Review Article

Systemic Inflammation and Vitamin D

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Abstract

Systemic inflammation is a fundamental component of many pathological processes, including autoimmune diseases, infections, metabolic disorders, and cardiovascular diseases, and is characterized by excessive and uncontrolled production of pro-inflammatory cytokines. Although vitamin D has traditionally been associated with calcium–phosphorus homeostasis and bone metabolism, the demonstration of vitamin D receptor (VDR) expression in numerous immune cells has led to its recognition as an important hormone involved in the regulation of the immune system and inflammatory responses. Low serum 25-hydroxyvitamin D concentrations have been reported to be associated with increased inflammatory cytokines, acute phase proteins, and systemic inflammatory indices in both humans and animals. In particular, studies in dogs and ruminants indicate that vitamin D deficiency may be linked to infection-related systemic inflammation, coagulation disturbances, and intestinal barrier dysfunction. Moreover, it has been suggested that vitamin D may behave as a negative acute phase protein, with its circulating levels decreasing as the severity of inflammation increases. In this context, vitamin D emerges as a potential biomarker that not only contributes to the pathogenesis of systemic inflammation but may also be useful in the assessment of disease severity and prognosis.

Keywords: Systemic inflammation, Vitamin D, Immune response, Acute phase response

INTRODUCTION

Systemic inflammation is regarded as both a risk factor and a fundamental characteristic of various pathological conditions, including autoimmune diseases, diabetes mellitus, cardiovascular disorders, and neurological diseases (Radzyukevich et al., 2021; Cecoro et al., 2020). It represents a state arising from the chronic and uncontrolled activation of the immune system in response to diverse internal and external stimuli and constitutes the basis of numerous pathophysiological processes. During this process, there is an increased production of pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukins (ILs), cytokines, and chemokines, whose concentrations may rise markedly in both the circulation and tissues (Pedersen et al., 2014). Key signaling pathways, including nuclear factor-kappa B (NF-ϰB), mitogen-activated protein kinase (MAPK), and Janus kinase/signal transducer and activator of transcription (JAK/STAT), play a central role in

the regulation of systemic inflammation (Pedersen et al., 2014). In particular, activation of the NF-κB and MAPK pathways via Toll-like receptors enhances the release of TNF-α, IL-6, and IL-12 from macrophages, thereby sustaining the inflammatory response (Coşkun et al., 2011). Moreover, cytokine-mediated activation of the JAK/STAT pathway leads to the translocation of STAT proteins into the nucleus, altering target gene expression and maintaining the pro-inflammatory response (Coşkun et al., 2013). Through these mechanisms, systemic inflammation exerts widespread effects on immune and metabolic homeostasis.

Vitamin D, whose active form is calcitriol (1,25-dihydroxycholecalciferol), is defined as an important hormone that regulates multiple biological processes in addition to calcium and phosphate metabolism (Mungai et al., 2021; Min et al., 2021). Although its primary sources are sunlight exposure and dietary intake, low vitamin D levels are frequently reported in patients (Mungai et al., 2021). In cats and, to a lesser extent, dogs, dermal concentrations of 7-dehydrocholesterol are too low to permit adequate vitamin D synthesis via UVB exposure; therefore, these species rely more heavily on a carnivorous diet rich in vitamin D from blood and fat, phosphorus from meat, and calcium from bones (Bouillon & Suda, 2014). Parathyroid hormone (PTH) plays a major role in calcium homeostasis in terrestrial vertebrates by increasing blood calcium concentrations through stimulation of osteoclastic bone resorption (Bouillon & Suda, 2014; Hardcastle & Dittmer, 2015). In addition, PTH strongly induces renal synthesis of $1,25(OH)_2D_3$, the hormonally active metabolite of vitamin D, which in turn enhances intestinal calcium absorption (Bouillon & Suda, 2014; Hardcastle & Dittmer, 2015).

