RESEARCH PAPER

Relationship between Serum 25-Hydroxyvitamin D Levels and Inflammatory and Oxidative Stress Biomarkers in Cervical Cancer Patients

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ABSTRACT
Background: Cervical cancer remains a major public health concern worldwide. Vitamin D, particularly its circulating metabolite 25-hydroxyvitamin D [25(OH)D], has been associated with the regulation of immune responses, inflammatory mechanisms, and oxidative stress pathways, which play important roles in carcinogenesis.
Objective: This study aimed to evaluate the association between serum 25(OH)D levels and inflammatory as well as oxidative stress markers among patients with cervical cancer.
Methods: A hospital-based case-control study was conducted in the Department of Obstetrics and Gynecology at PES Institute of Medical Sciences and Research. The study included 40 histopathologically confirmed cervical cancer patients and 40 age-matched healthy individuals as controls. Serum concentrations of 25(OH)D, the inflammatory marker interleukin-6 (IL-6), and oxidative stress markers including hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and superoxide anion ($O_2•^-$) were estimated using ELISA and spectrophotometric methods. Statistical analysis was performed using SPSS software, and a p-value <0.05 was considered statistically significant.
Results: Serum 25(OH)D levels were significantly reduced in cervical cancer patients compared with healthy controls ($p<0.05$). In contrast, levels of oxidative stress markers such as H_2O_2, •OH, and $O_2•^-$, along with the inflammatory marker IL-6, were markedly elevated in the cervical cancer group. An inverse relationship was observed between serum 25(OH)D concentrations and both oxidative stress as well as inflammatory markers.
Conclusion: The findings suggest that vitamin D may exert a protective role against cervical cancer through its influence on inflammatory responses and oxidative stress pathways. Further large-scale studies are required to determine the therapeutic and preventive potential of vitamin D supplementation in cervical cancer patients.
Keywords: Vitamin D, Cervical Cancer, Inflammatory markers and Oxidative stress
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INTRODUCTION

Cervical cancer remains a major global public health challenge and is one of the leading causes of cancer-related morbidity and mortality among women. Based on global cancer statistics reported by the World Health Organization and the International Agency for Research on Cancer, an estimated 604,000 new cases and 342,000 deaths due to cervical cancer were recorded worldwide in 2020[9]. Among all cancers affecting women, cervical cancer ranks fourth in terms of incidence[22]. The burden of this disease is especially high in low- and middle-income countries, where access to preventive strategies such as screening programs and vaccination against Human Papillomavirus (HPV) remains limited. Persistent infection with high-risk HPV genotypes, particularly types 16 and 18, is considered the primary etiological factor in the development of cervical cancer[23]. In addition, host-related factors such as oxidative stress, chronic inflammation, immune dysfunction, and nutritional

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deficiencies also contribute significantly to disease progression[4].

Vitamin D is a fat-soluble secosteroid hormone that plays an essential role in calcium homeostasis and immune system regulation. Its biologically active form, 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], exerts its effects by binding to the Vitamin D Receptor (VDR), a nuclear transcription factor involved in regulating genes associated with cell proliferation, differentiation, apoptosis, and immune responses. (Feldman et al.,2014)[8]. Increasing evidence suggests that low levels of serum 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D, are linked to an increased risk of several cancers, including breast, colorectal, and prostate malignancies. Recent findings also indicate a potential role of vitamin D signaling pathways in the development and immune regulation of cervical cancer[2].

Chronic inflammation is now widely recognized as a key factor in cancer initiation and progression. In cervical cancer, persistent HPV infection leads to the overexpression of viral oncogenes E6 and E7, which disrupt tumor suppressor mechanisms and promote malignant transformation. This process contributes to the establishment of a pro-inflammatory tumor microenvironment. Elevated levels of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) have been reported in cervical cancer patients and are associated with tumor progression, angiogenesis, and immune evasion. Vitamin D exhibits anti-inflammatory properties, primarily through inhibition of NF-κB signaling pathways, resulting in decreased production of pro-inflammatory cytokines. Deficiency of vitamin D may therefore enhance inflammatory responses and contribute to the development of cervical lesions and cervical cancer[21].

The current study was undertaken to measure serum 25-hydroxyvitamin D [25(OH)D] concentrations and to analyze their association with inflammatory mediators, especially interleukin-6 (IL-6), among newly diagnosed cervical cancer patients. Evaluating the interaction between vitamin D deficiency and inflammatory responses may improve understanding of cervical cancer progression and may also support the development of preventive and therapeutic strategies.

