DOI: 10.4149/BLL_2021_027

Bratisl Med J 2021; 122 (3)
172 – 178

CLINICAL STUDY

Low serum vitamin D levels are associated with a low percentage of TREM-2$^+$ monocytes in low-grade gliomas and poorer overall survival in patients with high-grade gliomas

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ABSTRACT
INTRODUCTION: Anti-inflammatory effect of vitamin D (VD) could be beneficial in improving the survival of glioma patients. The aim of our study was to analyse the serum levels of vitamin D in glioma patients and to find an association with the prognosis of glioma patients and other investigated parameters.
MATERIAL AND METHODS: The study included 63 patients with gliomas. Percentage of CD14$^+$ monocytes, TREM-1$^+$ and TREM-2$^+$ monocytes were determined by flow cytometry, serum levels of 25(OH)D were evaluated by electrochemiluminescent binding test.
RESULTS: Six patients out of 63 had normal levels of VD. A significant difference in the overall survival (OS) in the patients with severe VD deficiency, VD deficiency and insufficiency in grade IV was found. In grade II and III, the levels of vitamin D positively correlated with the percentage of TREM-2$^+$ monocytes, and in grade II also a negative correlation of VD with TREM-1/TREM-2 ratio was observed.
CONCLUSION: Levels of VD could influence the prognosis of patients with high-grade gliomas. Serum level of 25(OH)D in low-grade gliomas positively correlated with the percentage of anti-inflammatory acting TREM-2$^+$ monocytes and negatively with TREM-1/TREM-2 ratio. This could be protective against the progression to high-grade glioma, because TREM-2 is associated with protective functions such as: tissue repair, control of local inflammation, or phagocytosis *(Tab. 4, Fig. 4, Ref. 79)*. Text in PDF *www.elis.sk*
KEY WORDS: inflammation, glioma, prognosis, TREM-2, vitamin D.

Introduction

Gliomas belong to the most frequent primary brain tumours that have the third highest mortality and morbidity rates among cancer in human population. They occur in all age groups, but most of them emerge in adults older than 45 years. According to histological and genetic features defined by WHO (World Health Organization), they are classified into 4 grades (1). Grade I and II are referred to as low grade gliomas, grades III and IV as high-grade gliomas. More than half of patients present a diagnosis of glioblastoma (GBM, grade IV), the most frequent, aggressive, and lethal form of glioma. Despite an improvement in understanding glioma biology, this disease, especially high-grade forms, still have a bad prognosis. In 2019, Cantrell et al showed that despite improvements in the median and short-term overall survival, the percentage of patients with glioblastoma achieving 5-year overall survival remains very low - 4.6 % (2). The markers of survival prognosis in the patients with gliomas are still evaluated.

Inflammation develops as a defence mechanism to any damage caused by infectious agents, tissue injury or malfunction (3). Both chronic systemic and local inflammation in the tumour microenvironment can support cancer development. Under physiological state, the only cells with immune functions in the central nervous system (CNS) are microglia. However, after blood brain barrier (BBB) disruption induced by trauma, stress or other pathological conditions, the pro-inflammatory molecules and immune cells from the periphery can cross the BBB and enter the CNS (4). As gliomas can also lead to BBB disruption, circulating immune cells not normally found in the CNS – macrophages, various types of T and B cells, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) – gain access to tumour areas (5, 6). One of the potential molecules with anti-inflammatory effect is vitamin D (VD).

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Vitamin D is a neuro-hormone regulating bone calcium-phosphate homeostasis, which plays a major role in many aspects of cellular functions and immunomodulation (7–10). However, it has also a direct effect on the function of both innate and adaptive immunity via VD receptor expressed on several immune cells (11–14).

Anti-inflammatory effect of VD in human T cells is partially mediated by inhibitory effect of NFκB (15). VD also participates in the shifting of T helper (Th) cell response from Th1 (specific cell mediated immunity accompanied by inflammation) to Th2 (specific humoral immunity). Vitamin D inhibits the production of Th1 cytokine IFN-γ and it increases production of Th2 cytokines such as IL-4, IL-5 and IL-10 (16, 17).

