

Diagnostic Value of Serum Adenosine Deaminase in Type II Saudi Diabetic Patients

Keywords: Adenosine deaminase; Type 2 diabetes; Tabuk region

Abstract

Background: Diabetes mellitus (DM) is one of the most causative important factors of mortality in the developing countries. Adenosine deaminase (ADA) is a purine metabolizing enzyme that catalyzes the deamination of adenosine to inosine. The aim of the work was to evaluate the diagnostic value of serum ADA and its association with hyperglycemia in type II Saudi diabetic patients in Tabuk region at Kingdom of Saudi Arabia. Seventy one Type II Saudi diabetic patients and twenty two healthy controls were enrolled in this study. The diabetic patients were divided into four groups according to their fasting blood sugar. Serum levels of ADA, total cholesterol (TC), triglycerides (TG), glycosylated hemoglobin (HbA1c), alanine amino transferase (ALT), aspartate amino transferase (AST), urea, creatinine, uric acid, Malondialdehyde (MDA), Glutathione Peroxidase (GPx) and Superoxide dismutase (SOD) were measured.

Results: There was a significant increase ($p < 0.05$) in serum ADA, TC, TG, HbA1c, ALT, AST, urea, creatinine, uric acid and MDA in diabetic groups compared to the controls, while the levels of GPx and SOD were significantly decreased ($p < 0.05$) in diabetic groups compared to the controls.

Conclusion: The increasing of serum activity of adenosine deaminase was found as a good diagnostic marker for type II Saudi diabetes where it is highly significantly correlated with the glycemic status.

Introduction

Diabetes mellitus (DM) is one of the most causative important factors of mortality in the developing countries where it affects more than 170 million persons all over the world [1]. It is characterized by insulin deficiency either in secretion or action or both which leads to hyperglycemia and the disturbances of carbohydrate, lipid, and protein metabolism [2]. Hyperglycemia leads to increased oxidative stress by forming free radicals and superoxide ions and increases adenosine deaminase (ADA) activity [3]. ADA is a purine metabolizing enzyme that catalyzes the deamination of adenosine to inosine regulating intracellular and extracellular adenosine concentration [4]. ADA may play a role in insulin effect and glycemic control as adenosine acts directly to stimulate insulin activity via several processes such as glucose transport, pyruvate dehydrogenase activity, lipid synthesis, leucine oxidation and cyclic nucleotide phosphodiesterase activity [5]. Therefore, the activity of ADA in Type 2 DM is a marker for prognosis in Type 2 DM. Several studies have demonstrated the increase in adenosine deaminase in patients with type 2 diabetes mellitus. Insulin administration has been shown to reduce the elevated ADA activity in type 2 diabetics [6,7]. ADA has been shown to impair the insulin sensitivity for glucose transport and antilipolysis by inactivating extracellular adenosine, which adipocytes release spontaneously. ADA activates lipolysis and increase in cyclic AMP accumulation due to noradrenaline [8].



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The aim of this study is to assess the diagnostic value of serum ADA and other biochemical parameters such as lipid profile, and liver enzymes in type 2 Saudi diabetics and normal controls. This will help ascertain a correlation between serum ADA and glycemic status in type 2 DM.

Subjects and Methods

Study subjects

Seventy one Saudi patients both males and females in the age range of 40-65 years on oral hypoglycemic drugs, having uncomplicated type 2 diabetes mellitus were divided into four groups according to the level of their serum fasting sugar. The group I in sugar level up to 150 mg/dl, group II in sugar range 150-200 mg/dl, group III in sugar range 200-250 mg/dl and group IV their sugar level more than 250 mg/dl in addition to twenty two non-diabetic healthy individuals as control group, both males and females in the same age range. They were recruited from the local community in Tabuk city. The study was conducted at King Khalid Hospital at Tabuk City, Kingdom of Saudi Arabia between March to July 2014. All subjects gave written informed consent to participate. The study was approved by the Local Ethics Committee. All subjects were interviewed for details of their age, weight, height, and smoking. Also, blood pressure and body mass index (BMI) were measured for each subject.

Exclusion criteria: Individuals with diabetic complications (neuropathy/retinopathy/nephropathy/vascular complications etc.), hypertension/acute or chronic infection disease. Any medications other than the ones used for diabetic therapy/addictive habits/pregnancy will be excluded from the study [9].

Diagnostic criteria for type II diabetes mellitus: Thorough

clinical examination with appropriate investigations will be done before selecting the cases & controls for the study [10].

