ARTICLE

Poor glycemic control as a risk factor for pseudophakic cystoid macular edema in patients with diabetes

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Purpose: To specify the risk factors for pseudophakic cystoid macular edema (CME) in patients with diabetes.

Setting: Kymenlaakso Central Hospital, Unit of Ophthalmology, Kotka, Finland.

Design: Prospective case series.

Methods: Patients with type 1 or type 2 diabetes having routine cataract surgery were evaluated. Spectral-domain optical coherence tomography imaging was performed before surgery and 1 month postoperatively.

Results: The study comprised 93 patients (95 eyes). The central retinal thickness increase was 9.7 μm ± 1.7 (SEM) in diabetic patients with no retinopathy, 22.7 ± 8.6 μm in those who had nonproliferative retinopathy, and 73.8 ± 37.4 μm in those who had proliferative retinopathy ($P < .001$). The central retinal thickness increase was greater in the eyes of diabetic patients with insulin dependence than in eyes of patients using noninsulin medication (21.9 ± 5.9 μm versus 8.3 ± 1.8 μm, $P = .017$). Serum hemoglobin A_{1c} concentration and inversely, patient age, were associated with central retinal thickness increase, even after adjustment for confounding factors ($r = 0.607$, $P < .001$ and $r = 0.417$, $P = .001$, respectively). The central retinal thickness change was smaller in the eyes of patients who had a nonsteroidal antiinflammatory drug (NSAID) as their postoperative antiinflammatory medication than in eyes of patients who were not prescribed NSAID medication when retinopathy was analyzed as a covariant (8.2 ± 3.6 μm versus 13.6 ± 2.9 μm, $P = .016$).

Conclusions: Young patient age and poor glycemic control were risk factors for postoperative central retinal thickness increase. This study showed it is necessary to identify, effectively treat, and follow-up with patients with diabetes who are at a greater risk for pseudophakic CME.

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Cataract surgery is the most common surgical procedure worldwide and with modern phacoemulsification techniques, it is now safer than ever. However, the procedure is not risk-free and with the high number of operations, complications are occasionally seen. Pseudophakic cystoid macular edema (CME) (Irvine-Gass syndrome) is the most common postoperative complication of cataract surgery with an incidence rate of approximately 1.0% in patients with no known risk factors.[1,2] Diabetes itself, and its coexistence with diabetic macular edema and diabetic retinopathy (DR), have been linked to impaired visual outcomes after uneventful cataract surgery.[3,4] Despite improved systemic and ocular management of the disease, patients with diabetes have been identified to be at risk for pseudophakic CME, in particular those who have diabetic macular edema and/or DR, with the level of DR increasing the risk for pseudophakic CME.[1,2,5,6] To prevent pseudophakic CME, more aggressive antiinflammatory medications, nonsteroidal antiinflammatory drug (NSAID) eyedrops in particular, have been used before and after cataract surgery.[7,8] At present, there is no consensus on whether all patients with diabetes should receive more aggressive postoperative antiinflammatory medication; therefore, a wide variety of corticosteroid and NSAID treatments are used as singular drug therapies or in combination with varying treatment schedules.

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As the proportion of patients with type 1 or type 2 diabetes continues to increase,[9,10] the occurrence of pseudophakic CME can be expected to rise. The use of optical coherence tomography (OCT) has made the diagnosis of pseudophakic CME more accurate and convenient, reducing the need for fluorescein angiography (mainly used for ruling out differential diagnosis) to a minimum.[11] Previous studies with OCT[5,12,13] have shown that central retinal thickness increases postoperatively more in patients with diabetes, insulin dependence, and retinopathy, impairing visual acuity gain.

This study aimed to identify the patients with diabetes who are at the highest risk for pseudophakic CME. Specifically, these data might facilitate a surgeon's decision about whether a patient requires more extensive antiinflammatory medication for the prevention of pseudophakic CME and/or additional phase follow-ups.

PATIENTS AND METHODS

Study Design

Diabetic patients were admitted as per the national guidelines for the management of cataract in the Department of Ophthalmology, Kymenlaakso Central Hospital, Kotka, Finland. The patients were examined by an ophthalmologist on the day of surgery and at the 1-month postoperative visit. The mean central retinal thickness was recorded by spectral-domain OCT on both visits by an experienced ophthalmic nurse. The study was approved by the research director and chief medical officer of the Kymenlaakso Central Hospital. Oral consent was obtained from each participant before enrollment in the study, and all study participants were examined postoperatively at Kymenlaakso Central Hospital. Confidentiality of the patient records was maintained when the clinical data were entered in a computer-based standardized database for analysis.

Patients

Patients with type 1 or type 2 diabetes who were scheduled for cataract surgery were enrolled between September 2015 and December 2015. Exclusion criteria were patient withdrawal from the 1-month follow-up visit or omission of postoperative antiinflammatory medication and inability to obtain sufficient data from OCT imaging for the central retinal thickness comparisons.

