OPEN ACCESS International Journal of Applied Biology

ISSN : 2580-2410
eISSN : 2580-2119

Adenosine Deaminase Activity in Serum of Diabetics: A Reflection of Glycemic Profile?

Anirban Poddar [1*], and Devyani De [2]

[1]Demonstrator, Dept of Biochemistry,Deben Mahato Govt Medical College & Hospital,Purulia,West Bengal.
[2]Assistant Professor, Dept of Biochemistry, Calcutta National Medical College & Hospital,Kolkata,West Bengal.

Abstract

Diabetes presents with a constellation of symptoms,hyperglycemia being just one of them.The primary challenge faced by physicians is to achieve a control over this exorbitant blood sugar levels.Oral antidiabetic agents & insulin therapy are the primary modalities of treatment available presently. The most reliable diagnostic as well as prognostic marker used for this purpose is HbA1c. Adenosine Deaminase (ADA), an enzyme associated with purine metabolism is known to exert potent metabolic effects through its receptors. ADA is primarily an established inflammatory marker reflecting T lymphocyte activity .Adenosine,the substrate of ADA is known to affect cholesterol synthesis in liver,thereby serving as a key hinge in the fine balance between glucose & lipid homeostasis. Due to the association of ADA with glucose & lipid homeostasis ,the authors believe that studying ADA activity in serum of diabetics can reveal many important facts which might open a new dimension in diagnosis & treatment protocol for diabetes mellitus.The purpose of our study was to monitor ADA activity in serum of diabetic patients who are on oral antidiabetic drugs & do not have evidence of microvascular or macrovascular complications of diabetes & also determine if any correlation exists between fasting blood glucose,HbA1c & serum ADA activity.

Article History
Received December 16, 2022
Accepted June 14, 2023

Keyword
Adenosine; ADA; Diabetes; Glycemic marker; Glycemic profile.

Introduction

The unholy association of diabetes & obesity & its role in increasing cardiovascular risk is a well known fact(Stina Johanson,2007). Dyslipidemia or an elevated level of triglycerides & free fatty acids in blood is a commonly encountered phenomenon & is due to a jeopardised lipid metabolism(Dennis McGarry,2002). Adenosine's role as an antilipolytic agent is well established. Adenosine exerts multiple effects through its receptors. The A1 receptor of adenosine is expressed exclusively in the adipose tissue & it is through this receptor adenosine exerts its antilipolytic effect (Stina Johanson,2007). Adenosine Deaminase (ADA) catalyses the irreversible hydrolytic deamination of adenosine to inosine.

Many researchers have in the past have reported elevation of ADA activity in serum of patients suffering from diabetes mellitus (Madhavi Reddy A,1995). The exact reason for the elevation of ADA activity in diabetics has not been elucidated clearly till now. Insulin administration in diabetic subjects has shown to reduce ADA activity (Madhavi Reddy A,1995). Events such as hypoxia stimulate adenosine production & this increased adenosine production inturn acts as a stimulant for increased expression of ADA.This phenomenon inturn reveals how ADA acts, i.e by regulating the levels of intracellular & extracellular adenosine.

Diabetes mellitus is characterised by a gross imbalance in energy dynamics resulting in mitochondrial dysfunction,endoplasmic reticulum stress & hypertrophy of adipocytes (Sarah De Ferranti,2005).These hypertrophied adipocytes are capable of liberating large amount of inflammatory cytokines. The immune cells in close proximity of the adipocytes infiltrate the adipose tissue easily resulting in insulin resistance associated with inflammation.

Adenosine has been proved to be responsible for glucose uptake in cells(L.Vergauwen,1994). Therefore in an insulin sensitive tissue,if ADA activity is high,it will lead to depletion of adenosine & consequently glucose uptake in these cells will be compromised.ADA is a key player involved in lymphocytic proliferation & differentiation.T-lymphocytes have been found to posses high ADA activity. Thus an inference may be drawn that if ADA activity in insulin sensitive tissues is suppressed,it may facilitate glucose uptake in the cells resulting in a better utilisation of glucose at the cellular level.

Materials and Methods

Study Design

This case control study was carried out at Deben Mahato Govt Medical College & Hospital,Purulia,West Bengal over a period of 6 months. The subjects involved in the study were involved into two groups.

