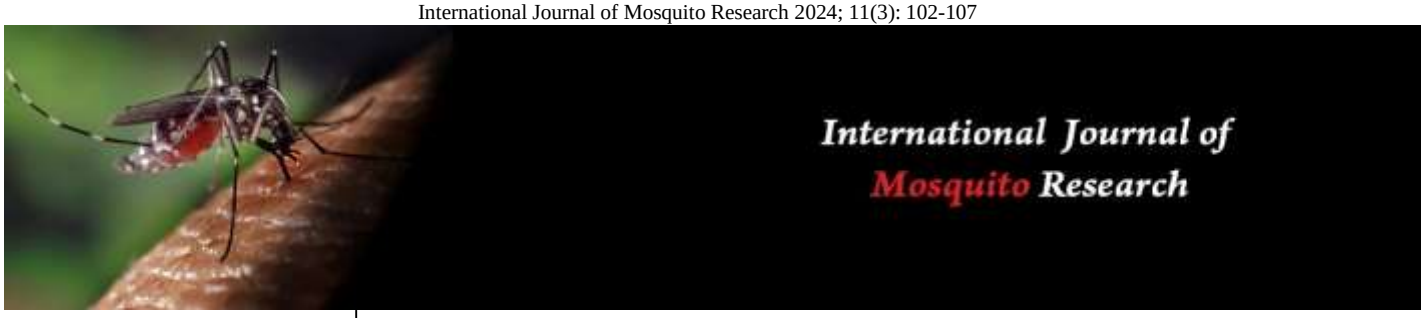

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Prevalence, severity and clinical impact of hypocalcemia in dengue fever patients

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Abstract
Background: Dengue fever, a viral infection transmitted by Aedes mosquitoes, poses a significant public health challenge in tropical and subtropical regions. The disease manifests in various forms, ranging from mild febrile illness to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Recent studies have highlighted hypocalcemia as a potential marker of disease severity in dengue patients.
Objectives: This study aimed to evaluate the prevalence of hypocalcemia in dengue fever and to assess its correlation with disease severity and patient outcomes.
Methods: A cross-sectional observational study was conducted at our tertiary care hospital, including 150 dengue patients diagnosed by NS1 antigen or Dengue IgM. Patients were stratified into categories based on dengue severity and calcium levels were monitored. Those with moderate and severe hypocalcemia received oral calcium supplementation.
Results: The study included a total of 150 dengue patients, consisting of 104 males and 46 females, with a mean age of 39.1 years. Hypocalcemia was observed in 40.7% of these patients, with 20% experiencing mild hypocalcemia, 14% moderate hypocalcemia, and 6.7% severe hypocalcemia. A notable correlation was found between hypocalcemia and the severity of dengue, as severe hypocalcemia was significantly associated with dengue shock syndrome (DSS). Patients with hypocalcemia generally had longer hospital stays.
Discussion: The findings suggest a strong correlation between hypocalcemia and dengue severity. Calcium supplementation appears to improve outcomes in hypocalcemic patients by reducing the duration of hospital stay.
Conclusion: Monitoring calcium levels in dengue patients can provide valuable insights into disease severity and guide treatment strategies. Calcium supplementation could be a beneficial intervention for hypocalcemic patients to improve clinical outcomes.

Keywords: Dengue fever, hypocalcemia, calcium supplementation, dengue severity, patient outcomes

Introduction

Dengue fever is a mosquito-borne viral disease that has become a major public health concern in tropical and subtropical regions worldwide. The disease is caused by the dengue virus (DENV), which belongs to the Flaviviridae family and is transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes [1-3]. Dengue fever presents a broad spectrum of clinical manifestations, ranging from asymptomatic infection and mild febrile illness to severe dengue, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [4].

Dengue fever has a long history, with the first recognized epidemics occurring in the late 18th century in Asia, Africa, and North America. Over the past five decades, the incidence of dengue has increased 30-fold, with significant outbreaks occurring in many countries. Today, dengue is endemic in over 100 countries, placing nearly half of the world's population at risk [5-7]. The World Health Organization (WHO) estimates that there are 390 million dengue infections each year, of which 96 million manifest clinically (with any severity of disease) [8].

