

Association of 25-hydroxyvitamin D with hematological profile and anthropometry in patients with glioma

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SUMMARY

OBJECTIVE: Gliomas are immune system suppressive tumors, and the role of vitamin D is pivotal in the immune system. This study aimed to observe if there is any significant association between the serum levels of 25-hydroxyvitamin D with hematological indices and anthropometric measurements.

METHODS: A total of 75 glioma patients were included, and the information was collected on gender, age group, area, socioeconomic status, intake of vitamin D and calcium in food and supplements, skin color, sunlight exposure, body mass index, and muscle strength. A nonparametric Kendall's tau-b correlation test was performed to find a correlation between 25-hydroxyvitamin D levels and blood counts, body mass index, and muscle strength.

RESULTS: The majority of patients (72%) were having low lymphocytes followed by high granulocytes and high white blood cells. The majority were having low levels of both 25-hydroxyvitamin D (84%) and calcium (73%). Patients were mainly from urban areas, and the majority belonged to middle-class families having sedentary lifestyles. The majority of patients were not taking vitamin D supplements. An insufficient amount of sunlight exposure was found in most of them. The majority of the patients were although had normal weight but weak muscle strength (74.6%). An insignificant correlation was found between 25-hydroxyvitamin D levels with the hematological indices or anthropometric measurements in brain tumor patients.

CONCLUSION: Vitamin D is a powerful immune modulator, and there is a great need for sufficient amounts of sunlight exposure and vitamin D-enriched diets to prevent cancer.

KEYWORDS: Glioma. Hydroxycholecalciferols. Lymphocytes. Body Mass Index. Muscle strength.

INTRODUCTION

Gliomas are immune suppressing tumors of the nervous system originating in the glial tissue of the brain generally notorious for carrying a poor prognosis and shorter survival. Vitamins may have a role in the etiopathogenesis of central nervous system (CNS) cancers¹. The anti-cancer activity occurs through the vitamin D receptor signaling mediated by 1,25-dihydroxyvitamin D². We conducted an epidemiological study to find the prevalence of vitamin D and calcium deficiencies in glioma patients. Vitamin D is a neurosteroid, and it regulates the production of neurotrophic factors, which are responsible for the differentiation and maturation of neurons. Moreover, vitamin D is also a neuroprotective agent as it stimulates phagocytosis of the amyloid-beta peptides and hence attenuates amyloid accumulation in the brain^{1,2}. Garland et al.³ suggested that the levels of calcifediol in a range of 40–60 ng/mL had reduced the risk of breast cancer by 25% and colonic cancer by 27%. Maintaining proper body weight and regular physical activity plays favorably. Notably, 30–50% of all cancers are preventable

by healthy dietary intake and lifestyle modification. A higher attained height and excessive body mass index (BMI) is related to a higher risk of gliomas⁴.

Hypovitaminosis is associated with decreased muscle strength, and its supplementation in the elderly has been known to increase muscle strength and help with gait⁵. A sedentary lifestyle resulted in a significant decrease in vitamin D levels in the body⁶. A higher BMI had also been related to the increased risk of gliomas⁷. Vitamin D modulates the adaptive immune system so are the leukocytes as immune cells, which participate in innate or adaptive immune systems. Therefore, we wanted to discover if there is any association between the altered levels of 25-hydroxyvitamin D [25(OH)D] and the hematological profile. BMI and muscle strengths are known to be impacted by decreased levels of calcifediol. We conducted a correlation between 25(OH)D levels and anthropometric measurements. There is not much literature available on such association. Some studies have reported the correlation between the grades of glioma and the counts of infiltrating and circulating neutrophils.

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on July 14, 2022. Accepted on July 29, 2022.

METHODS

Study design, setting, and patients: This cross-sectional epidemiological study was conducted from January to December 2019 and included 75 histologically confirmed glioma patients from the neurosurgical departments of Punjab Institute of Neurosciences (PINS), Lahore Pakistan, before surgery. Informed consent was taken from all patients for the data collection.

