Study of Serum Adenosine Deaminase and Transaminases in type 2 Diabetes Mellitus

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Abstract: Adenosine deaminase (ADA) is an enzyme present in most human tissues. It is also known as adenosine aminohydrolase and involved in purine metabolism. It is an important marker of inflammation. Elevation of the main serum transaminases, aspartate transaminase (AST) and alanine transaminase (ALT) levels indicates liver cell injury. Liver is the main organ that regulates carbohydrate metabolism. Diabetes mellitus is associated with increased risk of liver disease. The aims of the study is to measure serum ADA and transaminases levels in type 2 diabetes mellitus (T2DM) subjects and healthy controls. And to find out any correlation between ADA, fasting blood sugar (FBS), Glycated haemoglobin (HbA1c) and transaminases The study was carried out in 60 cases of T2DM and 30 healthy controls. Serum ADA was measured spectrophotometrically based on Guisti and Galanti method. FBS, HbA1c, ALT and AST were measured in all the study subjects. Statistical analysis was done by using SPSS version 20. In this study, the mean serum ADA was significantly increased in T2DM as compared to controls. Mean FBS, HbA1c, ALT and AST were also significantly increased (p < 0.05) in T2DM as compared to controls. Serum ADA was found to have significant positive correlation with FBS and glycemic status in T2DM. No significant correlation was found between serum ADA and transaminases. The present study shows that there may be ongoing inflammation and hepatic injury in diabetic patients. Estimation of liver enzymes along with serum ADA may help in early detection of derangement of liver function and to prevent further complications.

Keywords: Type 2 Diabetes Mellitus, Adenosine deaminase, Alanine transaminase, Aspartate transaminase, Glycated haemoglobin.

I. Introduction

Diabetes mellitus is a chronic non-communicable diseases. The disease is emerging as a major global health problem due to population growth and ageing, economic development, urbanization with associated sedentary lifestyle, physical inactivity and increased obesity.¹ According to International Diabetes Federation (IDF) Diabetes Atlas 8th edition, there were 425 million people with diabetes worldwide in 2017, with one in two remains undiagnosed. The incidence is expected to rise to 629 million by 2045. Currently, India has a total of 74 million people with diabetes which is expected to rise to 134.3 million by 2045.² Diabetes mellitus is associated with hyperglycemia due to defect in either or both insulin secretion or insulin action. Type 2 diabetes mellitus (T2DM) is due to the relative insulin deficiency or resistance to insulin action. Type 1 diabetes mellitus is due to the absolute deficiency of insulin due to destruction of β-cells of the pancreas. If hyperglycemia is not treated, diabetes can lead to complications.³

Adenosine deaminase (ADA) is also known as adenosine aminohydrolase. It is an enzyme found in purine metabolism. It converts adenosine to inosine and ammonia. The activity of ADA is present in most human tissues.⁴ Macrophages and monocytes are the major sources of serum ADA. Release of ADA by these cells into their surrounding environments contributes to the relative elevation of serum ADA activity seen following an inflammatory response. Therefore, it is suggested as a marker of inflammation.⁵ Inflammation is an important feature in chronic diabetes that leads to long term complication particularly retinopathy and nephropathy.⁵

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Increased serum ADA activity has been reported in various liver diseases. Type 2 diabetes mellitus has been associated with different chronic liver diseases such as abnormal liver enzymes, nonalcoholic fatty liver disease (NAFLD), cirrhosis, hepatocellular carcinoma, and acute liver failure in severe cases. Derangement in liver function test (LFT) in diabetic subjects is usually due to NAFLD. Mild to moderate elevation of serum transaminases, alanine transaminase (ALT) and aspartate transaminase (AST) are commonly found in NAFLD. Serum ALT and AST are the common liver enzymes which serve as the primary markers for hepatocellular injury.

It has been reported that NAFLD is characterized by insulin insensitivity and decreased effects of insulin on glucose. Impaired insulin sensitivity or insulin resistance, an important feature of metabolic syndrome plays a role in the development of NAFLD. Raised serum ALT may be an indication of liver fat accumulation. The prevalence of NAFLD in type 2 diabetes mellitus as reported in other studies was 28 to 55%. Type 2 diabetes mellitus is also regarded as a risk for cardiovascular diseases. The risk of mortality from heart diseases and hepatic failure in type 2 diabetes is markedly increased but it is a much neglected aspect. The present study will estimate serum ADA and transaminases in T2DM and find out any possible association between ADA, FBS, HbA1c and transaminases.

II. Materials And Methods

The study was a case control study. The study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Porompat, Manipur. The period of study was from January 2017 to December 2017. The study was done after getting approval from JNIMS Institutional Ethics Committee. A written informed consent of the patients or their relatives was taken prior to inclusion.

