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Original Article

Vitamin D receptor expression in hydatidiform mole and gestational trophoblastic neoplasia: A cross-sectional study

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المخلص

أهداف البحث: لدى مستقبلات فيتامين د أدوار كمضاد للسرطان لأنواع مختلفة من السرطانات. الهدف من هذه الدراسة هو تحديد الفروق في مستويات مستقبلات فيتامين د بين الورم الحويصلي المائي وورم النسيج التروفيي الحملي.

طرق البحث: هذه دراسة مقارنة شملت ستة وستين نسيجا تم جمعها من الورم الحويصلي المائي وورم النسيج التروفيي الحملي. تم إجراء اختبار "تي" واختبار "مان ويتني" لمقارنة التعبير المناعي لمستقبلات فيتامين د، بما في ذلك شدة مستقبلات فيتامين د، توزيع مستقبلات فيتامين د، والتقدير التاريخي بين الورم الحويصلي المائي وورم النسيج التروفيي الحملي.

النتائج: تم تضمين ما مجموعه ستة وستين عينة من الأنسجة في هذه الدراسة، تتألف من سبعة وثلاثين نسيجا تم تشخيصها بالورم الحويصلي المائي وأربعة وعشرين نسيجا تم تشخيصها بورم النسيج التروفيي الحملي. تمت المقارنة بين العمر والأعداد بين المرضى الذين يعانون من الورم الحويصلي المائي والمرضى الذين يعانون من ورم النسيج التروفيي الحملي، ولم يلاحظ وجود فروقات كبيرة في كلا المجموعتين. بالنسبة لحالات ورم النسيج التروفيي الحملي، كانت شدة مستقبلات فيتامين د أقل بشكل ملحوظ من شدة مستقبلات فيتامين د في نسيج الورم الحويصلي المائي. بالإضافة إلى ذلك، كان التقدير التاريخي في نسيج ورم النسيج التروفيي الحملي أقل بشكل ملحوظ من التقدير التاريخي في نسيج الورم الحويصلي المائي. ومع ذلك، لم يكن هناك فروقات كبيرة في توزيع مستقبلات فيتامين د بين نسيج ورم النسيج التروفيي الحملي ونسيج الورم الحويصلي المائي.

الاستنتاجات: كان التعبير المنخفض لمستقبلات فيتامين د مرتبطا بورم النسيج التروفيي الحملي. بالمقابل، كان التعبيرالعالي لمستقبلات فيتامين د مرتبطا بالورم الحويصلي المائي. تشير هذه النتائج إلى أن مستويات مستقبلات فيتامين د قد تلعب دورا في شدة مرض النسيج التروفيي الحملي.

الكلمات المفتاحية: فيتامين د؛ مستقبلات فيتامين د؛ مرض النسيج التروفيي الحملي؛ الورم الحويصلي المائي؛ ورم النسيج التروفيي الحملي

Abstract

Objective: Vitamin D receptor (VDR) exerts anti-cancer properties in a variety of cancers. The purpose of this study was to investigate the expression of VDR in patients with hydatidiform mole (HM) and gestational trophoblastic neoplasia (GTN).

Methods: This is a cross-sectional study involved 61 specimens of HM (n = 37, 60.7%) and GTN (n = 24, 39.3%) was collected from the biopsy. An immunohistochemistry was used to asses the VDR expression. Student's t-test and Mann–Whitney test were used to compare the expression of VDR, including VDR staining intensity, VDR distribution, and histoscore, between HM and GTN tissue specimens.

Results: No significant differences in age and parity were noted between patients with HM or GTN ($p > 0.05$). The VDR staining intensity of GTN tissue specimens was significantly lower than that of HM tissue specimens

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(2.3 ± 0.8 vs. 2.8 ± 0.5, p = 0.008). In addition, the histoscore for GTN tissues was significantly lower than that for HM tissues (7.3 ± 3.2 vs. 9.4 ± 28, p = 0.016). However, no significant differences in VDR distribution between GTN and HM tissues were observed (3.3 ± 0.8 vs. 3.3 ± 1.0, p = 0.525).