Inclusion/exclusion criteria: All consecutive histologically confirmed glioma patients aged between 25 and 70 years were included before surgery. The patients were not undergoing any chemotherapy or radiotherapy at the time of data collection. We did not include the metastasis cases. Patients with endocrinal abnormalities, previous operation, bone disease, and kidney or liver diseases were excluded. Patients on anti-tuberculous drugs, diuretics, anti-epileptics, bisphosphonates, hypnotics and opioids, chloroquine, and corticosteroids were also excluded.

Background and clinical information: The clinical information was collected through a self-designed proforma. The muscle strength was measured from an electronic, handy dynamometer (model CE-EH101). The dynamometer scale was to categorize muscle strength into normal, weak, or strong categories. A complete blood count (CBC) test was conducted in PINS Biochemistry Laboratory with “Sysmex Hematology Analyzer & Systems” through an automated hematology system. The serum 25(OH)D and calcium levels were conducted from the laboratory of PINS with the “I Chroma II Immune Assay Analyzer” through the kit method. The following normal ranges were considered for the blood counts: white blood cells (WBC): $5-10 \times 10^9/L$; red blood cells (RBC): $4-5 \times 10^{12}/L$; mean cell volume (MCV): $76-96 \times 10^{12}/L$; hematocrit (HCT): 36–50%; mean cell hemoglobin concentration (MCHC): 30–35 g/dL; mean corpuscular hemoglobin (MCH): 27–32 pg; lymphocytes (LYM): 25–40%; monocytes (MO): 3–7%; platelet (PLT): $150-400 \times 10^9/L$; and hemoglobin (HGB): 12–20 g/dL. Serum 25(OH)D levels were measured in ng/mL, and the normal range considered was 30–100. Serum calcium levels were measured in mg/dL with the normal range of 8.5–10.5.

Statistical analyses: A nonparametric Kendall’s tau-b correlation analysis was performed to find out if any significant association exists between 25(OH)D levels versus blood counts, BMI (underweight, normal weight, overweight, and obese), and muscle strength (weak, normal, and strong).

RESULTS

Demographics: There were 40 (53.3%) male and 35 (46.6%) female patients. The mean age of the patients was 41 years. In all, 20 (26.6%) patients belonged to the age group 25–40 years,

35 (46.6%) patients in 41–55 years, and 20 (26.6%) patients were in 56–70 years. Notably, 10 (13.3%) patients were from rural areas, 50 (66.6%) were from urban, and 15 (20%) were from suburban areas of Lahore. In total, 540 (55.5%) patients belonged to the middle class, 20 (26.66%) patients were poor, and 15 (20%) were from upper-class families.

Histopathology: The following glioma types were reported: astrocytoma (grades II/III), glioblastoma (GBM) (grade IV), ependymoma (grade III), and oligodendroglioma (grade III). Out of 75 patients, there were 22 (29.3%) cases of astrocytoma, 21 (28%) cases of GBM, 17 (22.6%) cases of ependymoma, and 15 (20%) cases of oligodendroglioma.

Vitamin D and calcium intake: Out of 75 patients, the majority (80%) did not take any vitamin D or calcium supplements. A total of 30 (40%) patients have darker skin tone, while 45 (60%) have a light skin tone. Notably, 54% of patients were having a good and regular intake of milk, ghee, fruits, vegetables, yogurt, cheese, and butter; 20% of patients also included the intake of fish with the food; and 26% of patients did not have a regular intake of all these foods.

Around 75% of patients were having exposure to sunlight in summers of up to 15 min only. Up to 25% of patients were having summer sunlight exposure of 30–40 min. In wintertime, around 75% of patients were having sunlight exposure of up to 30 min, whereas 25% were having exposure of 30–90 min.

BMI, muscle strength, and bone health: Table 1 shows the assessments. The majority of patients (51%) were having normal

Table 1. Glioma patients (n=75).

