

The Role of Serum Adiponectin Concentration in Diabetic Patients with Diabetic Retinopathy

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Abstract: Many factors are reported to affect the progression of diabetic retinopathy; there is general agreement that the duration of diabetes and the severity of hyperglycemia are the major risk factors for its development. An association between adiponectin and diabetic retinopathy was demonstrated. Adiponectin are involved in the development of diabetes and diabetic retinopathy. The aim of the study is to assess serum adiponectin concentrations in type 2 diabetic Egyptian patients with and without retinopathy and to assess the association between adiponectin and the severity of retinopathy. We studied 60 diabetic patients and 20 healthy subjects as control group. The diabetic patients were divided into 3 subgroups according to the severity of retinopathy. Subgroup I included those without diabetic retinopathy (DR), subgroup II included those with background DR and subgroup III included those with proliferative diabetic retinopathy (PDR). For all patients and control group, fasting blood glucose, serum total cholesterol, serum triglycerides, serum insulin and serum adiponectin were estimated and calculation of homeostasis model assessment of insulin resistance (HOMA-IR) for assessment of insulin resistance. There was a highly significant decrease in serum adiponectin concentration in diabetic patients compared to control group and there was lower levels in subgroups II & III compared to subgroup I and the concentration in subgroup III was lower significantly than in subgroup I. This study shows that the decrease in serum concentration of adiponectin was associated with the severity of diabetic retinopathy and suggests that adiponectin may play a role in the pathogenesis of diabetic retinopathy and its degree. We recommend the use of adiponectin in treatment of diabetes as a new era for possible glycemic control and reduction of diabetic complications

Key words: Adiponectin-type 2 diabetes- diabetic retinopathy.

INTRODUCTION

Diabetic retinopathy (DR) and diabetic macular edema (DME) are common micro vascular complications in patients with diabetes and may have a sudden and debilitating impact on visual acuity, eventually leading to blindness (Thomas *et al.*, 2003). Diabetic retinopathy progresses from mild nonproliferative abnormalities (characterized by increased vascular permeability) to moderate and severe nonproliferative diabetic retinopathy (NPDR)(characterized by vascular closure) to proliferative diabetic retinopathy (PDR) (characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous). Macular edema (characterized by retinal thickening from leaky blood vessels) can be developed at all stages of retinopathy. New blood vessels of DPR and contraction of all accompanying fibrous tissue can distort the retina and lead to tractional retinal detachment, producing severe and irreversible vision loss (Donald *et al.*, 2004).

Adiponectin is expressed in differentiated adipocyte and seems to be an essential modulator for metabolic and vascular diseases. Because adiponectin possesses anti-inflammatory properties and improve glucose tolerance, hypo adiponectinemia has been suggested to be a contributor to the pathogenesis of type 2 diabetes mellitus and its vascular complications (Beltowski, 2003).

Yilmaz *et al.*, (2004) reported that adiponectin plasma concentration are lower in patients with diabetic retinopathy than those without it and are involved in the development of diabetes and diabetic retinopathy.

The aim of the study is to assess the role of adiponectin in diabetic retinopathy and to investigate its association with diabetic retinopathy.

Patients and Methods:

This study was carried out on 80 subjects from Al-Zahraa University Hospital, approval of ethical committee and consent from the patients were done, 60 of them were type 2 diabetes and 20 apparently normal subjects as control group. The diabetic patients were grouped into 3 subgroups according to the severity of DR:

Subgroup I (those without DR), included 20 patients (8 males & 12 females) with mean age of 54.4 ± 4.43 years with mean body mass index (BMI) of 26.80 ± 2.69 Kg/m² with mean duration of diabetes 15.65 ± 3.48 years.

Subgroup II (those with background DR), included 20 patients (10 males and 10 females) with mean age of 55.55 ± 4.74 years with mean BMI of 26.65 ± 2.64 years and their mean duration of diabetes was 15.6 ± 5.04 years.

Subgroup III (those with PDR), included 20 patients (9 males and 11 females) with mean age of 54.65 ± 5.17 years, with mean BMI of 26.7 ± 2.45 Kg/m² and their mean duration of diabetes was 16.75 ± 4.93 years.

Regarding group IV was the control group (10 males & 10 females) with mean age of 55.0 ± 6.31 years with mean BMI of 26.05 ± 2.21 Kg/m².