Conclusion: Low VDR expression is associated with GTN, whereas high VDR expression is associated with HM, suggesting that the expression of VDR may regulate the severity of gestational trophoblastic disease.

Keywords: Gestational trophoblastic disease; Gestational trophoblastic neoplasia; Hydatidiform mole; Vitamin D; Vitamin D receptor

Introduction

Gestational trophoblastic disease (GTD) is defined as a spectrum of disorders ranging from premalignant to malignant abnormal trophoblastic proliferation. The premalignant form of GTD is hydatidiform mole (HM), and the malignant form is gestational trophoblastic neoplasia (GTN). HM can be further classified as complete and partial hydatidiform mole, whereas GTN can be classified into three malignant disorders, namely invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumor.[1]

The incidence of GTD varies across different regions of the world. The global incidence of HM, according to the International Federation of Gynaecology and Obstetrics (FIGO), is reported as 1 per 1000 pregnancies.[1] However, Indonesia has reported a higher incidence of 13 HM cases per 1000 pregnancies from 1977 until 1981.[2] According to FIGO 2000 staging and classification, GTN is classified based on risk. The classification distinguishes between low-risk and high-risk, with a risk score of 6 or below falling into low-risk GTN, while scores exceeding 6 are deemed high-risk GTN.[1] Low-risk GTN is estimated to have an incidence of 15.3 cases per 100,000 pregnancies, with approximately 9.8% of HM cases progressing to GTN.[3]

The progression of premalignant to malignant disorders involves a complex interplay of molecular factors that contribute to the development of cellular abnormalities.[4] One such disorder is GTN, which can arise from HM.[1] Understanding the mechanisms and identifying the treatments for this condition are important. Vitamin D has emerged as a potential anti-cancer agent due to its regulatory effects on cell growth, differentiation, and apoptosis.[5] In tissues, the vitamin D receptor (VDR) plays a crucial role in mediating the biological effects of vitamin D.[6] However, to the best of our knowledge, no study has investigated VDR expression in patients with GTD. This research gap highlights the need to explore the immunohistochemical expression of VDR in GTD, as this may provide valuable insights into the molecular pathways involved in the development and progression of the disorder.

Materials and Methods

Study design, setting, and duration

This was a cross-sectional study enrolling all cases of HM (n = 39) and GTN (n = 24) at Dr. Hasan Sadikin General Hospital in Bandung, Indonesia, between 2016 and 2021.

Patient characteristics, recruitment, and exclusion criteria

The specimens were collected from patients diagnosed with HM and GTN, according to the 2018 FIGO guidelines[1], who underwent a biopsy during evacuation of product of conception or hysterectomy. The exclusion criteria were as follows: (1) unusable paraffin blocks, (2) unsuccessfully stained specimens, (4) patients who underwent chemotherapy, and (5) patients with a history of vitamin D supplement use. All patients provided written informed consent before.

Sampling method and sample size estimation

Consecutive sampling was used in this study, in which all patients diagnosed with HM and GTN who sought medical attention at Dr. Hasan Sadikin General Hospital between 2016 and 2021 and underwent a biopsy during evacuation or hysterectomy, were included in the analysis. The sample size was not calculated in this study.

Laboratory procedures

Hematoxylin and eosin staining

The paraffin block, obtained after fixation in 10% neutral buffered formalin, was cut on a microtome to generate 4-μm-thick sections. These sections, derived from the paraffin-embedded biopsy tissue, were subsequently deparaffinized in xylene and rehydrated through a series of alcohol concentrations (90%, 80%, and 70% alcohol) for 5 min each. After rehydration, the tissue sections were stained with hematoxylin and counterstained with eosin. Following staining, the sections were dehydrated in increasing concentrations of alcohol. The dehydrated sections were then cleared with xylene and mounted with a coverslip for examination under a light microscope.

