Effect of Captopril on Aqueous Levels of Angiotensin II and Its Correlation with Macular Edema in Diabetic Patients

Morteza Shahshahan[1], MD; Mohammad-Reza Peyman[1], MD; Heshmatolah Ghanbari[2], MD; Ali-Reza Peyman[2], MD

[1]*Azad University, Najafabad Medical School, Najafabad, Iran;* [2]*Isfahan Medical University, Isfahan, Iran*

Purpose: To determine whether angiotensin II (AT II) levels in aqueous humor are related to diabetes mellitus and to evaluate the effect of captopril on this level. We also evaluated the correlation between severity of macular edema and captopril use.

Methods: In a case-control study, aqueous humor samples were obtained at the onset of cataract surgery from 58 eyes of 58 patients, of whom 37 were diabetic. From these latter subjects, 16 had taken captopril (captopril group) for at least six months and 21 had not taken any angiotensin converting enzyme inhibitor (non-captopril group). AT II level was assessed by radioimmunoassay. Severity of macular edema was evaluated by clinical examination after surgery.

Results: The aqueous level of AT II was significantly higher in diabetic patients (31.0 ± 7.3 pg/ml) compared to non-diabetics (6.28 ± 2.8 pg/ml) (Mann Whitney U test, $P < 0.0001$). In diabetic patients, aqueous concentration of AT II in the captopril group (16.3 ± 6.5 μg/ml) was significantly lower than the non-captopril group (75.73 ± 9.36 μg/ml) (Mann Whitney U test, $P < 0.0003$). The severity of macular edema was significantly less in the captopril group compared to the non-captopril group: 68.75% of the captopril group vs 33.3% of the non-captopril group had no macular edema ($P < 0.005$).

Conclusion: These findings suggest that the aqueous level of AT II is higher in diabetic eyes and is correlated with the severity of diabetic macular edema. Considering the possible role of AT II in the pathogenesis of diabetic macular edema, modulation of the ocular renin-angiotensin system may become an important target for its treatment.

Correspondence to: Mohammad-Reza Peyman, MD. Azad University, Najafabad Medical School, Najafabad, Iran; PO. Box: 81645/641, Esfahan; e-mail: drmpeyman@yahoo.com

INTRODUCTION

Diabetic macular edema (DME) is the most common cause of visual loss among diabetic patients.[1] The major mediators involved in the pathogenesis of diabetic retinopathy include vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), endothelin and nitric oxide.[2]

On the other hand a local renin-angiotensin system (RAS) exists in the eye that is independent of systemic RAS.[3] It has recently been shown that the local RAS is also involved in the pathogenesis of diabetic retinopathy.[4] In vitro studies have shown the effect of angiotensin II (AT II) as an angiogenic factor and also in promoting cell migration in culture media.[3]

Photocoagulation and vitrectomy have proven useful for treatment of DME but both are associated with adverse effects and may cause further loss of vision.[5] Regarding the lack of definite prevention or treatment for DME and the considerable adverse effects of currently used treatments, a safer noninvasive treatment for prevention and treatment of DME would be desirable. Modulation of the local RAS of the eye could theoretically be a very important target in this respect. We performed this study to evaluate the effect of captopril on the aqueous level of AT II and on the severity of DME.

METHODS

This study was performed on 58 eyes of 58 patients scheduled for cataract surgery including 37 patients with diabetes mellitus type 2 and 21 nondiabetic subjects (control group). Diabetic patients were recruited from two groups including 16 subjects under treatment with captopril (50 mg per day) for at least 6 months (captopril group) and 21 cases who did not use any angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor antagonist (non-captopril group). The control group did not use any ACE inhibitor or angiotensin receptor antagonist agent. Exclusion criteria included history of previous ocular surgery, ocular inflammation, proliferative diabetic retinopathy, rubeosis iridis, macular disorders other than DME, previous macular photocoagulation and uncontrolled systemic hypertension. Preoperative evaluations in diabetic patients included blood pressure measurement, the type of hyperglycemic treatment, Hb A_1C levels and proteinuria.

At the onset of cataract surgery, an undiluted sample of aqueous humor (0.1-0.2 ml) was obtained and immediately stored in a sterile tube at -80°C. A sample of venous blood was also obtained simultaneously and sent to the laboratory on an ice-bag. Plasma from the blood sample was separated and stored in a sterile tube at -80°C. AT II levels in the aqueous humor and plasma samples were measured using radioimmunoassay. The minimum measurable amount of AT II was 4 pg/ml with co-efficient of variant equal to 0.6%.

