Adiponectin may be used as a marker in prediction of diabetic retinopathy patients

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Objective To investigate the validity of serum adiponectin to differentiate diabetic retinopathy and to evaluate the relation between the tumor necrosis factor-alpha (TNFα) and adiponectin in this disease.

Methods A total of 120 persons were included in the study, 80 diabetic patients, which divided into two groups, 40 patients were with diabetic retinopathy and 40 patients without diabetic retinopathy and 40 healthy control subjects.

Results There was no significant difference in the age, BMI and gender between the studied groups. Serum levels of TNFα pg/ml was significantly higher in diabetic patients with retinopathy compared to without retinopathy and both groups were significantly higher compared to control, adiponectin ng/ml was significantly lower in diabetic patients with retinopathy compared to without retinopathy and both groups were significantly lower compared to control. In the control group, adiponectin inversely and significantly correlated with age, waist circumference, triglyceride, cholesterol and LDL. Both adiponectin and TNFα have excellent ability to discriminate between diabetic patients from normal to control. But only adiponectin found to have the ability to discriminate diabetic retinopathy from diabetic without retinopathy.

Conclusion We found decrease serum level of adiponectin in diabetic retinopathy patients and increase level of TNFα in this patients in compared with diabetic only and control subjects.

Keywords adiponectin, diabetic retinopathy, TNFα

Introduction

Diabetic retinopathy is the major cause that leads to disability and blindness in working age diabetic patients throughout the world.[1] This disease has affected about 93 million subjects around the world.[2] There are many risk factors that participate in the developing diabetic retinopathy, such as duration of the diabetic, prolonged elevated glucose level and dyslipidemia. Inflammation which defines as the nonspecific response of the body to the injury or damage and this response consist of many mediators and cytokines in addition to enhancement and activation of leukocytes. Many of the mediators and functional changes such as some of the cytokines and vessels damage that important characteristic of the inflammation process have been found in the retina of animals and human that are suffering from diabetic retinopathy.[3] The subclinical low degree of the inflammation for prolonged duration have a prominent role in the developing of microangiopathy in diabetic patients.[4] There are many studies that reports the role of the cytokines and other inflammatory mediator in the pathogenesis of diabetic retinopathy this low degree of inflammation and influx of leukocytes leading to destruction of retinal vessels and new vessels will formed. The causative correlation between angiogenesis and inflammation is largely agreeable.[5] In the vitreous fluid of the diabetic persons, there was increased amount of the tumor necrosis factor alpha (TNFα) found.[6] Many researches have been showed that there are prominent association between serum TNFα and the severity of retinopathy.[7] In the proliferative diabetic retinopathy, there have been shown the TNFα express in the endothelial cell and stromal cell, this enhanced the correlation between low degree of inflammation and diabetic retinopathy.[8] There are many studies that

found the expression of TNFα highly enhanced in retina of diabetic rats, and the closed of the TNFα lead to decrease leukocyte adhesion and reduce the damage of retinal blood barrier.[9] The endothelial destruction is highly induced by increased serum level of TNFα in patients with diabetic retinopathy.[10] Adiponectin is a good example for the prominent anti-inflammatory endogenous protein that secreted from adipocyte cell in the adipose tissue, which is consist of 244 amino acids and its structures resemble to the collagen, complement system and TNFα.[11,12] Adiponectin regarded as a key compound in the relation between adiposity, insulin resistance and inflammation process.[13] The adiponectin is the main adipocytokine that found to decrease the obesity, insulin resistance, diabetic macrovascular complication and coronary artery conditions.[14] By the improving insulin sensitivity and glucose level, the adiponectin decrease the developing and progression of microvascular complication in the diabetic patients. However, there are reverse relation between adiponectin and microvascular complications.[15] There was many research reported the beneficial effect of adiponectin on the retina this mediated through the suppression of the TNFα action on the retina and decrease the inflammatory response in retina.[16]

Materials and Methods

The study was conducted on 80 type 2 diabetes mellitus (T2DM) patients, which had been selected from those attending the specialized Imam AL-hussein center for endocrinology and diabetes from November 2016 to April 2017, the control group consist of 40 healthy persons.

