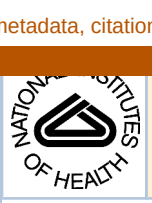

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Aqueous VEGF as a Predictor of Macular Thickening Following Cataract Surgery in Patients with Diabetes Mellitus

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Abstract

Purpose—To study associations between serum and aqueous vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) and macular edema measured with optical coherence tomography (OCT) following phacoemulsification in diabetic patients.

Design—Cohort study

Methods—A pilot study of 36 consecutive diabetic patients undergoing planned phacoemulsification with IOL in one eye by one surgeon at the University of North Carolina consented to preoperative and postoperative OCT central subfield thickness measurements (CSF) and aqueous and blood samples for VEGF and IGF-1. Four patients with CSME received laser preoperatively. Spearman Rank correlations were performed between growth factors and mean CSF or a clinically meaningful percent change in CSF (>11% of preoperative measurement) at one and 6 months postoperatively.

Results—There were no surgical complications or new cases of CSME following surgery. Mean aqueous VEGF in patients with retinopathy, determined preoperatively, increased with increasing level of severity. Patients with preoperative CSME also had severe or worse retinopathy and the greatest mean aqueous VEGF. Significant preoperative correlations existed between aqueous VEGF and more severe retinopathy, whether CSME was present or absent (r=0.49, *P*=.007), and between aqueous VEGF and CSME (r=0.41, *P*=.029). At one month postoperative, aqueous VEGF was positively correlated with >11% change from preoperative CSF, regardless of CSME status (r=0.47; *P*=.027). No noteworthy associations existed between CSF and IGF-1 values.

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C. Contribution of Authors: Design of Study (MEH); Conduct of the study (MEH, KLC); Collection, Management, Analysis and interpretation of the data (MEH, LP, GK, PG, PR); Preparation, review or approval of the manuscript (MEH, LP, GK, PG, PR, KLC) D.

B. MEH consults for Ophthalmic Research Associates. Dr. Koch is the principal investigator for cooperative agreements through the University of North Carolina at Chapel Hill with over 20 pharmaceutical and biotechnology companies, with the most substantial of these being with GlaxoSmithKline. None of these agreements have a specific relationship with the study reported in this paper. The primary objectives for the cooperative agreements noted here pertain to matters of statistical methodology for the design, analysis, and reporting of confirmatory clinical trials. Other authors have no financial disclosures.

D. This clinical study was approved by the University of North Carolina at Chapel Hill School of Medicine's Committee on the Protection of the Rights of Human Subjects and Institutional Review Board, and all research adhered to the tenets of the Declaration of Helsinki.

Conclusions—Aqueous VEGF was significantly positively associated with a clinically meaningful change in CSF in diabetic patients one month following cataract surgery. Accounting for preoperative CSF was important. Further study is indicated.

INTRODUCTION

Cystoid macular edema (CME) and exacerbated diabetic macular edema can adversely affect visual outcomes following cataract surgery in patients with diabetes mellitus[1,2,3,4,5]. With technical improvements in cataract surgery, better glycemic control in patients with diabetes, and preoperative laser treatment for clinically significant macular edema (CSME), long-lasting macular edema following cataract surgery is reported less often now than in the past, but the problem of postoperative macular edema still exists[3,6]. A 30% increase in the center point thickness as measured by optical coherence tomography (OCT) was reported in 22% of patients with diabetes at one month post-cataract extraction[7]. More than half had resolution at 3 months in this study. However, delay in treatment of macular edema has been shown to reduce visual improvement following cataract extraction in some patients[8,9]. Therefore, preoperative measurements that identify patients at risk for macular edema after cataract surgery may be beneficial to initiate treatment early and reduce vision loss from macular edema.

Vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) have been implicated in the pathogenesis of macular edema and diabetic retinopathy. VEGF is a vasopermeability factor[10] and has been associated with diabetic macular edema[11]. Intravitreous injections of agents that neutralize the bioactivity of VEGF have stabilized or improved visual acuity and reduced central subfield thickness (CSF) as measured by OCT in phakic patients with diabetic macular edema[12] and have had mixed reports in non-diabetic pseudophakic patients with cystoid macular edema[13,14]. Another study reported that elevated aqueous levels of VEGF, IL-6, and protein were associated with exacerbated fluorescein leakage in the maculas of diabetic patients 6 months following cataract surgery[15]. A recent report showed that 8 patients with diabetes who had had intravitreous bevacizumab for CSME prior to cataract surgery had reduced aqueous VEGF levels at the time of surgery two months later, but only a transient reduction in CSF[16]. The efficacy of anti-VEGF treatment for prevention or treatment of post-operative CME or exacerbation of CSME from cataract surgery in patients with diabetes remains indeterminate and may require further study.

Increased serum IGF-1 has been positively associated with increased severity of diabetic retinopathy[17,18]. High serum IGF-1 following intensive glycemic control was associated with rapidly progressive diabetic retinopathy, and the severity of retinopathy was reduced with ocreotide, a somatostatin analogue[19]. Transgenic mice that overexpress IGF-1 developed retinal features similar to human diabetic retinopathy[20]. Furthermore, transgenic mice expressing a growth hormone antagonist gene, or wild type mice treated with an inhibitor to growth hormone, had reduced retinal neovascularization in an angiogenesis model[21,22].

We performed a pilot study to determine the associations between the concentration of VEGF or IGF-1 at the time of surgery and clinically meaningful macular thickening measured by OCT at one month and 6 months following cataract surgery. Knowing relationships between preoperative growth factor values and a change in the macular thickening may be useful to determine if these factors increase the predictability of macular thickening and vision loss in a diabetic patient anticipating cataract surgery. This information may then be useful in designing future clinical studies to test the effect of treatments to prevent or treat macular edema in diabetic patients undergoing cataract surgery.

METHODS

Patient Selection/Preoperative assessment

Consecutive patients with type II diabetes mellitus (DM) who consented to have aqueous and blood samples obtained at the time of planned phacoemulsification and intraocular lens placement, were enrolled between August 2005 and August 2006 from the practice of one experienced cataract surgeon. Patients with known vein or artery occlusions, other retinovascular disease, uveitis or previous vitrectomy or eye surgery were excluded. There were 36 patients with diabetes, 20 female and 16 male. The average age was 67.5 years. Media opacity from cataracts precluded preoperative grading of retinopathy severity in one patient and accurate measurements by OCT in 7 patients because of low image saturation. All patients had uncomplicated phacoemulsification with posterior chamber intraocular lens implantations. Serum and aqueous samples from 3 patients were not received in the laboratory. An additional 4 patients had insufficient aqueous for analysis of some growth factors.

Preoperative assessments were performed within 2 weeks of surgery and included undilated LogMAR best corrected visual acuity (VA) using the ETDRS chart, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure measurement, and biometry to calculate IOL power. OCT was performed at the preoperative visit by a trained masked ophthalmic photographer using the Stratus OCT-3 (Carl Zeiss Meditec) and central subfield thickness (CSF) was recorded and analyzed.

The severity of diabetic retinopathy was diagnosed at the preoperative visit using slit-lamp funduscopic biomicroscopy and classified as no retinopathy, mild non-proliferative retinopathy (NPDR), moderate NPDR, severe NPDR, or proliferative retinopathy (PDR) based on the International Clinical Diabetic Retinopathy Disease Severity Scale[23]. A score (S) of 1 for no retinopathy (S1) to 5 for PDR (S5) was used in analyses. In binary analyses, patients with none or mild NPDR were collapsed into one category and compared to those with moderate NPDR or worse. CSME was defined by criteria in the Early Treatment Diabetic Retinopathy Study (ETDRS) as retina thickening within 500 μm of the fovea, hard exudates within 500 μm of the fovea in association with retinal thickening or retinal thickening one disc area or larger within one disc diameter of the fovea. Patients with CSME were treated with laser based on the ETDRS[24] at least one month before cataract surgery and were deemed to have had maximal treatment prior to cataract surgery. No patients had preoperative intravitreous triamcinolone or bevacizumab injections.

