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Research Article

Adenosine deaminase as marker of insulin resistance

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ABSTRACT

Background: Type-2 diabetes complications contribute to increased morbidity and mortality and hence early diagnosis and control of diabetes is necessary. Adenosine deaminase activity is present in almost all human tissues, but the highest levels are found in lymphoid system. Aim of the study was to identify the correlation between adenosine deaminase levels and insulin resistance in type-2 diabetics and serum adenosine deaminase levels and glycemic control.
Methods: In this case control study, patients with type-2 diabetes mellitus, attending out-patient department or admitted in the hospital during the study period, fulfilling the study criteria were taken up.
Results: 200 patients were included in the study, with 100 patients in the case and controls group respectively. The mean body mass index, waist circumference, fasting blood sugar, post prandial blood sugar, glycosylated hemoglobin, fasting serum insulin levels, quantitative insulin sensitivity check index values were found to be significantly elevated ($p<0.0001$) in case group compared to controls. Quantitative insulin sensitivity check index was significantly reduced ($p<0.0001$) in study group compared to controls. Adenosine deaminase levels were significantly high ($p<0.0001$) in the study group compared to the control group, with a mean value of 22.35 U/L against 4.38 U/L. Adenosine deaminase levels were found to have a linear association with elevated fasting blood sugar and post prandial blood sugar, with a statistical significance ($p<0.0001$).
Conclusions: We identified that the highest Adenosine deaminase levels were detected in poorly controlled type-2 diabetes mellitus. Adenosine deaminase levels were found to have positive correlation with body mass index, fasting blood sugar and post prandial blood sugar levels. Adenosine deaminase levels were also positively correlated with insulin resistance, as calculated by homeostasis model assessment of insulin resistance. Adenosine deaminase levels were found to have an inversely proportional correlation with quantitative insulin sensitivity check index.

Keywords: Adenosine deaminase, Diabetes mellitus, HOMA-INR, Insulin resistance, Insulin sensitivity, QUICKI

INTRODUCTION

Type-2 Diabetes Mellitus (DM) is one of the oldest known disorders now having increased incidence in the modern era. According to American Diabetic Association, HbA_{1C} >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.[1] It is estimated that 366 million people had DM in 2011, which is estimated to rise to 552 million by 2030.[2] The number of people with type 2 DM is increasing in every country with 80% of the people with DM living in low- and middle- income countries.[3] If uncontrolled, DM is associated with serious complications that can contribute to increased morbidity and mortality.[4] Hence the diagnosis and control of DM is necessary to prevent the complications associated with it. American Diabetes Association recommends the glycemic control of HbA_{1C} <7.0%, preprandial capillary

plasma glucose <130mg/dl, postprandial peak capillary plasma glucose <180mg/dl.[5]

Adenosine deaminase (ADA) is a metalloenzyme that catalyses the deamination of adenosine and deoxyadenosine to inosine and deoxyinosine respectively and is implicated in purine metabolism. ADA activity is present in almost all human tissues, but the highest levels are found in lymphoid system (monocyte and macrophages predominantly) such as lymph nodes, spleen and thymus.[6] Serum ADA levels are proven to be elevated in cases of infectious mononucleosis, hepatitis, tuberculosis (TB) due to various monocyte/macrophage related changes occurring in the diseases. Adenosine acts directly on tissues to stimulate insulin activity via several processes like increased glucose transport, lipid synthesis, pyruvate dehydrogenase (PDH) activity, leucine oxidation and cyclic nucleotide phosphodiesterase activity. Adenosine levels are in turn regulated by serum ADA and it has been proved that adenosine via ADA activity plays an important role in the modulation of glucose metabolism in different tissues.[7,8]

Insulin resistance syndrome is a cluster of three of five clinical and biochemical parameters: abdominal obesity, elevated blood pressure, elevated FBS, elevated TG and low high density lipoprotein-C levels.[4] This is time consuming, cumbersome and more expensive way to assess insulin resistance. If the level of ADA correlates well with these parameters, it will be simple, easy, less time consuming and inexpensive and hence useful for the assessing clinician and patient. Thus, the study aims to identify the association of serum ADA levels with insulin resistance (IR) and glycemic control in patients with type-2 DM. Another objective of the study was to identify the association of ADA levels with physical markers of IR and insulin sensitivity (IS) in Type-2 DM patients.

METHODS

This case control study was carried out in a tertiary care hospital on in-patients and patients visiting the out-patient department during the study period and meeting the inclusion and exclusion criteria.