Dengue fever is caused by four distinct but closely related serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4). Infection with one serotype provides lifelong immunity to that serotype but only partial and temporary protection against the others. Subsequent infections with different serotypes increase the risk of severe dengue due to antibody-dependent enhancement (ADE), where non-neutralizing antibodies facilitate viral entry into host cells,

leading to increased viral replication and severe disease manifestations [9-11]. The pathogenesis of dengue is complex and involves a combination of viral, host, and environmental factors. The virus targets various cells, including dendritic cells, macrophages, and hepatocytes, leading to a robust immune response characterized by high levels of cytokines and chemokines. This "cytokine storm" contributes to the vascular leakage, hemorrhage, and organ dysfunction observed in severe cases [12-14].

The clinical presentation of dengue can vary widely. After an incubation period of 4-10 days, the disease typically begins abruptly with high fever, severe headache, retro-orbital pain, severe muscle and joint pains (Hence the name "break bone fever"), nausea, vomiting, rash, and mild bleeding manifestations (Such as nose or gum bleeding) [15].

Severe dengue, previously known as DHF and DSS, is characterized by plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Warning signs of severe dengue include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement, and an increase in hematocrit with a rapid decrease in platelet count [16].

The diagnosis of dengue is primarily clinical, supported by laboratory tests. The detection of the NS1 antigen and IgM/IgG antibodies through enzyme-linked immunosorbent assay (ELISA) or rapid diagnostic tests (RDTs) are commonly used methods [17-18]. Real-time polymerase chain reaction (RT-PCR) is the gold standard for early detection and serotyping of the virus [19, 20].

Management of dengue involves supportive care, as there is no specific antiviral treatment for the disease. The primary focus is on maintaining fluid balance to prevent shock in severe cases. Hospitalization is recommended for patients with severe dengue, warning signs, or those with comorbid conditions that may complicate the disease course. Analgesics and antipyretics such as acetaminophen are used to manage pain and fever, while aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) are avoided due to the risk of bleeding [21].

Recent studies have identified hypocalcemia as a common biochemical abnormality in dengue patients. Hypocalcemia, defined as a total serum calcium level below 8.4 mg/dL, has been observed in various infectious diseases and is thought to result from multiple mechanisms, including decreased intake, increased losses, and redistribution. In dengue, hypocalcemia may be due to plasma leakage, binding of calcium to the viral particles, or secondary to other metabolic disturbances such as hypoalbuminemia and hypomagnesemia.

Calcium plays a crucial role in various physiological processes, including muscle contraction, blood coagulation, and signal transduction in cells. In the context of dengue, calcium is essential for maintaining vascular integrity and hemostasis. Low calcium levels have been associated with increased disease severity, including higher rates of DSS and prolonged hospital stays. Understanding the role of hypocalcemia in dengue can help improve patient management and outcomes [22].

Study Rationale

Given the high prevalence and impact of dengue worldwide, identifying factors that influence disease severity and outcomes is critical. Hypocalcemia has emerged as a potential marker for severe dengue, prompting the need for further investigation. This study aims to evaluate the prevalence of hypocalcemia in dengue patients and assess its correlation with disease severity and clinical outcomes. Additionally, the study explores the effects of calcium supplementation in hypocalcemic dengue patients, providing insights into potential therapeutic interventions.

The primary objectives of this study aims to determine the prevalence of hypocalcemia among patients diagnosed with dengue fever. Understanding how widespread this electrolyte imbalance is in dengue patients can provide insights into its potential role as a marker for disease progression. Second, the study seeks to assess the correlation between hypocalcemia and the severity of dengue. By evaluating the relationship between low calcium levels and the severity of clinical manifestations, the study aims to elucidate whether hypocalcemia can be used as a predictor of more severe forms of dengue, such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Methodology

Study Design and Setting

This cross-sectional observational study was conducted at our tertiary care hospital, over a period from October 2021 to August 2023. The study aimed to investigate the prevalence of hypocalcemia in dengue fever patients and assess its correlation with disease severity and clinical outcomes.

Study Population

The study included 150 patients diagnosed with dengue fever, confirmed by NS1 antigen or Dengue IgM serology. Patients were recruited from both outpatient and inpatient departments of the hospital. The inclusion and exclusion criteria were as follows:

The inclusion criteria for the study required patients to be diagnosed with dengue fever by NS1 antigen or Dengue IgM serology and to be aged 16 years or older. Exclusion criteria were applied to ensure a focused study population and included patients with autoimmune diseases, malignancy, those using medications that affect white blood cell count (Such as those for hematopoietic systemic disorders), pregnant women, and patients with concurrent infections other than dengue. This careful selection helped in minimizing confounding factors that could influence the study results.

