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ORIGINAL ARTICLE

Serum vitamin D3 (25-OH vit D3) concentrations and hemogram changes in calves with enzootic pneumonia

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Abstract

Background: Enzootic pneumonia is an important disease complex associated with insufficient colostrum intake after birth, adverse environmental conditions, and stress. Vitamin D deficiency may be an important predisposing factor for this disease.

Objective: This study aimed to investigate in calves with enzootic pneumonia.

Methods: A total of 30 calves, aged 3–5 months, under the same care and feeding conditions were used. Groups were formed according to Clinical Respiratory Scoring as the group with mild/moderate enzootic pneumonia ($n = 10$), the group with severe enzootic pneumonia ($n = 10$), and the healthy control group ($n = 10$) without any disease. Blood samples were collected from the jugular vein of animals in all groups on Day 0; a complete blood count was performed, and serum vitamin D levels were measured using the Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS) method.

Results: Although no statistical differences were observed in total leukocyte, lymphocyte, eosinophil, basophil, hemoglobin, and hematocrit levels between groups, statistically significant differences in blood neutrophil, monocyte, and erythrocyte counts were found between the groups. Monocyte counts were statistically decreased in the mild/moderate group compared with the control group. Neutrophil counts were significantly higher in the mild/moderate and severe groups than in the control group. Erythrocyte counts were increased in the mild/moderate and severe groups compared with the control group. Vitamin D concentrations were statistically lower in the mild/moderate and severe groups than in the control group. However, no statistical differences in Vitamin D concentrations were observed between the mild/moderate and severe groups. There was a negative and significant correlation between erythrocyte counts and vitamin D concentrations ($r = -0.64$, $P < .0001$). While erythrocyte counts increased in the severe group compared with the mild/moderate group, vitamin D concentrations decreased. Also, a negative and significant correlation was observed between platelet counts and vitamin D concentrations ($r = -0.74$, $P < .0001$).

Conclusions: The results of this study determined that serum vitamin D concentrations in calves with pneumonia were lower than those in healthy calves. Detailed studies on the etiologic and prognostic importance of low vitamin D levels in calves with enzootic pneumonia may provide valuable data for prevention and treatment.

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KEYWORDS
bovine, BRD, cattle, cholecalciferol, complete blood count, correlation analysis

1 | INTRODUCTION

Enzootic pneumonia is an important disease complex seen in calves aged 2–6 months, with high morbidity and mortality worldwide.[1,2] Enzootic pneumonia has a complex etiology, having both infectious and noninfectious etiologies. In addition, physical and environmental predisposing factors such as insufficient levels of active and passive immunity, as well as causes of stress, such as inadequate care and feeding, dusty weather, temperature changes, and overcrowding, have a role in pneumonia. In addition to these physical and environmental factors, various bacteria, viruses, and other infectious agents are found alone or together in the etiology of this disease.[2]

The diagnosis of enzootic pneumonia is based on clinical findings seen most often in 2-to 6-month-old calves[2–4]; manifestations include cough, breathing difficulties, varying degrees of fever, and nasal discharge, which are sufficient for clinical diagnosis. Deep nasal swabs and swabs of ocular discharge are recommended for the detection of viral pathogens, whereas transtracheal aspiration and bronchoalveolar lavages are recommended for the detection of bacterial and mycoplasma pathogens. Also, blood hemograms and serum biochemical data are usually evaluated with clinical findings in patients with pneumonia.[2] Depending on viral or bacterial factors, leukocytosis can be seen, including neutrophilia with left shift and a monocytosis. Eosinopenia and increased blood sedimentation rates can also be detected.[3] And, if enzootic pneumonia is not controlled, complications may occur due to multi-organ failure and increased mortality.[4]

