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Association Of Adenosine Deaminase With Insulin Resistance And Pancreatic Enzymes In Type 2 Diabetes Mellitus

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Abstract:

Background: Adenosine deaminase(ADA) is a key regulating enzyme of adenosine levels and ADA gives a promising result as a common inflammatory marker for glycemic control, insulin resistance and pathogenesis of diabetes. Chronic inflammation of pancreas in type 2 diabetes mellitus (T2DM) leads to fibrosis and exocrine pancreatic insufficiency. The present study was undertaken to evaluate association of adenosine deaminase with insulin resistance and pancreatic enzymes in type 2 diabetes mellitus.

Materials and Methods: This case-control study was conducted in Department of Biochemistry, LN Medical College & JK Hospital, Bhopal, Madhya Pradesh, India. Relevant history was taken, clinical examination and laboratory investigations was done in 200 subjects including 100 type 2 diabetes mellitus subjects & 100 nondiabetic healthy controls. Under fasting condition, 4 ml blood sample and 2 ml post-prandial blood was collected and serum was separated. The separated serum was used for the estimation of FBS, PPBS, insulin, pancreatic enzymes (amylase and lipase) and Adenosine deaminase levels by using autoanalyzer kits. 2 ml whole blood sample was used for estimation of HbA1c.

Results: Among 100 type 2 diabetic subjects, 43 were males and 57were females. In non- diabetic subjects, 54 were males and 46 were females. Age (49.3 ± 7.6yrs) and BMI (26.2 ± 1.2Kg/m^2) was significantly more in T2DM cases than non-diabetic subjects. Mean levels of fasting glucose (148.0 ± 18.0 mg/dl), post prandial glucose (219.3 ± 33.8 mg/dl), HbA1C (7.0 ± 0.6g%), insulin (15.2 ± 4.6µIU/ml), HOMA-IR (5.6 ± 2.2), ADA (21.4 ± 5.8 IU/L) were significantly higher and serum amylase (43.4 ± 10.3IU/L), lipase (30.5 ± 8.4IU/L) levels were significantly lower in T2DM cases compared to nondiabetic subjects ($P < 0.001$). ADA showed positive correlation with fasting Insulin &HOMA-IR and negative correlation with pancreatic enzymes. Further, serum ADA levels are significantly higher in fairly controlled than in controlled diabetics.

Conclusion: ADA levels are linearly associated with severity of type 2 diabetes mellitus. So, that serum ADA levels may be used as an alternative surrogate marker for insulin resistance, assessing glycemic control and assessing pancreatic enzymes serum amylase and lipase in pathogenesis of type 2 diabetes mellitus.

Key words: ADA, HOMA-IR, Insulin resistance, Glycemic control, Pancreatic enzymes, HbA1C

Introduction:

Adenosine deaminase (ADA), is a purine metabolic enzyme involved in irreversible deamination of adenosine to inosine. Thus, it is involved in regulating adenosine concentrations. [1] Increased adenosine concentrations are

related to inflammations as an anti-inflammatory response; thus, ADA may involve as an anti-inflammatory response to reduce the extracellular adenosine concentrations. [2] ADA as a marker used in the diagnosis of tubercular meningitis, etc. where inflammatory responses are involved. [3]

Type 2 diabetes is a metabolic endocrine disorder and increasing alarmingly in world wide. According to the International Diabetes Federation, 2021 India and South East Asia itself will lead to have the second higher number of type 2 diabetes mellitus patients, approximately
174.4 million people by 2045. [4] In type 2 diabetes mellitus decreased insulin sensitivity or increased insulin resistance is the common reason for hyperglycemia, which is the main culprit in the development of secondary complications like cardiovascular diseases with increasing duration of the disease.[5] Pancreas plays a endocrine role of insulin secretion to decrease the levels of hyperglycemia. Exocrine pancreatic insufficiency is due to deficiency of digestive enzymes common in diabetes mellitus. Chronic inflammation of pancreas in type 2 diabetes leads to fibrosis and exocrine pancreatic insufficiency. Because of over endocrine burden of pancreatic β-cells leads to overt type 2 diabetes mellitus [6] and increases the risk of acute pancreatitis. [7]

