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Vitamin D Deficiency As A Risk Factor For Mortality In Critically Ill Patients

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Abstract

Background: Vitamin D is produced in the skin upon sun exposure. Vitamin D is necessary to maintain serum calcium concentration within the normal physiologic range for musculoskeletal health. Currently one in five Americans dies in the ICU, and virtually every generation today will have an ICU encounter in their lifetime. Survivors of critical illness are at risk for subsequent hospitalization, outpatient evaluation and related health care costs.

Methodology: A systematic review was carried out through various databases from January 2010 to February 2022; the search and selection of articles was carried out in indexed journals in English. Key words used were: Vitamin D, Mortality, ICU, Critical patient.

Results: Vitamin D3 is produced in the skin from 7-dehydrocholesterol in a two-step process in which the B-ring is broken down under ultraviolet rays (e.g., sunlight) and the pre-D3 formed in this process is isomerized to D3 in a sensitive but non-catalytic thermo- process. Vitamin D deficiency could lead to major health impacts, including higher severity of illness scores and risk of death, longer ICU stay, longer duration of mechanical ventilation, higher rates of ventilator-associated pneumonia and positive blood cultures, and a higher incidence of organ dysfunction, particularly acute kidney injury.

Conclusions: The present review provides current and accurate information on the functions of vitamin D, what its deficiency entails and its impact on health and its role as a risk factor for mortality in critically ill patients.

Keywords: Vitamin D; Mortality; ICU; Critical patient; ICU; mortality

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Introduction

Vitamin D is labeled as the "sunshine vitamin" because it is produced in the skin upon exposure to the sun. Vitamin D is necessary to maintain serum calcium concentration within the normal physiologic range for musculoskeletal health **[1].**

The Endocrine Society, the National and International Osteoporosis Foundation and the American Geriatric Society define vitamin D deficiency as a 25-hydroxyvitamin (25 OH D) level below 30 ng/mL. The Endocrine Society recommends a preferred range of 40 to 60 ng/mL **[2].**

Vitamin D deficiency in children causes rickets and prevents children from reaching their maximum bone mass and genetically determined height. In adults, vitamin D deficiency causes abnormal mineralization of the collagen matrix in bone, known as osteomalacia. This collagen matrix is weak, does not provide adequate structural support, and increases the risk of fracture **[3].**

Vitamin D is a hormone obtained through dietary intake and skin

production. Ultraviolet B (UVB) radiation, wavelength (290 to 315 nm) converts 7- dehydrocholesterol in the skin to provitamin D. **[4, 5]** This provitamin D undergoes isomerization by heat and is converted to vitamin D. Vitamin D from skin and diet is metabolized in the liver to 25-hydroxyvitamin D (25 OH D), and 25-hydroxyvitamin D is useful for assessing vitamin D status. **[5].**

In the 1950s and 1960s, when the field of critical care developed, the primary focus was on survival: taking a patient who was dying imminently, providing vital organ support with infusions and pharmaceutical machines, and saving the patient from the agony of death **[5, 6].**

Currently one in five Americans dies in the ICU, and virtually all of today's generation will have an ICU encounter during their lifetime. Survivors of critical illness are at risk for subsequent hospitalization, outpatient evaluation, and related health care costs **[6, 7]** It is therefore appropriate to undertake this work in order to provide current and accurate information on the functions of vitamin D, what its deficiency entails and its impact on health and its role as a risk factor for mortality in critically ill patients.

Materials and Methods

A systematic review was carried out, searching PubMed, Scielo and Science Direct databases, among others. The collection and selection of articles was carried out in English-language indexed journals from 2010 to 2022. As keywords, the following terms were used in the databases according to DeCS and MeSH methodology: Vitamin D, Mortality, ICU, Critical patient. In this review, 80original and review publications related to the topic studied were identified, of which, articles28 met the specified inclusion requirements, such as, articles that were in a range not less than 2010, that were full text articles and that reported on vitamin D as a factor in the mortality of critical patients. Mortality risk in critically ill patients. Exclusion criteria took into account that the articles did not have sufficient information and that they did not present the complete text at the time of review.

Results

Results Vitamin D

Vitamin D3 is produced in the skin from 7-dehydrocholesterol in a two-step process.