Oxidative stress results from excessive generation of reactive oxygen species (ROS) beyond the neutralizing ability of antioxidant defense systems. Important ROS involved in this process include hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and superoxide anions ($O_2•^-$). Persistent oxidative stress can induce cellular injury, DNA mutations, genomic instability, and malignant transformation. Previous investigations in cervical cancer have reported elevated lipid peroxidation products such as malondialdehyde (MDA) together with decreased antioxidant enzyme activities, including superoxide dismutase (SOD) and catalase. Vitamin D is believed to possess antioxidant properties by enhancing endogenous antioxidant mechanisms and reducing oxidative damage under various pathological conditions. Experimental findings further indicate that vitamin D supplementation may decrease oxidative stress–related DNA injury and thereby reduce susceptibility to cancer development. However, studies specifically exploring the relationship between vitamin D levels and oxidative stress biomarkers in cervical cancer patients are still limited.

Several reports have demonstrated the involvement of vitamin D in the regulation of inflammatory and oxidative pathways; however, detailed studies correlating vitamin D status with these biochemical parameters in cervical cancer remain insufficient. Since vitamin D is increasingly recognized for its possible anticancer effects, investigating its relationship with inflammatory and oxidative stress markers could provide a better understanding of cervical cancer pathophysiology.

Hence, this study was conducted to estimate serum 25(OH)D levels and determine their association with inflammatory markers, particularly IL-6, and oxidative stress markers such as hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and superoxide anions ($O_2•^-$) in patients with newly diagnosed cervical cancer. Identifying these associations may contribute to the recognition of potential therapeutic targets and reinforce the importance of maintaining adequate vitamin D levels in the prevention and management of cervical cancer.

METHODOLOGY

Study Design and Setting

Examine the design and placement

The present hospital-based observational study was carried out in the Department of Obstetrics and Gynecology, PES Institute of Medical Sciences and Research. The purpose of this study was to assess the relationship between levels of serum 25-hydroxyvitamin D [25(OH)D] and inflammatory markers among cervical cancer patients. The participants of this study were recruited from patients who visited the hospital during the period of research. Before initiating the research ,ethical clearance was approved from the Institutional Ethics Committee. Written consent was taken from all participants before including them in the research.

Study Population and Sample Size

The study contains two groups:

A total of 80 participants were included in the study, which were divided equally into two groups: the case group, comprising 40 newly diagnosed cervical cancer patients, and the control group, consisting of 40 healthy individuals without a history of cancer or chronic inflammatory conditions.

Inclusion and Exclusion Criteria:

Patients were included in the case group if they were diagnosed with cervical cancer, were newly diagnosed, had not undergone previous chemotherapy or radiotherapy, and gave consent for the study. The control group consisted of healthy female volunteers without a

history of cancer, infections, or chronic inflammatory conditions.

Persons with autoimmune diseases, chronic renal or liver disease, endocrine disorders such as diabetes mellitus or thyroid disease, or previous use of vitamin D supplements in the preceding six months were excluded from the study. Patients on immunosuppressive drugs, pregnant, or lactating were also not included in the study.

Obtaining Clinical and Demographic Data
Demographic and lifestyle information were collected from all participants, including age, dietary habits, body mass index (BMI), sun exposure, and lifestyle factors such as smoking and alcohol consumption. In addition, detailed medical histories were obtained. For participants in the case group, clinical information including the stage of cervical cancer was retrieved from hospital medical records.

BIOCHEMICAL ANALYSIS

Blood Sample Collection:
5 mL of venous blood was collected from each participant under sterile conditions. The collected samples were immediately centrifuged for 10 minutes to separate the serum. The serum samples were then stored at −80 °C until further biochemical analysis.

Measurement of Biochemical Parameters:
Serum 25(OH)D levels were quantified using an enzyme-linked immunosorbent assay (ELISA) kit From BIOMERIEUX . Levels of the pro-inflammatory cytokine interleukin-6 (IL-6) were measured using ELISA kits ERBA company. Oxidative stress markers were analyzed using the following biochemical assays: Hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), and superoxide ($O_2^{\bullet-}$): Measured using an enzymatic colorimetric assay.

