Correlation of serum angiogenin level with various vascular complications in type 2 diabetic patients

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Introduction

Premature development of microvascular and macrovascular disease is the most frequent complication of diabetes. It is responsible for diabetic retinopathy, nephropathy, and neuropathy. Moreover, diabetes leads to reduced collateralization in ischemic tissues, which causes a three- to four-fold increase in cardiac mortality in diabetic individuals compared with nondiabetic individuals.

The pathophysiological mechanisms responsible for impaired angiogenic activity in diabetes remain unknown. The role of angiogenin in the physiological revascularization process has not been clarified.

Purpose

This work was carried out to determine the serum angiogenin level in type 2 diabetic patients and to determine its correlation with various microangiopathies, cardiovascular complications, and the duration in type 2 diabetic patients.

Patients and methods

This work was carried out on 88 individuals, 68 type 2 diabetic patients and 20 apparently healthy controls. All individuals were subjected to the following assessments: medical history taking; clinical examination including measurement of BMI; estimation of levels of fasting blood sugar, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, urea, low-density lipoprotein, and creatinine; determination of the albumin/creatinine ratio and complete lipid profile (total cholesterol, triglyceride, high-density lipoproteins); serum angiogenin estimation by enzyme linked immunosorbent assay; fundus examination; ECG and transthoracic echocardiography; and abdominal ultrasonography.

Results

Our results indicated a significant decrease in the serum angiogenin level in diabetic patients compared with the control group; an insignificantly low serum angiogenin level in diabetic patients with retinopathy and nephropathy compared with those without retinopathy and nephropathy, respectively; a significant decrease in the serum angiogenin level in patients with coronary artery disease (CAD) compared with diabetic patients without CAD; an insignificant inverse correlation of angiogenin with fasting blood sugar, duration of diabetes mellitus with urea, and creatinine with albumin/creatinine ratio; and an insignificant proportional correlation of angiogenin with ejection fraction in diabetic patients with complications of retinopathy, nephropathy, and CAD in each group separately.

Conclusion

This work concluded that the serum angiogenin level is lower in type 2 diabetic patients compared with the control group and it decreases with prolonged duration of diabetes, especially in uncontrolled patients and patients with microangiopathic and cardiovascular complications.

As angiogenin is one of most powerful angiogenic factors, we recommend further studies to evaluate the diagnostic, prognostic, and therapeutic value of angiogenin in various microangiopathic and cardiovascular complications of type 2 diabetes.

Keywords:

angiogenin, coronary artery disease, microangiopathy, type 2 diabetes mellitus

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Introduction

Type 2 diabetes is one of the greatest pandemics of our time, with 220 million individuals currently diagnosed and 366 million individuals expected to be affected by 2030 [1]. Diabetes mellitus (DM) is associated with angiopathy, which increases the risk of most complications [2]. Diabetes leads to reduced collateralization in ischemic tissues, which causes impaired wound healing and exacerbation of peripheral limb ischemia. Both coronary vessel formation and capillary density are poorer in diabetics than in healthy individuals [3].

Angiogenesis is a complex process regulated by stimulatory and inhibitory factors. It is well established in research that the expressions of different angiogenic growth factors are reduced in DM, whereas suppressive factors such as angiostatin and endostatin are high in diabetic patients, especially those with coronary artery disease (CAD) [4].

The pathophysiological mechanisms responsible for impaired angiogenic activity in diabetes remain unknown [2]. The risk of developing microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia [5]. Numerous authors have suggested that a high concentration of glucose causes endothelial cell dysfunction [6]. Production of inhibitors of angiogenesis is an important mechanism for the impairment of collateral development observed during hyperglycemia [3]. The results published in the last decade have shown that endothelial cells located in the eye apparatus of a healthy individual are not active mitotically and that vascular growth factors remain in equilibrium with antiangiogenic factors. However, under some conditions such as ischemia or inflammation, the equilibrium may be shifted in a proangiogenic direction, resulting in angiogenesis. This is a complex multistage process stimulated or inhibited by a vast number of mitogenic and chemotactic factors working together, thus increasing the number of divisions of endothelial cells and attracting migrating endothelium into the zones of ischemia. A vast number of cytokines, chemokines, and growth factors are classified as factors promoting angiogenesis. Angiogenin is a polypeptide with an amino acid sequence 33% identical to that of bovine pancreatic ribonuclease. It is a normal plasma component and a potent stimulator of angiogenesis. Its mRNA expression is detectable in epithelial cells, fibroblasts, and peripheral blood cells [7].

