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Original Research Article

Comparative study of Clinicolaboratory parameters of dengue in diabetic and non-diabetic from a tertiary care hospital

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ABSTRACT

Background: Dengue, neglected tropical disease, caused by a RNA virus belonging to Flaviviridae family. Comorbid conditions like diabetes mellitus, can lead to severe dengue leading to higher morbidity and mortality. This study was undertaken to compare the clinical and laboratory profile of dengue patients with and without diabetes mellitus.

Materials and Methods: A retrospective study conducted at the tertiary care hospital. The clinical and laboratory details of the adult patients diagnosed with dengue from January 2014 to March 2019 were included in the studied. The data was entered in Microsoft excel and analyzed.

Results: We have analyzed the hematological, hepatic and renal parameters in three groups: healthy individuals (n= 80), patients with diabetes (n= 66) and dengue (n= 422). Among the patients diagnosed with dengue, 393/422 (93. 12%) survived. Among the dengue patients who were diabetic (129), 115 (89. 14%) survived and 14 (10. 85%) succumbed. The most common symptoms in dengue patients were fever (100%), vomiting (53. 32%) and body ache (51. 9%). In deceased patients, symptoms of severe dengue like reduced urine output, bleeding manifestations, pedal oedema, altered sensorium were noted. Signs of fluid leak like ascites and pleural effusion were higher in deceased patients. Among the deceased patients, anaemia, thrombocytopenia, increased renal parameters were observed in diabetic patients.

Conclusion: Dengue in diabetic patients is associated with anemia, thrombocytopenia and higher mortality. There is no significant difference in hepatic and renal parameters in survived dengue diabetic and non-diabetic patients, but deceased patients had significant thrombocytopenia and increased renal parameters.

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1. Introduction

Dengue, a neglected tropical disease, is an arboviral infection caused by virus belonging to Flaviviridae family, transmitted by the infected Aedes mosquito.¹ There are five serotypes of Dengue virus (DENV 1-5), worldwide. Dengue, being endemic in tropical and subtropical countries, it is estimated that 2. 5 billion

people are at risk of getting infected in more than 100 countries.¹ The spectrum of disease caused by dengue can vary from asymptomatic seroconversion to symptomatic severe disease leading to death. Presently, symptomatic dengue is classified into three levels depending on severity as dengue without warning signs, dengue with warning signs (persistent vomiting, mucosal bleed, abdominal pain/tenderness, lethargy, liver enlargement, thrombocytopenia) and severe dengue (severe plasma leakage, severe bleeding, severe organ involvement).^{1,2} Vulnerable patients like,

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children, elderly and in pregnancy and patients with pre-existing co-morbidities like diabetes mellitus, hypertension and renal insufficiency have higher chances of developing severe dengue and higher fatality rates.³

Diabetes mellitus, being a metabolic disorder, is associated with deranged bone marrow functions. Anemia with reduced RBC levels, mean Corpuscular volume and packed cell volume is being reported in diabetic patients. This is postulated to the various toxic micromolecules causing bone marrow depression and altering the hematopoietic functions.⁴ Anaemia is reported with higher degree in diabetic patients developing nephropathy.⁵ It is also observed in few studies the relation between leucocyte count, packed cell volume and insulin resistance with increased triglycerides, insulin and lowered HDL in blood, and occurrence of central obesity.⁶ Diabetes is associated with higher total leucocyte count and lymphocytes, but lower neutrophil count compared to non-diabetics.⁷ Diabetes mellitus is associated with end stage renal failure associated with increased blood urea, serum creatinine, albuminuria and urine albumin to creatinine ratio.⁸ The change in the renal parenchyma and the blood vessels in diabetes mellitus is the caused for nephropathy in diabetes.⁸

Diabetes mellitus is one of the common causes for liver disease and one of the indications for liver transplantation in Western countries.^{9,10} The disease pattern has been studied with deranged hepatic enzymes, non- alcoholic fatty liver disease, cirrhosis and even hepatocellular carcinoma.^{9,11} There is imbalance in metabolism of fatty acid in liver. The mechanism of uptake, anabolism of fatty acid and its oxidation and export is associated with dyslipidemia (low HDL and high triglycerides).¹² This is attributed to insulin resistance in diabetes leading to lipolysis and increased circulating free fatty acids.¹² Various chemical mediators like tumor necrosis factor (TNF)- α , which are pro-inflammatory and adiponectin levels, anti-inflammatory, play a major role in liver disease in diabetes.¹² Increased insulin resistance is associated impaired glucose tolerance leading to fibrosis and hepatic cirrhosis.¹²