Parameters	Classes	n (%)
BMI	Underweight	8 (10.6)
	Normal weight	38 (50.6)
	Overweight	17 (22.6)
	Obese	12 (16)
Muscle strength	Weak	56 (74.6)
	Normal	16 (21.3)
	Strong	3 (4)
History of bone fracture	Yes	10 (13.3)
	No	65 (86.6)
Lifestyle	Moderately active	30 (40)
	Sedentary lifestyle	45 (60)
Vitamin D/calcium supplements	Yes	15 (20)
	No	60 (80)
25-Hydroxyvitamin D (ng/mL)	Normal levels	12 (16)
	Low levels	63 (84)
Calcium (mg/dL)	Normal levels	20 (26.6)
	Low levels	55 (73)
Skin color	Dark	30 (40)
	Light	45 (60)

weight (normal BMI), whereas 16% were obese. The majority (74.6%) of patients were having weak muscle strength. The majority (87%) of patients did not encounter any bone fracture. Most of the patients (60%) were having a sedentary lifestyle.

Laboratory findings: The majority of patients were having low levels (mean: 14 ng/mL) of serum 25(OH)D (84%) and calcium levels (73%; mean: 7 mg/dL) (Table 1). The majority patients were having low (mean: 13.233) LYM levels (72%), followed by high (mean: 85.164) granulocytes (GR) (59%) and high (mean: 14.57×10^9) WBCs (59%) and low (mean: 24.14) MCH and low (10.4) HGB (45%). Notably, 23% were having low (mean: 2) MO, 17% were having high (6.123×10^{12}) RBC and low MCHC (mean: 27.6), and 11% were having high (453×10^9) PLT. RBC (67%), MCV (74.6%), HCT (64%), MCHC (69%), MCH (48%), PLT (86%), and HGB (56%) were the most often reported normal values in glioma patients. Also, the normal values of WBC, LYM, MO, and GR were reported between 24 and 37% (see details in Table 2).

Kendall's Tau-b correlation analyses: Kendall's tau-b correlation analysis was conducted between dependent hemato-logical variables' levels (normal/low/high) and independent variables' levels (normal/low/high) of serum 25(OH)D levels. Kendall's tau-b correlation analysis was also conducted to see the correlations between ordinal dependent variables: BMI (underweight/normal weight/overweight/obese) and muscle strength (weak/normal/strong) and independent variables' levels (normal/low/high) of serum 25(OH)D. No statistically significant correlation was found. The detail of the correlations is mentioned in Table 3.

DISCUSSION

Vitamin D metabolites cross the blood-brain barrier, and its receptors are dispersed throughout the brain, examining its role in glioma formation is not implausible⁸. The function of blood vitamin D levels and hematopoietic markers in this

Table 2. Complete blood count profile.

Parameters	Normal range	Glioma patients (n=75)		
		Mean of normal values (n*, PP%**)	Mean of high values (n*, PP%**)	Mean of low values (n*, PP%**)
WBC ($\times 10^9$ /L)	5.00–10.00	8.214	14.57	4.9
		(28, 37.33%)	(44, 58.67%)	(3, 4%)
RBC ($\times 10^{12}$ /L)	4.00–5.50	4.707	6.123	3.816
		(50, 66.67%)	(13, 17.33%)	(12, 16%)
MCV (fL)	76.0–96.0	82.575	99.567	72.875
		(56, 74.67%)	(3, 4%)	(16, 21.33%)
HCT (%)	36.0–50.0	40.58		32.994
		(48, 64%)	–	(27, 36%)
MCHC (g/dL)	30.00–35.00	33.167	37.65	27.685
		(52, 69.33%)	(10, 13.33%)	(13, 17.33%)
MCH (pg)	27.0–32.0	28.636	32.2	24.144
		(36, 48%)	(5, 6.67%)	(34, 45.33%)
LYM (%)	25.0–40.0	29.722	43.2	13.233
		(18, 24%)	(3, 4%)	(54, 72%)
MO (%)	3.0–7.0	4.917	10.229	2.065
		(23, 30.67%)	(35, 46.67%)	(17, 22.67%)
GR (%)	50.0–75.0	65.4	85.164	22.853
		(22, 29.33%)	(44, 58.67%)	(9, 12%)
PLT ($\times 10^9$ /L)	150–400	274.554	453.5	118
		(65, 86.67%)	(2, 2.67%)	(8, 10.67%)
HGB (g/dL)	12.0–20.0	13.629		10.497
		(42, 56%)	–	(33, 44%)

*n=number of patients. **PP%=percentage prevalence.