Vitamin D, which is involved in the mineralization of the skeletal system in animals, is a fat-soluble steroid vitamin.[5] It is important in bone development, immune system regulation, cellular proliferation and differentiation, neurologic and cardiovascular systems, and prevention of infectious diseases.[6] The 25 (OH) vitamin D receptors have been identified in all immune system cells, especially in antigen-presenting cells such as T and B lymphocytes, macrophages, and dendritic cells.[7] Vitamin D has been reported to increase antimicrobial power and the expression of peptides (such as defensins and cathelicidins), which have direct antimicrobial effects against enveloped/non-enveloped viruses, thereby regulating innate immunity.[8] Also, studies reveal that vitamin D reduces the synthesis of proinflammatory cytokines (such as IL2, IL-6, and IFN-γ) by suppressing T helper 1 (Th1) cell function and increases the release of anti-inflammatory cytokines (such as IL4 and IL10) by stimulating T helper 2 (Th2) cells, and thus plays a role in the regulation of the acquired immune response.[9] In recent years, studies on lung diseases, especially COVID-19, have reported low vitamin D concentrations in patients with clinical symptoms.[10,11] A study by Charoenngam et al[12] on COVID-19 patients predicted that vitamin D could prevent cytokine storm and multi-organ failure in humans. Another study on enzootic pneumonia stated that vitamin D decreased due to the disease and its severity, and therefore, vitamin D supplementation is important in the treatment and prevention of infection.[4]

This study determined serum vitamin D concentrations in healthy calves and calves with enzootic pneumonia in the same age groups and environmental and care-feeding conditions. We also aimed to determine the relationship between serum vitamin D status and the severity of enzootic pneumonia.

2 | MATERIALS AND METHODS

2.1 | Animals

All experimental procedures were approved by the Bursa Uludağ University Ethics Committee (2020–10/05). The study was conducted at the Experimental Farm of the University (40° 13′ 8.0364″ N; 28° 52′ 12.0036″ E) between November and March.

The study animals consisted of a total of 30 Holstein calves, aged 3–5 months, under the same management and feeding conditions. The number of animals used in the study was determined based on previous studies.[13,14] All calves were group-housed in individual hutches outdoors during the study period and had ad libitum access to calf starter (Emek Feed Company, Turkey) and water. The starter ingredients were 17% crude protein, 10%–12% crude fiber, 10% crude ash, 0.25% sodium, 2%–3.50% crude fat, 15 000 U/kg vitamin A, 3000 U/kg vitamin D, and 30 mg/kg vitamin E. Calves were fed 3L of pasteurized milk twice a day for 60 days until weaning.

2.2 | Clinical Respiratory Scoring

The Wisconsin respiratory scoring system was used, according to McGuirk.[15] The calves were divided into three groups using a Scoring method, and Clinical Respiratory Scoring evaluations were performed by an operator (a veterinarian). Nasal and ocular discharge, position of ear and eye, presence of a cough/response to a tracheal pinch, and rectal temperature were all scored on a scale from 0 to 3, with 0 being normal and 3 being severely abnormal. The calves with a total score of ≤3 encompassed the control (healthy; $n = 10$) group; those with a total score of 4 encompassed the group with mild/moderate enzootic pneumonia ($n = 10$), and those with a total score of ≥5 encompassed the group with severe enzootic pneumonia ($n = 10$).

2.3 | Blood sample analyses

The farm visits were performed between November and March. At each visit, calves were examined according to Clinical Respiratory

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Scoring and symptoms, and blood samples were obtained from the vena jugularis in all groups into tubes with anticoagulant for complete blood counts and tubes without anticoagulant for vitamin D measurements. Complete blood counts (total leukocyte counts; lymphocyte, monocyte, neutrophil, eosinophil, basophil, erythrocyte counts; and hemoglobin, hematocrit, and thrombocyte counts) from blood samples taken were performed using an automatic blood count device (VH3, Hasvet, Turkey) within 2 h after sample collection.

The samples taken for vitamin D evaluation were centrifuged at 1008 *g* for 15 min, then serum was separated and immediately evaluated in an accredited laboratory according to the Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS) working principle using Mass Spectrometer (VidasPC, bioMérieux, France). The assay principle combines an enzyme immunoassay competition method with a final fluorescent detection (ELFA). All of the assay steps were performed automatically by the instrument. The reaction medium was cycled in and out of the Solid Phase Receptacle (SPR) several times. The sample was mixed with a pretreatment reagent to separate vitamin D from the binding protein. The conjugate enzyme catalyzed the hydrolysis of this substrate into a fluorescent product (4-methylumbelliferone) and was measured at 450 nm. The fluorescence intensity was inversely proportional to the concentration of vitamin D antigen present in the sample. At the end of the assay, results were automatically calculated by the instrument in relation to the calibration curve stored in memory and then printed out.

