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Original Research Article

To study the correlation of serum adenosine deaminase levels with hba1c in patients of type 2 diabetes mellitus

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Abstract

Background and Objectives: Immunological dysfunction is responsible for increased morbidity and mortality due to recurrent infections and hospital admission in Type 2 DM. There are limited studies and markers for the assessment of immunological dysfunction and serum ADA is one of the marker of immunological dysfunction as proven in several studies. The present study is an attempt to correlate ADA as a marker of altered immune function in diabetes mellitus with respect to glycemic control as assessed by HbA1C.

Methods: This cross sectional study was conducted in the hospitals attached to Bangalore Medical College and Research Institute. Relevant history taking, Clinical examination and laboratory investigations was done on 90 patients of Type 2 Diabetes mellitus, correlation of HbA1c and serum ADA was done in these individuals taking into consideration the glycemic control. Student t test was used to compare them. Spearman's correlation coefficient was used to see the relationship between the variables and p value of <0.05 was considered significant.

Results: Among 90 patients in our study 57 were males and 33 were females. Mean ± SD of HbA1C was 9.85 ± 2.73. Mean ± SD of serum ADA levels was 40.39 ± 4.69. Spearman's correlation coefficient in our study was 0.728 indicating a strong correlation between serum ADA and HbA1C. There was a linear correlation between HbA1C levels and serum ADA and the correlation was statistically significant P Value <0.001.

Conclusion: Metabolic and immunological disturbance are two important key factors in type 2 diabetes mellitus which is a leading cause of morbidity and mortality. ADA is an enzyme, which is considered as a good marker for cell mediated immunity. Our study showed elevated serum ADA activity in poorly controlled diabetic individuals and a strong correlation of HbA1C with serum ADA levels which was statistically significant indicating poor the glycemic control more the immunological dysfunction.

Keywords: ADA-Adenosine deaminase, HbA1C-Glycosylted hemoglobin, DM diabetes mellitus

Introduction

The number of people diagnosed with Type 2 Diabetes Mellitus is estimated about 380 million by the World Health Organization. This number is expected to increase to 592 million

people by the year 2035 [1].

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia [2]. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors [2]. It is characterized by high blood glucose levels resulting from defects in insulin production, insulin action, or both [4, 5]. Depending on the etiology of the DM, factors contributing to hyperglycaemia include reduced insulin secretion, decreased glucose utilization and increased glucose production [2].

The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system [2]. In the United States, DM is the leading cause of end-stage renal disease (ESRD), non-traumatic lower extremity amputations and adult blindness [1]. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be likely a leading cause of morbidity and mortality in the future [2].

Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide, accounting for 90% of cases globally. An epidemic of T2DM is under way in both developed and developing countries, although the brunt of the disorder is felt disproportionately in non-European populations [3].

It is a condition primarily defined by the level of hyperglycaemia giving rise to risk of micro-vascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related micro-vascular complications, increased risk of macro-vascular complications (ischaemic heart disease, stroke and peripheral vascular disease) and diminished quality of life [3].

Several pathogenetic processes are involved in the development of diabetes. These include processes, which destroy the beta cells of the pancreas with consequent insulin deficiency and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin.

Metabolic disturbance and immunological imbalance are two important key factors in type 2 diabetes mellitus [1, 6].

Immunological disturbance in type 2 diabetic individuals has been associated with cell-mediated immunity and inappropriate T-lymphocyte function [1, 7]. Adenosine deaminase (ADA) is an enzyme, which converts adenosine to inosine through an irreversible deamination reaction in the purine salvage pathway. The highest activity of ADA has been reported in lymphocytes and monocytes. Its chief role concerns the proliferation and differentiation of lymphocytes and activation of macrophages [1].

Hence it is considered as a good marker for cell mediated immunity it is also considered to be an important enzyme for modulating the bioactivity of insulin and some studies have reported it to be a predictive marker of insulin resistance [7]. As adenosine deaminase is associated with T-lymphocyte activity, its altered blood levels may help in predicting immunological dysfunction in diabetic individuals and might be one of the important biomarkers in predicting diabetes mellitus. Our present study aimed at correlation of serum ADA levels with glycemic control as indicated by HbA1C.

