Original paper

Serum Tnfα Levels Are Inversely Associated With Insulin Sensitivity in Diabetic Retinopathy Patients

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Abstract

Background: Diabetic retinopathy is the most important microvascular complication of diabetes mellitus and the inflammation have potent role in the pathogenesis and development of the disease .Tumor necrosis factor alpha is a prominent proinflammatory cytokine that mediated in all inflammatory process so it has unwanted role in diabetic complication, retina inflammation and endothelia disturbance. So the prediction of the TNFα role in the retinopathy will help to find the major treatment approach.

Objective: this study conducted to evaluate the effect of TNFα in diabetic retinopathy and to find the association between TNFα and insulin sensitivity.

Material & method: this study involved 120 persons were 40 healthy control subjects and 80 diabetic patients which divided into 40 type2 diabetic patients with retinopathy and 40 type2 diabetic patients without retinopathy .The serum level of TNFα ,insulin and lipid profile was measured for all patients and controls and used the SPSS program for the statistic calculation.

Results: The serum level of TNFα was significantly higher in diabetic retinopathy patients in comparison to diabetic only patients and control subjects. Also there was negative correlation between TNFα and insulin sensitivity, the lipid profile was significantly higher in diabetic patient compared to control subject and the LDL cholesterol was significantly high in diabetic retinopathy patients in comparison to diabetic only and control subjects.

Discussion: The inflammation play prominent role in the development of diabetic complication. TNFα is the most important inflammatory marker that present in the serum of diabetic patients. The TNFα affect mainly on the glucose and lipid metabolism and it worsen the insulin resistance and it correlate inversely with insulin sensitivity and due to this effect it will lead to develop of diabetic complication.

Conclusion: The serum TNFα level was elevated in type2 diabetic patients and it may have role in developed the complication of diabetes and it was inversely correlated with insulin sensitivity.

Keyword: TNFα, insulin sensitivity, diabetic retinopathy

Introduction

Diabetes mellitus is the most important metabolic syndrome that affect most peoples around the world and its characteristic by increased glucose level in the blood and decreased insulin amount or impaired insulin action (insulin resistance)[1].Also is characterized by state of increased inflammation that lead to many diabetic complication and this complication will affect the small and large blood vessels and nearly all diabetic patients will suffer from such complication during their life .This diabetic complication can be divided into acute complication such

as ketoacidosis and chronic complication such as nephropathy ,neuropathy and retinopathy.[2]

Diabetic retinopathy is the most potent diabetic complication that affect the eyes and lead to irreversible blindness [2].It characterized by dysfunction of the retina microvasculature and increased the adhesion molecules and the breakdown of the retina blood barrier. Inflammation is the most important factor in pathogenesis of the diabetic retinopathy[3] .Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes[3,4]. Many of the molecular and functional changes that are characteristic of inflammation have been detected in retinas from diabetic animals or humans, and in retinal cells under diabetic conditions[3].TNFα is an adipocytokine that participate in the inflammatory process and it involved in the acute phase of reaction and it is regarded the most important proinflammatory cytokine that present in retina of diabetic patient and have major role in the retinal vasculature damage and neovasculature formation[5,6,7]. TNFα also prevent the insulin transduction and have major role on glucose metabolism and this fact also appear in relation between TNFα and insulin sensitivity which are badly associated, when the TNFα increased the insulin sensitivity decreased as shown in many evidences [7]. There are many studies that found the serum level of proinflammatory cytokines and TNFα are present in higher concentration in diabetic retinopathy patients and its regard the major cause of the disease [8]. Also it has undesired effect on lipid homeostasis through its effect on free fatty acid uptake or stimulate the lipolysis process as well as increase the lipogenesis process in liver. There are many treatment approach that apply the anti-TNFα therapy to treat the patients with diabetic retinopathy [8,9] .

Material and method

The study was conducted on 80 type 2 diabetes patients (T2DM), who have 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≥ 126mg/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 group.

A- Group One: type 2 diabetic patients (T2DM) with diabetic retinopathy 40 patients.

B- Group two: type 2 diabetic patient s (T2DM) without diabetic retinopathy 40 patients.

We considerd the presence or absence of retinopathy ,the retinopathy was not graded.the duration of DM was noted for all 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 patients include in the study and store at -70c until TNF alpha and insulin measurement were performed. TNFα level were measured using Elabscience human TNFα ELISA kit.The insulin level was measured by using demeditic insulin Elisa kit based on sandwish principle and the insulin sensitivity was determined using the Quantitative Insulin Sensitivity Check Index (QUICKI).

Statistical analysis: the data was calculated by using the SPSS 20 version program, where the descriptive data expressed as mean standard deviation (SD).A p value was less than 0.05 consider statistically significant .The correlation measured by using Pearson correlatin coefficient.

Result

According to the result of this study there was no significant different between study groups in the age, BMI and sex as show in table 1.Also the serum TNFα level was significantly high in diabetic retinopathy patients in comparison to diabetic only and control subjects .And other variable are shown in the table2.

The lipid profile was significantly higher in diabetic retinopathy patients in comparison to diabetic only and controls as shown below.

There is a negative correlation between insulin sensitivity and TNFα as shown in table 3 and figure1.

Discussion

Diabetic retinopathy is the major microvascular complication of the diabetes and it's the microangiopathy of the retina that result from persistence inflammatory process that happen in all diabetes patients [10].

