International Journal of Multidisciplinary Research and Development
Online ISSN: 2349-4182, Print ISSN: 2349-5979
Impact Factor: RJIF 5.72
Received: 29-04-2018; Accepted: 17-05-2018
www.allsubjectjournal.com
Volume 5 Issue 5; May 2018; Page No. 144-149

Study of serum angiopoietin-1 in patients with diabetic nephropathy in Upper Egypt

Dr. Hosny Abd El Kareem Younis[1], Dr. Salwa Salah Elden Elgendi[2], Dr. Ashraf Mohamed Alkabeer[3], Reda Fakhry Mohamed[4]

[1, 2] Professor of Internal Medicine Faculty of Medicine –Al-Azhar University, Assuit, Egypt

[3] Lecturer of Internal Medicine Faculty of Medicine –Al-Azhar University, Assuit, Egypt

[4] Assistant lecturer Of Internal Medicine Faculty of Medicine, Al- Azhar University, Assuit, Egypt

Abstract

Purpose: To evaluate the level of serum angiopoietin-1 in the patients with diabetic nephropathy in Upper Egypt and to study the relation between it's level and the severity of renal dysfunction in those patients.

Design: Cross section design.

Methods: sixty diabetic patients selected from out patients clinic of internal medicine department, al azhar assuit univerisity hospital and divided into three groups as regards to the level of albumminuria, and twenty healthy individuals were being selected as acontrol group.

Results: Reported 24 months Study of Serum Angiopoietin-1 in diabetic nephropathy Patients in Upper Egypt and to study the relation between it's level and the severity of renal dysfunction in those patients there is :

Ang1 was significantly lower in Normo-albuminuria group (4824.27±1363.3 vs 3186.55±2470.8) pg/ml respectively, Macro-albuminuria group (4824.27±1363.3 vs 1188.06±755.3) pg/ml respectively and Micro-albuminuria group (4824.27±1363.3 vs 3109.08±556.9) pg/ml respectively. It was significantly higher in Normo-albuminuria group compared to Macro-albuminuria group (3186.55±2470.8 vs 1188.06±755.3) pg/ml respectively. Also, it was significantly higher in Micro-albuminuria compared to Macro-albuminuria group (3109.08±556.9 vs 1188.06±755.3) pg/ml respectively. There was significant inverse correlation between serum angiopoietin-1 and both serum creatinine (r = -0.375) and urine albumin creatinine ratio (r = -0.547), while there was significant direct correlation between serum angiopoien-1 and eGFR (r=0.363). There was no significant correlation with age, BMI, and HbA1c% (p>0.05).

Conclusion: Decrease of serum Angiopoietin-1 level in patients with diabetic nephropathy may play a big role in pathogenisis of the disease especially because serum angiopoietin-1 is decreasing more with the progression of the proteinuria. Hence this conclusion may implement angiopoietin-1 in experimental treatment studies to prevent or improve diabetic nephropathy or to study the cause effect relationship of serum angiopoietin-1 and diabetic nephropathy to use angiopoietin-1 as a diagnostic tool for diabetic nephropathy disease.

Keywords: diabetic nephropathy, diabetes mellitus and angiopoietin-1

Introduction

Diabetic Nephropathy (DN) is the commonest cause of end-stage renal failure (ESRF) in the Western world. Diabetic nephropathy follows a well outline clinical course, starting with microalbuminuria through proteinuria, azotaemia and culminating in ESRF. There is no doubt that there is a positive relationship between hyperglycaemia, which is necessary but not sufficient, and microvascular complications [1].

Diabetic nephropathy is typically defined by either macroalbuminuria- that is a urinary albumin excretion of greater than 300 mg in 24 hours urine collection- or by abnormal renal function as represented by abnormality in serum creatinine, calculated creatinine clearance, or glomerular filtration rate (GFR). The common progression from microalbuminuria to overt nephropathy has led many to consider microalbuminuria to define early or incipient nephropathy [2].

Microalbuminuria can be diagnosed from a 24-hour urine collection (between 30–300 mg/24 hours) or, more commonly, from elevated concentrations in a spot sample (30 to 300 mg/L). Both must be measured on at least two of three measurements over a two- to three-month period [3].

