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Original Article

Vitamin D Receptor and Role of Vitamin D Supplementation in Advanced Gallbladder Cancer: A Prospective Study from Northern India

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Abstract

Background: The proposed role of Vitamin D Receptor (VDR) in various cancers underscores the importance of vitamin D compounds as a novel therapeutic agent in the prevention of occurrence and progression of cancer. Vitamin D Receptor (VDR) expression in gallbladder cancer (GBC) has not been widely analyzed yet. In the present study, an attempt has been made to study VDR expression and the role of vitamin D supplementation during palliative chemotherapy in advanced GBC.

Methods: Expression of VDR was analyzed in benign cholecystectomy specimens (n=11), and GBC specimens (n=32). Thirty patients with advanced GBC were subjected to palliative chemotherapy. Out of them, 19 patients were supplemented with Vitamin D and 11 patients were not. Effect of vitamin D supplementation on the change in vitamin D scores and improvement in quality of life (QOL) were assessed by EORTC QLQ C30 version 3.0. and the difference in outcome between the two groups were studied.

Results: Mean intensity, staining and immunoreactivity scores signifying VDR expression were decreased in the studied population of GBC when compared to benign disease. In palliative setting, vitamin D supplementation significantly improved the quality of life. However, the effect on disease-specific survival, although present, was not statistically significant.

Conclusion: VDR expression downregulation is associated with increasing malignant process. Vitamin D may act as sensitizers for tumor cell death besides downplaying potential harmful effects of palliative chemotherapy thus reducing the associated morbidity. This study assumes importance as the first clinical study reporting VDR expression in GBC tissue and the possible role of vitamin D supplementation in patients with advanced disease.

Keywords: calcitriol receptor, gallbladder neoplasms, vitamin D supplementation, quality of life

Introduction

Gallbladder cancer (GBC) is the most common cause of malignant obstructive jaundice in the Indo—Gangetic region. Most of these patients in the Indian subcontinent belong to low socioeconomic statuses and a majority of them present in inoperable states. [¹] The precise etiology of GBC is still unknown. However, suspected incriminating factors include chronic inflammation, diet and environmental exposure to carcinogens. [¹,²] Epidemiologic studies have linked vitamin D deficiency as a possible causative factors in many human cancers. [³] The effects of vitamin D in a human body are mediated through the vitamin D receptor (VDR). [⁴] Besides calcium homeostasis, the molecules’ other actions include promoting cell differentiation, decreasing cancer cell growth and stimulating apoptosis in normal tissues. [⁴]

While present in almost all normal tissues of the body, its presence has also been confirmed in various malignancies such as breast, prostate, colon, skin and oral cavity. [⁵—¹⁰] There have been anecdotal reports of VDR expression in hepatobiliary malignancies like hepatic, pancreatic cancer and cholangiocarcinomas. [¹¹—¹³] Combining all clinical and laboratory research studies so far, the proposed role

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of VDR in various cancers underscores the importance of vitamin D compounds in the prevention of occurrence and progression of cancer as a novel therapeutic target.\[^7,14\]

In the present study an attempt has been made to study VDR expression and the role of vitamin D supplementation during palliative chemotherapy in advanced GBC.

**Materials and methods**

This prospective longitudinal interventional study was performed in the Department of Surgery, King George’s Medical University, Lucknow, India in collaboration with the Department of Pathology, RML Institute of Medical Sciences, Lucknow, India from April 2012 to October 2013 after approval from the institutional ethics committee no. IEC/2613/R–6.

Eleven (11) apparently normal, consenting patients of chronic cholecystitis, who underwent cholecystectomy at the hospital, were recruited in the benign control arm of the study.

GBC patients were chosen according to the following-

**Inclusion Criteria:**
1. Age >20 years, <70 years
2. Patients of histopathologically– proven GBC
3. Patients giving informed, written consent

**Exclusion Criteria:**
1. Patients not giving consent
2. Patients of chronic renal disease, metabolic bone disease
3. History of chemotherapy or radiotherapy in the past
4. Pregnant or lactating women

Tissue samples from GBC patients included histopathologically proven cases of GBC comprising of extended cholecystectomy specimens (n=2) or USG–guided core biopsies in inoperable/unresectable patients (n=30).