VD deficiency is associated with various disorders such as: diabetes, infections, myocardial infarction, autoimmune disease, chronic obstructive pulmonary disease, tuberculosis, and excess mortality in the general population (18–20). Vitamin D deficiency is common worldwide among healthy individuals (21, 22) and particularly among cancer patients (23–27). Laboratory studies demonstrated that $1,25(OH)_2D$ also has many anti-carcinogenic actions, including: anti-inflammation, anti-angiogenesis, and pro-apoptosis (28, 29). Despite such substantial experimental evidence, there are no formal recommendations for vitamin D supplementation for cancer prevention (30). Nonetheless, screening for vitamin D deficiency and vitamin D supplementation has increased dramatically since the early 2000s.

25-hydroxyvitamin D (25(OH)D) is the major circulating form of VD with a half-life of approximately 2–3 weeks. It is a metabolite of VD that is used to determine whether a patient is VD deficient, sufficient or intoxicated (31, 32). There is no absolute consensus about the normal range for 25(OH)D, but most experts now agree that VD deficiency should be defined as a 25(OH)D level less than 20 ng/mL (50 nmol/L), and levels between 20 and 29 ng/mL (50–74 nmol/L) are classified as insufficiency. Severe VD deficiency is characterized by values below 12 ng/mL. The normal level for 25(OH)D is now recommended to be more than 30 ng/mL (75 nmol/L) (31–34).

In recent years, the role of the modern inflammatory markers TREM-1 (triggering receptors expressed on myeloid cells) and TREM-2 in tumorigenesis has begun to be studied. The expression of TREM-1 receptor is associated with activated Th1 cell-mediated immunity, which is associated with anti-tumour immunity during the initiation phase of tumour growth. However, the long-lasting presence of this molecule supports the pro-inflammatory state at both systemic and local levels directly in the tumour microenvironment (TME), where it potentiates the tumour growth (35–37). TREM-2 is a negative regulator of inflammatory response. It is expressed in different tissues on dendritic cells, peritoneal and pleural macrophages, and microglia (38). Its expression on microglia is well known, but the exact role and signal pathways are the objects of further investigation (38, 39). The TREM-2 molecule has an anti-inflammatory effect, promotes phagocytosis, and is associated with Th2 immunity and cell-mediated immune suppression that could potentiate the tumour growth (40).

The aim of our study was to find an association of VD serum levels with the survival of glioma patients, with the percentage of pro-inflammatory TREM-1 positive and anti-inflammatory TREM-2 positive monocytes, TREM-1/TREM-2 ratio.

Subjects and methods

The study group included 63 patients older than 18 years (mean age: 53.29 ± 14.98 years) with partial or complete resection of CNS tumour. Patients with primary diagnosis and with relapse or progression of residual tumour were analysed. Only patients with histologically proven gliomas of grade II, III and IV were enrolled in our study, all other histological types of tumours or other diagnoses were excluded. Tumours of grade II with signs of grade III were taken as grade III, and one tumour of grade III with signs of glioblastoma was taken as grade IV. The diagnosis was approved by two neuropathologists according to the most recent WHO classification criteria. Blood samples were obtained from the patients, in the morning the day of surgery, before surgical treatment.

All investigations were carried out in accordance with the International Ethical Guidelines and the Declaration of Helsinki. The study was approved by the Ethical Committee of University Hospital in Bratislava, and a written informed consent for enrolling in the study and for personal data management was obtained from all examined cases.

The blood was obtained between the years 2015 and 2018. Percentage of $CD14^+$ monocytes (Mo) and TREM-1 and TREM-2 expressions on $CD14^+$ monocytes were measured by flow cytometry (Navios, Beckman Coulter France S.A.S). Both percentage and MFI (mean fluorescence intensity) of TREM expressions were analysed by KALUZA analysis software (Beckman Coulter France S.A.S) (antibodies used: CD14-PC7, TREM-1-PE, TREM-2-APC, and isotype controls; all from R&D System, Minneapolis, MN, USA). The TREM-1, TREM-2 analysis that we used in our previous studies (41, 42) was performed in compliance with Flow Cytometry Protocol recommended by the manufacturer. TREM-1 and TREM-2 expressions are presented as the percentage of TREM-1 and TREM-2 positive cells out of all $CD14^+$ cells. For each patient, we performed a negative control – sample stained with CD14, and isotype controls without TREM-1 and TREM-2 antibody. In addition, the serum levels of 25(OH)D were evaluated by electrochemiluminescence binding test (Elecsys Vitamin D total-cobas; Roche Diagnostics GmbH, Mannheim, Germany). Survival time was calculated from the time of diagnosis until April 2019 or the time of death. Patients were monitored from the 1th of December 2015 till 30th of April 2019.