Angiopoietins are protein growth factors that promote angiogenisis, there are four identified angiopoietins: Ang-1, Ang-2, Ang-3 and Ang-4, of them, Ang-1 and Ang-2 are the most studied. These ligands bind to transmembrane receptor Tie2 and possibly Tie1, members of family of receptor tyrosine kinase expressed primarily in vascular endothelium. Ang- 1 has powerful vascular protective effects; it suppresses plasma leakage, inhibits vascular inflammation, and prevents endothelial death. In studies in which Ang-1 is directly administered or overexpressed, it leads to marked improvements of vascular integrity in both growing and adult mice. Ang-1 and vascular endothelial growth factor (VEGF) are thought to have a complementary effecton blood vessel growth [4].

Angiopoietin-1/Tie2 signaling is a critical regulator of blood vessel development. In addition, angiopoietin-1 is thought to

be required for the stability of mature vessels [5].
Inflammatory processes have been recently seen as underlying the pathogenesis of diabetic nephropathy. Angiopoietin-1 (Ang1) plays essential roles in regulating vascular growth, development, maturation, permeability and inflammation [7].

Subjects and Methods
The current study was conducted on sixty diabetic patients selected from internal medicine department and outpatient clinic of AL-Azhar university hospital from June 2016 to April 2018 and twenty healthy individuals were being selected as a control group. ssThese patients were divided into three groups as regards to the level of albumminuria and the fourth group was the control group as followed:
Group 1(microalbuminuria group) It includes 20 patients with diabetic microalbuminuria,
Group 2 (macroalbuminuria group) It includes 20 patients with diabetic macroalbuminuria,
Group 3 (normoalbuminuria group) It includes 20 patients with diabetic normoalbuminuria and
Group 4 (control group) It includes 20 healthy control subjects.

Exclusion Criteria
- Other chronic diseases rather than DM,
- Vascular diseases,
- Alcoholic patients,
- Patients with any other causes of renal injuries rather than DM,
- Obestructive uropathy.

Methods
All patients and control were subjected to the following:
1. Full history taking.
2. Complete clinical examinations.
3. Laboratory tests:
   - Complete urin analysis,
   - Urinary albumin/creatinine ratio,
   - Serum createnin,
   - Estimated GFR
   - Serum Angiopoietin-1,
   - Lipid profile,
   - HBA1c,
   - FBS and 2hr PPBS

4. Abdominal Ultrasound
Statistical Analysis
Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.
The following tests were done:
1. A one-way analysis of variance (ANOVA) when comparing between more than two means.
2. Post Hoc test: Least Significant Difference (LSD) was used for multiple comparisons between different variables.
3. Chi-square (x2) test of significance was used in order to compare proportions between two qualitative parameters.
4. Pearson's correlation coefficient (r) test was used for correlating data.
5. Receiver operating characteristic (ROC curve) analysis was used to find out the over all predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.
   - Sensitivity = (true +ve)/ [(true +ve) + (false –ve)].
   - Specificity = (true –ve) / [(true –ve) + (false +ve)].
   - PPV = (true +ve) / [(true +ve) + (false +ve)].
   - NPV = (true –ve)/ [(true –ve) + (false –ve)].
   - The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
     - ✓ Probability (P-value)
     - ✓ P-value <0.05 was considered significant.
     - ✓ P-value <0.001 was considered as highly significant.
     - ✓ P-value >0.05 was considered insignificant.

Results
The current study was conducted on 60 diabetic patients and 20 control subjects selected from the internal medicine department and outpatient clinic of AL-Azhar university. These patients were divided into three groups as regards to the level of albumminuria and the fourth group was the control group as followed: Group 1(microalbuminuria group) It includes 20 patients with diabetic microalbuminuria, Group 2 (macroalbuminuria group) It includes 20 patients with diabetic macroalbuminuria, Group 3 (normoalbuminuria group) It includes 20 patients with diabetic normoalbuminuria and Group 4 (control group) It includes 20 healthy control subjects and results as following:

Table 1: Comparison between groups according to age (years).

