Δ.Ε.Β.Ε.

22ο ΕΤΗΣΙΟ ΣΥΝΕΔΡΙΟ
ΔΙΑΒΗΤΟΛΟΓΙΚΗΣ ΕΤΑΙΡΙΑΣ
ΒΟΡΕΙΑΣ ΕΛΛΑΔΑΣ

Νεότερες φαρμακευτικές θεραπείες στη διαβητική αμφιβληστροειδοπάθεια

Μαριάνθη Αρχανιωτάκη

Στο έργο της διαβητικής αμφιβληστροειδοπάθειας

υπάρχουν ρόλοι

-και ποιοί;-

για τους γιατρούς

που δεν είναι εξειδικευμένοι οφθαλμίατροι ;;

REVIEW

CME CREDIT

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Cleveland Clinic Journal of Medicine
Volume 71, Number 2, February 2004

The internist's role in managing diabetic retinopathy: Screening for early detection

REVIEW

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Diabetic retinopathy:

Treating systemic conditions aggressively can save sight

ABSTRACT

To control diabetic retinopathy, we need not only to detect it promptly, but also to manage common systemic comorbid conditions such as hypertension, hyperlipidemia, anemia, obstructive sleep apnea, and smoking—all of which tend to accelerate its course and increase its severity.

KEY POINTS

A target blood pressure of less than 130/75 mm Hg is recommended for any patient with evidence of retinopathy. In these patients, attributing elevated blood pressures to "white coat" hypertension is dangerous, as it may delay intervention.

Anemia often accompanies diabetic kidney disease and is thought to exacerbate the ischemic aspect of diabetic retinopathy. In patients with diabetes, it often occurs during the stage of overt proteinuria but before the onset of even moderate renal impairment.

Once lipid exudates collect in the fovea, treatment does not improve vision. Aggressive treatment of serum lipids and hypertension must be started early in the course of

d hypertension
aggravate

AS THE YEARS PASS WITH DIABETES, the risk of microvascular complications (retinopathy, nephropathy, and neuropathy) increases. We now know that care of these patients entails not only tight blood glucose control, but also aggressive treatment of systemic conditions that exacerbate or accelerate the course of diabetic microvascular and macrovascular disease: ie, hypertension, anemia, hyperlipidemia, obstructive sleep apnea, and smoking.

Studies continue to show that a comprehensive and aggressive approach to management significantly slows progression to end-organ failure. We discuss the rationale for aggressive and comprehensive management of diabetic patients and suggest how to implement such a program in primary care practice.

COURSE OF RETINOPATHY ACCELERATES

Within the retina, as in other organs, there is no observable microangiopathy during the first few years of diabetes. The first lesions are usually not seen until about 5 years after the onset of hyperglycemia, although about 20% of patients with type 2 diabetes may have observable microangiopathy at the time of diagnosis. Thereafter, retinal microvascular occlusion and leakage accelerates and progresses, so that after 15 years 80% of patients with type 2 diabetes and 97% of those with type 1 diabetes have some degree of retinopathy. Of those with type 1 diabetes, 14% develop vision problems from macular complications, and 40% develop proliferative retinopathy.[1,2]