Biochemical assays

Fasting blood samples were obtained from the patients as well as the controls. The blood sample was divided into two parts: the first part without anticoagulant to obtain serum and the second part was transferred into heparinized tube to obtain whole blood. Serum samples were frozen in dry ice prior to being stored at -80 °C and blood sample in refrigerator at 4 °C. The level of serum adenosine deaminase (ADA) was determined using a spectrophotometer based on the method by Giusti and Galanti [11]. Adenosine deaminase hydrolyses adenosine to inosine and ammonia. Ammonia then reacts with a phenol and hypochlorite in an alkaline medium to form a colored blue indophenol complex, using sodium nitroprusside as a catalyst. The degree of blue indophenol complex is directly proportional to the activity of ADA in the sample. The absorbance was read against water at 635 nm using a spectrophotometer. One unit of ADA is defined as the amount of enzyme required to release 1 mmol of ammonia per minute from adenosine at standard assay conditions.

The following biochemical parameters were determined using available Biodiagnostic kits (Randox): serum fasting blood sugar (FBS), Glycosylated hemoglobin (HbA1c), cholesterol, triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, uric acid, creatinine. Lipid peroxidation was estimated by measuring malondiadehyde (MDA), superoxide dismutase (SOD) and Glutathione-peroxidase (GPx).

Statistical analysis

The statistical analysis was performed using students’ t’ test to compare mean values of variables in control and different groups of type 2 diabetes mellitus. The correlations were assessed by Pearson rank correlation coefficient. Differences were considered statistically significant when p < 0.05 and highly significant when p < 0.001.

Results

The basal characteristics of the study groups are shown in (Table 1). There were no significant differences between diabetic patients and controls for almost variables. Non-significant differences were observed between the two groups in cystolic or diastolic blood pressure, while slightly significant decrease was observed in BMI in type 2 DM group compared to the control group.

The level of serum ADA was found significantly (P < 0.05) increased by 26%, 41.6%, 100.5%, and 118.6% respectively in all diabetic groups with respect to control group (Figure 1). As presented in table the levels of MDA were increased by 28.6% in group I up to 111.7 % in group IV compared with controls. These increases are directly proportional to the increases in the levels of glucose from group I to Group IV. However, highly significant decreases (P < 0.001) are found in the mean erythrocytes GPX and erythrocytes SOD activities of the patients of the four diabetic groups compared to the controls. These decreases are inversely proportional to the increases in the levels of glucose from group I to group IV (Table 2).

The levels of cholesterol were significantly (P < 0.05) increased from group I to group IV diabetic by 56.3%, 53.2%, 63.5% and 88.9%

Table 1: Demographic data and body measurements of the study groups.

Parameter	T2DM (n = 71)	Control (n = 22)
Sex (M/F)	38/33	13/9
BMI (kg/m ²)	22.47 ± 1.79*	24.15 ± 1.47
Age(years)	52.32 ± 7.55	50.45 ± 5.23
Blood Pressure		
a. Systolic (120 mm Hg)	120 ± 3	119 ± 3
b. Diastolic (80 mm Hg)	81 ± 2	78 ± 4

Values are expressed as Mean ± SD.
*P < 0.05 significantly different from controls.

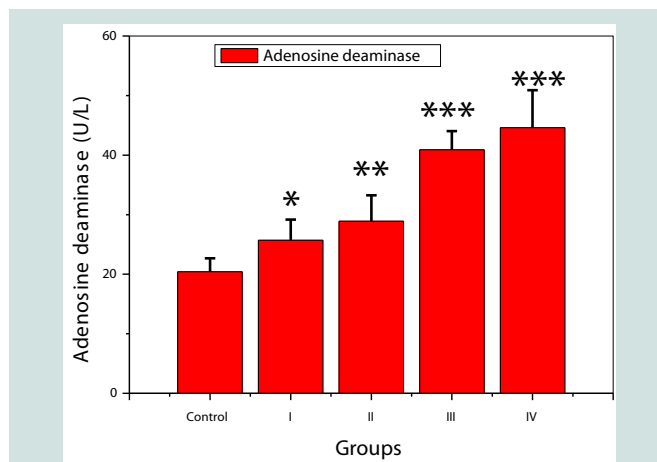


Figure 1: Serum adenosine deaminase activity in control and type II diabetic groups.

Groups are classified according to fasting blood sugar level: Control group up to 110 mg/dl, group I: up 150 mg/dl, group II: 150-200 mg/dl, group III: 200-250 mg/dl, group IV: more than 250 mg/dl.

Values are expressed as Mean ± SD.
*P < 0.05 significantly different from controls.

