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Original Article

Adenosine Deaminase as Inflammatory Marker in Type II Diabetes Mellitus

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Abstract

Objective: To evaluate the enzymatic activity of Adenosine Deaminase in type II diabetes mellitus (T2DM).

Methods: This study was conducted on 60 clinically diagnosed type II diabetes mellitus patients, with 60 healthy subjects as the control group. Subjects were enrolled in the study only after their written consent was obtained. The inclusion of diabetes mellitus cases (DM) was conducted as per the WHO guidelines. Estimation of enzymatic activity of serum ADA was performed by Kinetic method using a commercial kit.

Result: The observed serum ADA activity in DM patients was 48.34 ± 21.05 U/L, which was significantly higher in comparison to healthy controls (25.02 ± 5.78 U/L). The serum activity raised in about 80% of patients and they had higher values above the reference activity of 30 U/L. The increased activity of ADA among the diabetic subjects indicates inflammatory changes in these individuals.

Conclusion: It is possible that in the coming years, a new therapeutic strategy based on anti-inflammatory properties with beneficial effects on diabetic complications can be translated into real clinical treatments.

Keywords: Adenosine deaminase, inflammatory markers, type II diabetes mellitus

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized with hyperglycemia due to derangement in metabolism of carbohydrates, lipids and proteins. A large number of Diabetes Mellitus remains undiagnosed. This disorder is incurable and persists life-long. Type II Diabetes Mellitus is considered as a lifestyle disorder which develops due to sedentary lifestyle, lack of physical activities, low intake of dietary fibers, etc. Type II Diabetes Mellitus can lead to morbidity and mortality through various microvascular and macrovascular changes. Various other risk factors like environmental, genetically and behavioral factors contribute significantly for developing Type II Diabetes Mellitus.[1]

In type II Diabetes Mellitus, immune system functioning has also been found to be altered. T-cell mediated immunity is disturbed which further links to impairment in Insulin responses.[2] This results in adverse changes such as activation of leucocytes, elevated levels of cytokines in the circulation and increased apoptosis. These changes in the body system suggest mediation of inflammatory changes taking place in Diabetes Mellitus. A variety of pro-inflammatory mediators are released from different body tissues including activated Leucocytes, adipocytes and endothelial cells. The role of various biochemical products namely Interleukin-6, C- reactive protein (CRP), Tumor Necrosis Factor (TNFα), leptin, etc. have been studied widely and the researchers have proposed the potential involvement in inducing the pathogenesis of Type II Diabetes Mellitus. Also, some metabolic and inflammatory factors and their serum

levels directly relate with amount of adipose tissues in the body.[3, 4]

Adenosine Deaminase (ADA), a metabolic enzyme catalyzing metabolic reaction of deamination, deaminates Adenosine to Inosine and also acts as a regulatory enzyme for maintaining extracellular and intracellular concentration of Adenosine.[5] ADA being ubiquitously expressed, the activity of the enzyme is seen higher in the tissues like Thymus, GI tract, Brain tissues and Lymphoid tissues.[6] The enzymatic activity of ADA has been seen to be higher in lymphoid tissues and aids in increasing lymphocyte proliferation and differentiation. It has been found as a producer of oxygen derived reactive oxygen species (ROS) as well as a stimulator for lipid peroxidation.[7] Adenosine acts through a G protein- couples receptors and facilitates the regulation of normal cell physiology in various body tissues.[8] Adenosine is a suppressant of inflammation which inhibits the inflammatory mechanisms like inhibiting T-cell activation and proliferation. Meanwhile, Adenosine is supposed to mimic the activity of insulin on glucose and somehow might have role in causing insulin resistance. Since, the concentration of Adenosine is regulated by the activity of ADA; the insulin resistance can have ADA as a triggering factor. The increased ADA activity in the Diabetic subjects might be due to deranged insulin activity related to T-lymphocyte function.[9] The present study was aimed to evaluate the enzymatic activity of Adenosine Deaminase in Type II diabetes Mellitus and find out whether there might be any association between the inflammatory marker and Diabetic markers.

Methods

The study design is a case- control study. This study was conducted in Teerthanker Mahaveer Medical College & Research Center in 2019 after the approval from Institutional Ethical Committee (IEC/17-18/030). The study was conducted on 60 clinically diagnosed Type II Diabetes Mellitus patients and control group of 60 healthy subjects were also included. Sample size calculation was done using statistical formula. All the subjects were between the age group of 30 to 45 years. The subjects enrolled in the study were confirmed only after their written consent was obtained. The inclusion of Diabetes Mellitus cases was done according to WHO guidelines. The individuals having Fasting Plasma Glucose ≥ 126 mg/dl or Random Glucose ≥ 200 mg/dl on two occasions were included as the cases in this study. Those individuals having inflammatory diseases like Tuberculosis, Cancer, Gout, Liver and Kidney diseases were excluded from the study to rule out any increase in ADA activity due to other inflammation conditions. Pregnant female subjects were also excluded. Estimation of enzymatic activity of serum ADA was done by Kinetic assay method using commercially available kit.[10] Data Obtained was tabulated and analyzed using SPSS.