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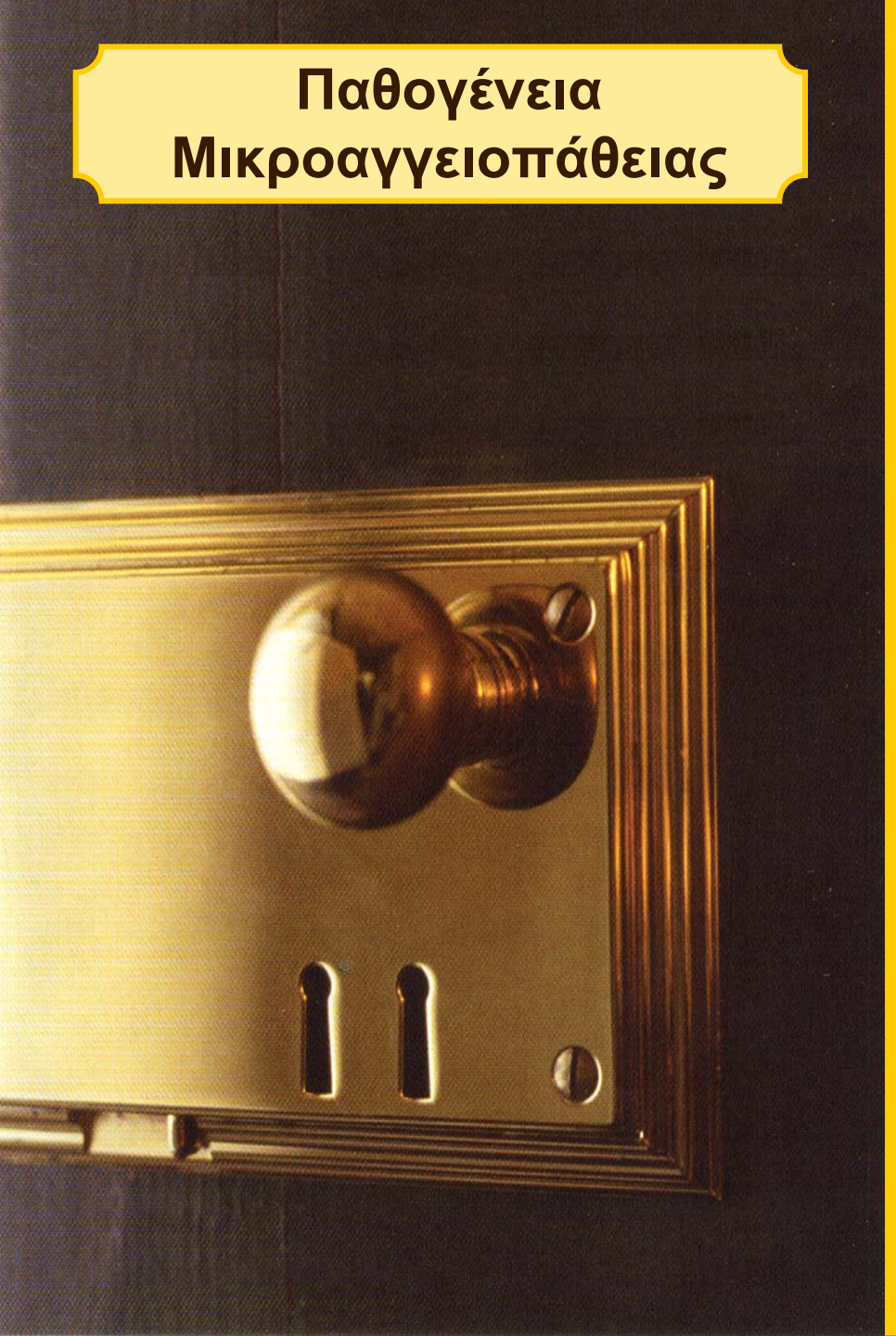
Παραλείψεις

γιατρών & ασθενών

Παθογένεια Μικροαγγειοπάθειας



Θεραπεία


αμφιβληστροειδοπάθεια
νευροπάθεια
νεφροπάθεια
ιστικές βλάβες
γενετική προδιάθεση
υπέρταση
υπερλιπιδαιμία
ΥΠΕΡΓΛΥΚΑΙΜΙΑ

Box. Summary of Risk Factors for Diabetic Retinopathy Identified in Epidemiologic/ Cohort Studies

Consistent Risk Factors

Duration of diabetes[3,5,6]

Hyperglycemia/glycated hemoglobin value[3,5-7]

Hypertension[3,8-10]

Hyperlipidemia[8,11-13]

Pregnancy[14]

Nephropathy/renal disease[15,16]

Less Consistent Risk Factors

Obesity[8]

Smoking[17]

Moderate alcohol consumption[18,19]

