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Original Research Article

SERUM ADENOSINE DEAMINASE AND ITS ASSOCIATION WITH TYPE 2 DIABETES MELLITUS

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Abstract

Background: Diabetes Mellitus is one of the largest global health emergencies of the 21st century. Adenosine deaminase (ADA) is an enzyme involved in purine metabolism and plays a vital role in maintaining adenosine concentrations. The aim is to assess and compare level of serum Adenosine deaminase in patients with Type 2 Diabetes Mellitus and normal controls. **Materials and Methods:** A case-control study was done on 120 subjects. Cases were divided into Group 1 and Group 2; Group 1: 40 Type 2 Diabetes Mellitus patients with good glycemic control (HbA1c <7%), Group 2: 40 Type 2 Diabetes Mellitus patients with poor glycemic control (HbA1c > 7 %); Controls: 40 normal healthy adults. Serum Adenosine deaminase, HbA1c, and Fasting blood sugar levels were measured. **Result:** In our study, fasting blood sugar (FBS), HbA1c, and serum Adenosine deaminase (ADA) were elevated in Type 2 Diabetes Mellitus patients. The mean serum ADA value in Group 2 patients is 35.46 ± 6.83 U/L which is higher when compared to the mean serum ADA value of 26.28 ± 4.72 U/L in Group 1 patients. The mean serum ADA value in controls is 12.03 ± 1.67 U/L. A significant positive association was found between serum ADA and HbA1c in Group 1 (r =0.949, P = 0.000). A significant positive association was found between serum ADA and HbA1c in Group 2 (r = 0.981, P = 0.000). **Conclusion:** Serum Adenosine deaminase levels were elevated in Type 2 Diabetes Mellitus patients and was higher in Type 2 Diabetes Mellitus patients with poor glycemic control than with good glycemic control. The increased ADA activity suggests an immunity imbalance which is one factor responsible for metabolic disturbances seen in Type 2 DM patients.

INTRODUCTION

Diabetes Mellitus (DM) is recognized as a chronic, debilitating and costly disease associated with severe complications, which poses severe risk for families and the entire world and serious challenges to the achievement of internationally agreed developmental goals. Diabetes Mellitus is the most common endocrinological disorder characterized by metabolic abnormalities and long-term complications. The incidence and prevalence of Type 2 DM is globally increasing and becoming a major public health problem for healthcare providers.[1]

In Diabetes Mellitus, there is either impaired synthesis and secretion of insulin (Type 1 diabetes mellitus, sometimes called juvenile-onset, or insulin-dependent diabetes) or impaired sensitivity of tissues to insulin action (Type 2 diabetes mellitus, sometimes called adult-onset or noninsulin-dependent diabetes).[2] Defects in carbohydrate metabolizing machinery and consistent efforts of the physiological system to correct the imbalance in carbohydrate metabolism place overexertion of endocrine system. Continuing deterioration of the endocrine system exacerbates the metabolic disturbances and leads primarily to hyperglycemia. Type 2 diabetes mellitus, the most prevalent form of the disease, is often asymptomatic in its early stages and can remain undiagnosed for many years. According to the American Diabetes Association (2008), individuals with undiagnosed Type 2 diabetes mellitus are also at significantly higher risk for stroke, coronary heart disease, and peripheral vascular disease than the nondiabetic population.[3]

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate.[3] Diabetes is projected to increase significantly in the coming period and it is estimated that 80 million people in India will be having diabetes by the year 2030. Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. This chronic disease is responsible for significant morbidity, mortality, and cost. Diabetes mellitus is the leading cause of treated end-stage renal disease, the most common cause of non-traumatic amputations, and the foremost cause of new blindness in adults ages 20-74 years.[4]

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Adenosine deaminase (also known as adenosine aminohydrolase, or ADA) is an enzyme (EC 3.5.4.4) involved in purine metabolism. ADA, an enzyme distributed in human tissues, is considered a good marker of cell-mediated immunity as well as a marker for insulin function. Adenosine deaminase (ADA), catalyzes the irreversible deamination of adenosine to inosine and 2‟-deoxyadenosine to 2‟deoxyinosine. ADA is a polymorphic enzyme and by irreversibly deaminating adenosine to inosine, it regulates intracellular and extracellular concentrations of adenosine. Various studies showing an increase in ADA activity in Type 2 diabetes mellitus patients have been reported.[5-7]

Reports available on serum Adenosine deaminase levels in Type 2 diabetes mellitus are still inconclusive. 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 levels in patients with Type 2 DM and to correlate it with blood glucose and glycated Hemoglobin levels (HbA1c).