Materials and Methods

Methodology of data collection

The present study was a cross sectional study conducted between November 2017 and May 2019 in hospitals attached to BMCRI. After obtaining approval from the Institutional Ethics Committee of BMCRI, written informed consent was taken from the patients. Patients with type 2 diabetes mellitus who were 18 years or older and diagnosed as per ADA criteria of diabetes mellitus were included in the study.

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Patients who were known alcoholics, on insulin treatment, had acute complications of Diabetes Mellitus, had liver diseases, were under the treatment of immunosuppressive drugs, type 1 diabetics, were diagnosed with Tuberculosis or on treatment for it were excluded from the study.
Demographic data and history was obtained and relevant clinical examination was done on 90 patients of type 2 Diabetes mellitus, as per study proforma (Annexure II). Relevant investigations were sent. Correlation of HbA1c and serum ADA was done in these individuals taking into consideration of the glycemic control. Further sampling or follow up was not done.

Statistical analysis

Data was analysed by the descriptive statistics. ANOVA was be used to compare 3 or more groups. Correlation coefficient was be used to see the relationship between the variables.

Results

The present study was conducted in the Department of Medicine, Bangalore medical college and research institute. A total of 90 cases of diabetes mellitus were taken according to the proforma detailed in the methodology and the data obtained thereby are presented and analysed below.
The present study was done to estimate serum ADA levels in individuals of Type 2 Diabetes Mellitus and to correlate Serum Adenosine deaminase levels with HbA1c.

1. Demographic details of study subjects

Table 1: Demographic details of study subjects

Demographic details	No. of subjects	Percentage
Sex		
Male	57	63.33%
Female	33	36.67%
Age (years)		
25-34	3	3.33%
35-44	14	15.56%
45-54	31	34.44%
55-64	24	26.67%
65-74	14	15.56%
75-85	4	4.44%

As observed from table 1 majority of the patients were between age group of 45 to 54 years (34.44%). It was observed from our study that three of the patients belonged to age group of 25-34. Fourteen out of ninety patients were of age group 35 to 44, twenty four of them to 55 to 64, fourteen to 65 to 74 and four of them belonged to 75 to 85 age group. We observe from table 1 that fifty seven subjects were males (63.33%) and thirty three were females.

2. Clinical history of study subjects

Table 2: Clinical history of study subjects

Clinical history	No. of subjects	Percentage
History of Diabetes Mellitus (years)		
0-5	46	51.11%

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5-10	29	32.22%
10-15	10	11.11%
15-20	2	2.22%
History of hypertension (years)		
1	11	12.22%
2	10	11.11%
3-4	6	6.67%
5-7	8	8.89%
Absent	55	61.11%
History of smoking		
Present	15	16.67%
Absent	75	83.33%

From the above table 2 it is observed that 46 patients in our study had disease for duration of less than 5 years (51.11%). Twenty nine patients had the disease for duration of 5 to 10 years (32.22%), ten of them had disease for duration of 10 to 15 years (11.11%) and only two of them had disease for a duration of 15 to 20 years.

It is observed from table 2 that 55 patients were non hypertensive and 35 patients had hypertension among them 11 of them had hypertension for duration of 1 year 10 of them had hypertension for 2 years six of them had hypertension for 3 to 4 years and 8 of them had hypertension for a duration of 5 to 7 years.

It is observed from the above table 2 that 75 patients out of 90 were non-smokers and 15 of them were smokers.

3. Hematological and biochemical parameters of study subjects

Table 3: Hematological and biochemical parameters of study subjects

Hematological Parameter	No. of subjects	Percentage
Hb (g/dl)		
5-10	7	7.78%
10-15	68	75.56%
15-20	15	16.67%
TLC (cells/cu mm)		
4000-5999	4	4.44%
6000-7999	26	28.89%
8000-9999	35	38.89%
10000-11999	18	20.00%
>12000	7	7.78%

It is observed from the table 3 that majority of the subjects 68 (75.56%) had their hemoglobin concentration in the normal range between 10 to 15g/dl. Seven had hemoglobin less than 10 g/dl and 15 had hemoglobin concentration more than 15g/dl (16.67%).

It is observed from the table 3 that majority of the patients had total counts within normal limits and only 7 patients (7.78%) had total count more than 12,000.