Angiogenin is an important and still poorly investigated angiogenic growth factor that has a great influence on the process of creation of new vessels [3].

This work aimed to measure the serum angiogenin level in type 2 diabetic patients and to determine its correlation with various microangiopathies, cardiovascular complications, and the duration in type 2 diabetic patients.

Patients and methods

The study was conducted on 88 individuals, 68 type 2 diabetic patients (diagnosed on the basis of fasting blood sugar > 126 mg/dl) and 20 apparently healthy controls who were recruited from the outpatient clinic and inpatient department of National Institute of Diabetes and Endocrinology and the Internal Medicine Department of Al-Zahraa University Hospital. They were divided into four groups: group A included 18 patients with recently diagnosed type 2 DM (11 women and seven men), mean age 47.7 ± 9.4 years and mean BMI 30.3 ± 3.3; group B included 25 patients with a duration of type 2 DM up to 10 years (18 women and seven men), mean age 52.4 ± 7.5 years and BMI 32.5 ± 3.1; group C included 25 patients with a duration of type 2 DM more than 10 years (14 women and 11 men), mean age 55.9 ± 5.2 years and BMI 33.8 ± 3.7; and the control group included 20 healthy individuals matched for sex and age (12 women and eight men), mean age 48.4 ± 7.5 years and BMI 28.2 ± 2.5. Consent was given by every participant recruited into this study.

Patients with a history of liver cirrhosis, malignancy infection, inflammation, bronchial asthma, heart failure, and those who were taking medications known to interfere with angiogenin action, such as neomycin, were excluded from the study.

All individuals were subjected to the following assessments: medical history taking; clinical examination including measurement of BMI [the weight (kg) divided by the square of height (m^2)]; laboratory investigations including estimation of complete blood count, erythrocyte sedimentation rate, and levels of fasting blood sugar (FBS), serum alanine aminotransferase, serum aspartate aminotransferase, serum alkaline phosphatase, total and direct serum bilirubin, urea, and creatinine; determination of the albumin/creatinine (A/C) ratio and lipid profile [including total cholesterol, triglyceride, high-density lipoproteins (HDL) and low-density lipoproteins (LDL)]; complete urine analysis with detection of microalbuminuria; serum angiogenin level estimation by enzyme linked immunosorbent assay; fundus examination; ECG and transthoracic echocardiography measuring left ventricular ejection fraction [LVEF = (end-diastolic volume – end-systolic volume)/end-diastolic volume]; and abdominal ultrasonography.

Fasting venous blood sample (10 ml) was withdrawn from every participant and divided into tubes; sera were separated and frozen until the time of assay at – 70°C. Serum angiogenin levels were measured in duplicate using the ELISA Quantikine kit (R&D System, Minneapolis, Minnesota, USA).

Statistical analysis

Results were expressed as mean ± SD or number (%). Comparisons were made between mean values of the two groups using an unpaired Student *t*-test. Comparisons between categorical data [*n*(%)] were made using the χ^2-test. The correlation between parameters was determined using the Spearman rank correlation coefficient. The SPSS computer program (version 14 windows; SPSS Inc., Chicago, Illinois, USA) was used for data analysis. A *P*-value less than 0.05 was considered significant and a *P*-value less than 0.01 was considered highly significant.

Results

The results of this work indicated that most of the diabetic patients had uncontrolled diabetes and were being treated with insulin and metformin, and only five patients were being treated with sulfonylureas and metformin.

Group A (recently diagnosed diabetic patients) included two patients with diabetic retinopathy (10%), one patient with diabetic nephropathy (5%), and four patients with ischemic heart disease (20%).

Group B (duration of DM up to 10 years) included three patients with diabetic retinopathy (12%), four patients with diabetic nephropathy (16%), and nine patients with ischemic heart disease (36%).

Group C (duration of DM >10 years) included 18 patients with diabetic retinopathy (72%), 13 patients with diabetic nephropathy (52%), and 14 patients with ischemic heart disease (56%).

