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RESEARCH ARTICLE

EVALUATION OF SERUM ADENOSINE DEAMINASE IN TYPE II DM AND ITS ASSOCIATION WITH GLYCAEMIC STATUS, LIPID PROFILE, SERUM URIC ACID & BMI

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ABSTRACT

Background: Type II Diabetes Mellitus & complication associated with it are major public health challenges worldwide. Studies have shown that Indian populations develop complication of diabetes at an early age (20-40 years) compared with Caucasians (>50 years), this indicates that diabetes must be carefully screened and monitored regardless of patient age within India. Adenosine deaminase (ADA) is suggested to be an important enzyme for modulating the bioactivity of insulin, but its clinical significance in Type II DM is not yet established. Adenosine Deaminase (EC 3.5.4.4) is an enzyme that catalyses the irreversible deamination of adenosine & deoxyadenosine to inosine & 2'deoxyinosine respectively which are further converted to hypoxanthine, xanthine & finally Uric acid. **Aims & Objective:** To estimate the levels of serum ADA & identify its correlation with glycaemic parameters, Lipid profile, serum Uric acid & BMI of patients of type II DM. **Material and Methods**: It is case - control study conducted at tertiary care teaching hospital. The subjects were divided into three groups –Group I consisted of 30 Controlled diabetics [HbA1c <7%], Group II consisted of 30 Uncontrolled diabetics [HbA1c >7%] and Group III consisted of 30 healthy Non diabetic individuals. Age & Sex matched belonging to age group of 35-65years. Estimation of serum ADA, FBS, PPBS, HbA1c, lipid profile, serum uric acid, serum total protein, SGOT & SGPT was carried out in all the study subjects. **Results**: Mean ADA in Group I, II, III are 29.60 +-5.86, 41.46+-6.2, 18.7+_5.27 respectively, Mean HbA1c in Group I, II, III are 6.27+_0.51, 9.09+_1.70, 4.8+_0.7 respectively & Mean Serum uric acid in Group I, II, III are 7.1+_0.54, 5.9+_0.48, 6.01+_049 respectively. Serum ADA was positively correlated with Glycemic parameters, TC, TAG, LDL, VLDL, BMI whereas negative correlation was observed with HDL. Serum uric acid levels were raised in control DM and decreased in uncontrolled DM. Also, no association was found between serum ADA and serum Total Protein, SGOT, SGPT, Blood Pressure in type II DM subjects. **Conclusion:** Serum ADA levels were significantly higher in Type II DM subjects compared to healthy individuals. This suggests that ADA plays a role in pathophysiology of Type II DM and its complications. Further studies are required to establish ADA as effective prognostic & pathological marker for early detection of complications in Type II DM.

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INTRODUCTION

Type II DM & complication related to it are major public health challenges worldwide. The etiology of diabetes in India is multifactorial and includes genetic factors coupled with environmental influences such as obesity associated with rising living standards, steady urban migration, and lifestyle changes.[1,2] According to American Diabetic Association, HbA1C >6.5% or FBS >126 mg/dl or symptoms of diabetes plus random blood glucose levels >200 mg/dl or two-hour plasma glucose >200 mg/dl during an oral glucose tolerance test are considered as criteria for diagnosis of DM [3-9]. Obesity is one of the major risk factors for diabetes, yet there has been little research focusing on this risk factor across India.[1,10-14]. Despite having lower overweight and obesity rates, India has a higher prevalence of diabetes compared to western countries suggesting that diabetes may occur at a much lower body mass index (BMI) in Indians compared with Europeans. Furthermore, Indians are genetically predisposed to the development of coronary artery disease due to dyslipidaemia