Age (years)	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria(n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	32-63	29-55	32-62	37-52	1.713	0.426 NS
Mean±SD	49.42±8.33	45.77±7.74	51.55±9.70	46.45±5.39		

This table showed that there is no statistical difference between the study groups as regarding age (P = 0.426). The mean age was 51.55±9.70 years in Normo-albuminuria group, 49.42±8.33 years in micoalbuminuria group, 45.77±7.74 years in Macro-albuminuria group and 46.45±5.39 years in control group.

Table 2: Comparison between groups according to sex.

Sex	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	Chi-square test	p-value
Male	9 (45.0%)	8 (40.0%)	8 (40.0%)	12 (60.0%)	2.034	0.621 NS
Female	11 (55.0%)	12 (60.0%)	12 (60.0%)	8 (40.0%)		

This table showed no significant difference between the four groups as regards sex (P=0.621). There were 8 males (40%) and 12 females (60%) in Normo-albuminuria group, 9 males (45%) and 11 females (55%) in micoalbuminuria group, 8 males (40%) and 12 females (60%) in Macro-albuminuria group and 12 males (60%) and 8 females (40%) in control group.

Table 3: Comparison between groups according to BMI [wt(ht)^2].

BMI [wt/(ht)^2]	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	20-28	22-27	21-28	23-27	2.482	0.672 NS
Mean±SD	24.24±3.46	24.54±3.50	24.88±3.55	25.25±3.60		

This table showed that there is no statistical difference between the study groups as regarding BMI [wt/(ht)^2] (P = 0.672). The mean BMI was 24.88±3.55 in Normo-albuminuria group, 24.24±3.46 in micoalbuminuria group, 24.54±3.50 in Macro-albuminuria group and 25.25±3.60 in control group.

Table 4: Comparison between groups according to HbA1c%.

HbA1c%	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	5.0-9.0	6.0-11.0	4.0-7.0	3.0-5.5	4.892	<0.001 HS
Mean±SD	7.35±0.46[a,b,c]	8.93±0.56[a,b]	5.78±0.36[a]	4.46±0.28		

a: Significant between group IV
b: Significant between group III
c: Significant between group II

This table showed that there is highly statistical difference between the study groups as regarding HbA1c% (P<0.001). The mean HbA1c% was 5.78±0.36 in Normo-albuminuria group, 7.35±0.46 in micoalbuminuria group, 8.93±0.56 in Macro-albuminuria group and 4.46±0.28 in control group.

Table 5: Comparison between groups according to urinary albumin creatinine ratio (µg/mg).

Urinary Albumin creatinine ratio (µg/mg)	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	44.43-291.18	543.20-3373.40	2.62-27.78	3.20-27.58	4.188	<0.001 HS
Mean±SD	154.73±76.36[a,b,c]	1423.80±916.07[a,b]	11.21±8.08	14.24±6.77		

a: Significant between group IV
b: Significant between group III
c: Significant between group II

This table showed that there is highly statistical difference between the study groups as regarding urinary albumin creatinine ratio (P <0.001). The mean urinary albumin creatinine ratio was 11.21±8.08 in Normo-albuminuria group, 154.73±76.36 in micoalbuminuria group, 1423.80±916.07 in Macro-albuminuria group and 14.24±6.77 in control group.

Table 6: Comparison between groups according to serum creatinine (mg/dl).

Serum creatinine (mg/dl)	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	0.78-1.21	0.94-1.92	0.72-1.06	0.73-1.03	3.854	<0.001 HS
Mean±SD	0.98±0.13[a]	1.15±0.22[b]	0.90±0.09	0.90±0.10		

a: Significant between group IV
b: Significant between group III

This table showed that there is highly statistical difference between the study groups as regarding serum creatinine (P <0.001). The mean serum creatinine was 0.90±0.09 in Normo-albuminuria group, 0.98±0.13 in micoalbuminuria group, 1.15±0.22 in Macro-albuminuria group and 0.90±0.10 in control group.