Inclusion criteria

- Patients diagnosed with type-2 DM

Exclusion criteria

- Patients with diagnosed TB, infectious mononucleosis, hepatitis at the time of study or ADA levels >40
- Patients with type-1 DM
- Patients with complications associated with DM
- Patients on insulin therapy
- Patients admitted with critical illness

Ethical approval was obtained from the institutional ethical committee located at the hospital.

Procedure for data collection

All the eligible subjects were included after into the study after obtaining informed consent. In situations where the potential subject was an illiterate, the consent was obtained from the impartial witness. In one arm, patients who were found fulfill the inclusion criteria were included and their physical examination followed by anthropometric data, FBS, PPBS, HbA_{1c}, fasting serum insulin levels, and serum ADA level estimation were collected. All the other relevant data was transcribed into the study data collection forms from the IP/OP cards, biochemistry reports and other relevant sources (interviewing other health care professionals and interacting with the subject and subject's care takers). In another arm, healthy subjects of similar age and sexes were included as control group.

Measurement of insulin resistance

There are multiple methods available to measure IR - dynamic test and static test.

A. Dynamic tests assess IS when the body is challenged with glucose or insulin. In this setting, glucose is primarily disposed of in skeletal muscle, and results largely reflects peripheral IR.
B. Static tests assess IS in the fasting state, in which IS is largely determined by the ability of insulin to regulate hepatic glucose production, thereby reflecting primarily hepatic IR.

Due to the complexity and time commitment of the dynamic methods, static methods were used. The two used methods were:

1. Homeostasis model assessment of insulin resistance (HOMA-IR) and
2. Quantitative insulin sensitivity check index (QUICKI).

Homeostasis model assessment of insulin resistance (HOMA-IR)

HOMA-IR has proved to be a good tool for the surrogate assessment of IR.[9,10] However, there is great variability in the threshold HOMA-IR levels to define IR. Population based studies for defining cut-off values of HOMA-IR for the diagnosis of IR had been conducted in different geographic areas.[11-18]

The cut-off point's determination was made on the percentile criterion (80 or 90 according to studies) of values in the general population (Figure 1). However, no studies have examined the ability of proposed cut-off points to identify risk of clinically relevant outcomes.[14] In

addition, in these studies the results have been reported without taking into account the possible effects of covariates on test results. However, it is well known that a biomarker's performance and, by extension, its discriminatory capacity can be affected by covariates.[19]

There are also age and gender-specific differences in HOMA-IR levels, with increased levels in women over fifty years of age.[20] On the other hand, the prevalence of cardio metabolic diseases such as diabetes or central obesity rises with age and shows gender differences.[21,22]

Quantitative insulin sensitivity check index (QUICKI)

This index correlates well with glucose clamp studies (r = 0.78), and is useful for measuring insulin sensitivity (IS), which is the inverse of IR. It has the advantage of that it can be obtained from a fasting blood sample, and is the preferred method for certain types of clinical research.[23] QUICKI is derived using the inverse of the sum of the logarithms of the fasting insulin and fasting glucose:

$$QUICKI = 1 / (\log(\text{fasting insulin } \mu U/mL) + \log(\text{fasting glucose mg/dL}))$$

Values typically associated with the QUICKI calculation for IR in humans fall broadly within a range between 0.45 for unusually healthy individuals and 0.30 in diabetics. So lower numbers reflect greater IR.[23]

Statistical analysis

Transcribed data was entered into Microsoft Excel 2010 for analysis. It was analyzed using SPSS software version 18.

Mean and Standard Deviation were worked out to estimate the various parameters of the study. Continuous variables were evaluated using parametric test like chi-squared test, also referred to as χ^2 test. Independent samples were evaluated using non parametric test like Student T test, Pearson correlation test and One-way ANOVA. The differences were interpreted statistically significant at $P<0.05$.

RESULTS

In Table 1, variables like age, duration of diabetes, BMI, waist circumference, creatinine, FBS, PPBS, HbA1c, fasting serum insulin level, HOMA-IR and QUICKI are compared between the case and control groups. We identified that the mean BMI, waist circumference, FBS, PPBS, HbA_{1c}, fasting serum insulin levels, HOMA-IR values were significantly elevated ($p < 0.0001$) in diabetic study group compared to controls. QUICKI was significantly reduced ($p < 0.0001$) in diabetic study group compared to controls based on Independent T test. There was no significant difference observed in creatinine levels of case and control group.

Table 1: Variables in type-2 diabetics (case) group and non diabetics (control) group.