and low levels of high density lipoproteins;[2-8] these determinants make Indians more prone to development of the complications of diabetes at an early age (20-40 years) compared with Caucasians (>50 years) and indicate that diabetes must be carefully screened and monitored regardless of patient age within India.[1,5,15,16] American Diabetes Association recommends the glycemic control of HbA1C <7.0%, preprandial capillary <130mg/dl , postprandial peak capillary plasma glucose <180 mg/dl.[1,17,18] Long term hyperglycaemia leads to glucotoxicity which further leads to poor glycaemic control and predisposes to long term micro and macro vascular complications. Hence more parameters are required which can elicit the risk of complications in diabetes[1,7,8,12]. Adenosine Deaminase (EC 3.5.4.4) is a enzyme that catalyses the irreversible deamination of adenosine & deoxyadenosine to inosine & 2' deoxyinosine respectively which are further converted to hypoxanthine, xanthine & finally Uric acid.[1,8,19] Uric acid is present as sodium urate in the extracellular fluid. Epidemiological studies had established the relationship between the serum uric acid and the increased risk of cardiovascular disease.[16,17,20] In addition to hyperglycemia, the type II diabetic individual almost invariably manifests a serious breakdown in lipid dynamics, often reflected by elevated levels of circulating free fatty acids (FFAs) and triglycerides (TG).[1,2] Studies have shown that ADA which reduces adenosine levels, increases basal and noradrenaline stimulated lipolysis in adipocytes.[4,5] Adenosine is an anti-lipolytic factor and lowers free fatty acid levels.[6] Several studies have demonstrated elevated levels of adenosine deaminase in individuals with type II diabetes mellitus, but the exact pathogenic role of elevated ADA activity in type II DM remains to be elucidated.[7,8,9,17-24] Insulin administration has been shown to reduce the elevated ADA levels in type II diabetics.[7] Adenosine Deaminase exerts its effects predominantly by regulating the concentration of intracellular and extracellular adenosine. Conditions which lead to elevated adenosine formation and release (e.g. hypoxia) have been shown to increase the expression of ADA.[10,18] Adenosine is known to exert potent metabolic effects acting through its receptors. Increased levels of serum ADA has been shown in individuals with type II diabetes mellitus[8,16,21]. However, it is difficult to conclude whether changes in ADA activity are the cause or result of actual insulin resistance. The present study was conducted to determine correlation of serum ADA with glycaemic parameters (FBS, PPBS, HbA1c), Lipid profile (T. Cholesterol, TG, LDL, VLDL and HDL), serum uric acid & BMI in patients with type II DM.

MATERIAL AND METHODS

The present study is a case-control study conducted at tertiary care hospital during the period August 2024 to March 2025 following institutional ethical committee approval. Written and informed consent was obtained from study participants. The study subjects were divided into three groups - Group 1 consisted of 30 Controlled diabetics (HbA1c <7%), Group 2 consisted of 30 Uncontrolled diabetic (HbA1c >7%) and Group 3 consisted of 30 healthy Non diabetic. Age & Sex matched belonging to age group of 35-65 years. The study included patient with type II DM both complicated & uncomplicated. The exclusion criteria include patients with Type I diabetic mellitus, Hepatitis, Hemolytic Anemia, Hemoglobinopathies, Immunocompromised disease like Tuberculosis, HIV, malignancy. Physical measurements of height and weight needed to calculate body mass index (BMI) and Blood pressure measurements were carried out in study subjects. A portable weight and height scale was used to measure the weight of the participant wearing light clothes and height in upright standing position on a flat surface. Body mass index (BMI) was calculated by weight in kilograms divided by height in meters squared formula. BMI < 18.5 kg/m^2 is considered as underweight, 18.5–24.9 kg/m^2 as normal, 25–29.9 kg/m^2 as overweight, and ≥30 kg/m^2 as obese. Blood samples were obtained from study subjects after an overnight fasting (≥8 hours) for Fasting blood glucose, triglyceride (TG), HDL, total cholesterol level measurements. For PPBS sample were collected 2 hours after meal. Total 5ml blood sample was collected under aseptic precaution for analysis of all parameters. Serum FBS, PPBS, T. Cholesterol, HDL, TAG, ADA, Uric Acid, SGOT, SGPT, Total protein, Urea, Creatinine, HbA1c were analyzed using commercially available kit. LDL and VLDL were calculated using Frederickson – Friedwald formula. Urine Protein & Sugar was determined by using dipstick method.

RESULTS

In the present study, as shown in Table No.1 mean age for Group 1 was 48.16, Group 2 was 54.33, Group 3 was 41.27. Each group consisted of15 males and 15 females.