Table 1 shows the following:

(1) Highly significant increase in FBS in group A compared with the control group.
(2) Highly significant decrease in the angiogenin level in group A compared with the control group.
(3) Significant increase in urea in group A compared with the control group.
(4) Insignificant increase in triglycerides, cholesterol, LDL, creatinine, and A/C ratio in group A compared with the control group.
(5) Insignificant decrease in ejection fraction (EF) and HDL in group A compared with the control group.

Table 2 shows the following:

(1) Highly significant increase in FBS, triglycerides, cholesterol, urea, and creatinine in group B compared with the control group.
(2) Highly significant decrease in HDL and angiogenin level in group B compared with the control group.
(3) Significant decrease in EF in group B compared with the control group.
(4) Insignificant increase in age, LDL, and A/C ratio in group B compared with the control group.

Table 3 shows the following:

(1) Highly significant increase in FBS, urea, creatinine, and A/C ratio in group C compared with the control group.
(2) Significant increase in cholesterol levels in group C compared with the control group.
(3) Insignificant increase in triglycerides and LDL in group C compared with the control group.
(4) Highly significant decrease in HDL, EF, and angiogenin level in group C compared with the control group.

Table 4 showed the following:

(1) Highly significant increase in the mean values of urea, creatinine, A/C ratio, and duration of diabetes in diabetic patients with retinopathy compared with diabetic patients without retinopathy.
(2) Insignificant increase in cholesterol and LDL in diabetic patients with retinopathy compared with diabetic patients without retinopathy.
(3) Insignificant decrease in the mean values of FBS, angiogenin, triglycerides, HDL, and EF in diabetic patients with retinopathy compared with diabetic patients without retinopathy.

Table 1 Comparison of the mean values of parameters between individuals of the control group and recently diagnosed diabetic patients (group A)

	Mean ± SD		
Parameters	Control group ($n=20$)	Group A ($n=18$)	*P*-value
Angiogenin	472.6 ± 45.6	331.3 ± 31.8	0.000
Triglycerides	111.5 ± 27	149.9 ± 62	>0.05
Cholesterol	179.6 ± 34.4	202.9 ± 34.6	>0.05
HDL	46.6 ± 5.83	40.33 ± 5.41	0.002
LDL	114.3 ± 24	125.2 ± 23.5	>0.05
Urea	15.7 ± 3.3	22.8 ± 11.5	0.044
Creatinine	0.68 ± 0.2	0.81 ± 0.26	>0.05
A/C ratio	13.7 ± 5.1	34.1 ± 79.5	>0.05
EF fraction (%)	72 ± 2.7	70.8 ± 7.5	>0.05
FBS	81.2 ± 8.5	209.4 ± 56.3	0.000

A/C, albumin/creatinine; EF, ejection fraction; FBS, fasting blood sugar; HDL, high-density lipoproteins; LDL, low-density lipoproteins.
Highly significant: $P<0.01$.
Significant: $P<0.05$.
Nonsignificant: $P>0.05$.

Table 2 Comparisons of the mean values of parameters between individuals of the control group and diabetic patients with durations up to 10 years (group B)

	Mean ± SD		
Parameters	Control group ($n=20$)	Group B ($n=25$)	*P*-value
Angiogenin	472.6 ± 45.6	287.6 ± 35.1	0.000
Triglycerides	111.5 ± 27	261.2 ± 280	0.002
Cholesterol	179.6 ± 34.4	217.6 ± 48.8	0.003
HDL	46.6 ± 5.83	40.64 ± 6.33	0.002
LDL	114.3 ± 24	126.6 ± 28.6	>0.05
Urea	15.7 ± 3.3	25.2 ± 7.4	0.004
Creatinine	0.68 ± 0.2	0.89 ± 0.2	0.005
A/C ratio	13.7 ± 5.1	31.6 ± 39.6	>0.05
EF fraction (%)	72 ± 2.7	67.2 ± 7.6	0.020
FBS	81.2 ± 8.5	284 ± 70.1	0.000

A/C, albumin/creatinine; EF, ejection fraction; FBS, fasting blood sugar; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Table 3 Comparisons of the mean values of parameters between individuals of the control group and diabetic patients with durations greater than 10 years (group C)