4. Diabetic parameters of study subjects

Table 4: Diabetic parameters of study subjects

Diabetic Parameter	No. of subjects	Percentage
FBS (mg/dl)		
50-149	34	37.78%
150-249	39	43.33%

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250-349	14	15.56%
>350	3	3.33%
PPBS (mg/dl)		
100-199	13	14.44%
200-299	42	46.67%
300-399	20	22.22%
>400	15	16.67%
100-199	13	14.44%
HbA1C		
5.7-6.4	23	1.11%
6.4-11.4	67	74.44%
11.4-16.4	19	21.11%
16.4-21.4	3	3.33%
Serum ADA levels		
25-29	1	1.11%
30-34	10	11.11%
35-39	24	26.67%
40-44	39	43.33%
45-49	15	16.67%
50-55	1	1.11%

It is observed from the above table 4 that 34 patients (37.78%) had fasting glucose levels less than 150 mg/dl. Thirty nine of them had fasting glucose levels between 150 to 249 mg/dl and fourteen of them had fasting glucose levels between 250 to 349 and only three of them had fasting blood glucose levels more than 350 mg/dl.

It is observed from the above table 4 that 42 of the subjects had post prandial blood glucose levels in the range of 200 to 299 mg/dl (46.67%), twenty subjects had postprandial sugars in the range of 300 to 399 (22.22%)and 15 of them had post prandial sugars more than 400mg/dl(16.67%).

It is observed from the table 4 that 67 patients had glycated hemoglobin of the range 6.4 to 11.4, nineteen of them had between 11.4-16.4 and 3 of them had glycated hemoglobin more than 16.4%.

It is observed from the table 4 that only one subject had serum ADA levels less than 30.Ten of them had serum ADA levels between 30 to 34(11.11%), twenty four of them had serum ADA levels between 35-39(26.67%), thirty nine subjects had serum ADA levels of the range 40-44(43.33%), 15 subjects had serum ADA levels between 45-49 and only one had serum ADA level more than 50.

5. Correlation between HbA1C and S. ADA levels among study subjects

Table 5: Correlation between HbA1C and S. ADA levels among study subjects

Descriptive statistics	HbA1C	S.ADA	Spearman's correlation coefficient
Mean	9.85	40.39	0.728
95% Confidence Interval	9.27-10.42	39.41-41.37	(p<0.001)
Median	9.10	41.00	
Std. Deviation	2.73	4.69	
Minimum	5.70	26.00	
Maximum	18.40	51.00	
Interquartile Range	3.55	7.00	

Mean HbA1C in our study was 9.85, median HbA1C level was 9.10 with a standard deviation of 2.73. The maximum and minimum HbA1C levels in our study were 18.40 and 5.70

respectively. Mean serum ADA level in our study was 40.39 with a standard deviation of 4.69 with median value of 41 and maximum and minimum value of serum ADA being 51 and 26 respectively. Spearman's correlation coefficient in our study was 0.728 indicating a strong correlation between serum ADA and HbA1C.

6. Serum ADA levels with reference to glycemic control

Table 6: Serum ADA levels with reference to glycemic control

	HbA1C		P Value
S.ADA	**<7**	**>7**	
25-34	4 (36.4%)	7 (63.6%)	<0.001
34-39	6 (25.0%)	18 (75.0%)	
39-44	0 (0.0%)	39 (100.0%)	
44-55	0 (0.0%)	16 (100.0%)	

It is observed from table 6 that people with well controlled glycemic state (HbA1C <7) had lower levels of serum ADA as compared with those of poorly controlled glycemic state (HbA1C>7) and the correlation was statistically significant P Value <0.001.

Discussion

In the present hospital based cross sectional study, patients of type 2 diabetes mellitus irrespective of duration of disease attending the Department of Medicine, Bangalore medical college were evaluated clinically and with required laboratory tests.

1. Age distribution

As discussed previously among 90 subjects in our study majority were of age group of 45 to 54 years (34.44%) which was comparable to a Study done by Hariprasath. G [7] *et al*. conducted from April to September 2016 at Rajah Muthiah Medical College & Hospital, Annamalai University which included a total number of 80 subjects of age group 40-55 years. Study done by Shiva Prakash [6] *et al*. on a group of thirty-six adult patients also had patients in the age group of 30 to 50 years. In a Study by Ramani NS [8] *et al*. on 101 study subjects in India the mean+ SD of Age (yrs.) in cases and controls were 49.12+9.177 and 48.4+ 8.822 respectively and they are age matched.

