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Surgical & Medical Retina, Uveitis, Macular Degeneration & Diabetic Eye Disease

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RETINA DIGEST®

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Anti-VEGF Therapy and Increased Intraocular Pressure

Development of intravitreal vascular endothelial growth factor (VEGF) inhibitors such as ranibizumab, bevacizumab and aflibercept has revolutionized the treatment of neovascular age-related macular degeneration (AMD), diabetic macular edema and macular edema caused by retinal vein occlusion. One secondary effect of any intravitreal injection is a transient elevation of intraocular pressure (IOP).

Dedania from the Albany Medical Center, New York, and Bakri from the Mayo Clinic, Minnesota, reviewed the literature evaluating sustained and delayed elevation of IOP in patients receiving intravitreal anti-VEGF therapy for neovascular AMD. They found 15 studies.

Reported incidence of sustained elevated IOP ranged from 3.45% to 11.6% in patients receiving anti-VEGF injections. The majority of patients with sustained elevated IOP were treated successfully with topical IOP-lowering medication.

Eight of the 15 studies included patients with a history of glaucoma and/or ocular hypertension, but conclusive data did not exist for an association with sustained elevated IOP after anti-VEGF injections. Several studies reported a correlation between increasing number of injections and sustained IOP elevation; again, other studies failed to support this correlation. Five studies reported prolonged elevated IOP in patients with previous or current systemic and/or topical steroid use. Patients receiving bevacizumab appeared to have a higher incidence of sustained elevated IOP, perhaps due to its higher molecular weight, which could cause outflow channel obstruction.

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Although insufficient data exist to establish a conclusive link between intravitreal anti-VEGF therapy and long-term elevated IOP, the current literature appears to support a connection. For now, patients undergoing intravitreal anti-VEGF therapy should be closely monitored for both immediate and prolonged increases in IOP.

Dedania VS, Bakri SJ. Sustained elevation of intraocular pressure after intravitreal anti-VEGF agents: what is the evidence? Retina *2015;35:841-858.*

Table 1. Logistic regression analyses of factors used to estimate risk of retinal toxicity

Variable	Odds ratio (95% CI)	*p* value
Multivariate analysis		
Daily use in 100-mg increments	5.11 (3.83–6.83)	<.001
Duration of use in 5-year increments	2.03 (1.72–2.40)	<.001
Tamoxifen citrate therapy	4.59 (2.05–10.27)	<.001
Kidney disease	2.08 (1.44–3.01)	<.001
Weight	0.96 (0.95–0.97)	<.001
Female sex	1.80 (0.95–3.36)	.08
Age at start of therapy	1.01 (0.99–1.02)	.64
Univariate analysis		
Daily use: >5.0 mg/kg	5.67 (4.14–7.79)	<.001
Cumulative use: >20 g/kg	8.13 (5.61–11.76)	<.001
Duration of use: >10 years	3.22 (2.20–4.70)	<.001

CI, confidence interval.

Retinal Toxicity Associated with Hydroxychloroquine

Physicians often use long-term hydroxychloroquine sulfate therapy to treat patients with lupus erythematosus, rheumatoid arthritis and other autoimmune conditions. Although hydroxychloroquine is effective and generally well tolerated, long-term use can lead to an irreversible and potentially blinding retinal toxicity. As a side effect, hydroxychloroquine retinopathy may be more widespread than previously believed. Melles from Redwood City Medical Center, California, and Marmor from Stanford University, California, conducted a retrospective case-control study to assess the prevalence of and risk factors for hydroxychloroquine retinal toxicity, and to determine optimal dosing standards.

Using Kaiser Permanente Northern California health organization's database of approximately 3.4 million members, the authors extracted the records of 3482 patients who had taken hydroxychloroquine for ≥5 continuous years (with no gaps of <1 year). Retinal toxicity was judged by characteristic damage: partial or full ring scotomas, parafoveal thinning of the outer retina and loss of photoreceptor outer segment marker lines. Retinal toxicity levels were graded as normal fundus, mild, moderate or severe.