The following method was employed for VDR estimation in tissue of benign and malignant gall bladder tissue.

**Technique of Vitamin D receptor expression estimation**

Paraffin–fixed specimens were incubated overnight at 60 degree Celsius, dewaxed in xylene, rehydrated in alcohol and subjected to antigen retrieval. The slides were incubated with a respective primary antibody (mouse monoclonal in 1:200 dilution Abcam, USA) for an hour and then treated with a secondary antibody (Dakopatts, Germany). The sections were incubated with DAB (3,3’–Diaminobenzidine tetra– hydrochloride), the most commonly used chromogen for immunohistochemistry (brown) and counterstained with hematoxylin (blue). The slides are finally mounted with DPX (Distyrene Plasticizer Xylene).

**Determination of Immunoreactivity Remmelle Score (IRS)**

Under light microscopy, a minimum of 500 malignant cells was counted. Brown–stained cells, suggestive of VDR staining, were recorded as follows: Score 0 for nil, score 1 for 1–10%, score 2 for 11–50%, score 3 for 51–80%.

For intensity, scores 1, 2 and 3 were given for weak, moderate and strong staining, The Immunoreactivity score (IRS) was assigned according to work of Remmelle and Stegner (1987).\[^15\] The assessment of the degree of staining and distribution patterns of specific immunohistochemical staining were evaluated using a semi–quantitative assay as semi–quantitative rather than qualitative expression of hormone receptors is a better representative of their predictive and prognostic capabilities.\[^16\]

The IRS was calculated as the by–product of the staining score and intensity score. Slides were considered negative when the immunoreactivity score (IRS), [score1 x score 2] was 0–1, moderately positive when IRS was 2–4, or highly positive when IRS was 6–12.

**Vitamin D supplementation with palliative chemotherapy**

Inoperable/unresectable GBC patients (n=30) were further assigned to two groups to treat either with vitamin D supplementation (1000 IU twice a day) (n=19) or without the supplementation (n=11) along with palliative chemotherapy (6 cycles of Gemcitabine 1000mg/m2 on day 1 and 8 with Cisplatin 25mg/m2 on day 1; 3 weekly regimen).

To objectivize the change in serum vitamin D levels, they were graded and divided into following groups:

<table>
<thead>
<tr>
<th>Vitamin D status</th>
<th>Serum Vitamin D (25 OH D) ng/ml</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very severe Vitamin D deficiency</td>
<td>&lt;5</td>
<td>−4</td>
</tr>
<tr>
<td>Severe Vitamin D deficiency</td>
<td>5–10</td>
<td>−3</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
<td>10–20</td>
<td>−2</td>
</tr>
<tr>
<td>Suboptimal level</td>
<td>20–30</td>
<td>−1</td>
</tr>
<tr>
<td>Optimal level</td>
<td>30–70</td>
<td>0</td>
</tr>
<tr>
<td>Over dose</td>
<td>70–150</td>
<td>+1</td>
</tr>
<tr>
<td>Vitamin D intoxication</td>
<td>&gt;150</td>
<td>+2</td>
</tr>
</tbody>
</table>
Similar supplementation was done in patients of benign gall bladder disease (n=11) to document the improvement in quality of life with vitamin D.

**Tumor Response and Quality of life assessment**

During the 6 months follow-up, only 15 survived in the supplemented group and 9 survived in non-supplemented group. The two groups were compared for tumor growth response on ultrasonography (assessed by RECIST criteria), change in vitamin D scores and improvement in quality of life (QOL) assessed by EORTC QLQ c30 version 3.0. [17] EORTC SF36 version 3.0 was sub-grouped into 2 domains for analysis: Domain 1 consisted of all questions from Q.1 to 28 (all included questions denote score 1 for no problem at all and 4 for very much). Domain 2 comprised of Q.29 and Q.30 demonstrating overall health and quality of life respectively (score 1 for very poor and 7 for excellent). QOL was assessed at the start of chemotherapy and at the end of 6 months.