2. Sex distribution

In our study 57 out of 90 subjects were males and 33 were females. In a Study by Ramani NS [8] *et al*. on 101 study subjects among the cases 45.1% were females and 54.9% were males and among the controls 46% were females and 54% were males. In a similar study by Tomoaki Hoshinoa [9] *et al*. on 53 Insulin dependent diabetic patients 20 were men and 33 women and 65 Non-Insulin dependent diabetic patients 41were men and 24 patients were women.

3. Duration of diabetes

46 patients in our study had disease for duration of less than 5 years (51.11%).

Twenty nine patients had the disease for duration of 5 to 10 years (32.22%), ten of them had disease for duration of 10 to 15 years (11.11%) and only two of them had disease for a duration of 15 to 20 years. However in similar other studies the HbA1C levels were given a priority to duration of diabetes as all previous studies correlated HbA1C values to serum ADA than duration of diabetes, But in a similar study by Tomoaki Hoshino [9] *et al*. all the study subjects had diabetes for a duration of more than 5 years.

4. Distribution of hypertensives

As previously mentioned 55 patients in our study did not have hypertension and 35 patients had hypertension among them 11 of them had hypertension for duration of 1 year 10 of them had hypertension for 2 years six of them had hypertension for 3 to 4 years and 8 of them had hypertension for a duration of 5 to 7 years. In a similar study by Shiva Prakash 6 *et al*. on a group of thirty-six adult patients of either sex none of them had hypertension.

5. Distribution of FBS and PPBS among study subjects

In our study 34 patients (37.78%) had fasting glucose levels less than 150 mg/dl,13 of them had fasting glucose levels between 150 to 249 mg/dl and fourteen of them had fasting glucose levels between 250 to 349 and only three of them had fasting blood glucose levels more than 350 mg/dl.

In a Study by Shiva Prakash [6] *et al*. on a group of thirty-six adult patients fasting glucose levels were normal in controls (86.05 ± 9.2) and significantly (p<0.001) higher in the diabetic subjects 146.8 ± 16.2(mg/dl). In a Study by Ramani NS [8] *et al*. on 101 study subjects the mean and SD of FBS in cases was 192.92 + 102.75 and controls was 98.36+17.90. In a study by Khemka [10] *et al*. FBS in (mg/dL) in controls was 80.91 ± 8.55 and in diabetics was 167.4 ± 60.3.

In our study we observed that 42 of the subjects had post prandial blood glucose levels in the range of 200 to 299 mg/dl (46.67%), 20 subjects had postprandial sugars in the range of 300 to 399 (22.22%) and 15 of them had post prandial sugars more than 400mg/dl(16.67%). In a Study by Ramani NS [8] *et al*. PPBS in cases were 261.24 + 109.05 and in controls were 142+ 35.16.

6. HbA1c in study population

In our study 67 patients had HbA1C in the range 6.4 to 11.4, 19 of them had between 11.4-16.4 and 3 of them had HbA1C more than 16.4%. The mean HbA1C in our study was 9.85, median HbA1C level was 9.10 with a standard deviation of 2.73.The maximum and minimum HbA1C levels in our study were 18.40 and 5.70 respectively. In a study by Khemka [10] *et al*. HbA1C (%) in controls was 4.82 ± 0.43 and in diabetics was 7.48 ± 1.08. In a Study by Ramani NS [8] *et al*. on 101 study subjects the mean and SD of HbA1C (%) in cases was 8.38 + 14.00 and in controls was 5.24+ 0.62.

7. Serum ADA levels among study population

In our study only one subject had serum ADA levels less than 30.10 of them had serum ADA levels between 30 to 34(11.11%), 24 of them had serum ADA levels between 35-39(26.67%), 39 subjects had serum ADA levels of the range 40-44(43.33%), 15 subjects had serum ADA levels between 45-49 and only one had serum ADA level more than 50. Mean serum ADA level in our study was 40.39 with a standard deviation of 4.69 with median value of 41 and maximum and minimum value of serum ADA being 51 and 26 respectively. In a Study by

Ramani NS [8] *et al*. on 101 study subjects the mean and SD of serum ADA in cases was 32.06 + 17.09 and in controls was 19.28+ 5.59. In a Study by Shiva Prakash [6] *et al*. on a group of thirty-six adult patients mean serum ADA (U/L) in controls was 18.2 ± 5.6 whereas in subjects was 37.2 ± 5.0.
Whereas in a similar study by Tomoaki Hoshino [9] *et al*. the Total ADA activity in the serum of healthy donors, insulin dependent diabetics and Non-Insulin dependent diabetic patients were 13.4, 23.1 (p<0.001 vs. HD) or 20.6 units/l (p<0.001 vs. HD), respectively.

