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Assessment of Hematological Laboratory Parameters between Diabetic and Non Diabetic Patients with Dengue

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Abstract:
Background: *Dengue (break-bone fever) is a vector-borne viral disease caused by the dengue virus (DENV) spreads through the infected female mosquito bite. Aedes aegypti mosquito act as vector in transmitting the disease to humans. The dengue virus initially replicates in the mosquito midgut later disseminate to secondary tissues, including the salivary glands. Diabetes Mellitus has been significantly linked to chronic inflammation is unambiguous. Our study aims to compare the severity of dengue infection among diabetic and non-diabetic populations in JSS hospital, Mysuru, Karnataka.*
Materials and methods: *We conducted observational study on 220 patients (75 diabetic and 145 non-diabetics) who suffered from dengue infection. The study involved the collection of data of the dengue patients and evaluation of the systolic blood pressure, glucose level, cholesterol level, triglycerides and hematocrit levels in patients with diabetes and non diabetes dengue patients.*
Results: *Regression model was created using serum albumin, total Protein, triglycerides, cholesterol, BUN, SGOT and SGPT as dependent variables and WBC, platelet count and haematocrit as independent variables. The present study reveals that the impact of type 2 diabetes (DM2) on severity of dengue had a higher rate of WBC count; haematocrit and platelet count in diabetes than non diabetic patients. Cholesterol ($p \leq 0.0132$), serum albumin ($p \leq 0.0458$) and BUN ($p \leq 0.0366$) were significantly impacting WBC count of dengue diabetics; Serum albumin ($p\_ \leq 0.0145$), SGOT ($p \leq 0.041$), triglycerides ($p \leq 0.019$) and total Proteins ($p \leq 0.0194$) were significantly impacting HCT dengue diabetics; Cholesterol ($p \leq 0.0186$) was significantly impacting Platelet count of dengue diabetics.*

Keywords: *Dengue virus; Diabetic; Thrombocytopenia; Leucopenia; Immunopathogenesis.*

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I. Introduction:

Globally, dengue has been identified by World Health Organization (WHO) as one of the four main life-threatening infections mosquito borne disease, which cause acute febrile illness and is highly prevalent in tropical as well as subtropical countries (Jentes et al., 2016). The dengue virus (DENV) has RNA as a genetic material and belongs to the genus *flavivirus*, and there are four serologically and genetically distinct serotypes (DENV 1–4) worldwide causing mild to severe dengue illness from asymptomatic to symptomatic dengue fever (DF) to dengue hemorrhagic fever (DHF) (Gould et al., 1998). The incidence of dengue has grown rapidly around the globe in recent decades, with cases reported to WHO increased from 505 430 cases in 2000 to 5.2 million in 2019, 1.2 million cases reported in 2021 and increased dengue infection seen in 2023 due to the widespread presence of vector mosquitoes, representing two-fold the risk of severe disease and even death (WHO report 2023). Recently, PAHO has reported 339 126 cases (March 2023) of dengue and 83 corresponding deaths, in the Americas. Clinically, dengue is characterized by high levels of inflammatory markers like CRP, endocan and IL-8 (Kalayanarooj et al., 1997). Multiple sequential infections may occur with any of the four dengue serotypes that are specifically increased by capillary permeability and shock (Lee et al., 2020; Singh et al., 2022). Currently, the immunopathogenesis of dengue is exceedingly complex, with the preliminary dengue infection with one serotype inducing homotypic antibodies (to the homologous infecting serotype), which known provide long-term immunity against the infecting serotype. (Shet & Kang, 2019). In addition, symptomatic dengue is classified into three levels based on severity: dengue without warning signs, dengue with warning signs, and dengue with severe warning signs (persistent vomiting, mucosal bleeding, visceral pain, tenderness, hepatomegaly, thrombocytopenia) and severe dengue (severe plasma leakage, bleeding and severe organ involvement).

