Original Article

Study of Circulatory Level of Serum Adiponectin in Patients with Type 2 Diabetes Mellitus: Effect of Antidiabetic Drugs and Association with Chronic Diabetic Complications

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Abstract

Background. The aim of this work was to study circulatory level of serum adiponectin in patients with type 2 diabetes mellitus and any possible effect of antidiabetic drugs or diabetic complication on serum level of adiponectin. **Subjects and methods.** This study involved 120 diabetic patients with type 2 diabetes mellitus. These patients were recruited from the outpatient clinic at Alexandria Main University Hospital, in addition to 60 non-diabetic healthy control group with matched age and sex. All participants were subjected to full history taking and detailed drug history, complete physical examination including,(body weight and height), waist circumference, vital signs (heart rate and arterial blood pressure), neurological and fundus examination. Blood was drawn for fasting serum glucose, insulin level for HOMA-IR assessment, glycated haemoglobin (HbA1C), total cholesterol, High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL- C), triglycerides and adiponectin level by using ELISA. Urinary albumin creatinine ratio and serum creatinine for calculation of eGFR and staging of chronic kidney disease were done. **Results**. The mean serum adiponectin levels was significantly higher in the diabetic group compared to the control group.There was significant positive correlation between adiponectin and age among diabetic group, significantly lower adiponectin in subjects with positive history of smoking, coronary artery disease and dyslipidemia but no significant difference in adiponectin among diabetic group as regard history of hypertension (HTN) or patient with or without peripheral neuropathy, but significantly lower adiponectin among diabetic group with diabetic retinopathy. No significant correlation with systolic blood pressure but negative correlation with diastolic blood pressure was present. There was positive correlation between serum adiponectin and estimated glomerular filtration rate (eGFR) but negative correlation with urinary Albumin/ Creatinine ratio (A/C ratio). Significant increase in adiponectin in patient using glitazon, dipeptidyl peptidase-4 inhibitors (DPP4) and statins was present, on the other hand there was numerical increase in adiponectin with renin-angiotensin enzyme blocking agents (ACEI), beta blockers (BB) and diuretics than in patients using angiotensin receptor blockers (ARBs), and calcium channel blockers (CCB) but this was not significant. **Conclusions:** The quantitative changes in adiponectin provide insight into how adiponectin is important while choice of different lines in management of type 2 diabetes and associated comorbidity.

Key Words: Adiponectin, Type 2 diabetes, Antidiabetic drugs, Diabetic complications

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by the presence of hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] Type 2 DM

is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. (2) Obesity has been found to contribute to approximately 55% of cases of type 2 DM. (3)

Adipose tissue is considered as endocrine structures because of their wide variety of chemical secretions (adipokines), which affect many diverse physiological functions and related pathological processes of the body, like metabolism of carbohydrates and lipids. (4) Adiponectin is one of the important adipokines which has remarkable insulin sensitizing property as well as antiatherogenic action thereby playing an important role in delaying and suppressing the metabolic derangements, which result in IR, T2DM, and metabolic syndrome. (5)

The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for macrovascular disease including ischemic heart diseases, cerebrovascular diseases, and peripheral arterial diseases. (1) Adiponectin by its insulin sensitizing property and antiatherogenic action can affect complications of diabetes including vascular and cardiac ones. (5)

Serum adiponectin levels can be affected by different lines of management of type 2 diabetes and may be negatively influenced by lifestyle, such as sedentarism, a high-fat diet causing obesity, or excessive smoking. (6) Some antidiabetic drugs are associated with increased adiponectin such as sulphonylureas (7)and thiazolidinediones (TZDs), (8) also incretin-based therapies, GLP-1 agonists, and DPP4 inhibitors can promote secretion of adiponectin. (9,10) In management of associated comorbidity with DM like hypertension and dyslipidemia, different antihypertensive drugs may have quite different effects on adiponectin, despite very similar or equivalent effects on blood pressure, (11-3) Also there is an association between statin therapy and adiponectin levels which vary upon statin type and dose. (14-6)

The aim of this work was to study circulatory level of serum adiponectin in patients with type 2 diabetes mellitus and any possible effect of antidiabetic drugs or diabetic complication on serum level of adiponectin.

