



Association of Serum Adenosine Deaminase with Glycaemic Indices in Patients with Diabetes Mellitus

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ABSTRACT

Background: Diabetes mellitus is an autoimmune disease which is characterized by hyperglycemia, insulin resistance, and abnormal metabolic and inflammatory changes. Adenosine Deaminase is an enzyme associated with purine metabolism and immunomodulation that can be affected by these changes. The study aimed to study the level of serum ADA and its relation with FPG, PPg, and HbA1c.

Methods: A cross-sectional design was applied to 110 subjects: 55 non-diabetics, 27 diabetics with satisfactory glycaemic control (HbA1c $\leq 7\%$) and 28 with unsatisfactory glycaemic control (HbA1c $> 7\%$). The parameters FBS, PPBS, HbA1c, and serum ADA were studied. ADA activity was determined by Giusti colorimetry. Statistical analysis was performed in SPSS version. 27. $p < 0.05$ was maintained for statistical significance.

Results: The diabetic participants showed significantly higher FBS, PPBS, and HbA1c values compared to the non-diabetic participants ($p < 0.0001$). The mean ADA level in the diabetic participants showed higher (49.36 ± 7.62 U/L) compared to non-diabetic participants (22.31 ± 5.08 U/L, $p < 0.0001$). Among diabetics, ADA values increased proportionally with increasing HbA1c values, from 42.78 ± 4.51 U/L for HbA1c $\leq 7\%$ to 62.58 ± 1.02 U/L for HbA1c $> 10\%$.

Conclusion: The study concluded that serum ADA levels were higher among diabetic rather than non-diabetic participants with high levels of HbA1c, indicated that ADA is considered as an adjunctive biochemical marker of glycaemic dysregulation.

Key-words: Adenosine deaminase; Diabetes mellitus; Glycaemic control; HbA1c; Hyperglycaemia

INTRODUCTION

Diabetes mellitus is a heterogeneous metabolic disorder defined as chronic hyperglycaemia caused by inadequate insulin production, insulin resistance or a combination of the two. The ongoing process of hyperglycaemia leads to progressive metabolic dysfunction, oxidative stress, endothelial damage, and low-grade chronic inflammation.

These pathological changes ultimately contribute to the development of microvascular and macrovascular complications ^[1]. In addition to glycated haemoglobin, fasting plasma glucose and postprandial plasma glucose, there has been a great deal of research interest in the development of markers of the inflammatory and metabolic abnormalities of diabetes. The enzyme adenosine deaminase, which plays a role in purine metabolism and immunomodulation, has emerged as a possible indicator for biochemical change in glucose homeostasis and inflammatory activity in this context ^[2]. Adenosine deaminase (EC 3.5.4.4) catalyses the irreversible deamination of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. Adenosine is known to modulate several

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physiological functions such as insulin secretion, peripheral glucose utilisation, lipolysis and inflammatory signalling. Changes in adenosine metabolism can then have a possible effect on insulin sensitivity and glucose regulation. ADA is found in a wide variety of tissues, and the two isoenzymes, ADA1 and ADA2, are present in different quantities, with ADA1 as the major intracellular isoenzyme, and ADA2 being mostly found on monocytes and macrophages [3]. The activity of ADA can increase as a result of improved cell-mediated activation and inflammatory responses. However, in DM, the presence of hyperglycemia, insulin resistance and low-grade inflammation could lead to changes in the activity of ADA, so that the estimation of ADA activity may be useful in the investigation of metabolic abnormalities in diabetes [4].

Since the biological (metabolic) link between ADA and glycaemic regulation is of special interest, as the adenosine signal affects insulin action in peripheral tissues. Modulation of insulin-mediated glucose uptake by adenosine, and degradation of adenosine by increased ADA activity, may result in decreased extracellular adenosine. This interaction is a possible biochemical connection between purine metabolism and glucose homeostasis [5]. However, the association is multifaceted and is related to tissue-specific adenosine receptor activity, insulin resistance, inflammatory pathways, and compensatory metabolic responses. Thus, high serum ADA cannot be relied upon as a direct and exclusive indicator of insulin resistance, but rather may reflect the overall metabolic and inflammatory environment of diabetes [6].

The proposed study is especially relevant in the Indian clinical scenario as the burden of chronic metabolic disease in India is significantly contributed by type 2 diabetes mellitus (T2DM). The assessment of serum ADA in combination with FPG, PPG and HbA1C may be useful in determining if there is a correlation between the degree of glycaemic dysregulation and the serum ADA activity [7]. Interpretation of the results in relation to clinical practice, however, must take into account the duration of diabetes, the antidiabetic treatment, renal and hepatic function, obesity and the presence of inflammatory or infectious diseases, which may affect biochemical measurements [8].

