic state. This results in the downregulation of immune responses mediated by T-helper-1 lymphocytes, the inhibition of pro-inflammatory cytokine production, and the promotion of regulatory T-cell maturation [23].

Vitamin D (VD) has been recognized for its significant involvement in various metabolic pathways related to musculoskeletal health [21]. Previous research has demonstrated that supplementation with VD has been shown to confer advantages in muscle recovery following periods of intense physical activity and tissue damage [24,25]. The studies found that VD levels were able to predict and exert an influence on the duration of illness and the time it took for recovery following

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an episode of acute severe pneumonia (Table 3). To this day, the role of vitamin D in the occurrence of Long-COVID has only been examined in a limited number of small-scale studies [26,27]. In a recent pilot study involving elderly patients recovering from acute COVID-19, the effectiveness of a six-week therapy with 2,000 IU/day of cholecalciferol compared to placebo was examined. The study found that cholecalciferol therapy resulted in a reduction in creatinine kinase values and demonstrated a positive trend in improving overall health and physical well-being [28–31].

### *4.4. Hypoparathyroidism*

The COVID-19 disease has been documented as a potential trigger for the decompensation of pre-existing primary hypoparathyroidism, which was previously well-tolerated by affected individuals. In their study, Bossoni et al. [10] documented a clinical case involving a 72-year-old female patient who had previously undergone thyroidectomy [32]. The patient exhibited a mild case of COVID-19 infection and presented with symptoms of acute perioral paresthesia and dysarthria. The laboratory analyses indicated a decrease in the concentration of calcium in the blood serum, an elevation in the concentration of phosphorus in the blood serum, and a decrease in the concentration of parathyroid hormone (PTH) in the blood serum [33–35]. These findings suggest that the infection caused by the SARS-CoV-2 virus led to a significant decrease in calcium levels, particularly in the presence of underlying, asymptomatic hypoparathyroidism after surgery [10].

### *4.5. Skeletal complications and vertebral fractures*

Morphometric vertebral fractures (VFs) are considered significant clinical manifestations of osteoporosis and skeletal fragility. Recent reports have indicated a high prevalence of these fractures in patients with COVID-19 [36–38]. VFs problems are associated with reduced survival rates, decreased respiratory function, and compromised quality of life in the general population [36].

Hospitalized patients with COVID-19 may experience an elevated risk of fractures due to various concurrent factors [39,40]. These factors involve advanced age and comorbidities like diabetes, cardiovascular diseases, and hypertension.

Also, it has been previously reported that individuals who are hospitalized due to COVID-19 regularly show hypovitaminosis D, a condition that is known to be linked to decreased bone mineral density (BMD) and an elevated risk of fractures [22,41].

Vertebral fractures (VFs) and reduced bone mineral density (BMD) have been identified as factors that elevate the likelihood of developing pneumonia and hinder respiratory function, resulting in restrictive pulmonary dysfunction within the general population [42]. VFs have been observed to have an impact on the respiratory function of individuals who have survived COVID-19 in the medium term. This influence, in turn, can have a substantial effect on their overall recovery process and may contribute to the occurrence of Long-COVID.

## 5. Incidence of phosphocalcium metabolism disorders related to COVID-19

The literature search revealed 240 studies, of which, ultimately, 31 studies were included in this review: 7 articles about hypocalcemia, 12 articles about hypophosphatemia and 12 articles about hypovitaminosis D.