Subject and Methods:

The study included 180 subjects classified into two groups, group I:120 type 2 diabetic patients who visit diabetes clinic at Alexandria Main University Hospital.,and group II: 60 non-diabetic healthy control group with matched age and sex with group I. Ethical approval was granted by ethics committee of Alexandria Faculty of Medicine. All participates were given written informed consent after explaining the nature and the aim of the study. The healthy control group included those without any chronic cardiovascular or metabolic disease and not receiving any long-term medication for both conditions. Exclusion criteria: Ischemic cardiovascular event in previous 3 month, severe liver or renal impairment, recent history of major trauma or surgery, hematological disorders or malignancy, chronic inflammatory or autoimmune diseases, as well as patients with recent history of sever significant infection at study entry, Alcoholics, HIV, HBV, HCV, under-weight (BMI $\leq$ 18.5 Kg\ m2). All participants were subjected to: Full history taking including: detailed analysis of different cardio-metabolic risk factors (family history of premature CAD, smoking, diabetes, hypertension or dyslipidemia) and detailed drug history, complete physical examination including :Body weight and height were measured in order to calculate body mass index (BMI), waist circumference, vital signs (heart rate and arterial blood pressure), neurological examination for detection of diabetic peripheral neuropathy and fundus examination was done for detection of diabetic retinopathy.

Laboratory investigations: Blood withdrawn for metabolic, biochemical and hematological parameters after a 10-12 hours overnight fasting and the following were estimated : fasting serum glucose, serum insulin level and Homeostasis Model Assessment 2 (HOMA2) calculator was used to estimate steady state beta cell function (%B) and insulin resistance (%S) (HOMA-IR) according to the updated computer based HOMA2 mode in subjects with normal or impaired glucose tolerance, glycated

haemoglobin (HbA1C),total serum cholesterol, HDL-C, LDL- C, serum triglycerides and serum level of adiponectin by using ELISA. Urinary A/C ratio and serum creatinine for calculation of e GFR and staging chronic kidney disease were done.

Statistical analysis of the data: data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp)(297) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level .

The used tests were Chi-square test for categorical variables, to compare between different groups, Fisher's Exact or Monte Carlo correction for chi-square when more than 20% of the cells have expected count less than 5, student t-test for normally distributed quantitative variables, to compare between two studied groups and Mann Whitney test for abnormally distributed quantitative variables, to compare between two studied groups.

Results

The study included 120 patients and 60 subjects as control group. There was no significant difference between the 2 groups as regard gender, age or smoking state. Patients had significant higher BMI, waist circumference, systolic and diastolic blood pressures, fasting plasma glucose, HbA1c., serum insulin and HOMA2-IR, total cholesterol, LDLC and triglycerides but lower HDLC eGFR were significantly lower and Urinary A/C ratio were significantly higher in patients in comparison to control group. Diabetic retinopathy was present in 23.3% of diabetics and peripheral neuropathy was present in 21.7% among them (Table I, II).

Table (I): Demographic data of the studied subjects

	Control (n = 60)		Patients (n = 120)		Test of Sig. χ^2	p
	No.	%	No.	%		
Sex						
Male	22	36.7	58	48.3		0.138
Female	38	63.3	62	51.7	2.205	
Smoking						
Non-smoker	50	83.3	92	76.7	1.067	0.302
Smoker	10	16.7	28	23.3		
Diabetic duration in years						
≤5			72	60.0		
>5			48	40.0		
History of						
Coronary artery disease (CAD)			12	10.0		
Hypertension (HTN)			64	53.3		
Dyslipidemia			56	46.7		
Family history(FH)						
CAD	4	6.7	24	20.0	5.414*	0.020*
HTN	12	20.0	50	41.7	8.316*	0.004*
DM	16	26.7	88	73.3	35.709*	<0.001*
Peripheral neuropathy (PN)			26	21.7		
Fundus examinatio						
Normal			92	76.7		
Retinopathy			28	23.3		
Non proliferative			18	15.0		
Proliferative			10	8.3		

χ^2: Chi square test
t: Student t-test
p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

Table (II): Laboratory and some clinical data of studied subjects in relation to adiponectin

Measures	Control (n = 60) Mean ± SD.	Patients (n = 120) Mean ± SD.	Test of sig.	P
BMI (kg/m^2)	24.94 ± 2.14	32.11 ± 3.26	t=17.664*	<0.001*
Waist circumference (cm)	94.83 ± 7.83	110.4 ± 10.21	t=11.321*	<0.001*
Systolic blood pressures(mmHg)	125.5 ± 10.36	137.4 ± 9.37	t=7.761*	<0.001*
Diastolic blood pressures(mmHg)	80.33 ± 4.10	82.93 ± 5.30	t=3.625*	<0.001*
FPG (mg/dl)	Mean ± SD.	86.77 ± 6.37	t=12.073*	<0.001*
Insulin (µIU/ml)	9.33 ± 3.01	13.37 ± 10.67	U =2584.0*	0.002*
HOMA –IR	1.35 ± 0.48	5.26 ± 3.26	U =414.0*	<0.001*
HbA1c (%)	5.06 ± 0.29	7.75 ± 1.66	t =17.313*	<0.001*
Total cholesterol (mg/dl)	173.6 ± 19.43	212.7 ± 49.79	t =7.526*	<0.001*
Triglycerides (mg/dl)	118.2 ± 16.49	175.0 ± 77.59	U =1238.0*	<0.001*
LDL (mg/dl)	85.77 ± 10.09	107.7 ± 33.65	t =6.574*	<0.001*
HDL (mg/dl)	57.97 ± 5.30	56.20 ± 6.44	t =1.835*	<0.001*
eGFR (ml/min/1.73 m^2)	94.37 ± 3.86	85.40 ± 11.26	U=1216.0*	<0.001*
A/C ratio (µgm/mg)	3.90 ± 1.55	35.62 ± 52.08	U=286.0*	<0.001*
Adiponectin (µg/ml)	4.07 ± 1.01	2.28 ± 1.72	U=958.0*	<0.001*

