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EC CLINICAL AND MEDICAL CASE REPORTS
Cross Sectional Study

Relation of Vitamin D Deficiency to Common Infections

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Received: August 08, 2025; **Published:** September 01, 2025

Abstract

Serum vitamin D deficiency or insufficiency has been observed to play a role as a risk factor in the development of infectious processes and the degree of morbidity thereof. This relationship has been attributed to the extra-skeletal actions of vitamin D through immunomodulatory mechanisms.

We conducted a systematic literature review and cross-sectional retrospective case studies, which confirmed this inverse correlation between hypovitaminosis D and specific infections (Pneumonia, urinary tract infection, cellulitis) in our primary care setting, which could be used as a basis for prognostic evaluation.

Keywords: *Vitamin D Deficiency; Infection; Pneumonia; UTI; Cellulitis*

Introduction

The association between low serum Vitamin D and infections or sepsis has been well documented in many observational studies. Patients with infectious processes or clinical sepsis have been found to have an inverse correlation with serum levels of Vitamin D. The mechanism for this association has been attributed to certain immune-based reactions like increased expression of T-cells, cytokine release, and antimicrobial peptides (AMP) [1]. Some researchers have concluded that hypovitaminosis D may indeed be a biomarker of susceptibility to sepsis [2], a similar conclusion reached by de Haan., *et al.* [3] in their meta-analysis of critically ill patients and vitamin D deficiency.

We conducted a systematic literature review and analyzed some case studies of selected patients from the Infectious Disease department of our ambulatory care practice to study the significance of this association in prognosticating the outcome of infection or sepsis. Three specific infections were chosen for this study, in a five-year window (2020 - 2025): Pneumonia, cellulitis, and urinary tract infection (UTI).

Background

Vitamin D (Cholecalciferol) is one of four fat-soluble vitamins (A, D, E, K) that is synthesized from two precursors, Ergocalciferol (D2) and 7-dihydroxycholecalciferol (D3) through ultraviolet radiation in the skin [4] and also directly from dietary intake [5].

Serum Vitamin D levels are usually measured as the concentration of 25-Hydroxyvitamin D (25(OH)D). Over the years, reference values for normal serum Vitamin D levels have been narrowly defined. However, a very recent extensive retrospective data analysis involving 130,030 subjects at a tertiary hospital in Barcelona, Spain [6], has provided more accurate, population-based reference intervals (RIs) and reliable definitions of normal and abnormal values of this vitamin, which accounted for demographics, seasonal as well as methodological differences. According to this study, normal serum vitamin D levels are 20 ng/mL and above; deficiency levels are ≤ 20 ng/mL or ≤ 50 nmol/L, and severe deficiency is ≤ 12 ng/mL or ≤ 30 nmol/L.

Physiology

The physiological effects of 25 (OH) D are primarily in bone health and calcium metabolism [7]; its deficiency is linked to diseases like Rickets in the pediatric population and osteomalacia in adults, secondary to bone demineralization and defective absorption of calcium and phosphorus.

The metabolism of Vitamin D involves a 2-step biochemical process; the first occurs in the liver, where it is converted to 25 (OH) D and secondarily to 1,25 (OH)2 D in the kidneys [8]. They bind to Vitamin D receptors (VDR) to exert these effects.

Some immunomodulatory and anti-proliferative effects of Vitamin D have also been observed and documented. Through these mechanisms, its deficiency is linked to multiple extra-skeletal disease conditions, such as prediabetes, diabetes mellitus [9], inflammatory bowel disease (IBD), multiple sclerosis [10], Rheumatoid Arthritis, and even Cancers [10,11]. At the molecular level, almost all tissues and cells have a Vitamin D receptor, which makes them more responsive to the active form, 1,25 (OH)2 D, and this is involved in regulating more than 200 genes linked to a wide range of biological processes [12]. The production of antimicrobial peptides like defensin and cathelicidin is enhanced by the active vitamin D [13].

Vitamin D and Pneumonia

For this review, we focused mainly on Community-acquired Pneumonia (CAP), i.e., pneumonia acquired from home, outside of an institution like a hospital, rehabilitation center, or Assisted Living Facility (ALF). The etiological agent could be bacterial, viral, or fungal. Bacterial pneumonia is the fifth most common cause of death globally [14] and accounts for about 2.5 million mortalities each year.

The increase in the expression of genes that code for antimicrobial peptides at sites of infection appears to be the immunological mechanism of the involvement of Vitamin D in the development and outcome of CAP [15].

Serum Vitamin D levels have been studied for their predictive value on the outcome of patients with pneumonia [16,17] and also on how its supplementation could be beneficial in the prevention and/or treatment of pneumonias [18,19]. An inverse relationship between low serum levels of Vitamin D and the risk of developing pneumonia or having worse outcomes from it has been documented [20].