Statistics

For the statistical analysis, we used programs InStat and SAS. We used Mann–Whitney test, Cox proportional hazard analysis, Kaplan–Meier survival analysis, Log Rank test, and Spearman correlation. The results were expressed as the median and interquartile range (IQR), mean ± standard deviation (SD), $p < 0.05$ was considered to indicate the statistical significance.

Results

1) Complete characteristics of patients are summarized in Table 1.
2) Number of patients with different vitamin D levels in each grade are shown in Table 2.
3) Levels of vitamin D were significantly higher in grade II gliomas than in grade III (p = 0.047) (Tab. 3). Interestingly, when we compared levels of vitamin D in grade IV with vitamin D in grade III or II, we did not find significant differences. In grade II the median of vitamin D was very similar to that in grade IV (20.4 vs 19.6 µg/L), in grade III the median was lower (13.7 µg/L), however, the difference was not significant (Tab. 3).

Tab. 1. Characteristics of glioma patients.

Patients	n	Mean age±SD
All gliomas	63	53.29±14.98
Sex (male/female)	38/25	
Grades (male/female)		
G. II	14/5	14/5 (40.47±12.30)
G. II–III	2/0	2/0 (30.5)
G. III	7/4	7/4 (48.55 ± 12.57)
G. III–IV	0/1	0/1 (55)
G. IV	15/15	15/15 (64.07 ± 8.70)
Primary diagnosis	49	
Relapse or progression of residual tumor	13	
Unknown	1	
Diagnosis		
Diffuse glioma II	4	
Oligodendroglioma II	7	
Oligoastrocytoma II	1	
Astrocytoma II	7	
Oligodendroglioma II–III	1	
Astrocytoma II–III	1	
Anaplastic astrocytoma	11	
Anaplastic astrocytoma with signs of GBM	1	
Primary GBM	28	
Unknown GBM	2	
Completely resected		
G. II	4	
G. II–III	0	
G. III	3	
G. III–IV	0	
G. IV	4	
IDH1/2 mutated	25	
G. II, III	24	
G. IV	1	
Steroid treated/untreated		
G. II	7/12	
G. III	9/4	
G. IV	28/3	

n – number of patients, G – grade, GBM – glioblastoma multiforme, IDH – isocitrate dehydrogenase

Tab. 2. Distribution of patients according to serum vitamin D levels.

	VD severe deficiency (<12 µg/L)	VD deficiency (12 – 19.99 µg/L)	VD insufficiency (20 – 29.99 µg/L)	Normal VD (≥30 µg/L)
G. II	1	7	9	2
G. II–III and III	2	8	2	1
G. III–IV and IV	5	11	12	3

G – grade, VD – vitamin D

Tab. 3. Comparison of serum 25(OH)D levels between different grades of gliomas.

Vitamin D	Gliomas G II	Gliomas G III	Gliomas G IV
n	19	13	31
Min	8.1	6.15	6.84
Max	61.5	35.1	43.4
Median	20.4	13.7	19.6
IQR	9.28	11.64	12.09
Mann-Whitney test	p=0.047 (II vs III)		

G – grade, n – number of patients, IQR – interquartile range

Tab. 4. Correlations of serum 25(OH)D level with percentage of TREM-2$^+$ monocytes and TREM-1/TREM-2 ratio.