1. Group A- This group comprised of 20 patients with history of diabetes mellitus who presented to the general medicine OPD.These patients were being treated with oral antidiabetic drugs & did not have any symptoms of microvascular or macrovascular complications of diabetes.
2. Group B - This group comprised of 20 age & sex matched healthy controls who presented to the institution for a regular health check up. This group served as the control group.

A valid written consent was obtained from all the participants in the study. The study was approved by the institutional ethics committee at Deben Mahato Govt Medical College & Hospital. The statistical data was analysed using SPSS v 17.0.

Inclusion Criteria:

1. Patients who are known cases of type 2 diabetes mellitus with no obvious symptoms of complications.
2. Age>35 years & < 65 years .
3. Patient being treated with oral antidiabetic drugs.
4. No H/O tuberculosis,psoriasis,viral hepatitis,rheumatoid arthritis.

Exclusion Criteria:

1. Diabetic patients who have symptoms of obvious complications of diabetes.
2. H/o rheumatoid arthritis,viral hepatitis,psoriasis,tuberculosis.
3. Diabetics on insulin therapy.
4. Pregnant women.

Method

7 ml of venous blood was collected with full aseptic precautions after 12 hours of fasting.2ml of this blood sample was collected in a fluorinated vacutainer for estimation of fasting blood sugar.Rest 5 ml was collected in a plain vacutainer which was processed ultimately to obtain serum.This was used for analysing serum ADA.

Estimation Of Glucose

Fasting blood glucose estimation was done by GOD-POD{Glucose oxidase peroxidase method}.This is an enzymatic method employed in the clinical laboratory for the estimation of glucose.Glucose is oxidized by glucose oxidase to gluconic acid and H2O2 is liberated. The colorimetric indicator, quinonemine is generated from 4 – amino antipyrene and phenol by H_2O_2 under the catalytic action of peroxidise. Intensity of colour generated is directly proportional to glucose concentration. Normal range in serum or plasma is 70-100 mg/dl.

Estimation Of ADA

ADA estimation was done by a commercially available kit by TULIP DIAGNOSTICS PVT LTD,Goa,which is based on the method described by Giusti & Galanti (Giusti & Galanti,1984). Adenosine deaminase hydrolyses adenosine to ammonia and inosine. The ammonia formed further reacts with a phenol and hypochlorite in an alkaline medium to form blue indophenols complex with sodium nitroprusside acting as a catalyst.Intensity of the blue coloured indo phenol complex formed is directly proportional to the amount of ADA present in the sample.

Table 1. Normal Reference Range of ADA in serum

Normal	<30 u/L
Strong Suspect	30u/L- 40 u/L
Suspect Positive	> 40 u/L- 60 u/L
Positive	>60 u/L

Results and Discussion

Adenosine deaminase activity was found to be elevated in the diabetic patients as compared to the healthy controls in our study.Increased adenosine deaminase activity would thus lead to depletion of adenosine.Adenosine through its receptors exerts potent metabolic effects. A_1 receptor agonists 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.This explains the hyperglycemia encountered in diabetic patients.

Our study also reveals a very strong correlation between fasting blood glucose levels & serum ADA activity in patients with uncomplicated type 2 diabetes.A similar correlation also exists between serum ADA levels & HbA1c. HbA1c is considered to be an established glycemic marker used to asses the glycemic status of a diabetic patient & also forms the diagnostic criteria for diabetes mellitus(HbA1c>6.5 gm%).Since a strong positive correlation exists between fasting blood glucose levels ,HbA1c & serum ADA,therefore estimation of serum ADA might serve as an inexpensive glycemic marker for assessing the glycemic status of a diabetic patient on oral antidiabetic agents who is free from symptoms of microvascular & macrovascular complications of diabetes & also chronic inflammatory conditions in which ADA activity tends to flare up.The data for the same is hereby depicted below:

Table 2. Data for Group A

Fasting blood sugar (FBS)	Serum ADA	HbA1C
167	15	7.2
185	18	6.8
165	17	7.9
220	25	8.2
200	20	7.3
178	19	6.5
189	20	7.0
168	17	7.2
148	15	6.8
210	21	7.9
235	21	8.2
189	19	7.3
176	18	6.5
192	19	7.0
190	17	7.1
165	15	6.8
193	19	7.3
182	17	6.9
176	17	6.7
180	18	7.0

