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ORIGINAL ARTICLE

Association of Vitamin D with Biochemical Severity Markers in Dengue Patients

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ABSTRACT

Background: Dengue fever is a common virus that has rapidly spread to all parts of the world. Dengue causes two critical disease dengue shock syndrome and dengue hemorrhagic fever.
Aim: To determine whether vitamin D levels and the severity of dengue are linked in any way.
Study design: Cohort study
Place and duration of study: Department of Medicine, Fauji Foundation Hospital Rawalpindi from 15-08-2022 to 15-11-2022.
Methodology: The patient's sample was collected to monitor the complete blood picture, including total leukocyte count and hemoglobin, hematocrit, platelets, etc. The severity of dengue was assessed by looking at platelet counts and hematocrit.
Results: The mean age was 29.19±16.80 years. There were 51% females and 49% males in the study. Vitamin D levels and platelet levels were weakly correlated with each other (rs= -.408, p= .000). There was a strong, negative correlation between Hb and Vitamin D levels, which was statistically significant (rs= -.704, p= .000). Similarly, hematocrit and highest MCHC also had a strong inverse significant correlation with Vitamin D level (rs= .698, p = .000 and rs= .751, p= .000, respectively). Surprisingly, there were significantly higher vitamin D levels in severe dengue patients than in non-severe ones (p<0.01).
Conclusion: Vitamin D levels were higher in severe dengue cases compared to less severe ones, indicating a possible role of vitamin D as a cofactor for predicting disease severity. It is suggested that maintaining an ideal vitamin D level can help avoid the progression of asymptomatic dengue to dengue hemorrhagic fever or dengue shock syndrome.
Keywords: Vitamin D, Biochemical severity markers, Dengue

INTRODUCTION

A mosquito is a vector for the widespread viral infection known as dengue fever. Four different dengue virus serotypes can infect people. Aedes aegypti and Aedes albopictus are two mosquito species linked to the transmission of the dengue virus[1,2]. Both of them favour daytime human bites. Compared to Aedes aegypti, Aedes albopictus is more resistant to cooler temperatures[2]. Dengue cases have been rising significantly each year[2,3]. The clinical manifestation of dengue varies widely. Simple asymptomatic sickness to fatal hemorrhagic fever or shock is a possible outcome. Additionally, dengue fever may harm the development of a fetus[4].

In all places, particularly where dengue is endemic, acute fever should be suspected to have a dengue component. It can be found using several tests. One way to identify dengue is by looking for NS1 antigenemia. Dengue is not treatable with a specific antiviral or vaccination[5].

Vitamin D levels regulate the immune response to the dengue virus in patients. Vitamin D's impact on miRNAs is one possible mechanism by which vitamin D plays this role[6]. Vitamin D has properties that make it an antiviral and an immune regulatory molecule. Many studies support its use in the measurement of dengue severity[7].

There are many clinical markers for the severity of dengue. Among these are platelet counts, which are a great indicator of severity[8]. Platelet counts have been suggested as a predictive indicator for the first three days of the disease by Huy et al.[9] According to a study; hematocrit levels may be a reliable indicator of the severity of dengue[10]. It can be used as an early marker to find patients who are at high risk. There is controversy over total leukocyte counts as a dengue indication. A high total leukocyte count (>20,000) was discovered to be a predictor of mortality.[11] According to a different study, total leukocyte counts do not predict prognosis[12].

It is unknown whether vitamin D and dengue virus severity are related. Numerous investigations have come to various findings about this. Low vitamin D levels were linked to a less severe variant of the dengue virus, according to research by Villamor et al[13]. According to a different study, taking vitamin D pills can lessen how bad the dengue virus affects people[14]. The evidence for the association between vitamin D and dengue seems ambiguous. According to Jaratsittisin et al[15], vitamin D receptor analog usage in dengue patients lowers the dengue virus load.

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MATERIALS AND METHODS

This cohort study was carried out at the Department of Medicine, Fauji Foundation Hospital Rawalpindi, Pakistan. The study duration was three month. With an anticipated prevalence of 0.37%[16], a confidence interval of 1.96, and a margin of 0.05, a sample size of 350 was determined using the WHO sample size calculator.