Physical inactivity[20]


RAS
Αγγειογενετικοί παράγοντες
Οξειδωτικό stress
Οδός εξοζαμίνης (τέλη ’90)
Ενεργοποίηση ισομορφών PKC (τέλη ’80)
Αυξημένος σχηματισμός AGEs (τέλη ’70)
Οδός πολυολών, AR (1966)


Θεραπευτικοί ορίζοντες...
πειραματικές θεραπείες

“Πειραματικές” θεραπείες

- Αναστολείς αναγωγάσης της αλδόζης, ARIs
- Αναστολείς AGEs: αμινογουανιδίνη, αμινοξέα
- Αναστολείς PKCβ: **RBX**
- Αντιοξειδωτικά: vit E, C και νεότερα
- Ανάλογα σωματοστατίνης: **οκτρεοτίδιο**
- Διεγέρτες τρανσκετολάσης: θειαμίνη & ανάλογα
- Αναστολείς PARP και MMP

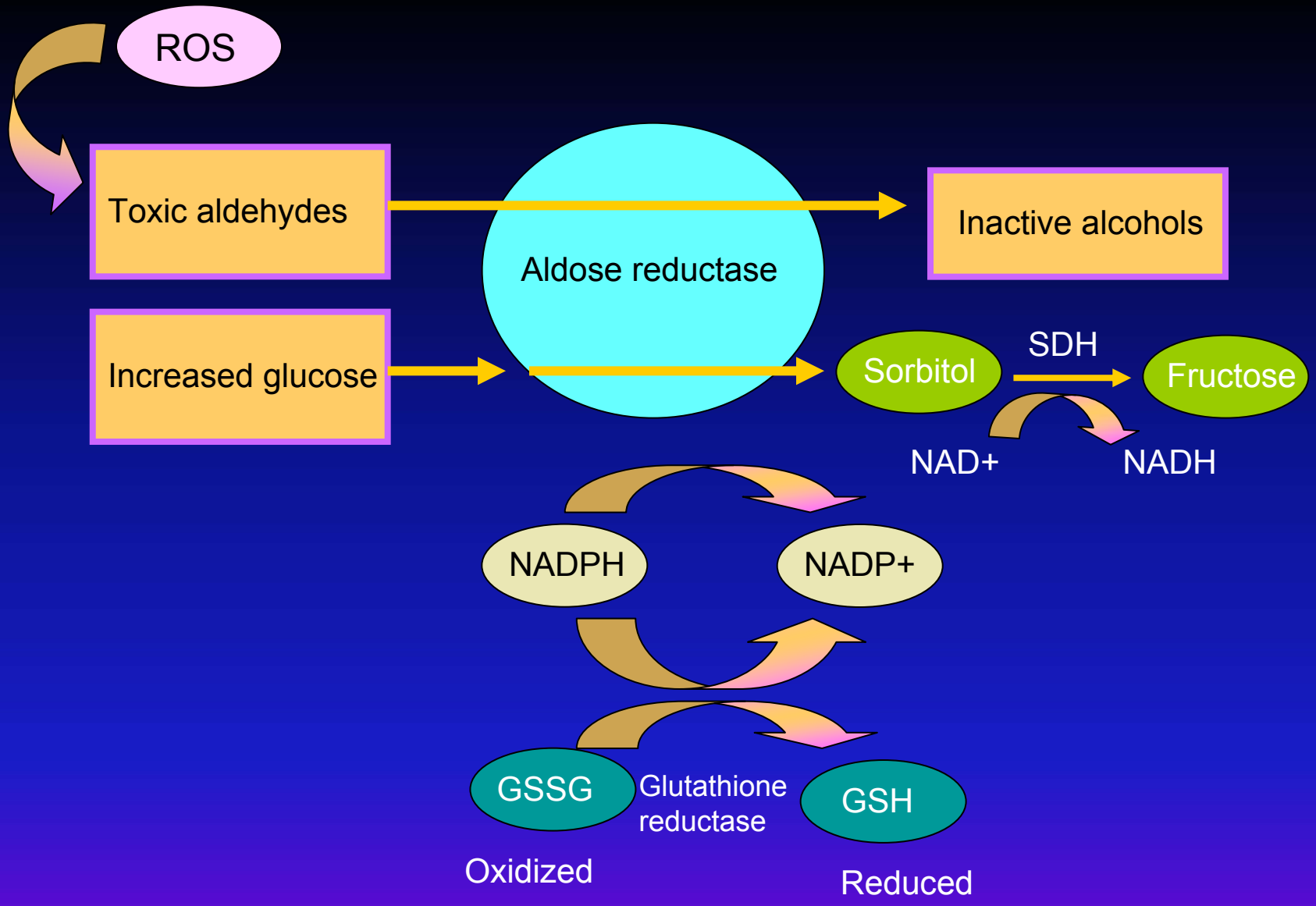
Συνεισφορά “κλασσικών” φαρμάκων στη ΔΑ

α-ΜΕΑ