MATERIALS AND METHODS

It was a Case-control study for 1 year. The study was conducted among the patients attending a diabetic clinic or admitted to the medicine ward at Government Medical College, Kozhikode.

Inclusion criteria

Cases:

1. Forty consecutive patients in each 2 groups of type 2 DM in the age group 35-65 years among both inpatient and outpatient.
2. Group 1-consist of patients having Type 2 diabetes mellitus both males and females with good glycemic control (HbA1c < 7 %).
3. Group 2-consist of patients having Type 2 diabetes mellitus both males and females with poor glycemic control (HbA1c > 7 %).

Controls:

1. Forty normal healthy individuals with no DM in the same age group from bystanders of other patients, medical and paramedical staff.
2. Persons giving written consent to participate in the study.

Exclusion criteria

Cases:

1. Patients with Type 1 DM, hemolytic anemia, hemoglobin variants.
2. Subjects less than 35 years and more than 65 years of age.
3. Participants who were suffering from other chronic illness in which ADA levels are also affected like – Tuberculosis, Enteric fever, Viral hepatitis, Nephrotic syndrome, Leprosy, Infectious mononucleosis, HIV, Chronic malnutrition.
4. Pregnant and lactating women.
5. Participants on drugs which affect ADA values like interferon alpha, deoxycoformycin, ribavirin and viramidine.
6. Participants not ready to give written consent.

Controls:

1. Patient not giving written consent.
2. Subjects not matched to the same age.
3. Pregnant ladies.
4. Bystanders genetically related to same patient as case.

Methodology:

The study was conducted in 120 subjects of either sex with prior informed consent. Detailed clinical history was taken considering age, sex, duration of illness and history of hypertension. Blood pressure was recorded.

Body mass index was calculated as weight (kg)/height (m2).

The following blood parameters were compared in the study groups.

Estimation of Fasting blood sugar- Glucose oxidase method

Estimation of glycated hemoglobin- Turbidimetric inhibition immunoassay

Estimation of serum Adenosine deaminase - Kinetic assay.

Statistical Analysis: All data analysis was done using Microsoft excel and statistical package of social sciences (spss-version 16) software for windows. Results were analyzed statistically for significance by one - way ANOVA and chi square test. At P value <0.05, results were considered significant.

RESULTS

A case control study was conducted among 120 subjects, with females comprising 45.8% and males comprising 54.2%. First group included 40 patients with diabetes mellitus under good glycemic control (HbA1C < 7%) with mean age of 53.93 years and second group included 40 patients with diabetes mellitus under poor glycemic control (HbA1c > 7 %) with mean age of 55.53 years (cases). Controls included 40 age and sex related apparently healthy individuals free of these events.

In total of 120 subjects, 54.2 % are males and 45.8 % are females. [Table 1]

Group 1: 20% are in the age group 35-45 yrs; 40% are in the age group 46-56 yrs; 40% are in the age group 57-65 yrs. Group 2:7.5% are in the age group 35- 45 yrs; 42.5% are in the age group 46-56 yrs;50% are in the age group 57-65 yrs. Controls:50% are in the age group 35-45 yrs;32.5% are in the age group 46-56 yrs;17.5% are in the age group 57-65 yrs. [Table 2]

Group 1: 7.5% are underweight; 37.5% are pre-obese;20% are obese class I; 5% are obese class II. Group 2: 30% are pre-obese; 27.5% belongs to obese class I. Controls: 2.5% -underweight,10% - Preobese,17.5 % -Obese class II. [Table 3]

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In Group 1, out of 40 patients 22.5% have FBS value in the range 100-120 mg/dL;62.5% have FBS value in the range 121-141 mg/dL;15% have FBS value in the range 142-162 mg/dL. In Group 2, out of 40 patients, 52.5% have FBS value in the range 170-240 mg/dL; 27.5% have FBS value in the range 241-311 mg/dL; 20% have FBS value in the range 312 -382 mg/dL. [Table 4]

In Group 2, out of 40 patients, 15% have HbA1c value in the range 5-5.4%; 40% have HbA1c value in the range 5-5.6%; 27.5% have HbA1c value in the range 6.1-6.5%;17.5 % have HbA1c in the range 6.6-7%. [Table 5]

In Group 1, out of 40 patients, 37.5% have serum ADA value in the range14.5-21.5 U/L; 42.5% have serum ADA in the range 21.6-28.6 U/L; 20% have serum ADA value in the range 28.7-35.7 U/L. In Group 2, out of 40 patients 37.5% have serum ADA value in the range 24-32.5 U/L;40% have serum ADA value in the range 32.6-41.1 U/L;22.5% have serum ADA in the range 41.2-49.7 U/L. In controls, out of 40 patients, 37.5% have serum ADA value in the range 9-11.5 U/L; 50% have serum ADA value in the range 11.6-14.1 U/L; 12.5% have serum ADA value in the range 14.2-16.7 U/L. [Table 6]