All newly diagnosed dengue patients with no endocrine or renal disease were considered eligible for inclusion in the study while patients with concurrent platelet disorder or dysfunction were excluded from the study sample. The subject or a close relative completed an informed consent form outlining the study's purpose. Patient's demographic and clinical characteristics were recorded. Serial blood samples were taken to monitor the complete blood picture, including total leukocyte count and hemoglobin, hematocrit, platelets, etc. The severity of dengue was assessed by looking at platelet counts and hematocrit.

The data was entered and analyzed through SPSS-22. A Spearman's rank-order correlation was applied to determine the correlation between vitamin D and biochemical severity marker levels. The factors were stratified, and a post-stratification Independent T-test was used. A p-values < 0.05 were regarded as significant.

RESULTS

The mean age of the patients were 29.19±16.80 years with 50.6% being males and 49.4% females. The biochemical estimations are presented in Table 1. A Spearman's rank-order correlation was run to determine the relationship between vitamin D and biochemical severity marker levels. There was a strong, negative correlation between Hb and Vitamin D levels, which was statistically significant (rs = -.704, p = .000). Similarly, hematocrit and highest MCHC also had a strong inverse significant correlation with Vitamin D levels (rs= .698, p= .000 and rs= .751, p= .000, respectively). While there was a weak negative correlation between platelet and Vitamin D levels, which was statistically significant, indicating the effect of other potentially important determinants (Table 2).

Patients with severe dengue had significantly lower white cell counts, platelet counts, and hematocrit (except those assessed for severity based on platelet count) than those with non-severe dengue. Furthermore, there were significantly higher vitamin D levels in severe dengue patients than in non-severe ones (p<0.01) [Table 3].

Table 1: Descriptive statistics of the patients

Variables	Mean±SD
Vitamin D Levels	52.78±47.22
TLC	5.89±4.87
Hb	13.60±2.03
Hematocrit	40.36±5.55
MCV	84.79±6.13
MCH	28.55±2.42
MCHC	33.66±1.12
Platelets	140.89±77.53
Neutrophil Percentage	49.67±22.08
Highest MCHC	40.39±7.03
Lymphocytes percentage	32.65±14.89
Lowest Platelets	59.56±50.25
Lowest Hematocrit	47.87±25.26

Table 2: Correlation of Vitamin D level with baseline and biochemical severity markers in dengue patients

Variables	Spearman's R-value	P value
Baseline characteristics		
Age	.493	0.000
Gender	.244	0.000
Biochemical severity markers		
TLC	.130	0.015
Hb	-.704	0.000
Hematocrit	-.698	0.000
MCV	-.408	0.000
MCH	-.483	0.000
MCHC	-.393	0.000
Platelets	-.408	0.000
Neutrophil Percentage	-.215	0.000
Highest MCHC	-.751	0.000
Lymphocytes percentage	.240	0.000
Lowest Platelets Count	-.451	0.000
Lowest Hematocrit	-.334	0.000

Table 3: Laboratory parameters concerning severity based on platelet count and hematocrit

Variable	The severity with respect to Platelet count		P value	The severity with respect to hematocrit		P value
	Severe Dengue	Non-severe Dengue		Severe Dengue	Non-severe Dengue	
Vitamin D Levels	95.93±79.68	38.50±7.92	.000*	94.97±79.97	38.82±9.15	.000*
TLC	5.59±1.95	5.98±5.50	.510	4.30±2.73	6.41±5.29	.000*
Hb	13.76±3.60	13.54±1.09	.385	11.07±1.69	14.44±1.30	.000*
Hematocrit	41±10.05	40.14±2.76	.212	33.59±4.84	42.59±3.61	.000*
MCV	85.80±9.56	84.45±4.42	.076	82.97±6.02	85.38±6.05	.001*
MCH	28.70±3.61	28.50±1.86	.512	27.33±2.44	28.95±2.27	.000*
MCHC	33.36±.77	33.75±1.19	.004*	32.95±.62	33.89±1.14	.000*
Platelets	105.33±56.71	152.65±79.95	.000*	38.36±25.03	174.80±56.17	.000*
Neutrophil %age	43.33±15.15	51.77±23.58	.002*	24.02±16.25	58.15±16.49	.000*
Highest MCHC	38.40±10.59	41.37±4.00	.008*	34.21±4.52	46.48±1.70	.000*
Lymphocytes %age	41.20±10.72	29.82±15.00	.000*	39.06±9.89	30.52±15.64	.000*
Lowest platelets	26.70±18.86	75.85±52.95	.000*	24.68±27.33	94.04±43.50	.000*
Lowest Hematocrit	63.60±38.73	40.06±5.92	.000*	31.23±4.29	64.30±26.61	.000*