t: Student t-test
p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$
U: Mann Whitney test

The mean serum adiponectin levels were statistically significant higher in the diabetic group compared to the control group (Fig 1)

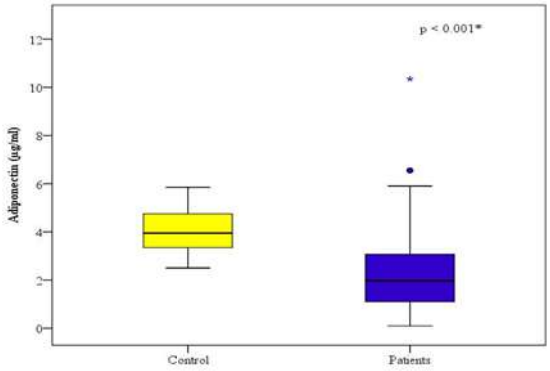

Fig. (1): Comparison between the two studied groups according to adiponectin

There was statistically significant positive correlation between serum adiponectin and the age among diabetic group but no statistically significant difference as regard gender, on the other hand there was statistically significant lower serum adiponectin levels, in subjects with positive history of smoking, coronary artery disease and dyslipidemia but no statistically significant difference in serum adiponectin levels among diabetic group as regard history of hypertension (HTN). No significant difference in serum adiponectin levels among diabetic group with or without peripheral neuropathy, but there were statistically significant lower serum adiponectin levels among diabetic group with diabetic retinopathy. No significant correlation among diabetes with systolic blood pressure (BP) but there was statistically significant negative correlation between serum adiponectin and diastolic BP (Table III, Fig.2- 5)

Table (III): Relation between adiponectin and clinical parameters of studied subjects

	N	Adiponectin (µg/ml)		U	p
		Mean ± SD.	Median		
Sex (control)					
Male	**22**	3.81 ± 0.94	3.90	328.0	0.167
Female	**38**	4.23 ± 1.02	4.0		
Smoking(control)					
Non-smoker	**50**	4.35 ± 0.87	4.25	4.0*	<0.001*
Smoker	**10**	2.70 ± 0.18	2.65		
FH (control)					
CAD					
No	**56**	4.05 ± 1.0	3.95	100.0	0.722
Yes	**4**	4.43 ± 1.24	4.43		
HTN					
No	**48**	4.12 ± 1.05	3.95	260.0	0.604
Yes	**12**	3.88 ± 0.81	4.05		
Dyslipidemia					
No	**44**	4.12 ± 1.01	4.13	302.0	0.403
Yes	**16**	3.94 ± 1.02	3.85		
Sex (Patients)					
Male	**58**	2.37 ± 1.64	2.35	1658.0	0.462
Female	**62**	2.20 ± 1.80	1.95		
Smoking(Patients)					
Non-smoker+++	**92**	2.56 ± 1.78	2.0	682.0*	<0.001*
Smoker	**28**	1.39 ± 1.09	0.70		
History (Patients)					
CAD					
No	**108**	2.49 ± 1.68	2.05	2.0*	<0.001*
Yes	**12**	0.41 ± 0.22	0.45		
HTN					
No	**56**	2.10 ± 1.29	1.73	U= 1696.0	0.613
Yes	**64**	2.45 ± 2.01	2.0		
Dyslipidemia					
No	**56**	3.57 ± 1.70	3.10	4.0*	<0.001*
Yes	**64**	1.16 ± 0.54	1.15		
FM (Patients)					
CAD					
No	**96**	2.28 ± 1.82	1.98	1062.0	0.555
Yes	**24**	2.31 ± 1.23	1.95		
HTN					
No	**70**	2.35 ± 1.99	2.0	1700.0	0.790
Yes	**50**	2.19 ± 1.25	1.90		
Dyslipidemia					
No	**32**	2.27 ± 1.37	2.30	1334.0	0.660
Yes	**88**	2.29 ± 1.83	1.93		
PN (Patients)					
No	**94**	2.31 ± 1.80	1.95	1210.0	0.939
Yes	**26**	2.18 ± 1.38	2.10		
Fundus (Patients)					
Normal	**92**	2.78 ± 1.66	2.48	0.00*	<0.001*
Retinopathy	**28**	0.65 ± 0.28	0.70		