**Table 1.** Summary of included articles with hypocalcemia.

| Study | Study design | Country | Patients(n) | Affected Organ/ System |
|---|---|---|---|---|
| Yiquin W et al. [43] | Retrospective | China | 125 | Lungs |
| Bálint D et al. [44] | Multicenter Study | Hungary | 451 | Liver |
| Wessam O et al. [25] | Prospective observational | Oman | 445 | Lungs |

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| | | | | |
|---|---|---|---|---|
| Meera M et al. [14] | Retrospective observational | England | 506 | Lungs |
| Berta T et al. [45] | Retrospective observational | Spain | 316 | Lungs |
| Jyot A et al. [46] | Prospective observational | India | 170 | Heart |
| Jingmei L et al. [12] | Prospective observational | China | 69 | Heart |

**Table 2.** Summary of included articles with hypophosphatemia.

| Study | Study design | Country | Patients(n) | Affected Organ/ System |
|---|---|---|---|---|
| Rourang W et al. [4] | Case series | China | 435 | Kidney |
| Zijin C et al. [47] | Retrospective | Hungary | 823 | Kidney |
| Maram H et al. [48] | Case series | UAE | 128 | Adrenal gland |
| Hannah W et al. [49] | Cross-sectional | Italy | 1226 | Lungs |
| Marina V et al. [50] | Prospective observational | Switzerland | 104 | Stomach |
| Baroncelli G et al. [51] | Retrospective | Italy | 26 | Kidney |
| Hadavi M et al. [52] | Retrospective | Iran | 1346 | Stomach |
| Kormann R et al. [53] | Retrospective | France | 42 | Kidney |
| Benson Y et al. [54] | Prospective observational | USA | 88 | Brain |
| Garcia F et al. [55] | Case series | Spain | 45 | Kidney |
| Charles L et al. [56] | Retrospective observational | Singapore | 83 | Kidney |
| Mnaff A et al. [57] | Case series | Kuwait | 78 | Lungs |

**Table 3.** Summary of included articles with hypovitaminosis D.

| Study | Study design | Country | Patients(n) | Affected Organ/ System |
|---|---|---|---|---|
| Saponaro F et al. [58] | Case series | Italy | 93 | Lungs |
| Luigi di F et al. [5] | Case series | Italy | 78 | Parathyroid |
| Singh S et al. [59] | Retrospective | India | 360 | Lungs |
| Mohammed A et al. [60] | Prospective observational | Egypt | 124 | Lungs |
| Manojlovic M et al. [61] | Cross-sectional | Serbia | 74 | Heart |
| Mazziotti G et al. [62] | Case series | Italy | 348 | Parathyroid |
| D'Alessandro A et al. [63] | Multicenter Study | Italy | 163 | Lungs |
| Rimesh P et al. [16] | Retrospective case | India | 72 | Bones |
| Rizaldy P et al. [64] | Case series | Indonesia | 10 | Heart |
| Carpagnano G et al. [65] | Retrospective | Italy | 42 | Lungs |
| Thiago J et al. [66] | Cross-sectional | Brazil | 176 | Heart |

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| | | | | |
|---|---|---|---|---|
| Nascimento R et al. [67] | Cross-sectional | Brazil | 1478 | Heart |

**Table 4.** Baseline characteristics of included patients (SD= standard deviation, COPD= chronic obstructive pulmonary disease).