In dengue patients with preexisting diabetes mellitus, Glucose metabolism can get impaired severely resulting in both hyperglycemia and hypoglycemia.¹³ The major complications seen are diabetic ketoacidosis and hyperosmolar hyperglycemia.¹³ These patients' presents mainly with nausea, vomiting and pain abdomen, overlapping symptoms between diabetic ketoacidosis and severe dengue. Similarly, hypoglycemia can occur in patients with oral hypoglycemic agents either due to poor oral intake or vomiting in dengue.¹³ Overall this leads to electrolyte imbalance complicating the treatment of dengue in diabetic patients.¹³ The hematological parameters Thus, this study was undertaken to compare the clinical and laboratory profile of dengue patients with and without

diabetes mellitus.

2. Materials and Methods

This was a retrospective observational study conducted in department of microbiology of a medical college with tertiary care hospital attached in India, after the obtaining clearance from institutional ethics committee (FMC/IMEC/253/2019) All the adults above 18 years who were diagnosed with dengue between January 2015 and December 2019 were included in the study. Details present in the files of patients who had succumbed to dengue were also noted. The case definition was based on the compatible history, confirmed by Dengue serology as either NS1 or IgM positive. These patients were categorized as one with diabetes and one without diabetes mellitus. The patients were diagnosed as diabetic, if their fasting blood sugar level was more than 126 mg %. The dengue patients were categorized into two groups one with diabetes mellitus and one without diabetes mellitus. Two more groups were included in the study; age and gender matched controls, who had no pre-existing diseases, who had come for general check up in the hospital and another group of patients who were known cases of diabetes mellitus included into the study. Patients diagnosed with other infectious disease like malaria, leptospirosis, tuberculosis, HIV, typhoid were excluded from the study. The demographic details, clinical features and laboratory parameters mainly hematology and biochemical, were studied among the four group of patients. The details were entered in Microsoft excel and analyzed with standard deviation.

3. Results

During the study period, a total of 422 patients were diagnosed with Dengue, among them, 129(30. 56 %) were diagnosed and were on treatment for Diabetes mellitus. The control group constituted for 80, age and gender matched patients and 66 Diabetic patients were included in the study (Table 1). The gender and age wise distribution of the study population is presented in the table. Fever (422,100%) was the most common symptoms, followed by vomiting (53. 32%) and headache (51. 9%). Out of 422 diagnosed with Dengue, 393(93. 12%) were successfully treated and discharged. Among the dengue patients who were diabetic (129), 115 (89. 14%) survived and 14 (10. 85%) succumbed. The mean age of diabetic dengue patients who succumbed were higher than compared to non-diabetic patients. A mean age difference of 10 years higher was observed among the survived diabetic dengue compared to non-diabetic dengue patients. Among the deceased patients, an age difference of 20 years was observed (Table 2).

Among the survived patients presented with mild symptoms like fever, vomiting, myalgia, headache and skin rashes, whereas the deceased patients presented with

Table 1: The details on gender, age, symptoms signs and radiological diagnosis of the people affected with Dengue with and without type II diabetes