Immunohistochemical staining of VDR

The paraffin-embedded biopsy tissues were subjected to antigen retrieval by incubation in EDTA solution at 96 °C for 45–60 min. Following antigen retrieval, the specimens were rinsed in phosphate buffered saline (PBS; pH 7.4) for 5 min. To block endogenous peroxidase activity, the specimens were incubated with 0.3% hydrogen peroxide for 10–15 min. The specimens were then treated with bovine serum albumin for 10 min to minimize non-specific binding,

followed by rinsing with PBS for 5 min. For primary antibody incubation, a mouse anti-human VDR antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA; cat. no. 13133; lot no. B1809) was used at a 1:500 dilution in PBS. Incubation was performed for 60 min at room temperature, followed by rinsing with PBS. Peroxide block and blocking serum were added so that the primary antibodies provided only bind to the corresponding epitopes. The slides were then incubated with a secondary antibody using horseradish peroxidase (HRP)-streptavidin biotin was added to the sections and incubated for 20 min at room temperature. The chromogen diaminobenzidine tetrahydrochloride was added to all sections. Next, the tissue sections were counterstained with Mayer's hematoxylin for 5 min. The VDR staining intensity and distribution were assessed using an immunoreactivity score. All laboratory procedures were performed by experienced pathologists with 32 years of experience.

Measurement of variables

VDR expression was assessed by immunohistochemical staining, and the VDR staining intensity, VDR distribution, and histoscore were evaluated. The VDR staining intensity was determined using an immunoreactivity score, where a score of 0 indicated no staining, 1 indicated weak, 2 indicated moderate, and 3 indicated strong. The VDR distribution was scored by the pathologist quantitatively based on the percentage of cells showing staining as follows: 0 for no staining, 1 for staining in <10% of cells, 2 for staining in 11%−50% of cells, 3 for staining in 51%−80% of cells, and 4 for staining in >81% of cells. The histoscore, which represented the overall expression of VDR, was calculated by multiplying the VDR intensity score by the VDR distribution score.[7]

Data collection

Patient data, including age, parity, and diagnosis, were collected from patient medical records. VDR expression was assessed by immunohistochemical staining, and this involved the evaluation of VDR staining intensity, VDR distribution, and calculation of the histoscore as described earlier.

Data analysis

Statistical analysis was conducted using SPSS version 24.0 for Windows (IBM, Armonk, NY, USA). Patient age, parity, and VDR expression were treated as continuous variables and presented as means ± standard deviation (SD). Patient diagnosis, either HM or GTN, was treated as a categorical variable. Bivariate analysis was performed to compare patient diagnosis with VDR expression using a t-test or Mann−Whitney test. A difference was considered statistically significant at $p < 0.05$.

Table 1: Characteristics of patients with gestational trophoblastic neoplasia or hydatidiform mole.

	Diagnosis		P value
	Gestational trophoblastic neoplasia (n = 24)	Hydatidiform mole (n = 37)	
Age, years			0.501
Mean ± SD	35.375 ± 3.46	35.67 ± 8.67	
Parity			0.412
Mean ± SD	2.5 ± 1.5	2.56 ± 1.55	

SD, standard deviation.

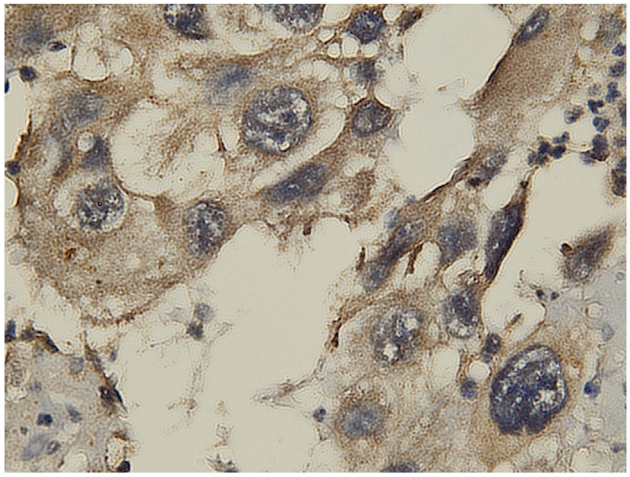

Figure 1: Immunohistochemical staining of gestational trophoblastic neoplasia tissue from a patient showing weak vitamin D receptor intensity (40× magnification).