Clinical studies already published have found elevated serum ADA levels in diabetic patients compared to

controls, and some studies have shown a positive correlation between ADA and glycaemic indices. However, between-study comparisons are limited by differences in study populations, methods of assaying ADA, glycaemic thresholds used, and treatment characteristics [9]. Furthermore, the evidence is not consistent regarding the ADA threshold to diagnose diabetes and/or control glycaemic parameters. So the purpose of the present study is to estimate the serum activity of ADA in diabetic patients and to study its correlation with glycaemic status, specifically with FPG, PPG and HbA1c [10]. The study aims to identify whether serum ADA can be used as a biochemical marker of metabolic dysregulation as an adjunct to the diagnostic and monitoring tools currently used, but not as a substitute for them.

MATERIALS AND METHODS

Research design- The study was a cross-sectional study to estimate the level of serum adenosine deaminase level and also to analyse the correlation of patients with glycemic status among diabetes mellitus patients. The study was conducted among 110 patients classified 55 as non-diabetic participants, 27 diabetic participants with good glycemic control (HbA1c $\leq 7\%$), and 28 diabetic participants with poor glycemic control (HbA1c $> 7\%$). The study was conducted in the Tertiary care Centre for 1 year. Glycemic status was evaluated by the use of FBS, PPBS, and HbA1c and serum ADA levels were compared between the groups of the study. Both verbal and written consent were taken for the study. Patient selection was done on the basis of certain predefined inclusion and exclusion criteria. Also the ethical approval was obtained and conducted according to the institutional ethical guidelines.

Inclusion criteria

- ✓ Patients with T2DM were included for the study.
- ✓ Age 35–70 years
- ✓ Both males and females were allowed
- ✓ Informed consent required for the study

Exclusion criteria

- ✓ Patients with previous history of tuberculosis, rheumatoid arthritis, viral hepatitis, or HIV
- ✓ Patients those who have received with insulin were excluded



- ✓ Patients with systemic hypertension (SBP >130 mmHg and/or DBP >80 mmHg) were excluded.

Procedure- Patients were selected and written informed consent was obtained, eligible patients were selected. Demographic and clinical parameters were recorded by the use of the proforma. Blood samples were collected aseptically in venous route. FBS, PPBS, HbA1c, and serum adenosine deaminase (ADA) levels were determined using laboratory methods. FBS was estimated after fasting state and PPBS after recommended postprandial period. HbA1c was estimated to find out the glycaemic status of patients. Diabetic patients were grouped into two categories based on their HbA1c status; good glycaemic control ($\leq 7\%$) and poor glycaemic control ($> 7\%$). Serum ADA levels were estimated by the colorimetric end point method explained by Giusti by quantitative ADA kit provided by Tulip Diagnostics. Laboratory reference values were 60–100 mg/dL for FBS, 80–140 mg/dL for PPBS, and $< 7\%$ for HbA1c.

Statistical analysis- Data obtained were entered in excel for analysis by the use of the statistical analysis. Data on continuous variables were presented as mean $\pm$ standard

deviation (SD). FBS, PPBS, HbA1c and serum ADA levels between diabetics and non-diabetics were compared by the use of the independent Student's t-test. Comparison between HbA1c and ADA levels among the different glycaemic control groups within the diabetic group was conducted. SPSS version 27 was used for statistical analysis. Statistical significance was maintained at $p < 0.05$.

RESULTS

Table 1 showed the marked difference in the glycemc parameters among the diabetic and non-diabetic participants. Diabetics showed the highest mean FBS values (153.26 ± 24.18 mg/dL) rather than non-diabetics (108.14 ± 9.72 mg/dL), with a t-value of 17.24 and p-value (< 0.0001). Diabetic patients showed a high PPBS value of 189.47 ± 27.16 mg/dL compared to non-diabetics (131.08 ± 14.38 mg/dL), with a t-value of 18.83. HbA1c level was $7.84 \pm 1.23\%$ among diabetics and $5.39 \pm 0.34\%$ among non-diabetics. Significant differences were noted among all three parameters, which highlighted 3 glycemc levels.

Table 1: Comparative Analysis of FBS, PPBS, and HbA1c Levels among Diabetic and Non-Diabetic Participants

Variable	Diabetics	Non-Diabetics	t-value	p-value
FBS (mg/dL)	153.26 ± 24.18	108.14 ± 9.72	17.24	< 0.0001
PPBS (mg/dL)	189.47 ± 27.16	131.08 ± 14.38	18.83	< 0.0001
HbA1c (%)	7.84 ± 1.23	5.39 ± 0.34	18.92	< 0.0001

Table 2 showed the difference in mean HbA1c levels on the basis of diabetes and glycemc control. The non-diabetic group (n=55) showed the lowest mean value of HbA1c at $5.41 \pm 0.35\%$. Patients with diabetes and good glycemc control (n=27) showed a high mean value of

HbA1c of $6.91 \pm 0.15\%$, rather than diabetes and poor glycemc control (n=28) had the highest value of $8.69 \pm 1.14\%$. A significant difference was noted for both of the diabetic groups. Overall, the table showed high levels of HbA1c values for the classification.