Of the 2361 patients showing characteristic changes, 177 (7.5%) showed clear signs of retinal toxicity. No primary medical indication for hydroxychloroquine therapy was significantly associated with an increased prevalence. Multivariate regression analysis of possible risk factors revealed that dosage, length of use, body weight, presence of kidney disease and concurrent tamoxifen therapy were significantly associated with retinal toxicity. The results of a univariate regression analysis were significantly associated with retinal toxicity (Table 1).

Real body weight predicted risk better than did ideal body weight. Patients with a mean daily use of >5.0 mg/kg had an approximately 10% risk of retinal toxicity within 10 years, rising to almost 40% after 20 years. Patients taking 4.0 mg/kg to 5.0 mg/kg had a <2% risk within 10 years, rising to almost 20% after 20 years. Breast cancer patients on tamoxifen had a 4.6× higher risk for retinal toxicity.

The 7.5% incidence of retinal toxicity among long-term hydroxychloroquine users is approximately 3× greater than that previously reported. Because risk appears to be dose- and duration-dependent, it is imperative that guidelines for prescribing this valuable medication be developed. Patients on long-term hydroxychloroquine therapy should be monitored for retinal toxicity.

Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol *2014;132:1453-1460.*

Association of Lipid Levels, Diabetic Retinopathy And Macular Edema

Patients with type 1 diabetes mellitus (DM) often suffer decreased vision due to proliferative diabetic retinopathy and macular edema. Although it has been suggested that serum lipid levels may be associated with the incidence and progression of diabetic retinopathy lesions and macular edema in these patients, the lack of systematic long-term follow-up data has prevented researchers from reaching conclusions about the relationship between lipid levels and visual outcomes. Klein et al from the University of Wisconsin School of Medicine and Public Health reported findings from a long-term study of patients with type 1 DM.

For >30 years, the Wisconsin Epidemiologic Study of Diabetic Retinopathy monitored a cohort of patients with type 1 DM for the presence and severity of retinal lesions. Each participant underwent stereoscopic color fundus photographs that were graded for diabetic retinopathy and macular edema. Proliferative diabetic retinopathy was defined as having an Early Treatment Diabetic Retinopathy Study (ETDRS) severity level of ≥60 in either eye; macular edema was defined as retinal thickening in the macular area in either eye. Demographic and medical information included age, time since diabetes diagnosis, medication use, serum cholesterol level (both total and high-density lipoprotein [HDL] cholesterol), and glycated hemoglobin A_{1c} (HbA_{1c}) levels.

Proliferative diabetic retinopathy incidence increased from 29% at 4 years to 49% at 32 years; macular edema incidence rose from 15% at 4 years to 29% at both 25 years and 32 years. Total serum cholesterol fell (from 203 mg/dL to 164 mg/dL) while serum HDL cholesterol rose (from 51 mg/dL to 61.5 mg/dL), which may have been related to the introduction of statin therapy as standard practice (statin use rose from 0% at 4 years to 71% at 32 years). HbA_{1c} declined from 9.5% to 7.8%.

An inverse association was found between levels of serum HDL cholesterol and proliferative diabetic retinopathy (odds ratio [OR], 0.87; 95% confidence interval [CI], 0.82–0.93). However, employing a covariate-adjustment model that used duration of DM as the time scale, this relationship ceased to be significant. The data indicated that only HbA_{1c} levels were significantly associated with proliferative diabetic retinopathy and macular edema (Table 2).

