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RESEARCH ARTICLE

ADIPONECTIN HORMONE, ADENOSINE DEAMINASE ENZYME AND INSULIN ADIPONECTIN HORMONE, ADENOSINE DEAMINASE ENZYME AND INSULIN HORMONE LEVELS IN TYPE 2 DIABETIC IRAQI PATIENTS

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ABSTRACT

A comparison was done for serum glucose, glycated hemoglobin, adiponectine and adenosine deaminase and insulin level with type 2 diabetes mellitus Iraqi patients. Sixty unrelated type 2 diabetes patients (age ≥35 years) who had a strong family history of diabetes (50 of 60 versus 0 of 40 for controls, $P < 0.001$) and 40 healthy subjects were study.it was obtained that adiponectin and insulin level was lowered significantly in diabetic patients as compared with control group while significantly elevated serum HbA1c and adenosine deaminase in patients group as compared with control.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases in which a person has high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced .There are three main types of DM, type 1 DM results from the body's failure to produce insulin, and currently requires the person to inject insulin, this form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". Type2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was previously referred to as non insulin-dependent diabetes mellitus (NIDDM) or "adult-onset diabetes". The third main form, gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level (AL-Kayatt *et al*., 2011; AL-Mukhtar *et al*., 2012a; AL-Mukhtar *et al.*, 2012b). Whereas type 2DM is the most common of diabetes, its specific etiology is not yet known .Its frequency varies in different racial and ethnic subgroups and is often associated with a strong familial, likely genetic, predisposition more than autoimmune type 1DM. Adiponectin is an abundant protein hormone which belongs to a family of so- called adipokines, adiponct in is expressed mostly by adipocytes and is important regulator of lipid and glucose metabolism. It is established that adiponect in is an insulin-sensitizing hormone with anti-diabetic, anti-inflammatory and anti- atherogenic properties. In recent years, it was shown that decreased serum adiponectin concentration indicates insulin resistance and type 2 diabetes associated with coronary artery disease. Accumulating evidence from animal and human studies shows that adiponectin plays an important role in insulin sensitivity and lipid metabolism, and this influences hyperlipidemia and diabetes. Adiponectin serum concentration were significantly lower in subjects with type 2 diabetes compared with controls subjects. This reduced levels may play a role in pathogenesis of obesity and diabetes type 2 through insulin resistance properties have made this novel adipocytokine a promising therapeutic tool for the future (Hamid *et al*., 2011; Nehal *et al*., 2011). Adenosine deaminase (ADA) is an enzyme catalyzing the deamination reaction from adenosine to inosine .The enzyme is widely distributed in human tissues,especially high in T-lymphocytes, elevated serum ADA activity has been observed in patients with acute hepatitis, liver cirrhosis and tuberculous effusions was considered as a good marker of cell mediated immunity. It plays a crucial role in lymphocyte proliferation and differentiation. It is an enzyme that has been suggested to be important for modulating the bioactivity of insulin and might be one of the important biomarkers in predicting bioactivity of insulin i.e, the role of serum ADA as a marker for insulin resistance. Some studies have shown that the significant elevation in the ADA levels in diabetic subjects when

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compared to this enzyme may be an important for immune-pathogenesis of type 2 diabetes mellitus (Baghanha *et al*., 1990; Kindt *et al.*, 2007; Bon *et al*., 2010).

MATERIALS AND METHODS

This study comprised of sixty Iraqi patients (26 females and 34 males) with Type 2 DM, they were attending the center of Endocrinology and Diabetes (Baghdad AL-Russafa Health Directorate) Permission from the respective center and Baghdad university institutional ethical committee for working on human subject was received properly. The patients were told about the purpose of the study and interested volunteers were enrolled with their oral information consent. All patients were selected on the basis of criteria for diabetes were used according to the American Diabetes Association 2007 guideline:Fasting plasma glucose (FPG) up to 7 mmol/l and above was considered to be diabetic and levels between 5.55 mmol/l and 6.9 mmol/l was considered as impaired fasting glucose (ADA, 2007). All investigations were carried out for patients as well as the control group according to the study protocol. Venous blood sample which have been collected from each fasting subject; blood was divided into two aliquot one for the biochemical tests.