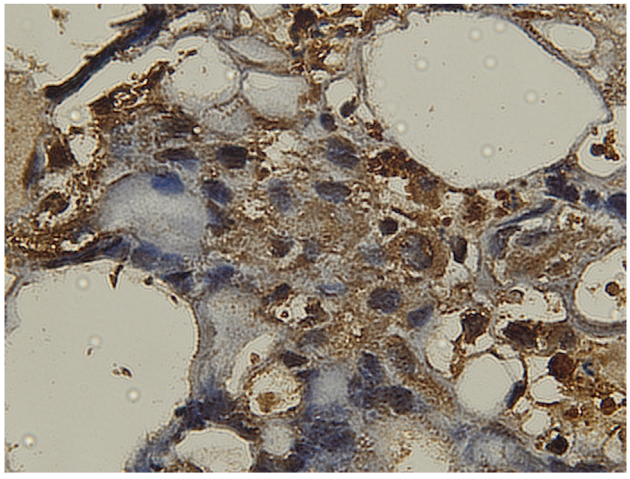

Figure 2: Immunohistochemical staining of hydatidiform mole tissue from a patient showing strong vitamin D receptor intensity (40× magnification).

Results

Characteristics of the patients

Sixty-three tissue specimens from patients diagnosed with HM and GTN were initially included in the study. However, two specimens were excluded due to unusable paraffin blocks as well as one specimen that was not stained successfully by immunohistochemistry. The final analysis included 61 specimens, namely 37 HM and 24 GTN specimens. The mean age

Table 2: Vitamin D receptor immunohistochemical staining analysis in patients with gestational trophoblastic neoplasia or hydatidiform mole.

	Diagnosis	
	Gestational trophoblastic neoplasia (n = 24)	Hydatidiform mole (n = 37)
VDR intensity		
Weak	6 (25.0%)	2 (5.4%)
Moderate	6 (25.0%)	5 (13.6%)
Strong	12 (50.0%)	30 (81.0%)
VDR distribution		
≤10%	0 (0.0%)	3 (8.1%)
11–50%	4 (16.7%)	4 (10.8%)
51–80%	9 (37.5%)	8 (21.7%)
>81%	11 (45.8%)	22 (59.4%)

VDR, vitamin D receptor.

Table 3: Vitamin D receptor expression analysis in patients with gestational trophoblastic neoplasia or hydatidiform mole.

	Histopathological diagnosis		P value
	Gestational trophoblastic neoplasia (n = 24)	Hydatidiform mole (n = 37)	
VDR intensity			**0.008**[a]
Mean ± SD	2.25 ± 0.846	2.75 ± 0.54	
VDR distribution			0.525[b]
Mean ± SD	3.29 ± 0.75	3.32 ± 0.97	
Histoscore			**0.016**[a]
Mean ± SD	7.33 ± 3.17	9.43 ± 3.28	

SD, standard deviation; VDR, vitamin D receptor.
The bold font indicate the significant value ($p < 0.05$).
[a] Student's t-test.
[b] Mann–Whitney test.

of the patients was 35.375 ± 3.46 years for the GTN group and 35.67 ± 8.67 years for the HM group. In addition, the mean parity values of the patients were 2.5 ± 1.5 for the GTN group and 2.56 ± 1.55 for the HM group. No significant differences in demographic data were observed between the two groups (Table 1).