The effects of statin use on lipid levels and the resultant benefits in fighting macrovascular disease are well established. Although patients with type 1 DM demonstrated significant

Table 2. Covariate-adjusted associations of serum total and HDL cholesterol and the incidence of PDR and macular edema[a]

Covariate	Model 3 HR (95% CI)	*p* value
Incident PDR		
Serum total cholesterol		
Serum total cholesterol per 20 mg/dL	1.02 (0.95–1.09)	.66
Glycated HbA_{1c} per 1%	1.54 (1.41–1.68)	<.001
Using statins (yes vs no)	0.76 (0.32–1.80)	.53
Serum HDL cholesterol		
Serum HDL cholesterol per 10 mg/dL	0.99 (0.89–1.11)	.91
Glycated HbA_{1c} per 1%	1.55 (1.43–1.68)	<.001
Using statins (yes vs no)	0.75 (0.32–1.77)	.51
Incident macular edema		
Serum total cholesterol		
Serum total cholesterol per 20 mg/dL	0.99 (0.91–1.08)	.81
Glycated HbA_{1c} per 1%	1.46 (1.31–1.63)	<.001
Using statins (yes vs no)	1.07 (0.41–2.78)	.89
Serum HDL cholesterol		
Serum HDL cholesterol per 10 mg/dL	0.87 (0.75–1.00)	.06
Glycated HbA_{1c} per 1%	1.44 (1.29–1.60)	<.001
Using statins (yes vs no)	1.01 (0.39–2.62)	.98

HR, hazard ratio; PDR, proliferative diabetic retinopathy; CI, confidence interval.
[a]Duration of DM was used as the time scale.

decreases in serum total cholesterol levels and significant increases in serum HDL cholesterol levels after the introduction of statin therapy, these changes did not result in any beneficial effect on the incidence of proliferative diabetic retinopathy or macular edema.

Klein BEK, Myers CE, Howard KP, Klein R. Serum lipids and proliferative diabetic retinopathy and macular edema in persons with long-term type 1 diabetes mellitus: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. JAMA Ophthalmol *2015;133:503-510.*

Diabetic Retinopathy Subsequent to Bariatric Surgery

According to a recent trial, bariatric surgery combined with medical therapy vs intensive medical therapy alone resulted in more remission of diabetes for patients with poorly controlled type 2 diabetes mellitus (DM). Significant improvement was noted within 3 months of surgery. Because a quarter of type 2 DM patients develop diabetic retinopathy (DR) within 2 years of diagnosis, these results should bode well for the visual health of these patients. However, several studies have shown that rapid improvements in glycemic control can result in the progression of DR.

Kim et al from Soonchunhyang University Seoul Hospital, South Korea, conducted a retrospective study of 20 patients without retinal vascular disease other than DR who underwent bariatric surgery to treat type 2 DM. All patients received preoperative ophthalmic examinations, which were then repeated every 3 months postoperatively. Fasting glucose, glycated hemoglobin A_{1c} (HbA_{1c}) and cholesterol levels, along with body mass index and renal function profile, were assessed at baseline and 3 months postoperatively.

At baseline, all patients had best-corrected distance visual acuity of 20/40 or better, with varying degrees of DR:

- 12 patients had no DR
- 2 had moderate nonproliferative DR (NPDR)
- 1 had severe NPDR
- 2 had proliferative DR

During follow-up (median duration, >2 years), DR progressed after bariatric surgery in 9 patients (45%); 5 patients required intervention. After surgery, 6 patients achieved an HbA_{1c} level of ≤6.0% and maintained that level without using oral hypoglycemic agents or insulin; DR progressed in 3 of these patients despite remission of their type 2 DM.

No patient whose DR did not progress demonstrated any visual loss during follow-up. No patient in either group experienced regression of DR. In the univariate and multivariate analyses, preexisting DR and albuminuria were identified as significant risk factors.

Patients with type 2 DM appear to be at an increased risk for DR progression after bariatric surgery, especially those patients who have some DR before surgery. All patients with DM who undergo bariatric surgery need regular ophthalmic follow-up regardless of how successfully their DM is controlled.

Kim YJ, Seo DR, Kim MJ, et al. Clinical course of diabetic retinopathy in Korean type 2 diabetes after bariatric surgery: a pilot study. Retina *2015;35:935-943.*

WINTER 2016

- Vascular occlusion and stroke
- Endophthalmitis after intravitreal injection
- Age-related macular degeneration treated with vascular endothelial growth factor inhibitors

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