Peripheral venous blood (7 - 10 ml) were collected from median cubital vein under good aseptic precautions using disposable, latex gloves and syringes following an overnight fast of at least 10 to 12 hours from all subjects. Three ml blood was transferred to 10 ml sterile plain tube, separated by subjecting the clotted blood was to centrifugation at 3000 rpm for 10 min. Serum of each individual sample was dispensed into small disposable sterile, screw capped frozen vial (Eppendorf) and than stored at -20ºC. Two ml of blood was transferred to an EDTA tube (1.5mg/ml) for estimation of HbA_{1c}

Measurement of body Mass Index (BMI)

Body mass index uses a mathematical formula based on a person's standing height and weight BMI equals weight in kilograms divided by height in square meter (BMI= Kg/m^2). It was suggested that a BMI of 18.5-24.9 indicates a person of normal weight, a person with a BMI of 25-29.9 is overweight, while a person with a BMI of ≥ 30 is obese (Prentice and Jebb, 2001).

Laboratory Investigations

Biochemical Tests

Quantitative Determination of Glucose

All Hormones tests were carried out in the hormones unit of the Center of Endocrinology and Diabetes (Baghdad Russafa Directorate) in Baghdad.

RESULTS AND DISCUSSION

Sixty Iraqi, diabetic patient were selected for this study with age ranged from (35 - 70) years, table (1) showed that the majority (41.7%) of patients were at the age group of (50-59) years, while the lowest (13.3%) at the age < 40 years with mean age 51.9 ±9.5 years, with no significant differences (P>0.05) in the gender distribution between type 2DM patients and control .The BMI revealed that (33.3%) of patients are overweight (Obese grade-I). No significant variation was noticed in mean value of BMI between diabetic patients (31 $Kg / m^2 \pm 6.4$) and control group (29.7$Kg / m^2 \pm 6$), (P =0.28).

Table 1. Case-control differences in gender, age and BMI

	Study group				
	Healthy controls		Cases (type-II DM)		
	N	%	N	%	P
Gender					0.38[NS]
Female	21	52.5	26	43.3	
Male	19	47.5	34	56.7	
Total	40	100.0	60	100.0	
Age group (years)					0.017
<40	11	27.5	8	13.3	
40-49	16	40.0	14	23.3	
50-59	7	17.5	25	41.7	
60+	6	15.0	13	21.7	
Total	40	100.0	60	100.0	
Range	(35 - 70)		(35 - 70)		
Mean +/- SD	46.9 +/- 10.8		51.9 +/- 9.5		
BMI categories (Kg/m2)					0.28[NS]
Normal (<25)	7	17.5	10	16.7	
Overweight (25-29.9)	15	37.5	19	31.7	
Obese grade-I (30-34.9)	13	32.5	20	33.3	
Obese grade-II (35+)	5	12.5	11	18.3	
Total	40	100.0	60	100.0	
Range	(18.4 - 51)		(20.5 - 58.1)		
Mean	29.7		31		
SD	6		6.4		

This finding is in agreement with other Iraqi studies such as (Mlaji, 2006; Ibrahim, 2013) and with a broad study (Reinauer *et al*., 2002). The prevalence of type 2 diabetes has increased dramatically in the Arabic countries over the last three decades, a trend that parallels increased industrial development .The wealth generated by oil-rich resources in countries of the Arabian Gulf have led to improved living standards, while there have also been accelerated urbanization, drastic changes in nutrition, reduced physical activity, and a greater reliance on mechanization and migrant workers (Badran and Laher, 2011). The BMI findings in this study are analogous to other studies done by Al-Mukhtar *et al*. (2012a) for Iraqi patients; Rizk *et al.* (2008) for Qatar subjects; Izadi *et al.* (2011) were BMI non modifiable risk factor in type 2DM, for Iranian subjects who showed that obesity is associated with several chronic condition these are risk factors that contribute to metabolic syndrome which in turn can lead to type 2 DM.

Frequency distribution of patients with type 2 DM by selected characteristics

Results in Table (2) are description for patients, and shown that (83.3%) of patients have positive family history of DM.