The diabetic patients were selected by specialized physician and diagnosed as diabetics according to the American Diabetes Association criteria [FSG ≥ 126 mg/dL (7.0 mmol/L)],[17] all participants underwent fundus eye examination carried out at advisory eye clinic in Imam AL Hussein medical city by ophthalmologist specialist, according to this eye examination the diabetic patients were divided into two groups: group one: T2DM patients with diabetic retinopathy 40 patients and group two: T2DM patients without diabetic retinopathy 40 patients. The duration of DM was noted for all the patients who were included in the study, fasting serum glucose, HbA1c, triglycerides, total cholesterol, HDL cholesterol and LDL cholesterol also measured.

Serum was collected from all the patients included in the study and store at −70°C until adiponectin and TNFα measurement were performed, adiponectin levels were measured using Cloud-clone corp human adiponectin ELISA kit, and TNFα level were measured using the Elabscience human ELISA kit.

Results

There was no significant difference in the age, BMI and gender between the studied groups. The rest of the variables are illustrated in Table 1. Serum levels of TNFα pg/ml was significantly higher in diabetic patients with retinopathy compared to without retinopathy and both groups were significant higher compared to control, adiponectin ng/ml was significantly lower in diabetic patients with retinopathy compared to without retinopathy and both groups were significantly lower compared to control as illustrated in Table 1.

In the control group, adiponectin inversely and significantly correlated with age, waist circumference, triglyceride, cholesterol and LDL. This significant relationship between adiponectin and the above-mentioned variables become non-significant in diabetic with or without retinopathy groups; however, in diabetic group with retinopathy there was direct significant relationship between duration of DM and adiponectin as illustrated in Table 2.

Table 1. **Demographic data, laboratory and disease characteristics of subject in the study**

	Control	DM only	Diabetic retinopathy	P value
Number	40	40	40	–
Age (years)	51.8 ± 4.7	52.5 ± 5.4	54.9 ± 8.7	0.079
BMI (kg/m²)	29.4 ± 1.5	29.7 ± 3.0	30.2 ± 3.8	0.517
Waist (cm)[a]	92.4 ± 8.3	104.2 ± 7.4	104.1 ± 7.9	<0.001[a]
DM duration	–	5.2 ± 3.7	12.1 ± 4.5	<0.001[a]
HbA1c	5.3 ± 0.5	9.0 ± 1.9	9.5 ± 1.7	<0.001[a]
FBS	99.2 ± 9.2	229.4 ± 90.6	227.3 ± 77.7	<0.001[a]
Triglyceride	107.9 ± 45.1	222.7 ± 133.4	218.9 ± 132.2	<0.001[a]
Cholesterol	176.4 ± 33.0	188.2 ± 44.5	212.0 ± 52.9	0.002[b]
LDL	100.7 ± 21.1	125.3 ± 27.8	149.8 ± 35.6	<0.001[b]
HDL	45.2 ± 10.8	40.0 ± 9.7	38.3 ± 8.9	0.006[a]
Gender, number (%)				0.149
Female	14 (35.0%)	22 (55.0%)	21 (52.5%)	
Male	26 (65.0%)	18 (45.0%)	19 (47.5%)	
TNFα pg/ml	16.0 (6.5–24.3)	70.6 (55.6–110.3)	107.1 (58.8-186.6)	<0.001[c]
Adiponectin ng/ml	16.66 (16.13–17.20)	14.58 (14.11–14.95)	13.50 (11.61–14.50)	<0.001[c]

Data presented as mean ± SD; [a]Between DM with or without retinopathy P > 0.05; [b]Between DM with or without retinopathy P < 0.05; [c]Data are presented as median (50%) and interquartile range (25–75%).