Result

As shown Table 1 and Fig. 2, the study parameter i.e serum ADA activity which has been studied as one of the inflammatory markers was found to be higher among Type II Diabetic subjects as compared to the healthy subjects and the difference in activity between

Table 1 Demographic distribution of the study population

S.N	Subject	Male	Female	Total
1.	Healthy Control	34	26	60
2.	Diabetes Mellitus	37	23	60

Table 2 Comparison of Study Parameters between Diabetic Patients and Healthy Controls

Parameters	Type II Diabetes Mellitus	Healthy Controls	p-value
Fasting Plasma Glucose (mg/dL)	178.96± 53.98	90.16 ± 12.23	<0.001*
HbAlc (%)	8.65 ± 1.83	5.26 ± 0.68	<0.05
Adenosine Deaminase (IU/L)	48.34 ± 21.05	25.02 ± 5.75	<0.001*

Table 3 Correlation of Serum ADA activity with Glycemic Status in Diabetic Individuals

Glycemic Status	r-value	p-value
Fasting Plasma Glucose	0.24	< 0.05
HbAlc	0.38	< 0.0.5

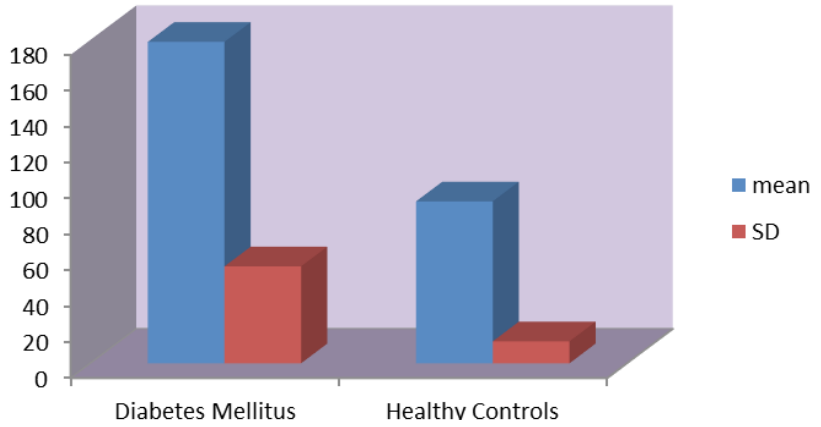

Fig. 1 Comparison of Fasting Plasma Glucose levels

the study groups was statistically highly significant ($p<0.01$). The correlation analysis between serum ADA activity and glycemic indices as shown in Table 2, also highlighted that serum ADA activity is significantly correlated with fasting blood sugar ($p<0.05$) and HbA1c levels ($p<0.05$).

Discussion

Type II Diabetes mellitus is a heterogeneous group of disorders featured by impaired insulin secretion and insulin resistance and increased blood glucose. This disorder is supposed to be associated with an acute phase reaction which suggests that a low-grade inflammation might also be involved in its pathogenesis.[11] Serum Adenosine Deaminase activity in this study has been found to be elevated among the Type II Diabetes Mellitus patients. On comparing the mean values using Student's t-test between the study groups, the serum activity of ADA