U: Mann Whitney test

p: p value for association between Adiponectin and different parameters

*: Statistically significant at $p \leq 0.05$

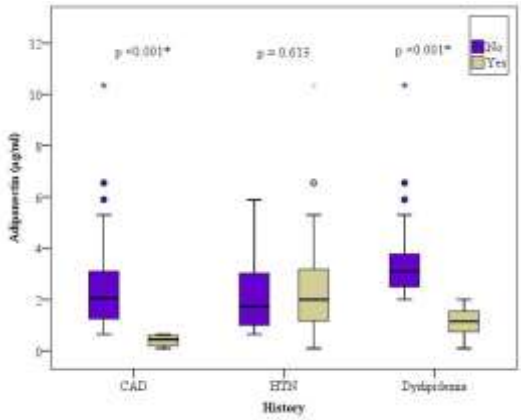

Fig. (2): Relation between adiponectin and history of CAD, HTN and dyslipidemia in patients group (n = 120)

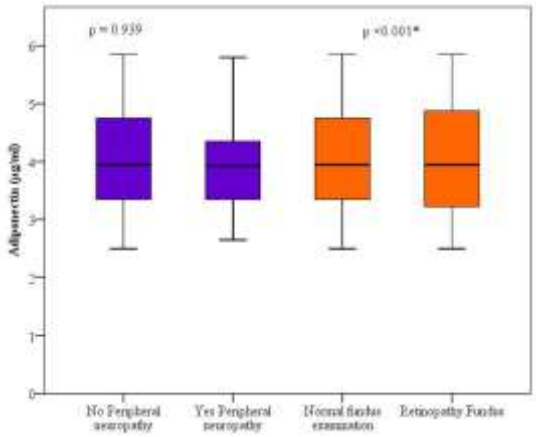

Fig. (3): Relation between adiponectin peripheral neuropathy and fundus examination in patients' group (n = 120)

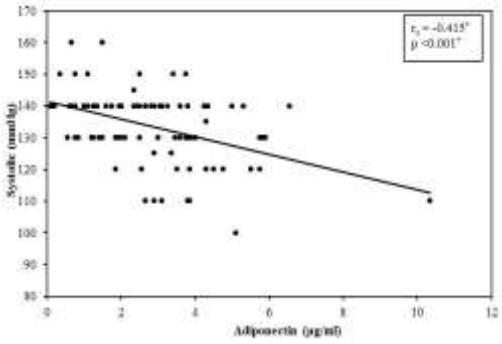

Fig. (4): Correlation between adiponectin and systolic BP

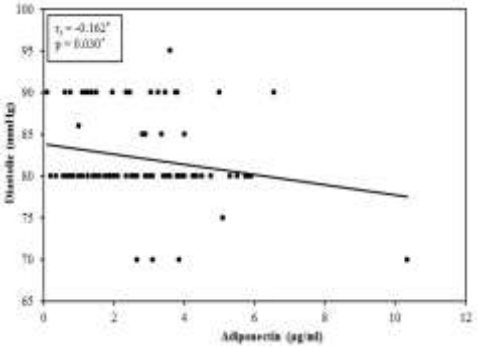

Fig. (5): Correlation between adiponectin and diastolic BP in total group.

There was statistically significant negative correlation between serum adiponectin BMI, waist circumference, fasting plasma glucose, HbA1c., serum insulin and HOMA2-IR, total cholesterol, LDL cholesterol and triglycerides but significant positive correlation with HDL cholesterol. No significant correlation between serum adiponectin and e GFR, also the same was observed among patients with diabetes with urinary A/C ratio but there was statistically significant positive and negative correlation between serum adiponectin and eGFR and also with urinary A/C ratio among the total group respectively (Table IV, Fig 6,7)

Table (IV): Correlation between adiponectin and different parameters in each group