All diabetic patients were evaluated for macular edema 48 hours postoperatively and were classified clinically as follows: stage 0- no macular edema; stage 1- focal macular edema (FME); stage 2- diffuse macular edema or cystoid macular edema (CME). FME was defined as focal capillary leakage (from microanenrysms and dilated capillaries) resulting in retinal thickening less than one disc area. Diffuse macular edema was defined as diffuse leakage from dilated retinal vessels at the posterior pole with retinal thickening of at least 1 disk area.[6]

Data analysis was performed using SPSS, version 10. Mean values of aqueous AT II were compared between the two groups by Mann-Whitney U test, other mean values were compared using t test between two groups and ANOVA among three groups. Frequencies were compared using the chi-square test. Spearman's rank-order correlation coefficient was calculated for evaluating the correlation between aqueous level of AT II and severity of macular edema. Significance was tested at $P< 0.05$.

RESULTS

Non-diabetic patients included 11 male and 10 female subjects with mean age of 55.6±8.2 years and diabetic patients included 22 men and 15 women with mean age of 55.5±6.6 years. Mean duration of diabetes was 10.1±3.7 years. Clinical characteristics of the 3 groups of patients are summarized in table 1.

There was no statistically significant difference between the captopril and non-captopril groups regarding age, sex, diabetes duration and Hb A_1C level. Diabetic patients had DME stage 0 in 18 cases (48.7%), stage 1 in 13 eyes (35.1%) and stage 2 in 6 eyes (16.2%). DME was significantly less severe in the captopril than the non-captopril group (table 2).

The aqueous level of AT II was 11.0 ± 7.3 pg/ml in diabetic patients with positive correlation with severity of DME (ρ=0.78, P=0.009). The aqueous level of AT II was less than 20 pg/ml in non-diabetics and less than 40 pg/ml in the captopril group but greater than 40

pg/ml in 24% of cases in the non-captopril group. (Fig. 1).

A positive correlation was found between Hb A_1C and aqueous AT II levels (ρ= 0.51, P=0.025). There was no correlation between aqueous humor and plasma levels of AT II (P=0.07) while both were significantly lower in the captopril vs non-captopril group (table 1).

Table 1 Clinical characteristics of patients

	Non-diabetics	Captopril	Non-captopril	P value
Age (year)	57±8.7	54±9.3	56±6.7	*P=0.75
BP (mmHg): Systolic	125±1.8	135±2.2	140±2.7	*P=0.06
Diastolic	80±0.8	85±1.3	90±1.1	*P=0.08
ATII (pg/ml): Aqueous	5.2±2.7	16.3±6.5	45.7±9.4	**P_1=0.02 P_2<0.001
Serum	14.8±3.5	12.4±4.1	29.±5.6	**P_1=0.01 P_2<0.001

BP: blood pressure, ATII: angiotensin II, P_1: Non-captopril group versus non diabetics
P_2: Non-captopril group versus captopril group, *ANOVA **Mann-Whitney U test

Table 2 Clinical characteristics of diabetic patients in relation with consumption of captopril

	Group		*P value
	Captopril	Non-captopril	
Gender (M/F)	10/12	6/9	0.08
DM duration (years)	9.1±3.9	11.2±4.3	0.08
Treatment: Dietary regimen	3 (18.75%)	4 (19.1%)	
Oral antiglycemic	5 (31.25%)	7 (33.3%)	0.5
Insulin	8 (50.0%)	10 (47.6%)	
Hb A_1C (%)	7.3±2.4	8.5±3.2	0.1
Proteinuria (+/-)	7/9	14/7	0.002
Stage of DME: 0	11 (68.75%)	7 (33.3%)	
1	4 (25.0%)	9 (42.9%)	0.007
2	1 (6.25%)	5 (23.8%)	

DM: diabetes mellitus, DME: diabetic macular edema
* Chi square for frequencies and t test for mean values

DISCUSSION

Breakdown of the blood-retinal barrier increases capillary permeability resulting in DME and visual loss in diabetic patients. Previous studies have demonstrated high levels of VEGF and IL-6 in the aqueous humor and vitreous of these patients and have suggested that these mediators play a role in the pathogenesis of DME.[1] A direct correlation has been found between the aqueous and vitreous regarding the levels of these mediators and some abnormalities have also been reported in ocular RAS in eyes with DME.[7] Funatsu et al[8] have reported a rise in the aqueous level of AT II in association with incr-eased VEGF concentration in the vitreous.