Correlation is significant at the 0.01 level (2-tailed). Correlation is significant at the 0.05 level (2-tailed). [Table 7]

Positive correlation was seen in parameters of group 1 and ADA. [Table 8]

Positive correlation with HBS abd FBS but negative correlation with BMI and age with ADA [Table 9]

As per controls except BMI all parameters showed positive correlation with ADA. [Table 10]

Table 1: Gender distribution among groups

	Groups	N =120	Gender	
			Male	Female
CASES	GROUP 1 GROUP 2	40 40	22 22	18 18
CONTROLS		40	21	19

Table 2: Age wise distribution

Groups		No: of subjects	Mean (years)	Standard Deviation
Cases	Group 1 Group 2	40 40	53.93 55.53	7.287 6.656
CONTROLS		40	47.03	8.951

Table 3: Distribution as per BMI

	Groups		No: of subjects	Mean	Standard Deviation
BMI (kg/m2)	Cases	Group 1 Group 2	40 40	26.65 26.05	4.932 5.074
	Controls		40	23.92	4.239

Table 4: FBS distribution in both groups

Category	No of subjects	Mean (mg/dL)	Standard deviation
GROUP 1	40	129.40	11.158
GROUP 2	40	257.77	55.329
CONTROLS	40	83.25	9.963

Table 5: HbA1c distribution

Category	No: of subjects	Mean	Standard deviation
Group 1	40	5.988	0.502
Group 2	40	10.628	2.201
Controls	40	5.215	0.2815

Table 6: Distribution of Serum ADA

Category	No of subjects	Mean (U/L)	Standard deviation
Group 1	40	26.277	4.7187
Group 2	40	35.457	6.8335
Controls	40	12.030	1.6760

Table 7: Correlation of different parameters with ADA

		Serum ADA (U/L)
HbA1c (%)	Pearson Correlation Sig. (2-tailed)	0.877** 0.000
FBS (mg/dL)	Pearson Correlation Sig. (2-tailed)	0.904** 0.000
Duration of DM(YRS)	Pearson Correlation Sig. (2-tailed)	0.098 0.388
BMI (kg/m2)	Pearson Correlation Sig. (2-tailed)	0.216* 0.018
AGE	Pearson Correlation Sig. (2-tailed)	0.392** 0.000

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Table 8: Correlation of different parameters with serum ADA in group 1

Group 1:DM with Good Glycemic control(HbA1c < 7 %)		Serum ADA(U/L)
HbA1c (%)	Pearson Correlation Sig. (2-tailed)	.949 .000
FBS (mg/dL)	Pearson Correlation Sig. (2-tailed)	.877 .000
BMI (kg/m2)	Pearson Correlation Sig. (2-tailed)	.329 .038
AGE	Pearson Correlation Sig. (2-tailed)	.103 .527

Table 9: correlation of different parameters with serum ADA in group 2

Group 2:DM with poor glycemic Control (HbA1c > 7 %)		Serum ADA(U/L)
HbA1c (%)	Pearson Correlation Sig. (2-tailed)	0.981 0.000
FBS (mg/dL)	Pearson Correlation Sig. (2-tailed)	0.884 0.000
BMI (kg/m2)	Pearson Correlation Sig. (2-tailed)	-0.031 0.849
AGE	Pearson Correlation Sig. (2-tailed)	-0.030 0.853

Table 10: correlation of different parameters with serum ADA in controls

CONTROLS		SERUM ADA(U/L)
HbA1c (%)	Pearson Correlation Sig. (2-tailed)	0.905 0.000
FBS (mg/dL)	Pearson Correlation Sig. (2-tailed)	0.892 0.000
BMI (kg/m2)	Pearson Correlation Sig. (2-tailed)	-0.036 0.824
AGE	Pearson Correlation Sig. (2-tailed)	0.064 0.695

DISCUSSION

Diabetes mellitus, a chronic metabolic disorder is a cluster of abnormal metabolic paradigm having a common feature of hyperglycemia. It has assumed an epidemic proportion and its long term complications could have devastating consequences.[8] Adenosine deaminase (ADA) is suggested to be an important enzyme for modulating the bioactivity of insulin, but its clinical significance in diabetes mellitus (DM) is not yet characterized.