Time from diagnosis of diabetes; topical and systemic medication; glycemic control (hemoglobin A_{1c} [HbA_{1c}]); history of laser photocoagulation, intravitreal treatment, and surgery; posterior segment status (eg, the degree of DR, existence of diabetic maculopathy, existence of age-related macular degeneration [AMD]); and other ocular comorbidities were recorded. The latest HbA_{1c} level was used and patients without an HbA_{1c} measurement within 1 year were not included in the study. Intraoperatively, axial length (AL), duration of the surgery, cumulative dissipated energy, and use of an intraocular surgical aid—a capsular tension ring (CTR) (Stabileyes, Abbott Medical Optics, Inc.) or a 6.25 mm pupil-expansion device (Malyugin Ring, Microsurgical Technology)—were recorded.

Postoperative Antiinflammatory Medication

The postoperative antiinflammatory medication was corticosteroid (dexamethasone sodium phosphate 1.32 mg/mL, Oftan Dexa) 3 times a day for 3 weeks. The decision to use an NSAID (nepafenac 10 mg/mL, Nevanac) 3 times a day for 3 weeks in combination with a corticosteroid (15 eyes of 15 patients) was made by the operating physician. One of the patients did not tolerate dexamethasone sodium phosphate as a postoperative antiinflammatory medication and was treated only with nepafenac.

Surgical Technique

A standardized phacoemulsification technique was used in all cataract surgeries. A 2.75 mm clear cornea incision was followed by capsulorhexis, phacoemulsification (divide-and-conquer), and intraocular lens (IOL) placement in the capsular bag. An Ozil phacoemulsification handpiece and a 0.9 mm 30-degree beveled Kelman tip were used in the phacoemulsification system (Infiniti, Alcon Surgical, Inc.). In all cases, anesthesia was topical. Hyaluronic acid 1.6%–chondroitin sulfate 4.0% (Discovisc) was used as the ophthalmic viscosurgical device. Aspheric hydrophobic single-piece monofocal IOLs were used (Tecnis, PCB00, Abbott Medical Optics, Inc. or Acrysof IQ, SN60WF, Alcon Surgical, Inc.). Antimicrobial medication included intraoperative intracameral cefuroxime (Aprokam) and postoperative levofloxacin 5 mg/mL (Oftaquix) eyedrops 3 times a day for 1 week.

Clinical Evaluation

The corrected distance visual acuity (CDVA) was evaluated preoperatively by the referring ophthalmologist and postoperatively with an autorefractometer (AR-1s, Nidek Co. Ltd.) at standardized light conditions. Intraocular pressure was measured with rebound tonometry (iCare tonometer, Revenio Group Oyj).

The biometry was evaluated on the day of surgery using the IOLMaster 500 (Carl Zeiss Meditec AG), and the Haigis formula[14] was used for IOL power calculations.

Diabetic retinopathy was evaluated by clinical assessment and graded on a 5-stage severity classification as none, background, moderate nonproliferative, severe nonproliferative, or proliferative DR according to international clinical classification systems for DR.[15,16] For statistical purposes, DR was graded as 0 = none, 1 = nonproliferative (background, moderate, and severe nonproliferative), and 2 = proliferative DR.

Follow-up 30-frame scans were performed with Autorescan software and preoperative OCT analyses were compared with those obtained 1 month after surgery (Heidelberg Eye Explorer, version 1.9.10.0 and HRA Spectralis Viewing Module, version 6.0.9.0, Heidelberg Engineering GmbH).

Pseudophakic CME was diagnosed by a clinician at the control visit. The diagnosis of pseudophakic CME was based on clinical signs and typical OCT findings.[12]

Statistical Analyses

Data are given as means ± SEM, except for the absolute numbers and proportions for the nominal scale. Statistical analysis was performed using IBM SPSS Statistics software (version 24, IBM Corp.). For 2-group comparisons, qualitative data were analyzed with the 2-factor chi-square test (or with the Fisher exact test when values in any of the cells of a contingency table were below 5) and ordinal measurement scale, and continuous variables with the nonparametric Mann-Whitney *U* test. Multiple groups were compared with the control by using the nonparametric Kruskal-Wallis with the Dunn test. The Dunn post hoc test was applied only if the Kruskal-Wallis test showed an overall statistically significant difference. A linear regression model was used to estimate the relationships between variables, and multiple regression was used to include specific variables in the model, such as type of diabetes and existence of posterior segment comorbidities (diabetic maculopathy, level of DR, dry AMD). A *P* value of 0.05 or less was considered statistically significant.

RESULTS

The study recruited 103 patients (105 eyes) with type 1 or type 2 diabetes. Of these, 2 patients were excluded because they were unable to meet the 1-month follow-up, 1 patient was excluded because of omission of postoperative antiinflammatory medication, and 7 patients were excluded

Table 1. Baseline variables of 93 patients (95 eyes).