Diabetes Mellitus is a highly prevalent disease, and is proposed host risk factors for the development of severe dengue. Diabetes mellitus is known to increase a person's susceptibility to infection. It has been found to have adverse effects on the immune system, such as leukocyte adherence, phagocytosis and reduced chemotaxis. In endemic areas of dengue, concurrence between dengue and diabetes is possible (Singh et al., 2022). Diabetes mellitus is linked to impaired bone marrow function with lower RBC levels, mean corpuscular volume, and packed cell volume. This is thought to be due to the various toxic micromolecules that cause bone marrow depression and alter hematopoietic functions. Few studies have found a link between leucocyte count, packed cell volume, and insulin resistance, as well as higher triglycerides, insulin, and lower HDL in blood (Saeedi et al., 2020). Diabetes is associated with an increase in total leucocyte count and lymphocytes when compared to non-diabetics. Furthermore, it is linked to end-stage renal failure, which is characterized by elevated blood urea, serum creatinine, albuminuria, and urine albumin to creatinine ratios; it also causes nephropathy by causing changes in the renal parenchyma and blood vessels (Jaaban et al., 2021). In hyperglycemia and hypoglycemia conditions of dengue patients with preexisting diabetes mellitus have resulted in severely impaired glucose metabolism. The most common complications are diabetic ketoacidosis and hyperosmolar hyperglycemia. These patients primarily present with nausea, vomiting, and abdominal pain, symptoms that overlap with diabetic ketoacidosis and severe dengue (Thadchanamoorthy et al., 2020). In addition, hypoglycemia can occur in patients receiving oral hypoglycemic agents due to poor oral intake or vomiting in dengue patients. Individuals with diabetes tend to have higher risk for morbidity and mortality from commonly found infections (Baretic & Bralic Lang, 2020). Some studies have focused on bacterial infection, and some have focused on the interaction between diabetes and severity of viral infection. The relationship between severe dengue and co-morbidities such as diabetes mellitus must be determined because the prevalence of both diseases is increasing globally, and awareness can help to reduce morbidity and mortality. In this study, we have compared hematological laboratory parameters between diabetic and non-diabetic dengue patients because thrombocytopenia is one of the vital clinical features in dengue disease and can be functional indicator of severity of dengue infection.

II. Materials And Methods:

This retrospective study was carried at a tertiary care - JSS hospital, Mysore, Karnataka, South India from March 2019 to March 2020. All febrile patients with any one of the symptoms of dengue, like severe headache, retro orbital pain, severe myalgia, arthralgia, and rash were considered for the study. Dengue infection was further confirmed by Dengue NS1 antigen (DENV Detect™ NS1 ELISA Kit) or Dengue IgM Antibody ELISA (DENV Detect™IgM Capture ELISA Kit) as per the manufacturer's instruction. A total of 220 admitted dengue positive cases were recruited under this study. Pregnancy cases, patients with chronic infections or autoimmune diseases were excluded from the study.

The demographic details, their co-morbid conditions, blood pressure, duration and medication received for diabetes and blood pressure were obtained in a detailed proforma with prior patient consent. Institutional Ethical Clearance was obtained from the Institute. Based on the clinical manifestations as per CDC guidelines dengue positive cases were further divided into Dengue without warning signs (febrile illness with more than two clinical symptoms of dengue), with warning signs (abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, and liver enlargement) and majority of the times dengue with warning signs acts a predictor for severe dengue and severe dengue (severe plasma leakage leading to shock or fluid accumulation with respiratory distress; severe bleeding; or severe organ impairment such as elevated transaminases ≥1,000 IU/L, impaired consciousness, or heart impairment). The data of Random Blood sugar lever, glycated hemoglobin (HbA1c), Creatinine, BUN, Serum albumin, SGOT, SGPT, Cholesterol, Trigylcerides and total proteins, Hematocrit, Platelet counts, WBC count etc were obtained from their medical records. Data obtained from the study were analyzed by IBM SPSS software version 20. Majority of the data are presented in Mean ± standard deviation (SD). Student t- test was used to compare the variables between diabetic and non-diabetic dengue patients. Multiple linear regression analysis was used to analyze platelet counts, WBC counts and hematocrit percentage as independent variables against serum albumin, total protein, triglycerides, cholesterol, BUN, SGOT and SGPT as dependent variables between diabetic and non-diabetic dengue patients.