Sixty (60) confirmed case of type 2 diabetes mellitus in the age group 30-70 years of either sex on oral hypoglycemic drugs attending out-patient and ward of Medicine department were included. Another thirty (30), age and sex matched non-diabetic healthy subjects who came for routine medical checkup were also included as controls. A detail history was taken and a thorough physical examination was carried out in each subject.

Exclusion criteria:
1. Type 1 diabetes mellitus
2. Patient with acute illness such as hepatitis, tuberculosis
3. Patients with underlying liver, kidney and lung diseases
4. Obesity
5. Hypertension
6. Chronic alcoholic patient
7. Patients on insulin therapy.

After taking informed consent, about 3 ml of venous blood was drawn under aseptic precaution after an overnight fasting. For the estimation of serum ADA, AST and ALT, plain vials were used. The blood was allowed to clot for 30 minutes and the serum was separated by centrifugation. Serum ADA was estimated based on the method described by Guisti and Galanti using spectrophotometer. For the estimation of HbA1c, EDTA vials were used. HbA1c was estimated by Fast Ion-Exchange resin separation method using spectrophotometer. For the estimation of blood glucose, fluoride vials were used. Plasma FBS was measured by glucose oxidase-peroxidase method (GOD-POD) by Trinder. ALT and AST was estimated by International Federation of Clinical Chemistry (IFCC) method on semi-automated Biochemical analyser. Serum AST and ALT levels < 45 U/L was considered normal.

Statistical analysis:

Data was analyzed using IBM SPSS version 22 software. Student T-test was used to find the difference in the parameters between the study group and controls. Analytical test such as Pearson Correlation was applied to find out the correlation between parameters. Data were presented as mean ± standard deviation (SD). P-value < 0.05 was set as statistically significant level.

III. Result

The mean serum ADA level was 36.80 ± 7.66 U/L in study group and that of controls was 19.70 ± 4.84 U/L. The increase in serum ADA level in type 2 diabetes mellitus was highly significant. Serum FBS and HbA1c concentration were also significantly increased (p < 0.05) in type 2 diabetes than controls. Both the transaminases were significantly increased in diabetic subjects as compare to healthy controls (Table 1).
**Study of Serum Adenosine Deaminase and Transaminases in Type 2 Diabetes Mellitus**

### Table 1: Biochemical parameters in T2DM and controls.

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>CASES (n=60)</th>
<th>CONTROLS (n=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.27 ± 8.17</td>
<td>42.66 ± 10.82</td>
<td>0.131</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>24.06 ± 1.87</td>
<td>22.87 ± 1.86</td>
<td>0.006</td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td>7.96 ± 4.69</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ADA (U/L)</td>
<td>36.80 ± 7.66</td>
<td>19.70 ± 4.84</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>152.80 ± 52.30</td>
<td>86.40 ± 7.72</td>
<td>0.006</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>9.60 ± 2.82</td>
<td>4.15 ± 0.78</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>34.60 ± 9.86</td>
<td>25.66 ± 5.77</td>
<td>0.036</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>36.09 ± 8.33</td>
<td>25.41 ± 4.73</td>
<td>0.017</td>
</tr>
</tbody>
</table>

**T2DM**: Type 2 diabetes mellitus, **ADA**: Adenosine deaminase, **FBS**: Fasting blood sugar, **AST**: Aspartate transaminase, **ALT**: Alanine transaminase.

Serum AST level was found to be elevated in 8.3% (5 out of 60 cases) and serum ALT level in 10.0% (6 out of 60 cases). Both serum ALT and AST levels were elevated in 5% (3 out of 60 diabetic subjects).

A significant correlation was found between serum ADA and FBS. There was also significant correlation between ADA and HbA1c concentration. The correlation between serum ADA and transaminases was insignificant (Table 2). No correlation was found between serum transaminases with FBS and HbA1c.

### Table 2: Pearson correlation between ADA and different parameters in T2DM.

<table>
<thead>
<tr>
<th>T2DM cases</th>
<th>FBS</th>
<th>Hb1Ac</th>
<th>AST</th>
<th>ALT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>.587**</td>
<td>.382*</td>
<td>.096</td>
<td>.003</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.000</td>
<td>0.048</td>
<td>0.597</td>
<td>0.985</td>
</tr>
<tr>
<td>N</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

**p < 0.01 highly significant, *p < 0.05 significant**

**T2DM**: Type 2 diabetes mellitus, **ADA**: Adenosine deaminase, **FBS**: Fasting blood sugar, **AST**: Aspartate transaminase, **ALT**: Alanine transaminase

The diabetic subjects were divided into 2 groups according to glycated hemoglobin level, Group 1 with HbA1c < 7% and Group 2 with HbA1c > 7%. Serum ADA, FBS, HbA1c % and transaminases of the two groups were compared. The levels of serum ADA, FBS and HbA1c were found to be significantly increased in diabetic subjects with poor controlled of blood glucose as compared to diabetic subjects with good controlled of blood glucose. The serum AST and ALT were also increased in diabetic subjects with poor blood glucose control as compared to diabetic subjects with good blood glucose control but it was not significant (Table 3).