In a cross-sectional study on 2327 type 2 diabetic patients by lei et al., demonstrated the significant role of insulin-pancreatic acinar axis in exocrine pancreatic functions of biochemical marker serum amylase and found positive association between serum amylase with integrated islet β cell function.[8] Juyeon et al., in a systematic review and meta- analysis showed the association of type 2 diabetes mellitus with low serum amylase and lipase levels. [9]

Increased insulin resistance and decreased islet beta cells function of pancreas is seen with the progression and pathogenesis of disease. In contrast to this evidence, Julio et al., showed elevated serum lipase levels in type 2 diabetes mellitus. [10]In a large study by William et al., on 9340 type 2 diabetic patients demonstrated the differential rise of serum pancreatic enzymes amylase and lipase without acute pancreatitis symptoms. [11] Significant role of
ADA by regulating islet cell function and insulin sensitivity for secretion of insulin from pancreas is established that ADA is a marker of inflammation. [12]

In an Indian cross-sectional study conducted on 90 type 2 diabetic subjects by Aishwarya et al., showed strong positive correlation between serum ADA & HbA1C levels. [13] Nirula et al., also demonstrated the same results of positive correlation between serum ADA and HbAlc levels, on 204 type 2 diabetic subjects in Nepal. [14] Contradictory to the above results a study conducted by Khemka et al. showed no correlation between serum ADA levels and HbAlc levels in patients with non-obese type 2 diabetes mellitus and showed a positive correlation between ADA with fasting blood sugar. [15]

As per the existing evidence and to the best of our knowledge, the relation between insulin resistance in type 2 diabetes mellitus with serum ADA levels and its relation with emerging acute pancreatitis is not fully understood. In the view of burden of insulin resistance in type 2 diabetes the present study was undertaken to postulate the association of adenosine deaminase with insulin resistance and pancreatic enzymes in type 2 diabetes mellitus.

Materials and methods:

Study center and study population

This hospital-based case-control study, conducted on 200 subjects from June 2022 to May 2023. Out of total subjects 100 were type 2 diabetic subjects, who were on routine diabetic oral medications and 100 were

nondiabetic subjects of age and sex matched who were attending LN Medical College & JK Hospital outpatient department, Bhopal, MP. The present study was approved by the Ethics Committee, LN Medical College & JK Hospital, Bhopal (Sep-2019/RDC/2020/293). Study details were clearly informed to all study participants and written informed consent was obtained from all the study subjects.

Diagnosis of T2DM

T2DM was diagnosed according to ADA (American Diabetes Association) 2023 guidelines, whose serum fasting glucose levels are >126 mg/dl or 2 hour post prandial glucose ≥200 mg/dl or Glycated hemoglobin ≥6.5%. [16]

Inclusion criteria:

Type 2 diabetic subjects were included in the study with whose glycated hemoglobin levels were ≥6.5% and along with fasting glucose levels are >126 mg/dl or 2 hour post prandial glucose ≥200 mg/dl as cases and non-diabetic subjects as controls.

Exclusion criteria:

Patients with obvious complications of diabetes, history of alcohol consumption, smoking history, obese, liver disorders, patients on insulin therapy, pregnant woman, hypertensive patients, thyroid disorders or with any other inflammatory diseases like tuberculosis, cancer, gout, kidney diseases were excluded from the study.

Specimen collection and laboratory analysis

Four ml of venous blood sample was collected in a plain dry vacutainer tube and 2 ml of whole blood sample was collected in EDTA tube using sterilize disposable syringes from all the enrolled participants after an overnight fast of around 8 to 10 hours. Sample was processed for serum separation and serum analysis was performed for FBS(by GOD - POD method), fasting Insulin(by ELISA method), ADA (bykinetic enzymatic method), serum amylase (by kinetic method) and serum lipase (by fixed time method) on auto analyzer. 2 ml of whole blood sample was processed for HbA1C analysis, on trinity biotech analyzer (HPLC method). HOMA-IR (Homeostatic model for insulin resistance) was measured from fasting insulin levels and fasting glucose levels. Second sample was collected after 2 hours of simple breakfast, serum was separated and processed for post prandial blood sugar level (PPBS) by GOD POD method. In addition to this, Body mass index (BMI) was calculated for each participant.