VDR expressions

Immunohistochemical staining revealed distinct VDR expression patterns in patients with GTN or HM. In the GTN group, 6 out of 24 specimens (25%) exhibited weak VDR staining intensity (Figure 1). Conversely, in the HM group, 2 out of 37 specimens (5.4%) showed weak VDR staining intensity. Furthermore, most HM specimens (30 out of 37) showed strong VDR staining intensity (Figure 2). In terms of VDR distribution, 11 out of 24 specimens (45.8%) in the GTN group were positive for VDR in >81% of cells (Table 2), whereas in the HM group, 22 out of 37 specimens (59.5%) were positive for VDR in >81% of cells.

Comparison of VDR staining intensity, VDR distribution, and histoscore for GTN and HM

Comparative analysis revealed that the mean VDR staining intensity in the GTN group was significantly lower than that in the HM group (2.25 ± 0.846 vs. 2.75 ± 0.54, $p = 0.008$). On the other hand, no significant difference in the mean VDR distribution was noted between the groups ($p = 0.525$). However, the mean VDR distribution was slightly lower in the GTN specimens than that in the HM specimens (3.29 ± 0.75 vs. 3.32 ± 0.97). The histoscore was significantly lower in the GTN group than that in the HM group (7.33 ± 3.17 vs. 9.43 ± 28, $p = 0.016$) (Table 3).

Discussion

This study aimed to evaluate the expression of VDR in HM and GTN tissue specimens. Our results demonstrated notable differences in VDR expression between the two groups. We found that a higher proportion of tissues from patients with HM exhibited strong VDR staining intensity compared to those from patients with GTN (30 patients vs. 12 patients, respectively), suggesting that the expression of VDR may play a role in the pathogenesis of HM by contributing to its distinctive biological behavior. In addition, an examination of the VDR distribution revealed intriguing patterns among the patients. Specifically, within the HM group, a substantial number of patients (22 out of 37) demonstrated VDR distribution in >81% of cells, indicative of widespread VDR expression throughout the tissue. By contrast, the GTN group exhibited a lower proportion of patients (11 out of 24) with a similar distribution pattern. Although the difference in VDR distribution between the two groups did not reach statistical significance, the higher prevalence of extensive VDR distribution in the HM group suggests a plausible association between the expression of VDR and the development of HM.

In our study, the mean age of patients with GTN was 35 years, consistent with the findings of a study conducted by Winarno et al., where the mean age of 129 patients with GTN was also reported to be 35 years.[8] The mean age of the patients with HM in our study was 35.6 years. This finding diverges from an epidemiological study conducted in Finland from 1975 to 2001, which reported a higher incidence of HM in women younger than 20 years and older than 39 years.[9] However, another study has reported that age under 20 and above 40 years are risk factors for GTD.[10] These trends in different age groups raise a hypothesis that GTD may be associated with the pathological conditions of premature and postmature ova. The observed variations in GTD incidence across age groups prompt speculation about potential links to specific characteristics or conditions related to the maturation status of ova during conception.[11]

Abnormal trophoblast differentiation is one of the etiologies for GTD, and proto-oncogenes and tumor suppressor genes may play essential role in the pathophysiology of

GTD.[12] Several studies have investigated the roles of proto-oncogenes and tumor suppressor genes in the cell cycle and apoptosis. For instance, Nabiha et al. revealed that a proto-oncogene, *BCL-2*, which is important in placental growth, can preserve the trophoblast mass during pregnancy by reducing apoptotic activity.[13] Another protein, BAX, can promote apoptosis and tumor regression.[14] A study in patients with complete hydatidiform mole revealed that a high BAX:BCL-2 ratio is associated with a high apoptotic rate.[14] The tumor suppressor, P53, has an essential role in regulating BAX and BCL-2 by inducing BAX and inhibiting BCL-2 to reach the threshold for apoptosis.[15] P53 mutations can suppress apoptosis and even promote cancer cell activity.[16] A retrospective study revealed that alterations of P53 expression are implicated in the development of HM.[13] Therefore, it is evident that P53 plays a crucial role in regulating apoptosis and its alterations are associated with the development of HM.