Vitamin D deficiency is commonly associated with low-grade systemic inflammation, a condition that may be alleviated by vitamin D supplementation (Ao et al., 2021; Shah et al., 2021). Numerous studies have demonstrated that vitamin D modulates immune responses and exerts anti-inflammatory effects (Min et al., 2021; Ao et al., 2021). Granulocytes, dendritic cells, monocytes/macrophages, and lymphocytes play critical roles in immune regulation, inflammatory responses, and bone remodeling. As early as the 1980s, Abe et al. reported that vitamin D induces the differentiation of monocytes and macrophages (Abe et al., 1981). In a study conducted in calves with pneumonia, evaluation of the relationship between vitamin D levels and parameters related to coagulation and inflammation demonstrated that vitamin D influences inflammatory processes and the accompanying coagulation response; notably, changes in the D-dimer/fibrinogen ratio suggested that vitamin D levels may reflect the biochemical manifestations of disease-associated inflammation (Manulboga et al., 2024). Furthermore, dendritic cells, monocytes/macrophages, and T and B lymphocytes have been shown to express vitamin D as well as 1α-hydroxylase (CYP27B1), the enzyme responsible for vitamin D activation (Hart et al., 2011). In another study, the immunomodulatory effects of vitamin D were evaluated through humoral immune responses following vaccination, and puppies receiving vitamin D supplementation exhibited significantly higher antibody titers against canine parvovirus after the first booster dose, indicating that vitamin D may enhance adaptive immune responses and support vaccine-induced immunity (Saridag et al., 2023).

Vitamin D Metabolism

Vitamin D metabolism in animals has been recognized for nearly a century due to its fundamental role in skeletal health. Classical studies demonstrated that cod liver oil prevented rickets in dogs and that this effect was attributable to vitamin D (Mellanby, 1976; Elder & Bishop, 2014). Unlike humans, cattle, and sheep, dogs and cats are unable to synthesize vitamin D in the skin and therefore must meet their vitamin D requirements primarily through dietary intake (How et al., 1995; Hurst et al., 2020b). Vitamin D exists in two forms, D_2 (ergocalciferol) and D_3 (cholecalciferol), and the majority of commercial pet foods are supplemented with vitamin D_3 (Parker et al., 2017b).

Following intestinal absorption, vitamin D_2 and D_3 enter the circulation and bind predominantly to vitamin D-binding protein (VDBP) and, to a lesser extent, to albumin; less than 1% of circulating vitamin D is present in the free form and directly available for cellular uptake (Herrmann et al., 2017; Bikle et al., 2017; Schwartz et al., 2018). Vitamin D_2/D_3 are biologically inactive prohormones that undergo sequential hydroxylation steps mediated by cytochrome P450 (CYP) enzymes (Jones et al., 2014). The first hydroxylation occurs in the liver at the C25 position, producing 25-hydroxyvitamin D [25(OH)D] (calcifediol), a reaction catalyzed mainly by CYP2R1 and, to a lesser extent, by CYP27A1 (Zhu et al., 2013). Subsequently, in the proximal tubules of the kidney, C1α-hydroxylation yields the hormonally active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (calcitriol), a step mediated by CYP27B1 (Zehnder et al., 1999). The expression of CYP27B1 in extra-renal tissues has contributed to the recognition of the extra-skeletal biological roles of vitamin D (Adams & Hewison, 2012).

Regulation of active vitamin D metabolism is tightly controlled by parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23), and negative feedback mechanisms. While $1,25(OH)_2D$ suppresses CYP27B1, it induces CYP24A1, which is responsible for its own degradation (Murayama et al., 1999; Shimada et al., 2004). C24 hydroxylation via CYP24A1 converts $1,25(OH)_2D$ through multiple steps into calcitroic acid, which is excreted in bile; the same pathway also produces $24,25(OH)_2D_3$, a metabolite that may possess biological activity (Jones et al., 2014; Boyan et al., 2016; Martineau et al., 2018).

Vitamin D metabolites may also undergo C3 epimerization, a process involving a change in the spatial configuration of the hydroxyl group on the A ring, after which the resulting epimers can be further metabolized through classical pathways (Bailey et al., 2013; Tuckey et al., 2019). Ultimately, $1,25(OH)_2D$ binds to the vitamin D receptor (VDR) to exert genomic and non-genomic effects, with its principal function being the maintenance of calcium homeostasis in concert with PTH and calcitonin (Elder & Bishop, 2014; Christakos et al., 2016). These effects include enhancement of intestinal calcium absorption, support of renal calcium reabsorption, and mobilization of calcium from skeletal stores under conditions of hypocalcemia (Christakos et al., 2016).