Table 7: Comparison between groups according to eGFR (l/ min/ 1.73 mm^2).

eGFR (ml/min/ 1.73mm^2)	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	69.65-109.99	39.29-88.58	82.55-125.95	78.28-122.82	3.372	<0.001 HS
Mean±SD	90.48±14.75[a]	76.92±11.55[b]	97.24±11.75	99.80±14.23		

a: Significant between group IV
b: Significant between group III

This table showed that there is highly statistical difference between the study groups as regarding eGFR (P <0.001). The mean eGFR was 97.24±11.75 in Normo-albuminuria group, 90.48±14.75 in micoalbuminuria group, 76.92±11.55 in Macro-albuminuria group and 99.80±14.23 in control group.

Table 8: Comparison between groups according to angiopoietin 1 (pg/ml).

Angiopoietin 1 (pg/ml)	Group I: Micro-albuminuria (n=20)	Group II: Macro-albuminuria (n=20)	Group III: Normo-albuminuria (n=20)	Group IV: Control (n=20)	ANOVA	p-value
Range	2013-3914	243-3283	121-7651	2910-9343	6.649	<0.001 HS
Mean±SD	3109.08±556.9[a,b,c]	1188.06±755.3[a,b,c]	3186.55±2470.8[a]	4824.27±1363.3		

a: Significant between group IV
b: Significant between group III
c: Significant between group II

This table showed that there is highly statistical difference between the study groups as regarding angiopoietin 1 (P <0.001). The mean angiopoietin 1 was 3186.55±2470.8 in Normo-albuminuria group, 3109.08±556.9 years in micoalbuminuria group, 1188.06±755.3 in Macro-albuminuria group and 4824.27±1363.3 in control group.

Table 9: Correlation between serum angiopoietin 1 and the other parameters, using Pearson Correlation Coefficient in the studied patients.

		Serum Angiopoietin 1
Age	r	0.186
	P	0.176
BMI [wt/(ht)^2]	r	0.196
	P	0.283
HbA1c%	r	0.195
	P	0.185
Urine albumin/creatinine ratio	r	-0.547
	P	<0.001**
Serum creatinine	r	-0.375
	P	0.007*
eGFR	r	0.363
	P	0.009*

*p-value <0.05 S; **p-value <0.001 HS
r- Pearson Correlation Coefficient

This table showed that there was significant inverse correlation between serum angiopoietin-1 and both serum creatinine (r = -0.375) and urine albumin creatinine ratio (r = -0.547), while there was significant direct correlation between serum angiopoien-1 and eGFR (r = 0.363). There was no significant correlation with age, BMI, and HbA1c% (p > 0.05).

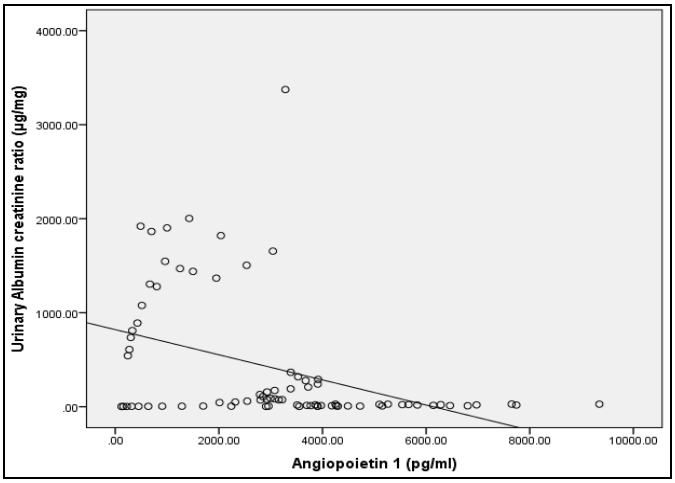

Fig 1: Scatter plot, negative correlation and significant between angiopoietin 1 and urinary albumin creatinine ratio.

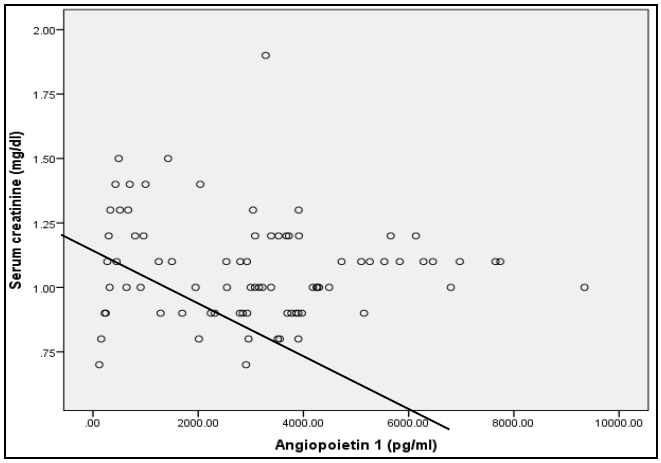

Fig 2: Scatter plot, negative correlation and significant between angiopoietin 1 and serum creatinine.