Table1. demographic characteristic and laboratory measurement of subjects in this 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/m^2)	29.4 ± 1.5	29.7 ± 3.0	30.2 ± 3.8	0.517
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%)	
TNF α pg/ml	16.0 (6.5-24.3)	70.6 (55.6-110.3)	107.1 (58.8-186.6)	<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 presented as median (50%) and interquartile range (25% to 75%)

**Table2.** Pearson correlation between TNF-alpha and various variables in each study group

	Control		DM only		Diabetic retinopathy	
	β	P value	β	P value	β	P value
Age	0.111	0.494	-0.176	0.278	-0.049	0.766
Duration of DM	-	-	-0.070	0.669	0.026	0.876
BMI	0.011	0.944	0.149	0.358	0.174	0.282
HbA1c	-0.034	0.836	0.215	0.183	0.229	0.156
FBS	0.165	0.310	0.268	0.095	0.043	0.794
Triglyceride	-0.011	0.948	0.147	0.364	0.371	0.019 [S.]
Cholesterol	-0.043	0.794	0.043	0.791	0.335	0.035 [S.]
LDL	0.212	0.189	-0.045	0.781	0.290	0.070
HDL	0.010	0.950	-0.031	0.851	-0.033	0.839
Insulin	-0.282	0.078	-0.121	0.457	-0.017	0.918

β = Correlation coefficient
Linear regression

Table3. Pearson correlation between insulin sensitivity and various variables in each study group

	Control		DM only		Diabetic retinopathy	
	β	P value	B	P value	β	P value
Age	-0.063	0.699	-0.084	0.607	0.192	0.235
Duration of DM	-	-	-0.231	0.151	0.250	0.119
BMI	-0.048	0.768	-0.037	0.819	-0.162	0.317
HbA1c	0.016	0.924	-0.372	0.018 [S.]	-0.443	0.004 [S.]
FBS	-0.354	0.025 [S.]	-0.476	0.002 [S.]	-0.534	0.000 [S.]
Triglyceride	-0.182	0.261	-0.215	0.183	-0.086	0.599
Cholesterol	0.109	0.504	-0.133	0.413	-0.087	0.594
LDL	0.177	0.274	-0.273	0.088	-0.192	0.235
HDL	0.256	0.110	0.087	0.592	0.037	0.820
Insulin	-0.698	0.000 [S.]	-0.485	0.002 [S.]	-0.614	0.000 [S.]
β = Correlation coefficient Linear regression analysis						
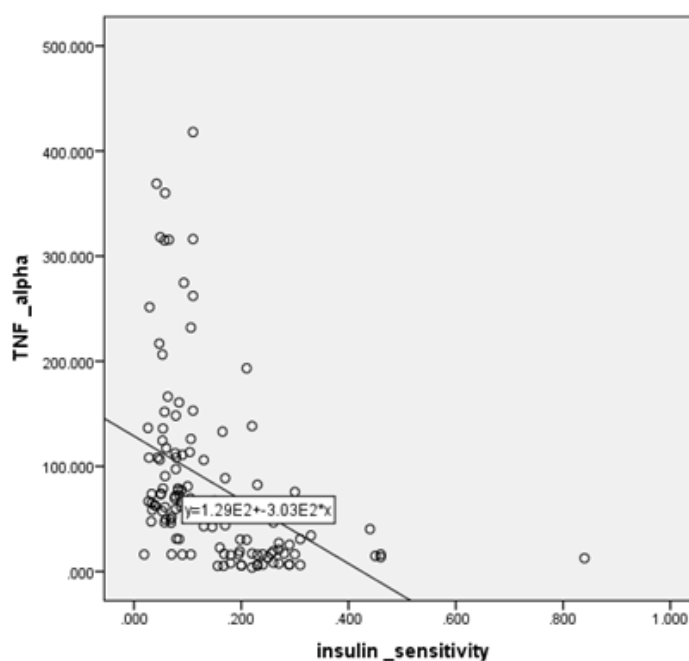
Figure1. Correlation between TNFα and insulin sensitivity in total patients where r=-.413 and p value 0.001

TNFα is the proinflammatory cytokine that have prominent role in the diabetic complications especially the pathogenesis of retinopathy through its effect on the glucose and lipid metabolism as well as its role in the inflammation [11,12]. In the current study we found that there was considerable increase in the serum TNFα level in diabetic retinopathy patients in comparison to the diabetics without retinopathy and control subject .The high level of the TNFα in the diabetic patient for prolong time may indicate there was a low grade of inflammation in this patients and this inflammatory process will lead to all diabetic complication that may appear in this patients through the next time of the life [13,14]. This result of the present study is agree with many other evidence that found the serum TNFα increased in diabetic patients[10,12].The insulin resistance which is the state of improper response of the body to insulin in which TNFα have a potent role through its effect on insulin receptor[17,16], the current study found that there is inverse correlation between insulin sensitivity and

TNFα.Also there was significant increase in the triglycerides and LDL in diabetic retinopathy patients and this may be attributed to the high level of the TNFα that found in this patients [18]. The high lipid content in the blood and decrease insulin sensitivity which lead to hyperglycemia and increase the inflammatory state which represent by high level of TNFα all this condition create a suitable environment for the developed the diabetic complication[19,20]. And all these factors may regarded as a risk factors for diabetic retinopathy [16].

The limitation of our study was the small sample size that included in the study and short duration of time .In conclusion the TNFα through its effect on lipid profile, insulin sensitivity and inflammatory process it may be regard as risk factor for retinopathy and we recommend more future studies to confirm this result.

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