

Original Article

Increased levels of serum Adenosine deaminase (ADA) enzyme and increased risk of T cell activation markers in type 2 diabetes



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ABSTRACT

Diabetes Type 2 is the most common type of diabetes, a common disorder of glucose homeostasis and accounts for 90% of cases. The prevalence of diabetes type 2 is increasing. Adenosine deaminase is an enzymatic polymorphism that plays an important role in modulating the biological activity of insulin. It seems that excessive activity of the adenosine A1 receptor has caused adiposity in diabetes type 2. In this study, we examined the correlation of ADA enzyme with diabetes type 2. This investigation was performed on 80 men and women between 40 and 80 years old in District 2 of Tehran with diabetes. Venous blood samples were collected after 12 hours of fasting blood was centrifuged. Then fasting blood glucose and HbA1c, Triglyceride, and total Cholesterol were measured for enzyme activity respectively by COBAS MIRA. Insulin was measured by ELISA and serum ADA enzyme activity was measured by photometry. The results of this study were done by SPSS software. A significant increase in serum ADA levels was observed in diabetic patients compared with the control group. A positive correlation was observed between ADA activity and FBS and HbA1c. The amount of HOMA-IR in diabetics was higher than in the control group, but no positive correlation was observed between serum levels of ADA and HOMA-IR. The enzyme adenosine deaminase can act as an immunological marker and the results of this study show that diabetes is associated with increased T cell activation markers and immune disequilibrium. Serum ADA level has a positive correlation with glycemic control status in patients.

1. Introduction

Type 2 diabetes, called adult-onset diabetes or non-insulin-dependent diabetes, is a debilitating metabolic disorder characterized by high blood glucose in conditions of insulin resistance and relative insulin deficiency. Type 2 diabetes is common. It is the most common type of diabetes in the world and 90% of people with diabetes have type 2 diabetes and the other 10% have type 1 diabetes mellitus and gestational diabetes, respectively [1, 2].

Type 2 diabetes, in which the body produces some insulin but the cells do not respond to insulin. In the later stages of the disease, the body may not produce enough insulin. Uncontrolled type 2 diabetes can cause high blood sugar, which can cause several symptoms and eventually serious complications [2].

Risk factors for type 2 diabetes are varied; these factors include family history, obesity, age, gestational diabetes lifestyle, hypertension, and hyperlipidemia [3-5]. Type

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2 diabetes is the most common type of diabetes and accounts for most cases of the disease. The prevalence of type 2 diabetes is constantly increasing. Although the incidence of type 1 and type 2 diabetes is increasing worldwide, it is expected that the rate of increase in type 2 diabetes is due to lifestyle changes, which lead to a decrease [6]. The global prevalence of type 2 diabetes is currently 8.8%, which is expected to increase worldwide. In Canada, the prevalence of diabetes has increased by 70% in the last decade [7]. Recognizing the factors influencing the occurrence of this disorder can lead to a better understanding of the damage. Diagnosis of the disease and, consequently, the invention of diagnostic and therapeutic methods new help.

Adenosine deaminase (ADA) is a glycoprotein enzyme composed of a polypeptide strand of 311 amino acids. The ADA gene is located on the long arm of the human chromosome 20 [8]. This enzyme was sequenced in 1984. The Km of the enzyme is 45 μ M for adenosine and 34 μ M for deoxyadenosine. The optimum pH for enzyme activity is in the neutral pH range. ADA is one of the key enzymes in purine metabolism. A high degree of amino acid sequence protection indicates the critical nature of ADA in the purine rescue pathway [9].

Adenosine is a purine nucleoside found in extracellular fluids and plasma and is involved as a hormone in regulating blood flow, smooth muscle physiology, nerve conduction, and platelet aggregation [10]. Adenosine can also affect the function of the hormone insulin [11]. Studies have shown that adenosine facilitates glucose uptake into the cell [12]. Therefore, increasing ADA activity reduces the amount of adenosine and subsequently glucose uptake into the cell. It has been shown in several studies with blood sugar control status [13, 14]. In a study, serum ADA changes in type 2 diabetes have not been studied [15] and in addition, The relationship between these changes in serum ADA and blood glucose control and insulin resistance indices has not been studied. Therefore, in this investigation, the serum concentration of ADA in type 2 diabetes and its relationship with

glycemic control and insulin resistance indices were investigated.