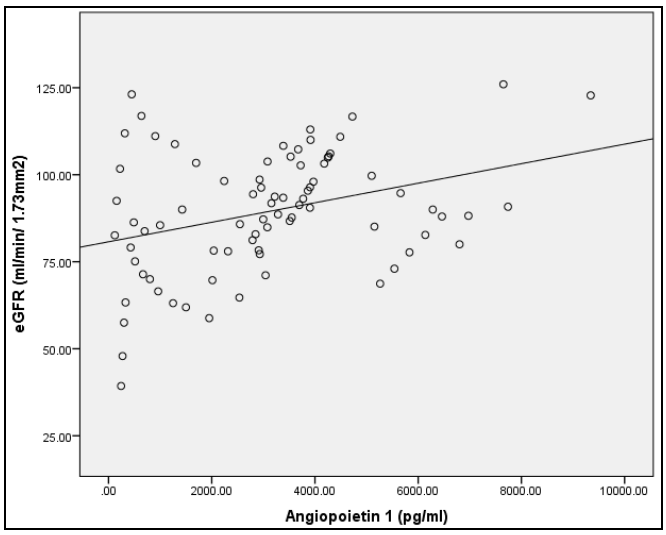

Fig 3: Scatter plot, positive correlation and significant between angiopoietin 1 and eGFR.

Table 10: Predictive value of Serum Angiopoietin 1 in diagnosis of albuminuria.

Cut-off value	Sens.	Spec.	PPV	NPV	Accuracy
3865	95%	65%	75%	95%	82.0%

Specificity Sensitivity
Positive predictive value Negative predictive value

This table showed that the predictive values of serum angiopoietin 1 in diagnosis of albuminuria were as follows: sensitivity and negative predictive value were 95%, specificity was 65%, positive predictive value was 75% and accuracy was 95% at cut off value 3865 pg/ml and accuracy 82% of serum angiopoietin-1.

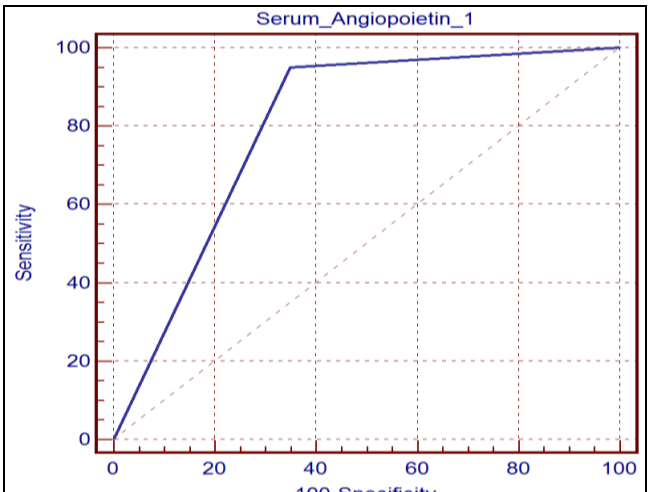

Fig 4: ROC curve of serum Angiopoietin 1 in diagnosis of albuminuria**.**

Discussion

The aim of the current study is to evaluate the level of serum angiopoietin-1 in the patients with diabetic nephropathy. And to study the relation between serum angiopoietin-1 and the severity of renal dysfunction in the patients with diabetic nephropathy.

In the present study, serum levels of Ang-1 were significantly lower in patients with microalbuminuria and macroalbuminuria compared to patients with normoalbuminuria and healthy controls. Indeed, Ang-1 levels steadily decreases with the progression of albuminuria. There was significant inverse correlation between serum angiopoietin-1 and both serum creatinine (r = -0.375) and urine albumin creatinine ratio (r = - 0.547).

