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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 (ADA) 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 known chronic metabolic disorders characterized by the presence of hyperglycemia caused by the derangements in the metabolism of carbohydrates, lipids, and proteins. A large number of diabetes mellitus cases remains undiagnosed. This disorder is deemed incurable and persists life-long. Type II diabetes mellitus is considered as a lifestyle disorder, which develops due to a sedentary lifestyle, lack of physical activities, low intake of dietary fibers, etc. Type II diabetes mellitus can lead to morbidity and mortality through numerous microvascular and macrovascular changes. Various other risk factors that have significant contributions to the development of this disease include the environmental, genetical, and behavioral factors.[1]

In type II diabetes mellitus, alterations in the functions of the immune system is also observed. The T-cell mediated immunity is disturbed, leading to the impairment in the insulin responses.[2] This results in adverse changes such as the activation of leucocytes, elevated levels of cytokines in the circulation, as well as increased apoptosis. These changes suggest that inflammatory changes occur in diabetes mellitus. Various pro-inflammatory mediators are released from different tissues including activated leucocytes, adipocytes, and endothelial cells. The role of various biochemical products, i.e., Interleukin-6, C-reactive protein (CRP), Tumor Necrosis Factor (TNFα), leptin, and others have been studied widely and many researchers have proposed their potential involvement in inducing the pathogenesis of Type II diabetes mellitus. Also, some metabolic and inflammatory factors and their serum levels has also been shown to have

a direct effect on the amount of adipose tissues in the body.[3, 4]

Adenosine deaminase (ADA), a metabolic enzyme catalyzing deamination, has been shown to deaminate adenosine into inosine while also acting as a regulatory enzyme that maintains the extracellular and intracellular concentrations of adenosine.[5] ADA is an enzyme that is expressed ubiquitously and its activity is seen higher in tissues like thymus, GI tract, brain, 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 also been found as a producer of oxygen derived reactive oxygen species (ROS), as well as a stimulator for lipid peroxidation.[7] Adenosine acts through G protein-couples receptor and facilitates the normal cell physiology regulation in various tissues.[8] It also plays the role of a suppressant of inflammation for its ability to inhibit the inflammatory mechanisms, such as inhibiting T-cell activation and proliferation. Meanwhile, adenosine is supposed to mimic the activity of insulin on glucose and might somehow play a role in causing insulin resistance. Since, the concentration of adenosine is regulated by the activity of ADA, the insulin resistance can have ADA as the triggering factor. The increased ADA activity in diabetic subjects might be due to deranged insulin activity linked to the T-lymphocyte function.[9] This study aimed to evaluate the enzymatic activities of adenosine deaminase in type II diabetes mellitus and whether there is a possibility of an association between inflammatory and diabetic markers in this disease.

Methods

This study was a case-control study performed at the Teerthanker Mahaveer Medical College and Research Center in 2019 after receiving the approval from the Institutional Ethical Committee of the college under the ethical clearance number IEC/17–18/030. The study was conducted on 60 clinically diagnosed type II diabetes mellitus patients with 60 healthy subjects as the control group. Sample size calculation was performed using the statistical formula. All subjects aged between 30 and 45 years old and were only enrolled in the study after their written consent was obtained. The inclusion of diabetes mellitus cases was done according to the WHO guidelines. Individuals having a fasting plasma glucose level of ≥ 126 mg/dl or a random glucose level of ≥ 200 mg/dl on two occasions were included as cases in this study. Those individuals having inflammatory diseases like tuberculosis, cancer, gout, liver diseases, and kidney diseases were excluded from the study to rule out any increase in the ADA activities due to other inflammation conditions. Pregnant female subjects were also excluded. The estimation of enzymatic activity of serum ADA was performed using the Kinetic assay method with commercially available kits.[10] Data obtained were tabulated and analyzed using the SPSS.

Results

Table 1 and Table 2 describe the demographic distribution of the participant and the study parameter comparisons between subjects and

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 Control	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