Parameter	Value
Sex	
Male	43
Female	50
Age (y)	
Mean	72.7
Range	44, 88
DM (n)	
Type 1	7
Type 2	86
Insulin medication (n)	
Yes	35
No	58
Maculopathy	
Yes	9
No	86
Retinopathy	
None	84
NPDR	7
PDR	4
Duration of DM (y)	
Mean	14.8
Range	<1, 53
HbA_{1c} (%)	
Mean	7.0
Range	4.6, 15.2
CDVA (Snellen decimal)	
Mean	0.32
Range	HM, 0.50
CRT (μm)	
Mean	287.9
Range	186, 562

CDVA = corrected-distance visual acuity; CRT = central retinal thickness; DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}; HM = hand movement; n = number of patients; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

because of inability to obtain sufficient data from OCT imaging for the central retinal thickness comparisons. Thus, the analysis comprised 93 patients (95 eyes).

Seven patients (7 eyes) had type 1 diabetes, and 86 patients (88 eyes) had type 2 diabetes. The mean duration of diabetes was 14.8 years and the mean level of HbA_{1c} was 7.0% (53 mmol/mol). Overall, 35 patients were insulin dependent. Eleven study eyes had DR of which 4 had background, 3 had preproliferative, and 4 had the proliferative form. Diabetic maculopathy was present in 9 eyes and clinically relevant diabetic macular edema in 5 eyes. Six eyes had partial or panretinal laser photocoagulation treatment based on the form of retinopathy, and 4 eyes were treated with macular grid laser photocoagulation. Dry AMD was diagnosed in 17 eyes and epiretinal membrane or vitreomacular traction was diagnosed in 11 eyes.

Table 1 shows the patients' baseline characteristics. Preoperatively, the mean CDVA was 0.32 ± 0.01 decimals in the Snellen chart and the mean central retinal thickness was 287.9 ± 5.8 μm. The mean operation time was 19.6 ± 0.9 minutes and the phaco energy (cumulated dissipated energy) was 16.4 ± 2.0 seconds. A pupil-expansion device was used in 3 surgeries and CTR in 2 surgeries. No eye had iris prolapse or vitreous loss.

Central Retinal Thickness

Diabetic Patients with Insulin Dependence The mean central retinal thickness increase was 21.9 ± 5.9 μm in the eyes of diabetic patients with insulin dependence and 8.3 ± 1.8 μm in those with noninsulin medication ($P = .017$) (Figure 1, *A*). The mean central retinal thickness increase was 34.9 ± 13.6 μm in type 1 diabetes and 18.6 ± 6.5 μm in type 2 diabetic patients with insulin dependence (Figure S1, *A* and *B*, available at: www/jcrsjournal.org). The time from the diagnosis of diabetes was not associated with the central retinal thickness change ($r = 0.032$, $P = .765$) (Figure 1, *B*).

Hemoglobin A_{1c} Serum Concentrations Serum HbA_{1c} concentration, reflecting poor glycemic control, was associated with central retinal thickness increase ($r = 0.523$, $P < .001$) (Figure 1, *C*). The HbA_{1c} concentration was higher in patients who had type 1 diabetes than in patients with type 2 diabetes ($P < .001$) (Table S1, available at: www/jcrsjournal.org), and the association between serum HbA_{1c} and central retinal thickness increase remained significant in regression analysis of patients with type 2 diabetes only ($r = 0.518$, $P < .001$) (Figure 1, *C*). Moreover, in the multivariate linear regression model with diabetic posterior segment manifestations (maculopathy and level of retinopathy) and type of diabetes as confounding factors, the association between serum HbA_{1c} and central retinal thickness increase remained significant ($r = 0.607$) ($P < .001$).

Proliferative Diabetic Retinopathy In patients having diabetic maculopathy, the mean central retinal thickness increase was 37.3 ± 20.6 μm compared with those with no maculopathy 10.7 ± 1.6 μm ($P = .647$) (Figure 2, *A*). The mean

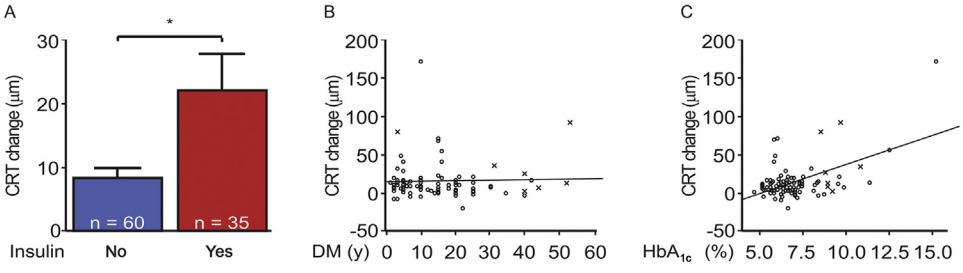

Figure 1. The effect of (*A*) insulin dependence on the central retinal thickness change 1 month after uncomplicated cataract surgery. Correlation between (*B*) duration of diabetes in years since diagnosis and (*C*) serum level of HbA_{1c} on the central retinal thickness change (* = $P \leq .05$; CRT = central retinal thickness; DM = diabetes mellitus; HbA_{1c} = hemoglobin A_{1c}).