	Group	N	Mean	Standard Deviation	P value
Age	Diabetes	100	58.5000	10.83065	1
	No diabetes	100	58.5000	10.83065	
Duration of diabetes	Diabetes	100	5.6000	4.15118	
	No diabetes	0[a]	.	.	
BMI (in kg/m2)	Diabetes	100	28.1614	4.48230	<0.0001
	No diabetes	100	21.6370	1.21518	
Waist circumference (in Cm)	Diabetes	100	100.8600	11.90028	<0.0001
	No diabetes	100	80.5200	3.65558	
Creatinine	Diabetes	100	1.0860	0.24205	0.1
	No diabetes	100	1.0370	0.16917	
Fasting blood sugar (FBS)	Diabetes	100	159.5900	56.47778	<0.0001
	No diabetes	100	82.6600	6.17460	
Postpradial blood sugar (PPBS)	Diabetes	100	276.2200	85.51952	<0.0001
	No diabetes	100	128.5900	5.74385	
HbA1C	Diabetes	100	8.4040	1.44802	<0.0001
	No diabetes	100	5.3060	0.18522	
Fasting serum insulin level miu/L	Diabetes	100	9.2217	2.08846	<0.0001
	No diabetes	100	5.1704	0.41770	
HOMA-IR	Diabetes	100	3.5620	1.13707	<0.0001
	No diabetes	100	1.0576	0.14013	
QUICKI	Diabetes	100	0.3192	0.01402	<0.0001
	No diabetes	100	0.3806	0.00822	

Table 2: Correlation of ADA with FBS, PPBS, HbA1C, fasting serum insulin levels, HOMA-IR, QUICKI.

		FBS	PPBS	HbA1C	Fasting serum insulin level (in mIU/L)	HOMAIR	QUICKI
ADA	r	0.795**	0.877**	0.892**	0.836**	0.944**	-0.975**
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	N	200	200	200	200	200	200

Table 3: Correlation between ADA levels with BMI and waist circumference.

		ADA	BMI (kg/m^2)	Waist circumference (in cm)
ADA	r	1	0.795**	0.812**
	p		<0.0001	<0.0001
	N	200	200	200
BMI (kg/m^2)	r	0.795**	1	0.873**
	p	0.000		0.000
	N	200	200	200
Waist-circumference (in cms)	r	0.812**	0.873**	1
	p	0.000	0.000	
	N	200	200	200

Table 4: Correlation of ADA with HbA1C level.

HbA_{1c}	N	Mean	Standard deviation	95% Confidence Interval for mean	
				Lower bound	Upper bound
<5.7	100	4.3800	2.03891	3.9754	4.7846
6.4-7.0	12	15.3333	4.63844	12.3862	18.2805
7.1-8.0	38	20.7105	4.86525	19.1114	22.3097
>8.0	50	25.2800	3.79064	24.2027	26.3573
Total	200	13.3650	9.89806	11.9848	14.7452

Table 5: Correlation of HOMA-IR with HBA1C.

HbA_{1c}	N	Mean	Standard Deviation	95% Confidence Interval for Mean	
				Lower bound	Upper bound
< 5.7	100	1.0576	0.14013	1.0298	1.0854
6.4-7.0	12	2.5930	0.89600	2.0237	3.1623
7.1-8.0	38	3.1253	1.01248	2.7925	3.4581
> 8.0	50	4.1264	0.97728	3.8486	4.4041
Total	200	2.3098	1.49292	2.1016	2.5179

Table 6: Correlation of BMI with insulin resistance and insulin sensitivity.

		HOMA-IR	BMI (kg/m^2)	QUICKI
HOMA-IR	Pearson Correlation	1	0.761**	-0.953**
	Sig. (2-tailed)		0.000	0.000
	N	200	200	200
BMI (kg/m^2)	Pearson Correlation	0.761**	1	-0.782**
	Sig. (2-tailed)	0.000		0.000
	N	200	200	200

Gender distribution of study subjects are depicted in the figure 2. Both the groups had equal patient distribution with 60 male and 40 female type-2 DM patients in the study group and 60 male and 40 female non-diabetic patients in the control group. ADA levels were significantly elevated ($p < 0.0001$) in study group as compared to the control group, with a mean value of 22.35 U/L in case group and 4.38 U/L in control group based on Independent T test (Figure 3).

The association between ADA with FBS, PPBS, HbA_{1c}, fasting serum insulin levels, HOMA-IR and QUICKI is

shown in Table 2. ADA levels were linearly elevated along with FBS, PPBS, $HbA_{1c,}$ fasting serum insulin levels, HOMA-IR and QUICKI values with statistical significance (p<0.0001) based on Pearson correlation test.

BMI and waist circumference was linearly elevated when compared to ADA levels with a statistical significance (p<0.0001) based on Pearson correlation test (Table 3).