2. Materials and Methods

This case-control study was performed on 80 men and women between 40 and 80 years old in Tehran Region 2 with diabetes. The control group was healthy men and women who did not meet the criteria for diabetes and whose first- and second-degree relatives had a family history of diabetes. In this study, written consent was obtained from all participants.

Laboratory evaluations: Venous blood samples were collected after 12 hours of fasting. After blood sampling, the serum of all samples was collected after centrifugation and stored at -20 ° C.

Fasting blood glucose was measured by glucose oxidase method biosystem kit, triglyceride by the enzyme-photometry method by Pars test kit, total cholesterol by the enzyme-photometry method by Pars test kit, the amount of HbA1c was measured enzymatically with Axis-Shield kit by autoanalyzer and insulin concentration by ELISA technique and MONO BIND kit. HDL by one-point enzymatic colorimetric method using Biosystem kit. LDL was calculated using the Fried Wald formula as follows.

$$\text{CHOL} - (\text{TG}/5 + \text{HDL}) = \text{LDL}$$

2.1. Measurement of Adenosine Deaminase Activity

Serum enzyme activity was measured by photometric method with Biosystem kit. The basis of this measurement is the conversion of adenosine to inosine and ammonia in the direct purine pathway by the ADA enzyme. Inosine produced by the enzyme nucleoside phosphorylase is converted to hypoxanthine. Hypoxanthine is oxidized by the enzyme H xanthine oxidase to produce H₂O₂. The amount of H₂O₂ produced is measured by the colorimetric method.

2.2. Measuring insulin resistance

(HOMA-IR) index was used to measure insulin resistance it was calculated based on fasting blood sugar concentration and fasting

insulin concentration using the following equation.

$$\text{HOMA-IR} = \frac{\text{insulin} \times \text{fasting plasma glucose}}{22.5}$$

Statistical analysis: Statistical tests were performed with SPSS software. Quantitative variables were compared between the control group and the patient using Student t-test, $P > 0.05$ was considered as a significant degree.

3. Results

According to Figure 1, a positive correlation was between serum ADA enzyme levels and glycemic control status indices, suggesting that elevated serum ADA may be involved in the pathogenesis of diabetes. The results of this study show that the serum level of ADA enzyme increases in type 2 diabetes and there is a positive correlation between the serum level of ADA, FBS and in diabetics, the level of FBS (fasting blood sugar) increased compared to the control group. According to Figure 2, serum ADA activity in patients with type 2 diabetes with high HbA1c was significantly higher than in the healthy group. This investigation showed a significant positive correlation between serum ADA activity and HbA1c hemoglobin. There is a significant positive relationship between ADA activity and total cholesterol in hypercholesterolemia and HDL-cholesterol in HDL-cholesterol individuals Figure 3. However, there was a stronger positive relationship between ADA and LDL-cholesterol in LDL-cholesterol individuals. Findings showed that the level of cholesterol in diabetics was higher than in the control group. According to Figure 4, ADA enzyme activity was significantly increased in patients with diabetes compared to the control group, and a positive correlation was observed between serum ADA enzyme activity and HbA1c and FBS levels, which are indicators of glycemic control. The insulin resistance index (HOMA-IR) in diabetics increased compared

to the control group, indicating higher insulin resistance in this group. According to Figure 5, serum ADA activity in patients with type 2 diabetes and triglycerides was significantly higher than in the healthy group. We showed a significant positive correlation between serum ADA and triglyceride activities.