Acquisition of serum and aqueous samples

At the time of surgery, 100–200 μL of aqueous humor was withdrawn from the anterior chamber using a tuberculin syringe attached to a 30 gauge needle via a paracentesis prior to instillation of viscoelastic. Blood samples were drawn into serum separation tubes (BD, Franklin Lakes, NJ) and allowed to clot for 30 to 60 minutes at room temperature. The sterile aqueous sample was placed on ice for transfer. Both samples were labeled with a unique identification number and transferred to the laboratory where they were centrifuged at 14000 rpm for 10 minutes at 4°C. The supernatants were rapidly frozen and stored at −80°C until analyses were performed.

Measurement of VEGF and IGF-1

VEGF and IGF-1 levels were measured in aqueous and serum samples by an experienced masked lab technician using commercially available enzyme-linked immunosorbent assay (ELISA) kits for human VEGF or IGF-1 (R&D Systems, Minneapolis, MN; mean minimum detectable dose: VEGF [6.4 pg/mL, catalog number DVE00], IGF-1 [0.026 ng/mL, catalog number DG100]) according to manufacturer's instructions. IGF-1 serum samples were

incubated with pretreatment reagents supplied with the kit prior to assay to release IGF-1 from binding proteins. Sample values were expressed as pg/mL (VEGF) or ng/mL (IGF-1) based on standard curves plotted using protein standards supplied with the kits. In cases in which aqueous collection was less than 150 μL, a dilution with phosphate buffered saline of up to 1:4 was used. The effect of dilution was then corrected when determining final values.

Postoperative assessment

The main outcome measures were LogMAR visual acuity and CSF variables determined postoperatively at 1 month and 6 months (mean CSF, and change in CSF >11% of preoperative CSF measurement).

Statistical analysis

At the time of designing this pilot study, there were few data on associations between OCT parameters and growth factor values in patients with diabetes. Also since the inception of the study, the Diabetic Retinopathy Clinical Research Network published that preoperative values of the CSF of the OCT are important when interpreting postoperative measurements. Specifically, a clinically meaningful change in CSF was equivalent to 11% of preoperative CSF[25], rather than an absolute value, such as 25 μm, used in previous studies (> 2 S.D. of baseline OCT[26]). This guideline has not yet been universally accepted; therefore, we determined associations between mean growth factor values and mean CSF as well as the percent change in postoperative CSF of at least 11% of the preoperative value.

Means and standard deviations are used to describe continuous variables and frequency distributions are used to describe categorical variables.

Retinopathy was analyzed by the category of severity or as a binary variable comparing no and mild NPDR to moderate NPDR or worse. Associations among preoperative mean CSF, change in CSF >11% of preoperative value, LogMAR visual acuity, serum and aqueous growth factors, and severity of retinopathy determined categorically or as a binary variable were assessed using Spearman rank correlations.

For all analyses of this pilot study, a criterion of $p \leq 0.05$ was used as a guideline to identify associations of potential interest for future study. All analyses were performed with SAS system software (SAS Institute Inc., Cary, N.C.).

RESULTS

Preoperative variables of all patients, categorized as those with and without CSME and by level of retinopathy severity, are shown in Table 1. When considering diabetic patients regardless of CSME status, the average HbA1C was 6.7± 1.2 % (range: 5.2 – 9.8) with a median value of 6.4%. Of diabetic patients without CSME, 19 had no retinopathy; 6 had mild NPDR; 5 had moderate NPDR; and 1 had PDR. Of those 4 with CSME, 3 had severe NPDR and 1 had PDR. (The media opacity from cataract precluded accurate classification of retinopathy in one patient.) All patients with CSME had been treated with laser prior to cataract surgery based on ETDRS recommendations[24]. Aqueous IGF-1 was below detection by ELISA in all patients (binding proteins had been released with pretreatment reagents to maximize the measurement of IGF-1). There was a progressive increase in mean aqueous VEGF levels from mild NPDR to severe PDR and to CSME, which included eyes with severe NPDR and PDR (Table 1). The increase in mean aqueous VEGF levels with increasing levels of retinopathy severity existed when the CSME group was removed and these values were included in appropriate retinopathy severity groups (data not shown).