	Mean ± SD		
Parameters	Control group ($n=20$)	Group C ($n=25$)	*P*-value
Angiogenin	472.6 ± 45.6	286.4 ± 42.2	0.000
Triglycerides	111.5 ± 27	195.7 ± 79.3	>0.05
Cholesterol	179.6 ± 34.4	210.7 ± 42.3	0.014
HDL	46.6 ± 5.83	40.04 ± 6.56	0.001
LDL	114.3 ± 24	132.8 ± 42.2	>0.05
Urea	15.7 ± 3.3	38.6 ± 15.7	0.000
Creatinine	0.68 ± 0.2	1.18 ± 0.31	0.000
A/C ratio	13.7 ± 5.1	98.7 ± 114.9	0.000
EF fraction (%)	72 ± 2.7	66.2 ± 7.4013	0.005
FBS	81.2 ± 8.5	252.1 ± 50.17	0.000

A/C, albumin/creatinine; EF, ejection fraction; FBS, fasting blood sugar; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Table 4 Comparison of the mean values of various parameters in diabetic patients with and without retinopathy

	No retinopathy ($n=45$)		Retinopathy ($n=23$)			
Parameters	Mean	SD	Mean	SD	*t*-test	*P*-value
Angiogenin	302.2	38.5	292.0	47.0	0.900	0.374
Triglycerides	213.4	219.6	196.3	69.4	0.479	0.634
Cholesterol	204.3	43.6	224.5	38.6	−1.952	0.057
HDL	41.1	5.8	38.9	6.6	1.328	0.192
LDL	123.0	30.0	139.3	36.3	−1.855	0.071
Urea	25.7	11.9	36.9	14.7	−3.166	0.003
Creatinine	0.9	0.3	1.2	0.3	−4.263	0.000
A/C ratio	29.0	56.2	111.6	114.5	−3.266	0.003
EF fraction (%)	68.2	8.4	67.1	5.8	0.627	0.533
Duration of diabetes	6.1	5.5	13.7	6.6	−4.788	0.000
FBS	252.9	74.2	251.9	46.9	0.068	0.946

A/C, albumin/creatinine; EF, ejection fraction; FBS, fasting blood sugar; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Table 5 showed the following:

(1) Highly significant increase in the mean values of urea, creatinine, A/C ratio, and duration of diabetes in diabetic patients with nephropathy compared with diabetic patients without nephropathy.
(2) Significant increase in the mean values of FBS in diabetic patients with nephropathy compared with diabetic patients without nephropathy.
(3) Insignificant increase in triglycerides, cholesterol, and LDL in diabetic patients with nephropathy compared with diabetic patients without nephropathy.
(4) Insignificant decrease in the mean levels of angiogenin, HDL, and EF in diabetic patients with nephropathy compared with diabetic patients without nephropathy.

Table 6 showed the following:

(1) Highly significant increase in the mean value of creatinine in diabetic patients with CAD compared with diabetic patients without CAD.
(2) Insignificant increase in the mean values of FBS, triglycerides, cholesterol, LDL, urea, A/C ratio, and duration of diabetes in diabetic patients with CAD compared with diabetic patients without CAD.
(3) Highly significant decrease in the mean value of EF in diabetic patients with CAD compared with diabetic patients without CAD.
(4) Significant decrease in the angiogenin serum level in diabetic patients with wall motion abnormality compared with those without wall motion abnormality.
(5) Insignificant decrease in the mean values of HDL and alanine aminotransferase in diabetic patients with CAD compared with diabetic patients without CAD.

There was a significant decrease in the serum angiogenin level in diabetic patients compared with the control group. There was an insignificant inverse correlation of angiogenin with the duration of DM (Fig. 1).

There was a low serum angiogenin level in diabetic patients with retinopathy compared with diabetic patients without retinopathy, but it was insignificant (Fig. 2), and also in diabetic patients with nephropathy compared with diabetic patients without nephropathy (Fig. 3).