Table 2: Average levels of MDA, GPx and SOD in control subjects and diabetic patients.

Groups	MDA(nmol/ml)	GPx (U/g Hb)	SOD(U/g Hb)
Control	2.65 ± 0.5	40.3 ± 4.75	10.5±0.906
Group I	3.41 ± 0.49*	33.50 ± 3.54*	8.46 ± 0.670*
Group II	3.78 ± 0.48*	30.6 ±2.79*	7.68 ± 0.764*
Group III	4.95 ± 0.59*	24.0 ± 2.63*	6.42 ± 0.61*
Group IV	5.61 ±0.76*	22.0 ±1.8*	5.43 ± 0.54*

Values are expressed as Mean ± SD.
*P < 0.05 significantly different from controls.

respectively compared with control group. Similar elevations were observed in the levels of triglycerides from 50.5% in group I up to 78.4% in group IV diabetic group compared to controls. The level of glycosylated hemoglobin (HbA1c) was significantly (P < 0.05) increased from 53% in group I up to 88% in group IV. These increases are directly proportional to the increases in the levels of glucose from group I to Group IV (Table 3).

The levels of serum ALT and AST were increased by 8.2% and 11.3% respectively in diabetic group I up to 38.1% and 41.6%

respectively in diabetic group IV comparing with control group. The levels of uric acid, creatinine, and urea were increased by 20.7%, 13.6% and 17.1% respectively in diabetic group I up to 31.8% , 40.8% and 74.2% respectively in diabetic group IV comparing with control group. The levels of MDA were increased by 28.6% in group I up to 111.7% in group IV compared with controls. These increases are directly proportional to the increases in the levels of glucose from group I to Group IV. However, highly significant decreases ($P < 0.0001$) are found in the mean erythrocytes GPX and erythrocytes SOD activities of the patients of the four diabetic groups compared to the controls. These decreases are inversely proportional to the increases in the levels of glucose from group I to group IV (Table 4).

Level of Serum ADA was significantly ($P < 0.001$) and positively correlated with FBS, MDA and HbA1c concentration in type 2 diabetes, However, negative significant correlation ($P < 0.001$) were found in the mean erythrocytes GPX and erythrocytes SOD activities of the patients of the diabetic groups (Table 5).

Discussion

Diabetes mellitus is type 2 is a heterogeneous disease characterized by altered carbohydrate, fat and protein metabolism secondary to insulin resistance. It is characterized by hyperglycemia leading to increased oxidative stress and dyslipidemia. Identifying the resistance of insulin helps in minimizing the complications at an early stage. ADA estimation as a simple, inexpensive marker which

can identify insulin resistance without actually requiring estimation of serum insulin is required in current methods for measuring insulin resistance.

All subjects were interviewed for details of their age, weight, height, and smoking. Also, blood pressure and body mass index (BMI) were measured for each subject.

Individuals with uncomplicated Type 2 DM with a BMI in the range of 19-25 kg/m² were included in our study.

Our results show, that adenosine deaminase (ADA) activities were significantly increased in all the four diabetic groups as compared to control group (Figure 1). This increase was more than two times in 3rd and 4th diabetic groups with respect to controls. It was a positive significant correlation between FBS and serum ADA as shown in Table 5.

Our results were in agreement with results obtained in previous studies that concluded the increased in adenosine content make similar effect to insulin on glucose and lipid metabolism in adipose tissue [12,13]. The increasing of Serum ADA levels in our study may be due to insulin resistance or increased secretion of adenosine [14]. Decreased tissue adenosine levels is due to increased ADA activity which is related to the degree of hyperglycemia and lipid peroxidation in diabetes mellitus due to insulin resistance in the target organs and also the increased in production of free radicals and oxidative stress.

Table 3: Average levels of cholesterol, triglycerides and HbA_{1c} in control subjects and diabetic patients.

Groups	Cholesterol(mg/dl)	Triglyceride(mg/dl)	HbA1c(mg/dl)
Control	126.0 ±15.4	111.0 ±15.9	3.85± 0.621
Group I	197.0 ±28.3*	167.0 ± 15.8*	6.97 ±1. 01**
Group II	193.0 ±24.9*	169.0 ±26.2*	8.31 ±1.81**
Group III	206.0 ±22.9**	182.0 ±28.2*	9.09 ±1.32 **
Group IV	238.0 ±62.3**	198.0 ±42**	12.1 ±1.56 **

Values are expressed as Mean ± SD.

*P < 0.05 significantly different from controls.