| | | Healthy individuals (healthcare check up) | | dengue (n=422) | | | |
|----------------------------|---------------|--|---------------------|------------------------------------|-----------------------|--------------------------------------|----------------------|
| | | | | Survived Dengue (n=393, 93.12%) | | Succumbed to Dengue (n=29, 6.87%) | |
| | | Healthy individuals (n=80) | Diabetics (n=66) | No DM (n=278, 70.73%) | DM (n=115, 29.26%) | No DM (n=15, 51.72%) | DM (n=14, 48.27%) |
| Gender | Male | 58 (72.5) | 54 (81.82) | 217 (78.06) | 98 (85.22) | 7 (46.67) | 7 (50) |
| | Female | 22 (27.5) | 12 (18.18) | 61 (21.94) | 17 (14.78) | 8 (53.33) | 7 (50) |
| Age (Yrs) | >18-30 | 46 (57.5) | 17 (25.76) | 101 (36.33) | 18 (15.65) | 3 (20) | 0 |
| | 31-45 | 12 (15) | 20 (30.30) | 80 (28.78) | 26 (22.61) | 6 (40) | 1 (7.14) |
| | 46-60 | 13 (16.25) | 22 (33.33) | 73 (26.26) | 40 (34.78) | 6 (40) | 3 (21.43) |
| | >61 | 9 (11.25) | 7 (10.61) | 24 (8.63) | 31 (26.96) | 0 | 10 (71.43) |
| | Fever | | | | 278 (100) | 115 (100.00) | 15 (100) |
| Symptoms | Vomiting | | | 156 (56.12) | 57 (49.57) | 8 (53.33) | 4 (28.57) |
| | Headache | | | 113 (40.65) | 99 (86.09) | 3 (20) | 4 (28.57) |
| | Body ache | | | 77 (27.70) | 83 (72.17) | 5 (33.33) | 4 (28.57) |
| | Pain | | | 69 (24.82) | 29 (25.22) | 6 (40) | 8 (57.14) |
| | Abdomen | | | | | | |
| | Skin Rashes | | | 47 (16.91) | 19 (16.52) | 0 | 0 |
| | Reduced | | | 9 (3.24) | 24 (20.87) | 8 (53.33) | 9 (64.29) |
| | Urine Output | | | | | | |
| | Joint Pain | | | 48 (17.27) | 2 (1.74) | 0 | 0 |
| | Bleeding | | | 0 | 0 | 4 (26.67) | 4 (28.57) |
| | Manifestation | | | | | | |
| | Pallor | | | 5 (1.80) | 3 (2.61) | 8 (53.33) | 8 (57.14) |
| | Signs | Hypotension | | | 10 (3.60) | 4 (3.48) | 4 (26.67) |
| Pedal Oedema | | | | 8 (2.88) | 0 | 4 (26.67) | 4 (28.57) |
| Altered | | | | 0 | 0 | 6 (40) | 2 (14.29) |
| USG Abdomen Findings | Sensorium | | | | | | |
| | Ascites | | | 47 (16.91) | 9 (7.83) | 2 (13.33) | 5 (35.71) |
| | Pleural | | | 32 (11.51) | 5 (4.35) | 2 (13.33) | 4 (28.57) |
| | Effusion | | | | | | |
| | Hepatomegaly | | | 15 (5.40) | 4 (3.48) | 3 (20) | 4 (28.57) |
| | Splenomegaly | | | 4 (1.44) | 4 (3.48) | 3 (20) | 4 (28.57) |

reduced urine output and bleeding manifestations. Among the signs, pallor, hypotension, pedal oedema and altered sensorium were seen in higher percentage in deceased patients. Signs of fluid leakage in interstitial space like ascites and pleural effusion were also reported in higher percentage in deceased patients especially in diabetic patients (Table 1). The comparison of fasting blood sugar, there was higher fasting blood sugar in diabetic dengue, both in survived and deceased groups (Table 2). The diabetic patients were anaemic, had higher total leucocyte count, neutrophils, monocytes, platelets and packed cell volume; lower lymphocytes, eosinophils compared healthy control group (Table 2). Both the hepatic and renal parameters were increased in diabetic patients.

Among the survived Dengue patients, the diabetic group were anemic, had higher total leucocytes, lymphocytes, eosinophils; lower neutrophils, monocytes, platelet counts and packed cell volume. The liver enzymes were increased but no difference was observed in total bilirubin among

the two groups. The blood urea and serum was increased in diabetic patients. The deceased diabetic dengue patients were significantly anaemic, had higher neutrophils; lower lymphocytes, monocytes, platelets, packed cell volume compared to non-diabetic. They had higher total bilirubin, lower liver enzymes and higher renal parameters.

4. Discussion

Diabetes mellitus is one of the leading causes of morbidity and mortality among the non-communicable disease, worldwide.⁶ Diabetes is associated with higher total leucocyte count and lymphocytes, but lower neutrophil count compared to non-diabetics.⁷ The complications associated with DM are mainly due to metabolic derangement and immune dysfunction.¹⁴ Diabetic Neuropathy is associated with urinary incontinence, gastroparesis, erectile dysfunction and nocturnal diarrhea.¹⁵ The macrovascular pathology commonly seen in DM is accelerated macrovascular atherosclerosis causing

