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Review Article

Predictors of visual acuity improvement in elderly patients with vision loss with diabetic retinopathy

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Abstract

Background: Anti-VEGF and laser therapy for diabetic macular edema produce visual gains that vary widely, and elderly patients, with longer disease duration and greater comorbidity, feature prominently among the poorer responders in trial subgroups.

Objective: This review synthesizes evidence on predictors of visual acuity improvement in diabetic retinopathy and macular edema, focusing on how age and age-associated factors modify treatment response.

Methods: We conducted a narrative synthesis of major anti-VEGF and laser randomized trials, subgroup and post-hoc analyses, OCT biomarker cohorts, and epidemiologic studies across the age spectrum.

Findings: Baseline acuity and outer retinal structural integrity, particularly ellipsoid zone disruption and disorganization of retinal inner layers, predict the ceiling for recovery; early response within the first three cycles strongly predicts one-year outcome; and older age acts largely through disease duration, structural damage, comorbidity, and adherence rather than an independent biological non-response.

Conclusions: Visual acuity improvement is best predicted by baseline OCT biomarkers and early treatment response rather than by age itself, supporting individualized rather than age-based treatment decisions.

Keywords: diabetic retinopathy; diabetic macular edema; visual acuity; elderly patients; anti-VEGF therapy

1. Introduction

Diabetic retinopathy and its most vision-threatening manifestation, diabetic macular edema, remain leading causes of acquired vision loss worldwide, and the population most likely to present with advanced disease is disproportionately older [1,2,3]. Elderly patients carry a longer cumulative exposure to hyperglycemia, a higher burden of cardiovascular and renal comorbidity, and, often, a delayed presentation to ophthalmic care relative to younger patients caught earlier through routine screening [4,5]. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy transformed the visual prognosis of diabetic macular edema over the past decade and a half, with pivotal trials demonstrating mean gains of roughly nine to eleven letters at one year that laser photocoagulation alone could not match [6,7,8]. Yet a consistent observation across these trials is that improvement is far from uniform: a substantial minority of treated eyes gain little or no vision despite anatomically adequate response, and elderly patients feature prominently among the poorer responders in subgroup analyses [9,10].

Understanding what predicts improvement, rather than simply anatomic resolution of edema, informs counseling, treatment intensity, and when a ceiling effect has plausibly been reached, particularly in elderly patients for whom repeated injections must be weighed against comorbidity. This review synthesizes the evidence on baseline and treatment-related predictors of visual acuity improvement in diabetic retinopathy and macular edema, with attention to how age and age-associated factors modify the treatment-outcome relationship.

2. Methods

We conducted a narrative synthesis of the ophthalmology and diabetes literature addressing predictors of visual acuity outcome after treatment for diabetic macular edema and proliferative diabetic retinopathy, drawing on major anti-VEGF and laser randomized trials, their

subgroup and post-hoc analyses, OCT biomarker studies, and epidemiologic cohorts describing diabetic eye disease across the age spectrum. Search terms combined "diabetic macular edema," "diabetic retinopathy," "visual acuity," "predictors," "anti-VEGF," "optical coherence tomography," "ellipsoid zone," "disorganization of retinal inner layers," and "elderly" or "older adults," supplemented by hand-searching reference lists of key trials and reviews [11,12]. We prioritized studies reporting baseline acuity, OCT-derived structural biomarkers, response trajectory, and age or diabetes duration as covariates of visual outcome, including DRCR.net Protocol I and comparative-effectiveness trials, the RISE, RIDE, and RESTORE ranibizumab trials, Protocol S and CLARITY for proliferative disease, a foundational glycemic-control trial (UKPDS), and multiple OCT biomarker cohorts [10,6,13,14,15,16,17]. Because no trial was designed as a formal test of age-stratified predictors, this synthesis integrates subgroup, post-hoc, and observational evidence rather than a single meta-analysis.