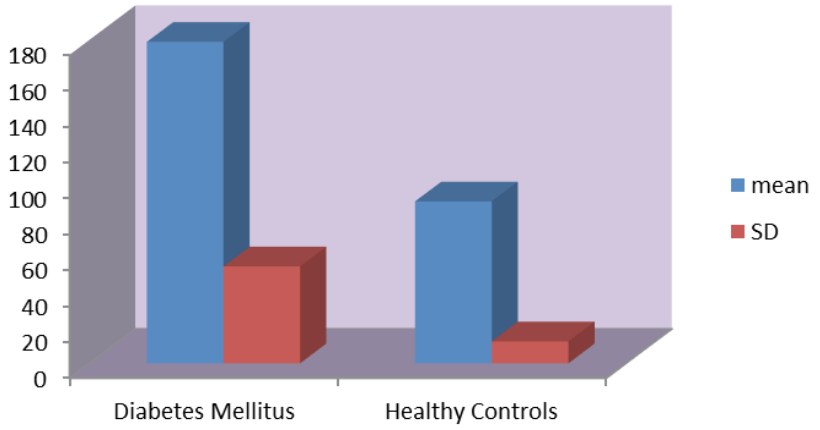

Fig. 1 Comparison of Fasting Plasma Glucose Levels

control. As described in Table 1 and Fig. 2, the study parameter, i.e serum ADA activities as one of the inflammatory markers, was found to be higher among type II diabetic subjects compared to the healthy subjects, and the difference in activity between the study groups was highly significant statistically ($p<0.01$). The correlation analysis between serum ADA activities and glycemic indices as shown in Table 2 also highlighted the fact that serum ADA activity was 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 that is featured by impaired insulin secretion and insulin resistance, as well as increased blood glucose. This disorder is supposed to be associated with an acute phase reaction, suggesting that a low-grade

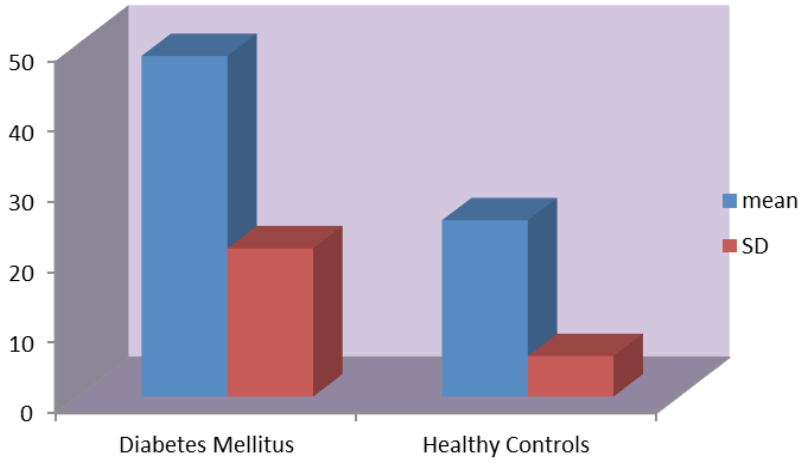

Fig. 2 Comparison of Adenosine Deaminase Activity

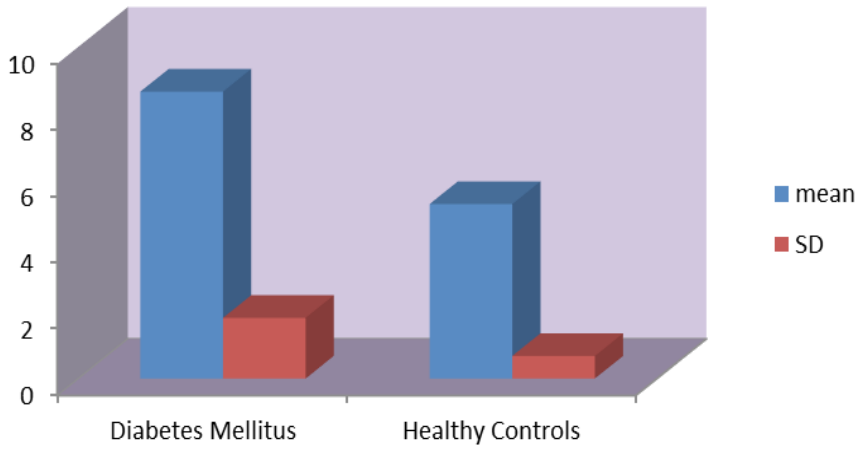

Fig. 3 Comparison of Glycosylated Hemoglobin Level

inflammation might also be involved in its pathogenesis.[11] Serum adenosine deaminase activity in this study was 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 in diabetic patients was seen to be 48.34±21.05 U/L, which was significantly higher than that of healthy controls of 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 the value was higher than the reference activity, i.e., up to 30 U/L. An attempt to analyze the relationship of ADA as an inflammatory marker with the glycemic status of an individual was also made in the current study by applying the Karl Pearson's correlation coefficient. As a result, a positive and statistically significant correlation was observed with r= 0.385 ($p<0.05$).

