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Association Of Insulin Resistance With Adenosine Deaminase In Type 2 Diabetes Mellitus & Their Correlation With Liver Enzymes

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Background: Type 2 diabetes mellitus (T2DM), chronic metabolic disorder and its prevalence is raising globally. The micro and macrovascular complications in T2DM increases with duration of disease and prevailing of chronic hyperglycemia. Adenosine deaminase, a key regulating enzyme of adenosine levels and concerned with cell mediated immunity. ADA gives a promising result as a common marker for glycemic control, insulin resistance and pathogenesis of disease. The present study was undertaken to evaluate association of insulin resistance with adenosine deaminase levels in type 2 diabetes mellitus and their correlation with liver enzymes.

Materials and Methods: This case-control study was conducted in Department of Biochemistry, LN Medical College & JK Hospital, Bhopal, Madhya Pradesh, India. The present study was approved by the Ethics Committee, LN Medical College & JK Hospital, Bhopal (Sep-2019/RDC/2020/293). In this study, 200 subjects were included, among them 100 were type 2 diabetes mellitus subjects and 100 were nondiabetic subjects. Detailed clinical and physical examination was done to all the study subjects. 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, Liver enzymes and Adenosine deaminase by using autoanalyzer kits. 2 ml whole blood sample was used for estimation of HbA1c. in addition to family history, duration, BMI also recorded.

Results: In this study, among 100 T2DM cases, 46were males and 54 were females. Mean levels of fasting glucose, post prandial glucose, HbA1C, insulin, HOMA-IR, Liver enzymes (AST, ALT, ALP) and ADA were significantly higher in T2DM cases compared to nondiabetic subjects ($P < 0.001$). ADA showed positive correlation with fasting Insulin, HOMA IR and liver enzymes. Further, Serum ADA levels are significantly higher in fairly controlled than in controlled diabetics.

Conclusion: The present study results may conclude that serum ADA levels may be used as an alternative surrogate marker for insulin resistance, assessing glycemic control and assessing liver functioning deformities in pathogenesis of type 2 diabetes mellitus.

Key words: ADA, HOMA-IR, Insulin resistance, Glycemic control, Liver enzymes, HbA1c

Introduction:

Type 2 Diabetes Mellitus (T2DM), most common form of diabetes. According to the International Diabetes Federation (IDF), prevalence of T2DM is increasing and it was estimated that 537 million people worldwide had diabetes in 2021, and this

number is projected to reach 643 million by 2030, and 783 million people by 2045.[1] India, is in second position with largest number of Diabetes patients and the scenario will rise to 134.3 million by the year 2045.[2]

In T2DM, insulin resistance & dysfunction of islet beta cells of pancreas is a known fact for the condition of chronic hyperglycemia. The micro and macrovascular complications increase with duration of disease, prevailing of chronic hyperglycemia which is mainly caused by abnormality in insulin secretion, insulin action or both. Glycemic control is the key therapeutic goal in prevention of complications in type 2 diabetes. There is a potential need of new methods of glycemic control assessing and its implications in pathogenies of disease with time and cost effective were under evaluation nowadays. [1,3]

ADA (Adenosine deaminase) is a purine metabolic enzyme and its concentration is rich in thymus, spleen & other lymphoid tissues mainly concerned with cell medicated immunity. In addition, ADA also plays a significant role in insulin secretion by regulating islet cell function and insulin sensitivity. Increased serum ADA levels are strongly associated with autoimmune diseases, cancers and inflammatory diseases. There is an increased evidence of serum ADA levels as an inflammatory marker. [4] In a study conducted by Niraula et al., in Nepal on 204 type 2 diabetic patients, reported significant positive correlation between serum ADA and HbA1C levels.[5] Aishwarya et al., conducted a study on 90 type 2 diabetic patients in India and also reported strong positive correlation between serum ADA and HbA1C levels. [6]

Liver is the central organ of metabolic homeostasis. Metabolic disorders like obesity, insulin resistance, dyslipidemia, T2DM, hypertension and nonalcoholic fatty liver disease are interconnected with each other through molecular, biochemical and complex immune mechanisms. Altered liver functions are established in T2DM with increased insulin resistance.[7] A few studies by Shiful Islam et al., [8], Yaru Bi et al., [9], Sana Alam et al., [10] demonstrated the elevated liver enzymes in type 2 diabetes mellitus.

Khemka et al., showed that there was a positive correlation of ADA with FBS but showed no correlation between serum ADA levels and HbA1C in patients with non-obese type 2 diabetes mellitus. [11] Moreover, to the best of our knowledge, the relationship between serum insulin levels, insulin resistance and ADA levels in type 2 diabetes mellitus are not fully elucidated as most of the previous studies designed to analyze the possible relationship of serum ADA levels with glycemic status of type 2 diabetic population. In the view of increasing insulin resistance in type 2 diabetes the present study was undertaken to postulate the relationship of altered serum ADA levels with insulin resistance and its association with liver enzymes in type 2 diabetes mellitus.