	Adiponectin (µg/ml)					
	Control		Patients		Total sample	
	r_s	P	r_s	p	r_s	p
Age (years)	-0.125	0.340	0.235*	0.010*	0.047	0.527
DM since years	-	-	0.021	0.821	0.021	0.821
BMI (kg/m^2)	0.003	0.980	-0.240*	0.008*	-0.569*	<0.001*
Waist circumference (cm)	0.062	0.637	-0.226*	0.013*	-0.518*	<0.001*
Systolic (mmHg)	0.034	0.799	-0.163	0.075	-0.415*	<0.001*
Diastolic (mmHg)	-0.089	0.499	0.002	0.979	-0.162*	0.030*
FPG (mg/dl)	-0.124	0.345	-0.339*	<0.001*	-0.608*	<0.001*
Insulin (µIU/ml)	0.088	0.503	-0.096	0.296	-0.146*	0.049*
HOMA – IR	0.225	0.084	-0.343*	<0.001*	-0.566*	<0.001*
HbA1c (%)	0.089	0.497	-0.274*	0.002*	-0.582*	<0.001*
Total cholesterol (mg/dl)	0.040	0.760	-0.173	0.058	-0.386*	<0.001*
Triglycerides (mg/dl)	-0.033	0.802	-0.306*	<0.001*	-0.487*	<0.001*
LDL (mg/dl)	-0.088	0.505	-0.222*	0.015*	-0.356*	<0.001*
HDL (mg/dl)	0.069	0.599	0.247*	0.007*	0.204	0.006*
eGFR (ml/min/1.73 m^2)	-0.105	0.425	-0.054	0.555	0.276*	<0.001*
A/C ratio (µgm/mg)	-0.048	0.715	-0.132	0.151	-0.515*	<0.001*

r_s: Spearman coefficient

*: Statistically significant at $p \leq 0.05$

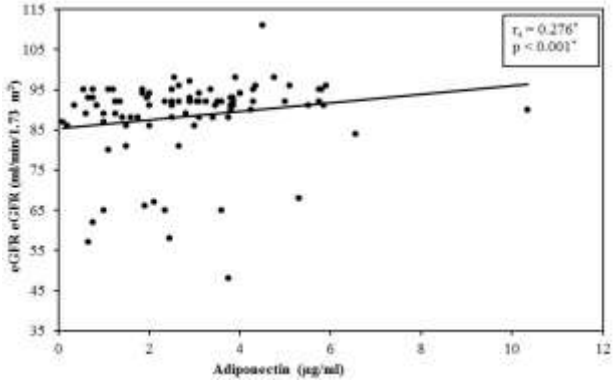

Fig. (6): Correlation between adiponectin and eGFR in total group

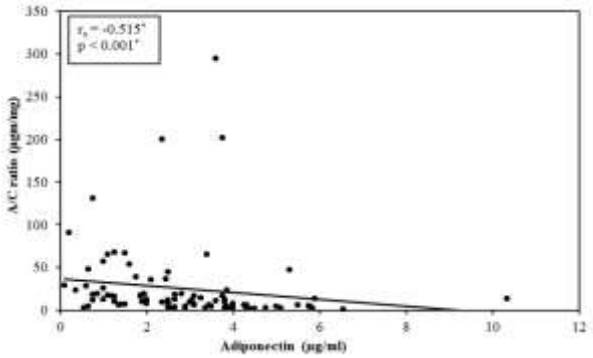

Fig. (7): Correlation between adiponectin and A/C ratio in each group

As regard the relations between serum levels of adiponectin and antidiabetic drugs in patients' group, there was statistically significant increase in serum adiponectin levels in patient using glitazon and DPP4, but there was no statistically significant difference in those using or not using metformin, sulphonylureas or insulin. On the other hand, regarding the relations between serum levels of adiponectin and antihypertensive drugs, there was increase in serum adiponectin levels among diabetic group using ACEI, BB and diuretics than in patients using ARBs, and CCB but this was not statistically significant. There was statistically significant increase in serum adiponectin levels among diabetic group using statins in comparison with those who didn't use statin (Table V, Fig 8-9).

Table (V): Relation between adiponectin and drug history in patients group (n = 120)

Drug history	N	Adiponectin (µg/ml)			U	p
		Min. – Max.	Mean ± SD.	Median		
Metformin						
No	**14**	0.65 – 2.65	1.84 ± 0.79	2.10	660.0	0.502
Yes	**106**	0.10 – 10.35	2.34 ± 1.80	1.95		
Sylphnylurea						
No	**56**	0.10 – 3.80	1.96 ± 1.16	1.98	1566.0	0.234
Yes	**64**	0.55 – 10.35	2.56 ± 2.05	1.95		
Glitazon						
No	**108**	0.10 – 10.35	2.0 ± 1.52	1.85	24.0*	<0.001*
Yes	**12**	3.80 – 6.55	4.87 ± 1.16	4.85		
DPP4						
No	**98**	0.10 – 10.35	2.16 ± 1.73	1.85	776.0*	0.040*
Yes	**22**	0.55 – 6.55	2.81 ± 1.58	2.50		
Insulin						
No	**92**	0.10 – 10.35	2.23 ± 1.83	1.88	1074.0	0.184
Yes	**28**	0.60 – 5.30	2.46 ± 1.31	2.40		
ACE.I						
No	**95**	0.10 – 10.35	10.35 ± 10.35	10.35	1032.50	0.316
Yes	**25**	0.10 – 10.35	2.73 ± 2.21	2.35		
ARBS						
No	**100**	0.10 – 10.35	2.35 ± 1.82	2.0	916.0	0.554
Yes	**20**	0.35 – 3.75	1.94 ± 1.02	1.93		
CCB						
No	**103**	0.10 – 10.35	2.33 ± 1.80	1.95	814.50	0.646
Yes	**17**	0.35 – 3.80	1.97 ± 1.08	2.0		
BB						
No	**112**	0.10 – 10.35	2.21 ± 1.57	1.98	364.0	0.377
Yes	**8**	0.10 – 10.35	3.25 ± 3.13	2.55		
Diuretics						
No	**91**	0.10 – 10.35	2.22 ± 1.78	1.85	1139.50	0.270
Yes	**29**	0.35 – 6.55	2.48 ± 1.50	2.35		
Statin						
No	**68**	0.10 – 3.80	1.88 ± 1.09	1.95	1375.0*	0.037*
Yes	**52**	0.65 – 10.35	2.81 ± 2.19	2.10		