Statistical Analysis:
All statistical analyses were carried out using SPSS software version 26.0. Continuous data were represented as mean ± standard deviation (SD), whereas categorical data were expressed in percentages. Differences in mean values between the cervical cancer group and healthy controls were evaluated using the independent sample t-test. Pearson's correlation analysis was applied to determine the association between serum 25(OH)D concentrations and inflammatory as well as oxidative stress markers. A p-value less than 0.05 was considered statistically significant.

RESULTS
Table 1 demonstrates that patients with cervical cancer had significantly lower serum 25-hydroxyvitamin D [25(OH)D] levels than the healthy control subjects ($p<0.05$). This finding indicates a possible association between reduced vitamin D status and cervical cancer.

A significant rise in the inflammatory biomarker interleukin-6 (IL-6) was observed among cervical cancer patients in comparison with controls ($p<0.05$), suggesting increased inflammatory activity in the disease condition.

The analysis also revealed markedly elevated oxidative stress parameters in the cervical cancer group. Levels of hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and superoxide anions ($O_2^{\bullet-}$) were significantly higher than those observed in healthy individuals ($p<0.05$). These observations indicate enhanced oxidative stress, which may contribute to the initiation and progression of cervical cancer.

Table 1: Comparison of Serum 25(OH)D, Inflammatory, and Markers of Oxidative Stress Between Controls and Cases

Parameter	Controls (Mean ± SD)	Cases (Mean ± SD)	p-value
Vitamin D (25(OH)D) (ng/mL)	40.5 ±10.9	20.6± 8.6	<0.05*
IL-6 (pg/mL)	2.1 ±0.8	38.2 ±7.1	<0.05*
Hydrogen Peroxide (H_2O_2) (µM)	0.8±0.4	7.0±1.4	<0.05*
Hydroxyl Radical (•OH) (µM)	0.16±0.9	4.8±1.3	<0.05*
Superoxide ($O_2^{\bullet-}$) (µM)	0.10±0.05	2.2±0.57	<0.05*

Note: Values expressed as **Mean ± SD**. *$p<0.05$ indicates statistical significance.

Table 2 demonstrates a negative correlation between serum 25-hydroxyvitamin D [25(OH)D] levels and the inflammatory marker IL-6 ($r = -0.02$, $p<0.05$), indicating that reduced vitamin D levels are associated with increased inflammatory activity.

Similarly, a significant inverse relationship was observed between serum 25(OH)D and oxidative stress biomarkers, including hydrogen peroxide (H_2O_2) ($r = -0.03$, $p<0.05$), hydroxyl radical (•OH) ($r = -0.18$, $p<0.05$), and superoxide anion ($O_2^{\bullet-}$) ($r = -0.10$, $p<0.05$). These findings suggest that lower vitamin D status is linked with higher oxidative stress levels.

Table 2: Correlation Analysis of Serum **25(OH)D with Inflammatory and Oxidative Stress Markers**

Parameter	Correlation Coefficient (r)	p-value	Interpretation
IL-6 (pg/mL)	-0.02	<0.05*	Negative correlation
Hydrogen Peroxide (H_2O_2) (µM)	-0.03	<0.05*	Negative correlation
Hydroxyl Radical (•OH) (µM)	-0.18	<0.05*	Negative correlation
Superoxide ($O_2^{\bullet-}$) (µM)	-0.10	<0.05*	Negative correlation

Note: *$p<0.05$ indicates statistical significance.

DISCUSSION

The present study demonstrates a clear association between serum 25-hydroxyvitamin D [25(OH)D] concentrations and inflammatory activity in individuals diagnosed with cervical cancer. A significant decline in vitamin D levels was observed among patients, while inflammatory cytokines were markedly elevated. This pattern indicates a potential interaction between vitamin D status and inflammatory processes that may contribute to cervical tumor development[1,5].

The role of vitamin D deficiency in cancer has been widely investigated, with multiple studies reporting a negative association between circulating 25(OH)D levels and cancer incidence[7,8]. The findings of this study are consistent with these observations, as reduced vitamin D levels were evident in cervical cancer patients compared to healthy controls. This supports the concept that inadequate vitamin D availability may increase vulnerability to malignancy[9]. In addition, vitamin D is known to influence essential cellular mechanisms, including regulation of cell growth, differentiation, apoptosis, and immune responses, which collectively contribute to its protective role[8].