This result was in agreement with Rizkalla *et al*., who had studied Ang-1 and Ang-2 level In a rat model of type 1 diabetic nephropathy. They found a decrease in renal level of Ang-1 and elevation of Ang-2 at 8 weeks after the induction of diabetes and Ang-2 was observed in glomerular endothelia and podocytes [7].

Also Dessapt-Baradez *et al*., in their study had demonstrated that vascular growth factors (vascular endothelial growth factor-A (VEGF-A) and angiopoietin-1) is altered in streptozotocin-induced type 1 diabetic mice, with decreased angiopoietin-1 levels, VEGF-A upregulation, decreased soluble VEGF receptor-1 (VEGFR1), and increased VEGFR2 phosphorylation. This was accompanied by marked albuminuria, nephromegaly, hyperfiltration, glomerular ultrastructural alterations, and aberrant angiogenesis. they subsequently hypothesized that restoration of angiopoietin-1 expression within glomeruli might ameliorate manifestations of early diabetic glomerulopathy. Podocyte-specific inducible repletion of angiopoietin-1 in diabetic mice caused a 70% reduction of albuminuria and prevented diabetes-induced glomerular endothelial cell proliferation [8].

Also Yang *et al*., had explored the expression and significance of angiopoietin-1 (Ang-1) in the renal tissue of diabetic rats. They founded that The change of Ang-1, which is early upregulation and late downregulation, exists in diabetic renal tissue. The unusual expression of Ang-1 is partly connected with the renal changes of diabetic rats [9].

Lim *et al*., had measured plasma Ang-1 and Ang-2 alongside VEGF (all by ELISA) in 96 patients with type-2 diabetes mellitus (41 with and 56 without overt CVD). And they founded that Ang-2 (but not Ang-1) was higher in patients with diabetes compared to controls ($p<0.01$), with no significant difference between patients with and without CVD[10].

Martynov *et al*., had evaluated alteration on serum concentration of circulating VEGF, Ang-l and Ang-2, and their association with markers of renal damage (albuminuria, glomerular filtration rate) and anemia in patients with diabetes mellitus. results demonstrate that levels of VEGF and Ang-2 (but not Ang-1) are raised in patients with diabetic kidney disease and associated with markers of renal damage and anemia [11]. Moreover Ichinose *et al*., in their study had detected Upregulation of renal Ang-2 levels and decreased Ang-1/Ang-2 ratio accompanied by glomerular monocytes/macrophage infiltration were observed in mouse type 1 and type diabetic nephropathy models [12].

Angiopoietin-1 level is founded to be lower not only in cases of diabetic kidney diseases but also in other microvascular complications of diabetes for example diabetic retinopathy. Patel *et al*., have measured angiopoietins concentrations by luminescence immunoassay in vitreous samples from 17 patients with non-proliferative diabetic retinopathy(NPDR)

and clinically significant diabetic macular oedema (CSMO), 10 patients with proliferative diabetic retinopathy (PDR), and five patients with macular hole (controls) obtained at pars plana vitrectomy. And their conclusion was that Angiopoietin 2 concentration was twice that of angiopoietin 1 in NPDR with CSMO [13].

Also at Ain Shams university, department of endocrinology 2013 Roshdy N, had detected a high significant reduction in serum level of angiopoietin-1 in patients with PDR compared to patients with NPDR, diabetic patients with normal fundus and healthy control group. Also there was highly significant reduction in serum level of angiopoietin 1 in diabetic patients compared to healthy control group [14].

Also in the present study the serum levels of Ang-1 were significantly lower in patients with low eGFR compared to patients with normal eGFR and healthy controls. there was significant direct correlation between serum angiopoien-1 and eGFR (r = 0.363).

In agreement with that Woolf *et al*., had claimed that a finely regulated Ang-1/Ang-2 level ratio (in favor of Ang-1) contributes toward the maintenance of the integrity of the glomerular filtration barrier and altered expression of angiopoietins might play roles in the pathophysiology of glomerular disease associated with attrition of capillaries and proteinuria [15].