In analyzing preoperative variables for all diabetics regardless of CSME status, there was a strong positive correlation between aqueous VEGF and more severe retinopathy when analyzed by category of retinopathy severity (r=0.43; *P*=.020; Table 2) and a very strong positive correlation with moderate NPDR or worse in a binary analysis (r=0.49; *P* =.007). The same relationships were not found for serum VEGF or IGF-1. When analyses were performed on diabetic patients without CSME, there was a trend toward increased mean aqueous VEGF and moderate or worse retinopathy in a binary analysis (r=0.35; *P* =.085), but no significant difference was found in a categorical analysis (Table 2). There was a positive correlation between mean aqueous VEGF and the presence of CSME (r=0.41; *P* =.029) and a positive trend between mean serum VEGF and CSME (r=0.30; *P*=.091).

Descriptive statistics for postoperative outcomes at one and 6 months are presented in Table 3 for all diabetic patients, divided into those with or without CSME, and categorized by level of retinopathy severity. Of note, the one month postoperative increase in CSF >11% of the preoperative measurement was found in 6 patients, 2 without CSME and in 4 with CSME.

Analyses of postoperative correlations of all patients with diabetes, regardless of CSME status, are shown in Table 4. Of note, aqueous VEGF was positively correlated with change in CSF > 11% of the preoperative measurement (r=0.47; *P* =.027) at one month after surgery. There were also strong positive correlations between more severe retinopathy, analyzed categorically, and mean CSF at one (r=0.64; *P* =.0003), 6 months (r=0.47; *P* =.017) and change in CSF >11% of the preoperative measurement at one month (r=0.53; *P* =.009). Similar relationships were present when retinopathy severity was analyzed in binary fashion. There was a trend toward increased mean serum VEGF and percent change in CSF >11% from the preoperative value at one month (r=0.37, *P* =.092).

Discussion

In this pilot study, we determined associations between VEGF or IGF-1 levels at the time of surgery with macular thickening measured as central subfield thickness (CSF) by OCT at one month following uncomplicated phacoemulsification. We found that aqueous VEGF correlated positively with a clinically meaningful change in CSF (>11% of preoperative value), suggesting it may have predictive value in determining diabetic patients at risk for macular edema following cataract surgery. We included diabetic patients with and without CSME because both CME and CSME can lead to vision loss following cataract surgery, and there are common factors in the pathogenesis (for example, inflammatory cytokines). However, we also divided out patients with CSME in some of our analyses. In patients with retinopathy, we found greater mean aqueous VEGF levels at progressively more severe levels of retinopathy in accordance with other investigators[27]. Patients with CSME had the highest mean aqueous VEGF levels, but these patients also all had severe NPDR or worse retinopathy. There were too few events in which a change in CSF >11% from baseline occurred in this pilot study to distinguish the influence of CSME or severity of retinopathy on the positive association with mean aqueous VEGF or other factors.

We chose to measure CSF at one month since previous investigators found CSF following cataract surgery to be greater at one month than at later time points[7], but we also evaluated those patients who were available for examination at 6 months. In a study from the Diabetic Retinopathy Clinical Research Network, baseline or preoperative CSF values were found to be important when analyzing postoperative values, specifically that a change in CSF of >11% of the preoperative measurement was clinically significant and outside the error of measurement present when using the Stratus OCT-3[25]. This study also found that there was better reproducibility in CSF than in foveal center point thickness measurements. In our study, no growth factor measurement (serum VEGF, aqueous VEGF, or IGF-1) was strongly

correlated with mean postoperative CSF at 1 month. However, even though only 6 patients had a > 11% change from preoperative CSF at one month, aqueous VEGF was strongly associated with a change in CSF >11% from the preoperative value at one month.