Table 5 Comparison of the mean values of various parameters in diabetic patients with and without nephropathy

	A/C<30 ($n=50$)		A/C>30 ($n=18$)			
Parameters	Mean	SD	Mean	SD	*t*-test	*P*-value
Angiogenin	301.7	40.5	290.3	44.3	0.958	0.346
Triglycerides	203.0	207	220.6	86.3	−0.494	0.623
Cholesterol	208.8	42.1	217.7	45.3	−0.732	0.470
HDL	40.7	5.7	39.2	7.2	0.807	0.427
LDL	124.1	29.0	140.8	40.4	−1.617	0.119
Urea	24.9	10.0	42.2	15.3	−4.463	0.000
Creatinine	0.9	0.2	1.3	0.3	−6.070	0.000
A/C ratio	19.3	5.8	161.3	124.4	−4.839	0.000
EF fraction (%)	68.2	8.3	66.7	5.5	0.882	0.383
Duration of diabetes	6.5	5.8	14.6	6.2	−4.862	0.000
FBS	244.5	70.0	274.7	47.6	−2.017	0.050

A/C, albumin/creatinine; EF, ejection fraction; FBS, fasting blood sugar; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

Table 6 Comparison of the mean values of various parameters in diabetic patients with and without coronary artery disease

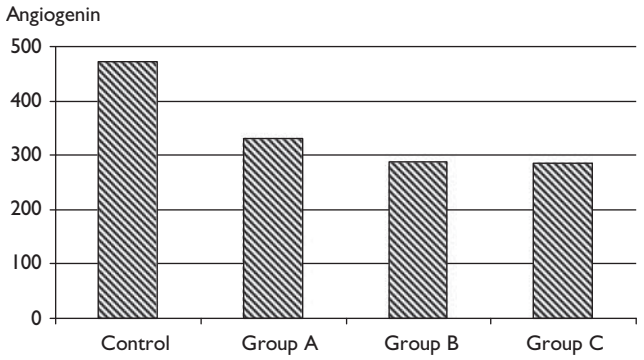
	No CAD ($n=41$)		CAD ($n=27$)			
Parameters	Mean	SD	Mean	SD	t-test	*P*-value
Angiogenin	308.4	38.6	284.0	42.2	2.416	0.019
Triglycerides	169.1	76.0	266.2	266.6	−1.845	0.075
Cholesterol	205.9	38.5	219.2	48.3	−1.204	0.234
HDL	41.1	5.6	39.1	6.7	1.305	0.198
LDL	126.1	29.5	132.1	37.8	−0.692	0.492
Urea	27.2	13.5	33.0	14.0	−1.700	0.095
Creatinine	0.9	0.2	1.1	0.3	−3.353	0.002
A/C ratio	38.1	62.2	85.5	114.4	−1.969	0.057
EF fraction (%)	70.9	5.2	63.2	8.4	4.247	0.000
Duration of diabetes	7.5	7.2	10.4	6.0	−1.810	0.075
FBS	244.2	77.3	265.1	41.3	−1.444	0.154

A/C, albumin/creatinine; CAD, coronary artery disease; EF, ejection fraction; FBS, fasting blood sugar; HDL, high-density lipoproteins; LDL, low-density lipoproteins.

There was a significant decrease in the serum angiogenin level in patients with CAD compared with diabetic patients without CAD (Fig. 4).

There was an insignificant inverse correlation of angiogenin with FBS (Fig. 5) and creatinine (Fig. 6) in diabetic patients with complications of retinopathy, nephropathy, and CAD.

Figure 1



Mean levels of angiogenin in the groups of the study.

There was an insignificant proportional correlation of angiogenin with EF in patients with complications of retinopathy, nephropathy, and CAD.

Table 7 indicates an insignificant correlation between angiogenin and EF in groups A, B, and C.

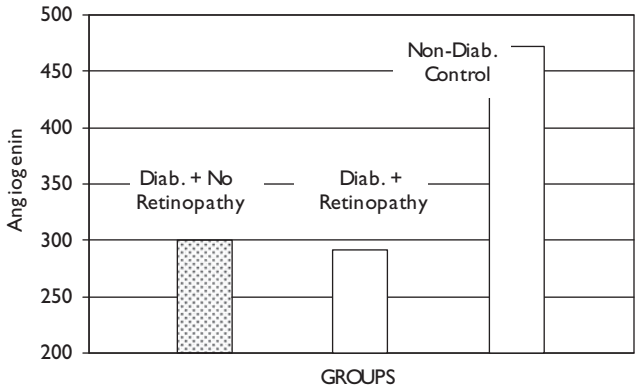
Table 8 indicates an insignificant decrease in the angiogenin level in diabetic patients with diastolic dysfunction compared with diabetic patients without diastolic dysfunction; however, both diabetic groups showed a highly significant decrease in the angiogenin level when compared with the control group.

