Relation of elevated serum adenosine deaminase levels to glycated hemoglobin and serum uric acid in type 2 diabetes mellitus

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Abstract

Background: Adenosine deaminase (ADA) is suggested to be an important enzyme for modulating the bioactivity of insulin, but its clinical significance in Type 2 diabetes mellitus is not yet established. The present study was undertaken to evaluate serum ADA activity and serum uric acid levels in patients of Type 2 DM**.** It is widely reported that immunological imbalance is one of the key factors associated with the metabolic disturbances in type 2 diabetes mellitus. **Aims**: The present study aimed to evaluate the serum Adenosine Deaminase level and to correlate ADA levels with Blood Glucose and **HbA1c** levels in Type-2 Diabetes Mellitus patients. **Material and Method:** It is a case control study. The subjects included in this study were divided into 3 groups. Group I consisted of 50 normal healthy individuals who served as controls with no history of DM. Group II consisted of 50 patients of Type 2 Diabetes Mellitus both males & females in the age group of 40-65 years on oral hypoglycemic drugs with $HbA1_c$ <7%. Group III consisted of 50 patients of Type 2 Diabetes Mellitus both males & females in the age group of 40-65 years on oral hypoglycemic drugs with $HbA1_c$ >7 %. Serum levels of fasting blood sugar, $HbA1_c$, ADA and uric acid were estimated in all the subjects under study. **Results:** All the three parameters, FBS, $HbA1_c$**,** ADA and serum uric acid levels were found to be increased in the patients of Type 2 DM as compared to controls. The mean serum uric acid levels showed a bell shaped relation with glycemic control. **Conclusion:** From the present study, it is concluded that there is an increase in serum ADA levels with increase in $HbA1_c$ levels. It was found that the serum uric acid levels increased with increasing levels of $HbA1_c$ <7% and then decreased with further increasing levels of $HbA1_c$ >7% (a bell-shaped relation).

Key words: Type 2 Diabetes mellitus, Adenosine deaminase, Glycated Hemoglobin, Uric acid.

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Introduction

Over the past 30 years, the status of diabetes has changed from being mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people. The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025 [1]. Diabetes Mellitus is a common endocrinological disorder characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism [2]. Chronic Hyperglycemia in diabetes causes long-term damage, dysfunction, and failure of various organs specially the eyes, kidneys, nerves, heart and blood vessels [3]. Type-2 diabetes is characterized by insulin resistance where there is impaired ability of hormone to suppress hepatic glucose output and to promote peripheral glucose disposal and compromised function of pancreatic β-cells such that insulin secretion is insufficient to match the degree of insulin resistance. Also Immunological disturbances such as the cell mediated immune system and improper T-lymphocyte

function play a role in the pathophysiology of T2DM [4].

Adenosine deaminase, an enzyme, which is present in red cells and the vessel wall catalyses the irreversible hydrolytic deamination of adenosine to inosine and 2'-deoxyadenosine to 2'- deoxyinosine. Inosine and 2'-deoxyinosine are converted to hypoxanthine, xanthine and finally to uric acid [5]. ADA is considered as a good marker of cell mediated immunity [6]. High lymphocyte ADA activities were found to be elevated in diseases in which there is cell mediated immune response [7]. It plays a crucial role in lymphocyte proliferation and differentiation [5], and shows its highest activity in T- lymphocytes [6]. Previously, adenosine deaminase has been reported to be a marker for insulin function [7]. But its connection with the immune system was not yet established in diabetic subjects. Even though there are some reports available on adenosine deaminase levels in diabetic subjects, these are all inconclusive.

In a study, Hoshino T et al [8] reported elevated ADA activity in the serum of Type 2 DM patients whereas Angielski S et al [9] demonstrated that 5'-nucleotidase and ADA activities were not changed in isolated glomeruli of streptozocin diabetic rats.