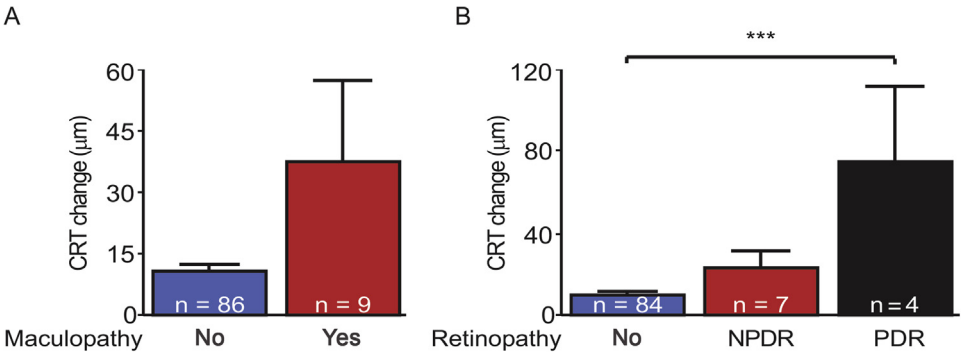

Figure 2. The effect of diabetic (*A*) maculopathy and (*B*) retinopathy on the central retinal thickness change (*** = $P < .001$; CRT = central retinal thickness; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy).

central retinal thickness change was 9.7 ± 1.7 µm in patients with no DR, 22.7 ± 8.6 µm in those with the nonproliferative DR form, and 73.8 ± 37.4 µm in those with proliferative DR ($P < .001$) (Figure 2, *B*).

Use of Postoperative Antiinflammatory Medication

Fourteen eyes were treated with a combination of corticosteroid (dexamethasone sodium phosphate 1.32 mg/mL) and NSAID (nepafenac 10 mg/mL) eyedrops postoperatively. In addition, 1 eye was treated with only nepafenac 10 mg/mL eyedrops postoperatively. The mean age of the patients was 70.5 years and the mean HbA_{1c} was 7.3% in patients receiving NSAID drops. The central retinal thickness change in those not receiving NSAID treatment was 13.6 ± 2.9 µm and 8.2 ± 3.6 µm in those receiving NSAID ($P = .227$) (Figure 3, *A*). Two of the 15 eyes were of patients with type 1 diabetes. Maculopathy coexisted in 3 eyes, and DR in 4 eyes. Baseline variables did not differ from the group with no NSAIDs, except the level of DR ($P = .020$). When the level of DR was analyzed as a covariant (analysis of covariance), the central retinal thickness change was less in the eyes in the NSAID group than in the eyes with no NSAID treatment ($P = .016$).

Effect of Central Retinal Thickness Change

Visual Outcomes 1 Month After Surgery At 1 month, the mean decimal CDVA was 0.86 ± 0.03 (mean CDVA gain 0.54 ± 0.03) and the mean central retinal thickness was 301.1 ± 6.7 µm (mean CRT increase 13.2 ± 2.5 µm). In eyes with the mean central retinal thickness at 1 month that was more than 30% greater than preoperatively, the postoperative CDVA decreased from 0.89 ± 0.03 to 0.29 ± 0.04 ($P = .049$) and the CDVA gain was (0.05 ± 0.05 versus 0.57 ± 0.04) ($P = .048$) compared with eyes with a central retinal thickness increase of less than 20% (Figure 3, *B*). Based on the clinical evaluation and OCT analysis, pseudophakic CME was refractory and longstanding in 3 (3.2%) of the 95 eyes, and these were treated with intravitreal injections with a sustained delivery of 0.7 mg dexamethasone. All 3 were insulin dependent ($P = .047$) and did not receive NSAID treatment primarily after the surgery (the difference was not statistically significant). In non-pseudophakic CME eyes, the mean central retinal thickness increase was 10.0 ± 2.9 µm (range 22 to 69 µm) and in eyes with refractory pseudophakic CME, the mean central retinal thickness increase was 113.7 ± 28.9 µm (range 79 to 171 µm).

Patient Age and Diabetic Patients with Dry Age-Related Macular Degeneration The age of the diabetic patients at surgery was inversely associated with central retinal thickness change ($r = 0.392$, $P < .001$) (Figure 4, *A*). Patients with type 1 diabetes were younger than patients with type 2 diabetes ($P < .001$) (Table S1, available at: www.jcrsjournal.org). The inverse association between patient age and central retinal thickness change remained