Stages in which the B-ring is cleaved under ultraviolet rays (e.g., sunlight) and the pre-D3 formed in this process is isomerized to D3 in a sensitive but non-catalytic thermo-process **[8].**

The three main steps in vitamin D metabolism, 25-hydroxylation, 1a-hydroxylation and 24- hydroxylation are carried out by cytochrome P450 mixed function (CYP) oxidases. The first step toward activation is the conversion of vitamin D to 25-hydroxy-D. **[9]** In addition to UV activation, small amounts of vitamin D, either as D2 or D3, can enter the body from intestinal absorption from dietary intake and progress to activation by hydroxylation **[10].**

The next step towards full activation is dihydroxy-vitamin1, 25 D (1, 25 (OH) 2 D) Through CYP27B1 (also known as 1-alpha hydroxylase), a mitochondrial P450 enzyme in the proximal renal tubule of the kidney. 25-hydroxyvitamin D 24 hydroxylase, also known as CYP24, can hydroxylase both 25-hydroxy-D and 1, 25(OH) 2 D. In addition to 1, 25(OH) 2 D, the kidney also produces 24, 25 dihydroxyvitamin D, a relatively inactive metabolite **[11].**

Functions of Vitamin D

(OH) D. The regulation of this conversión at the tissue level differs from the conventional activation occurring in the kidney in that it is more substrate dependen and, therefore, more susceptible to vitamin D deficiency. **[12, 13],** The non-skeletal actions of vitamin D are mediated by the control of gene expression in a number of organs such as brain, prostate, colon and immune cells, which may be of particular relevance in critical illness **[14].** These non-skeletal actions result in the regulation of cell proliferation, differentiation, apoptosis and angiogénesis. In fact, the mechanism of action of vitamin D in these contexts is analogous to the way steroid hormones act. As a result of this contemporary knowledge, vitamin D is considered more of a hormone than a vitamin. In we can see other functions of vitamin D found in animal models. **[14-18] (Figure 1)**

Vitamin D Deficiency And Its Impact On Health

Several population studies have shown that low vitamin D levels are associated with poor outcomes. However, causality is more difficult to establish given that a low vitamin D level itself could be a marker of poor general health and deficiency is seen in people with limited physical activity and little exposure to sunlight, advanced age, obesity, poor diet, and other comorbid diseases **[19].**

In the general population, mortality risk appears to decrease with increasing 25 hydroxy-D levels, with optimal levels of 75 to 87.5 nmol/l. A large meta-analysis of community dwelling adults showed that the lowest observed 25-hydroxy-D quintile was associated with increased mortality **[19].**

Conditions that have been associated with vitamin D deficiency include certain malignancies such as colon, breast, ovarian, prostate, and lymphoma. Some studies also report an increased risk of mortality with these cancers in people with vitamin D deficiency **[20].**

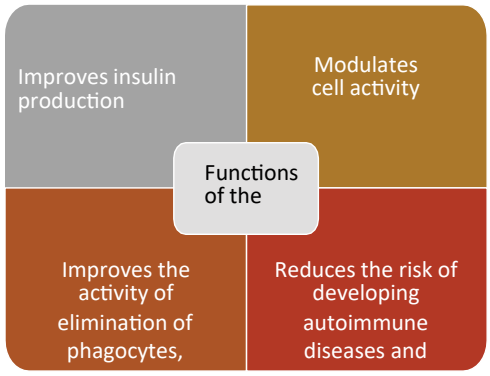

Figure 1 Functions 1. Of 1,25(OH) $_2$D in animal models.

Similarly, low vitamin D levels have been associated with cardiovascular conditions, such as poor control of hypertension and congestive heart failure **[21].**

Subjects with vitamin D deficiency who have multiple sclerosis, diabetes, depression, and certain infections such as influenza, tuberculosis, and other conditions have shown a similar association with adverse outcomes. **[21].** Several observational studies in critically ill patients have shown an association between vitamin D deficiency and adverse outcomes, in Figure 2 we can identify the main conditions **[19-23] (Figure 2).**

Associated ICU and hospital costs are also higher in patients with vitamin D deficiency **[20].**

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Which deficiency could contribute to these outcomes, such as immune dysfunction, cardiovascular disease, dysglycemia, and endothelial and mucosal barrier disruption **[25]**

It is possible, therefore, that the low levels observed are simply a marker of poor overall health resulting in limited sunlight exposure, chronic disease, and poor diet and, therefore, are associated with adverse outcomes with vitamin D deficiency being the innocent by stander of this inevitable trajectory **[15].**

Therefore, vitamin D deficiency could not be considered as the cause of the clinical picture of the patient, but rather the detection of this vitamin could contribute to determine the patient's prognosis. In Table 1 we can identify other functions of vitamin D in different organs **[12, 27, 22, 23,25, 26]. (Table 1).**