Materials and methods:

Study center and study population

This case-control study, conducted from June 2021 to May 2022. In this study, 200 subjects were included. Out of 200 subjects, 100 were type 2 diabetic subjects, who were on routine diabetic oral medications and 100 were nondiabetic individuals of age and sex matched attending LN Medical College & JK Hopsital outpatient department, Bhopal, Madhya Pradesh, India. 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%. [12]

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 fasting venous blood sample was collected in a plain vacutainer and 2 ml of whole blood sample was collected in EDTA tube from the enrolled participants. Sample was processed for serum separation and serum was used for estimation of FBS (by GOD – POD method), fasting Insulin (by ELISA method), ADA (by kinetic enzymatic method), Aspartate Transaminase (by modified IFCC method), Alanine Transaminase (by modified IFCC method), Alkaline phosphatase (by kinetic method) on auto analyzer. 2 ml of whole blood sample was used 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 breakfast, serum was separated and processed for post prandial blood sugar level (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 48.8 ± 7.6 years and 45.8 ± 8.9 years for nondiabetic subjects. BMI (26.42 ± 1.02 kg/m^2), FBS (142.6 ± 21.3 mg/dl), PPBS (211.8 ± 32.1 mg/dl), HbA1c (7.0 ± 0.5 %), fasting Insulin (14.65 ± 5.39 µIU/ml), HOMA-IR (5.2 ± 2.3), AST (32.5 ± 7.8 IU/L), ALT (33.4 ± 13.3 IU/L), ALP (97.9 ± 28.8 IU/L) ADA (23.5 ± 9.5 IU/L) were significantly higher 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

Parameters	Type 2 Diabetic Subjects Mean ± SD (n=100)	Nondiabetic Subjects Mean ±SD (n=100)	p-Value

Age (yrs)	48.89 ± 7.68	45.88 ± 8.94	0.019
Males	46 (46%)	54 (54%)	-
Females	54 (54%)	46 (46%)	-
BMI (Kg/m^2)	26.42 ± 1.02	23.46 ± 1.18	0.000
FBS (mg/dl)	142.61 ± 21.36	90.48 ± 7.94	0.000
PPBS (mg/dl)	211.89 ± 32.16	119.43 ± 12.79	0.000
HbA1C (g%)	7.06 ± 0.56	4.98 ± 0.26	0.000
Fasting Insulin (µIU/ml)	14.65 ± 5.39	6.82 ± 1.77	0.000
HOMA IR	5.29 ± 2.37	1.52 ± 0.43	0.000
Serum AST (IU/L)	32.50 ± 7.80	24.22 ± 5.06	0.000
Serum ALT (IU/L)	33.40 ± 13.33	21.19 ± 2.82	0.000
Serum ALP (IU/L)	97.92 ± 28.82	78.62 ± 16.87	0.000
Serum ADA (IU/L)	23.53 ± 9.54	9.14 ± 1.71	0.000

In the present study, fasting Insulin levels were significantly positively correlated with FBS (r= 0.474), PPBS (r=0.267), HbA1c (r=0.571), AST (r=0.316), ALT (r=0.389), ALP (r=0.384) and ADA (r=0.515) 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)	0.474	0.000
PPBS (mg/dl)	0.267	0.007
HbA1c (g%)	0.571	0.000
AST (IU/L)	0.316	0.001
ALT (IU/L)	0.389	0.000
ALP (IU/L)	0.384	0.000
ADA (IU/L)	0.515	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= 0.330), PPBS (r=0.388), HbA1c (r=0.630), fasting insulin (r=0.515), HOMA-IR (r=0.516), AST (r=0.299), ALT (r=0.398) and ALP (r=0.414) 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)	0.330	0.001
PPBS (mg/dl)	0.388	0.000
HbA1c (g%)	0.630	0.000
Fasting Insulin (µIU/ml)	0.515	0.000
HOMA-IR	0.516	0.000
AST (IU/L)	0.299	0.003
ALT (IU/L)	0.398	0.000
ALP (IU/L)	0.414	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 controlled type 2 diabetic subjects whose mean values were 31.4 ± 12.4 IU/L *vs* 19.6 ± 5.2 IU/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)	9.14 ± 1.71	0.000
Good Controlled type 2 Diabetic Subjects (n=63)	19.65 ± 5.23	
Fair Controlled type 2 Diabetic Subjects (n=37)	31.48 ± 12.41	

Discussion:

T2DM, metabolic disorder characterized with metabolic disturbances, mainly of Insulin resistance, associated with hyperinsulinemia and hyperglycemia.[13] Insulin resistance impairs glucose utilization leads to hyperglycemia, resulting in increase in β- cell insulin production and hyperinsulinemia. The resultant hyperinsulinemia further aggravates the insulin resistance and the cycle continues till to the ending of β- cell functioning of pancreas, seen in poor glycemic controlled chronic type 2 diabetes mellitus. [14] Therefore, early detection of insulin resistance will be helpful for managing of emerging chronic complication of type 2 diabetes mellitus.