Vitamin D exerts its biological effects through interaction with the vitamin D receptor (VDR), which is expressed in cervical epithelial tissues. The active metabolite, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], binds to VDR and regulates gene expression involved in controlling cell proliferation and programmed cell death. A deficiency in vitamin D may disrupt these regulatory pathways, thereby facilitating abnormal cell growth and tumor progression[8].

Persistent inflammation is another major contributor to cervical carcinogenesis, particularly in the context of long-standing human papillomavirus (HPV) infection[15,23]. Elevated levels of interleukin-6 (IL-6) observed in this study further support the involvement of inflammatory mediators in disease progression[11].

IL-6 plays a central role in tumor biology by promoting angiogenesis, suppressing immune responses, and facilitating epithelial–mesenchymal transition. Increased IL-6 levels have also been linked with poorer clinical outcomes in cervical cancer patients[23]. Similarly, tumor necrosis factor-alpha (TNF-α) contributes to tumor development by activating NF-κB signaling, which enhances cell survival and inhibits apoptosis[20].

Beyond its classical functions, vitamin D acts as a regulator of immune responses. It can reduce the production of pro-inflammatory cytokines and help maintain immune balance. Evidence suggests that vitamin D suppresses IL-6 and TNF-α expression through inhibition of NF-κB signaling via VDR activation[19]. Therefore, reduced vitamin D levels may lead to an exaggerated inflammatory response, which could promote tumor progression.

Oxidative stress, defined as an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense system, is recognized as an important contributor to HPV-associated cervical carcinogenesis[1]. In the present study, cervical cancer patients showed significantly elevated levels of hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and superoxide anions ($O_2•^-$), indicating increased oxidative burden and disturbed redox homeostasis. These findings suggest enhanced cellular oxidative injury and weakened antioxidant protection in affected individuals.

Previous studies have reported that persistent HPV infection promotes oxidative stress through excessive ROS production, which subsequently leads to DNA damage, chromosomal instability, and malignant transformation[2]. Increased malondialdehyde (MDA) levels observed in cervical cancer patients further support the role of lipid peroxidation in cervical carcinogenesis[3].

Vitamin D has been shown to improve antioxidant defense mechanisms by regulating oxidative stress pathways and reducing ROS-mediated cellular injury[4]. Experimental evidence also indicates that vitamin D can attenuate oxidative stress-induced DNA damage in cervical epithelial cells by modulating ROS levels and enhancing cellular protective responses[5]. Therefore, the observed vitamin D deficiency in cervical cancer patients may further aggravate oxidative stress, thereby contributing to disease progression.

Clinical Implications and Future Directions

The results of this study carry meaningful clinical implications. Considering the high prevalence of vitamin D deficiency among cervical cancer patients, routine assessment of vitamin D status and appropriate supplementation may be considered as a supportive approach in the prevention and management of cervical cancer. Evidence from several clinical studies suggests that vitamin D supplementation may help reduce inflammatory responses, strengthen immune function, and potentially improve overall cancer outcomes.

Future research should aim to clarify the underlying molecular mechanisms through which vitamin D influences inflammatory and oxidative stress pathways in cervical cancer. In addition, large-scale prospective studies are required to determine whether vitamin D supplementation can lead to improved clinical outcomes in patients with cervical cancer.

LIMITATIONS OF THE STUDY

This study has useful clinical relevance; however, certain limitations should be acknowledged. The findings may not be widely generalizable due to the relatively small sample size. In addition, the cross-sectional design restricts the ability to establish a causal relationship between vitamin D deficiency and the development of cervical cancer. Therefore, longitudinal studies with larger populations are needed to confirm these associations and to further investigate the potential therapeutic role of vitamin D supplementation in cervical cancer management.

CONCLUSION

In conclusion, the present study demonstrates a significant relationship between vitamin D deficiency, elevated inflammatory cytokines, and increased oxidative stress in patients with cervical cancer. The results indicate that reduced serum 25(OH)D levels may play a role in cervical carcinogenesis by promoting inflammatory activity and oxidative damage. Considering the immunomodulatory and antioxidant properties of vitamin D, supplementation may represent a potential preventive and adjunct therapeutic approach in the management of cervical cancer. However, further studies are required to elucidate the underlying molecular mechanisms and to evaluate the clinical benefits of vitamin D intervention in cervical cancer patients.

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