Table 2. **Pearson correlation between adiponectin and various variables in each study group**

Variables	Control		DM only		Diabetic retinopathy	
	β	P value	β	P value	β	P value
Age	−0.457	0.003 [S.]	−0.120	0.459	0.036	0.823
Duration of DM	–	–	−0.182	0.262	0.318	0.045 [S.]
BMI	−0.051	0.754	−0.188	0.245	0.003	0.983
Waist	−0.414	0.008 [S.]	−0.077	0.638	−0.101	0.536
HbA1c	−0.095	0.561	−0.203	0.208	−0.172	0.289
FBS	−0.057	0.727	−0.125	0.441	−0.175	0.281
Triglyceride	−0.372	0.018 [S.]	0.102	0.532	−0.032	0.844
Cholesterol	−0.382	0.015 [S.]	−0.127	0.436	−0.118	0.469
LDL	−0.414	0.008 [S.]	−0.093	0.570	0.005	0.976
HDL	0.159	0.327	−0.277	0.084	−0.052	0.752
TNFα	−0.135	0.405	−0.213	0.188	−0.118	0.470

β, Correlation coefficient; Linear regression analysis.

Table 3. ROC analysis of investigated marker to discriminate between control and DM

	AUC	P value	Cut point	Sensitivity	Specificity	PPV	NPV
Adiponectin	0.992	<0.001	≤15.17	96.3%	97.5%	98.7%	95.9%
TNFα	0.943	<0.001	>40.33	90%	92.5%	96%	82.2%

ROC analysis performed.

Table 4. ROC analysis of investigated marker to discriminate between diabetic retinopathy and DM

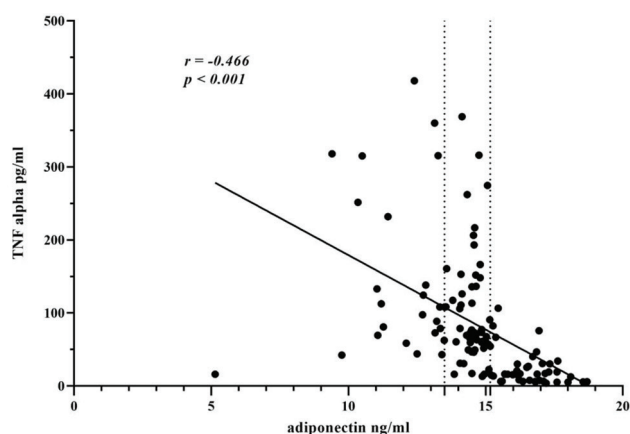|	AUC	P value	Cut point	Sensitivity	Specificity	PPV	NPV
Adiponectin	0.780	<0.001	≤13.5	52.5%	90.0%	84.0%	65.5%
TNFα	0.620	0.062	>78.92	62.5%	65.0%	64.1%	63.4%

ROC analysis performed.

Fig. 1 **The relationship between TNFα and adiponectin in all the patients.**

Both adiponectin and TNFα have excellent ability to discriminate between diabetic patients from normal control as illustrated in Table 3 and Fig. 2, but only adiponectin found to have ability to discriminate diabetic retinopathy from diabetic without retinopathy (fair ability) as illustrated in Table 4 and Fig. 1. Only adiponectin was correlated significantly (inversely) with diabetic retinopathy as illustrated in Fig. 3.