Discussion

Angiogenin is a protein implicated in immunological and inflammatory angiogenesis. It is a normal constituent of blood, and its level usually remains unchanged. However, under some pathological conditions, such as peripheral vascular disease, inflammatory bowel disease, rheumatoid arthritis, obesity, proliferative diabetic retinopathy, and proliferative vitreopathy, it can intensify the induction of new blood vessel formation [2]. Angiogenin promotes the invasiveness of cultured endothelial cells by stimulation of cell-associated proteolytic activities [3]. It appears to respond as an acute-phase reactant and acts as an inhibitor of polymorphonuclear leukocyte degranulation; in this way, it avoids the conversion of plasminogen into angiostatin, which is a potent inhibitor of angiogenesis, by human neutrophil elastase [8]. Angiogenin binds to actin and this complex is more effective than actin alone in stimulating the production of plasmin, which plays an essential role in processes such as wound healing, inflammation, and even tumor cell metastasis [9], by t-PA. It also activates nitric oxide synthase by interacting with the cell nucleus [10].

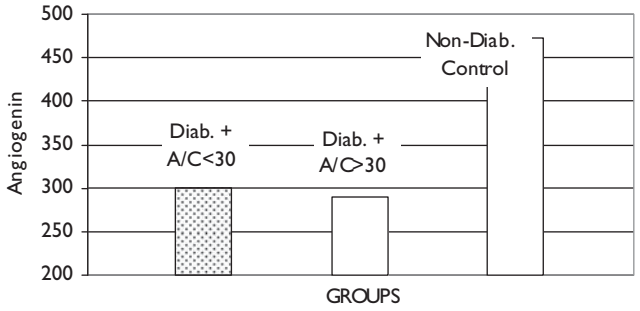
Patel *et al.* [11] hypothesized that plasma indices associated with angiogenesis (angiogenin, vascular endothelial growth factor, angiopoietin 1, and angiopoietin 2) would be abnormal in patients with left ventricular systolic dysfunction, being correlated with EF and wall motion abnormalities independent of underlying CAD.

Figure 2



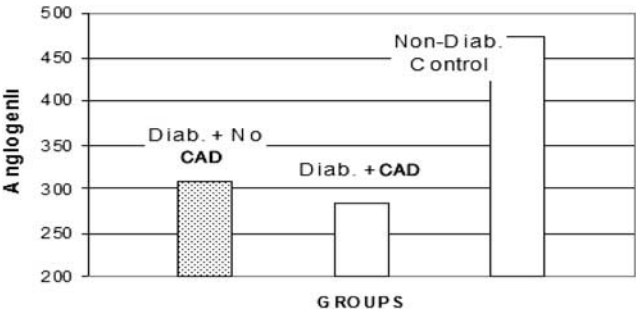
Mean levels of angiogenin in the control group and in diabetic patients with and without retinopathy.

Figure 3



Mean levels of angiogenin in the control group, in diabetic patients with an albumin/creatinine (A/C) ratio greater than 30, and in diabetic patients with an A/C ratio less than 30.

Figure 4

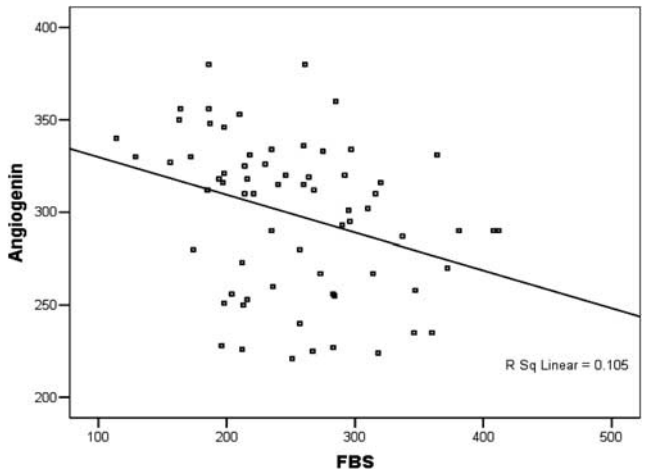


Mean levels of angiogenin in the control group and in diabetic patients with and without coronary artery disease.

Plasma angiogenin levels are significantly increased in acute coronary syndrome and may be involved in the pathogenesis of this condition. High angiogenin levels were predictive of adverse events during follow-up [12].