Table 2: Comparative Analysis of HbA1c Levels among Non-Diabetic Participants and Diabetic Participants According to Glycemc Control (N = 110)

Group / Classification	N (110)	Mean $\pm$ SD HbA1c (%)	Comparison	p-value
Non-Diabetic	55	5.41 ± 0.35	Diabetic Group with good glycemc control vs. non-diabetic	< 0.0001
Diabetic with good glycemc control	27	6.91 ± 0.15	Diabetic Group with good glycemc control vs non-diabetic	< 0.0001
Diabetic with poor glycemc control	28	8.69 ± 1.14	Diabetic with poor glycemc control vs. non-diabetic	< 0.0001



Table 3 demonstrated the difference in the level of serum ADA between diabetic and non-diabetic participants. Diabetic patients showed a high mean ADA level of 49.36 ± 7.62 U/L rather than non-diabetics at 22.31 ± 5.08 U/L. The mean value of the difference was 27.05 U/L, which indicated a high level of ADA. The

comparison showed a t-value of 29.74, with and the $p < 0.0001$. Overall, the result findings showed the strong difference in the group for the serum ADA, with diabetic patients indicated high mean value of ADA value than non-diabetic patients.

Table 3: Comparison of ADA Levels between Diabetic and Non-Diabetic Participants

Variable	Diabetics	Non-Diabetics	t-value	p-value
Serum Adenosine Deaminase (ADA) (U/L)	49.36 ± 7.62	22.31 ± 5.08	29.74	<0.0001

Table 4 showed the consistent increase in mean serum ADA levels among the 55 diabetic subjects in increasing HbA1c categories. Patients with $\text{HbA1c} \leq 7.0\%$ ($n=25$), there was a mean serum ADA level of 42.78 ± 4.51 U/L. The mean serum ADA level rose to 51.84 ± 2.06 U/L among the group with HbA1c 7.1-8.0% ($n=10$) and again

further to 55.79 ± 0.87 U/L for the category with HbA1c 8.1-9.0% ($n=10$). For the category with HbA1c 9.1-10.0% ($n=7$) the mean serum ADA level was 58.14 ± 2.21 U/L, and for $\text{HbA1c} > 10\%$ ($n=3$), the mean serum ADA level was the highest at 62.58 ± 1.02 U/L.

Table 4: Comparison of ADA Levels across Different HbA1c Categories among Diabetic Participants

HbA1c Level (%)	ADA Level Range (U/L)	Total Patients (N)	ADA Levels (Mean $\pm$ SD) (U/L)
≤ 7.0	30.3–49.2	25	42.78 ± 4.51
7.1–8.0	49.3–53.0	10	51.84 ± 2.06
8.1–9.0	53.1–56.1	10	55.79 ± 0.87
9.1–10.0	55.2–59.0	7	58.14 ± 2.21
> 10.0	58.2–62.7	3	62.58 ± 1.02
Total	-	55	-

DISCUSSION

Increasingly, serum adenosine deaminase activity has become a target for interest as a biochemical correlate of glycaemic dysregulation in diabetes mellitus. In this context, the present study aims to assess serum activities of ADA and the correlation between the two and glycaemic status, thus exploring the link between purine metabolism, chronic hyperglycaemia, and metabolic inflammation. The findings should be interpreted in the light of the magnitude of the ADA elevation in the diabetic patients, its relationship with FPG, PPG, and HbA1c, and how well this relationship is supported by previously published clinical evidence.

Serum ADA activity is elevated in patients with T2DM in several clinical studies. Hoshino *et al.* showed that the activities of ADA1 and 2 were significantly higher in patients with diabetes than in healthy donors.

In insulin-dependent diabetes mellitus patients, the ADA1 activity was 8.1 U/L, and in patients with non-insulin-dependent diabetes mellitus, the activity was 9.5 U/L, while in healthy donors, it was 6.5 U/L. The activity of ADA was also high in both diabetic groups (14.9 and 11.2 U/L) compared to 7.0 U/L in controls. The results suggest that the activity of ADA can be changed in various types of diabetes, but not all isoenzymes necessarily are involved to the same extent ^[11].

In another hospital-based cross-sectional study, Niraula *et al.* found that the level of serum ADA was significantly higher in diabetic patients (40.44 ± 17.97 U/L) than in healthy controls (10.55 ± 2.20 U/L) ($p < 0.001$). The considerable difference between the groups is correlated with the association between diabetes and an increase in circulating ADA activity. The size of the elevation of ADA should not be assumed to be the same for all



populations; however, due to understudy variability, assay methodology, clinical characteristics and co-occurring inflammatory diseases can all play a role [12].