Table 2. Frequency distribution of patients with type 2DM by selected characteristics

	N	%
Family history of DM		
Negative	10	16.7
Positive	50	83.3
Total	60	100.0
Duration of DM (years)-categories		
<5	16	26.7
5-9	17	28.3
10+	27	45.0
Total	60	100.0
Age of onset (years)-categories		
<40	16	26.7
40+	44	73.3
Total	60	100.0

This result may indicate strong evidence that type 2 DM is inherited and has a genetic origin. These disease are heritable, but what is inherited is not the (Prabhavath *et al*., 2012), its disease itself, but rather the susceptibility of it agreement with that first degree relatives of individuals with type 2 DM are about three times more likely to develop the disease than individuals without a positive family history of the disease (Flores *et al*., 2003; Hansen, 2003; Gloyn, 2003). Moreover, most of patients are ≥ 40 years of age of onset (73.3%) also most of patients are ≥ 10 years of duration of DM (45%). This finding is in agreement with other Iraqi studies such as (Al-Kayatt *et al*., 2011; Al-Mukhtar *et al*., 2012b) and with abroad studies (Reinauer *et al.*, 2002; Perry *et al*., 2002) who reported that this variation in the age incidence reflects the interaction of both environmental and genetic factors in different social, racial, and geographical areas in the world (Ghodke *et al.*, 2005). Regarding the age of onset of the disease which is analogous to other Iraqi study (Ibrahim, 2013). The explanation of higher incidence of this age group may be related to physiological changes occurring at this time of maturity, exposure to many infectious agents ,environmental risk factor such as obesity which affect the activation status of β-cells function (Shaw and Chisholm, 2003).

Laboratory Findings

Biochemical parameters

Screening diagnostic tests for Type 2 DM patients

In the present study, several important biochemical parameters that are of great value in glucose metabolism were evaluated in comparison to healthy control. Serum levels of fasting HbA_{1c} and blood sugar were highly significant in comparison to healthy control (P<0.001), as shown in Table (3).

Table 3. The case control difference in serum fasting blood glucose and glycated hemoglobin

	Study group		
	Healthy controls	Cases (type-II DM)	P
HbA1c %			<0.001
Range	(4 - 6)	(6.5 - 13.8)	
Mean	5.5	9	
SD	0.6	1.5	
SE	0.09	0.19	
Number	40	60	
Fasting blood glucose (mmol/L)			<0.001
Range	(4 - 6.8)	(7.1 - 28.8)	
Median	5.9	11.6	
Inter-quartile range	(5.5 - 6.5)	(9.1 - 15.6)	
Number	40	60	
Mean rank	20.5	70.5	

It is generally agreed that FBG is the traditional basis for the diagnosis, but to be more accurate HbA_{1c} should be done to assess glycemic control in patients with diabetes because both test have related to glucose metabolism. Glygated hemoglobin reflects the blood glucose level during the preceding two to three months. Thus HbA_{1c} is suitable to monitor long-term blood glucose control in individuals with DM. Levels of HbA_{1c} are not influenced by daily fluctuations in the blood glucose concentration but reflect the average glucose levels over the prior six to eight weeks. Therefore, HbA_{1c} is a useful indicator of how well the blood glucose level has been controlled which may be used to monitor the effects of diet, exercise, and drug therapy on blood glucose in diabetic patients (Perry *et al.*, 2002; Roche, 2004; Al-Mukhtar *et al*., 2012a). This study revealed highly significant level of serum fasting sugar and HbA_{1c} among patients (p<0.001). Also, this finding is in agreement with other Iraqi studies such as (Mlaji, 2006; Salih, 2007; Ibrahim, 2013) and with abroad studies (Lee *et al*., 2011).

Estimation of HOMA2-IR and HOMA2-β cells function.

Depending on the differences in serum concentration of fasting glucose and insulin hormone by using especial computerized mathematic calculation formula, HOMA2-β-cells function was highly significant (p<0.001) with median of (29.4) in patients in comparison with healthy control (121.1), while no significant difference (P>0.05) were observed between HOMA2-IR patients and healthy control with median (2.1) for both case study as shown in the Table (4).

Many studies revealed that pancreatic β-cells dysfunction is the main cause for DM, β-cells gradually reduced to produce insulin hormone for different reasons such as viral infection, obesity and some genetic diseases (Bakari and Onyemelukwe, 2002). It is unclear if insulin resistance is the only explanation for why fasting serum hyperinsulinemia predicts diabetes or whether fasting serum hyperinsulinemia may have a pathogenic role independent of insulin resistance, there are several evidences suggest that fasting

hyperinsulinemia can be a primary metabolic defect and not simply a secondary consequence of insulin resistance (Mile *et al.,* 1998; Jeanrenaud,1994), these studies are in agreement with our finding in which there is no significant difference in HOMA2-IR between control and patients group.