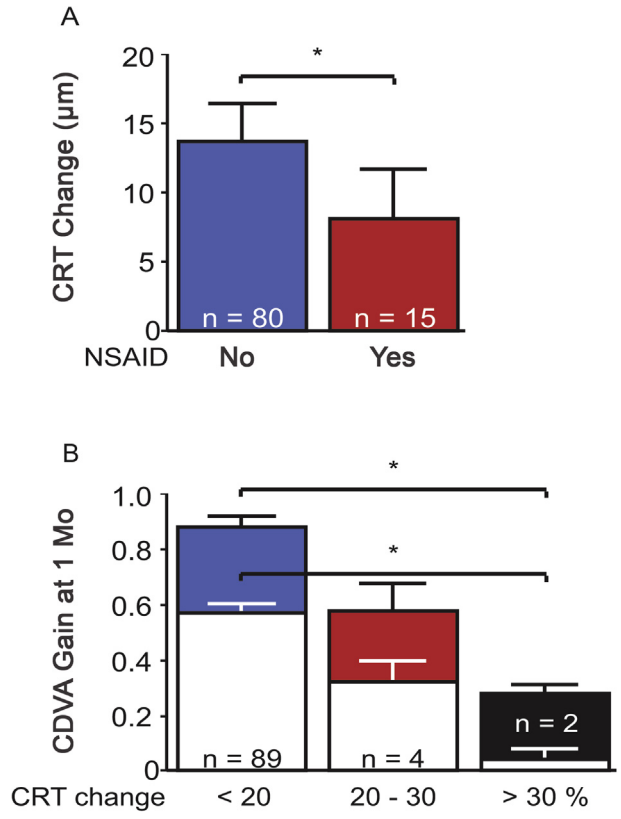

Figure 3. The effect of (*A*) use of postoperative NSAID eyedrops on the central retinal thickness change and (*B*) the level of central retinal thickness change on postoperative CDVA (*colored bars*) and CDVA gain (*white bars*) 1 month after uncomplicated cataract surgery (* = $P \leq .05$; CDVA = corrected-distance visual acuity; CRT = central retinal thickness).

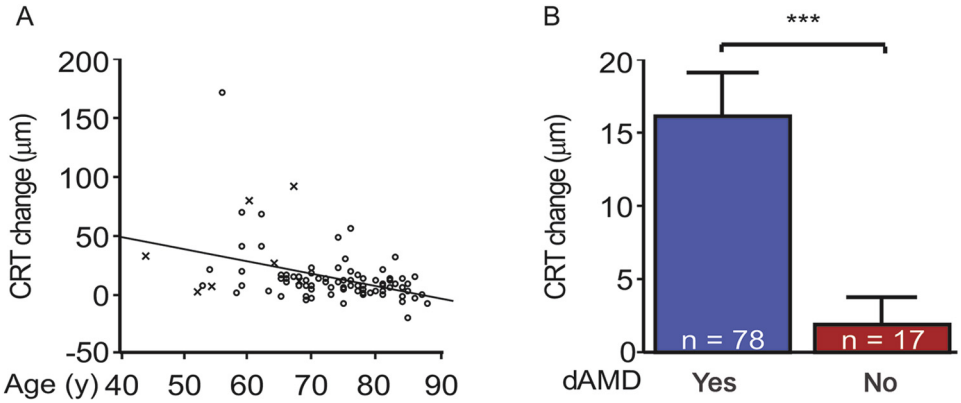

Figure 4. *A*: Correlation between patient age and the central retinal thickness change at 1 month. *B*: The effect of dry AMD on the central retinal thickness change (*** = $P < .001$; CRT = central retinal thickness; dAMD = dry age-related macular degeneration; DM = diabetes mellitus).

significant in regression analysis only in type 2 diabetic patients ($r = 0.406$, $P < .001$) (Figure 4, *A*).

Eyes with dry AMD were associated with less central retinal thickness increase than eyes with no dry AMD (1.9 ± 1.9 µm and 16.1 ± 3.0 µm) ($P = .001$) (Figure 4, *B*). However, the inverse association between age and central retinal thickness change remained significant when analyzing the eyes with no dry AMD only ($r = 0.367$, $P = .001$). In the multivariate linear regression model with the type of diabetes and presence of dry AMD as confounding factors, inverse correlation between patient age and central retinal thickness change remained significant ($r = 0.417$, $P = .001$).

Effect of Topical Nonsteroidal Antiinflammatory Drugs on Central Retinal Thickness

In patients having non-insulin medication, the mean central retinal thickness increase was 9.2 ± 1.9 µm without NSAIDs and 1.5 ± 3.1 µm with topical NSAIDs ($P = .029$). In patients with insulin dependence, the mean central retinal thickness increase was 21.7 ± 7.3 µm with no NSAIDs and 15.9 ± 5.8 µm with topical NSAIDs ($P = 0.040$ compared with those using non-insulin medication) (Figure S2, *A*, available at: www/jcrsjournal.org).

In eyes with no maculopathy, the mean central retinal thickness increase was 10.9 ± 1.8 µm with no NSAIDs and 9.7 ± 4.3 µm with topical NSAIDs. In eyes with maculopathy, the mean central retinal thickness increase was 52.4 ± 35.1 µm with no NSAIDs and 2.3 ± 3.8 µm with topical NSAIDs (Figure S2, *B*, available at: www/jcrsjournal.org).