Table 3. Correlation between serum 25-hydroxyvitamin D levels and blood counts, body mass index, and muscle strength.

Dependent variables	25-Hydroxyvitamin D levels (normal/low/high)	
	Kendall's tau-b coefficient	p-value
WBC	0.117	0.308
RBC	-0.006	0.959
MCV	0.104	0.362
HCT	-0.134	0.250
MCHC	0.022	0.844
MCH	0.101	0.372
LYM	-0.163	0.154
MO	-0.068	0.536
GR	0.210	0.061
PLT	0.062	0.589
HGB	-0.086	0.459
BMI	0.124	0.258
Muscle strength	-0.035	0.757

setting is debatable and requires a bigger cohort of patient data. Furthermore, the net effect of elevated vitamin D levels above the typical threshold on hematopoiesis is not clearly understood. According to certain studies, there is even a detrimental relationship between hematological parameters and increasing levels of vitamin D⁹. The current study sought to determine whether there is a link between blood counts and aberrant levels of calcifediol in glioma patients prior to surgery. We wanted to affirm these correlations, as some studies reported such results. There could also be links between altered levels of vitamin D with blood counts, or the deficiency of vitamin D can impact blood counts, but in the present data, we did not find any statistically significant correlations. Weak and insignificant results are reported because most of the patients (48–86%) reported normal RBC, MCV, HCT, MCHC, MCH, PLT, and HGB. Some more altered values were found in WBC, MO, and GR, but not greater than 58%. However, the LYMs were depressed in 72% of glioma patients. However, BMI and muscle strengths can be impacted by altered levels of calcifediol. Therefore, we were interested to know whether BMI and muscle strength are interrelated to the low levels of both calcifediol. Half of the patients had a normal range of BMI. We did not report any significant variations in BMI or muscle strength from altered levels of calcifediol. The majority of our patients with GBM were having low levels of serum 25(OH) D (84%) and calcium (73%).

Under normal homeostatic settings, leukocytes remain in the cerebrospinal fluid (CSF) and blood arteries and do not penetrate brain tissue. The only immune cells found in the CNS are macrophages or microglia. For a long time, neutrophils were assumed to have protumoral functions. In many malignancies, the presence of neutrophils and high NLR (neutrophil-to-lymphocyte ratio) is associated with a poor prognosis¹⁰. In gliomas, the severity of the disease correlates with the counts of infiltrating and circulating neutrophils. This indicates a prognostic and possible protumoral role for these leukocytes. One research identified a significant connection between key hematological measures and vitamin D levels in patients (with restrictive inclusion/exclusion criteria), but with no significant confounders, such as chronic illnesses or disorders that may affect hematological parameters⁹. However, we did not find any significant association between serum 25(OH)D levels with blood indices. On the contrary, other studies have shown that neutrophils orchestrate anti-tumor responses and directly kill tumor cells¹¹. GBMs are heavily infiltrated with MO, which are derived from circulation and not from some local transformation. Patients with brain tumors had reported a decreased macrophage-to-lymphocyte ratio. This was attributed to a reduced MO count as the cell-mediated immunity gets suppressed¹². A significant prognostic indicator reported was the altered HGB level before radiotherapy in cancer patients¹³. Cure et al.¹⁴ reported a strong association between a low vitamin D level and a high mean platelet volume (MPV). Increased PLT indices and deficiency of vitamin D are known to be associated with a higher risk of metabolic syndromes and cardiovascular disease as well¹⁵. Regarding the relationship between vitamin D and anemia, 25(OH)D and 1,25-dihydroxyvitamin D are found to be linked with low HGB during stages of chronic kidney disease (CKD)¹⁶.