Table 4. Case-control difference in mean and median of HOMA2 β-cells function and HOMA2-IR related to glucose metabolism

	Study group		
	Healthy controls	Cases (type-II DM)	P
HOMA2 percent Beta cell function			<0.001
Range	(74.8 - 300.1)	(5 - 234.2)	
Median	121.1	29.4	
Inter-quartile range	(92.9 - 171.2)	(15.6 - 48.9)	
Number	40	57	
Mean rank	76.0	30.1	
HOMA2 insulin resistance			0.37[NS]
Range	(1.3 - 8.2)	(0.8 - 15.2)	
Median	2.1	2.1	
Inter-quartile range	(1.9 - 2.9)	(1.4 - 3.4)	
Number	40	57	
Mean rank	52.1	46.9	

Estimation of serum hormones level

Estimation of serum fasting insulin level

Table (5) showed that the range of serum fasting insulin in patients was from (4-116 uIU/mL) while, in healthy control (10.2-67), and median serum levelwas (12.1) for patient and was (16) for control with statistical significant differences between two groups (P= 0.001). The level of serum insulin measures how much insulin is being produced in the body this hormone highly related to glucose metabolism, fasting hyperinsulinemia is widely used surrogate measures insulin resistance and predicts type 2 DM in various populations (Weyer *et al*., 2000).Both hypoinsulinaemia and hyperinsulinaemia have been reported among type 2 DM patients (Defronzo *et al*., 1983; Bakari and Onyemelukwe, 2002).In this study, the median insulin concentration was (12.1uIU/ml) for patients, while, (16uIU/ml) in healthy control, this could be explained by the failure of pancreatic β-cells in most patients who respond appropriately to the prevailing blood glucose levels. In this study the hypoinsulinaemia has been observed among type 2 diabetic patients is in agreement with earlier studies in Africa (Omar and Asmal,1983;Wicks and Jones,1973; Bakari and Onyemelukwe, 2005) and African-American type 2 diabetic populations (Osei *et al.*, 1993) but in contrary, findings in most European studies suggest a role for racial factor in this difference (Aronoff *et al*., 1977). Hyperinsulinemia is a common characteristic of several ethnic groups with a high prevalence of diabetes, such as Native American (Lillioja *et al.*,1993). Mexican-Americans (Haffner *et al.*, 1995) and Pacific Islanders (Sicree *et al.*, 1987). In Pima Indians ,plasma insulin concentration are increased at an early age (Pettit *et al.*,1993) and are higher than those in Caucasians ,even after adjusting for the higher degree of insulin resistance, despite their hyperinsulinemia, Pima Indians have one of the highest reported prevalence rate of diabetes in the world (Lillioja *et al.*,1993).

Table 5. The case-control difference in concentration of serum insulin

	Study group		
	Healthy controls	Cases (type-II DM)	P
Serum Insulin (uIU/ml)			0.001
Range	(10.2 - 67)	(4 - 116)	
Median	16	12.1	
Inter-quartile range	(14 - 22.5)	(8.1 - 20.2)	
Number	40	60	
Mean rank	62.0	42.8	

Estimation of serum adiponectine hormone

The mean serum level of adiponectin in sera of patients was significantly lower than that in healthy control (20.7±15.2ng/mL vs. 34±18.7ng/mL), (p<0.001) as observed in Table (6).

Table 6. The case-control difference in mean serum Adiponectin hormone

	Study group		
	Healthy controls	Cases (type-II DM)	P
Serum Adiponectin ng/mL.			<0.001
Range	(15 - 100)	(3 - 83)	
Mean	34	20.7	
SD	18.7	15.2	
SE	2.95	1.96	
Number	40	60	

It was observed that adiponectin level was lowered significantly in patients group of this study with mean (20.7±15.2) while, in healthy control (34±18.7) which is compatible with Iraqi studies (Al-Kayatt *et al*., 2011) and abroad studies reported by (Cruz *et al.*,2004;Koenig and Meisinger, 2006; Umar and Adam, 2009; Hsu *et al*., 2012). Those studies have concluded that adiponectin is independently associated with a reduced risk of type 2 diabetes in apparently healthy individuals. Many studies outcomes joined between reduced plasma levels of adiponectin as role in pathogenesis of obesity and diabetes type 2but, physiological role for adiponectin had not yet been fully established (Statnick *et al.*,2000; Haluzik *et al*., 2004). The trend towards increased adiponectin on a high fat diet in more insulin sensitive subjects is suggestive of increased capacity for fat oxidation and may be protective against development of type 2 DM (Berk *et al.*, 2003).