Table 7: Relationship of HOMA-IR with number of people with and without *Acanthosis nigricans.*

HOMA-IR				
Acanthosis nigricans	**Mean**	**N**	**Standard Deviation**	**P value**
N	1.4732	120	1.01419	<0.0001
Y	3.5647	80	1.18619	
Total	2.3098	200	1.49292	

Table 8: Relationship of HOMA-IR with number of people with and without skin tags.

HOMA-IR				
Skin tags	**Mean**	**N**	**Standard Deviation**	**P value**
N	1.0598	74	0.28009	<0.0001
Y	3.0439	126	1.42625	
Total	2.3098	200	1.49292	

Study	Characteristics of study population	Threshold value	Criteria
Hedblad, 2000 [15]	N = 4,816 Sweden, population-based sample	≥ 2.0	75th percentile
Summer, 2008 [16]	N = 2804, U.S. NHANES population, age ≥ 20 yr, normal BMI and fasting glucose	≥2.73	66th percentile
Geloneze, 2006 [17]	N = 1317 Brazilian, age: 40 ± 12 yr, BMI: 34 ± 10 kg/m^2	≥ 2.77	90th percentile
Esteghamati, 2009 [18]	N = 1,276 Iranian,	≥1.80	ROC
	Age: 38 ± 12 yr, non-diabetic, normotensive	≥1.95	ROC
	IDF-MetS	≥1.6	75th percentile
	ATPII-MetS	≥1.8	80th percentile
		≥ 2.3	90th percentile
Marques-Vidal, 2002 [19]	N = 1153, France, age: 35–64 yr, population based sample	≥3.8	75th percentile
Do, 2010 [20]	N = 738 Thailand, age: ≥35 yr, normal BMI and fasting glucose	1.55	90th percentile
Miccoli, 2005 [38]	N = 225 Italian, age: 40–79 yr, healthy subjects	≥ 2.77	80th percentile
Nakai, 2002 [22]	N = 161 Japanese, age: 41.6 ± 0.4 yr, healthy subjects	≥ 1.7	90th percentile
Ascaso, 2001 [39]	N = 140 Spanish, age: 7–16 yr	3	ROC
Tome, 2009 [40]	N = 2860 Spanish, population based age: 18–104 yr, BMI: 26.2 ± 4.9 kg/m^2	2	ROC

Figure 1: HOMA-IR cut-off in different populations.

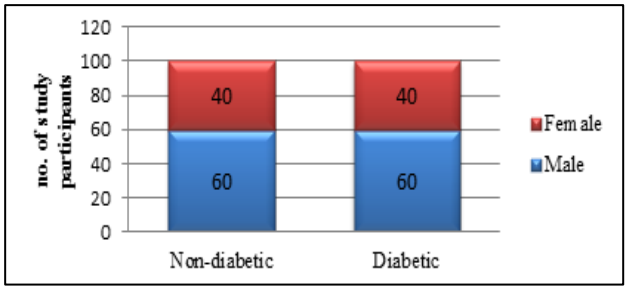

Figure 2: Distribution of the sex in case and control groups.

In the study, HOMA-IR levels were linearly elevated when compared to HbA_{1c} levels with a statistical significance (p<0.0001) based on Pearson correlation (Figure 4). The mean values of ADA level in different groups of HbA_{1c} were compared and found a significant elevation of ADA levels with the poorer glycemic control based on one-way ANOVA (Table 4). HOMA-IR levels were compared to glycemic control by HbA_{1c} and were found to be significantly elevated with poorer control of diabetes, based on One-way ANOVA (Table 5). As shown in table 6, HOMA-IR was linearly elevated with BMI in a statistically significant manner (p < 0.0001) based on Pearson correlation.

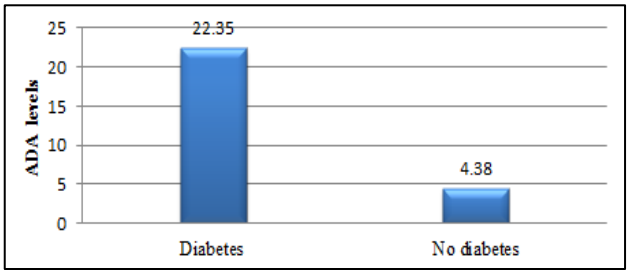

Figure 3: Correlation between ADA levels in the diabetic and non-diabetic group.

In this study, *Acanthosis nigricans* was correlated with mean HOMA-IR levels and subjects who had Acanthosis nigricans had mean HOMA-IR level of 3.5647 compared to subjects who didn't have *Acanthosis nigricans* who had a mean HOMA-IR level of 1.4732 signifying statistical significance based on Independent 't' test (Table 7).