Insulin resistance is the first detectable abnormality found in type 2 diabetes mellitus. Adenosine potentiates insulin and contraction stimulated glucose transport in skeletal muscles by enhancing the increase in GLUT-4 at the cell surface. Increased level of adenosine deaminase could play a causative role in insulin resistance.[9]

In our study, the mean serum ADA levels of Group 2 patients with poor glycemic control were significantly higher than Group 1 patients with good glycemic control. Also, the levels of ADA were significantly higher in both groups 1 and 2 than controls. A study conducted a study on altered adenosine deaminase activity and its immunological significance in a group of thirty-six adult patients of either sex who had history of not less than six years of diabetes mellitus and equal number of healthy non-diabetics as controls, showed a significant ($P < 0.001$) increase in adenosine deaminase activity with a mean ± SD of 37.2 ± 9.29 U/L in diabetic subjects when compared to controls who had normal mean ± SD values of 18.2 ± 5.6 U/L. This study hypothesised that increased ADA activity may be due to altered immunity.[10]

A study evaluated ADA, IL-6 and TNF-alpha level in type 2 diabetes mellitus with and without hypoglycemic drugs. The study was conducted in 150 subjects. It was observed that there was a significant ($P<0.001$) tremendous increase in ADA,IL-6,and TNF-α levels (47.32 U/L ,29.04 pg/mL ,and 98.23 pg/mL, respectively) in diabetes mellitus patients not on hypoglycemic drugs than those on hypoglycemic drugs.[11] This study concluded that ADA, IL-6, and TNF-α levels are good glycemic markers associated with type 2 DM and that intake of hypoglycemic drugs decreases the levels of these markers.

A similar study was conducted on 96 newly diagnosed Type 2 diabetes mellitus patients on oral hypoglycemic medication and 46 healthy non-diabetics were enrolled as cases and controls, respectively. This study was conducted in order to make a contribution to the understanding of the effect of DPP-4 inhibitors on the ongoing immune disturbances in Type 2 DM by analyzing their serum ADA level and comparing the effect of other commonly prescribed oral anti-diabetic drugs on the activity of this enzyme. Serum ADA activity was investigated in the whole study group.[12] 50 patients (Group 2) receiving triple drug therapy i.e. SU + Met + DPP-IV inhibitors showed a significant difference ($p< 0.001$) in HbA1c levels (7.68 ±0.11 %) when

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compared to 42 patients (Group 1) (9.58 ±0.26 %) on SU + Met only. A significant difference ($p<0.001$) in serum ADA levels was observed in group-2 patients (24.77 ± 0.40 U /L) in comparison to group-1 patients (33.12 ± 0.55 U/L), indicating the potential effects of DPP-IV inhibitors on the immune function. A strong positive correlation between HbA1c and ADA was also observed in both group-1($r = + 0.951$) and group-2 ($r = + 0.964$).

In our present study Group 1 patients with good glycemic control showed a significant correlation between HbA1c and serum ADA ($r = +0.949$, $p = 0.000$) and Group 2 patients with poor glycemic control showed a positive significant correlation between HbA1c and serum ADA ($r = +0.981$, $P = 0.000$). Our study showed a positive correlation ($r = 0.329$) between serum ADA and BMI in Group 1 patients with good glycemic control, but it was statistically not significant (P value = 0.038). A negative correlation was found between serum ADA and BMI in Group 2 patients with poor glycemic control ($r = - 0.031$) in our study. Increased adenosine deaminase activity in diabetic individuals could be due to altered insulin related T-lymphocyte function. Increased activity of ADA in type 2 DM might be a marker for insulin indication. However, further studies are required to determine the pathogenic role of elevated ADA activity in type 2 DM.

CONCLUSION

In the present study a significant elevation in Adenosine deaminase levels have been observed in diabetic subjects as compared to controls. This high plasma Adenosine deaminase levels in diabetic subjects might be due to abnormal T- lymphocyte responses or proliferation which in turn are due to altered insulin related T- lymphocyte function. Our study showed a positive association between adenosine deaminase levels with HbA1c and FBS. This study also shows that when glycemic control was good, ADA activity was relatively low. The positive correlation between ADA level with good and poor glycemic control suggest its important role in glucose and lipid metabolic derangements seen in Type 2 DM patients. Elevated adenosine deaminase activity might be used as an important indicator of immunological disturbances seen in Type 2 diabetes mellitus. Increased activity of ADA in Type 2 DM might be considered as a marker for insulin indication.

The suppression of ADA activity may help to improve insulin sensitivity, inflammation, cell proliferation, and T-lymphocyte activity, all of which are associated with the pathophysiology of Type 2 DM. Since a positive association has been observed between ADA and glycemic status in our study, ADA might be used as an important prognostic tool, which may be helpful in early prediction and prevention of long term complications of Type 2 diabetes mellitus.

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