8. Correlation between HbA1C and S. ADA levels among study subjects

We observed in our study that people with well controlled glycemic state (HbA1C <7) had lower levels of serum ADA as compared with those of poorly controlled glycemic state (HbA1C>7) and the correlation was statistically significant P Value <0.001 and there was a linear correlation between serum ADA and HbA1C.
In a Study conducted by Bagher L [1] *et al*. on 33 patients with type 2 diabetes at Diabetes Center of Shariati Hospital, Iran 2016 found significant differences between total serum ADA (tADA) and ADA2 activities in the diabetic groups with HbA1c < 8 (%) and HbA1c ≥ 8 (%) with respect to the values in healthy individuals.
In a Study by Shiva Prakash [6] *et al*. on 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 in 2005 in India found a significant increase in adenosine deaminase activity in diabetic subjects when compared to controls.
In a Study by Hariprasath. G [7] *et al*. conducted from April to September 2016 at Rajah Muthiah Medical College & Hospital, Annamalai University which included a total number of 80 subjects of age group 40-55 years in the study out of which 30 were healthy Controls with no history of diabetes mellitus, 25 were Type 2 Diabetics with Good glycemic control (HbA1c ≤7) and 25 were Type 2 Diabetics with Poor glycemic control (HbA1c ≥7) found elevation of plasma ADA activity in Type 2 diabetic subjects as compared to controls. In particular much higher ADA activity was observed in Type 2 diabetic patients with poor glycemic control than Good Glycemic control. Significant Positive correlation was also observed between ADA & HbA1c in both good and poor glycemic controls.
In a Study by Ramani NS [8] *et al*. on 101 study subjects in India concluded that serum ADA was significantly elevated in individuals of Type 2 diabetes and ADA could be used as a marker of glycemic status in individuals of Type 2 diabetes mellitus.
In a Study by Pinnelli [11] *et al*. on 100 subjects with T2DM and 100 healthy controls conducted in India in 2015 concluded ADA level was significantly higher in patients with Type 2 DM than controls. A significant positive correlation was observed between serum ADA and HbA1c among subjects with Type 2 diabetes mellitus but not among non-diabetic controls.
In a cross-sectional study by Lokendra BS [12] *et al*. on 80 type 2 diabetes mellitus (DM) patients and same number of age-matched and sex-matched healthy controls concluded that Serum ADA activities were significantly higher in type 2 diabetic patients compared with controls having significant positive correlation with glycemic parameters. Serum ADA and its isoenzymes could be used as biomarkers for assessing glycemic status in patients with type 2 DM.
However in a study by Khemka [10] V *et al*., serum ADA levels showed a significant positive correlation with fasting plasma glucose (r = 0.657; p<0.0001) level among non-obese T2DM subjects, but no significant correlation was observed in controls (r = −0.203; P = 0.180) and also no correlation was observed between serum ADA levels with BMI and HbA1c levels.

Conclusion

Metabolic and immunological disturbance are two important key factors in type 2 diabetes mellitus which is a leading cause of morbidity and mortality. ADA is an enzyme, which is considered as a good marker for cell mediated immunity. Our study showed that serum ADA levels are raised in diabetic individuals compared to general population and there was a linear correlation of serum ADA with HbA1C. As observed serum ADA was elevated more in poorly controlled diabetics with HbA1C **>7** as compared to well controlled diabetics with HbA1C <7. Spearman's correlation coefficient in our study was 0.728 indicating a strong correlation between serum ADA and HbA1C which was statistically significant indicating poor the glycemic control more the immunological dysfunction.

Serum ADA estimation is simple and inexpensive marker which can be used for assessment of immunological dysfunction in diabetic individuals and It is also considered to be an important enzyme for modulating the bioactivity of insulin and some studies have reported it to be a predictive marker of insulin resistance.

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