In eyes with no retinopathy, the mean central retinal thickness increase was 10.5 ± 1.9 µm with no NSAIDs and 4.5 ± 3.0 µm with topical NSAIDs. In eyes with retinopathy, the central retinal thickness increase was 50.8 ± 27.4 µm with no NSAIDs ($P = .045$ compared with those with no retinopathy) and 20.5 ± 9.2 µm with topical NSAIDs (Figure S2, *C*, available at: www/jcrsjournal.org).

When NSAIDs were included as a covariant in the multivariate linear regression model with maculopathy, level of retinopathy, and type of diabetes as confounding factors, the association between serum HbA_{1c} and central retinal thickness increase remained significant ($r = 0.639$, $P < .001$). In addition, the inverse relationship between patient age and central retinal thickness remained significant when NSAIDs were included as a covariant in the multivariate linear regression model with dry AMD and type of diabetes as confounding factors ($r = 0.422$, $P < .001$).

Central Retinal Thickness Change Correlations

In eyes with an epiretinal membrane and eyes with no epiretinal membrane and/or vitreomacular traction, the central retinal thickness change was comparable ($P = .525$, Figure S3, available at: www/jcrsjournal.org). Neither AL ($r = 0.019$, $P = .862$), phaco energy ($r = 0.089$, $P = .485$), operation time ($r = 0.105$, $P = .334$) (Table 2), use of a pupil-expansion device or a CTR ($P = .510$), nor the educational level of the operating physician (experienced resident versus specialist in ophthalmology, $P = .244$) (Figure S3, available at: www/jcrsjournal.org) had an effect on the central retinal thickness change.

DISCUSSION

Pseudophakic CME remains a common cause of reduced visual acuity gain after cataract surgery, especially in patients with diabetes. This study identifies unreported clinical characteristics that predispose diabetic patients to a high risk for developing pseudophakic CME. Supporting previous data, the level of DR was identified as a risk factor for central retinal thickness increase. Moreover, central retinal thickness increase was greater in patients with type 1 diabetes than in patients with type 2 diabetes, and the central retinal thickness increase was greater in type 2

Table 2. Correlation between surgical parameters and the mean central retinal thickness change.*

Parameter	Range	*r* Value	*P* Value
Axial length (mm)	21.1, 26.5	0.019	.862
Phaco energy (CDE)	4.1, 127.0	0.089	.485
Surgical procedure time (min)	6, 56	0.105	.334

CDE = cumulative dissipated energy
*Linear regression model

diabetic patients who were insulin dependent than in type 2 diabetic patients who were not using insulin medication.

Glycemic oscillations postprandial (after mealtime) and during fasting might activate oxidative stress, systemic proinflammatory, and proapoptotic signaling pathways and promote microvascular endothelial dysfunction and pericyte dropout.[17,18] Patients with type 1 diabetes have a higher glycemic variability than patients with type 2 diabetes, regardless of overall glycemic control.[19] Given that glucose fluctuation might differ between insulin-dependent and non-dependent diabetic patients, and glycemic variability might promote inflammation and vascular complications, patients with type 1 or type 2 diabetes with insulin dependence seem to be at greater risk for pseudophakic CME.

With univariate and multivariate regression analyses, we found a correlation between serum levels of HbA_{1c} and central retinal thickness increase. This is in accordance with the recently published data.[20] The HbA_{1c}, a simple quantitative measure, might be used as 1 of the tools to estimate an individual's risk for developing pseudophakic CME. The mechanisms behind the correlation between HbA_{1c} and central retinal thickness are likely multifactorial and might include secretion of inflammatory and vasoactive factors, such as angiopoietin-2 and vascular endothelial growth factor, microvascular dysfunction, and blood–retinal barrier breakdown.[21–23] Poor glycemic control not only encourages more aggressive antiinflammatory medication in cataract surgery, but also better management of the disease preoperatively.

In concurrence with the literature, dry AMD was associated with reduced macular changes after cataract surgery.[2] However, the presence of dry AMD did not explain the inverse association between patient age and central retinal thickness increase. Use of vasoactive medications in older patients with diabetes might play a protective role; therefore, further studies evaluating the relationship between systemic medication and posterior segment changes after ocular surgery might prove fruitful.[24–26]

Our present study has some limitations. First, although the study has a prospective design, it was not tightly controlled. A non-diabetic control group was not included in the study design that focused on recruiting a high number of diabetic patients. Although the study population included only 7 eyes from type 1 diabetic patients, 3 of the 4 proliferative DR eyes were from patients with type 1 diabetes. Multivariate analyses were performed to minimize effect of confounding factors. Second, the postoperative use of NSAID eyedrops in combination with corticosteroids was left to the operating surgeon's clinical discretion, and seemed to be based more on the operating surgeon's preference than on the known risk factors in the patient population. According to covariance analysis, postoperative use of topical NSAIDs reduced central retinal thickness increase. This parallels the finding that the use of an NSAID and corticosteroid combination reduced the incidence of pseudophakic CME after uneventful cataract surgery in a retrospective chart review of unselected patients and in a double-masked randomized clinical trial of patients with nonproliferative diabetic retinopathy in comparison to corticosteroid monotherapy.[27,28] Third, late phase follow-ups 3 to 12 months after surgery would have been warranted to better evaluate the kinetics of central retinal thickness and pseudophakic CME. These were, however, not included in the study protocol monitoring the clinical practice because clinical practices in government-based units are recommended to adhere to the Current Care Guidelines of Cataract Surgery of the Finnish Medical Society, Duodecim, which state that a 1-month follow-up is sufficient after uncomplicated cataract surgery.