Adenosine increases glucose uptake inside the cells. Thus, higher ADA activity will decrease adenosine levels and this in turn decreases glucose uptake into cells. Thus, a suppression of ADA activity may help improve various factors associated with the pathophysiology of T2DM like insulin sensitivity and inflammation, cell proliferation and T-lymphocyte activity [4] Moreover chronic hyperglycemia leads to increased oxidative stress by forming enediol radicals and superoxide ions by NADPH oxidase system and increases ADA levels, both leading to insulin resistance [6]. If activity of ADA is suppressed, insulin sensitivity may be improved, and cellular proliferation, inflammation and T-cell activity which are associated with the pathophysiology of insulin resistance, can also be improved. Thus insulin resistance may have an important relationship with ADA activity [10].

Since a relationship exists between Adenosine Deaminase, cell mediated immunity and Type-2 Diabetes Mellitus, the present study was undertaken to determine Serum Adenosine Deaminase and serum uric acid levels in patients with Type 2 diabetes mellitus and to find correlation between blood glucose and Glycated Hemoglobin levels.

Materials and Methods

The subjects included in the present study were 100 patients of Type 2 diabetes mellitus in age group of 40-65 years of either sex, on oral hypoglycemic drugs, attending the OPD of Department of Medicine of the institute. A group of 50 normal healthy individuals, age and sex matched from the same population served as controls.

These 150 subjects were divided into 3 groups: GROUP I comprised of 50 normal healthy individuals both males and females in the age group of 40-65 years. GROUP II comprised of 50 patients of Type 2 Diabetes Mellitus both males & females in the same age group on oral hypoglycemic drugs with HbA1c<7 %.GROUP III comprised of 50 patients of Type 2 Diabetes Mellitus age and sex matched on oral hypoglycemic drugs with HbA1c>7 %.

Ethical clearance was obtained from Institution, Medical College, Kolkata. All the subjects were in the category of type 2 diabetes mellitus. Neither of the subjects were on insulin treatment, nor did they have a history of infection or other ailments at the time of the study Patients with type 1 diabetes mellitus, acute complications of diabetes mellitus and history of acute infection or other ailments like gross congestive heart failure, tuberculosis, gout, rheumatoid arthritis, skeletal muscle injury and renal failure were not included in this study. Subjects on insulin treatment, on drugs like sulfonylureas, thiazolidinediones, glucocorticoids, thyroid hormones, thiazides, diazoxides, pentamidine, phenytoin, interferons or having a history suggestive of any infections, known complications of diabetes mellitus, liver disease, immunological disorders, trauma or malignancy were excluded.

A complete clinical examination of subjects was done. About 2 ml of fasting blood was collected for the determination of different biochemical parameters. The plasma obtained was analyzed for biochemical parameters such as fasting blood sugar (GOD-POD Method), serum adenosine deaminase (Erba), serum uric acid (uricase method) and glycated hemoglobin (immunoinhibition method), cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, SGOT, SGPT, creatinine, total proteins and gamma glutamyl

transferase. These were measured with the kits provided by Erba, Manheim, Germany.

Determination of adenosine deaminase (ADA): The ADA levels were estimated using a commercially available kit (Erba, Manheim, Germany) [11]. The assay is based on the enzymatic deamination of adenosine to inosine which is converted to hypoxanthine by purine nucleoside phosphorylase (PNP). Hypoxanthine is then converted to uric acid and hydrogen peroxide by xanthine oxidase. Hydrogen peroxide is further reacted with N-Ethyl-N-(2-hydroxy-3sulf-opropyl)-3-methylaniline (EHSPT) and 4-

aminoantipyrine in the presence of peroxidase to generate quinine dye which is monitored at 546nm. One unit of ADA is defined as the amount of ADA that generates one micromole of inosine from adenosine per min at 37°C.