A previous study found no correlation in aqueous VEGF and CSF at the time of cataract surgery in 17 patients with diabetes[16]. This study also found no correlation in CSF and aqueous VEGF, both measured postoperatively, in 8 patients who had had an intravitreous injection of anti-VEGF antibody, bevacizumab, 2 months prior to cataract surgery to treat CSME. In these patients, aqueous VEGF was lower than in the 9 who had not had previous treatment with intravitreous bevacizumab. The study differed from ours in that we determined associations between preoperative aqueous VEGF levels and postoperative CSF at one and 6 months and analyzed clinically meaningful measurements of > 11% change in CSF[25]. Few patients in our study had increases in CSF that were >11% of preoperative values. This finding may be because patients in our study had good glycemic control, and most had no or mild NPDR. Few had CSME and of those who did, all had had preoperative laser treatment. Also, no patients developed new onset CSME during the follow up period, and all cataract surgery was uncomplicated.

High inter-patient variability in growth factor measurements has been reported in other studies[28,29,27,15]. To minimize variability in growth factor measurements, we strove to keep the time between collection of the sample and processing and storage at −80°C to within 2 hours of surgery. The mean serum VEGF in our study (283 pg/mL) was similar to studies in the oncology (mean values ranging from 240 to 327 pg/mL) and ophthalmology literature (mean 305 pg/mL). There is debate about whether serum or plasma samples should be obtained to measure circulating VEGF levels. Many studies in the oncology literature report serum VEGF values, because obtaining VEGF from the serum, rather than the plasma, includes that bound to platelets, whereas platelet-bound VEGF is underrepresented in plasma samples[30,31,32]. Several of these studies concluded that serum provided more useful data after direct comparison with plasma measurements[32,33], whereas others disagreed and favored plasma measurements[34]. In addition, in the ophthalmology literature, there is disagreement, but several studies[35,36] reported serum measurements of VEGF as valuable in the management of diabetic retinopathy. Therefore, we chose to measure serum VEGF in order to capture both bound and unbound VEGF. We used commercially available ELISA kits with standard curves to determine VEGF and IGF-1 protein in serum or aqueous and these analyses were completed by the same masked laboratory technician. In future studies, it may be helpful to measure both plasma and serum levels. However, we found that aqueous VEGF measurements appeared to be of greater benefit than serum VEGF or IGF-1 measurements in our analyses.

In summary, our study found that aqueous VEGF was positively correlated with a clinically meaningful percent change in CSF (>11% from the preoperative measurement[25]) at one month following cataract surgery in diabetic patients. Our study suggests that aqueous VEGF may lend predictive value when determining postoperative macular thickening in diabetic patients undergoing cataract surgery and may be a useful measure in future trials. Larger studies are recommended, particularly to dissect the potential value of aqueous VEGF and severity in retinopathy as predictors.

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Biography

Mary Elizabeth Hartnett, MD is a board-certified ophthalmologist, specializing in adult and pediatric vitreoretinal surgery, and professor of ophthalmology. She is involved in clinical and clinical trials research and is also Principal Investigator of an NIH-funded laboratory to study mechanisms of aberrant angiogenesis in retinal and choroidal diseases. Besides NEI/NIH, she has been funded through the March of Dimes, American Diabetes Association, Research to Prevent Blindness, and the Juvenile Diabetes Research Fund.

Table 1

Description of Preoperative Variables by Severity of Diabetic Retinopathy

	ALL	Without CSME				With CSME
	All Diabetes	No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR (Severe + PDR)
Number of pts	36	19	6	6 (5+0+1)		4 = (3+1)
HTN	22	9	6	4 (4+0+0)		3
Preop LogMAR VA	0.67(0.66)	0.55(0.45)	0.851(1.06)	0.91(0.94)		0.61(0.29)
Preop CSF	220(42)	205(26)	234 (53)	236(23)		242(78)
Serum VEGF	284 (187)	257(107)	235(155)	231(100)		648 (392)
Aqueous VEGF	698(647)	570(706)	467 (295)	981 (663)		1293 (23)
Serum IGF-1	102(33)	94 (33)	117(32)	112 (35)		92 (23)
HbA1C	6.7(1.2)	7.0 (1.4)	6.9 (0.8)	6.2 (0.7)		5.9(0. 5)

Media opacity precluded accurate classification of retinopathy severity in one patient Means (and standard deviations) are reported for continuous variables and frequency distributions are reported for categorical variables. pts – patients; NPDR – non-proliferative diabetic retinopathy; PDR – proliferative diabetic retinopathy; CSME – clinically significant macular edema; CSF – central subfield thickness measured on time-domain OCT3; VEGF – vascular endothelial growth factor; IGF-1 – insulin-like growth factor 1; HbA1c – hemoglobin A1C; VA – visual acuity (LogMAR); HTN - hypertension