**Statistical Analysis**

Data were summarized as Mean ± SD. Two independent groups were compared by independent Student’s test. Two independent groups were also compared by nonparametric Mann–Whitney U test. Groups were also compared by nonparametric Kruskal–Wallis (H) analysis of variance (ANOVA) by ranks and the significance between the groups was done by Z test. Two dependent groups were compared by Wilcoxon (W) matched pairs test. Discrete (categorical) groups were compared by chi–square (χ2) test. A two–sided (α=2) p<0.05 was considered statistically significant. All analyses were performed with SPSS software (version 23.0 for MAC).

**Results**

The baseline demographic, anthropometric, performance statuses and serum vitamin D levels of malignant and benign groups were matched and found to be similar. They are summarized in Table 1. The IHC profile (intensity, staining and IRS) is summarized in Table 2. The mean intensity and IRS scores did not differ statistically between malignant or benign groups. However, in isolation, the mean staining was significantly decreased (59.3%) in carcinoma specimens as compared to benign disease. (p=0.03) While the majority of GBC patients showed very low VDR expression (n=21), one third of the population had moderate or high VDR expression. (Figure 1)

**Tumor Response, Quality of life and Serum vitamin D scores**

With supplementation, the mean serum Vitamin D levels improved from suboptimal levels to optimal levels in all patients, cases and controls alike. While 77.8% of cases with GBC who did not obtain supplementation had progressive disease, 60% of cases with Vitamin D supplementation had stable disease. However, there was no statistical difference in the tumour growth rate in either groups (p=0.07).

In Domain I QLQ there was a significant decrease in score in the supplemented group in comparison to non-supplemented group demonstrating a marked improvement in extent of problems. Domain II QLQ showed significant increase in score in the supplemented group denoting overall improvement in quality of life. [Table 3]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Malignancy (n=32)</th>
<th>Benign Disease (n=11)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs): Mean ± SD</td>
<td>47.43 ± 9.27</td>
<td>43.18 ± 9.24</td>
<td>0.200</td>
</tr>
<tr>
<td>Sex: Females</td>
<td>23 (71.8%)</td>
<td>8 (72.7%)</td>
<td>0.957</td>
</tr>
<tr>
<td>Males</td>
<td>9 (28.2%)</td>
<td>3 (27.3%)</td>
<td></td>
</tr>
<tr>
<td>Height (cm): Mean ± SD</td>
<td>149.60 ± 12.11</td>
<td>156.55 ± 9.54</td>
<td>0.817</td>
</tr>
<tr>
<td>Weight (kg): Mean ± SD</td>
<td>47.17 ± 5.03</td>
<td>43.73 ± 7.36</td>
<td>0.096</td>
</tr>
<tr>
<td>Performance status (ECOG): 1+</td>
<td>1+ 0.89</td>
<td>1+ 0.56</td>
<td>0.116</td>
</tr>
<tr>
<td>BMI (kg/m²): Mean ± SD</td>
<td>21.34 ± 3.40</td>
<td>17.91 ± 2.99</td>
<td>0.107</td>
</tr>
<tr>
<td>Rural</td>
<td>19 (59.3%)</td>
<td>3 (27.3%)</td>
<td>0.066</td>
</tr>
<tr>
<td>Urban</td>
<td>13 (40.7%)</td>
<td>8 (72.7%)</td>
<td></td>
</tr>
<tr>
<td>Baseline Serum Vitamin D Levels (ng/ml)</td>
<td>24.89 ± 10.81</td>
<td>32.70 ± 17.38</td>
<td>0.171</td>
</tr>
</tbody>
</table>

Table 1: Comparative Details of Two Groups

<table>
<thead>
<tr>
<th>IHC (scores)</th>
<th>Malignancy (n=32)</th>
<th>Benign disease (n=11)</th>
<th>p– value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity</td>
<td>0.63 ± 0.89</td>
<td>1.27 ± 1.27</td>
<td>0.136</td>
</tr>
<tr>
<td>Staining</td>
<td>0.67 ± 0.99</td>
<td>1.64 ± 1.29</td>
<td>0.036</td>
</tr>
<tr>
<td>IRS</td>
<td>1.20 ± 1.92</td>
<td>3.27 ± 4.10</td>
<td>0.118</td>
</tr>
</tbody>
</table>

Table 2: Mean Intensity, Staining and IRS scores of control and cancer patients
The QLQ conducted on patients with benign disease did not show any improvement upon 6 months of Vitamin D supplementation.