2.4 | Statistical analyses

Statistical analyses were performed with SPSS (Version 20.0; Chicago, IL). Data were examined for normality distribution and variance homogeneity assumptions (Shapiro–Wilk test). If normally distributed, a one-way ANOVA test was applied, and the differences between groups were analyzed with the post hoc Tukey's test. The differences were considered significant at $P < .05$, and the means and standard errors were calculated. Nonparametric tests were used as the data did not provide normal assumptions. Therefore, the differences between the groups were analyzed with the Kruskal–Wallis and Mann–Whitney U tests. Additionally, the differences were considered significant at $P < .05$, and the median values (minimum-maximum) were calculated. The correlation coefficients and their significance were calculated using Spearman's test. The erythrocyte counts and vitamin D concentrations were used in the correlation analyses.

3 | RESULTS

In the study, according to Clinical Respiratory Scoring, rectal temperature (38.3–38.6°C), heart rate, and respiratory rate were normal in the control group. The general condition and appetite of the control animals were good, and depression and dyspnea were not observed. Also, no nasal or ocular discharge was observed, and lung auscultations were normal. In the mild/moderate group, no significant depression was observed. However, there were varying rectal temperatures (38.3–39.8°C), a slight increase in heart and respiratory rates, good appetites, and a lack of dyspnea. There was also a dry cough and serous-seromucinous ocular discharge, and varying degrees of wet rales were clearly audible on auscultation. In the severe group, heart rates, respiratory rates, body temperatures (38.6–40°C), and cough rates were increased in all animals. There was also purulent-mucopurulent nasal and ocular discharge and dyspnea, which were not seen in the other groups. Appetite and depression, and friction, rales, and crackling sounds on lung auscultation were found on clinical exam.

The hemogram variables observed in the study are shown in Table 1. The total leukocyte counts in calves of the severe group ($13.27 \pm 1.09 \times 10^9$/L) were increased compared with the control ($10.63 \pm 0.43 \times 10^9$/L) and mild/moderate groups ($11.12 \pm 0.83 \times 10^9$/L), although the increase was not significant. However, neutrophil counts were significantly increased in the

TABLE 1 Complete blood count and vitamin D findings of all groups (Mean ± S.D).

	Groups		
Variables	**Control ($n = 10$)**	**Mild/moderate ($n = 10$)**	**Severe ($n = 10$)**
Total leukocytes (10^9/L)	10.63 ± 0.43	11.12 ± 0.83	13.27 ± 1.09
Lymphocyte (10^9/L)	6.74 ± 0.42	6.94 ± 0.42	5.98 ± 0.46
Monocyte (10^9/L)	1.01 ± 0.12^{a}	0.49 ± 0.17^{b}	1.20 ± 0.08^{a}
Neutrophil (10^9/L)	2.93 ± 0.30^{a}	3.68 ± 0.62^{ba}	6.08 ± 0.87^{b}
Eosinophil (10^9/L)	0	0	0
Basophil (10^9/L)	0	0	0
Erythrocyte (10^{12}/L)	9.07 ± 0.29^{b}	10.93 ± 0.33^{c}	12.05 ± 0.35^{a}
Hemoglobin (g/dL)	11.29 ± 0.23	10.33 ± 0.28	10.96 ± 0.31
Hematocrit (%)	29.97 ± 1.05	29.26 ± 0.71	30.76 ± 0.70
Platelets (10^9/L)	269.90 ± 20.10	408.40 ± 30.74	451.10 ± 21.73

Statistical difference was determined between the letters on the same line ($P < .05$) and the values indicated. (a, b; $P < .05$).