U: Mann Whitney test p: p value for association between Adiponectin and drug history

*: Statistically significant at $p \leq 0.05$

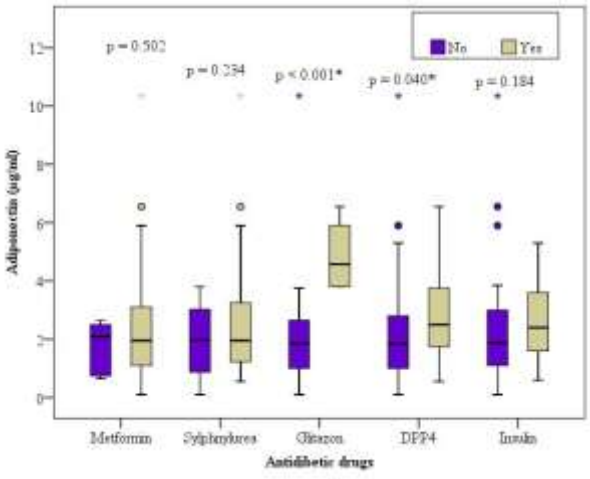

Fig. (8): Relation between adiponectin and antidibetic drugs.

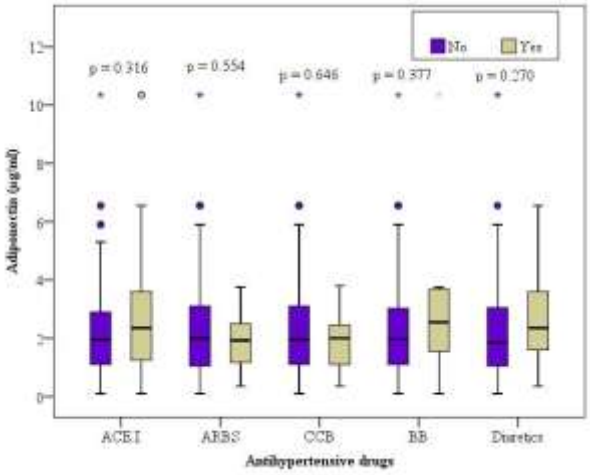

Fig. (9): Relation between adiponectin and antihypertensive drugs history.

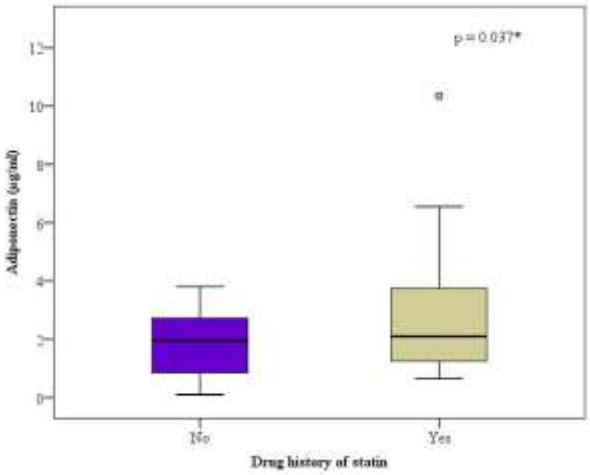

Fig. (10): Relation between adiponectin and drug history of statin.

Discussion

Central obesity appears to play an important role in metabolic syndrome and insulin resistance. [17] In the present study, type 2 diabetics had significantly ($p<0.001$) higher BMI and WC than non-diabetics, also statistically high significant increase in FBG levels, HBA1c and Insulin resistance, measured as HOMA-IR ($p<0.001$) in comparison with control group.