In recent years, the number of studies related to the role of vitamin D in preventing cancer has increased. Some of the mechanisms of vitamin D as an anti-cancer agent include the regulation of the cell cycle, induction of apoptosis, and prevention of metastasis by decreasing metalloproteinase and increasing E-cadherin expression.[17] The effects of vitamin D emerged after it was found that vitamin D binds to the nuclear receptor superfamily, VDR. VDR functions as a specific receptor for vitamin D; therefore, the biological activity of vitamin D is potentially determined by the level of VDR in the tissue. A previous study revealed that P53 has a direct role in regulating VDR expression.[17] Given VDR's role as a specific receptor for vitamin D, the biological activity of vitamin D in tissues may be contingent on VDR levels. In connection with P53, research has demonstrated P53's direct involvement in regulating VDR expression.

No study has investigated the association between VDR expression and GTN or HM. In the present study, we found that VDR expression was lower in patients with GTN than in those with HM. The levels of VDR are usually high in the placenta, decidua, and ovary during pregnancy, in accordance with the important role of vitamin D in pregnant women.[18] However, a previous study has reported that 25(OH) vitamin D serum levels in patients with GTN were significantly lower than those in women with normal pregnancies. Another study compared vitamin D serum levels in women with GTD to women with normal pregnancies and found that women with the disorder had lower vitamin D levels than women without the disorder.[19]

The mechanisms responsible for the lower VDR expression in GTN than HM remains unclear, although we propose two hypotheses to explain this phenomenon: (1) alterations of P53; as described earlier, P53 regulates the expression of VDR, and changes in P53 levels or P53 activity may directly or indirectly downregulate VDR function in GTN, and (2) low levels of circulating vitamin D. A randomized controlled trial revealed that vitamin D supplementation by 2000 IU increased VDR expression,[20] suggesting that inadequate levels of vitamin D may be associated with the lower expression of VDR observed in GTN.

Even though this study does not provide a direct mechanism to explain the relationship between vitamin D insufficiency and low VDR expression, our findings have important clinical implications. Our findings emphasize the importance of maintaining vitamin D sufficiency to prevent the progression of HM to GTN as well as the prevention of HM itself. Furthermore, our data suggests that VDR can potentially serve as a marker for detecting HM in the early stages of the disorder.

This study has several limitations that should be acknowledged. Firstly, the sample size was relatively small; this may have limited the generalizability of our findings. Secondly, the dietary intake of vitamin D from various food sources was not included in the present study; this could have provided valuable insights into the potential influence of diet on VDR expression. Furthermore, there was no comparison of VDR expression in the trophoblast villi of patients with GTD with that in the trophoblast villi of patients without GTD. Therefore, the recommendations for future research are as follows: (1) examine the association of P53 and VDR expression in GTD; (2) evaluate the association of vitamin D supplementation and VDR expression in GTD; and (3) compare VDR expression in women with GTD to those without GTD. Addressing these recommendations in future research will provide a more comprehensive understanding of the role of VDR in GTD and its potential clinical implications.

Conclusion

Low VDR expression is associated with GTN, whereas high VDR expression is associated with HM, suggesting that the expression of VDR may play a role in the severity of GTD. Further research with larger sample sizes and molecular analyses is needed to explore this phenomenon. Understanding the relationship between VDR expression and circulating vitamin D levels and their association with different GTD subtypes can lead to enhanced diagnostic and therapeutic approaches in managing GTD in the future.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This study was approved by the Institutional Review Board of Hasan Sadikin Hospital (approval no. LB.02.02/X.6.5/154/2021) on June 8, 2021.

Consent

All participants provided written informed consent.

Authors contributions

RMSS and YMH conceptualized the study. AK acquired the data and drafted the manuscript. AIM drafted and revised the manuscript for important intellectual content. JSE, WP, BSH, and ABH contributed to the data curation and formal analysis. All authors reviewed and approved the final draft of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Chat GPT to improve language and readability. After using this tool, the authors reviewed and edited the content and take full responsibility for the content of the publication.

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