The chronic complications of type 2 diabetes mellitus are driven by metabolic and immunological disturbances and their prevalence. Increasing incidence of type 2 diabetes mellitus and insight knowledge of disease strives the researchers and their approach towards the immunological disturbances. ADA is an enzyme, which is considered as a good marker for cell mediated immunity and raised levels were observed in type 2 diabetes mellitus as a result of increased inflammation which is secondary to insulin resistance. ADA converts adenosine to inosine, thus decreases the adenosine levels. Adenosine mimics the action of insulin on glucose and is a promotor for glucose uptake into cells, whose decreased levels strongly associated with hyperglycemia and decreased insulin sensitivity.[15]

Because of complexity in insulin testing methods and time-consuming procedures, it was not frequently used in clinical practice. Parallel to insulin resistance, serum ADA showed a positive correlation, so it can be used as marker for insulin resistance in type 2 diabetes mellitus [4] for managing the emerging complications like diabetic kidney disease [16] and cardiovascular disease. [15] Our study reported increased levels of glycemic parameters (FBS, PPBS and HbA1C), fasting insulin levels, insulin resistance (HOMA IR) and serum ADA levels in type 2 diabetic subjects compared with nondiabetic subjects. Niraula *et al.*, reported significant positive correlation between serum ADA and HbA1C, Fasting plasma glucose and post-prandial glucose in type 2 diabetes mellitus. [5] In a study conducted by Aishwarya *et al.*, on 90 type 2 diabetic subjects including 57 males and 33 females found strong positive correlation between serum ADA and glycated hemoglobin levels. [6]

This 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. Cao *et al.*, in their

cross-sectional study demonstrated the independent association of serum ADA levels with islet β-cell function in type 2 diabetes mellitus.[4] Another study Bagher *et al.*, showed the diagnostic value of ADA and its isoforms in type 2 diabetes mellitus. [17]

Liver is the central metabolic organ of the body which is also affected by the pathogenesis of type 2 diabetes. Progression of insulin resistance can lead to nonalcoholic fatty liver disease (NAFLD). [14] The exact nature of altered liver enzymes in type 2 diabetes mellitus is still unclear. Study conducted by Liu C et al., on 7066 subjects including normal weight, overweight, and obese groups of non-diabetic individuals, showed insulin resistance is a significant predictive factor for abnormal liver enzymes. [18] Earlier studies clearly established that liver cirrhosis and development of diabetes and their bidirectional relationship [19,20]. Bi y et al., in their cross-sectional study demonstrated the association between liver enzymes and type 2 diabetes. [9] Islam et al., conducted a study on 270 subjects compromising of 110 type 2 diabetic and 160 nondiabetic healthy controls showed the high prevalence of elevated liver enzymes in subjects having type 2 diabetes mellitus.[8]

Romina et al., in their study showed that the moderate to advanced liver fibrosis in type 2 Diabetes Mellitus.[21] The increased liver enzymes AST, ALT and ALP were used mostly in analysis of liver function, which will reflect liver inflammation, impaired glucose tolerance associated insulin resistance in type 2 diabetes mellitus. [22,10] This study also reported the same results like earlier studies that liver enzymes were elevated significantly but within normal range in type 2 diabetic subjects when compared with nondiabetic subjects.

Previous studies mainly focused to draw the possible positive correlation between serum ADA levels and fasting plasma glucose, post prandial glucose and glycemic control with prevalence of dyslipidemia. [5,6,23-26] Very few studies were reported the correlation of insulin resistance with serum ADA levels in type 2 diabetes, [4,27-29] The present study found strong positive correlation between serum fasting insulin, insulin resistance and serum ADA levels. Present study also shows the positive correlation of serum ADA levels with glycemic parameters, fasting insulin, insulin resistance and liver enzymes. 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.[5]

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 elevated levels of ADA from good control to fair control in T2DM cases. these findings were supported by A Niraula et al and Aishwarya R et al. [5,6] The present study depicts that there is strong association of ADA with glycemic control, duration of disease and incidence of abnormal liver enzymes secondary to severity of inflammation and poor glycemic control.

Limitations of the study

Any imaging techniques were not used to investigate the liver abnormality and its association with type 2 diabetes mellitus and more over this study design is case control study, therefore it is not possible to know whether the duration of diabetes preceded abnormal liver function or not. The limited geographical distribution and sample size of study population limits to draw concrete conclusions. Future studies are needed aiming isoforms of ADA activity in pathogenesis and prognosis of type 2 diabetes mellitus.

Conclusion:
The present study results may conclude that significantly elevated glycemic parameters, liver enzymes and serum ADA in T2DM subjects. Serum ADA levels were positively correlated with glycemic parameters. Serum ADA levels may be used as an alternative surrogate marker for insulin resistance, assessing glycemic control and assessing liver functioning deformities in pathogenesis of T2DM. Further studies are needed with larger sample size to make the concrete conclusions.

Conflict of interest: Nil

Financial support: Nil

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