25(OH)D in gliomas			
G. II	% of TREM-2 monocytes	Spearman r	0.5083
		p	0.0312
	TREM-1/TREM-2	Spearman r	–0.4681
		p	0.0581
G. III	% of TREM-2 monocytes	Spearman r	0.6648
		p	0.0390
	TREM-1/TREM-2	Spearman r	
		p	NS

G – grade

4) In grade II and III gliomas, a significant positive correlation of vitamin D level with percentage of TREM-2$^+$ monocytes was found (G. II: p = 0.0312, G. III: p = 0.0390) (Tab. 4).
5) In grade II glioma patients, we saw a trend to a negative correlation of vitamin D level with TREM-1/TREM-2 ratio (p = 0.0581) (Tab. 4).
6) In the Cox proportional analysis, serum level of vitamin D showed no association with overall survival in any grade. However, grade IV glioma patients with vitamin D lower than 20 µg/L survived significantly shorter time than the patients with vitamin D higher than 20 µg/L (p = 0.0027) (Fig. 1).
7) When we divided the patients into the three subgroups: 1, with vitamin D < 12 µg/L; 2, VD level between 12 and 20 µg/L and 3, VD level > 20 µg/L, we observed that patients with severe vitamin D deficiency (<12 µg/L) and vitamin D deficiency (12–20 µg/L) survived significantly shorter time than patients with vitamin D higher than 20 µg/L (p = 0.0099) (Fig. 2). Three patients had VD in normal range – more than 30 µg/L (Tab. 2).
8) When we omitted the patients with normal levels of vitamin D in grade IV, we observed significant differences in the overall survival with very similar p as shown in results 6 and 7 (Figs 3 and 4).
9) We did not see significant differences in VD levels comparing the primary diagnosed glioma patients with the patients with relapse or progression of residual tumour (primary diagnosis: median: 19.6 µg/L; median 23.6 µg/L in relapses or progression of residual tumour).
10) Regarding steroid therapy, we did not see differences in vitamin D levels and the percentage of TREM-2$^+$ monocytes.

Discussion

VD deficiency is common among the general population. It is also observed in up to 76 % of critically ill patients (43). In recent years, there has been a great deal of enthusiasm regarding the potential role of vitamin D in the primary and secondary prevention of cancer (44).

The serum/plasma level of 25(OH)D vitamin is the best indicator of overall vitamin D status, because it reflects the total vitamin D from dietary intake and sunlight exposure (45).

In our study we observed, that only 6 patients out of 63 had normal levels of vitamin D. Blood samples of our glioma patients were collected after diagnosis of CNS tumour was proven and many of the patients were at the time of blood collection under steroid treatment. However, we did not observe differences in 25(OH)D serum levels between steroid treated and steroid not treated patients. Patients with relapses were also included in our study, however, we did not observe differences in vitamin D levels between glioma patients with primary diagnosis and patients with relapse or progression. In grade IV, 5 patients out of 31 suffered from severe VD deficiency. In grade II, there was only one patient and in grade III there were two patients.

Low VD levels were associated with a higher risk of various types of cancer − colorectal (46–48), breast (49, 50), pancreatic (51), ovarian (52), and skin cancer (53). Many of these analyses highlight the importance of prospective studies with blood collected years in advance of diagnosis and treatment. Studies of different designs examined the level of 25(OH)D and cancer mortality/survival and are included in several reviews and meta-analyses. Blood samples were collected years prior to diagnosis, at the time of diagnosis or in some cases after diagnosis or treatment (54–59). In literature, we did not find studies about vitamin D levels and prognosis of gliomas, however, we found one study that investigated the association between vitamin D levels and glioma risk. Zigmont et al in 2015 published the first study in which they evaluate a potential association between pre-diagnostic serum vitamin D and glioma risk. They found that men older than 56 years with higher levels of serum 25(OH)D had a reduced risk of glioma (60).

In our study, in grade IV glioma patients, we observed significant differences in overall survival of patients with severe VD deficiency, VD deficiency and VD insufficiency; with increasing levels, the overall survival was better. This finding was not observed in grade II or III of gliomas.