We did not find any statistically significant link between serum 25(OH)D levels with anthropometric measures in our glioma patients. However, few studies reported that obesity was strongly associated and reported with lower levels of vitamin D¹⁷. BMI and vitamin D levels are inversely proportional as reported by Delle Monache et al.¹⁸. A significant correlation exists between deficiency of vitamin D and increased risk of bone fractures and poor muscle strength in elders¹⁹. Vitamin D supplementation is associated with a better prognosis in GBMs. Studies that explain a relationship between the vitamin D receptor protein and the outcome of gliomas are still lacking. In French adults in an urban setting, lack of sunlight exposure and relatively low dietary intake of vitamin D require attention owing to the prevalence of vitamin D deficiency in that community²⁰. Klement et al.²¹ suggested that low vitamin

D in cancer patients can be enhanced with proper exposure to the sunlight and intake of supplements. They investigated the levels of calcifediol with blood counts and some anthropometric measurements. A strong negative correlation is found between 25(OH)D with leukocytes and C-reactive protein (CRP). A recent study by Disney-Hogg et al.²² explored the association between dietary factors of vitamin D, immunity, and obesity. However, they did not find any significant link of risk of glioma development with obesity, BMI, type 2 diabetes mellitus, and lipids. Vitamin D deficiency and the reduction of telomere length have also been investigated in some research. Mixed results are observed; therefore, further investigation is recommended. For example, Zigmont et al.⁸ found no overall effect of serum 25(OH)D concentration on glioma risk. Mazidi et al.²³ supported a positive correlation of calcifediol with telomere length. Julin et al.²⁴ reported that age and BMI were inversely associated with telomere length. However, neither 25(OH)D nor 1,25-dihydroxyvitamin D was found to be linked with telomere length²⁵.

Women showed a stronger linear association between vitamin D and moderate-to-severe physical activity in the highest tertile of activity²⁶. A higher BMI had also been related to the increased risk of gliomas⁷. In this study, we gathered information on calcifediol through information on the intake of vitamin D and calcium in foods/supplements, skin color, sunlight exposure, BMI, muscle strength, history of bone fracture, and lifestyle. Vitamin D modulates the adaptive immune system, so are the leukocytes as immune cells, which participate in innate or adaptive immune systems. Therefore, we wanted to discover if there is any association between the altered levels of 25(OH)D and the hematological profile. BMI and muscle strengths are known to be impacted by decreased levels of calcifediol. Therefore, we also included a correlation between 25(OH)D levels and anthropometric measurements (i.e., BMI and muscle strength). There is no much literature available on such association. Some studies have reported the correlation between the grades of glioma and the counts of infiltrating and circulating neutrophils. A decrease in HGB levels, a relative increase in PLT counts, and a reduction in MO counts have also been seen in brain tumors¹². Moreover,

decreased MPV and increased RBC distribution width both are associated with brain tumors²⁷.

CONCLUSION AND RECOMMENDATIONS

There could be links between altered levels of vitamin D with blood counts, and with anthropometry (BMI and muscle strength), but in the present data, we did not find any statistically significant correlations. Since most of the patients (48–86%) reported normal blood counts, around half patients reported altered WBC, MO, and GR. However, the most disturbed parameter was the LYM (72%). Also, half of the patients had a normal range of BMI. The correlations can also depend on the type of cancer included. We reported data on brain cancer. The majority of glioma patients had low 25(OH)D and calcium levels. The patients usually did not use vitamin D or calcium supplements. As a result, we highly advise patients with brain tumors to take vitamin D supplements. Larger investigations are needed to investigate the possible involvement of vitamin D in glioma patients in conjunction with the other immune busters. Clinical trials to determine optimal dosages are required before they may be used as a supplement in cancer patients. As vitamin D is a powerful immune modulator, there is a great need for sufficient amounts of sunlight exposure and vitamin D-enriched diets as low-cost and cost-effective cancer prevention methods.

ETHICAL CONSIDERATIONS

The study conformed to institutional ethical standards.

AUTHORS' CONTRIBUTIONS

SS: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft. **MAC:** Data curation, Resources, Validation, Visualization, Writing – review & editing.

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