Data Collection

After obtaining informed consent, each patient was followed daily during their hospital stay. Clinical and laboratory parameters recorded included vital signs (Heart rate, blood pressure), symptoms (Fever, headache, retro-orbital pain, myalgia, arthralgia), and laboratory tests (Complete blood count, platelet count, hematocrit, liver function tests, renal function tests, serum calcium levels). Additionally, abdominal ultrasound was performed to assess for signs of plasma leakage, such as ascites or gallbladder edema. This comprehensive monitoring ensured a detailed assessment of each patient's clinical status and response to treatment.

Stratification

Patients were stratified into categories based on the severity of dengue fever: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) 1 & 2, DHF 3, and Dengue Shock Syndrome (DSS). Serum calcium levels were measured, and hypocalcemia was categorized as mild (8.0–8.39 mg/dL), moderate (7.5–7.99 mg/dL), or severe (<7.5 mg/dL). Patients with moderate to

severe hypocalcemia received oral calcium supplementation.

Outcome Measures

The primary outcome measure was the duration of hospital stay. Secondary outcome measures included the time to achieve normocalcemia, resolution of shock, normalization of platelet count, and resolution of transaminitis. The impact of calcium supplementation on these outcomes was analyzed.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software (version 20.0, Chicago, IL, USA). Descriptive statistics were used to summarize demographic and clinical parameters. Continuous variables were expressed as mean with standard deviation (SD), and categorical variables were expressed as numbers and percentages. The significance of differences between groups was assessed using appropriate statistical tests, including the chi-square test for categorical variables and t-test or ANOVA for continuous variables. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee. Written informed consent was obtained from all participants before their inclusion in the study. The study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki and its later amendments.

Results

Demographic and Clinical Parameters

The study included a total of 150 dengue patients, consisting of 104 males (69.3%) and 46 females (30.7%), with ages ranging from 18 to 80 years and a mean age of 39.1±12.4 years. The mean BMI of the population was 21.97±1.81 kg/m². Heart rate ranged from 59 to 148 beats per minute, with a mean of 89.26±24.60 bpm. The mean systolic blood pressure was 117.43±15.65 mmHg, and the mean diastolic blood pressure was 72.29±10.99 mmHg. The mean calcium level at admission was 8.717±0.8708 mg/dL. Hematocrit levels ranged from 33 to 56%, with a mean of 44.27±6.033%. The mean hemoglobin level was 12.482±1.2579 g/dL, and the mean platelet count was 140,300±79,641 cells/cumm (Fig 1) (Table 1).

Prevalence of Hypocalcemia

Hypocalcemia was observed in 40.7% of the patients. Among these, 30 patients (20%) had mild hypocalcemia (8.0–8.39 mg/dL), 21 patients (14%) had moderate hypocalcemia (7.5–7.99 mg/dL), and 10 patients (6.7%) had severe hypocalcemia (<7.5 mg/dL). The remaining 89 patients (59.3%) had normal calcium levels (≥8.4 mg/dL) (Fig 2) (Table 2).

Severity Correlation

Hypocalcemia was more prevalent in severe dengue cases. Among the patients with severe hypocalcemia, a significant association was observed with dengue shock syndrome (DSS). Specifically, of the 10 patients with severe hypocalcemia, 6 had DHF 1 & 2, and 2 had DSS. In contrast, the majority of patients with normal calcium levels were categorized under Dengue Fever (DF) (Table 3).

Outcomes

The duration of hospital stay was longer for patients with hypocalcemia compared to those with normal calcium levels. In patients with mild hypocalcemia, those who received calcium supplementation had a reduced mean hospital stay of 3.13 days compared to 3.6 days for those who did not receive supplementation, indicating an improvement in outcomes with calcium supplementation (Table 4).

Duration to Achieve Normocalcemia

The mean duration to achieve normocalcemia varied with the severity of hypocalcemia. For patients with mild hypocalcemia, the mean duration to achieve normocalcemia was 1.67±0.994 days. For those with moderate hypocalcemia, it was 2.9±0.7 days, and for those with severe hypocalcemia, it was 4.5±0.527 days (Table 5).