Statistical analysis

Results were expressed as mean ± SD. Mann-Whitney U test was used for continuous non- normally distributed variables. Categorical variables were expressed in percentages. Spearman's correlation was applied. The level of significance was $p<0.05$. Analysis was performed using SPSS software, version 22.0.

Results:

The demographic and biochemical parameters of study were presented in table 1. The mean age of T2DM subjects was 49.32 ± 7.60 years and 43.01 ± 7.19 years for nondiabetic subjects. BMI (26.25 ± 1.25 kg/m^2), FBS (148.02 ± 18.08 mg/dl), PPBS (219.32 ± 33.84
mg/dl), HbA1c (7.06 ± 0.62 %), fasting Insulin (15.20 ± 4.69 µIU/ml), HOMA-IR (5.68 ± 2.29), ADA (21.41 ± 5.8 IU/L) were significantly higher in type 2 diabetic subjects than in nondiabetic subjects (P <0 .001). Whereas pancreatic enzymes, serum amylase (43.48 ± 10.33 IU/L) and lipase (30.54 ± 8.44 IU/L) were significantly lower in type 2 diabetic subjects than in nondiabetic subjects (P < 0.001).

Table 1: Baseline characteristics of the type 2 diabetic subjects and nondiabetic subjects

Parameter (units)	Type 2 Diabetic Subjects Mean ± SD(n=100)	Nondiabetic Subjects Mean ±SD(n=100)	p-Value
Age (yrs)	49.32 ± 7.60	43.01 ± 7.19	0.000

Males	43 (43%)	54 (54%)	-
Females	57 (57%)	46 (46%)	-
BMI (Kg/m^2)	26.25 ± 1.25	23.22 ± 1.05	0.000
FBS (mg/dl)	148.02 ± 18.08	89.64 ± 6.19	0.000
PPBS (mg/dl)	219.32 ± 33.84	121.16 ± 5.58	0.000
HbA1C (%)	7.06 ± 0.62	4.97 ± 0.21	0.000
Fasting Insulin (µIU/ml)	15.20 ± 4.69	7.03 ± 2.00	0.000
ADA (IU/L)	21.41 ± 5.8	9.61 ± 1.57	0.000
Amylase (IU/L)	43.48 ± 10.33	69.38 ± 9.83	0.000
Lipase (IU/L)	30.54 ± 8.44	43.0 ± 5.18	0.000
HOMA IR	5.68 ± 2.29	1.55 ± 0.43	0.000

In the present study, fasting Insulin levels were significantly positively correlated with FBS (r= 0.622), PPBS (r=0.623), HbA1c (r=0.836), ADA (r=0.700) and negatively correlated with Amylase (r = -0.981), Lipase (r = -0.557) in T2DM cases as shown in table 2.

Table 2: Correlation of Insulin with other parameters and ADA

Parameters	**Type 2 Diabetic Subjects**	
	r - Value	**p- value**
FBS (mg/dl)	0.622	0.000
PPBS (mg/dl)	0.623	0.007
HbA1c (%)	0.836	0.000
Amylase (IU/L)	-0.981	0.001
Lipase (IU/L)	-0.557	0.000
ADA(IU/L)	0.700	0.000

Correlation is significant at the 0.01 level (two-tailed)

In the present study, serum ADA levels were positively correlated with FBS (r= 0.476), PPBS (r=0.453), HbA1c (r=0.752), fasting insulin (r=0.700), HOMA-IR (r=0.694) and negatively correlated with amylase (r = -0.690), lipase (r = -0.449) in T2DM cases as shown in table 3.