### Table 3: Comparison of serum ADA, FBS and HbA1c between group 1 and group 2.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 HbA1c &lt; 7% (n=27)</th>
<th>Group 2 HbA1c &gt; 7% (n=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADA (U/L)</td>
<td>31.44 ± 5.83</td>
<td>38.25 ± 7.53</td>
<td>0.025</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>106.14 ± 9.15</td>
<td>165.46 ± 52.00</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>6.40 ± 0.87</td>
<td>10.46 ± 2.52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>33.28 ± 4.3</td>
<td>38.03 ± 11.10</td>
<td>0.090</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>32.42 ± 7.89</td>
<td>37.07 ± 8.31</td>
<td>0.202</td>
</tr>
</tbody>
</table>

**ADA**: Adenosine deaminase, **FBS**: Fasting blood sugar, **AST**: Aspartate transaminase, **ALT**: Alanine transaminase

### IV. Discussion

In the present study, serum ADA was significantly increased in type 2 diabetic subjects as compared to controls which is consistent with previous studies done by Kurtul N et al 18. There was also positive correlation between serum ADA with glycemic status. Similar result was also reported by Ramani NS et al 19. Chronic low-grade inflammation usually due to obesity is a probable cause of insulin resistance. As diabetes is associated with low grade inflammation, ADA could be specific inflammatory marker of diabetes mellitus. 20 It is suggested ADA modulates the bioactivity of insulin and may play role in insulin effect and glycemic control. Serum ADA level was found to be decreased by injection of insulin in diabetic subjects as reported by Hoshino T et al 21.

In this study, elevated serum ADA level was detected in 8.3% and elevated serum ALT level in 10.0% of diabetic subjects which is in consistent with other studies. Judi L et al 22 in their study reported elevated serum ALT level in 10.4% and elevated serum AST level in 5.4% of diabetic subjects. Similarly, Forlani G et al 23 found 16.0% and 5.4% of diabetic subjects have elevated serum ALT and AST respectively. Frequently, mild
chronic elevation of transaminases was found in type 2 diabetes mellitus mainly due to underlying insulin resistance.5

In the present study, both serum ADA and transaminases levels were increased in diabetic subjects. However, correlation between serum ADA and transaminases was insignificant. Lee JG et al24 in their study observed correlation between serum transaminases and ADA in type 2 diabetes mellitus. In another study, serum ALT was found to have significant positive correlation with FBS and HbA1c which is in contrast to this study.25

Association of liver injury with diabetes was observed in a study done by Hanley AJ et al26. Concentration of AST and ALT were associated with diabetes risk and serum transaminases were suggested as the predictor of type 2 diabetes mellitus. One possible mechanism that explained for the link between liver function and risk of diabetes is chronic subclinical inflammation. Vozarova et al in their study reported that a raised serum ALT level may indicate inflammation. Increased serum ALT level may be due to impaired insulin signaling and it is a risk for the development of T2DM.27 In a prospective study done by Kim HC et al, increased transaminases was positively associated with FBS and family history of liver disease. A slightly increased but still normal transaminases concentration was associated with mortality from liver disease.28 The role of the liver in the pathogenesis of type 2 diabetes has gain much interest. Several studies have reported associations of ALT with type 2 diabetes mellitus and elevated ALT as a feature of metabolic syndrome and type 2 diabetes mellitus.29

Nonalcoholic fatty liver disease often leads to nonalcoholic steatohepatitis which can result in cirrhosis and liver failure.30 Present of NAFLD among T2DM patients increases the risk of developing cardiovascular diseases.31 Elevated transaminases have also been reported as an independent risk factor of cardiovascular diseases (CVD).32 The present study shows that estimation of serum liver enzymes, ALT and AST along with the inflammatory marker serum ADA should be considered in type 2 diabetes mellitus since there may be ongoing hepatic injury in diabetes. Estimation of liver enzymes along with serum ADA may help in early detection of liver abnormalities and to prevent further complications. The limitations of the study were less number of subjects included and liver imaging was not done.

V. Conclusion

The present study shows that serum level of ADA and transaminases were significantly increased in T2DM as compared to healthy controls. Increased ADA activity was associated with poor controlled of blood glucose in T2DM. So, serum ADA could be a marker of inflammation and glycaemic status in type 2 diabetes mellitus. Estimation of serum transaminases as a part of routine LFT should be considered in diabetic patients for early detection of liver abnormalities. Further studies on larger number of subjects are required.

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References

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