Table 1: Demographic and Clinical parameters of study population

Parameter	Mean ±SD (Range)	N = 150
Age (years)	39.1±12.4	18-80
BMI (kg/m²)	21.97±1.81	18.9-29
Heart Rate (bpm)	89.26±24.60	59-148
Systolic BP (mmHg)	117.43±15.65	78-142
Diastolic BP (mmHg)	72.29±10.99	38-90
Calcium (mg/dL)	8.717±0.8708	7.2-10.7
Hematocrit (%)	44.27±6.033	33-56
Hemoglobin (g/dL)	12.482±1.2579	9.2-15.1
Platelet Count (x10³/cumm)	140.3±79.641	21-430

Table 2: Prevalence of hypocalcemia in dengue patients

Calcium Level	Frequency (n)	Percentage (%)
Normal (≥ 8.4 mg/dL)	89	59.3
Mild Hypocalcemia (8.0–8.39 mg/dL)	30	20.0
Moderate Hypocalcemia (7.5–7.99 mg/dL)	21	14.0
Severe Hypocalcemia (< 7.5 mg/dL)	10	6.7
Total	150	100.0

Table 3: Severity of dengue fever and hypocalcemia

Severity of dengue	Normal calcium	Mild hypocalcemia	Moderate hypocalcemia	Severe hypocalcemia	Total
Dengue Fever	71	18	12	2	103
DHF 1 & 2	15	8	3	6	32
DHF 3	3	4	6	2	15
Total	89	30	21	10	150

Table 4: Duration of hospital stay based on calcium supplementation in mild hypocalcemia

Group	Mean Hospital Stay (days)	Number of Patients (n)
Supplemented with Calcium	3.13	15
Not Supplemented with Calcium	3.6	15
Total	3.36	30

Table 5: Duration to Achieve Normocalcemia Based on Severity of Hypocalcemia

Severity of Hypocalcemia	Mean Duration to Achieve Normocalcemia (days)	Standard Deviation (SD)	Number of Patients (n)
Mild	1.67	0.994	30
Moderate	2.9	0.7	21
Severe	4.5	0.527	10
Total	2.23	1.407	61