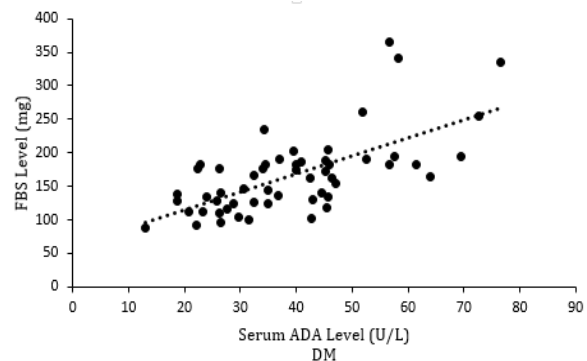


Fig. 1. Study of FBS (fasting blood sugar) and ADA enzyme

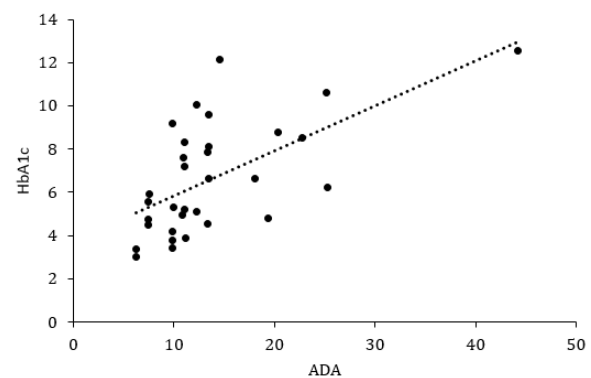


Fig. 2. Study of HbA1c hemoglobin and ADA enzyme

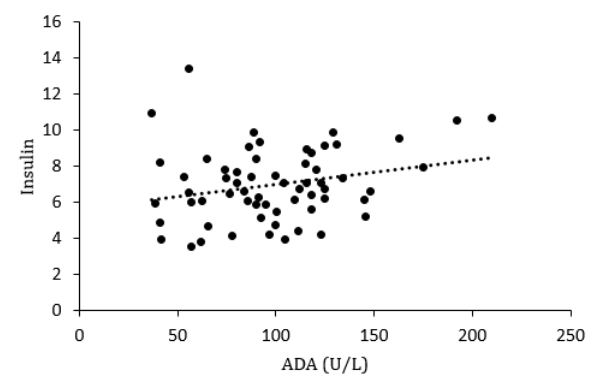


Fig. 3. Review of insulin and ADA enzymes

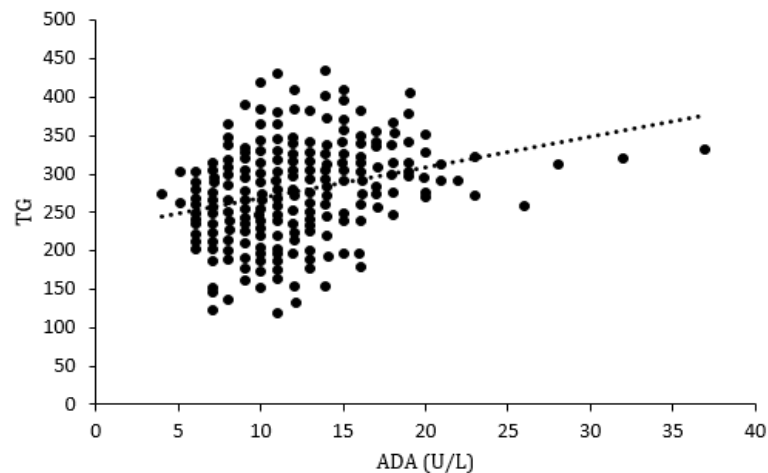


Fig. 4. Evaluation of triglyceride and adenosine deaminase enzyme

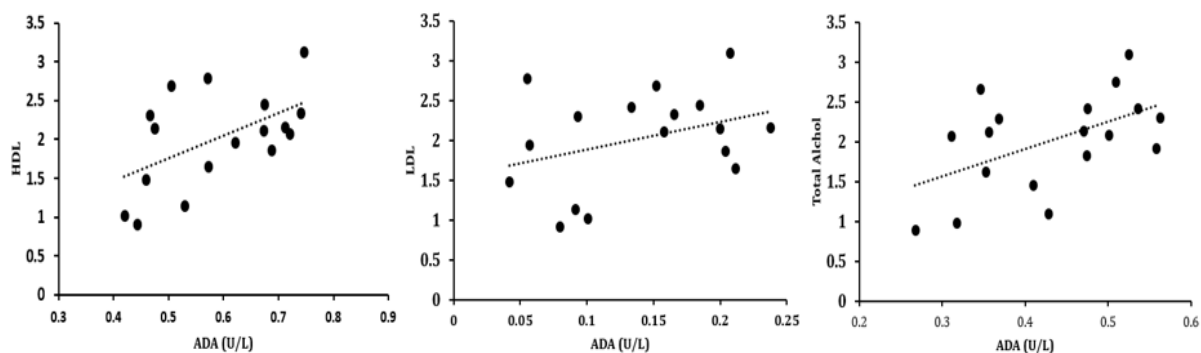


Fig. 5. Examination of cholesterol (HDL, LDL, Total alcohol) and ADA enzyme

4. Discussion

The present study was performed to investigate the correlation between adenosine deaminase and type 2 diabetes. In this section on diabetes, we discuss the role of adenosine deaminase and its effect on type 2 diabetes and compare the results of our research with the results of previous studies. Type 2 diabetes is a metabolic disease caused by hyperglycemia (high blood sugar). This is because the body can no longer use the insulin produced, which is known as insulin resistance, or the body can no longer produce insulin. Is created [16]. The prevalence of type 2 diabetes in the world is currently more than 100 million people, about 95% of whom are type 2 diabetics. It is estimated that by 2010, more than 230 million people worldwide will have diabetes [17].

Adenosine is a purine nucleoside. It is present in extracellular fluid and plasma and is involved as a hormone in smooth muscle

physiology, blood flow regulation, platelet aggregation, and nerve conduction. Other effects of adenosine include its effect on insulin function. ADA adenosine deaminase plays an important role in controlling adenosine concentration and its effects by converting adenosine to inosine. Adenosine facilitates the entry of glucose into the cell. Therefore, increasing ADA activity reduces the amount of adenosine and, consequently, the entry of glucose into the cell. This enzyme is involved in the proliferation and differentiation of T lymphocytes [18].

