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Review Study On Lifestyle Intervention and the Prevention of Diabetic Retinopathy in Prediabetes

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Abstract: Diabetic retinopathy (DR) is a leading cause of vision loss worldwide and begins to develop long before the clinical diagnosis of type 2 diabetes mellitus (T2DM), during the preceding state of impaired glucose tolerance (IGT). This review examines the evidence that structured lifestyle intervention — weight loss, dietary change, and increased physical activity — can reduce early microvascular retinal injury in people with prediabetes, centered on a post-hoc ocular sub-study of the Finnish Diabetes Prevention Study (DPS). In that analysis, 211 participants of the original DPS trial underwent fundus photography five or more years after a four-year lifestyle intervention had ended. Retinal microaneurysms (MAs), the earliest clinically visible sign of DR, were significantly less frequent among former intervention participants (24%) than former controls (38%), and this protective association persisted after adjustment for age, sex, diabetes status, and body mass index. Notably, glycemic and blood pressure measures did not independently predict microaneurysm occurrence; instead, baseline serum triglycerides emerged as the only significant biomarker of risk. This review situates these findings within the broader literature on diabetes prevention trials, including the Diabetes Prevention Program and the China Da Qing study, discusses the proposed role of triglyceride-driven microvascular injury, and considers the clinical and public health implications of intervening early — during prediabetes rather than after diabetes is diagnosed — to prevent visionthreatening retinal disease.

Keywords: diabetic retinopathy; prediabetes; lifestyle intervention; microaneurysms; triglycerides; diabetes prevention

1. Introduction

Diabetes is among the most consequential chronic metabolic disorders worldwide, with global prevalence estimated at 415 million people in 2015 and projected to reach 642 million by 2040, with the sharpest increases expected in low- and middle-income countries [1]. A substantial share of the disease burden associated with diabetes stems not from hyperglycemia alone but from its microvascular complications, chief among them diabetic retinopathy (DR). An estimated 93 million people with diabetes have some form of DR, which is conventionally classified as non-proliferative (NPDR) or proliferative (PDR) disease [1,2]. DR is the fifth leading cause of visual impairment and blindness globally, and historically the leading cause of blindness among working-age adults; between 1990 and 2010, the global burden of visual impairment and blindness attributable to DR rose measurably [1].

The earliest clinically detectable sign of NPDR is the retinal microaneurysm (MA) — a focal dilation of retinal capillaries — which, along with hemorrhages, hard exudates, and intraretinal microvascular abnormalities, marks the beginning of a disease process that can progress to vision-

threatening proliferative disease if unaddressed [1]. Established risk factors for DR include the duration of diabetes, chronic hyperglycemia, and hypertension, while elevated total cholesterol and triglycerides have been linked to diabetic macular edema specifically [1,2]. Because these risk factors are, in principle, modifiable through lifestyle change well before diabetes is diagnosed, an important open question is whether intervening during the prediabetic stage — specifically in individuals with impaired glucose tolerance (IGT) — can forestall the earliest retinal changes rather than merely delaying the onset of diabetes itself.

This review focuses on a post-hoc analysis of the Finnish Diabetes Prevention Study (DPS), a landmark randomized trial of lifestyle intervention in adults with IGT, which examined retinal outcomes years after the active intervention phase had concluded [1]. The DPS itself had already established that intensive lifestyle counseling improves insulin sensitivity and preserves pancreatic beta-cell function, translating into a markedly lower incidence of T2DM [3,4]. The ocular sub-study extends this evidence by asking a more specific question: does earlier participation in lifestyle intervention also reduce the downstream occurrence of retinal microvascular injury, and if so, through which metabolic pathway [1].

2. Study Design and Methods

2.1 The Parent Trial

The DPS enrolled 522 adults with IGT (mean age 55 years, range 40–64) across five Finnish study centers between 1993 and 1998, randomizing 265 to a structured lifestyle-intervention arm and 257 to a control arm receiving general lifestyle advice [1,3]. The intervention was intensive during its first year, comprising seven individual sessions with a clinical nutritionist targeting weight loss of 5% or more, reduced total and saturated fat intake, increased dietary fiber, and at least 30 minutes of moderate daily exercise; it was reinforced by quarterly counseling visits over a subsequent 2–5-year maintenance period, for a median total intervention duration of four years and a median of 20 counseling sessions per participant [1,4].