Hypertriglyceridemia, in conjunction with increased small dense LDL C and low HDLC levels, is an important contributor to accelerated atherosclerosis in DM and insulin-resistant conditions. [18] The results of lipid profile in the present study, showed that there was a significant ($P <0.0001$)* increase in serum triglyceride, total serum cholesterol and LDLC but a significant ($P <0.0001$) decrease in HDLC levels in diabetic patients in comparison with its values in the control group.

Adiponectin which is a bioactive adipocytokine exclusively secreted by mature adipocytes in adipose tissue possesses anti-inflammatory, antiatherogenic, and insulin-sensitizing properties. It is the most abundant adipocytokine synthesized by adipocytes. [19–21] So, adiponectin plays an important role in pathogenesis of DM and its complications. In the present study, lower level of serum adiponectin was seen in diabetics (Median =1.98 µg/ml) in relation to control subjects (Median=3.95 µg/ml), which was statistically significant ($p <0.001$) and serum adiponectin levels in diabetic patients had a negative correlation with HbA1c and fasting blood glucose. Also, serum levels of adiponectin were strongly correlated with insulin sensitivity and low adiponectin was found in patients with IR which is supported by the previous studies that found adiponectin to be a major modulator of insulin action and insulin resistance. [22] Jung CH.et al, [23] showed in concordance with the present study significant negative correlations with serum fasting insulin, and HOMA-IR and serum adiponectin levels.

The association between low adiponectin levels and obesity have been documented. [5] In the present study, there was a negative correlation between adiponectin levels and both BMI and WC. Also, there was a negative correlation with total cholesterol, LDLC, triglycerides and positive correlated with HDLC. In agreement with the results of the present study, Jung CH.et al [23] found that serum adiponectin levels was negatively correlated with total cholesterol, LDLC, triglycerides and positively correlated with HDLC.

Adiponectin can affect diabetic complications through its multiple anti-inflammatory and antiatherogenic effects which can involve vascular endothelial cell survival. [19–21]

In the present study, diabetic subject with hypertension had numerically higher serum adiponectin levels but it was non-significant. Mallamaci et al [24] et al showed similar results had significantly higher plasma adiponectin levels in hypertensive men than normotensive ones and he mentioned that plasma adiponectin levels may be affected by arterial pressure, but may also be affected by total body fat, hormones and so on. On the other hand, Murakami et al. [25] reported that low adiponectin levels can only be present in insulin resistant hypertensive patients.

Lower serum levels of adiponectin was detected among patient with positive history of CAD in the present study and this relation was statistically significant. In concordance with this, Hotta et al. [26] found that plasma levels of adiponectin in diabetic individuals with CAD were lower than in diabetic patients without CAD, while, Nakamura et al. [27] noted significantly lower adiponectin plasma levels in patients with acute myocardial infarction and unstable angina pectoris but not with stable angina pectoris, compared to the control group.

Adiponectin, were positively correlated with eGFR and negatively correlated with UACR in the present study, which are well known markeres of diabetic kidney disease (DKD). [28] In disagreement with these results, CH.et al. [23] found the mean levels of adiponectin were significantly lower in patients with DKD. While, Galovicova et al. [29] (who studied 120 patients with type 2 DM found higher plasma adiponectin levels in those with macroalbuminuria, compared to those who had normoalbuminuria,

microalbuminuria, as well as compared to controls (patients with normoalbuminuria had the lower levels of adiponectin). He concluded that diabetic nephropathy potentially plays a very important role in increasing the synthesis and secretion of adiponectin. So, adiponectin may be lower in early stages of DKD but higher in advanced stages.

Adiponectin was significantly lower in patients with diabetic retinopathy (DR) compared to those with normal fundus examination in the present study. Hatef ZS et al. [30] showed similar results among diabetic patients with retinopathy than those without. On the other hand, Jung CH.et al. [23] serum adiponectin levels were significantly higher in type 2 diabetes patients with retinopathy. A number of studies have shown that adiponectin is upregulated in damaged tissues. For example, adiponectin mRNA is detected in the liver of a mouse model of hepatic injury. So, an explanation for the increased concentration of adiponectin in DR is a possible role in tissue injury and repair. [31] Consequently, the relationship between adiponectin and DR may be different from early and advanced stages DR and it is possible that adiponectin is a marker for retinal injury, mediates angiogenesis, or elevated adiponectin may represent a state of adiponectin resistance.

Peripheral neuropathy (PN) in the present study in relation to adiponectin was positively correlated but this associations were not significant. In concordance with the present study, Cha J J et al. [32] found that high adiponectin levels were associated with increased risk of PN, but the significance of this association was lost after adjusting for confounding factors, while, Jung CH.et al [23] found that higher serum adiponectin levels were associated with increased risk of PN. In a study by Kato et al. [33] serum adiponectin was not correlated with neuropathy. So, the relationship between diabetic neuropathy and serum adiponectin, is controversial.