**Survival**

The overall survival of the two groups was also found to be similar (Log rank test: $\chi^2=0.72$, $p=0.396$) though it was 1.85 times better in patients of vitamin D supplemented group as compared to those without supplementation (Hazard ratio=1.85; 95% CI=0.38 to 11.26). (Figure 2).

<table>
<thead>
<tr>
<th>Response to Tumor (at the end of 6 months)</th>
<th>Groups</th>
<th>PD</th>
<th>SD</th>
<th>$\chi^2$ value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With  vit D (n=9)</td>
<td>7 (77.8%)</td>
<td>2 (22.2%)</td>
<td>3.23</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>With  vit D (n=15)</td>
<td>6 (40%)</td>
<td>9 (60%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EORTC Domain I</th>
<th>Groups</th>
<th>Pre supplementation</th>
<th>Post supplementation</th>
<th>Change (Pre to Post supplementation)</th>
<th>Wilcoxon matched pairs test (W) value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without vit D (n=9)</td>
<td>131.00 ± 11.43</td>
<td>128.00 ± 18.00</td>
<td>3.00 ± 8.47</td>
<td>12.00</td>
<td>0.496</td>
<td></td>
</tr>
<tr>
<td>With vit D (n=15)</td>
<td>132.07 ± 11.16</td>
<td>122.13 ± 18.72</td>
<td>9.93 ± 9.96</td>
<td>92.00</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>U value</td>
<td>66.50</td>
<td>53.50</td>
<td>38.00</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.976</td>
<td>0.421</td>
<td>0.084</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EORTC Domain II</th>
<th>Without vit D (n= 9)</th>
<th>5.56 ± 1.33</th>
<th>6.67 ± 2.87</th>
<th>1.11 ± 1.76</th>
<th>20.00</th>
<th>0.109</th>
</tr>
</thead>
<tbody>
<tr>
<td>With vit D (n=15)</td>
<td>5.87 ± 1.30</td>
<td>8.07 ± 2.31</td>
<td>2.20 ± 1.66</td>
<td>105.00</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>U value</td>
<td>57.50</td>
<td>43.50</td>
<td>45.50</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.568</td>
<td>0.160</td>
<td>0.198</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

| Serum Vitamin D scores                     | Without vit D (n = 15) | –1.41 ± 0.87 | 0.13 ± 0.74 | 1.47 ± 0.52 | 120.00 | <0.001 |

Table 3: Comparison of two groups in relation to tumor response, change in Vitamin D scores and QOL
**Discussion**

**VDR expression**

VDR is involved in multiple pathways that are important in the pathogenesis of cancer. The vitamin D receptor is expressed in both normal tissue and tumor cells. It has been hypothesized that a less active VDR could be associated with either an increased susceptibility to cancer risk or to a more aggressive disease. [18, 19] Evans et al. have reported the VDR downregulation linking with colon tumorigenesis, and mentioned that absence or low levels of VDR expression correlate with poor prognosis. [20] There have been only a handful of reports documenting vitamin D receptor expression in hepatobiliary cancers. VDR is reported to rarely express in normal bile duct epithelium and only 20% of normal bile ducts showed positive staining with low expression. In a study by Seubwai et al., however, VDR was shown to express more frequently and significantly in precancerous biliary epithelium and cholangiocarcinoma tissue cell lines compared to normal bile epithelia. [13] In our study, we found that the mean intensity, staining and IRS scores were decreased in gallbladder cancer patients compared to healthy controls. However, the difference in expression was not statistically significant. This disparity in the expression of the receptor between tumour tissue and benign control may well be denoting a link in the pathway to neoplasia, as hypothesized previously in colon tumorigenesis. This hypothesis is further substantiated by reports of ex-vivo studies in oral [10] and breast cancer [21] that has linked decreased VDR expression with increasing stages of malignancy. Although a similar trend was observed in our study among gallbladder cancer patients, one third of the GBC population displayed moderate or high VDR expression.