2.2 The Ocular Sub-Study

Between 2002 and 2006 — at least five years after the structured intervention had ended — surviving participants at four of the five original study centers were invited to undergo dilated fundus photography [1]. Of 532 initial photographs, 145 were excluded for inadequate quality, leaving 211 evaluable participants (113 former intervention, 98 former control). Photographs were independently graded for retinal microvascular signs, including microaneurysms, hemorrhages, macular edema, exudates, and intraretinal microvascular abnormalities, by ophthalmologists masked to original group assignment. Statistical analysis used t-tests or chi-square/Fisher's exact tests for baseline comparisons and binary logistic regression, adjusted for age, sex, diabetes status, and BMI, to model the odds of microaneurysm occurrence [1].

3. Key Findings

3.1 Reduced Microaneurysm Occurrence in the Former Intervention Group

Retinal microaneurysms — present in 27 of 113 (24%) former intervention participants versus 37 of 98 (38%) former controls ($p = 0.029$) — were significantly less common in those who had received structured lifestyle counseling years earlier [1]. This association held in a multivariable model adjusting for age, sex, diabetes diagnosis, and BMI, with intervention-group assignment associated with roughly half the odds of microaneurysm occurrence (OR 0.52, 95% CI 0.28–0.97, $p = 0.039$) [1]. The protective association was independent of whether participants had gone on to develop overt diabetes, and diabetes incidence itself did not differ significantly between those with and without microaneurysms during the five-year ocular followup period, suggesting the lifestyle effect on retinal microvasculature was not simply a proxy for reduced diabetes incidence [1].

3.2 Serum Triglycerides as the Dominant Risk Marker

Among the metabolic variables examined — fasting and 2-hour glucose, fasting insulin, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and triglycerides — only baseline serum triglycerides differed significantly between participants who later developed microaneurysms and those who did not (1.9 ± 0.9 mmol/L vs. 1.6 ± 0.7 mmol/L, $p = 0.003$) [1]. A tertile analysis reinforced this finding: participants in the middle and highest triglyceride tertiles had substantially higher odds of microaneurysms than those in the lowest tertile (OR 2.95, $p = 0.010$ and OR 2.58, $p = 0.024$, respectively), with the increase in risk apparent even at only modestly elevated triglyceride levels [1]. In a fully adjusted

regression model, triglycerides remained an independent predictor of microaneurysm occurrence (OR 1.92, 95% CI 1.12– 3.35, p = 0.018), whereas fasting glucose did not [1].

3.3 Absence of Glycemic and Blood Pressure Associations

Contrary to expectations based on established DR risk factors in overt diabetes, neither fasting nor 2-hour plasma glucose, nor systolic or diastolic blood pressure, showed a significant independent association with microaneurysm occurrence in this prediabetic cohort [1]. The study authors proposed that because all participants shared a broadly similar degree of impaired glucose tolerance at baseline, the relatively narrow range of glycemic variation within this specific population may have limited the ability to detect a glucosedriven signal, even though glucose control is a well-documented risk factor for retinopathy progression once diabetes is established [5,6].

4. Discussion: Interpreting the Evidence

4.1 A Novel Link Between Lifestyle Intervention and Early Retinal Protection

This ocular sub-study is notable for being among the first to connect lifestyle-intervention trial participation directly to a reduced incidence of early retinal microvascular disease, rather than diabetes incidence alone [1]. Prior evidence on this question has been mixed: the Diabetes Prevention Program Outcomes Study found that lifestyle intervention did not significantly reduce a composite of microvascular outcomes (nephropathy, neuropathy, and retinopathy) over 15 years [7], whereas the China Da Qing Diabetes Prevention Outcome Study reported a 47% reduction in severe, vision-threatening retinopathy over 20 years of follow-up in combined lifestyle-intervention groups, an effect the Da Qing investigators attributed largely to the reduced incidence of diabetes itself in those groups [8]; extended 30-year followup of the same cohort has continued to report reduced diabetes-related morbidity and mortality in the former intervention groups [9]. The DPS ocular findings differ somewhat from both: the protective effect on microaneurysms was independent of eventual diabetes status, pointing toward a direct metabolic pathway rather than one mediated solely through diabetes prevention [1].