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severe group ($6.08 \pm 0.87 \times 10^9$/L) compared with the control group ($2.93 \pm 0.30 \times 10^9$/L; $P < .05$). Monocyte counts ($0.49 \pm 0.17 \times 10^9$/L) were statistically lower in the mild/moderate group than in the control group ($1.01 \pm 0.12 \times 10^9$/L; $P < .05$) and the severe group ($1.20 \pm 0.08 \times 10^9$/L; $P < .05$). No statistical differences were found in lymphocyte, eosinophil, and basophil counts among the groups.

Erythrocyte counts were significantly higher in the mild/moderate ($10.93 \pm 0.33 \times 10^{12}$/L) and severe ($12.05 \pm 0.35 \times 10^{12}$/L) than in the control group ($9.07 \pm 0.29 \times 10^{12}$/L; $P < .05$) and were significantly higher in the severe group ($12.05 \pm 0.35 \times 10^{12}$/L) than in the mild/moderate group ($P < .05$).

Serum vitamin D concentrations are shown in Figure 1. Vitamin D concentrations in the calves of the mild/moderate (25.50 ± 1.23 ng/mL) and severe (20.80 ± 1.71 ng/mL) groups were significantly lower than those of the control group (43.50 ± 2.33 ng/mL) ($P < .05$). Vitamin D concentrations were also lower in the severe group than in the mild/moderate group, although this finding was not significant.

As for correlation studies, we found a negative and significant correlation between erythrocyte counts and vitamin D concentrations ($r = -0.64$, $P < .0001$). While erythrocyte counts increased in the severe group compared with the mild/moderate group, vitamin D concentrations decreased. A negative and significant correlation was also found between platelet counts and vitamin D concentrations ($r = -0.74$, $P < .0001$).

4 | DISCUSSION

Respiratory diseases are one of the most critical problems in cattle breeding that can cause serious yield losses and deaths. Studies have stated that besides bacterial and viral factors, hygienic conditions, environmental changes, age, and stress factors also play a role in the emergence of enzootic pneumonia, which has no specific etiology. Variable degrees of cough, increased body temperature, dyspnea, various pathologic lung sounds, and nasal discharge are generally sufficient for diagnosing enzootic pneumonia in 2-to 6-month-old calves.[2] In this study, we measured vitamin D concentrations in calves diagnosed with mild/moderate and severe enzootic pneumonia based on clinical findings and compared these findings with those of healthy animals, as well as between the severity of disease.

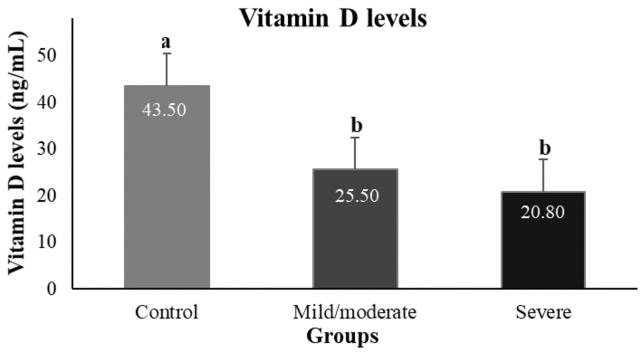


FIGURE 1 Vitamin D levels of all groups. Groups: Control, Mild/moderate, Severe. Statistical difference was determined between the letters (a, b; $P < .05$).

Vitamin D levels tend to decrease in winter, although these levels vary according to the seasons. Some studies reported lower serum 25(OH) vitamin D levels in winter months, suggesting that low Vitamin D levels could be important factors in respiratory diseases since these diseases are more common in the winter months.[7,16] Therefore, vitamin D concentrations should be measured in the same season to ensure accurate diagnoses. Enzootic pneumonia was diagnosed during the autumn months in the current study.