Higher 25(OH)D status in cancer patients at the time of diagnosis has generally been reported in reviews to be associated with an improved survival for most malignancies − breast, colorectal, stomach, lung, prostate and head/neck cancers (54–57). The majority of studies included in these reviews measured the levels of 25(OH)D in patients after diagnosis. Only three studies measured the 25(OH)D in pre-diagnostic blood samples and their conclusion was similar – the reduced risks of mortality from colorectal and prostate cancer with higher levels of 25(OH)D (61, 62, 48). Maalmi et al conducted a meta-analysis of colorectal and breast cancer survival and reported a lower overall and disease-specific mortality with higher vitamin D status. 25(OH)D was measured in blood samples taken after diagnosis for all of the breast cancer studies and three of the five colorectal cancer studies (63). Other published data are more mixed in their findings and conclusions. For example, higher pre-diagnostic vitamin D status was associated with a significantly lower lung cancer mortality in two Danish cohorts, but not with colorectal cancer mortality (64). High post-diagnostic level of 25(OH)D was associated with a lower colorectal cancer mortality (65, 27), ovarian cancer mortality (66), and Merkel cell carcinoma mortality (although not significant) (67). This was observed also in one study concerning pancreatic cancer (68).

Vitamin D levels measured after diagnosis were not associated with a prostate cancer mortality in two studies (69, 70), however, a higher pre-diagnostic 25(OH)D status was associated with a lower prostate cancer mortality in the Swedish Malmo cohort (71) and the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort (72). In 2014, Salomón et al observed an improved overall survival associated with vitamin D receptor expression in human glioblastoma tissues (73).

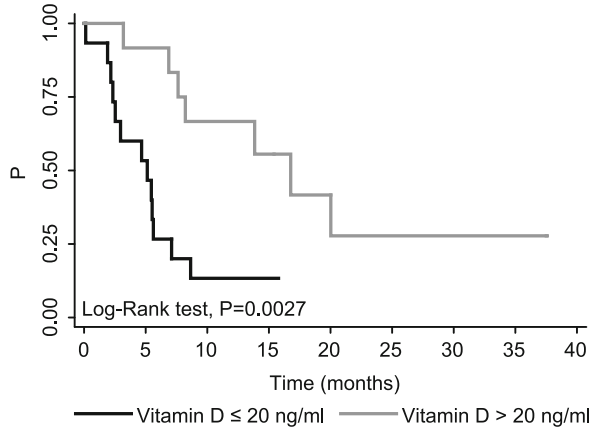

Fig. 1. Kaplan-Meier survival curves of patients with different serum vitamin D levels in grade IV (two subgroups)

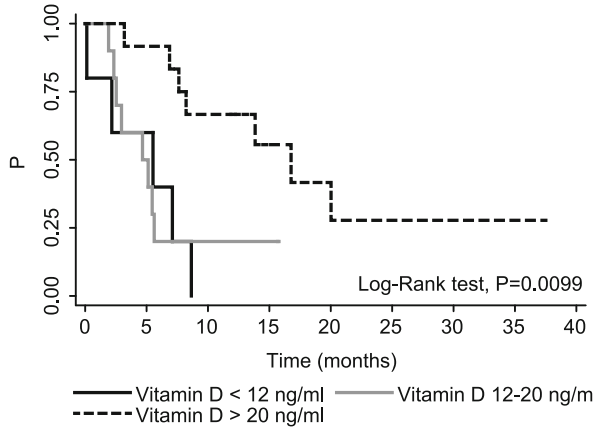

Fig. 2. Kaplan-Meier survival curves of patients with different serum vitamin D levels in grade IV (three subgroups)

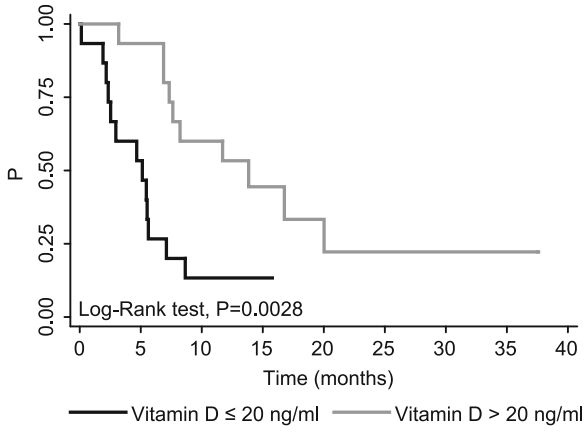

Fig. 3. Kaplan-Meier survival curves of patients with different serum vitamin D levels in grade IV (two subgroups, patients with normal VD omitted)