Skin tags was correlated with mean HOMA-IR levels and subjects who had skin tags had mean HOMA-IR level of 3.04 compared to subjects who didn't have skin tags who had a mean HOMA-IR level of 1.06 signifying statistical significance based on Independent 't' test (Table 8).

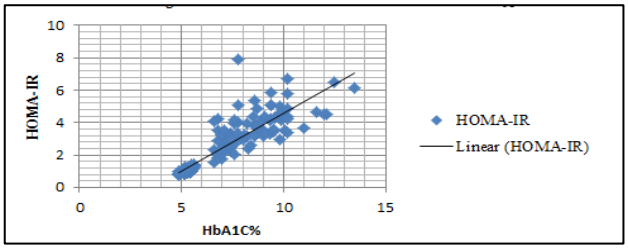

Figure 4: Correlation between HOMA-IR and HbA1C.

DISCUSSION

Fasting, post-prandial blood sugar levels and adenosine deaminase levels

In this study, FBS levels had a positive correlation with ADA levels with non-diabetics having mean FBS levels of 82.66 mg/dL and mean ADA levels of 4.38 U/L when compared to Type-2 diabetics having a mean FBS levels of 159.59 mg/dL and mean ADA levels of 22.35 U/L. We identified that PPBS levels had a positive correlation with ADA levels with non-diabetics having mean PPBS levels of 128.59 mg/dL and mean ADA levels of 4.38 U/L when compared to type-2 diabetics having a mean PPBS levels of 276.22 mg/dL and mean ADA levels of 22.35 U/L. We found significant increases in ADA levels in patients with increasing FBS, PPBS levels as previous studies by Sangeeta et al and Dong Gu Kang et al have shown. But in contrast to our findings, Naciye Kurtulet al observed no relationship between FBS, PPBS and serum ADA.[24-26]

Glycemic control according to glycosylated hemoglobin and adenosine deaminase levels

In this study, the mean ADA levels in controls was around 4.38 U/L in non-diabetics (HbA_{1c}<5.7%), 15.33 U/L in well-controlled diabetics (HbA_{1c} 6.4% - 7%), 20.71 U/L in unsatisfactorily controlled diabetics (HbA_{1c} 7.1%-8.0%) and 25.28 U/L in poorly controlled diabetics (HbA_{1c} >8.0%) and there was significant increase in the values of ADA in comparison with higher HbA1c levels (poorer glycemic status).

We found significant increases in ADA levels in patients with increasing HbA_{1c} levels as previous studies Dharamveer et al, Jae-GeunL et al, Nisha et al and Amandeep et al, have shown.[25-28] But in contrast to our findings, Pence et al observed no relationship between HbA_{1c} and serum ADA.[24]

Body mass index and adenosine deaminase levels

We found significant increase in ADA levels in patients with increasing BMI as the previous studies Bottini et al and Ashish et al [have] shown in normal individuals.[29,30]

Insulin resistance (HOMA-IR) and adenosine deaminase levels

We found significant increase in ADA levels in patients with increasing HOMA-IR levels as seen in as previous studies Amrita et al and Vanitha et al.[31,32]

Insulin sensitivity (QUICKI) and adenosine deaminase levels

We found significant reduction in ADA levels in patients with increasing QUICKI levels as seen in as Vanitha et al have shown. [32] We had a few limitations. The exact role of ADA in pathogenesis of Type-2 DM was not completely clear, for which further studies at molecular level are needed. This cross-sectional study also limited the interpretation of a causal link between the ADA and insulin resistance. Prospective studies are required to fully assess the role of ADA in the development of Insulin resistance.

Moreover, ADA was measured from serum, reflecting only systemic changes and may not reflect the local concentrations in the tissue level of adipocytes, muscles and liver. Hence, studies involving estimation of adenosine and ADA concentrations at tissue level might shed more light at the level of tissue pathology. We measured total ADA levels rather than its different isoforms (ADA_1, ADA_2). In this study, we could not rule out whether or not a specific isoform, such as ADA_1 or ADA_2 isoforms, were involved in DM progression.

CONCLUSION

Type-2 DM is a major public health problem worldwide. The incidence and prevalence of diabetes is increasing at an alarming rate. We found that the highest ADA levels were present in poorly controlled type-2 DM patients who had the highest HbA1c. ADA was positively correlated with BMI, FBS and PPBS.

ADA was also positively correlated with insulin resistance as calculated by HOMA-IR. ADA levels were found to have inversely proportional correlation with QUICKI. Although a positive correlation was identified, larger prospective studies are required to fully assess the role of ADA in the development and progression of type-2 DM.

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