MEAN:-

1. FBS- 185.4000±20.22089
2. SERUM ADA-18.3500±2.39022
3. HbA1C-7.1550±0.49362

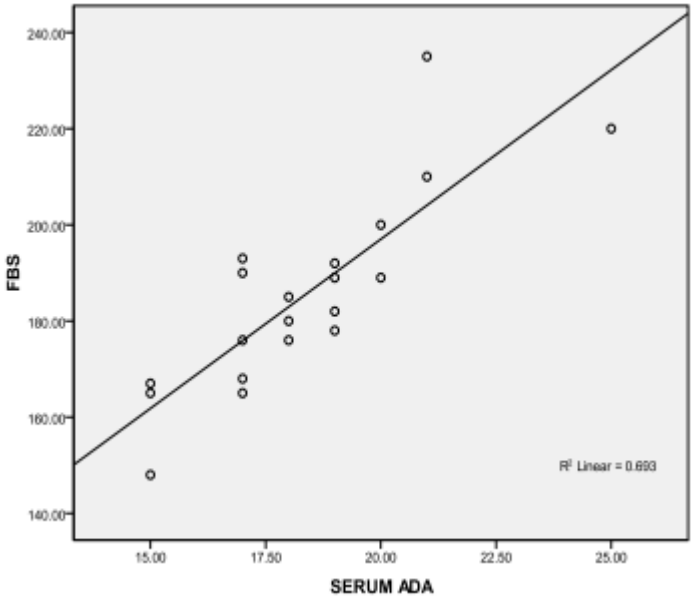

Figure 1. Scatter plot showing correlation between fasting blood sugar levels & serum ADA levels in patients with uncomplicated type 2 diabetes mellitus (Group A).

'r' VALUE: -0.832

'p' VALUE: <0.01(SIGNIFICANT)

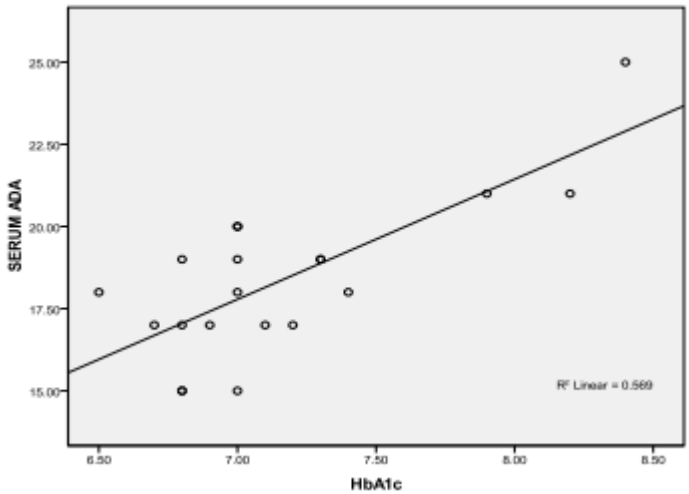

Figure 2. Scatter plot showing correlation between serum ADA levels & HbA1c in patients with uncomplicated type 2 diabetes mellitus (Group A).

'r' VALUE: -0.755

'p' VALUE: <0.01(SIGNIFICANT)

Table 3. Data for Group B

Fasting blood sugar(FBS)	Serum ADA	HbA1c
80	5	5.0
76	8	6.1
74	9	5.3
70	7	5.0
69	6	5.3
79	9	5.6
96	9	4.7
90	8	6.0
84	8	5.2
90	9	5.3
69	6	5.0
88	8	6.0
84	7	5.8
90	7	6.1
75	9	4.6
77	8	6.1
72	7	5.8
71	7	5.7
70	9	5.2
73	8	5.1

MEAN:

1. FBS- 78.8500±8.42474
2. SERUM ADA-7.9500±1.27630
3. HbA1C-5.4450±0.48175

Conclusion

Our study revealed a positive correlation between serum ADA activity and HbA1c levels as well as with fasting blood glucose levels. This raises an important question as to whether ADA activity in serum is actually a reflection of the glycemic status of an individual.Although our study goes in favour of this hypothesis,but it was done with a very limited sample size over a short span of time .More elaborate studies over longer period of time with a substantially larger sample size at different geographic locations are required to establish the above hypothesis.

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