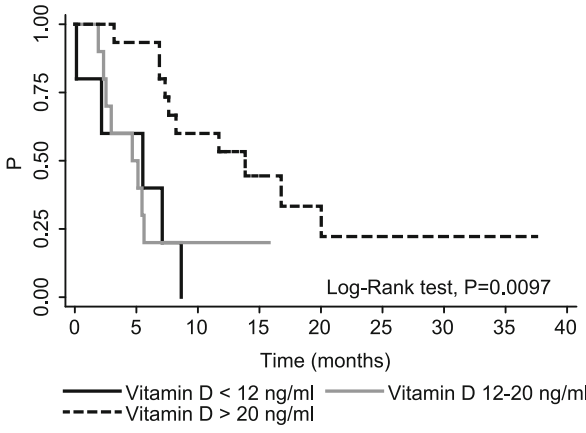

Fig. 4. Kaplan-Meier survival curves of patients with different serum vitamin D levels in grade IV (three subgroups, patients with normal VD omitted)

The expression of TREM-1 receptor is associated with activated Th1 cell-mediated immunity, which is associated with anti-tumour immunity during the initiation phase of tumour growth. However, the long-lasting presence of this molecule supports the pro-inflammatory state and it potentiates the tumour growth (35–37). The TREM-2 molecule has an anti-inflammatory effect, promotes phagocytosis, what might have a positive impact in the prevention of tumour growth, however, it is also associated with Th1 cell-mediated immune suppression and activation of Th2 immunity, what in the case of longer lasting state also to our opinion could potentiate the tumour growth (40).

In our study we showed that vitamin D levels positively correlated with the percentage of TREM-2^+ monocytes in grade II and III glioma patients. Moreover, in grade II gliomas a negative correlation with TREM-1/TREM-2 ratio was found. The positive correlation of plasma vitamin D with percentage of TREM-2 positive monocytes and the negative correlation with TREM-1/TREM-2 ratio could be protective. While TREM-1 molecule acts pro-inflammatory and could potentiate the tumour growth, TREM-2 positive monocytes/ macrophages are associated with alternative type of inflammation, act anti-inflammatory and have potentiated phagocytic activity. It means that vitamin D potentiated cell mediated innate immunity might account for immune protection in low grade gliomas. These TREM-2 positive cells are important not only in control of local inflammation, phagocytosis, but also in tissue repair (74).

As only a few studies (75, 76, 42) analysed the effect of vitamin D level on anti-inflammatory TREM-2 receptor expressions, we cannot compare in a broader sense our results with the findings of other authors. Bucova et al observed an increase of TREM-2 receptor expression with VD serum level in pulmonary sarcoidosis (42). Zhao et al in 2018 investigated the effect of active vitamin D on the expression of TREM-1, but not TREM-2 in the renal tissues of diabetic nephropathy (DN) rats. Their results demonstrated that VD could suppress macrophage adhesion and migration by reducing the expression of TREM-1 (77). Addula et al in 2018 investigated the effect of VD on TREM-1 and TREM-2 expression in inflammatory bowel diseases in 8 cases and 11 healthy controls. They concluded that insufficient VD levels were associated with an increased inflammatory state, which was accompanied by an increase of TREM-1 (pro-inflammatory molecule) and decrease of TREM-2 (anti-inflammatory) expressions (78). Results of Kim et al in 2013 showed that $1,25(OH)_2D_3$ could affect the innate and inflammatory responses by up-regulating TREM-1 expression and suggested the possibility that $1,25(OH)_2D_3$ might function as an enhancer of innate immune response in chronic inflammatory conditions (79).

Conclusion

The levels of vitamin D could influence the prognosis of patients with high-grade gliomas. We observed significant differences in the overall survival of grade IV glioma patients with severe VD deficiency, VD deficiency and VD insufficiency; with increasing levels, the overall survival was better. Supplementation of VD might be helpful in improving OS and quality of life of these patients. Vitamin D in plasma correlated positively with the percentage of anti-inflammatory TREM-2^+ monocytes and negatively with TREM-1/TREM-2 ratio in low grade gliomas, what might account for potentiated phagocytosis, decreased inflammation, and tissue repair.

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Received June 30, 2020.
Accepted November 11, 2020.