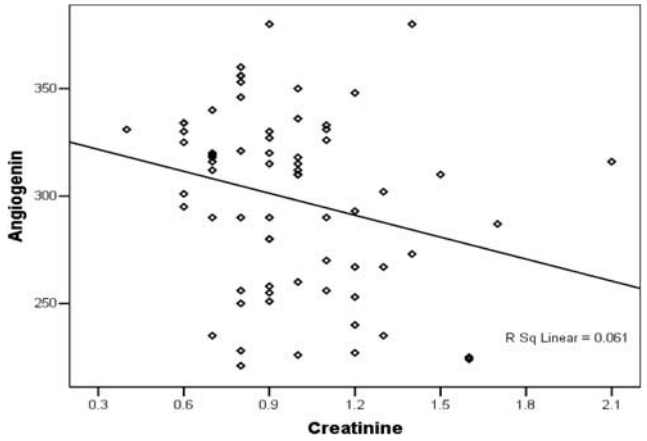
This study indicated that serum angiogenin levels showed an inverse correlation with FBS in all diabetic patients included in the study, irrespective of the duration of diabetes, and an inverse correlation in each complicated group separately, but this was insignificant.

Figure 5



Correlation of angiogenin and fasting blood sugar in diabetic patients ($N=68$; inverse). $r=-0.763$, $P<0.001$ (highly significant).

Figure 6



Correlation of angiogenin and creatinine in diabetic patients ($N=68$; inverse). $r=-0.248$, $P<0.05$ (significant).

Table 7 Pearson correlation of angiogenin with ejection fraction in the studied groups

Groups	Mean ± SD	*r*	*P*-value
A	70.8 ± 7.5	0.218	>0.05
B	67.2 ± 7.6	0.063	>0.05
C	66.2 ± 7.4013	−0.146	>0.05

This is in agreement with the findings of Weihrauch *et al.* [6], who reported that the production of inhibitors of angiogenesis is an important mechanism in the impairment of collateral development observed during hyperglycemia, and Stitt *et al.* [13], who found that sera of type 2 diabetic patients have strong antiangiogenic effects. The poorer the glycemic control of patients, the greater the inhibition of angiogenesis. The authors documented that advanced glycation end products and their receptors may be mediators in the inhibition of retinal angiogenesis. In addition, Siebert *et al.* [14] found that the angiogenin level is markedly decreased in patients with A1C greater than 7% in comparison with well-controlled patients and their healthy counterparts. Furthermore, poorly controlled patients had a higher proportion of hypertension and ischemic heart disease and greater BMI. Several authors have suggested that a high concentration of glucose causes endothelial cell dysfunction [15].

This study showed that the angiogenin level decreases with increased duration of diabetes and increased vascular complications as it was higher in recently discovered diabetic patients with a low incidence of vascular complications and better control of blood glucose levels compared with type 2 diabetic patients with a longer duration of diabetes and increased incidence of vascular complications and uncontrolled hyperglycemia.

These data are comparable to the results of different observational studies [16]. The longer the duration of diabetes, the poorer the control and the lower the serum angiogenin level. Moreover, Zorena *et al.* [7] reported a significant positive correlation between the serum level of angiogenin and duration of type 1 DM longer than 5 years after diagnosis.

In terms of the lipid profile, the present study showed a highly significant inverse correlation of angiogenin with triglycerides in group A, but an insignificant inverse correlation in groups B and C. There was an insignificant inverse correlation of angiogenin with cholesterol and LDL in groups A and B. Chahil and Ginsberg [17] described the characteristic features of a diabetic phenotype as a high plasma triglyceride concentration, a low HDL cholesterol concentration, and an increased concentration of small dense LDL cholesterol particles.

In the present study, an insignificant decrease in the angiogenin level was found in diabetic patients with an A/C ratio greater than 30 compared with diabetic patients with an A/C ratio less than 30; however, both diabetic groups showed a highly significant decrease in the serum angiogenin level compared with the control group.

There is growing evidence that an increased urinary albumin excretion rate in type 2 diabetic patients is both a predictor of progression to chronic renal failure and an independent risk factor for cardiovascular disease [18].

In the present study it was found that there was an insignificant decrease in angiogenin levels in diabetic patients with nephropathy compared with those without nephropathy; however, the angiogenin level showed a highly significant decrease in both groups compared with the control group.