| Study | Study design | Patients (n) | Age (Mean ± SD) | COVID-19 Severity | Duration of Hospitalization (Days) | Phosphocalcium Findings | Other Complications | Comorbidity |
|---|---|---|---|---|---|---|---|---|
| Yiquin W et al. [43] | Retrospective | 125 | 55 ± 8.9 years | Mild | 13 ± 3.9 | Hypocalcemia: 64% | Pneumonia | Diabetes type 2<br>Hypertension<br>Coronary heart disease |
| Bálint D et al. [44] | Multicenter study | 451 | 58.2 ± 10.3 years | Severe | 14 ± 3.9 | Hypocalcemia: 45% | Severe respiratory failures | Cirrhosis |
| Wessam O et al. [25] | Prospective | 445 | 50 ± 12.1 years | Mild | 7.5 ± 2.1 | Hypocalcemia: 75%<br>Hypovitaminosis D: 5% | Chronic respiratory diseases | Diabetes<br>Hypertension |
| Meera M et al. [14] | Retrospective | 506 | 65 ± 7.2 years | Severe | 25.6 ± 4.7 | Hypocalcemia: 53% | Lymphopenia<br>Hypoxia | Obesity<br>Hypertension<br>Cancer |
| Berta T et al. [45] | Retrospective | 316 | 65 ± 9.5 years | Severe | 19.3 ± 3.5 | Hypocalcemia: 63% | ICU admission | Cardiopathy<br>Dyslipidemia<br>Diabetes |
| Jyot A et al. [46] | Prospective | 170 | 62 ± 11.7 years | Critical | 23.7 ± 5.2 | Hypocalcemia: 80% | Acute respiratory distress syndrome | Hypertension<br>Diabetes mellitus type 2 |
| Jingmei L et al. [12] | Prospective | | 68 ± 6.8 years | Severe | 14.1 ± 1.9 | Hypocalcemia: 62% | Pneumonia | Coronary heart disease<br>Hypertension |
| Rourang W et al. [4] | Case series | 435 | 57 ± 10.5 years | Severe | 10 ± 4 | Hypophosphatemia: 7.6% | Chronic liver disease | COPD<br>Hypertension<br>Diabetes mellitus |
| Zijin C et al. [47] | Retrospective | 823 | 60.9 ± 14.9 years | Severe | 14.8 ± 6.3 | Hypophosphatemia: 10% | Acute liver injury | COPD<br>Diabetes mellitus |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Hannah W et al. [49] | Cross sectional | 1226 | 61.2 ± 8.3 years | Severe | 13.5 ± 2.8 | Hypophosphatemia: 26% | Pneumonia | Cardiovascular disease Septic shock |
| Marina V et al. [50] | Prospective | 104 | 59 ± 14 years | Critical | 20.3 ± 9 | Hypophosphatemia : 33% | Gastrointestinal problems | Diabetes Obesity |
| Hadavi M et al. [52] | Retrospective | 1346 | 65.9 ± 1.1 years | Severe | 14 ± 6 | Hypophosphatemia : 10% | Respiratory failure | Cardiovascular disease Hypertension Autoimmune disease |
| Kormann R et al. [53] | Retrospective | 42 | 63.4 ± 8 years | Severe | 19 ± 12.2 | Hypophosphatemia : 29% | Kidney disease | Hypertension Dyslipidemia COPD |
| Charles L et al. [56] | Retrospective | 83 | 58 ± 12.7 years | Severe | 14 ± 3.1 | Hypophosphatemia : 18% | Gastrointestinal problems | Hypertension Diabetes Cancer |

The results from the reviewed studies indicate a high prevalence of phosphocalcium metabolism disorders among individuals with COVID-19, and there is often a correlation between the severity of these disorders and the clinical manifestation of the disease. Hypocalcemia and hypophosphatemia are frequently observed disturbances, particularly in patients with severe cases of COVID-19.

Multiple factors contribute to the occurrence of phosphocalcium abnormalities, encompassing the length and intensity of hospitalization, coexisting medical conditions, and the occurrence of additional complications like acute respiratory distress syndrome and acute kidney injury (refer to Table 4). There is evidence to suggest that individuals diagnosed with chronic kidney disease or chronic heart disease may be more susceptible to the development of phosphocalcium disorders in the context of COVID-19.

The duration of hospital stay, and the severity of the disease are important variables that have a significant impact on phosphocalcium abnormalities in individuals diagnosed with COVID-19. Extended durations of hospitalization, particularly in cases of critical illness, have the potential to disrupt the balance of minerals in the body. This can be attributed to various factors such as reduced ability to move, changes in dietary consumption, and the presence of systemic inflammation. Consequently, it is imperative to closely monitor phosphocalcium levels during the entire duration of hospitalization in order to promptly intervene and mitigate complications associated with imbalances in these vital minerals.