Lately Li et al. described the interaction between VDR polymorphisms and risk of GBC in a Chinese cohort by analyzing serum samples for genotyping using polymerase chain reaction techniques. [22] To the best of our knowledge, for the first time in clinical setting, our study attempts to quantify the expression of VDR in GBC tissue specimens based on immunohistochemistry.

**Tumor Response**

Vitamin D has shown potential in enhancing the antitumor activities of a number of cytotoxic agents. [23] Zeichner et al. were one of the earliest to report a significant improvement in patients who received vitamin D supplementation concurrently with chemotherapy for breast cancer. [24] In our study, though vitamin D supplementation showed no effect on objective tumor response statistically, 60% of patients in the supplemented group had stable disease, as opposed to only 22.2% in the unsupplemented group. Seubwai et al. showed that expression of VDR was compatible with an overall favorable prognosis for cholangiocarcinoma and treatment with active metabolite of vitamin D3 and that cholangiocarcinoma cell lines with high expression of VDR showed significantly reduced cell proliferation on exposure to vitamin D. However, this effect was not demonstrated in the cell lines that had lower VDR expression, further establishing the anti–tumor effect of vitamin D and its metabolites in hepatobiliary cancers. [13] Albrechtsson et al. [12] showed that the VDR was expressed in all pancreatic cancers cells and cell lines derived from these cancers responded with a decrease in cell number to high concentrations of a vitamin D analogue. Lastly, Grimm et al. showed that VDR expression occurs in oral cancer and vitamin D and its synthetic analogues could be useful for inducing apoptosis in these lesions. [25]

**Quality of life Assessment**

Not much has been published regarding the effect of vitamin D supplementation on quality of life as documented in a recent systematic review. [26] The physiologic manifestations of the disease states are important considerations, not only from a physician’s perspective, but also from that of the patient. All of these factors play an important role in overall quality of life and well being since ‘health’ has to be taken in a holistic intellect. Marked improvements were observed in decreased pain and improved well being in patients supplemented with oral vitamin D in this study. As stated by Hoffman et al. 2 [26] present–day evidence directs that vitamin D supplementation may have a small to moderate effect on quality of life when used on a short–term basis in diseased populations with role of long–term supplementation still an avenue of research. The combination treatment studies with calcitriol do provide evidence and support for the continued study of calcitriol in cancer chemotherapies, however, there is scarcity of exclusively designed clinical trials particularly to evaluate role of vitamin D supplementation with concomitant chemoradiation, with effect of vitamin D on toxicity in a palliative setting.

**Survival**

Vitamin D supplementation along with palliative chemotherapy failed to surge the overall survival in inoperable GBC patients statistically but there was a 1.85– times improved survival in these patients. Higher vitamin D levels have been allied to significantly reduced mortality in patients with colorectal and breast cancer. [27] A meta–analysis of randomized controlled trials found
that intake of ordinary doses of vitamin D supplements was associated with reduction in total mortality rates from any cause.\(^{[28]}\) Since GBC tends to present late because of its vague clinical course, further studies with large sample size are needed on role of vitamin D supplementation in inoperable GBC as an adjunct to palliative care so as to establish whether its supplementation can dent the disease progression in addition to improving health-related quality of life.

**Conclusion**

VDR expression is present in GBC and its reduced quantitative expression is linked with severe and progressive disease. Vitamin D supplementation has a favorable effect on improving quality of life, especially in a palliative setting. Supplementation may have a role in restricting tumor proliferation in GBC. However, definite roles need to be further studied in a bigger population of patients and tumour growth response needs to be documented with objective cross-sectional imaging for tangible results.

This study assumes importance as the first clinical study reporting vitamin D receptor expression in GBC tissue and the suggestive beneficial role of vitamin D supplementation in patients with advanced gallbladder cancer.

**Previous presentation**

This study was previously presented (Oral Presentation) to the 46th World Congress of Surgery, International Surgical Society, Bangkok, Thailand, August 23–37th 2015: “Expression Of Vitamin D Receptor (VDR) In Gallbladder Cancer (GBC), Immunoreactivity Scoring (IRS), Serum Vitamin D Levels (SVDL) And Effect Of Vitamin D Supplementation With Gemcitabine Chemotherapy.”

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