Discussion

Diabetic retinopathy is the major microvascular complication that affect most of the diabetic patients. It is the microangiopathy of the retina. Adiponectin is regard as "a key adipokines in T2DM and DR."[18] It is a noval protein that secreted from adipose tissue and have important role as an anti-inflammatory and anti-diabetic agent, when its serum level decrease this will lead to increase insulin resistance, T2DM, obesity and other metabolic disturbance will appear. There are many studies that report the anti-inflammatory properties of the adiponectin.[19,20] The result of the previous studies that take the relation between adiponectin and diabetic retinopathy are controversial. In this study, found that the serum adiponectin level were low in diabetic retinopathy patients compared to diabetic only and control subjects (P < 0.001). This result agrees with the Yilmaz et al.,[21] and Yuan Zhang et al.,[22] and Tasci et al.[23] The hypoadiponectinemia was very closely association with DR, due to the anti-inflammatory properties of the adiponectin, it will prevent the retinal vessels damage that cause by inflammation process that occur along time in diabetic patients. There are
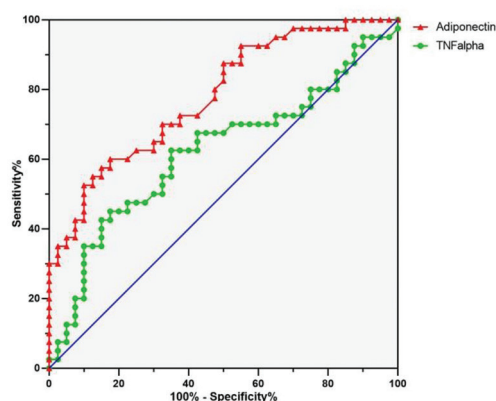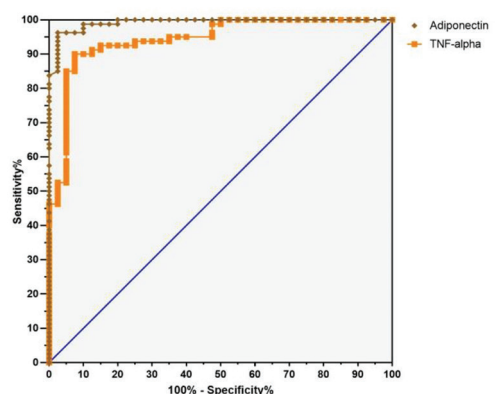

Fig. 2 **ROC curve of adiponectin and TNFα as predictor of diabetic compared to control (left) and as predictor of diabetic retinopathy compared to non-retinopathy (right).**

a negative correlation between adiponectin and DR as found in the recent meta-analysis study by Fan et al.[24] In this study, we found there was a significant negative correlation between adiponectin and waist circumference, triglyceride, total cholesterol and LDL.

It is obviously known that the inflammation play a major role in the pathogenesis of DR, the proinflammatory cytokine TNFα which found in higher amount in the diabetic retinopathy and diabetic patients in comparison to control subjects as in result of the present study. The TNFα have a prominent role in pathogenesis of T2DM by its effect on the insulin sensitivity, it will lead to disturbance in glucose metabolism. There is a large evidence of body that report the involvement of the TNFα in the pathogenesis of retinopathy, and it's found in the
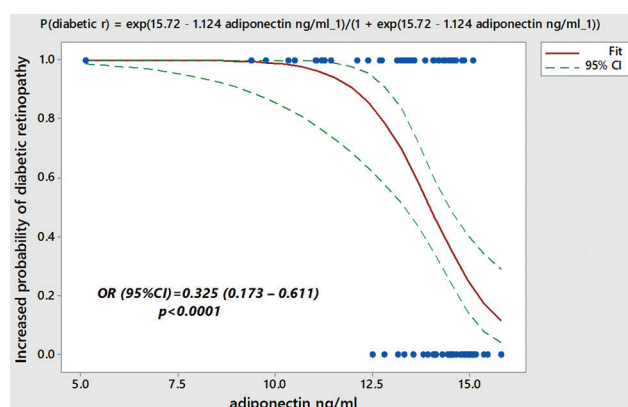
Fig. 3 **Increased probability of having diabetic retinopathy as we have lower adiponectin.**

endothelial and vessel wall of vascular tissue of PDR, also the TNFα found in high concentration in the vitreous fluid of diabetic eyes. In the present study, we found there was a significant negative correlation between TNFα and adiponectin and these results are agree with previous study. According to the result of conditional logistic regression analysis, adiponectin is likely to be one of the major contributors to the pathogenesis of both type 2 diabetic and diabetic retinopathy. However, the ROC curve analysis reveal a threshold concentration of adiponectin for existence of diabetic retinopathy and thus can used to discriminate the presence of diabetic retinopathy from all diabetic patients .

Conflict of Interest

None. ■

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