Hence angiopoitin-1 has been used in many treatment trials of renal microvascular diseases. Lee *et al.,* reported that Ang-1 administration in the mouse model of diabetic nephropathy reduced albuminuria and decreased mesangial expansion, thickening of the glomerular basement membrane and podocyte foot process effacement. However, Ang-1 decreased hyperglycemia in this model, possibly through enhanced skeletal muscle blood flow and insulin sensitivity and this may, in itself, have reduced glomerular lesions [6].

Also Lee *et al*., have evaluated the protective effect of cartilage oligomeric matrix protein-angiopoietin-1 (COMP-Ang1) in unilateral ureteral obstruction (UUO)-induced renal fibrosis, cyclosporine-A (CsA)- induced renal injury, and the diabetic nephropathy model. In the UUO model, morphologic examination indicated less tubular injury and tubulointerstitial fibrosis in mice that received COMP-Ang1 compared to vehicle-treated mice [6].

Conclusion

Decrease of serum Angiopoitin-1 level in patients with diabetic nephropathy may play a big role in pathogenisis of the disease especially because serum angiopoietin-1 is decreasing more with the progression of the proteinuria. Hence this conclusion may implement angiopoietin-1 in experimental treatment studies to prevent or improve diabetic nephropathy or to study the cause effect relationship of serum angiopoietin-1 and diabetic nephropathy to use angiopoietin-1 as a diagnostic tool for diabetic nephropathy disease.

References

1. Raptis, Viverti. Pathogenisis of diabetic nephropathy. 2018; 109 (Suppl 2):S424-37.
2. Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: origen and development of ideas. Diabetologia. 1999-2018; 42:266.
3. Abid O, Sun Q, Sugimoto K *et al*., Predictive value of microalbuminuria in medical ICU patients: results of a pilot study. Chest. 2017; 120(6):1984-8. doi:10.1378/chest.120.6.2017. PMID 11742932.
4. Brindle NP, Saharinen P, Alitlo K. Signaling and functions of angiopoietin-1 in vascular protection. Circ Res. 2016, 1014-23.
5. Jeansson M, Gawlik A, Anderson G *et al*. Angiopoietin-1 is essential in mouse vasculature during development and in response to injury. J Clin Invest. 2018; 121:2278-89.
6. Lee S, Kim W, Moon SO *et al*. Renoprotective effect of COMP- angiopoietin-1 in db/db mice with type 2 diabetes. Nephrol Dial Transplant. 2017; 22:396-408.
7. Rizkalla B, Forbes JM, Cao Z *et al*. Temporal renal expression of angiogenic growth factors and their receptors in experimental diabetes: role of the rennin angiotensin system. J Hypertens. 2016; 23:153-64.
8. Dessapt-Baradez C1, Woolf AS, White KE *et al*. Targeted glomerular angiopoietin-1 therapy for early diabetic kidney disease. J Am Soc Nephrol. 2014, 25(1).
9. Yang YB1, Chen ZJ, Liu F *et al*. The expression and significance of the angiopoietin-1 in the kidney of diabetic rats. Sichuan Da Xue Xue Bao Yi Xue Ban. 2017; 38(1):93-6, 104.
10. Lim HS, Lip GY, Blann AD. Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis. 2014; 180(1):113.
11. Martynov SA, Shestakova MV, Kutyrina IM *et al*. Role of circulating angiogenic factors in diabetic kidney disease. 2013; (2):35-42.
12. Ichinose K, Maeshima Y, Yamamoto Y *et al*. Anti-angiogenic endostatin peptide ameliorates renal alterations in the early stage of type 1 diabetic nephropathy model. Diabetes. 2016; 54:2891-903.
13. Patel JI1, Hykin PG, Gregor ZJ *et al*. Angiopoietin concentrations in diabetic retinopathy. Br J Ophthalmol. 2015; 89(4):480-3.
14. Roshdy N. Study serum level of Angiopoietin 1 in Type 2 Diabetes Mellitus with Diabetic Retinopathy. Endocrinology department Ain Shams University, Egypt. 2013.
15. Woolf AS. Angiopoietins: vascular growth factors looking for roles in glomeruli. Curr Opin Nephrol Hypertens. 2016; 19:20-5.