Table 1. Age And Sex Distribution of subjects in three Groups

	Group 1 [n=30]	Group2 [n=30]	Group 3 [n=30]
Mean of age in year	48.16	54.33	41.27
Sex (M/F)	15/15	15/15	15/15

Table 2. Showing comparisons of biochemical parameters of Group 1, Group 2 & Group 3. ANOVA test was applied for comparison of means between the three groups

Parameters	Group1 [n=30] Mean ±SD	Group2 [n=30] Mean ±SD	Group3 [n=30] Mean ±SD	P value
ADA	29.60 ±5.86	41.46 ±6.2	18.7 ±5.27	0.0001
FBS	144 ±8.59	211.63 ±48.72	86.93 ±10.78	0.0001
PPBS	229±46.46	334.4 ±86.95	124.43 ±11.02	0.001
TC	192.01 ±46.97	276.6 ±47.75	132.1 ±12.13	0.001
TAG	204.86 ±55.63	289.03 ±47.57	107.5 ±13.05	0.001
HDL	38.16 ±7.57	33.90 ±7.01	48.26 ±7.5	0.001
LDL	112.82 ±42.33	152.49 ±31.78	62.42 ±14.17	0.001
VLDL	40.96 ±11.12	51.12 ±10.37	21.40 ±2.81	0.001
Hb1Ac	6.27 ±0.51	9.09 ±1.70	4.8 ±0.7	0.001
Uric acid	7.1 ±0.54	5.9 ±0.48	6.01 ±049	0.001
Urea	27.05 ±5.24	59.25 ±28.42	30.46 ±7.9	0.001
Creatinine	0.93 ±0.23	1.78 ±0.89	0.82 ±0.16	0.001
BMI	24.37 ±3.77	28.59 ±3.26	21.72 ±1.42	0.001
SGOT	21.03 ±4.03	31.71 ±11.37	14.26 ±5.34	0.001
SGPT	20.76 ±4.02	32.21 ±13.79	15.43 ±5.14	0.001
Total protein	6.61 ±0.55	5.68 ±0.48	6.98 ±0.62	0.001
Systolic BP	124 ±6.8	141.20 ±12.81	120.86 ±7.34	0.001
Diastolic BP	80.86 ±5.81	85 ±53 ±756	74.33 ±5.40	0.001

Table 3. Showing correlation between ADA and other biochemical parameters in Group I & Group II

Parameters	Group1 [n=30] Control DM	Group2 [n=30] Uncontrol DM
FBS	r=0.423 p=0.05	r =0.484 p=0.01
PPBS	r =0.481 p= 0.01	r =0.635 p=0.01
TC	r =0.534 p=0.01	r =0.749 p=0.01
TAG	r =0.488 p=0.01	r =0.597 p=0.01
HDL	r =-0.698 p=0.01	r =-0.648 p=0.01
LDL	r =0.584 p=0.01	r =0.501 p=0.01
VLDL	r =0.485 p=0.01	r =0.391 p=0.05
Hb1Ac	r =0.828 p=0.01	r =0.659 p=0.01
Uric acid	r =0.546 p=0.01	r =-0.586 p=0.01
Urea	r =0.644 p=0.01	r =0.534 p=0.01
Creatinine	r =0.575 p=0.01	r =0.623 p=0.01
BMI	r =0.670 p=0.01	r =0.488 p=0.01
SGOT	r =0.266 p=0.06	r =-0.154 p=0.06
SGPT	r =0.135 p=0.06	r =-0.251 p=0.06
Total protein	r =-0.257 p=0.06	r =-0.401 p=0.06