Statistical Analysis: Results were analyzed by Oneway ANOVA, Students' t-test, Post Hoc Turkey HSD and a probability of less than 5% ($p < 0.05$) was considered to be statistically significant. All variables were expressed as mean ± SD (standard deviation). Pearson's correlation coefficient was used to find out the correlation between two variables.

Results

The sex and number distribution in both controls (n=50), and cases (n=100) shown in Table- 1A. The age, anthropometric measurements and blood pressure is depicted in Table -1B. The values of the biochemical parameters evaluated in the present study for both normal healthy individuals (controls) and type 2 diabetic subjects (cases) are represented in Table-6. The mean FBS levels of Group I were 88.00±10.00 mg/dl, Group II were 129.18±21.67 mg/dl and the corresponding values among Group III subjects were 137.04±20.97 mg/dl. In the present study, the mean FBS levels of Group II and Group III were found to be highly significantly higher than Group I (p <0.001). Although the mean FBS levels of Group III were higher than Group II but the difference was statistically not significant (p=0.114). It was further observed that the mean HbA1$_c$ levels in Group I were 5.70±0.40%, in Group II were 6.10±0.49% and the corresponding values among Group III were 8.90±1.02 %. From this study it was observed that the difference in the levels of HbA1$_c$ was found to be insignificant between Group II and Group I (p= 0.310) [Table-2].

Table- 1A: Showing sex and number distribution.

Number	Group I(n=50)	Group II(n= 50)	GroupIII(n= 50)
Male/Female (%)	60/40	70/30	50/50

Table- IB: Baseline characteristics of the participants.

	Mean ± SD	Mean ± SD
	Controls	**Subjects**
	(n = 50)	**(n = 100)**
Age	43.2 ± 6.0	44.0 ± 5.1
Height (cm)	164 ± 4.8	169 ± 6.0
Weight (kg)	61.8 ± 7.5	71.0 ± 8.0
Blood pressure		
a. Systolic (120 mm Hg)	118 ± 4	129 ± 4
b. Diastolic (80 mm Hg)	76 ± 5	84 ± 2

Table-2: Showing FBS & Hb1AC In control and study groups.

Group n=50	FBS Mean± 2SD Comparison P value			Hb1AC Mean ±2SD Comparison P value		
I.	88.00±10.00	Gp I v/s Gp II	<0.001***	5.70±0.40%	Gp I v/s Gp II	0.310
II.	129.18±21.67	Gp I v/s Gp III	<0.001***	6.10±0.49%	Gp I v/s Gp III	<0.001***
III.	137.04±20.97	Gp II v/s Gp III	0.114	8.90±1.02%	Gp II v/s Gp III	<0.001***

Table- 3: Comparison of ADA levels in three groups.

Group	n=50	Mean ± 2SD	Comparison	p value
I.	50	17.30±7.08	Gp I v/s II	<0.001
II.	50	31.05±9.49	Gp I v/s III	<0.001
III.	50	44.03±15.10	Gp II v/s III	<0.001

Table-4: Comparison of serum Uric Acid in three groups.

Group n=50	Mean ± 2sd	Comparison	P Value
A.	6.29±1.58	Gp I v/s II	0.383
B.	7.88±1.82	Gp I v/s III	0.015
C.	5.20±1.29	Gp II v/s III	<0.001***

Table-5: Comparison of serum ADA, Uric Acid and Hb1AC in group II and Group III.

Parameter		Group I		Group II	
		Hb1AC	ADA	Hb1AC	ADA
ADA	R value	0.003		0.122	
	P value	0.908		0.509	
Uric Acid	R value	0.190	0.000	-0.012	0.200
	P value	0.309	0.991	0.989	0.278

Table-6: Biochemical parameters expressed in Mean±2SD.