This study encourages strict preoperative diabetes management and in select cases, intensive management for pseudophakic CME prophylaxis. The use of more extensive antiinflammatory medication postoperatively and perhaps preoperatively, in particular NSAID eyedrops as a monotherapy or in combination with conventionally used corticosteroid eyedrops, could be justified to diminish the risk for developing pseudophakic CME.[1,8,27–29] Intraoperative bevacizumab injection might also be considered as an adjunct treatment, and additional phase follow-ups might be appropriate in patients at high risk for pseudophakic CME.[30,31] Research on the risks for and prevention of pseudophakic CME is still required to minimize postoperative complications of uneventful cataract surgery, especially concerning patients with diabetes.

To conclude, the findings in this study suggests considering serum HbA_{1c} when assessing a patient's risks for pseudophakic CME. Clinical characteristics such as patient age, type of diabetes and insulin dependency, and posterior segment manifestations of disease should also be considered.

WHAT WAS KNOWN

- Diabetes is a risk factor for pseudophakic CME.
- The extent of diabetic posterior segment manifestations adds to the risk for pseudophakic CME.

WHAT THIS PAPER ADDS

- A diabetic patient's risk for pseudophakic CME was associated with poor glycemic control, which was determined by the high serum HbA_{1c} level.
- It is necessary to identify, effectively treat, and follow-up with patients who have diabetes and are at a greater risk for pseudophakic CME.

REFERENCES

1. Grzybowski A, Sikorski BL, Ascaso FJ, Huerva V. Pseudophakic cystoid macular edema: update 2016. Clin Interv Aging 2016; 11:1221–1229. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5025006/pdf/cia-11-1221.pdf. Accessed August 11, 2017
2. Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC, for the United Kingdom Pseudophakic Macular Edema Study Group. Risk factors and incidence of macular edema after cataract surgery; a database study of 81 984 eyes. Ophthalmology 2016; 123:316–323. Available at: http://www.aaojournal.org/article/S0161-6420(15)01146-X/pdf. Accessed August 11, 2017
3. Zaczek A, Olivestedt G, Zetterström C. Visual outcome after phacoemulsification and IOL implantation in diabetic patients. Br J Ophthalmol 1999; 83:1036–1041. Available at: http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1723171&blobtype=pdf. Accessed August 11, 2017