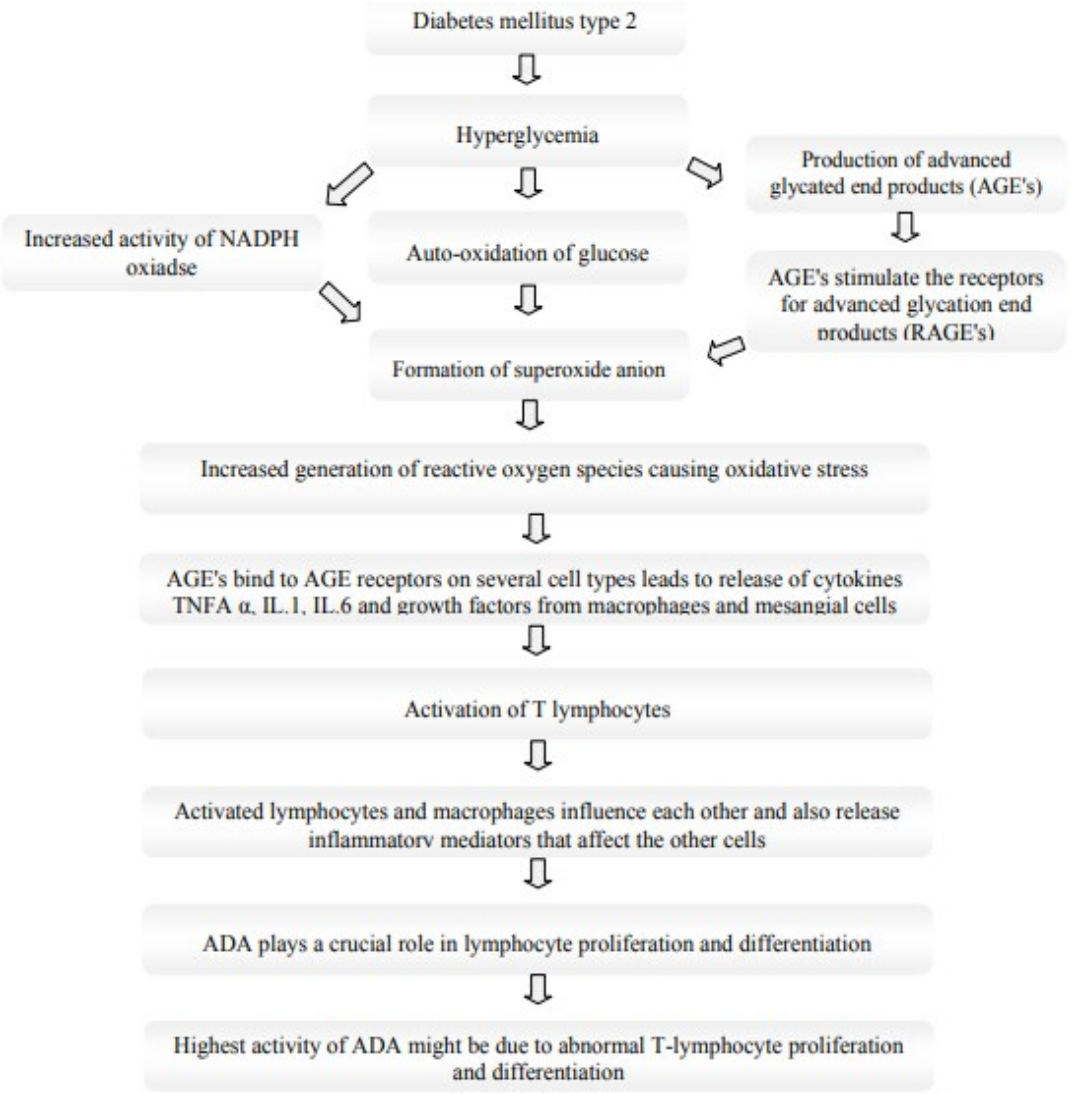

Figure 1. Possible Mechanism of high activity of ADA in type 2 diabetic patients

Table 2 shows Mean ±SD of all biochemical parameters in Group 1, Group2 and Group 3. One way analysis of variance (ANOVA) test was applied and results show that the difference in mean value of all parameters were statistically significant between all the three groups. Correlation was observed by using Pearsons correlation coefficient**.** Table 3 shows serum ADA was positively correlated with FBS, PPBS, TC, TAG, LDL, VLDL, HbA1c, urea, creatinine and BMI. ADA is negatively correlated with HDL in the Group 1 and Group 2. ADA is positively correlated with serum uric acid levels in control DM and a negative correlation was found with serum uric acid levels in uncontrolled DM. There was no association between serum ADA and systolic/ diastolic BP, serum total protein, SGOT, SGPT.

DISCUSSION

The relationship between the serum adenosine deaminase and the serum uric acid with the glycaemic parameters (HbA1c, FBS, PPBS), parameters of lipid profile (TG, T.Cholesterol, LDL, VLDL, HDL) & BMI in type II diabetes mellitus individuals was evaluated. There was a significant ($p < 0.01$) increase in serum ADA in individuals with type II diabetes mellitus in both controlled diabetes & uncontrolled diabetes in comparison with control group. Dyslipidemia which is characterized by abnormal levels of lipid profile is a common feature of Type II DM and is linked to development of cardiovascular disease. In present study, a significant proportion of Type II DM subjects had abnormal lipid profile. The most frequent was hypertriglyceridemia. It was observed that with increase in serum Triglyceride level there was an increase in serum ADA levels. Moreover, immunological disturbances of cell-mediated origin are believed to initiate from T lymphocyte dysfunction.[14,21-23] Recent in vitro studies implicated that in Type II DM, inappropriate immune responses may result from the defects in the action of insulin required for the function of T-lymphocytes. [8,16,21,24] ADA plays a crucial role in lymphocyte proliferation and differentiation [24] and shows its highest activity in T-lymphocytes.[23] In the present study, a significant elevation in the ADA levels was observed in Type II DM subjects compared to the controls. High plasma ADA activity might be due to abnormal T lymphocyte responses or proliferation and may point to a mechanism that involves its release into circulation.[21] Therefore, as presented in Figure 1, increased ADA activity in diabetic individuals could be due to altered insulin related T-lymphocyte function. Mokhtari et al documented that ADA activity is significantly higher in gestational diabetes mellitus and pregnant individuals than normal group.[24] ADA contributes to regulation of intracellular and extracellular concentration of adenosine. Adenosine on the other hand functions to increase glucose uptake in tissue and also inhibits proliferation of T- cells and cytokines synthesis. Thus, if ADA