Epidemiologic studies have recently suggested that vitamin D and respiratory diseases may be related to one another, as vitamin D levels have been shown to be especially low in people with respiratory diseases.[17,18] Bartley reported that respiratory tract infections increased in patients with vitamin D deficiency,[17] and Altınel Açoğlu et al stated that vitamin D deficiency is more common in patients with severe respiratory diseases.[18] It has been suggested that the immunomodulatory properties of vitamin D may affect the severity of respiratory diseases in children in pediatric intensive care units.[19] Although there are limited studies in calves, a study conducted in calves with enzootic pneumonia reported that vitamin D concentrations were decreased in diseased animals.[4] What we do know is that vitamin D concentrations are lower in calves from birth until they are 3 months old that serum vitamin D concentrations may not increase despite vitamin supplementation during this early age, and that there is a lack in the development of immunity, making these young animals prone to lung diseases.[13] Accordingly, it has been suggested that serum vitamin D concentrations should be measured in young calves. In this study, we found that serum vitamin concentrations were decreased in the mild/moderate and severe groups compared with the control group; however, there were no differences between the concentrations in the mild/moderate group compared with the severe group. The slightly lower serum vitamin D concentrations in the severe group compared with the mild/moderate group, although not significant, might be due to an increasing vitamin D deficiency with increasing severity of enzootic pneumonia. Serum vitamin D concentrations of the control group agreed with the reference value of 30 ng/mL ≤ for healthy calves.[20] In people with COVID-19 infection, it was shown that vitamin D deficiency increases due to the increasing severity of respiratory disease.[21,22] However, some studies reported that vitamin D concentrations are not related to the severity of pneumonia.[23] Our study did not show a statistical difference between mild/moderate disease and severe disease, but concentrations were lower than those in the control group.

In enzootic pneumonia, hemograms can vary depending on the severity of infection and the primary pathogen and can be used as markers for diagnosis, treatment, and prognosis.[24] In a recent study on calves with enzootic pneumonia, erythrocyte counts were found to be higher in the severe group than in the control and mild/moderate groups and were higher in the mild/moderate group than in the control group.[25] In this same study, the degree of leukocytosis varied in the mild/moderate and severe

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groups, and neutrophil counts were statistically higher in the severe group than in the control group. The neutrophilia in our study was similar to that published in previous bovine respiratory and human COVID-19 studies[24–27] Monocyte counts were increased in the severe group compared with the control group, although these differences were not found to be statistically significant. The significant decrease in monocyte counts in the mild/moderate group compared with the severe and control groups in our study was consistent with the results of a study of infection-induced acute bacterial respiratory tract infection in calves.[25] Also, $CD16^{+}$ monocytes may enter the circulation of the lungs in patients with COVID-19 infection, increasing a cytokine storm and causing inflammation in the lungs.[27] In this context, it can be suggested that the high serum monocyte counts in the severe group might be related to increased cytokine production in calves, exacerbating the infection.

In this study, we found a negative and significant correlation between erythrocyte counts and vitamin D concentrations. Although there are limited studies examining correlations between vitamin D concentrations and complete blood counts, vitamin D deficiency has been associated with structural erythrocyte changes in COVID-19 patients; increased erythrocyte aggregation and decreased deformation in erythrocytes have been reported.[28] However, a study of healthy adult people in Korea found no correlation between erythrocyte counts and vitamin D concentrations.[29] The negative correlations between platelet counts and vitamin D concentrations seen in this study may be associated with the antithrombogenic, anti-inflammatory, antioxidant, and anticoagulant activities of vitamin D.[30] Protein synthesis and thrombocyte synthesis have also been shown to be regulated through the vitamin D receptors located in the mitochondria of platelets. Moreover, megakaryocyte maturation and increased platelet counts have been shown to occur in patients with vitamin D deficiency.[31]

Enzootic pneumonia is an important disease due to immunosuppression in young calves. Evidence shows that serum vitamin D deficiency increases susceptibility to respiratory infections. Thus, demonstrating vitamin D deficiency in young calves with associated enzootic pneumonia is important in terms of diagnosis and susceptibility to infection. Therefore, we believe that determining serum vitamin D concentrations in young calves can contribute to animal health and breeding, with improved economic outcomes.

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CONFLICT OF INTEREST STATEMENT

The authors indicated that they have no affiliations or financial involvement with any organization with a financial interest in, or in financial competition with, the subject matter or materials discussed in this article.

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