This correlation has also been confirmed even in the pediatric age group [21-23], where it was found that serum Vitamin D levels were significantly lower in children with pneumonia and that levels greater than 75 nmol/L were associated with reduced risk of and lower morbidity from acute pneumonia.

Vitamin D and urinary tract infection (UTI)

Over 400 million people worldwide were diagnosed with UTI in 2019 [24]. In adults, there is a significant female preponderance, with women 30 times more likely to develop a UTI than men [25]. Although this has geographic variations, it still presents an enormous healthcare burden on a global scale [26]. The term includes all infections along the whole urinary tract, including the urethra (Urethritis), the bladder (Cystitis), and the kidneys (Pyelonephritis). This paper focused primarily on acquired rather than nosocomial UTI.

Like in most other inflammatory processes and infections, low serum Vitamin D levels have been observed in patients with UTI [27]. The immunomodulation factors implicated in the association of serum Vitamin D levels and UTIs include the increase in production of cytokines, Tumor Necrosis Factor (TNF)-alpha, and Immunoglobulins (IgM, IgG, IgA) [28].

Vitamin D and cellulitis

Cellulitis is a skin infection involving the deep dermis and subcutaneous tissues that presents with the classical symptoms of swelling, expanding area of redness, increased warmth, and pain [29]. In the United States, an estimated 14.5 million cases are treated annually, with about 650,000 requiring hospital admission [29].

Host immunity status plays a key role in risk stratification for developing the condition, which is why cellulitis is not uncommon in immune-deficient conditions (like HIV, poorly-controlled diabetes, chronic steroid therapy, and malignancies), lymphatic dysfunction, and chronic edema from venous insufficiency [30].

Case Studies

Cross-sectional retrospective case studies for UTI, Pneumonia, and Cellulitis were conducted in our Primary Care Center, correlating them with serum Vitamin D levels, over 5 years from 2020 to 2025. The cases were drawn from multiple specialties, deriving a majority of the patient population from our Infectious Disease Clinic.

A total of 91 patients were included in the study (Pneumonia n = 27, making up 29.6% of the total population studied); (UTI n = 40, making up 43.9% of the total population studied); (Cellulitis n = 23, making up 25.2% of the total study population). There was a female preponderance of 58 (63.7%) to 33 males (36.2%). In the female population, the conditions were 32 UTIs (55.1%), 11 Pneumonias (18.9%), and 15 Cellulitis (25.8%). The male group included 8 UTIs (24.2%), 16 Pneumonias (48.4%), and 9 Cellulitis (27.2%).

Results

As a percentage of their total numbers, UTIs were more common in females at a > 2:1 ratio. A reverse relationship was apparent in the pneumonia group, where a 2.5:1 male preponderance was noted. The percentage of cellulitis was almost similar in both genders.

Group	Total patients	Vit D assessed	Vit D deficient	Not deficient
Pneumonia	27	10	7	3
Cellulitis	23	15	8	7
UTI	40	21	13	8
Total	90	46	28	18

Table: *Data summary for three arm infections in ambulatory care (PMA, Florida).*

In the UTI group, only 21 out of the 40 patients had initial serum vitamin D levels, and of this number, 13 (61.9%) were vitamin-deficient or insufficient, while 8 had normal values.

The pneumonia group had 10 patients out of 27 with serum vitamin D levels. Analysis revealed vitamin D deficiency or insufficiency in 7 (70%) of the 10 patients studied, while 3 were normal.

Serum vitamin D levels were drawn on 15 out of the 23 patients in the cellulitis group, and 8 (53.3%) showed deficiency/insufficiency, while 7 were within the normal range. As raw percentages from the three groups, it is apparent that more patients with pneumonia had vitamin D deficiency (70%) than UTI (61.9%), followed by cellulitis (53.3%).

Conclusion

These findings suggest that vitamin D deficiency may represent a more significant risk factor in the development and clinical outcomes of pneumonia than in cases of UTI or cellulitis. However, when the data was subjected to statistical analysis using the Chi-square with 2 degrees of freedom, the p-value = 0.56. Therefore, based on this sample size, there was no statistically significant difference in the rates for vitamin D deficiency among the three patient groups.

This study demonstrates that, despite published evidence correlating Vitamin D deficiency with various non-skeletal diseases, including the infectious processes analyzed in this study, Vitamin D assays are not being routinely ordered in patients with these conditions or as part of the follow-up to provide some degree of prognosis to their outcomes.

Although in general, a plurality of patients with these conditions had hypovitaminosis D before or during the infectious process, a larger population of study would have provided better statistical significance. Every patient being newly established ought to have a serum vitamin D level drawn to obtain a baseline for future reference, since the clinical importance of this vitamin has increasingly come into view as previous studies have confirmed.

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Volume 8 Issue 9 September 2025