III. Results:

Off the 220 dengue positive patients, 75 (34.09%) were diabetic and 145 (65.90%) were non diabetics. Majority of dengue diabetics and non-diabetics were in the age group of 40-60 years and their mean age was 56.51+ 9.87 and 44.23+ 16.05 respectively as given in the Table 1. Among the both dengue diabetic and non-diabetic male preponderance was observed, sixty five percent of the diabetic patients had dengue with warning signs followed by severe dengue (20%), however in non-diabetics 77.24% of the patients had dengue without

warning signs, followed by 20.68 % of dengue with warning signs (table 2), suggesting that diabetes could be attributed to dengue with warning signs and severe dengue.

BUN, SGOT, SGPT, cholesterol, triglycerides are some of the Hematological parameters showed a significant changes whereas creatinine, serum albumin, SGPT and total proteins did not show much difference between the two groups as shown in the Table 2. Also, significant changes were noted in platelet count, WBC count in the first three days of hospitalization especially in diabetic dengue patients. Though we did not observe 20% increase in the hematocrit percentage but we noticed downfall in the percentage of hematocrit in case of dengue diabetic patients especially in the first two days of hospitalization as mentioned in Table 3.

From the Regression analysis it was noticed that, though we tested several blood parameters only few parameter showed significant impact on WBC, HCT and platelet count. Cholesterol, serum albumin and BUN were significantly impacting WBC count of dengue diabetics; Serum albumin, SGOT, triglycerides and total Proteins were significantly impacting HCT dengue diabetics; Cholesterol was significantly impacting Platelet count of dengue diabetics as in table 4.

IV. Discussion:

Increased blood sugar level is established to reduce the defense mechanism of the host by altering the functions of phagocytosis, intracellular killing and chemotaxis of polymorphonuclear leukocytes leading to accelerating the morbidity and mortality due to life threatening infections (Alexiewicz, 1995; Delamaire et al., 1997). Majority of studies are available to elucidate the role of diabetes on bacterial infection however limited studies are available with respect to viruses (Bravo, 1987; Sangiorgio et al., 2000). Therefore the current study is aimed to attribute the role of diabetes in dengue patients. Nevertheless we studied several haemtological parameters among diabetic and non-diabetic dengue positives, only few parameters like WBC, Hematocrit and platelets turned to show a strong association between diabetes and dengue. On a global scale, both the cases of dengue and diabetes are surging (removed our study). Based on the inclusion criteria 220 positive dengue samples were included in the study. The prevalence of diabetes among the dengue positives was 34.09% (75/220). The prevalence of diabetes in our study was high when compared to other studies conducted by Lattetal from Bangkok; Lee et al from Taiwan; Figueiredo et al from Brazil; Pang et al from Singapore, they all noted the prevalence of 2.65%, 16.8%, 5.3%, 6.4% respectively (Lee et al., 2006; Figueiredo et al., 2010; Pang et al., 2012 and Latt et al., 2020). Our results were in concordance with study conducted by Karunakaran et al, from Kerala, South India; they witnessed 40% of positivity in their study. The mean age of the dengue positives among the diabetic patients was 56.51$\pm$ 9.87, whereas in case of non-diabetic it was 44.23$\pm$ 16.0. Similar to Singh et al, we noticed maximum number dengue positive diabetes patients in the age group of 46-60 years (Singh et al., 2022). Considerable number of studies noted that adult diabetic dengue patients are more prone to develop DHF. A case control study conducted by Pang et al., revealed the same, when they adjusted the odd ratio of 1.78 (1.06 - 2.97) at the time of the epidemic; to correlate the role of co-morbidities with DHF, multivariate regression analysis was used by them (Pang et al., 2012). The inflammatory markers like IL-6, IL-10 and CRP in the serum were positively associated with dengue severity in diabetic dengue positive patients (Marimoutou et al., 2012). Similar results were also observed by Singh et al especially with CRP there was double fold increase in diabetic dengue (35.308 ± 1.32) mg/dl compared to non-diabetic dengue (18.6365 ± 0.64) mg/dl (Singh et al., 2022). In diabetic dengue patients the WBC count was suboptimal (3.51$\pm$2.32) compared to non-diabetic dengue patients (4.01$\pm$1.14) Table 3. In both the cases though the WBC count started increasing after two days of hospitalization. Chen et al., on the other hand did not find much difference of WBC count among the diabetic and non-diabetic dengue groups. However in their study also, a rise in WBC count was witnessed after three days of hospitalization (Chen et al 2015). Similarly, leukopenia was noticed in first two days of hospitalization and a steady recovery has been observed by Chaloemwong et al., 2018 and Ananda Rao et al., 2020. The probable reason for developing leukopenia could be due to, in the first seven days of fever there will be disruption of myeloid progenitor cells with hypo cellular bone marrow cells. From the fifth day of fever to ninth day of fever, atypical lymphocyte starts emerging and peaks up on the seventh day of fever. Generally, hematocrit level in dengue patients either increases or decreases by 20% than the haemoconcentration because of plasma leakage and it normalizes as soon as plasma leakage stops. Plasma leakage is mainly due to apoptosis of endothelial cells by the cross reaction tumor necrosis factor (TNF)-alpha a pro-inflammatory mediators and anti-NS1 antibodies with surface proteins present on endothelial cells (Martina et al., 2009). HCT is one of the important parameters involved to decide the severity of dengue and also helps in the management of dengue (CDC). In the present study the HCT was decreased in diabetic (35.57$\pm$4.94) when compared to non-diabetic dengue (41.26$\pm$4.21) and HCT started to recover within two to three days of hospitalization. Contradictory results were observed with respect to HCT percentage among them (Chen et al 2015). In good number of studies, thrombocytopenia is considered as the proficient marker for the severity of dengue (Sekaran et al., 2022). In dengue, the research is still going on to understand the steps involved in the pathophysiology of thrombocytopenia. Several theories have been put forwarded to explain the