Estimation of serum adenosine deaminase enzyme activity

The current study revealed that the mean level of serum ADA in patients was significantly higher than that in healthy control (106.6ng/ml±15.9 vs.59.3ng/mL±14.9) with (p<0.001) as shown in Table (7).

Table 7. Case-control difference in mean serum adenosine deaminas

	Study group		
	Healthy controls	Cases (type-II DM)	P
Serum Adenosine Deaminase Enzyme activity ng/mL.			<0.001
Range	(25 - 77)	(79 - 149)	
Mean	59.3	106.6	
SD	14.9	15.9	
SE	2.36	2.06	
Number	40	60	

Previously, ADA has been reported to be a marker for insulin function or modulating the bioactivity of insulin (Hoshino *et al*., 1994). Since a relationship exists between adenosine deaminase and cell mediated immunity (Baghanha *et al*., 1990). The present study was observed a significant elevation in the ADA levels in diabetic patients when compared to controls also used as test for evaluation state of patients group. Turkish study conducted by Kurtul *et al.* (2005) is in agreement with our finding who found significant correlating of ADA with HbA_{1C}, suggest that ADA may play a great role in insulin effect and glycamic control, on the other hand increased activity of ADA in type 2 DM might be a marker for insulin indication.

Prakash *et al.* (2006) obtained same finding and interpreted the alteration in serum levels may help in predicting immunological dysfunction in diabetic individuals and might be one of the important biomarkers in predicting DM. Another study was done in Korea reveled that ADA were significantly higher in diabetes patients than in the control group and had positive correlation with both FBG and HbA_{1C} (Lee *et al*., 2011). Recently, study conducted by Kaur *et al.* (2012) reveled that three parameters (FBG, HbA_{1C} and ADA) levels were found to be increased in patients with type 2 DM as compared to controls, they were mentioned that ADA plays a crucial role in lymphocyte proliferation and differentiation and showed its highest activity in T-lymphocytes. Therefore, high serum ADA activity might be due to abnormal T-lymphocyte responses or proliferation.

Interestingly Table (8) and Figure (1) revealed a significant area under curve with elevation of serum glucose, serum ADA, serum adiponectine, HOMA2-IR and HOMA2-β-cell function as tests for diagnose of type 2 DM and differentiate it from healthy controls. The ROC analysis displays the pairs of sensitivity and specificity for different tests, it could be clearly shown that ADA by ELISA provided the best combination of sensitivity and specificity for detecting DM type 2.

Table 8. ROC area for selected parameters when used as test to diagnose type2 DM differentiating them from healthy controls

	AUC	P
Serum Adenosine Deaminase Enzyme activity(ng/mL)	1.000	<0.001
Fasting blood glucose (mmol/L)	1.000	<0.001
HOMA2 percent Beta cell function	0.973	<0.001
Serum Adiponectin (ng/mL)	0.753	<0.001
Serum Insulin (uIU/ml)	0.697	0.001
HOMA2 insulin resistance	0.554	0.37[NS]

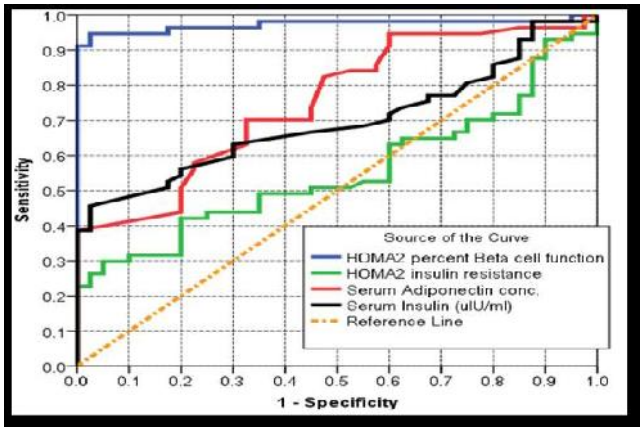

Figure 4-1. ROC curve showing the trade-off between sensitivity (rate of true positive) and 1-specificty (rate of false positive) for selected parameters when used as test to diagnose type 2 DM differentiating them from healthy controls