Serum adiponectin levels can be affected by different lines of management of type 2 DM and associated comorbidity. In the present study, a regard anti-diabetic drugs thiazolidinediones and DPP4 inhibitors were associated with significant increase serum adiponectin levels, while serum adiponectin levels were numerically increased but not significant in patients on metformin and sulphonylureas.

In agreement with the results of the present study, Phillips SA et al [34] observed no change in serum adiponectin with metformin but troglitazone treatment increased serum adiponectin levels nearly threefold. Also in a systematic review which summarizes the evidence of the effect of thiazolidinediones on circulating adiponectin levels was performed, a significant increase in adiponectin (80-178%) after thiazolidinediones treatment was observed in all included studies. [8] In ten RCTs, evaluating DPP4i (sitagliptin and vildagliptin) versus placebo or an active control drug in type 2 diabetic patients including 1495 subjects. DPP4i (sitagliptin and vildagliptin) treatment were associated with significantly elevated adiponectin levels. [9] AmetovAS and Gusenbekova DG [10] studied the effect of sitagliptin in combination with metformin as well as of metformin monotherapy. After24 weeks of therapy, adiponectin content in blood increased by 27.06% in the group receiving sitagliptin and metformin combination, and by 7.16% in the group receiving metformin monotherapy. In disagreement with the results of the current study, a meta-analysis was done to investigate and determine the role of metformin on serum adiponectin levels in patients with type 2 DM, post-treatment serum adiponectin levels were higher than pre-treatment levels. [35] Also, Tsunekawa T et al. (7) reported a highly significant elevation in plasma adiponectin concentration after 8 weeks of glimepiride treatment. By contrast, the control group treated with glibenclamide did not show change in plasma adiponectin concentration.

Different types of antihypertensive drugs which are used for control of hypertension may have different effects on adiponectin. ACEI and angiotensin converting enzyme inhibitors was found to increase adiponectin levels and improve insulin sensitivity without affecting the degree of body adiposity,[36] Calcium channel blockers may impair insulin release, but this effect on glucose metabolism appears to be balanced by their action to increase peripheral glucose uptake [12,13] on the other, hand beta-blockers

differ in terms of their mechanism of action and their effects on glucose and lipid metabolism. [37]

In the present study, there was numerical increase in serum adiponectin levels among diabetic group using ACEI, BB and diuretics than in patients using ARBs, and CCB but this was not statistically significant. YILMAZ MI et al. [38] observed that plasma adiponectin concentrations significantly increased with ramipril and valsartan. Derosa, G., et al (2010) [39] Within CCBs, candesartan, but not Olmesartan therapy, over the period of a year resulted in increased adiponectin and insulin sensitivity in T2DM hypertensive patients, even though BP lowering was similar in both treatment groups. Piecha, G., et al. [11] In a comparison of enalapril, metoprolol, amlodipine, and indapamide, no changes in adiponectin level were seen with enalapril, amlodipine, or metoprolol, whereas a reduction in adiponectin was seen with indapamide. This reduction in adiponectin with the thiazide-like diuretic correlated with increased insulin resistance. Patients treated with nebivolol and carvedilol were found to had a trend toward more improvement in insulin sensitivity and glucose tolerance. Nebivolol and carvedilol therapy significantly improved glycemic profile, which may improve prognosis. [40] Nebivolol and metoprolol were shown to have similar reductions in blood pressures but differ in their effects on plasma adiponectin levels. Nebivolol improved insulin resistance and oxidative stress while there were no significant alterations in the metoprolol group. [40] Also, Hara Y et al. [41] showed that, there was a significant worsening of insulin resistance in patients receiving atenolol.

In the present study, there was statistically significant increase in serum adiponectin levels among diabetic group using statins. The association between statin therapy and adiponectin levels vary upon statin type and dose.[14-6]

Chrusciel P et al. [14] showed in the results of their meta-analysis significant increase in plasma adiponectin levels following statin therapy and the pleiotropic adiponectin-elevating effect of statins may be explained, at least in part, the putative benefits of these drugs in reducing cardiovascular risk in diabetic patients. Atorvastatin and pravastatin were more effective (numerically) than other statins in increasing plasma adiponectin concentrations. Simvastatin and atorvastatin were found to improve insulin sensitivity in diabetic patients; [15] However, others have reported that simvastatin either did not change or worsened insulin sensitivity in diabetic patients. [16,42] So, statin in most of studies improve adiponectin levels.

Conclusion

The quantitative changes in adiponectin provide insight into how serum adiponectin levels can be affected by different lines of management of type 2 diabetes and associated comorbidity. Thus, medications that improve insulin sensitivity and glucose control, as well as blood pressure control, have a significantly beneficial role beyond blood glucose or blood pressure control.

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