pathophysiology. 1) It is believed that the dengue viruses curtail the capacity of progenitor cells to replicate by directly acting on these cells present in the bone marrow. 2) Dengue viruses are known to play a consequential role by altering the plasma-kinin system resulting in the abnormal immunological response, resulting in more and more depletion of platelets by disseminated intravascular coagulation (DIC). 3) Platelets undergoing apoptosis and formation of antiplatelet antibodies also escalate the damage (Ledika et al., 2015). Delay in the admission of dengue cases to hospital greater than 5 days from the onset of fever was also associated with dengue severity (Agarwal et al., 2018). In majority of the studies, among the DHF/DSS substantial number of cases had diabetes and had thrombocytopenia, proposing that diabetes may influence the dengue infection severity. Nonetheless, the pathophysiological role of diabetes in the subsequent development of DHF/DSS is yet to be elucidated. Various studies ascertained that the diabetes could be sequel of immune and endothelial dysfunction (Kaye etal., 1986; Geerlings et al., 1999; Dandona et al., 2004 and Hsueh et al., 2004). In the present study, a significant difference in platelet count has been noticed among the diabetic dengue and non-diabetic dengue. Our results are also associated with low platelet count and diabetes emphasizing the role of diabetes in thrombocytopenia and our results were in accordance with Chen et al., 2015. Akin to WBC count, platelet count also gradually started increasing after third day of hospitalization.

V. Conclusions

It is very important for the physicians to be aware of the role of hematological parameter which acts an indicator in developing the severity of dengue disease in order to start the treatment modalities as the treatment for dengue is mainly symptom based. Based on the results of our study we could say that among the dengue diabetics thrombocytopenia and leukopenia played a significant role in developing severe dengue. Also other blood parameters especially cholesterol played a critical role with severe thrombocytopenia and leukopenia.

Conflicts of Interest:
The authors declare no conflict of interest.

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