Table 4: Average levels of ALT, AST, uric acid, creatinine and urea in control subjects and diabetic patient.

Groups	ALT(U/L)	AST(U/L)	U A(mg/dl)	Creat(mg/dl)	Urea(mg/dl)
Control	20.70 ± 6.0	20.2 ± 4.15	4.5 ± 0.97	0.696 ± 0.16	25.2± 4.59
Group I	22.4 ± 4.27	22.50 ± 6.7	5.43 ±1.04*	0.791 ± 0.19*	29.50 ± 8.50
Group II	24.5 ± 6.7	23.8 0 ± 6.4	5.66 ±1.27*	0.955 ± 0.31*	36.68 ± 9.57
Group III	25.9 ±12.7*	25.95 ±9.5*	5.87 ±1.26*	0.974± 0.14*	8.42 ± 9.61*
Group IV	28.6± 11.8*	28.61 ±9.76	5.93 ±1.23*	0.98 ± 0.234*	43.90±9.5**

Values are expressed as Mean ± SD.

*P < 0.05 significantly different from controls.

Table 5: Correlation between serums ADA in different parameters in the whole group of type 2 DM.

Parameters	r	p
Serum ADA and FBS	0.825	P <0.001
Serum ADA and MDA	0.727	P <0.001
Serum ADA and HbA1c	0.449	P <0.001
Serum ADA and GPx	-0.721	P <0.001
Serum ADA and SOD	-0.741	P <0.001

In other words the increase in ADA activity may lead to the decrease in adenosine content that requires to formation of ATP for the first step in glycolysis, therefore the level of glucose increases in the blood [15]. Our results showed a significant increase in HbA1c among all the four diabetic groups (Table 2); in addition to positive correlation between HbA1c and ADA (Table 4). These results are in accordance with other studies [16,17].

Our results showed that the oxidative stress parameters such as MDA, GPx and SOD were significantly increased in all diabetic groups compared with the healthy controls (Table 4). These observations were similar to that obtained by other investigators [18-22]. The observed high levels of plasma MDA in diabetic groups reflected lipid peroxidation resulted from oxidative stress. We also found significant decreases in glutathione peroxidase (GPX) and superoxide dismutase (SOD) activities in all diabetic groups compared to the controls. These results are in agreement with other reports reported by other authors [23]. These disturbances in these parameters may result in a number of deleterious effects due to the accumulation of superoxide radicals and hydrogen peroxides [24]. The increase in the level of MDA correlated directly with hyperglycemia in these patients because of auto oxidation of glucose, which causes the generation of free radicals. Hence complications of diabetes may be a result of the elevations in levels of free radicals and the reduction in antioxidant defenses (GSH, GPx, GR and SOD) [25].

Adenosine binds to its receptors on various tissue cells then stimulates glycogenolysis, gluconeogenesis leading to hyperglycemia that is associated with the increase inactivity of ADA, which is one of the factors that lead to the increase in production of oxidative stress by generation of reactive oxygen species [26].

The adipocytes stores triglycerides leading to adipocyte hypertrophy. This exposure leads to cellular dysfunction, increased circulating free fatty acids (FFA) and a pro-inflammatory state. Exposure of hepatocytes to excess fats and glucose leads to steatohepatitis and insulin resistance. Thus, there is elevation of free fatty acids in diabetes which leads to worsening of insulin receptors and β -cell dysfunction [27-31].

Hyperglycemia affected the liver functions. The values of the liver enzymes AST and ALT in our study show that, these enzymes were significantly higher in all diabetic groups than of the controls. This is accordance with Idris et al. [32].

As can be seen from the present study, the serum level of uric acid was significantly increased in diabetic patients compared to the healthy individuals. This is similar to Kuo-Liong suggesting a positive association between the plasma concentration of uric acid and the incidence of type 2 diabetes Chinese individuals [33].

The significant increase of serum urea and creatinine in our study was in accordance with results of Viswanathan [34], who reported a positive association between these parameters and diabetic disease. Hyperuricemia is a strong predictor of stroke events in middle-aged patients with type 2 diabetes independently of other cardiovascular risk factors [35]. Our results show that the values of cholesterol and triglycerides were higher in diabetics compared with the normal individuals. It was reported that dyslipidemia is an important distributor to the increased cardio-vascular disease (CVD) risk in

patients with type 2 diabetes and is characterized by elevated levels of triglycerides and low levels of HDL cholesterol [36].

Conclusion

The increasing of serum activity of adenosine deaminase was found as a good diagnostic marker for type II Saudi diabetes where it is highly significantly correlated with the glycemc status.

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