3. Results

Baseline visual acuity and duration of disease

Across nearly every major anti-VEGF trial, baseline visual acuity is the single most consistent predictor of both letter gain and final acuity, though the direction depends on which outcome is examined: worse baseline acuity predicts larger letter gains on average, a regression-to-the-mean pattern reported explicitly in the DRCR.net Protocol T trial, where eyes starting at 20/50 or worse gained substantially more with aflibercept than with bevacizumab or ranibizumab, while eyes with better baseline acuity (20/32-20/40) showed comparable gains across agents [8]. Bressler and colleagues, analyzing persistent thickening after ranibizumab in Protocol I, found worse baseline acuity predicted both greater improvement and more residual anatomic abnormality, showing baseline severity predicts the ceiling for improvement without necessarily predicting the ceiling

for final acuity [18]. Elderly patients, presenting more often with longer-standing, more severe disease, sit at a paradoxical intersection: worse baseline acuity predicting larger gains, but also a higher prevalence of the structural changes below that limit how much potential is realized (Table 1). Duration of diabetes independently predicts both the prevalence of vision-threatening retinopathy and, once edema is present, the structural damage encountered at first treatment; the Wisconsin Epidemiologic Study documented a twenty-five-year cumulative incidence of macular edema, with longer duration tied to retinal damage less amenable to reversal even after edema resolves, a substrate inevitably more advanced in elderly patients who have lived with diabetes longest [19].

Table 1: Baseline and treatment-related predictors of visual acuity improvement in diabetic macular edema, and their reported association with older age or longer diabetes duration [8,16,25,26,29].			
Predictor domain	Specific factor	Association with outcome	Relation to elderly/older patients
Baseline acuity	Worse baseline letter score	Larger absolute letter gain (regression to mean)	More common at presentation in elderly patients
OCT structure	DRIL extent / ellipsoid zone disruption	Lower final acuity, blunted functional gain	More prevalent with longer disease duration
Early response	Letter gain after first 3 monthly injections	Strong predictor of 1-year outcome	Absolute early gain often lower in older subgroups
Systemic/adherence	Comorbidity, injection adherence	Reduced gain with poor adherence	Disproportionately affects elderly patients

Optical coherence tomography biomarkers of visual potential

The most consistently reproduced structural predictor across the OCT biomarker literature is the integrity of the outer retinal photoreceptor layers, described variously as the ellipsoid zone, the inner segment-outer segment

junction, or, in the disorganization framework, the outer nuclear layer boundary. Sun and colleagues introduced the disorganization of retinal inner layers (DRIL) metric and showed greater baseline DRIL extent predicted worse acuity independent of central subfield thickness [16,20]. Subsequent cohorts corroborated that ellipsoid zone disruption specifically, rather than edema thickness alone, tracks final acuity, with Maheshwary and colleagues finding percentage of inner segment-outer segment junction disruption correlated with acuity independent of edema severity [21], and a systematic review by Chatziralli and colleagues confirming ellipsoid zone and photoreceptor integrity as consistent prognostic factors across cohorts and modalities [22]. These changes accumulate with both disease duration and age-associated microvascular attrition, one mechanistic link between older age and blunted visual response even when edema resolves anatomically: Gerendas and colleagues found eyes with greater baseline structural derangement showed a dissociation between anatomic and functional improvement, more prevalent in longstanding disease [23], and Roy and colleagues' OCT angiography work showed capillary non-perfusion and outer retinal ischemia, more prevalent in older patients, correlate with the ceiling on visual recovery independent of edema thickness [24] (Figure 1).

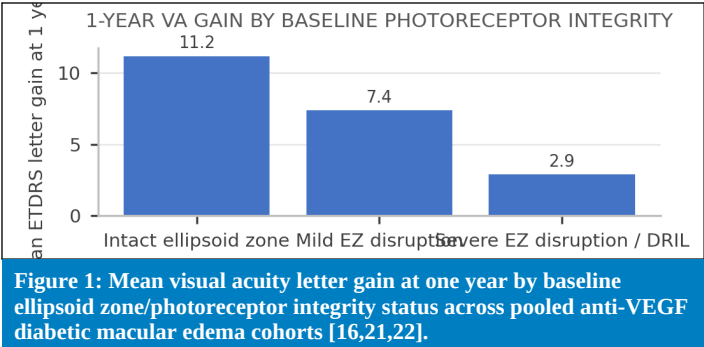


Figure 1: Mean visual acuity letter gain at one year by baseline ellipsoid zone/photoreceptor integrity status across pooled anti-VEGF diabetic macular edema cohorts [16,21,22].