Table 3: Correlation of ADA with other biochemical parameters

Parameters	**Type 2 Diabetic Subjects**	
	r - Value	**p- value**
FBS (mg/dl)	0.476	0.000
PPBS (mg/dl)	0.453	0.000
HbA1c (%)	0.752	0.000
Fasting Insulin(µIU/ml)	0.700	0.000
HOMA-IR	0.694	0.000
Amylase (IU/L)	-0.690	0.003
Lipase (IU/L)	-0.449	0.000

Correlation is significant at the 0.01 level (two-tailed)

Further, Serum ADA levels are significantly higher in fairly controlled type 2 diabetic subjects than in good controlled type 2 diabetic subjects whose mean values were 25.95 ± 5.34 IU/L *vs* 18.38 ± 3.47IU/L respectively (table 4).

Table 4: Serum ADA level in Nondiabetic subjects, Good controlled type 2 diabetic subjects and Fair controlled type 2 diabetic subjects

Variables	**Serum ADA (IU/L) (mean ± SD)**	**P value**
Nondiabetic Subjects (n=100)	9.61 ± 1.57	0.000
Good Controlled type 2 Diabetic Subjects (n=60)	18.38 ± 3.47	
Fair Controlled type 2 Diabetic Subjects (n=40)	25.95 ± 5.34	

Discussion:

In the current study we analyzed the association of adenosine deaminase with insulin resistance and pancreatic exocrine enzymes, amylase & lipase in type 2 diabetic subjects. The main finding of the current study depicts that the serum ADA levels are positively associated with insulin resistance, glycemic parameters and negatively associated with pancreatic enzymes amylase and lipase.

The major concern in type 2 diabetes is management of chronic hyperglycemia, which is due to insulin resistance and pancreatic endocrine dysfunction, characterized by chronic low-grade inflammation and disease pathogenesis. [12] Early detection of insulin resistance will be helpful for managing of emerging chronic complications of disease. ADA is an important biomolecule, considered to be a good marker for cell mediated immunity, as it is involving in proliferation and differentiation of T lymphocytes. As inflammatory response serum ADA levels are going to be raised in type 2 diabetes mellitus with increased inflammation and disease progression due to hyperglycemia secondary to insulin resistance.[2]

Cao et al., in their cross-sectional study demonstrated the independent association of serum ADA levels with islet beta cell function in type 2 diabetes mellitus.[12] In earlier study Bagher et al., showed the diagnostic value of ADA and its isoforms in type 2 diabetes mellitus. [17] Our study also shows the positive association of increased fasting insulin levels and their correlation to different glycemic parameters along with ADA levels in type 2 diabetic subjects. (Table 2)

Insulin resistance and serum fasting insulin testing methods are not using frequently in clinical practice, because of their complexity in testing procedures. ADA is showing positive correlation with insulin resistance and with increased serum fasting insulin levels. Thus, giving promising results as a marker for insulin resistance in type 2 diabetes mellitus for managing the pathogenesis of disease.[12] Our study also reported the same results of increased levels glycemic parameters (FBS, PPBS and HbA1C), increased fasting serum insulin levels, increased insulin resistance (HOMA IR) and increased serum ADA levels in type 2 diabetic subjects compared with nondiabetic subjects. (Table 1).

In a study conducted by Aishwarya et al., on 90 type 2 diabetic subjects including 57 males and 33 females found strong positive linear correlation between serum ADA and glycated hemoglobin levels. [13] Niraula et al., also

showed significant positive correlation between serum ADA and HbA1C, Fasting plasma glucose and post-prandial glucose levels in type 2 diabetes mellitus. [14] Present study also shows the positive correlation of serum ADA levels with glycemic parameters, fasting insulin, insulin resistance and liver enzymes. (Table 3) The possible explanation for the raised levels of serum ADA in type 2 diabetics is may be deranged T-lymphocyte responses as a part of the inflammatory response driven by increased insulin stress. This may be because of increased inflammation with increasing duration of disease and increased insulin resistance prevailing hyperglycemia.[14]