The increased aqueous level of AT II in diabetic patients in the current study provides further evidence suggesting that the ocular RAS plays a role in the pathogenesis of DME. Funatsu et al[9] have reported the probable effect of ACE inhibitors on ocular RAS in DME. A pilot study revealed that low dose of an ACE inhibitor has beneficial effect on microvascular complications of diabetic retinopathy.[10]

An interesting finding in our study is the positive correlation between aqueous levels of AT II and the severity of DME and the observation that captopril treated patients had lower aqueous levels of AT II and also less severe

DME. These findings suggest that ACE inhibitors may modulate the ocular RAS and decrease DME. Considering the availability of different ACE inhibitor agents, this seems to be a promising idea.

Another finding of our study is the significant positive correlation between Hb A_1C (an indicator for long term glycemic control) and aqueous levels of AT II. This may indicate that better glycemic control may suppress ocular RAS. Interestingly we found no correlation between aqueous and plasma levels of AT II in spite of decrease in both levels in response to captopril. This can be explained by the fact that the local RAS in the eye is independent of the systemic RAS and responds differently to ACE inhibitors.
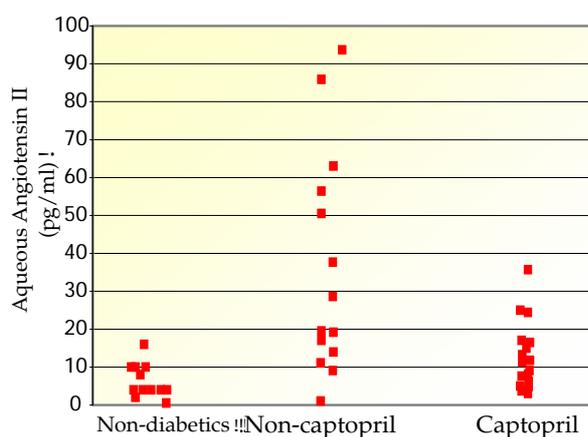

Figure 1 Distribution of the patients regarding the level of aqueous angiotensin II

One possible confounding factor causing less severe macular edema in the captopril group may be better control of hypertension.

The results of this study support the idea that AT II, in addition to other cytokines may play a role in the pathogenesis of DME. We speculate that modulation of these mediators could be a potential target for prevention and treatment of diabetic macular edema.

REFERENCES

1- Funatsu H, Yamashita H, Ikeda T, Mimura T, Eguchi S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor are related to diabetic macular edema. *Ophthalmology* 2003;110:1690-1696.

2- Funatsu H, Yamashita H. Pathogenesis of diabetic retinopathy and the renin-angiotensin system. *Ophthalmic Physiol Opt* 2003;23:495-501.

3- Funatsu H, Yamashita H. Modulation of the renin-angiotensin system and retinopathy. *Heart* 2000;84(Suppl.1):i29-31.

4- Funatsu H, Yamashita H, Ikeda T, Nakanishi Y, Kitano S, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with diabetic macular edema and other retinal disorders. *Am J Ophthalmol* 2002;133:537-543.

5- Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 2003;26:2653-2664.

6- Funatdu H, Yamashita H, Noma H, Mimura T, Yamashita T, Hori S. Increased levels of vascular endothelial growth factor and interleukin-6 in aqueous humor of diabetics with macular edema. *Am J Ophthalmol* 2002;133:70-77.

7- Funatsu H, Yamashita H, Noma H, Mimura T, Nakamura S, Sakata K, et al. Aqueous humor levels of cytokines are related to vitreous levels and progression of diabetic retinopathy in diabetic patients. *Graetes Arch Clin Exp Ophthalmol* 2005;243:3-8. Epub 2004 Jul 17.

8- Funatsu H, Yamashita H, Nakanishi Y, Hori S. Angiotensin II and vascular endothelial growth factor in the vitreous fluid of patients with proliferative diabetic retinopathy. *Br J Ophthalmol* 2002;86:311-315.

9- Funatsu H, Yamashita H, Shimizu E, Mimura T, Nakamura S, Hori S. Quantitative measurement of retinal thickness in patients with diabetic macular edema is useful for evaluation of therapeutic agents. *Diabetes Res Clin Pract* 2004;66:219-227.

10- Pradhan R, Fong D, March C, Jack R, Rezapour G, Norris K, Davidson MB. Angiotensin-converting enzyme inhibition for the treatment of moderate to severe diabetic retinopathy in normotensive Type 2 diabetic patients. A pilot study. *J Diabetes Complications* 2002;16:377-381.