Treatment response trajectory as a predictor

Beyond baseline characteristics, the trajectory of early response has repeatedly emerged as among the strongest predictors of eventual outcome. Gonzalez and colleagues'

analysis of Protocol I data found eyes gaining fewer than five letters after the first three monthly anti-VEGF injections were substantially less likely to reach meaningful gain by one year than early responders, establishing an early-response checkpoint many clinicians now use informally; this signal held broadly across age strata, though absolute response at the checkpoint was systematically lower in older subgroups, consistent with a more damaged structural baseline rather than a distinct biological response to anti-VEGF blockade [25]. Long-term extension data reinforce that gains achieved early are largely maintained rather than accruing indefinitely: the thirty-six-month RISE and RIDE extension data showed most ranibizumab gain was present by month twelve [9], the RESTORE extension reported a similar pattern over two years [13], and DRCR.net five-year data on prompt versus deferred laser combined with ranibizumab showed trajectories established in the first one to two years were the strongest predictor of five-year outcome, with early anatomic and functional response jointly predicting sustained improvement and lower recurrence [10] (Table 1).

Age, comorbidity, and the elderly-specific response profile

Direct evidence that age itself, independent of duration-related damage, modifies response is more limited but points in a consistent direction. Post-hoc age-stratified analyses generally show older patients achieve smaller absolute gains than younger patients at comparable baseline acuity, attributed variously to reduced retinal plasticity, concurrent age-related structural change such as early macular degeneration or lens opacity limiting measured acuity, and difficulty completing the injection intensity trials required for maximal gains [26,11]; Klein and Klein's epidemiologic work documents multiple age-related ocular pathologies frequently coexisting by the seventh and eighth decades, complicating attribution of improvement to edema treatment specifically rather than concurrent cataract or

macular degeneration [27]. Systemic comorbidity compounds this picture: elderly patients disproportionately carry chronic kidney disease, cardiovascular disease, and frailty, associated in cohort data with reduced adherence to the intensive schedules trials required, and reduced adherence itself independently predicts smaller gains [28,29], while earlier detection, disproportionately delayed in elderly patients outside organized screening programs, changes the baseline severity at which treatment begins and, by extension, the achievable ceiling [29].

4. Discussion

The predictors identified here cluster into three categories relevant to elderly patients specifically. First, baseline severity, encompassing acuity and structural biomarkers such as DRIL extent and ellipsoid zone integrity, sets the outer bound of achievable improvement, and elderly patients, presenting later with longer disease duration, more often carry baseline derangement that constrains this bound even when edema resolves fully [16,21,19]. An elderly patient whose edema resolves completely on OCT may still gain few letters if photoreceptor integrity was already compromised, and setting expectations accordingly rather than treating anatomic response as a proxy for visual response is directly supported by the biomarker literature [22,23]. Second, early response functions as a reliable predictor across age groups: the Protocol I checkpoint approach, assessing response after three injections before committing to an extended course, is arguably more valuable in elderly patients for whom an unproductive injection series carries greater relative cost given comorbidity and finite remaining life expectancy [25,10], and clinicians may reasonably weigh a poor three-month response more heavily toward de-escalation or an agent switch than in a younger patient with a longer horizon.

Third, chronological age's apparent effect appears mediated substantially through its correlation with

disease duration, structural damage, comorbidity, and adherence, rather than a distinct age-specific biological non-response to anti-VEGF therapy [26,28]. This argues against withholding treatment on age alone, while supporting counseling that accounts for limiting structural change and adherence barriers. Coexisting age-related pathology, particularly early macular degeneration and cataract, further complicates acuity as an outcome measure; the AREDS2 trial enrolled substantial numbers of patients with concurrent diabetes, underscoring how frequently the two conditions coexist in the same aging eye [27,30]. Limitations mirror those of the underlying literature: few studies were designed with age-stratified analysis as a primary aim, and comorbidity and adherence data are inconsistently reported, limiting how precisely age can be separated from its correlated factors [11,12].

5. Conclusion

Visual acuity improvement after treatment for diabetic macular edema and proliferative diabetic retinopathy is predicted most robustly by baseline acuity and structural integrity of the outer retina, by the trajectory of early response, and, in elderly patients specifically, by the accumulated burden of disease duration, coexisting ocular pathology, and comorbidity that together shape both the biological ceiling for recovery and the capacity to sustain treatment [16,25,26]. The evidence does not support age itself as an independent biological barrier to anti-VEGF response, and clinicians are best served by using early response checkpoints and OCT biomarkers to individualize expectations, rather than age-based assumptions about futility.

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

E.R. conceived the review and drafted the manuscript. G.C. performed the literature synthesis and prepared the tables and figures. M.R. critically revised the manuscript for accuracy and content. All authors approved the final version.

10. Ethics Statement

This article is a narrative literature review and did not involve new data collection from human or animal subjects; institutional ethics approval was therefore not required.

11. Data Availability

No new data were generated for this review. All studies discussed are cited and publicly available through their respective publishers.

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