5. The Triglyceride Pathway

The prominence of triglycerides, rather than glycemia, as the key predictor of microaneurysm risk in this cohort is consistent with other lines of evidence linking hypertriglyceridemia to retinal and macular pathology. Elevated serum triglycerides and hypertriglyceridemia have been proposed elsewhere as a surrogate marker for macular tissue change in type 2 diabetes [10], and pharmacologic triglyceridelowering with fenofibrate reduced retinopathy and albuminuria progression in the ACCORD and FIELD trials [11,12]. The DPS findings extend this triglyceride-retinopathy link into the prediabetic period [1], suggesting that elevated triglycerides may contribute to microvascular injury even before diabetes is clinically diagnosed, consistent with independent effects of triglycerides on early retinopathy reported in type 1 diabetes [13], and that lifestyle measures — which are well established to lower triglycerides alongside their effects on weight and glucose — may confer retinal benefit through this lipid pathway specifically.

Why Glucose and Blood Pressure Did Not Predict Risk Here

The absence of a significant glucose or blood pressure association in this cohort should be interpreted cautiously rather than as evidence against their established roles in DR. The study population was, by design, uniformly affected by impaired glucose tolerance, which may have compressed the range of glycemic exposure and reduced the study's power to detect a glucose-driven effect; similarly, the frequent use of antihypertensive medication in this trial population may have minimized between-group blood pressure differences relevant to retinal autoregulation. Well-established data from other cohorts, including the UK Prospective Diabetes Study, continue to demonstrate a linear relationship between updated mean HbA1c, updated mean blood pressure, and retinopathy risk once diabetes is present [5,6], so these findings should be read as specific to the prediabetic transition rather than as contradicting the broader glycemiaretinopathy relationship.

Limitations

- The ocular sub-study analyzed only 211 of the original 522 DPS participants — those who survived, remained enrolled, and produced evaluable fundus photographs — introducing potential survivorship

or selection effects, although baseline characteristics were largely comparable to nonparticipants apart from a lower fasting glucose among participants.

- No baseline retinal photographs were available, so the analysis characterizes the prevalence of microaneurysms at a single post-intervention time point rather than tracking their incident development from a documented retinal baseline.
- The cross-sectional timing of fundus photography (2002–2006) occurred at variable intervals after the intervention ended for different participants, and multiple testing across the five-year followup period was not corrected with post-hoc analysis.
- As a post-hoc, hypothesis-generating analysis of a trial originally designed to assess diabetes incidence, the study cannot establish causality between triglyceride levels and microaneurysm formation, only association.

Clinical and Public Health Implications

These findings reinforce the rationale for initiating lifestyle-based prevention during the prediabetic window, rather than deferring intervention until diabetes is diagnosed. If confirmed in larger and more diverse populations, the specific role of triglycerides suggests that lipid-focused counseling — encouraging dietary patterns and physical activity known to lower triglycerides — may be a particularly important component of prediabetes management for protecting long-term retinal health, alongside its recognized benefits for diabetes prevention itself. In patients for whom lifestyle measures alone are insufficient to normalize triglycerides, these results also raise the question of whether adjunctive triglyceride-lowering pharmacotherapy could offer additional microvascular protection during the prediabetic period, an approach that has shown benefit for retinopathy progression in the setting of established diabetes [11,12] but has not yet been directly tested in prediabetes.

Future Research Directions

- Prospective, adequately powered trials with baseline fundus photography are needed to establish incident (rather than prevalent) microaneurysm development in relation to lifestyle intervention, allowing more definitive causal inference.
- Mechanistic studies exploring how triglyceride metabolism contributes to early retinal microvascular injury — independent of glycemia — would help clarify whether triglyceridelowering itself, rather than a correlated factor, drives the observed protective association.
- Trials directly testing lipid-targeted interventions (dietary, behavioral, or pharmacological) specifically for retinal microvascular endpoints in IGT/prediabetic populations would help determine whether this pathway can be therapeutically exploited.
- Longer-term, multi-center replication in more diverse populations (the DPS cohort was Finnish, with a mean age of 55) would clarify the generalizability of these findings to younger and more ethnically diverse prediabetic populations.

Conclusion

This review of the Finnish Diabetes Prevention Study's ocular sub-analysis indicates that structured lifestyle intervention delivered during the prediabetic stage confers a durable reduction in early diabetic retinal microvascular injury, evident even five or more years after active intervention ended. Unlike in established diabetes, where glycemia and blood pressure are dominant risk factors for retinopathy, this analysis identified serum triglycerides as the key modifiable predictor of microaneurysm occurrence in a prediabetic population. Together, these findings support prioritizing lifestyle-based prevention — with particular attention to lipid metabolism — as early as the prediabetic stage, well before glycemic thresholds for diabetes are met, as a strategy for preventing the earliest stages of diabetic retinopathy.

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