*p<0.05 is considered significant

DISCUSSION

According to this study, high vitamin D levels are linked to more abnormal laboratory measures of dengue severity, such as platelet count and hematocrit. Vitamin D levels were highly correlated with hemoglobin concentrations, and participants with higher vitamin D levels typically had a lower hematocrit percentage. Furthermore, we discovered that the lowest hematocrit and platelet counts throughout the dengue fever sickness were very weakly correlated with vitamin D levels. Our findings were in contrast to the existing literature, where the likelihood of vitamin D deficiency was shown to be higher in children with severe dengue compared to healthy controls in a case-control investigation.[17] Various plausible explanations exist for the potential link between dengue and vitamin D insufficiency. First, high cytokine concentrations generated by T cells, monocytes/macrophages, and endothelial cells in response to high virus loads are known to be associated with severe dengue. Second, vitamin D promotes macrophage differentiation, which limits the reproduction of viruses. Additionally, it has been demonstrated that vitamin D therapy dramatically reduces cytokine production in dengue-infected macrophages compared to control groups[18].

Platelets and hematocrit are significant predictive predictors of the severity of dengue infection. Their response to vitamin D suggests that it might be to blame for the escalation of dengue infection. Our findings imply that increased vitamin D levels were linked to decreased platelets and hematocrit levels, which suggested a greater chance of developing severe dengue indirectly. In contrast, a Sri Lankan study revealed that children with acute dengue had reduced vitamin D levels[19]. The age ranges being considered could cause the disparity. Our study was more focused on adults than the pediatric group in other studies.

Vitamin D use may trigger a strong immunological response that puts the patient at risk for dengue shock or hemorrhagic syndromes. In our culture, vitamin D pills are widely used. In research on vitamins, 3465 of the 4224 outpatient visits involved supplement use[20]. This indicates that a sizable portion of the populace is susceptible to severe dengue. According to Alagarasu, vitamin D's immunoregulatory effects can be employed to fight the dengue virus. They have advocated for the therapeutic use of vitamin D in dengue patients. Villamor et al[7] also found a similar finding to our investigation. They discovered that lower vitamin D levels were linked to a lower risk of suffering from dengue shock syndrome or hemorrhagic fever.

The amount of vitamin D in the body may play a role in molecular processes that affect immune response or dengue virus pathogenesis. The dengue virus's ability to survive or spread and the host's response to it may all be enhanced by vitamin D. This ultimately leads to fewer platelets and impaired hemostasis, which causes hemorrhage, or plasma leakage, which causes shock.

CONCLUSION

Vitamin D levels were higher when comparing severe dengue cases to less severe ones. A better understanding of vitamin D's function as a cofactor for predicting disease severity may result from more research correlating vitamin D levels with pro-inflammatory/anti-inflammatory cytokines. It is suggested that Vitamin D level may play a role in the progression of dengue, and maintaining an optimum vitamin d level will help prevent the progression of asymptomatic dengue to dengue hemorrhagic fever or dengue shock syndrome. Moreover, the potential for genetic susceptibility research in dengue will increase as more identified variants exist in the human genome, opening the door to creating viable therapeutic approaches. Furthermore, carefully planned multi-country randomized controlled studies with sizable populations of varied racial, cultural, and genetic backgrounds are required to further fill up the knowledge gaps regarding the impact of vitamin D on the course of dengue disease.

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