ADA also stimulates the release of stimulatory amino acids in addition to adenosine breakdown and is essential for the binding of adenosine A1 receptors and heterotrimeric G proteins. Adenosine deaminase deficiency leads to pulmonary fibrosis, indicating chronic exposure. High levels of adenosine can exacerbate inflammatory responses rather than suppress

them [19]. As a result, in this study, we examined the correlation between adenosine deaminase enzyme and type 2 diabetes. The increased pathogenesis of ADA levels in type 2 diabetes is explained by the additional CAMP-adenosine cell pathway. ADA inactivates adenosine and increases lipolysis. It also enhances the accumulation of CAMP [20].

It has been examined the activity of the enzyme adenosine deaminase as a diagnostic marker in type 2 diabetes and found that total serum activity, especially ADA2, was increased in diabetics compared to the control group. As a result, they found that ADA could be a useful test for the diagnosis of type 2 diabetes [21, 22], which was consistent with the results of our work. It has been examined the correlation between serum adenosine deaminase levels and blood glucose levels in gestational diabetes. 70 healthy pregnant women were measured. Insulin resistance was also measured with the Homeostasis Model of Assessment (Insulin Resistance) (HOMA-IR) index.

The results of the present study showed that gestational diabetes was associated with increased T-cell activation markers. Blood was present in these patients and a significant increase was observed in serum ADA level in women with gestational diabetes) in comparison with the control group. A positive correlation was observed between ADA activity with FBS and HbA1c. - IR was not observed [23-25], this study is consistent with our results that adenosine deaminase enzyme had a positive correlation between glucose and HbA1c, and serum ADA level in patients with diabetes was higher than the control group.