Table (9) revealed the optimum cut-off value of most selected parameters when used as tests for diagnoses of type 2 DM and differentiate it from healthy control that performed the accurate diagnosis of disease are (95.9) for HOMA2 β-cell function with highly specificity (97.5) and sensitivity (94.7), in HOMA2-IR (54.6), (100), (22.8) in serum adiponectin (59.8), (100), (2.2); and in serum insulin(63.9),(100), (38.6) respectively also table (4-9) shows the correlation coefficient PPV and NPV probability. The optimum cut-off value performed accurate diagnosis of serum adenosine deaminase and serum glucose when used as tests diagnose type 2 DM differentiating them from healthy control are represented in table (10) as well as showed optimum cut-off value for sensitivity (100),specificity (100); accuracy (100) for both serum ADA and serum glucose respectively. There was no significant differences in serum adiponectin level according to disease duration categories (P>0.08) whereas, this study noticed significant differences in the level of ADA according to disease duration (P0.047). ADA can be detected very early in DM although this outcome, it can conclude that ADA as a significant diagnostic marker. This finding prove the role of ADA in type 2 DM to be one of the important biomarkers in predicting DM (Prakash *et al*., 2006) and with expending duration time of disease serum level activity of ADA will be increase significantly. This result is in agreement with Kaur *et al*. (2012). Thus, the level of ADA in patients group was elevated in comparison with healthy group explained this increased may possibly related to hyperglycemic state of diabetic subject which could induced the secretion of these ADA.

Table 9.Validity parameters for selected measurements when used as test to diagnose type2 DM differentiating them from healthy controls

Positive if < cut-off value	Sensitivity	Specificity	Accuracy	Matthew's correlation coefficient	PPV at pretest probability = 50%	PPV at pretest probability = 90%	NPV at pretest probability = 10%
HOMA2 percent Beta cell function							
<74.7 (Highest specificity cut-off)	91.2	100.0	94.8	0.901	100.0	100.0	99.0
<80.5 (optimum cut-off value)	94.7	97.5	95.9	0.916	97.4	99.7	99.4
<238.1 (Highest sensitivity cut-off)	100.0	5.0	60.8	0.173	51.3	90.5	100.0
HOMA2 insulin resistance							
<1.33 (Highest specificity and optimum cut-off value)	22.8	100.0	54.6	0.33	100.0	100.0	92.1
<7.89 (Highest sensitivity cut-off)	94.7	2.5	56.7	-0.068	49.3	89.7	81.0
Serum Adiponectin conc.							
<14.5 (Highest specificity and optimum cut-off value)	38.6	100.0	63.9	0.454	100.0	100.0	93.6
<91.5 (Highest sensitivity cut-off)	100.0	2.5	59.8	0.122	50.6	90.2	100.0
Serum Insulin (uIU/ml)							
<10.1 (Highest specificity cut-off)	38.6	100.0	63.9	0.454	100.0	100.0	93.6
<11.7 (optimum cut-off value)	45.6	97.5	67.0	0.474	94.8	99.4	94.2
<63.5 (Highest sensitivity cut-off)	98.2	2.5	58.8	0.026	50.2	90.1	92.8

Note: The whole cutoff values in the appendix PPV: positive predictive value NPV: negative predictive value

Table 11. The mean serum adiponectin and adenosine deaminase by duration of DM categories among cases with type 2 DM

	Duration of DM (years)-categories			
	<5	(5-9)	10+	P
Serum Adiponectin conc.				0.29[NS]
Range	(3 - 42)	(5 - 36)	(5 - 83)	
Mean	17.3	18.5	24.1	
SD	10.8	11.1	18.9	
SE	2.71	2.69	3.63	
Number	16	17	27	
r=0.147 P=0.26[NS]				
Serum Adenosine Deaminase Enzyme activity.				0.047
Range	(89 - 149)	(87 - 140)	(79 - 130)	
Mean	114.7	101.9	104.7	
SD	16.1	15.4	14.9	
SE	4.02	3.73	2.87	
Number	16	17	27	
r=-0.203 P=0.12[NS]				

Adiponectin is independently associated with a expending duration time to increase risk of type 2 diabetes in patient. However, physiological role for adiponectin had not yet been fully establishedit is not entirely clear if the adiponectin pathway is influenced in type 2 diabetes with duration time (Kubota *et al*., 2002; Haluzik *et al.,* 2004).

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