Systemic Inflammation

Systemic inflammation is a complex pathophysiological process that is most commonly initiated by tissue injury and extends beyond a localized response to affect the entire organism (Muckart & Bhagwanjee, 1997). Direct tissue damage resulting from mechanical or thermal trauma, as well as cellular injury caused by ischemia–reperfusion, leads to the acute release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Muckart & Bhagwanjee, 1997). When tissue injury is severe or widespread, large amounts of cytokines and non-cytokine inflammatory mediators are released into the circulation, triggering a systemic inflammatory response (Wolf et al., 1997; Kelly et al., 1997). The clinical course of this response depends on both the magnitude and duration of inflammation as well as the host's adaptive capacity; if the response becomes dysregulated, early development of multiple organ dysfunction may occur.

Two major sensing systems are involved in the initiation of trauma-associated inflammation at the cellular and molecular levels. Toll-like receptors (TLRs) recognize both pathogen-associated molecular patterns (PAMPs) of microbial origin and damage-associated molecular patterns (DAMPs) released during cellular injury, thereby activating the innate immune response. Endogenous molecules such as heat shock proteins, high mobility group box-1 (HMGB1), histones, and mitochondrial DNA can activate TLRs and induce transcription of inflammation-related genes (Osterloh & Breloer, 2008; Zhang et al., 2010; Fontaine et al., 2016). The second sensing system involves cytoplasmic nucleotide-binding oligomerization domain-like receptors (NLRs), which promote inflammasome activation when cellular integrity is disrupted. Inflammasome assembly results in caspase-1 activation, leading to the generation of biologically active forms of IL-1 and IL-18 and amplification of the pro-inflammatory response (Fontaine et al., 2016; Schroder et al., 2010).

During systemic inflammation, inflammatory and coagulation pathways are closely interconnected. Tissue injury and inflammation activate the coagulation cascade, particularly through the extrinsic pathway via tissue factor, resulting in increased thrombin generation. Beyond its role in clot formation, thrombin and the tissue factor–VIIa complex also enhance the production of pro-inflammatory cytokines such as TNF-α, thereby intensifying the inflammatory response (Pawlinkski et al., 2003; Lippi et al., 2010). Conversely, regulatory mechanisms including antithrombin, the protein C system, and tissue factor pathway inhibitor (TFPI) limit uncontrolled coagulation activation and exert anti-inflammatory effects (Messori et al., 2002; Shorr et al., 2006; Bernard et al., 2001).

Another hallmark of systemic inflammation is increased microvascular permeability. Enhanced vascular permeability leads to extravasation of protein-rich fluid, intravascular volume depletion, and interstitial edema. In the absence of timely and adequate fluid resuscitation, this condition may progress to hypovolemia, hypotension, and impaired tissue perfusion (Demling, 2005; Nakazawa et al., 1993). Endothelial cells function not only as targets of inflammation but also as active regulators by expressing adhesion molecules such as E-selectin and releasing pro-inflammatory cytokines, thereby facilitating leukocyte adhesion and migration (Oliver, 1992).

In a study conducted on dogs with diarrhea, intestinal inflammation was associated with disruption of the intestinal barrier, as evidenced by significantly increased serum zonulin and lactate levels related to metabolic stress; these biomarkers were suggested to be useful indicators of inflammation severity and intestinal damage (Şen et al., 2025). Similarly, in animals

with distemper, plasma zonulin levels were significantly elevated compared to healthy controls, particularly in cases with neurological signs, suggesting increased blood–brain barrier permeability associated with systemic inflammation (Çöllü et al., 2024). Collectively, these mechanisms indicate that systemic inflammation represents a multilayered, dynamic, and potentially destructive biological response.

