RESEARCH ARTICLE

Impaired glucose tolerance in dengue fever: A case–control study

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ABSTRACT

Background: Studies on dengue fever demonstrated that the dengue viral infection of pancreas is often associated with disease morbidity and complication. Aims and Objectives: The pancreas-pathogen interactions in dengue-infected persons were evaluated using endocrine deregulation as an investigation marker of complication. Materials and Methods: A prospective observational study was conducted in a tertiary care medical college and hospital of West Bengal, over 1 year and 4 months. Blood samples from 286 cases and 258 controls were collected on day 2. After plasma glucose determination, 44 cases and 39 controls were excluded as frank cases of diabetes mellitus. On day 6, fasting and 2 h postprandial plasma glucose estimation were done in 73 cases and 61 controls by glucose oxidase-peroxidase method using autoanalyzer. Data were analyzed using the Statistical Package for the Social Sciences version 20.0. Results: The prevalence of impaired glucose tolerance was higher in cases on day 2 than on follow-up on day 6 (12.3% vs. 8%). There existed no statistical difference in terms of fasting plasma glucose between cases and control on day 2 and day 6 and postprandial (PP) plasma glucose on day 2. However, the PP values on day 6 in cases were significantly higher in comparison to controls (P = 0.006). Among cases, day 6 values were higher than day 2 values (0.016). Conclusion: Dengue viral infection correlates with the involvement of the pancreas in terms of impaired tolerance to glucose which has implications for understanding disease pathogenesis in terms of developing chronic complications.

KEY WORDS: Dengue Virus; Fasting Plasma Glucose; Postprandial Plasma Glucose; Impaired Glucose Tolerance

INTRODUCTION

Dengue, important arthropod-borne viral disease, affects more than 100 countries worldwide.¹ Since the 1990s, dengue outbreaks are occurring every few years in India with a post-monsoon peak.²³ Classical dengue fever presents with fever, headache, abdominal pain, diarrhea, bleeding, and skin rash, however, in few cases leads to severe dengue hemorrhagic fever and dengue shock syndrome.⁴⁵ Since dengue cases are increasing, atypical findings and complications are gradually appearing which are coined as expanded dengue by the World Health Organization.⁶ Pancreatic involvement has been reported in dengue infections.⁷⁸ With this background, we assessed plasma glucose in dengue cases to determine the glucose tolerance status.

MATERIALS AND METHODS

This was a prospective observational study conducted in the department of microbiology, in collaboration with the department of biochemistry of a tertiary care medical college
RESULTS

The plasma glucose levels in fasting and PP state of all the cases and controls were expressed in terms of mean and standard deviation [Table 2]. The prevalence of impaired glucose tolerance (IGT) was higher in cases on day 2 than on follow-up on day 6 (12.3% vs. 8% [Table 1]). There existed no statistical difference in terms of fasting plasma glucose between cases and control on day 2 and day 6 and PP plasma glucose on day 2. However, the PP values on day 6 in cases were significantly higher in cases in comparison to controls (P = 0.006 [Table 3]). Among cases, day 6 values were higher than day 2 values (P = 0.016 [Table 4]).

DISCUSSION

In the present study, there was no statistically significant difference between fasting glucose levels of cases and controls on day 2, between PP glucose levels of cases and controls on day 2, between fasting glucose levels of cases and controls on day 6, between fasting glucose levels of cases on days 2 and 6, between PP glucose levels of controls on days 2 and 6, and between PP glucose levels of controls on days 2 and 6 [Tables 3 and 4]. However, there was a statistically significant difference between PP glucose levels of cases on days 2 and 6 and statistically highly significant difference between PP glucose levels of cases and controls on day 6 [Tables 3 and 4]. Furthermore, within the cases, percentage of patients having IGT increased from 8.0% on day 2 to 12.3% on day 6 [Table 2]. Thus, in the present study, there was increase in glucose levels in the PP but not in fasting state, with progression of duration of dengue.

Development of Type 1 DM in human beings has been incriminated in the past to viral infection. On the basis of temporal and geographical associations, the common offending agents were enteroviruses, Coxsackie B virus, retroviruses, rubella, mumps, cytomegalovirus, Epstein–Barr, and varicella zoster virus. In cases of recently diagnosed diabetes, there has been serological evidence of infection and isolation of viruses from the pancreas of reported cases.\[9\,10\]

Table 1: Division of cases and controls according to plasma glucose levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 2</th>
<th>Day 6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DM</td>
<td>IGT</td>
</tr>
<tr>
<td>Cases</td>
<td>44 (15.4%)</td>
<td>23 (8.0%)</td>
</tr>
<tr>
<td>Controls</td>
<td>39 (15.1%)</td>
<td>21 (8.1%)</td>
</tr>
</tbody>
</table>