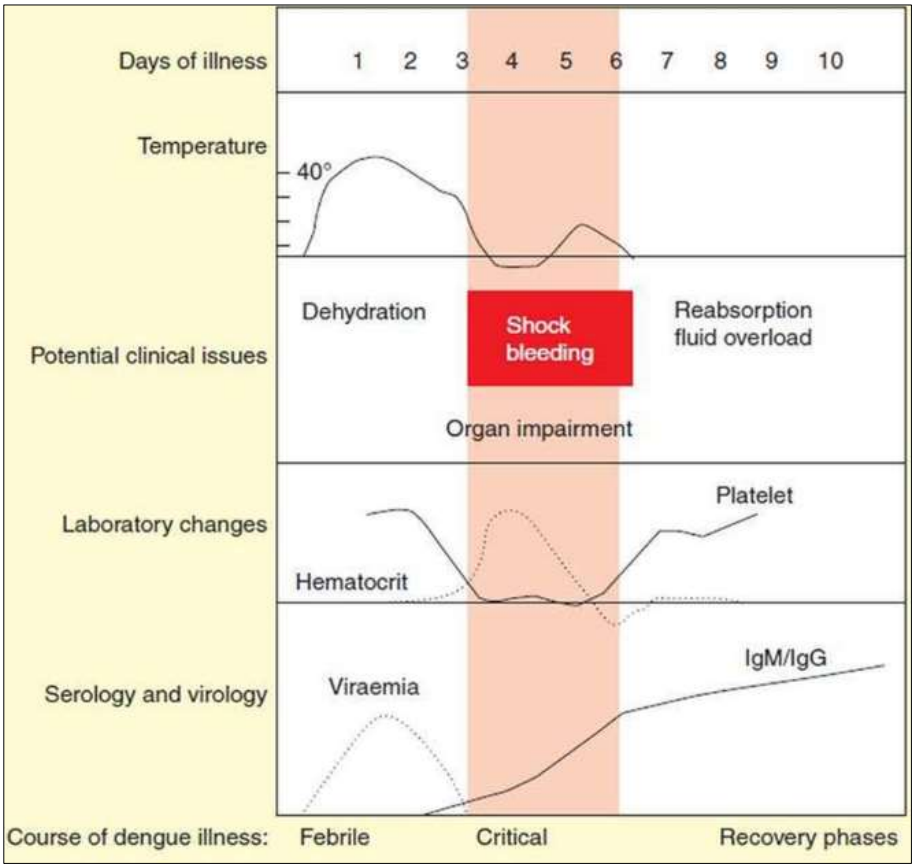

Fig 1: Course of dengue illness

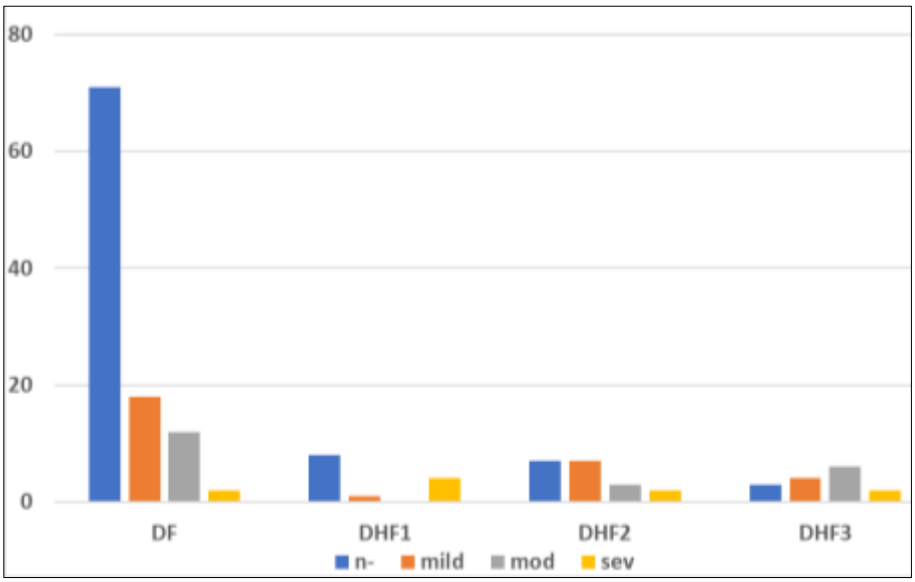

Fig 2: Severity of dengue with hypocalcemia

Discussion

Prevalence of Hypocalcemia in Dengue Patients

The present study highlights the significant prevalence of hypocalcemia among dengue patients, observed in 40.7% of the study population. This finding aligns with existing literature indicating hypocalcemia as a common biochemical abnormality in dengue fever [23]. The high prevalence underscores the need for routine monitoring of calcium levels

in dengue patients to identify those at risk of severe disease early.

Correlation between Hypocalcemia and Dengue Severity

A notable finding of this study is the strong correlation between hypocalcemia and the severity of dengue fever. Severe hypocalcemia was significantly associated with dengue shock syndrome (DSS) and more severe forms of dengue hemorrhagic fever (DHF). This correlation supports the hypothesis that hypocalcemia may serve as a marker for severe dengue, potentially due to its role in various physiological processes disrupted during severe infection [24]. The significant association between low calcium levels and severe disease outcomes emphasizes the importance of electrolyte monitoring in dengue management protocols [25].

Mechanisms of Hypocalcemia in Dengue

The mechanisms underlying hypocalcemia in dengue fever are multifaceted. Dengue-induced plasma leakage, binding of calcium to viral particles, and secondary metabolic disturbances such as hypoalbuminemia and hypomagnesemia have been proposed as contributing factors [29]. The role of the immune response, particularly the cytokine storm associated with severe dengue, may also contribute to alterations in calcium homeostasis [30]. Further research is needed to elucidate these mechanisms and determine how best to address them therapeutically.

Clinical Implications

The clinical implications of this study are significant. Identifying hypocalcemia as a prevalent and impactful factor in dengue fever can help refine treatment protocols and improve patient outcomes. Routine monitoring of calcium levels in dengue patients could become a standard practice, enabling early intervention and potentially reducing the incidence of severe disease manifestations.

Limitations

This study, while comprehensive, has certain limitations. The sample size, though adequate, could be expanded in future studies to confirm these findings across larger and more diverse populations. Additionally, the study's observational nature means that while correlations can be drawn, causation cannot be definitively established. Randomized controlled trials are necessary to conclusively determine the efficacy of calcium supplementation in improving clinical outcomes in dengue patients.

Future Directions

Future research should focus on larger, multi-center studies to validate these findings and explore the mechanisms behind hypocalcemia in dengue fever more deeply. Investigating the role of other electrolytes and their interactions with calcium in the context of dengue could also provide valuable insights. Moreover, exploring the timing and dosage of calcium supplementation in clinical trials could help establish standardized treatment protocols.

Conclusion

In conclusion, this study underscores the significant prevalence of hypocalcemia in dengue patients and its strong correlation with disease severity. Routine monitoring and early intervention for hypocalcemia could enhance patient care, reduce morbidity, and improve recovery times, ultimately contributing to better health outcomes in dengue-endemic regions.

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