Inflammatory biomarkers have gained importance in monitoring various diseases due to their potential to predict disease severity and treatment outcomes, particularly following systemic inflammatory response syndrome (SIRS) (Rejec et al., 2017; Pierini et al., 2019). Several novel inflammatory indices have been described, including the systemic inflammatory response index (SIRI), aggregate index of systemic inflammation (AISI), and systemic immune-inflammation index (SII), which are based on well-established inflammatory components such as neutrophils, monocytes, lymphocytes, and platelets (Hamad et al., 2019; Pierini et al., 2019). In dogs with monocytic ehrlichiosis, the presence of SIRS was associated with significant increases in SIRI and SII, supporting the utility of these indices in monitoring systemic inflammatory responses (Erdoğan et al., 2025).

Systemic Inflammation and Vitamin D

Although vitamin D is classically associated with calcium homeostasis and bone metabolism, the expression of vitamin D receptors (VDR) on numerous immune cells has revealed its important role in the regulation of inflammation and immune responses (Christakos et al., 2003). A negative association between serum 25-hydroxyvitamin D [25(OH)D] levels and inflammatory markers has been reported, with elevated circulating pro-inflammatory cytokines and acute phase proteins being linked to low vitamin D concentrations in conditions such as obesity, inflammatory polyarthritis, diabetes mellitus, autoimmune diseases, inflammatory bowel disease, and HIV infection (Codoner-Franch et al., 2012; Bellia et al., 2013; Patel et al., 2007; Shih et al., 2014). Even in apparently healthy individuals, vitamin D deficiency has been associated with increased inflammatory markers (De Vita et al., 2014; Peterson et al., 2008).

Mechanistically, vitamin D exerts immunomodulatory effects through VDR-mediated actions on macrophages, dendritic cells, and T and B lymphocytes, promoting immune tolerance by increasing regulatory T cells, suppressing pro-inflammatory cytokine production, and enhancing anti-inflammatory cytokine synthesis (Prieti et al., 2013; Martineau et al., 2007). In addition, vitamin D strengthens innate immunity by stimulating the production of antimicrobial peptides such as cathelicidin (Martineau et al., 2007; Korf et al., 2012).

In dogs, decreased serum 25(OH)D concentrations have been reported in various inflammatory conditions including congestive heart failure, protein-losing enteropathy, and renal disease (Kraus et al., 2014; Gow et al., 2011; Gerber et al., 2003). In a study evaluating neonatal calf diarrhea, reduced vitamin D levels were accompanied by increased fibrinogen and platelet-to-lymphocyte ratio (PLR), indicating a close association between vitamin D insufficiency, dysregulation of immune responses, and exacerbation of systemic inflammation (Özalp et al., 2025). Similarly, another study on calf diarrhea demonstrated a marked inverse relationship between elevated fibrinogen concentrations and decreased 25(OH)D_3 levels, suggesting that vitamin D may behave as a negative acute phase reactant and that declining vitamin D levels may reflect the presence and severity of systemic inflammation (Özalp & Erdoğan, 2019).

While some studies have reported a negative correlation between vitamin D and C-reactive protein (CRP) levels (Selting et al., 2014), others have observed a positive association in specific populations, underscoring the complex nature of this relationship and highlighting the need for further investigation, particularly in dogs with chronic enteropathy (Spoo et al., 2015; Day et al., 2008). In goat kids with diarrhea caused by Giardia duodenalis, significantly reduced serum 25-hydroxyvitamin D_3 levels were observed compared to healthy controls, likely as a result of inflammation-related intestinal damage and malabsorption, further supporting the link between vitamin D deficiency and inflammatory processes accompanying giardiasis (Erdoğan et al., 2020).

Conclusion

The available evidence indicates that vitamin D is not limited to its role in mineral metabolism but also functions as an important immunomodulator involved in the regulation of systemic inflammation. The association between reduced vitamin D levels and increased cytokine responses and acute phase proteins in inflammatory diseases suggests that vitamin D may be considered a negative acute phase reactant. In veterinary medicine, further elucidation of the relationship between vitamin D and inflammation across different species and disease conditions may contribute to improved diagnostic and prognostic approaches.

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