Insulin was administered to patients with type 2 diabetes. Serum levels of adenosine deaminase (ADA), insulin, and fasting plasma glucose (FPG) were assessed. Data were analyzed by SPSS software in 50 patients with type 2 diabetes and 50 healthy individuals. Serum adenosine deaminase and insulin levels in the case group were very significant compared to the control group. As a result, they found that serum adenosine deaminase activity and insulin levels were significantly increased in type 2 diabetes. Adenosine

deaminase and insulin were positively correlated with each other as well as with fasting plasma glucose. This is consistent with our finding that serum ADA levels in people with type 2 diabetes increased compared to controls [26-28].

It has been studied the expression of genes related to the A2A and A2B subgroups of adenosine receptors in a sample of human breast cancer tissue. The collected samples included 11 cancer samples and 4 normal samples, all of which were pathologically confirmed to be normal or pathogenic. Using RT-PCR, the RNA of the cells was first isolated and transcribed into a cDNA sequence. Using the corresponding cDNA sequences, a specific primer pair was designed and synthesized. PCR was performed under favorable conditions for each subgroup. PCR products were electrophoresed on agarose gel with a concentration of 7.1% [29].

Samples were measured by semi-quantitative methods using Relative intensity software in Photoshop. The results showed that the role of adenosine receptors in different estrogen receptor-dependent 7-MCF and estrogen receptor-dependent cell lines MDA-MB231 and MDA-MB488 could be expressed as inhibitors of the inguinal cortex. The breasts are different, and their signaling pathways are also different. As a result, they found that, on average, A2B receptors in tumor tissue were 1.5 times more pronounced than in normal tissue adjacent to the tumor, while there was no slight difference between the expression of adenosine A2A receptors in normal tissue [29].

Out of 26 patients with pulmonary tuberculosis, 17 suspected TB patients with negative smear and culture results, and 67 healthy individuals were sampled. ADA Total test using Shim Enzyme Company kit and ADA2 test using inhibitor EHNA was performed. The results of the present study indicate a significant difference between the concentrations of ADA and ADA2 in patients with tuberculosis and non-tuberculous lung diseases in healthy individuals. And found that ADA serum activity in patients with pulmonary tuberculosis was higher than in

healthy individuals, which was consistent with the present study [30].

It has been studied the activity of adenosine deaminase enzyme on type 2 diabetes in 2 samples of type 2 diabetic patients and health control in Nepal hospital. Used independently. Analysis of variance (ANOVA) was used to compare ADA levels between healthy controls and controlled and uncontrolled type 2 diabetes. Correlation of serum ADA levels with different markers used to control glycemia, HbA1c, FPG, and PPG, respectively. The results showed that the mean serum ADA in diabetic patients was significantly higher than healthy controls. In addition, ADA levels were significantly higher in uncontrolled type 2 diabetes than in diabetics. The correlation of FPG, PPG, and HbA1c with ADA serum had a positive and significant correlation with all glycemic parameters. This suggests that the use of ADA as an alternative marker of glycemic control in diabetic patients. Serum ADA showed a significant positive correlation with HbA1c, which is considered a good marker for long-term glycemic control [31-34], which is consistent with our results.

5. Conclusion

In this study, a positive correlation was observed between serum ADA enzyme levels and glycemic control status indices, suggesting that elevated serum ADA may play a role in the pathogenesis of diabetes. The results of this study show that the serum level of ADA enzyme increases in type 2 diabetes and there is a positive correlation between the serum levels of ADA, FBS, HbA1c, and HOMA-IR.

It can also be suggested that hyperglycemia is a possible cause of elevated serum ADA levels in type 2 diabetes. Increasing the serum level of ADA intensifies hyperglycemia by increasing the breakdown of adenosine and decreasing its effects, including the role of adenosine in facilitating the effects of insulin. Increased serum adenosine deaminase levels have been shown to be involved in metabolic abnormalities and immune disequilibrium, which may in turn contribute to inflammatory diseases.

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Informed Consent

The authors declare not used any patients in this research.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by M.T.M., Gh.E. The first draft of the manuscript was written by Gh.E., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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