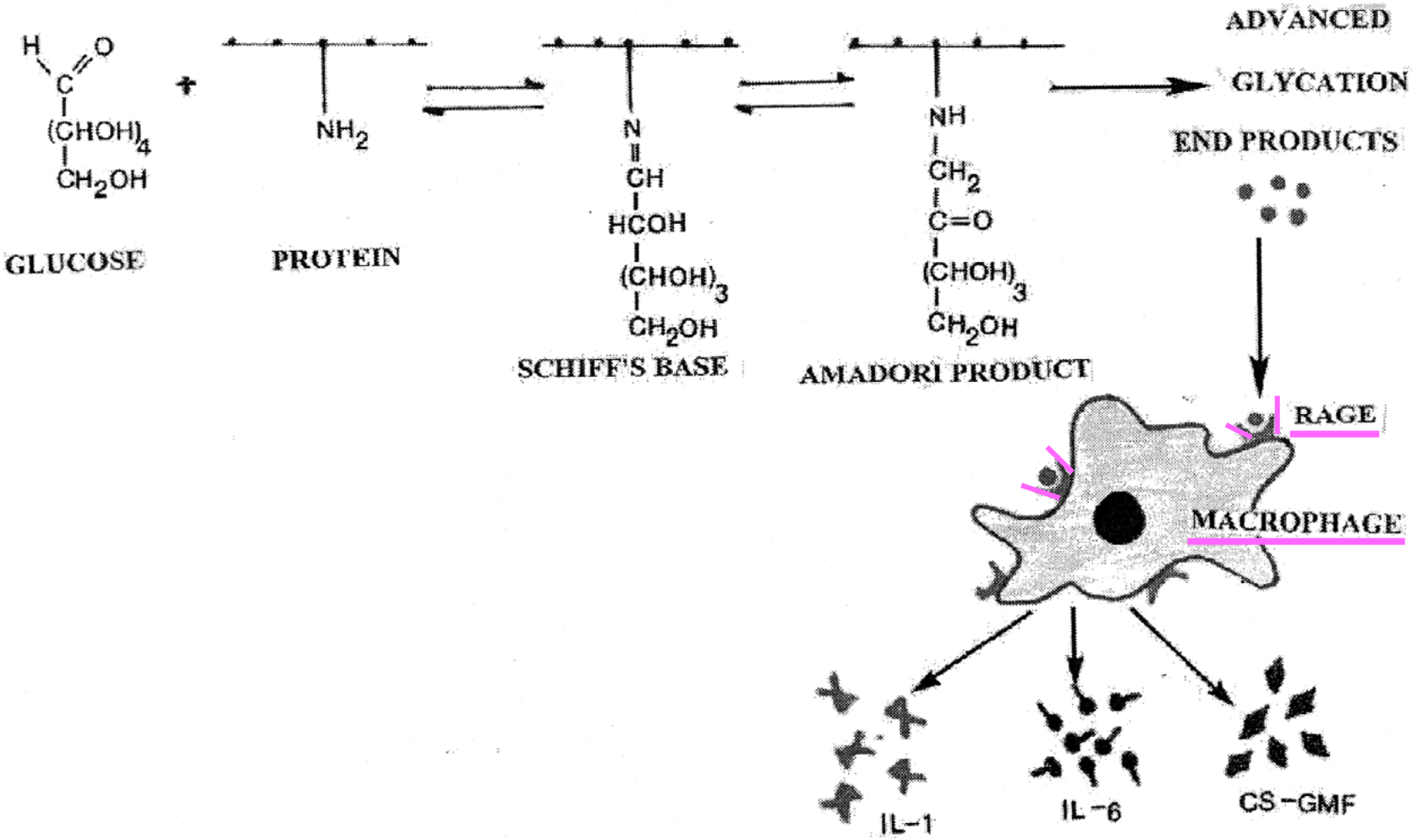
ARBs

Στατίνες

Φενοφιμπράτη



Hyperglycemia increases flux through the polyol pathway. *From Brownlee M. Biochemistry and molecular cell biology of diabetic complications.* Nature 414: 813-820, 2001.



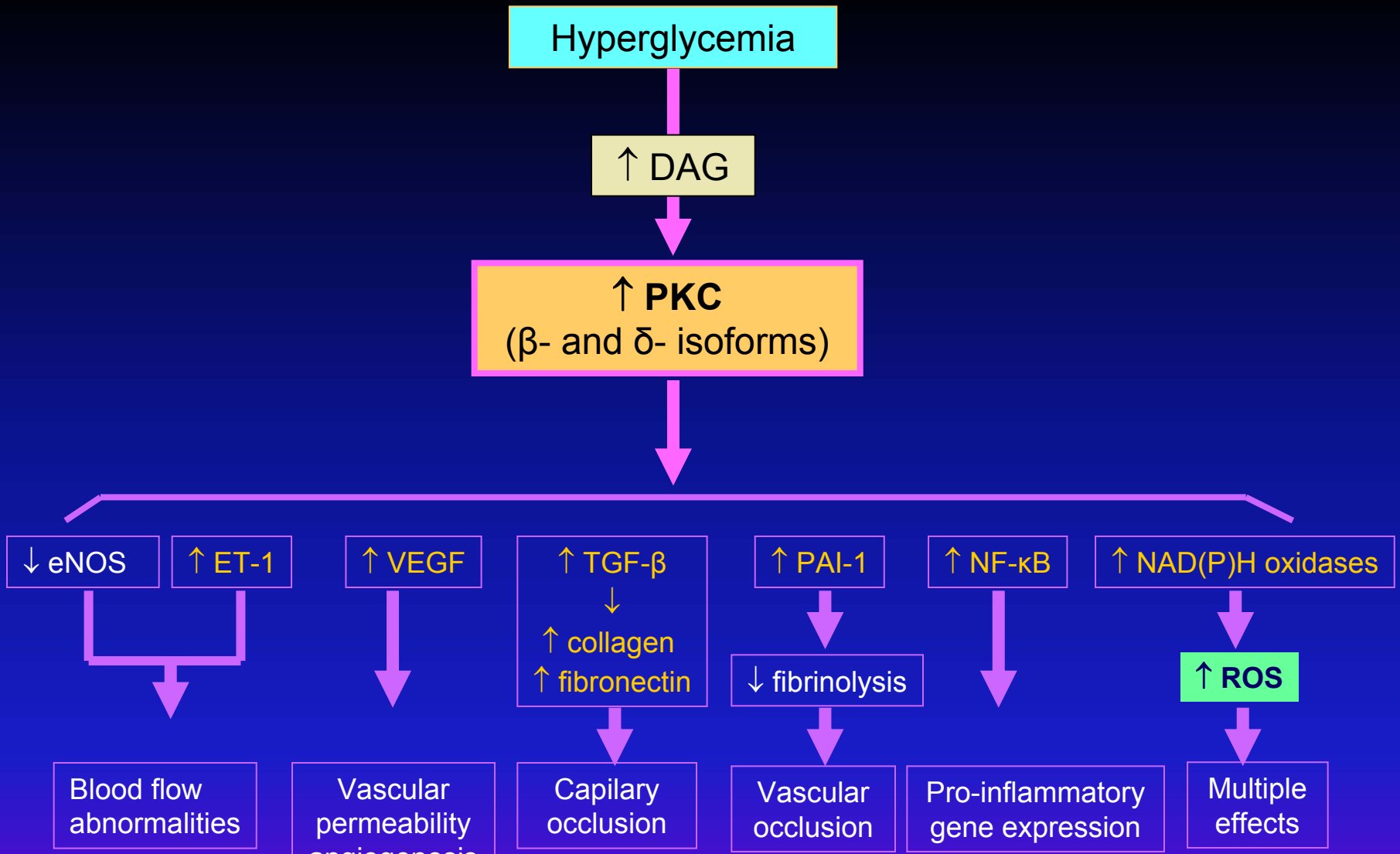
↑AGEs → RAGE ⇒ τροποποίηση λειτουργίας κυττάρων-στόχων