Table 2: haematological, hepatic and renal parameters in various groups of the study

| Parameters studied | No dengue infection | | Dengue (n=422) | | | | F value P Value |
|---|----------------------------|---------------------------|---------------------------------|-----------------------------|------------------------------|-----------------------------------|-----------------|
| | Healthy individuals (n=80) | Diabetics (n=66) | Survived Dengue (n=393, 93.12%) | DM (n=115) | No DM (n=15) | Succumbed to Dengue (n=29, 6.87%) | |
| Age (in years) | 36.51±16.78 | 42.2±13.30 | 39.67±14.83 | 49.91±16.80 ^Z | 42.33±10.75 | 62.36±9.54 ^Z | 19.913 <0.001 |
| Fasting Blood Sugar (mg%) | 84.61±14.74 | 187.05±52.41 ^Z | 87.14±14.77 | 209.62±84.55 ^Z | 164±25.11 ^Z | 316.64±113.93 ^Z | 127.422 <0.001 |
| Haemoglobin (g%) | 12.59±1.50 | 11.93±2.1 | 14.21±1.86 ^Z | 13.7±2.38 ^X | 13.85±3.05 | 10.74±2.43 | 24.211 <0.001 |
| Total Leucocyte Count (/mm ³) | 7949.75±2386.90 | 9757.56±3039.9 | 5828.42±5370.18 ^T | 7187.74±5794.1 | 12366.67±8641.1 ^U | 12257.14±11612.7 | 13.92 <0.001 |
| Neutrophils (%) | 64.44±14.52 | 70.65±14.69 | 83.93±315.6 | 56.77±20.71 | 69.93±19.11 | 74.43±22.51 | 0.283 0.923 |
| Lymphocytes (%) | 29.25±14.07 | 18.94±12.57 ^W | 26.16±16.49 | 32.37±19.29 | 22.79±16.78 | 18.43±21.84 | 7.665 <0.001 |
| Eosinophils (%) | 4.18±5.04 | 3.52±3.65 | 1.81±2.26 ^Z | 7.24±4.10 ^Z | 1.73±1.79 | 1.25±0.62 | 43.529 <0.001 |
| Monocytes (%) | 2.46±1.72 | 6.86±3.13 ^Z | 8.43±4.02 ^Z | 2.08±1.93 | 6.55±5.03 ^X | 5.43±2.87 | 105.825 <0.001 |
| Platelet count (/mm ³) | 225175±86707 | 236151.52±112998 | 93311.15±63153 ^Z | 78192.17±83367 ^Z | 66060±119434 ^Z | 83571.43±102818 ^Z | 50.457 <0.001 |
| PCV | 39.66±4.04 | 42.18±5.89 | 42.45±5.45 ^Y | 41.77±6.84 | 43.16±9.12 | 33.11±6.79 ^Y | 9.21 <0.001 |
| Total Bilirubin (mg%) | 0.62±0.41 | 3.34±2.97 ^Z | 1.06±1.11 | 1.07±1.18 | 2.05±3.07 | 5.24±9.47 ^Z | 8.595 <0.001 |
| Apartate aminotransferase (IU/ml) | 26.62±11.15 | 85.26±74.44 | 120.62±283.54 | 305.44±748.44 ^Z | 549.93±530.73 ^Z | 582.75±630.89 ^Z | 39.813 <0.001 |
| Alanine aminotransferase (IU/ml) | 25.66±19.86 | 48.11±40.58 | 80.9±154.35 | 147.91±264.59 ^W | 402.80±453.52 ^Z | 450.36±527.09 ^Z | 22.105 <0.001 |
| Blood Urea (mg%) | 20.86±8.46 | 36.63±19.2 | 24.79±10.08 | 29.72±19.12 | 71.07±63.71 ^Z | 77.57±59.27 ^Z | 8.118 <0.001 |
| Serum Creatinine (mg%) | 0.75±0.25 | 1.23±0.81 | 1.04±0.24 | 1.27±1.23 ^V | 2.90±2.10 ^Z | 2.89±1.99 ^Z | 15.37 <0.001 |

Statistical comparison with Health individuals: z = P < 0.001, y = P < 0.001; X = 0.002; w = 0.003; v = 0.005, u = 0.04; t = 0.02.

ischemia in myocardium, cerebral cortex and lower extremities.¹⁶ Microvascular pathology causes mainly nephropathy and retinopathy.¹⁷ There is increased release of gamma-interferon and tumor necrosis factor- α , from the activated T lymphocytes, due to endothelial inflammation.¹⁸ Both being pro-inflammatory cytokines, causes increased capillary permeability leading to plasma leakage. This increases the risk of dengue hemorrhagic fever in diabetic patients.¹⁹ Thus, uncontrolled hyperglycemia is a confounding factor in development of complications in dengue like Dengue hemorrhagic fever, renal failure and mortality.^{20–22}

The viral infection like dengue is controlled by the host defense by phagocytosis and intracellular lysis of the virus, which is impaired in patients with uncontrolled diabetes leads to higher morbidity and mortality.^{23–25} In a study conducted in South Indian population, there was significantly higher incidence of severe dengue in patients with diabetes.²⁶ In this study we have tried to correlate the clinical, haemato- biochemical parameters among dengue patients, with and without diabetes mellitus.