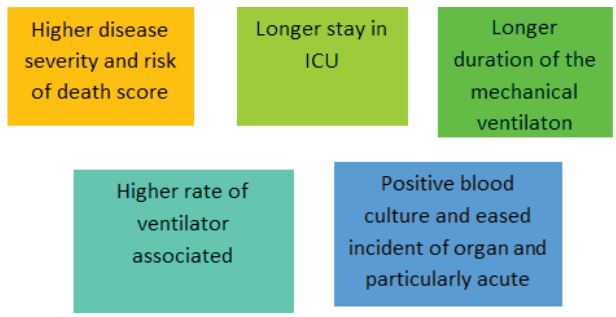

Figure 2 Main conditions of vitamin D deficiency in critically ill patients.

Discussion

The retrospective study of a medical intensive care unit in a community hospital by Sindhaghatta et al report on a large cohort of patients with 25(OH) D deficiencies and insufficiency in an ICU setting. This study shows a clear association between 25(OH)D levels and hospital mortality in critically ill patients. 25(OH) D levels of 10 ng/dL predicted hospital mortality in 83.6% of this cohort. The hospital mortality observed for patients with 25(OH)D deficiency was higher than the mortality predicted by the APAC HE IV score on admission **[27]**

Another study by Rafael et al, in which they prospectively measured vitamin D on admission of 125 intensive care unit patients, and weekly until discharge from the ICU, analysing the parameters of 28-day mortality, mechanical ventilation, length of stay, infection rate and culture positivity. They concluded That low vitamin D levels on ICU admission are an independent risk factor for mortality in critically ill patients and that low vitamin D levels on ICU admission may have a causal relationship with mortality and may serve as a marker for vitamin D replacement among critically ill patients **[28].**

Strength of the current study is the methodology implemented, with respect to the literature search, and steps in the selection of relevant articles, quality assessment and data extraction. However, this study has several limitations, which should be taken into account before reaching a conclusion, among these are the little evidence of clinical trial analysis to determine the relationship between deficiency and the percentage of mortality in patients hospitalized in an intensive care unit, hospitalized in general ward or critical patients, so more studies are needed to answer these questions.

Conclusion

Vitamin D3 is produced in the skin from 7-dehydrocholesterol in a two-step process in which the B-ring is cleaved under ultraviolet

Table 1. Vitamin D identify other functions of vitamin D in different organs.

Organ	Function
Immune system	Vitamin D metabolites act as modulators of innate and adaptive system cells.
Cardiac function	Vitamin D may play a role in the prevention of atrial fibrillation by negatively regulating the renin-angiotensin- aldosterona system (RAAS), mediating calcium homeostasis, binding to vitamin D receptors (VDRs) on cardiac myocytes and, in addition, having antioxidant properties that may reduce levels of reactive oxygen species (ROS) in the atria, which contribute to inflammation and the formation of proarrhythmic substrates.
Pulmonary function	Lack of vitamin D receptors in the barrier. Epithelial lung tissue appeared to compromise its defense, which Caused more severe lipopolysaccharide (LPS)-induced lung injury. Thus, vitamin D could be a therapeutic approach in different types of lung conditions.
Function muscular metabolic	Some animal models have confirmad that the Vitamin D deficiency and congenital abnormalities in the vitamin D endocrine system can cause muscle weakness.
Bone	Limited available data in ICU survivors suggest impaired bone health and a high risk of fracture in patients with vitamin D deficiency.

rays (e.g., sunlight) and the pre-D3 formed in this process is isomerized to D3 in a thermo-sensitive but non-catalytic process. There is a growing appreciation of the many functions of vitamin D beyond its classic actions on calcium metabolism and musculoskeletal health.

The non-skeletal actions of vitamin D are mediated by the control of gene expression in a number of organs such as brain, prostate, colon and immune cells, which may be of particular relevance in critical diseases. There are other functions of Vitamin D described in animal models, such as Enhances insulin production, Modulates T and B cell activity, Enhances the activity of elimination of phagocytes, improves vascular smooth muscle resistance and reduces the risk of developing autoimmune diseases and inhibits the growth of cancer cells.

Vitamin D deficiency could have a major impact on health, including higher severity of illness scores and risk of death, longer ICU stay, longer duration of mechanical ventilation, higher rates of ventilator-associated pneumonia and positive blood cultures, and a higher incidence of organ dysfunction, particularly acute kidney injury.

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