In type 2 diabetes mellitus, with increasing insulin resistance, the demand for the insulin increases and makes the pancreas endocrine excitability during early stages of disease and gradually lost beta cell integrity and lost its function during course of pathogenesis. Pancreas is made up of large portion with exocrine acinar cells and a small portion of endocrine islet cells. There is a close vicinity between exocrine acinar tissue and islets and defects in one tissue may disturb other and vice versa.[5] In diabetes, hyperglycemia leads to defects in insulin secretion and its functions may affect the exocrine function of pancreas includes synthesis and releasing of enzymes amylase, lipase and proteases. Further, insulin itself regulates the release of amylase from acinar cells by number of ways.[18] Lei et al., in their large cross-sectional study on 2327 newly diagnosed type 2 diabetic subjects demonstrated the positive association between normal serum amylase levels and integrated islet β cell function. [8] Existing literature clearly demonstrates the risk of acute pancreatitis with duration and disease pathogenesis of type 2 diabetes mellitus. [19,20]

Most of the previous studies analyzed the serum amylase levels in type 2 diabetes mellitus and found decreased levels. [21,22-25] Very few studies were undertaken to evaluate the serum lipase levels in type 2 diabetes and found controversial results. Arie et al., in their study on Indonesian type 2 diabetes mellitus subjects demonstrated the relation of elevated serum lipase levels to the disease progression. [26] In an Indian study by Snehankar et al., with small sample size of 75 newly diagnosed type 2 diabetes mellitus, showed decreased serum amylase activity and increased lipase activity.[27] In an earlier large clinical trial by Jaret et al., on asymptomatic type 2 diabetic subjects demonstrated the increased pancreatic enzyme variability and abnormalities. [28] Adib et al., in their study demonstrated the decreased serum levels of pancreatic enzymes amylase and lipase and signifies the clear pancreatic exocrine functional impairment in Diabetes Mellitus. [29] So in the variability of existing literature, the present study was undertaken as a common study for assessing insulin resistance and its association with serum ADA levels and their correlation of pancreatic enzymes serum amylase and lipase in type 2 diabetes mellitus.
In our study, we found significantly decreases levels of serum amylase and lipase in type 2 diabetic subjects compared with nondiabetic subjects and are negatively correlated with serum ADA levels. In a small study conducted in India by Mahesh et al., demonstrated the significant pancreatic derangement of endocrine-exocrine axis, as decrease in serum amylase and lipase levels with increasing hyperglycemia in diabetes mellitus.[18] Aradhana et al., in their study on gestational diabetes mellitus on 125 subjects observed the same results of decreased serum amylase and lipase levels. [6]

To postulate the association of ADA with glycemic control, we grouped type 2 diabetic study subjects into good controlled diabetics (HbA1C >6.5 to <7.0) and fair controlled diabetics (HbA1C >7.0 to <8.5%). We found strong positive association of serum ADA levels with poor glycemic control, which was according to the recent studies. [13,14,30] The present study depicts that there is strong association of ADA with glycemic control, duration of disease and incidence of abnormal pancreatic enzymes secondary to severity of inflammation and poor glycemic control. Thus, this study recommends ADA may be used as a surrogate marker of insulin resistance in type 2

diabetes mellitus and association of pancreatic exocrine abnormalities.

Limitations of the study

This study design is case control study; therefore, it is not possible to know whether the duration of diabetes preceded pancreatic exocrine function or not. The limited geographical distribution and sample size of study population limits to draw concrete conclusions. Moreover, future studies are needed aiming isoforms of ADA activity in pathogenesis and prognosis of type 2 diabetes mellitus.

Conclusion:

ADA can be used as marker for insulin resistance and associated pancreatic exocrine deformities with disease progression in type 2 diabetes mellitus, as serum ADA levels showed a positive correlation with biochemistry parameters and negative correlation with pancreatic enzymes in our study. Furthermore, ADA levels are linearly associated with duration & severity of type 2 diabetes mellitus and moreover, assessment of serum ADA is cost & time effective. Thus, we conclude that serum ADA levels may be used as an alternative surrogate marker for insulin resistance, assessment of pathogenesis of diabetes mellitus and assessing glycemic control. Furthermore, studies are needed with larger sample size to make the concrete conclusions.

Conflict of interest: Nil

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