The correlation between phosphocalcium disorders and specific comorbidities, such as chronic kidney disease and chronic heart disease, presents significant clinical implications. Individuals who have pre-existing medical conditions may exhibit increased susceptibility to disturbances in phosphocalcium metabolism after being infected with COVID-19. The management of phosphocalcium levels in these individuals may necessitate customized strategies, considering their pre-existing conditions and prescribed medication protocols.

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## 6. Discussion

The COVID-19 pandemic has not only impacted the respiratory system, but it has demonstrated systemic implications, such as modifications in phosphocalcium metabolism. The objective of this article review was to provide a comprehensive summary and critical analysis of existing research about disorders in phosphocalcium metabolism following COVID-19 [2,16,26]. The review aimed to offer valuable insights into the potential underlying mechanisms and clinical implications associated with these disorders.

The results derived from the examined studies highlight the frequency of phosphocalcium metabolism disorders among individuals in the process of recuperating from COVID-19. Various research studies have documented a variety of disruptions, such as hypophosphatemia, hypocalcemia, and secondary hypoparathyroidism [19,24,33]. The results of this study suggest that COVID-19 has the potential to disturb the intricate equilibrium of phosphorus, calcium, and parathyroid hormone concentrations within the human body.

One possible mechanism that may contribute to the development of phosphocalcium metabolism disorders following COVID-19 is the direct impact of the virus on organs responsible for maintaining phosphocalcium balance. Multiple research studies have provided evidence regarding the existence of viral particles and the manifestation of viral receptors within the renal and parathyroid tissues [33,34]. This observation implies that SARS-CoV-2 has the potential to directly impact these organs, resulting in changes to phosphocalcium metabolism.

The COVID-19 infection has the potential to induce systemic inflammation and immune dysregulation, which in turn can have an impact on the regulation of phosphocalcium metabolism. The imbalances of phosphorus, calcium, and parathyroid hormone levels can occur because of the activation of the immune system and the release of inflammatory cytokines [2,3]. In addition, the administration of medications in the context of COVID-19 therapy, such as corticosteroids, has the potential to induce metabolic disruptions.

The clinical ramifications of disorders related to phosphocalcium metabolism following a COVID-19 infection are of considerable importance. The presence of hypophosphatemia and hypocalcemia may result in various clinical manifestations, such as muscle weakness, fatigue, bone pain, muscle cramps, tingling sensations, and potential cardiac arrhythmias [3,4,16,24].

The effective management of phosphocalcium metabolism disorders in individuals undergoing recovery from COVID-19 necessitates diligent monitoring and the implementation of suitable interventions. Systematic monitoring of phosphorus, calcium, and parathyroid hormone concentrations can facilitate the detection and management of any deviations from the optimal levels. The restoration and maintenance of optimal levels may require the utilization of nutritional supplementation, such as vitamin D and calcium. Furthermore, the restoration of phosphocalcium homeostasis could potentially be facilitated by the management of systemic inflammation and immune dysregulation.

Recognizing the constraints of the examined studies holds significance. Numerous studies exhibit limited sample sizes and heterogeneity concerning patient characteristics and methodologies. Additional investigation utilizing larger groups, standardized methodologies, and extended monitoring periods is imperative to enhance our comprehension of the frequency, underlying mechanisms, and medical consequences associated with disturbances in phosphocalcium metabolism post-COVID-19.

## 7. Conclusions

In conclusion, this review has explained the profound influence of COVID-19 on phosphocalcium metabolism, resulting in a range of metabolic dysfunctions. The results obtained from the examined studies highlight the high occurrence of disruptions in phosphocalcium metabolism among individuals in the process of recovering from COVID-19. These disruptions include hypophosphatemia, hypocalcemia, and secondary hypoparathyroidism.

The perturbations in phosphocalcium metabolism following COVID-19 are presumably influenced by a variety of factors, encompassing the direct impact of the virus on the kidneys and

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parathyroid glands, systemic inflammation, immune dysregulation, and the administration of medications during COVID-19 treatment. These mechanisms have the potential to disturb the intricate equilibrium of phosphorus, calcium, and parathyroid hormone, leading to imbalances and subsequent clinical manifestations.