Table 2

Correlations of Growth Factor Values with Preoperative Diabetic Retinopathy Severity and Clinically Significant Macular Edema

	Diabetic patients, including CSME		**Diabetic patients without CSME**		**CSME only**
	Categorical analysis of DR severity	**Binary analysis (moderate or worse DR vs. none or mild)**	**Categorical analysis of DR severity**	**Binary analysis (moderate or worse DR vs. none or mild)**	
Serum VEGF (pg/mL)	0.08	0.11	−0.09	−0.05	0.30[a]
Aqueous VEGF (pg/mL)	0.43[b]	0.49[c]	0.27	0.35[a]	0.41[b]
Serum IGF (ng/mL)	0.19	0.08	0.30	0.15	−0.10

[a] $0.05 < p \leq 0.10$

[b] $0.01 < p \leq 0.05$

[c] $0.001 < p \leq 0.01$

[d] $p \leq 0.001$

DR –diabetic retinopathy; CSME – clinically significant macular edema; VEGF – vascular endothelial growth factor; IGF-1 – insulin-like growth factor 1

Table 3

Description of Postoperative Outcomes by Severity of Diabetic Retinopathy and Clinically Significant Macular Edema

	ALL	Without CSME				With CSME
	All Diabetes	No retinopathy	Mild NPDR	Moderate NPDR	Severe NPDR	PDR (Severe+PDR)
LogMAR VA (1 month)	0.28(0.40)	0.10 (0.13)	0.50(0.66)	0.38 (0.44)		0.38(0.41)
LogMAR VA (6 months)	0.12 (0.24)	0.09(0.15)	0.04(0.03)	0.13 (0.27)		0.35(0.52)
CSF (1 month)	274(153)	207(25)	246(34)	417(283)		313(103)
CSF (6 months)	237(49)	215(30)	232 (25)	267(51)		273(91)
CSF>11% at 1 month (N:Y)	17:6	10:1	3:1	4:0		0:4
CSF>11% at 6 months (N:Y)	18:2	8:1	4:0	4:0		2:1

Means (and standard deviations) are reported for continuous variables and frequency distributions are reported for categorical variables CSME – clinically significant macular edema; NPDR – non-proliferative diabetic retinopathy; PDR – proliferative diabetic retinopathy; VA – visual acuity (LogMAR); CSF – central subfield thickness measured on time-domain OCT3

Table 4

Spearman Rank Correlations Between Growth Factor Values and Postoperative Variables in Diabetic Patients

	CSF (1 month)	CSF (6 months)	Change in CSF> 11% at 1 month	Change in CSF> 11% at 6 months	LogMAR VA at 1 month	LogMAR VA at 6 months
Serum VEGF (pg/mL)	−0.17	−0.10	0.37[a]	−0.35	−0.17	−0.10
Aqueous VEGF (pg/mL)	0.11	−0.06	0.47[b]	−0.12	−0.04	−0.05
Serum IGF-1 (ng/mL)	−0.03	−0.09	0.15	−0.38	0.15	−0.35
Retinopathy severity (categorical)	0.64[d]	0.47[b]	0.53[c]	0.08	0.37[a]	0.22
Retinopathy severity (binary[e])	0.51[c]	0.47[b]	0.40[a]	0.10	0.25	0.18
CSME	0.24	0.15	0.77[d]	0.33	0.14	0.18

[a] $0.05 < p \leq 0.10$

[b] $0.01 < p \leq 0.05$

[c] $0.001 < p \leq 0.01$

[d] $p \leq 0.001$

[e] binary analysis between none and mild non-proliferative diabetic retinopathy (NPDR) vs. moderate and worse retinopathy.

CSF – central subfield thickness measured on time-domain OCT3; VA – visual acuity (LogMAR); VEGF – vascular endothelial growth factor; IGF-1 – insulin-like growth factor 1; CSME – clinically significant macular edema;