A recent Indian study by Ghosh *et al.* also showed that the T2DM patients in this group had a significantly higher level of serum ADA activity than non-obese patients. The mean ADA concentration was 38.77 ± 14.29 U/L in diabetic cases compared with 17.02 ± 5.74 U/L in healthy controls ($p < 0.0001$). This is important, especially given the fact that the association remained with non-obese diabetic individuals, so further research is needed to determine whether the increased activity of the ADA is simply due to obesity-related inflammation. However, the cross-sectional design does not allow for the determination of whether ADA elevation is a cause or a consequence of metabolic dysfunction or of prolonged hyperglycaemia [13].

It is especially important to note the relationship between serum ADA and HbA1c since HbA1c is a measure of glycaemic load over the past 2–3 months. In the study done by Hoshino *et al.*, there was a direct correlation between ADA2 activity and HbA1c in poorly controlled NIDDM patients ($p < 0.002$). Moreover, a reduction in activity of ADA2 was reflected by the improvement in blood glucose levels in 11 of 12 poorly controlled NIDDM patients during hospitalisation. The observations indicate that activity of ADA might be affected by the degree of metabolic control, but this is limited to a small number of patients in whom glucose normalisation has been achieved [11].

Niraula *et al.* reported a positive correlation between serum ADA and HbA1c ($r = 0.417$, $p < 0.001$), FPG ($r = 0.333$, $p < 0.001$), and PPG ($r = 0.306$, $p < 0.001$). The relationship with HbA1c compared to the glucose measurements implies that rather than fluctuations in circulating glucose, ADA activity may relate to sustained glycaemic exposure. But these correlations suggest only a moderate to relatively weak relationship – not enough to make ADA an independent measure of glycaemic control [12].

Ghosh *et al.* confirmed a higher correlation between ADA and FPG in non-obese T2DM patients ($r = 0.657$, $p < 0.0001$), suggesting that FA may be associated with the severity of fasting hyperglycaemia in non-obese T2DM patients [13]. In another study, Khemka *et al.* found that there was a significant relationship between total ADA activity and HbA1c ($r = 0.60$, $p < 0.0001$), and ADA2

activity was significantly higher in patients with HbA1c $\geq 8\%$ compared with those with lower values of HbA1c [14]. All these findings indicate the need to explore the association of ADA with glycaemic control groups in the current study. If there is a similar positive correlation, then this will give more credence to the evidence of association between increased ADA activity and decline in glycaemic status. But the strength and statistical significance of this relationship should be confirmed by the actual data of the study.

Partly, this correlation between ADA activity and glycaemic dysregulation could be explained by the interaction of adenosine signalling and insulin action. There is evidence that elevated ADA activity leads to a greater breakdown of adenosine, which may alter the regulation of glucose uptake, insulin secretion and inflammatory responses mediated by adenosine. Furthermore, ADA2 has been linked to monocyte–macrophage activity, and this suggests that immune activation would be a likely connection between chronic low-grade inflammation in T2DM and altered immune activation. Such mechanisms are plausible, but it is only through observation that associations between higher ADA activity and insulin resistance or hyperglycaemia can be established [15].

This interpretation was supported by Lee *et al.*, who reported that the activity of ADA was elevated in T2DM patients compared with non-diabetic controls (23.1 ± 0.6 versus 18.6 ± 0.8 U/L, p -value < 0.05). There was a positive correlation between ADA activity and FPG ($r = 0.258$) and HbA1c ($r = 0.208$). Patients with HbA1c $> 9\%$ also had higher ADA activity compared to patients with lower HbA1c.

CONCLUSIONS

The study concluded that variations are noted between diabetics and non-diabetics regarding glycemic parameters and serum Adenosine Deaminase (ADA). The mean values of FBS, PPBS, and HbA1c in diabetics were much higher than those in non-diabetics. All three parameters differed significantly between the groups ($p < 0.0001$). Moreover, there were evident differences in HbA1c levels depending on the level of glycemic control, with the highest mean value being seen in people with poor glycemic control. Along with this, serum ADA was highly elevated in diabetics compared with non-diabetics, thus showing a considerable intergroup

difference. The mean serum ADA levels in diabetics rose increasingly with HbA1c level elevation from 42.78 ± 4.51 U/L in individuals with $HbA1c \leq 7.0\%$ to 62.58 ± 1.02 U/L in patients with $HbA1c > 10\%$. Overall, the study shows a correlation between increased HbA1c and increased serum ADA.

CONTRIBUTION OF AUTHORS

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