Several previous studies have reported an 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 the oxidative stress as well as raises ADA activity, which may be due to the local insulin resistance in the target organs. In the present study, since the serum activity of ADA was significantly highest among 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 plays an important role in the proliferation and differentiation of lymphocytes, especially for T-lymphocytes. A higher activity of ADA is due to deranged T-lymphocyte responses, pointing towards the mechanism to release ADA into the circulation.[12] It is also speculated that an altered insulin related T-lymphocyte function could be the reason for the increased ADA activity in diabetes mellitus. Also, with the role of adenosine in the inhibition of lipolysis through the A1 receptors, as well as due to increased adenosine deaminase, the inactivation of adenosine and activation of lipolysis are observed .[13,14] This markedly potentiates the increment in the cAMP accumulation via nor-epinephrine action. Thus, deregulated lipid metabolism and consequent elevation of free fatty acids might lead to the pathogenesis of the type II diabetes mellitus.[15, 16] In this study, it was found that the activity of ADA was higher in diabetic patients. Meanwhile, this particular inflammatory marker was also found to be positively correlated with the glycemic status of a diabetic patient. Furthermore, the Pearson's correlation coefficient results showed a significant and positive correlation with the HbA1c levels of these patients. The positive significant correlation between serum ADA activity with the 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. Nevertheless, this present study was limited in a way that only ADA is included as a marker for inflammation, and a small sample size also have weaken the findings of the study. A large extended prospective study at the molecular level is suggested to explore the pathophysiological processes that are involved in the mediation of inflammation in diabetes mellitus circulatory levels that underlie the inflammatory mediators correlation with insulin resistance and the significant increase in groups at risk of type II diabetes mellitus.

The present study has shown that inflammatory marker like ADA is linked 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. The role of several other inflammatory markers like hs-CRP, Interleukins, etc. in metabolic disorders would be an open area for future studies.

References

1. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J. 2012;27(4):269–73.
2. Sapkota LB, Thapa S, Subedi N. Correlation study of adenosine deaminase and its isoenzymes in type 2 diabetes mellitus. BMJ Open Diabetes Res Care. 2017;5(1):e000357.
3. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 diabetes and its impact on the immune system. Curr Diabetes Rev. 2020;16(5):442–9.
4. Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr. 2019;13(2):1165–72.
5. Yu M, Zhou H, Li Q, Ding J, Shuai H, Zhang J. Serum adenosine deaminase as a useful marker to estimate coronary artery calcification in type 2 diabetes mellitus patients. Clin Appl Thromb Hemost. 2021;27: 1-5.
6. Sauer AV, Brigida I, Carriglio N, Aiuti A. Autoimmune dysregulation and purine metabolism in adenosine deaminase deficiency. Front Immunol. 2012;3:265.
7. Costa LR, Souza AKY, Scholl JN, Figueiró F, Battastini AMO, Jaques JADS, et al. Biochemical characterization of adenosine deaminase (CD26; EC 3.5.4.4) activity in human lymphocyte-rich peripheral blood mononuclear cells. Braz J Med Biol Res. 2021;54(8):e10850.
8. Sheth S, Brito R, Mukherjea D, Rybak LP, Ramkumar V. Adenosine receptors: expression, function and regulation. Int J Mol Sci. 2014;15(2):2024–52.
9. Khemka VK, Bagchi D, Ghosh A, Sen O, Bir A, Chakrabarti S, et al. Raised serum adenosine deaminase level in nonobese type 2 diabetes mellitus. ScientificWorldJournal. 2013;2013:404320.
10. Giusti G, Galanti B. Rapid colorimetric method for determination of some deaminase activities. Boll Soc Ital Biol Sper. 1966;42(19):1312–6.
11. Cruz NG, Sousa LP, Sousa MO, Pietrani NT, Fernandes AP, Gomes KB. The linkage between inflammation and Type 2 diabetes mellitus. Diabetes Res Clin Pract. 2013;99(2):85–92.
12. Flinn AM, Gennery AR. Adenosine deaminase deficiency: a review. Orphanet J Rare Dis. 2018;13(1):65.
13. Hariprasath, G., Ananthi, N. Glycemic control and raised adenosine deaminase activity in type 2 diabetes mellitus. IOSR J Dent Med Sci. 2017; 16(01): 53–6.
14. Patel B, Taviad D, Malapati B, Chhatriwala, M, Shah R. Serum adenosine deaminase in patients with type-2 diabetes mellitus and its relation with blood glucose and glycated haemoglobin levels. Int J Biomed Res. 2014; 5(9):556.
15. Athyros VG, Doumas M, Imprialos KP, Stavropoulos K, Georgianou E, Katsimardou A, et al. Diabetes and lipid metabolism. Hormones (Athens). 2018;17(1):61–7.
16. Aron-Wisnewsky J, Warmbrunn MV, Nieuwdorp M, Clément K. Metabolism and Metabolic Disorders and the Microbiome: The Intestinal Microbiota Associated With Obesity, Lipid Metabolism, and Metabolic Health-Pathophysiology and Therapeutic Strategies. Gastroenterology. 2021;160(2):573–99.