Parameters	Controls(n=50)		Subjects(n=100)
Cholesterol (mg/dl)	196.4	± 6.8	210.4 ± 6.8
HDL Cholesterol (mg/dl)	66 ±	4.2	61 ± 4.2
LDL Cholesterol (mg/dl)	110 ± 9.8		126.2± 11.2
Triglyceride (mg/dl)	122.5	± 7.2	143.2 ± 6.8
SGOT (units/L)	16.7 ± 0.9		22.1± 1.6
SGPT (units/L)	21.2 ± 1.6		17.2± 1.4
Creatinine (mg%)	0.67 ± 0.06		0.8 ± 0.01
Total protein (g/dl)	6.6 ± 0.78		7.2 ± 0.9

In the present study the mean serum ADA levels in Group A were 17.30±7.08 U/L, in Group II were 31.05±9.49 U/L whereas in Group III were 44.03±15.10 U/L. Statistical analysis showed that the mean serum ADA levels of Group III were significantly higher than Group II (p<0.001) and the levels of ADA were significantly higher in both Group II and Group III as compared to Group I (p<0.001) [Table-3]. The mean serum uric acid levels in Group I were 6.29±1.58 mg/dl, in Group II were 7.88±1.82 mg/dl and in Group III were 5.20±1.29 mg/dl. The mean serum uric acid levels of Group II were significantly higher than Group III (p<0.001) whereas levels of mean serum uric acid in Group III were significantly lower than Group I (p=0.015) but no significant difference was observed between Group I and Group II (p=0.383) [Table-4].

The Pearson's correlation coefficient for the relationships between serum ADA, Uric acid and HbA1$_c$ levels in Group II showed positive correlation between HbA1$_c$ and ADA (r=0.003). Similarly when the comparison was made between serum uric acid levels and HbA1$_c$ there was positive correlation (r=0.190) but when the comparison was made between serum ADA and uric acid there was no correlation (r=0.000) [Table-5]. The Pearson's correlation coefficient for the relationships between serum ADA, Uric acid and HbA1$_c$ levels in Group III showed positive correlation between HbA1$_c$ and ADA (r=0.122). When the comparison was made between serum uric acid levels and HbA1$_c$ there was negative correlation (r= -0.012) [Table-5].

Discussion

In the present study, the mean serum ADA levels of group III were significantly higher than group II ($p<0.001$). Also, the levels of ADA were significantly higher in both groups II and III than Group I ($p<0.001$). Similar results were reported by and Kaur et al [12] & Kurtal et al [13]. The pathogenesis of increased ADA levels in Type 2 D.M is explained by extra cellular CAMP – adenosine pathway. ADA inactivates adenosine and enhances lipolysis. It also potentiates increase in CAMP accumulation. In the deficiency of insulin postprandial lipids and glucose circulate through blood and are taken up by Pancreas, to liver and adipose tissue. The adipocytes stores TAG (Triacylglycerol) leading to adipocyte hypertrophy. This exposure leads to cellular dysfunction, increased circulating FFA and a proinflammatory state. Exposure of Hepatocytes to excess fats and glucose leads to steatohepatitis and Insulin resistance. Thus, there is elevation of free fatty acids in diabetes which leads to worsening of IR and β-cell dysfunction. Chronic Hyperglycemia leads to increased oxidative stress by forming enediol radical and super oxide ions with NADPH oxidase system and increases ADA levels both leading to Insulin resistance. GLUT4 receptors are down regulated in the absence of adenosine. This is one of the reasons for Insulin resistance. Hyperglycemia leads to activation of NADPH oxidase, that catalyses O_2^- formation by one electron reduction of O_2 using NADPH or NADH as electron donor [14].

$$2O_2 + NADPH(\text{or NADH}) \rightarrow 2O_2^- + NADP\ (\text{or NAD}) + H^+$$
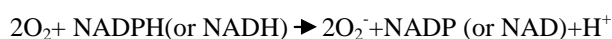
Another source of superoxide anion formation could be auto-oxidation of glucose which is subjected to enediol rearrangements that result in the formation of an enediol radical ion, which is capable of reducing molecular oxygen to form superoxide anion [19]. Hyperglycemia also causes formation of Advanced glycation End Products (AGEs) as result of non-enzymatic reactions between intra-cellular glucose-derived dicarbonyl precursors with the amino group of both intracellular and extracellular proteins. The AGEs stimulate receptors for advanced glycation end products (RAGE). Their interaction is believed to initiate and aggravate the diabetic complications. In addition they increase the generation of reactive oxygen species in macrophages thereby causing oxidative stress [15].