Hohenstein *et al.* [19] reported that in type 2 diabetic patients an increased endothelial number was observed and early glomerular lesions were caused by a combination of increased proliferation and decreased apoptosis in glomerular endothelial cells.

In addition, the present study showed an insignificant decrease in the angiogenin level in diabetic patients with

Table 8 Comparison of the mean levels of angiogenin using the analysis of variance test in the study groups divided into diabetic and control groups and according to the presence or absence of diastolic dysfunction

			ANOVA (multiple comparison tests)		
Groups	*N*	Angiogenin (mean ± SD)	1 vs. 2	1 vs. 3	2 vs. 3
1 Diabetes + No diabetic dysfunction	13	315.4 ± 29.7	NS	< 0.01**	< 0.01**
2 Diabetes + diabetic dysfunction	55	294.8 ± 43.1			
3 Nondiabetic control	20	472.6 ± 45.6			

ANOVA, analysis of variance.
**Highly significant.

retinopathy compared with diabetic patients without retinopathy; however, the angiogenin level showed a highly significant decrease in both diabetic groups compared with the control group.

On the other hand, Marek *et al.* [20], who reported that angiogenin was found to be significantly more abundant in serum than in the vitreous in both diabetic groups. In addition, patients with retinopathy had two-fold lower vitreous angiogenin levels than diabetic individuals without complications. The low vitreous concentration of angiogenin in diabetic patients indicates that this factor is not responsible for pathological neovascularization in eyes of diabetic patients; thus, angiogenin can be used to improve the insufficient angiogenesis in diabetic patients and prevent retinal ischemia after treatment of retinopathy with anti-vascular endothelial growth factor agents.

In the present study, a significant decrease was found in the angiogenin level in diabetic patients with CAD compared with those without CAD.

This is not in agreement with the findings of Mena *et al.* [21], according to whom levels of serum vascular endothelial growth factors Ang-1 and Ang-2 in patients with CAD were significantly higher than those in healthy control individuals.

There was an insignificant correlation between angiogenin and EF in groups A, B, and C. In terms of the diastolic dysfunction in this study, there were 55 diabetic patients with left ventricular diastolic dysfunction and 13 diabetic patients without diastolic dysfunction, most of them in group A. In addition, there was an insignificant decrease in the angiogenin level in diabetic patients with diastolic dysfunction compared with diabetic patients without diastolic dysfunction; however, both diabetic groups showed a highly significant decrease in the angiogenin level compared with the control group. In contrast to this study, Patel *et al.* [11] reported abnormal indices of angiogenesis in patients with chronic heart failure.

Conclusion

Serum angiogenin levels are lower in type 2 diabetic patients compared with the control group and they decrease with prolonged duration of diabetes, especially in patients with uncontrolled diabetes and patients with microangiopathic and cardiovascular complications.

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Conflicts of interest

There are no conflicts of interest.

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العلاقة بين مستوى الأنجيوجنين فى مصل الدم

ومضاعفات الأوعية الدموية فى مرضى البول السكرى

من النوع الثانى

يعد ضعف الاوعية الدموية الدقيقة وأمراض الأوعية الكبيرة السابق لأوانه هي المضاعفات الأكثر شيوعا لمرض السكري وهي مسئولة عن اعتلال الشبكية السكري ، وأمراض الكلى ، والاعتلال العصبي. وعلاوة على ذلك فان مرض السكري يؤدي إلى خفض اوعية الضمانات في الأنسجة التى تعانى من نقص التروية ، والذي يسبب ضعف التئام الجروح ، وتفاقم نقص تروية أوعية الأطراف ، وزيادة من ثلاثة الى أربعة أضعاف معدل وفيات القلب بالمقارنة مع المرضى غير المصابين بالسكري و تعد الآليات الفسيويولوجية المرضية المسؤولة عن ضعف الاوعية الدموية في مرض السكري ما زالت غير معروفة على الرغم من أن ضعف الأوعية الدموية قد يكون بسبب تغييرات في شبكة الجينات التنظيمية ، والتي يمكن أن تشارك في عملية إعادة تكوين الأوعية الدموية فسيولوجيا ، فقد يعد الانجيوجنين أحد العوامل التى لم يعرف دورها فى توضيح تلك الآليات حتى الآن.

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