4. Somaiya MD, Burns JD, Mintz R, Warren RE, Uchida T, Godley BF. Factors affecting visual outcomes after small-incision phacoemulsification in diabetic patients. J Cataract Refract Surg 2002; 28:1364–1371
5. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology 2007; 114:881–889
6. Diabetic Retinopathy Clinical Research Network Authors/Writing Committee. Macular edema after cataract surgery in eyes without preoperative central-involved diabetic macular edema. JAMA Ophthalmol 2013; 131:870–879. Available at: http://archopht.jamanetwork.com/article.aspx?articleid=1679509. Accessed August 11, 2017
7. Henderson BA, Kim JY, Ament CS, Ferrufino-Ponce ZK, Grabowska A, Cremers SL. Clinical pseudophakic cystoid macular edema; risk factors for development and duration after treatment. J Cataract Refract Surg 2007; 33:1550–1558
8. Wielders LHP, Lambermont VA, Schouten JSAG, van den Biggelaar FJHM, Worthy G, Simons RWP, Winkens B, Nuits RMMA. Prevention of cystoid macular edema after cataract surgery in nondiabetic and diabetic patients: a systematic review and meta-analysis. Am J Ophthalmol 2015; 160:968–981.e33
9. Tuomilehto J. The emerging global epidemic of type 1 diabetes. Curr Diab Rep 2013; 13:795–804
10. Jaacks LM, Siegel KR, Gujral UP, Narayan KMV. Type 2 diabetes: a 21st century epidemic. Best Pract Res Clin Endocrinol Metab 2016; 30:331–343
11. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol 2012; 23:26–32
12. Kusbeci T, Eryigit L, Yavas G, Inan UU. Evaluation of cystoid macular edema using optical coherence tomography and fundus fluorescein angiography after uncomplicated phacoemulsification surgery. Curr Eye Res 2012; 37:327–333
13. Chen X-Y, Song W-J, Cai H-Y, Zhao L. Macular edema after cataract surgery in diabetic eyes evaluated by optical coherence tomography. Int J Ophthalmol 2016; 9:81–85. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4768508/pdf/ijo-09-01-081.pdf. Accessed August 11, 2017
14. Haigis W, Lege B, Miller N, Schneider B. Comparison of immersion ultrasound biometry and partial coherence interferometry for intraocular lens calculation according to Haigis. Graefes Arch Clin Exp Ophthalmol 2000; 238:765–773
15. Davis MD, Fisher MR, Gangnon RE, Barton F, Aiello LM, Chew EY, Ferris FL III, Knatterud GL, for the Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: Early Treatment Diabetic Retinopathy Study Report #18. Invest Ophthalmol Vis Sci 1998; 39:233–252. Available at: http://iovs.arvojournals.org/article.aspx?articleid=2180992. Accessed August 16, 2017
16. Wilkinson CP, Ferris FL III, Klein RE, Lee PP, Agardh CD, Davis M, Dills D, Kampik A, Pararajasegaram R, Verdaguer JT, representing the Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003; 110:1677–1682
17. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002; 106:2067–2072. Available at: http://circ.ahajournals.org/content/106/16/2067. Accessed August 11, 2017
18. Beltramo E, Arroba AI, Mazzeo A, Valverde AM, Porta M. Imbalance between pro-apoptotic and pro-survival factors in human retinal pericytes in diabetic-like conditions. Acta Ophthalmol 2017 [Epub ahead of print]. Available at: https://iris.unito.it/retrieve/handle/2318/1623624/292412/Beltramo_MS_IRIS_4aperto.pdf. Accessed August 11, 2017
19. Sechterberger MK, van Steen SCJ, Boerboom EMN, van der Voort PHJ, Bosman RJ, Hoekstra JBL, DeVries JH. Higher glucose variability in type 1 than in type 2 diabetes patients admitted to the intensive care unit: a retrospective cohort study. J Crit Care 2016; 38:300–303
20. Yang J, Cai L, Sun Z, Ye H, Fan Q, Zhang K, Lu W, Lu Y. Risk factors for and diagnosis of pseudophakic cystoid macular edema after cataract surgery in diabetic patients. J Cataract Refract Surg 2017; 43:207–214
21. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, Pasquale LR, Thieme H, Iwamoto MA, Park JE, Nguyen HV, Aiello LM, Ferrara N, King GL. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994; 331:1480–1487. Available at: http://www.nejm.org/doi/pdf/10.1056/NEJM199412013312203. Accessed August 11, 2017
22. Hammes H-P, Feng Y, Pfister F, Brownlee M. Diabetic retinopathy: targeting vasoregression. Diabetes 2011; 60:9–16. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012202/pdf/zdb9.pdf. Accessed August 11, 2017
23. Tuuminen R, Haukka J, Loukovaara S. Poor glycemic control associates with high intravitreal angiopoietin-2 levels in patients with diabetic retinopathy [letter]. Acta Ophthalmol 2015; 93:e515–e516. Available at: http://onlinelibrary.wiley.com/doi/10.1111/aos.12401/epdf. Accessed August 11, 2017
24. Tuuminen R, Sahanne S, Loukovaara S. Low intravitreal angiopoietin-2 and VEGF levels in vitrectomized diabetic patients with simvastatin treatment. Acta Ophthalmol 2014; 92:675–681. Available at: http://onlinelibrary.wiley.com/doi/10.1111/aos.12363/epdf. Accessed August 11, 2017
25. Tuuminen R, Sahanne S, Haukka J, Loukovaara S. Improved outcome after primary vitrectomy in diabetic patients treated with statins. Eur J Ophthalmol 2016; 26:174–181
26. Tuuminen R, Yegutkin GG, Jalkanen S, Loukovaara S. Simvastatin use associated with low intraocular ADP levels in patients with sight-threatening diabetic retinopathy [letter]. Graefes Arch Clin Exp Ophthalmol 2016; 254:1643–1644
27. Wolf EJ, Braunstein A, Shih C, Braunstein RE. Incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated with nepafenac. J Cataract Refract Surg 2007; 33:1546–1549
28. Singh R, Alpern L, Jaffe GJ, Lehmann RP, Lim J, Reiser HJ, Sall K, Walters T, Sager D. Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy. Clin Ophthalmol 2012; 6:1259–1269. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3422154/pdf/opth-6-1259.pdf. Accessed August 11, 2017
29. Kessel L, Tendal B, Jørgensen KJ, Erngaard D, Flesner P, Lundgaard Andresen J, Hjortdal J. Post-cataract prevention of inflammation and macula edema by steroid and nonsteroidal anti-inflammatory eye drops; a systematic review. Ophthalmology 2014; 121:1915–1924. Available at: http://www.aaojournal.org/article/S0161-6420(14)00389-3/pdf. Accessed August 11, 2017
30. Funatsu H, Yamashita H, Noma H, Shimizu E, Mimura T, Hori S. Prediction of macular edema exacerbation after phacoemulsification in patients with nonproliferative diabetic retinopathy. J Cataract Refract Surg 2002; 28:1355–1363
31. Takamura Y, Kubo E, Akagi Y. Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery. Ophthalmology 2009; 116:1151–1157

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