The management of disorders related to phosphocalcium metabolism following a COVID-19 infection is of major significance to enhance patient outcomes. The regular monitoring of phosphorus, calcium, and parathyroid hormone levels is imperative for the timely identification and implementation of appropriate measures. The restoration and maintenance of optimal levels may require the utilization of nutritional supplementation, such as vitamin D and calcium. The restoration of phosphocalcium homeostasis can be facilitated by addressing systemic inflammation and immune dysregulation.

Nevertheless, it is crucial to recognize the constraints inherent in the examined studies, including limited sample sizes, variability in participant characteristics, and the necessity for additional investigations employing standardized methodologies and extended periods of observation. Future research endeavors should strive to enhance our comprehension regarding the frequency, underlying mechanisms, and medical ramifications of phosphocalcium metabolism disorders after the COVID-19 infection.

In summary, this manuscript review highlights the importance of phosphocalcium metabolism disorders in the population undergoing recovery from COVID-19. The results underscore the significance of surveillance, interventions, and additional investigation in this domain. Healthcare professionals have the potential to enhance the comprehensive care and outcomes of individuals after COVID by addressing these metabolic disturbances.

## 8. Future Perspectives

The review on phosphocalcium metabolism disorders post-COVID-19 provides valuable insights into the impact of SARS-CoV-2 infection on calcium, phosphorus, and vitamin D homeostasis in patients. Building on the existing knowledge, several future perspectives can guide further research and clinical practice in this area:

### *8.1. Long-term monitoring*

Conducting longitudinal studies with extended follow-up periods is essential to understand the long-term consequences of phosphocalcium disorders post-COVID-19. Tracking patients beyond the acute phase will help assess the persistence of abnormalities and potential late-onset complications, such as osteoporosis and cardiovascular events.

### *8.2. Impact on bone health*

Investigating the effects of phosphocalcium disorders on bone health is crucial. Long-term studies assessing bone mineral density, bone turnover markers, and fracture risk in post-COVID-19 patients can provide valuable insights into bone-related complications and guide preventive measures.

### *8.3. Optimal vitamin D supplementation*

Conducting randomized controlled trials to determine the most effective and safe dosage of vitamin D supplementation in post-COVID-19 patients is essential. Understanding the optimal timing, duration, and formulation of supplementation can improve patient outcomes and reduce complications.

### *8.4. Immune system dysregulation*

Exploring the immunological mechanisms underlying phosphocalcium metabolism disorders post-COVID-19 is critical. Investigating the role of immune dysregulation, cytokine storm, and

chronic inflammation in disrupting calcium and phosphorus homeostasis can provide potential therapeutic targets.

*8.5. Multidisciplinary care teams*

Establishing multidisciplinary care teams involving endocrinologists, nephrologists, infectious disease specialists, and rehabilitation experts can provide comprehensive management for post-COVID-19 patients with phosphocalcium disorders. Collaboration among specialties can address the complexity of these conditions.

*8.6. Global collaboration and data sharing*

Encouraging international collaboration and data sharing among researchers and institutions can enhance the collective understanding of phosphocalcium disorders post-COVID-19. Large-scale, multinational studies can yield robust findings and facilitate more comprehensive guidelines.

*8.7. Preparing for future outbreaks*

Applying the knowledge gained from studying phosphocalcium disorders post-COVID-19 can help healthcare systems prepare for future infectious disease outbreaks. Lessons learned from managing these disorders can inform strategies for preventing and managing similar complications in future pandemics.

In conclusion, the future perspectives outlined above offer a roadmap for furthering our understanding of phosphocalcium metabolism disorders in the context of COVID-19 recovery. By addressing these perspectives through dedicated research and collaboration, we can optimize patient care, mitigate long-term consequences, and enhance public health measures to improve the overall well-being of post-COVID-19 patients.

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