DM: Diabetes mellitus, IGT: Impaired glucose tolerance, n: Normal

Table 2: Mean plasma glucose levels (mg/dl) in subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Fasting</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>86.9±12.8</td>
<td>117.3±14.1</td>
</tr>
<tr>
<td>Control</td>
<td>89.2±14.6</td>
<td>115.6±17.2</td>
</tr>
</tbody>
</table>

Fasting and 2 h postprandial (PP) (after intake of 75 g of glucose) blood were collected from all participants. Plasma glucose was estimated by enzymatic colorimetric assay (glucose oxidase and peroxidase) method using biochemistry autoanalyzer (Erba XL360, Transasia). All the relevant data were analyzed by appropriate statistical tests using the Statistical Package for the Social Sciences version 20.0. \( P < 0.05 \) and 0.001 were considered as significant and highly significant.

Table 3: Division of cases and controls according to plasma glucose levels

<table>
<thead>
<tr>
<th>Plasma glucose</th>
<th>Fasting</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases versus controls</td>
<td>0.71</td>
<td>0.61</td>
</tr>
<tr>
<td>PP: Postprandial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Division of cases and controls according to plasma glucose levels

<table>
<thead>
<tr>
<th>Plasma glucose</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2 versus day 6</td>
<td>0.559</td>
<td>0.0162</td>
</tr>
<tr>
<td>PP: Postprandial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Previous reports have suggested that hyperglycemia was an independent predictor of death, and patients with even mild severe active respiratory syndrome (SARS) receiving no glucocorticoid medications during the course had a higher level of FPG. Follow-up study showed that diabetes occurred during the hospitalization of 20 of 39 patients who received no corticosteroids during the course of SARS. The previous case reports in two individuals presenting with acute insulin-dependent DM have revealed a causal relation between varicella zoster virus and the onset of DM. These studies establish a cause–effect relationship between viral infection and dysfunction of endocrine pancreas. Dengue is associated with the development of numerous complications including pancreatic disorders. Literature survey revealed one case report of dengue shock syndrome complicated by new-onset DM. This had made the authors to propose that these were due to direct inflammation and destruction of pancreatic acinar cells as an autoimmune response to pancreatic islet cells with viral infection as a triggering factor. Similarity between viral and islet cells antigens induces an autoimmune response causing edema of the ampulla of Vater, thereby obstructing the outflow of pancreatic fluid.

Other mechanisms responsible for increase in plasma glucose might include insulin resistance where chronic low-grade inflammation releases several mediators from various cell types, including several pro-inflammatory cytokines. Increase in interleukin (IL)-1 production in human macrophages during dengue infection was found by Cheung et al. Rachman and Rinaldi implicated high concentrations of IL-6 in coagulopathy in dengue. On the other hand, elevated TNF was detected in dengue fever and dengue hemorrhagic fever by Vitarana et al. Similarly, elevated plasma IL-10 levels in acute dengue were found to correlate with disease severity as proposed by Green et al. Mustafa detected increased levels of IL-13 and IL-18 in patients with dengue hemorrhagic fever. The proposed signaling pathways involved in dengue-2 virus infection are virus-induced over expression of RANTES, a member of IL-8 superfamily which acting as a selective attractant for memory T lymphocytes and monocytes causing tissue inflammation. Thus, several cytokines associated with IR are increased in dengue, and this also might lead to higher plasma glucose levels, which is a finding of the present study. In the present study, patients with apparent pancreatic complications were excluded from the study. However, in the opinion of the authors, the endocrine pancreas might have been involved, with resultant decrease in secretion of insulin, leading to rise in plasma glucose.

At this point, few limitations of the present study might be considered. Only patients attending the outpatient department were enrolled. However, in our country, most people visit district, sub-divisional, and lower-tier hospitals for treatment. Hence, results of this study might not reveal the true picture of the population as a whole, and data from the study should not be extrapolated blindly to the general population. Rather, a multicentric study with cosmopolitan population and larger number of subjects need to be taken up, to confirm the present findings. Further, more detailed investigations are warranted to evaluate pancreatic or other pathology so that the exact mechanism of hyperglycemia could be revealed. Moreover, long-term prospective studies are warranted to follow-up both the diabetic and newly discovered impaired cases during dengue infection to fathom the progress in terms of glycemia control. Despite these limitations, we believe that the study points toward IGT as an important, novel feature in dengue with far-reaching consequences. Hence, IGT may be taken into consideration when planning treatment strategy and monitoring.

CONCLUSION

The results of our study suggest that hyperglycemia may be related to dengue infection. This problem should be further investigated and assessed thoroughly.

REFERENCES


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