About 5 ml of fasting (12-16 hours) venous blood samples, the serum was separated by centrifugation and fasting blood glucose was determined immediately by glucose oxidase (Siest *et al.*, 1981) and the rest of the serum stored at -20°C for determination of total cholesterol, triglyceride, insulin and adiponectin

Lipid Profile:

Total cholesterol was carried out using Trinder's reaction (Allain *et al.*, 1974). Triglyceride was carried out using enzymatic hydrolysis of glycerol (Fossati and Principe *et al.*, 1982).

Serum insulin was determined using radioimmunoassay kit (Hotamisligil, 2003)

Adiponectin Determination:

By quantitative sandwich enzyme immunoassay technique and the kit of adiponectin and insulin were supplied by LINCO Diagnostic (Linco Research Inc., 6 Research Park Drive, St Charles, Missouri, USA.) (Faraj *et al.*, 2003).

Insulin resistance was also assessed using the homeostasis model (Wallace *et al.*, 2004) in which the index of insulin resistance was calculated as Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) = fasting plasma glucose (mg/dl) x fasting serum insulin (μIU/ml)/405.

RESULTS AND DISCUSSION

Highly significant increase in FBG serum, total cholesterol, triglycerides, insulin and HOMA-IR ($P < 0.01$) and a highly significant decrease in adiponectin in diabetic patients compared with control group ($P < 0.01$) (Table 1).

Results recorded a highly significant decrease in serum adiponectin in subgroup II ($P < 0.01$) compared to subgroup I and III ($P < 0.01$) compared to subgroup I and significant decrease in subgroup III ($P < 0.05$) compared to subgroup II. There were a non-significant difference in serum insulin and HOMA-IR in different patient groups ($P > 0.05$) (Table 2)

There were no significant correlations between serum adiponectin and age, duration of diabetes, BMI and insulin ($P > 0.05$) (Table 3).

A significant negative correlation between serum adiponectin and serum insulin in-subgroup I ($P < 0.05$), between serum adiponectin and BMI in-subgroup II patients ($P < 0.05$) but in-subgroup III no significant correlation was found between adiponectin and age, duration of diabetes, BMI and insulin ($P > 0.05$) (Table 4).

Adiponectin is a protein product of adipose tissue and is considered as an essential modulator for metabolic and vascular diseases. Several studies have indicated that adiponectin possesses anti-inflammatory properties and may negatively modulate the process of atherogenesis (Diaz and Iglesias, 2003).

Many factors are reported to affect the progression of diabetic retinopathy; however, there is general agreement that the duration of diabetes and the severity of hyperglycemia are the major risk factors for its development (Aiello *et al.*, 2001). Because adiponectin possesses anti-inflammatory properties and improve glucose tolerance, hypo adiponectinemia has been suggested to be a contributor to the pathogenesis of type 2 diabetes mellitus and its vascular complications (Beltowski, 2003).

Table 1: The clinical and laboratory characteristics of diabetic patients and control group (Mean±SD).

Parameters	Groups		P
	Diabetic group (n=60)	Control group (n=20)	
BMI (kg/m ²)	26.72± 2.55	25.05± 2.21	>0.05
FBG (mg/dl)	195.68±67.63	80.85±9.53	<0.01
Total serum cholesterol (mg/dl)	211.02±52.23	169.05±41.45	<0.01
Serum triglycerides (mg/dl)	135.32±43.26	97.30±29.15	<0.01
Serum Insulin (µIU/ml)	25.39±3.51	15.03±1.46	<0.01
Serum adiponectin (µg/ml)	5.97±1.44	8.39±1.2	<0.01
HOMA-IR	12.33±4.5	2.96±0.61	<0.01

P>0.05: Non significant. P<0.01: Highly significant.

Table 2: The serum levels of adiponectin, insulin and HOMA-IR index in different patients subgroups (Mean ± SD).

Parameters	Groups			P
	Subgroup I	Subgroup II	Subgroup III	
Serum insulin (µIU/ml)	25.64±3.04	25.25±3.04	25.3±4.44	Pa>0.05 Pb>0.05 Pc>0.05
Serum adiponectin (µg/ml)	7.05±1.09	5.90±0.99	4.98±1.04	Pa<0.01 Pb<0.01 Pc<0.05
HOMA-IR	12.19±4.58	11.80±5.69	12.00±2.88	Pa>0.05 Pb>0.05 Pc>0.05

Pa: subgroup I versus subgroup II. Pb: subgroup I versus subgroup III. Pc: subgroup II versus subgroup III.