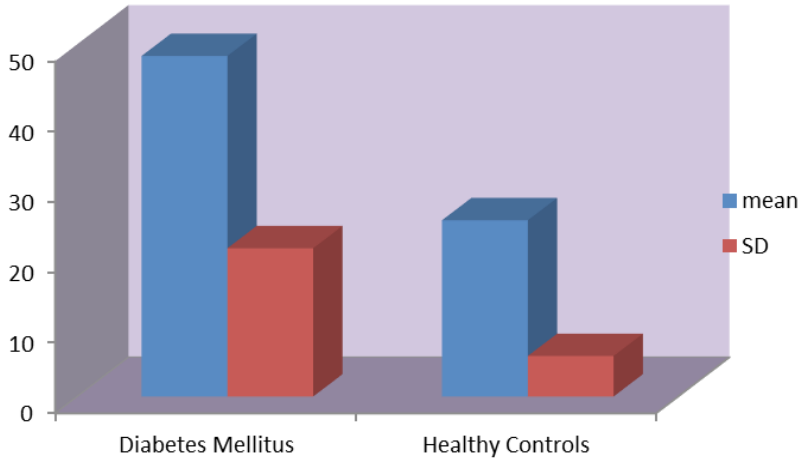

Fig. 2 Comparison of Adenosine Deaminase activity

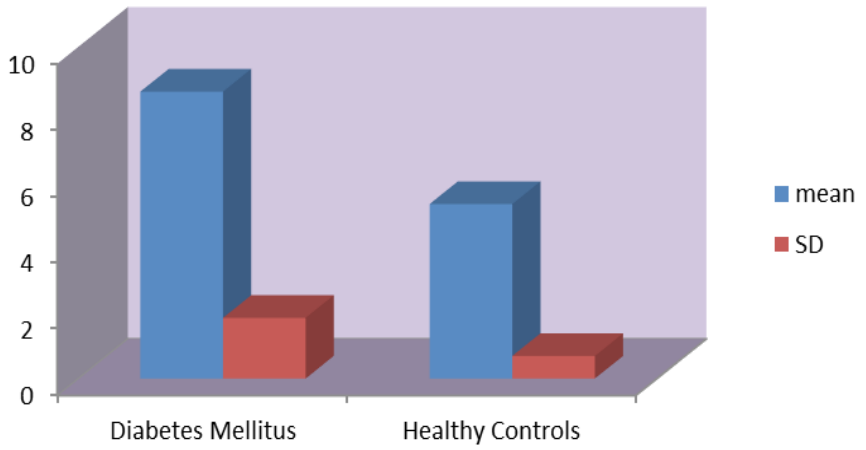

Fig. 3 Comparison of Glycosylated Hemoglobin

in the Diabetic patients was seen to be 48.34 ± 21.05 U/L which was significantly higher in comparison to that of healthy controls which was seen to be 25.02 ± 5.78 U/L as shown in Table 2 and Fig. 2. The Serum activity was raised in about 80% of the patients and had higher values than the reference activity i.e., up to 30 U/L. An attempt to analyze the relationship of this inflammatory marker ADA with Glycemic status of an individual was also made in the current study by applying Karl Pearson's correlation coefficient. It showed a positive and statistically significant correlation coefficient of r= 0.385 ($p< 0.05$).

Some studies have reported altered Serum ADA activity which is quite variable. Kurtul N *et al* have shown increased level of serum ADA activity in Diabetic patients and its correlation with HbA1c and suggested that ADA might be an important enzyme for modulating the bioactivity of insulin effect and glycemic control. ADA may serve as an immune-enzyme marker in the etiopathology of Type II Diabetes Mellitus according to some researchers. A study by Gitanjali G *et al* have reported an elevated serum activity of ADA and concluded that higher blood glucose levels aggravate oxidative stress as well as raises ADA activity which may be due to local insulin resistance in the target organs. In the present study, since the serum activity of ADA was significantly highest among the Diabetic cases in comparison to non-Diabetic subjects, it can be suggested that ADA is an effective marker for inflammation in the case of Type II Diabetes Mellitus.

Adenosine Deaminase has an important role in proliferation and differentiation of lymphocytes, especially T-lymphocytes. Higher activity of ADA is due to deranged T- lymphocyte responses pointing towards the mechanism to release ADA into the circulation.[12] It is speculated that altered insulin related T- lymphocyte function could be the reason of increased ADA activity in Diabetes Mellitus. Also, the role of Adenosine in inhibition of lipolysis through A1 receptors and due to increased Adenosine Deaminase, there is inactivation of Adenosine and activation of lipolysis.[13,14] This markedly potentiates the increment in cAMP accumulation via nor-epinephrine action. Thus, deregulated lipid metabolism and consequent elevation of free fatty acids might lead to pathogenesis of Type II Diabetes Mellitus.[15, 16] In this study, it was found that ADA was higher in activity in Diabetic patients. Meanwhile, this particular inflammatory marker was also found to be positively correlated with the glycemic status of a Diabetic patient. Also, the Pearson's correlation coefficient was significantly and positively correlated with HbA1c levels of those patients. A positive significant correlation between serum ADA activity with short term and long-term glycemic control indicates the important role of ADA in glucose and lipid metabolism derangements seen in Type II Diabetes Mellitus. The present study was limited in a way that we included only ADA as a marker for inflammation and a small sample size also have weaken the findings of the study. A large extended prospective study is suggested at molecular level to explore the pathophysiological processes involved

in mediation of inflammation in Diabetes Mellitus Circulatory levels of inflammatory mediators correlate with insulin resistance and are raised in significant amount in groups at risk of Type II Diabetes Mellitus.

The present study has shown that inflammatory marker like ADA is related to the development of insulin resistance and progression to Diabetes Mellitus Type II. It is possible that in the coming years, the hope of new therapeutic strategies based on anti-inflammatory properties with beneficial effects on diabetic complications can be translated into real clinical treatments. The present study was limited to the sample size and a larger sample size studies would help in extrapolating the inflammatory role of ADA in T2DM. Few more inflammatory markers like hs-CRP, Interleukins, etc. in metabolic disorders by researchers would be an open area for study.

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