In our study population, the dengue infection was seen mainly in adult males below 45 years, as observed in few studies conducted in South Indian Population.^{24–27} All patients presented with fever, followed by other common complaints like headache, retroorbital pain as reported by earlier studies.^{24,28} Eventhough not much difference were noted among the symptoms of diabetic and non-diabetic deceased patients, signs like pedal edema, pleural effusion, ascites were noted higher in deceased diabetic patients. Similarly, signs of reticulo-endothelial system involvement like hepatosplenomegaly were higher again in deceased diabetic patients. The diabetic dengue patients were found to be hyperglycaemic in both the survived and deceased groups due to stress hyperglycemia. The development of stress hyperglycemia is caused by a highly complex interplay of counter-regulatory hormones such as catecholamines, growth hormone, cortisol, and cytokines.²⁹ Corticosteroid treatment was associated with a slightly higher risk of hyperglycemia, but no adverse effects or prolongation of viremia.

We have observed that the non-diabetic dengue patients had higher hemoglobin and packed cell volume compared to diabetic dengue patients. This may be attributed to the plasma leakage, causing haemoconcentration, due to the release of proinflammatory cytokines like Tumor necrosis factor- α caused by anti-NSI antibodies interacting with surface proteins on the endothelial cells.³⁰ The deceased diabetic dengue patients were also had significant thrombocytopenia and DHF/DSS, which lead to multiple hemorrhage and thus anemia.

The absolute lymphocyte count in diabetic patients found to be lower to healthy individuals. The exact mechanisms of the effects of hyperglycemia on lymphocytes and T

lymphocytes are unclear. For dengue patients with T2DM, there is already an imbalance of T lymphocyte subsets. Moreover, patients with T2DM have decreased CD3+ T cells, which may be related to adaptive immune activation and chronic inflammation during the pathogenesis of T2DM.³¹ The diabetic with DHF/ DSS are prone for sepsis which causes neutrophilia and lymphocytopenia as observed in our patients.

The Diabetic dengue patients were significantly thrombocytopenic compared to non-diabetic dengue patients. Many studies have reported severe thrombocytopenia in diabetic dengue patients.^{24,32} The thrombocytopenia in diabetic dengue patients is not clearly understood, but suggested hypothesis is due to endothelial dysfunction.³³ The current hypothesis is that the immune mediated clearance of antibody coated platelets has been proposed. The cross reactivity of antibodies directed against NS1 antigen and platelets suggests the role of antiplatelet antibody in the pathogenesis of thrombocytopenia. In addition, complement-mediated platelets destruction plays an important role during dengue infection.³⁴

Being an antioxidant, bilirubin levels are increased to ameliorate the oxidative stress in diabetic patients compared to healthy individuals.³⁵ The liver enzymes were increased but no difference was observed in total bilirubin among the two groups. But, in Chinese patients, LFT was positively correlated platelet counts.³² Severe forms of dengue like DHS/ DSS are characterized by the presence of haemorrhages, hypotension, thrombocytopenia and plasma leakage, also accompanied by neurological alterations, conditions that could eventually lead to shock and multi-systemic failure and that could worsen in presence of comorbidities. Thus as a part of MODS and end stage the liver and renal functions are deranged among the deceased diabetic dengue patient.¹³ The deceased diabetic dengue patients were significantly anaemic and thrombocytopenia compared to non diabetic patients. The thrombocytopenia may be due to T cell activation causing release of inflammatory cytokines like tumor necrosis factor alpha and interferon gamma, leading to increased mortality.¹⁹

5. Conclusion

Dengue in diabetic patients is associated with higher mortality. Signs/ symptoms of severe dengue like reduced urine output, bleeding manifestations, altered sensorium and fluid leak like pedal edema, ascites and pleural effusion need to be looked for and treated appropriately for preventing mortality among the diabetic patients. The hematological parameters like anemia, thrombocytopenia is seen in deceased diabetics. There is no significant difference in hepatic and renal parameters in survived dengue diabetic and non-diabetic patients, but deceased patients have significantly increased renal parameters. The biggest drawback of the study is that as this was a

retrospective study, the data on HbA1c of the patients was not available to be collected for analysis. The detailed study on the other biochemical parameters like cholesterol which gets altered in diabetic patients was not available.

6. Conflict of Interest



The authors declare no conflict of interest with regards to the publication of this research review article.

7. Source of Funding

None.

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