Thus, increased adenosine deaminase activity leads to increased depletion of adenosine. Adenosine is both a metabolic precursor for nucleic acids and a significant signaling molecule involved in regulation of various physiological processes which linked to its localized release. Adenosine modulates the action of insulin on various tissues differently and its concentration in tissues is affected by ADA levels. It mimics the action of insulin on glucose and lipid metabolism in adipose tissue and the myocardium. Adenosine potentiated insulin and contraction stimulated glucose transport in skeletal muscles by enhancing the increase in GLUT-4 at the cell surface. A1 receptor agonists of adenosine have been found to be associated with increased insulin sensitivity. Thus, depletion of adenosine due to increased adenosine deaminase activity would mean increase in insulin resistance in the body & subsequent hyperglycemia, which is a hallmark feature of diabetes mellitus [14].

AGEs bind to AGE receptors on several cell types (endothelial cells, mesangial cells and macrophages) and lead to release of cytokines; TNF-α, IL-1, IL-6 and growth factor from macrophages and mesangial cells resulting in activation of T lymphocytes [16].

ADA plays a crucial role in lymphocyte proliferation and differentiation and shows its highest activity in T-lymphocytes [17]. High ADA activity might be due to abnormal T-lymphocyte responses or proliferation and may point to a mechanism that involves its release into circulation. Therefore, in the present study, we report that increased ADA activity in diabetic individuals could be due to altered insulin related T-lymphocyte function.

Singh P. *et al* in 2013 also studied the activity of ADA in type 2 diabetes mellitus and reveals that increase in serum ADA levels was associated with increase in HbA1c levels, which may play an important role in determining the glycemic status in diabetes [18]. The reason for increased uric acid levels could be due to increased activity of ADA, an enzyme responsible for converting adenosine to uric acid in patients of type 2 Diabetes Mellitus. Another reason behind the increase in serum uric acid levels could be due to hyperinsulinemia in insulin resistant individuals. Studies showed that Insulin can stimulate the urate-anion exchanger or the Na-dependent anion co-transporter in brush border membranes of the renal proximal tubule and increase renal urate reabsorption [19]. However, a negative correlation of uric acid in

poor glycemic status may be related to the inhibition of uric acid reabsorption in the proximal tubule by high glucose levels in diabetic individuals.

The correlation between serum ADA and HbA1c levels in Group II & Group III revealed that there is positive correlation between HbA1c and ADA and this shows with the increase in glycated haemoglobin levels, levels of serum ADA also increases. This positive correlation between ADA level with short and long term glycemic control suggest its important role in glucose and lipid metabolic derangements seen in type 2 DM patients. This finding was similar with the study done by Kurtul et al [13], Singh et al [18] and Ramani et al [20].

However, this study has a few limitations. A concomitant lymphocytic/plasma adenosine deaminase and its activity on insulin or vice versa, and a correlation with oral glucose tolerance test (OGTT) are to be carried out to strengthen this concept.

Conclusion

The use of adenosine deaminase is a cost-effective process and the efficient exploitation of this strategy may help in better establishing this enzyme as a good marker for assessing CMI in diabetic individuals.

Therefore, we conclude that elevated adenosine deaminase activity may be an important indicator in the immuno-pathogenesis of type 2 diabetes mellitus.

Further studies on ADA activity in lymphocytes are required to consider ADA as an effective prognostic and pathological marker in type 2 diabetes mellitus.

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