P>0.05: Non significant. P<0.05: significant. P<0.01: highly significant.

Table 3: Correlation between serum adiponectin and different clinical parameters and serum insulin in diabetic patients.

	Adiponectin	
	r	P
Age	-0.167	>0.05
Duration	-0.017	>0.05
BMI	-0.125	>0.05
Serum insulin	-0.142	>0.05

Table 4: Correlation between serum adiponectin and different clinical parameters and serum insulin in different subgroups of diabetic patients.

	Adiponectin					
	Subgroup I		Subgroup II		Subgroup III	
	r	P	r	P	r	P
Age	-0.241	>0.05	0.041	>0.05	-0.301	>0.05
Duration	-0.249	>0.05	-0.028	>0.05	-0.369	>0.05
BMI	-0.362	>0.05	-0.577	<0.05	-0.294	>0.05
Serum insulin	-0.404	<0.05	-0.365	>0.05	-0.213	>0.05

The present study was conducted on 60 patients with type 2 diabetes mellitus with or without diabetic retinopathy and divided into 3 subgroups according to the severity of DR: subgroup I include those patients without DR, subgroup II include those with background DR and subgroup III include those with PDR as well as twenty apparently healthy subjects as control group. For all subjects fasting blood glucose, serum total cholesterol, triglycerides, insulin and adiponectin were determined and HOMA-IR was calculated.

The present study showed that a highly significant decrease in serum adiponectin levels in diabetic patients compared to control group (<0.01), with significant decrease in its serum level with the severity of DR, serum adiponectin levels in subgroup II is highly significant decreased than in subgroup I (P<0.01), in subgroup III is highly significant decrease than in subgroup I (P<0.01) and a significant decrease in subgroup III compared to subgroup II (P<0.05). These results were in agreement with Hotta *et al.*, 2000 and Lindsay *et al.*, 2002, where the concentration of adiponectin was lower in diabetic patients than in controls and individuals with high concentration of adiponectin were less likely to develop type 2 diabetes than those with low concentration supporting the fact that adiponectin might protect against diabetes. The observed proportionate decrease in adiponectin levels to the severity of retinopathy in our study is similar to that observed by Mahmut *et al.*, 2005, where they suggested that a critical adiponectin level is needed for the development of retinopathy. Also our results was in agreement with study done by Yilmaz *et al.*, 2004, as they reported a similar proportionate decrease in adiponectin with the severity of DR.

Diabetes reduces angiogenic potential in the retinal microvasculature and this is an important finding since it suggests that apart from inactive proliferative retinopathy, the angiogenic potential of retinal micro vascular endothelial cells is significantly compromised by the diabetic state (Tamarat *et al.*, 2003). Inhibition of angiogenesis could be involved in the anti-atherogenic effect of adiponectin. In type 2 diabetes, the decreased levels of adiponectin may contribute to several severe complications (Brakenhielm *et al.*, 2004).

The present study showed that adiponectin showed non-significant correlation with age, duration of diabetes, BMI and serum insulin in different patients subgroups except BMI in subgroup II and serum insulin in subgroup I and this result was challenged with Yamamoto *et al.*, 2002 and Diez and Iglesias, 2003, they demonstrated negative correlation between adiponectin and BMI and insulin. Our results was in agreement with study done by Yilmaz *et al.*, 2004, as they reported no significant correlation between adiponectin and BMI. Our study failed to determine a correlation between adiponectin and BMI may be because of the selection of patients with near normal BMI

In-subgroup I (patients without DR), serum adiponectin was negatively correlated with serum insulin, In-subgroup II (patients with background DR), there was significant negative correlation between adiponectin and BMI which is in agreement with other studies as Yamamoto *et al.*, 2002; Matsubara *et al.*, 2002 and Diez and Iglesias, 2003.

CONCLUSION

This study shows that serum adiponectin concentration are lower in diabetic patients compared to control group and are lower in diabetic patients with DR than those without DR suggest that serum adiponectin may play role in the pathogenesis of DR. Three therapeutic strategies may be recommended, first regulation of adiponectin levels which have several therapeutic advantages over antidiabetic drugs used. The second may be regulation of adiponectin receptors or to stimulate adiponectin receptor using small molecule agonists. The third is the use of adiponectin as anti-atherogenic agent. So the use of adiponectin in treatment of diabetes may be a new era for glycemic control and reduction of diabetic complications. New studies of adiponectin on type 2 diabetes with other complications may express its role in pathogenesis and as a therapy is recommended.

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