activity is increase; insulin insensitivity/resistance, cellular proliferation, inflammation, T-cells also increase. As a marker of assessment of cell-mediated immunity in humans adenosine deaminase modulate cell growth and carbohydrate metabolic pathway through adenosine modulation.[10,21] This modulation includes concomitant downward and upward regulation of adenosine A1 and A2 receptor respectively.[16] Recent studies have indicated that defective signaling from the insulin receptors is an important component of the insulin resistance associated with obesity in both animal model and humans.[14,15,16] Kaur et al showed that there is an increase in serum ADA as the glycated hemoglobin level increased. Also, serum uric acid levels increased with moderate increase in HbA1c and then decreased with further increasing levels of HbA1c.[21] These findings are similar to the results obtained in the present study. Furthermore, it is hypothesized that adenosine has got insulin like activity on glucose and lipid metabolism particularly in adipose tissue and skeletal muscles.[4,14] ADA is found as a producer of reactive oxygen species (ROS), stimulator of lipid peroxidation and marker of both T-cell activation and glycemic status in diabetes mellitus (DM), Glucagon like peptide-1 (GLP-1), an incretin, promotes insulin secretion in a glucose concentration-dependent manner in pancreatic beta cells, inhibits glucagon secretion in alpha cells, decreases the gastric discharge rate, and mediates appetite suppression. GLP-1 is rapidly degraded by dipeptidyl peptidase-4 (DPP-4).[19,22,23] DPP-4 is an enzyme that acts as an important immune regulator by interacting with CD3 and acting as a co-stimulator for CD4+ T cells. It also regulates glucose homeostasis by hydrolysing integrins. DPP-4 binds ADA with high affinity and as adenosine causes apoptosis and inhibits differentiation of T lymphocytes by activating P1 adenosine receptors, interaction of ADA with DPP-4 can lead to T cell proliferation and increased cytokine production which can interfere with insulin signaling, there were several reports that DPP4 might increase the incidences of some infectious diseases (e.g. nasopharyngitis and urinary tract infection), so further experimental and clinical studies are needed to determine the effects of DPP-4 on immune cell function. Thus, if ADA activity 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 be affected.[4,7,8,11,19,22.] The reason behind increase in uric acid levels could be due to increase activity of ADA, enzyme responsible for converting adenosine to uric acid. Another reason could be due to hyperinsulinemia in insulin resistant / Type II DM individuals. Also, previous studies have shown that Insulin can stimulate the urate – anion exchanger or Sodium- dependent anion co- transporter in brush border membranes of renal proximal tubule and thus lead to increase renal urate reabsorption. Furthermore, the negative correlation of uric acid in poor glycemic status (uncontrolled DM) may be related to inhibition of uric acid reabsorption in proximal tubule by high glucose level in diabetic individuals.[16,17,21,]

CONCLUSION

In present study, significantly higher levels of ADA were found in Type II DM patients compared to healthy individuals. These findings suggest that ADA plays a role in pathophysiology of Type II DM & its complications. Also, serum ADA levels positively correlated with the levels of serum triglyceride which might be associated with insulin resistance in Type II DM subjects. The use of ADA is cost effective & efficient exploitation of this strategy may help in better establishing of this enzyme as a good marker for assessing insulin resistance in Diabetic individual. Further studies are required to consider ADA as effective prognostic & pathological marker for early detection of complications in type II DM.

LIMITATION

Estimation of different isoforms of ADA [ADA1 &ADA2] would have shown specific isoform responsible for progression of T2DM, were not performed. Serum insulin level known to be related to ADA was not estimated. Moreover, a correlation between serum ADA levels & OGTT were not estimated. Prediabetics were not considered in present study.

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