π.χ. ενεργοποίηση μονοκυττάρων και μακροφάγων, προφλεγμονώδεις κυττοκίνες

μετανάστευση και υπερπλασία ενδοθηλιακών κυττάρων,

μεσολαβητές νεοαγγείωσης

απόπτωση περικυττάρων



Consequences of hyperglycemia – induced activation of PKC

Ruboxistaurin and Retinopathy

An oral presentation session on diabetic retinopathy was entitled "More than VEGF and PKC"; however, the most important paper in this session actually was about protein kinase C (PKC). Lloyd Paul Aiello, MD, PhD,[10] Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts, reported on a combined analysis of the trials with the PKC inhibitor ruboxistaurin in diabetic patients. The final analysis was done on 608 patients with the following characteristics: 59 years of age (SD 11); 85% had type 2 diabetes, with an average duration of 15 years; mean glycated hemoglobin (A1C) was 8.2%; 10% had retinopathy ETDRS level < 47, and 60% had ETDRS level of 47. The primary aim was prevention of retinopathy progression; the secondary aim was the prevention of vision loss. Although the primary target was not met, the reduction in sustained moderate vision loss was 4.2% (relative risk reduction, 41%; $P = .011$). Safety and tolerability were shown to be excellent in light of the need for long-term administration.

ΚΛΙΝΙΚΕΣ ΔΟΚΙΜΕΣ RUBOXISTAURIN (RBX)

Table 3. Randomized Controlled Trials of Medical Interventions in Diabetic Retinopathy

Source	No.	Diagnosis	Intervention	Follow-up	Outcome	Comments
PKC-DRS,[69] 2005	252	Moderately severe to very severe NPDR (ETDRS severity level between 47B and 53E; visual acuity ≥20/125 and no previous scatter photocoagulation)	Ruboxistaurin (8, 16, or 32 mg/d) vs placebo	36-46 mo	No significant effect on DR progression Ruboxistaurin (32 mg) delayed occurrence of MVL (P = .038) and SVL (P = .226) In multivariable Cox proportional hazard analysis, ruboxistaurin (32 mg) decreased risk of MVL vs placebo (HR, 0.37 [95% CI, 0.17-0.80]; P = .012)	Decrease of SVL by ruboxistaurin observed only in eyes with definite DME at baseline (10% ruboxistaurin vs 25% placebo, P = .017)
PKC-DRS2,[70] 2006	685	Moderately severe to very severe NPDR (ETDRS severity level between 47B and 53E; visual acuity ≥20/125 and no previous scatter photocoagulation)	Ruboxistaurin (32mg/d) vs placebo	3 y	No significant effect on DR progression Treatment decreased risk of sustained MVL (5.5% treated vs 9.1% placebo, P = .034)	
PKC-DME,[71] 2007	686	DME >300 μm from center (ETDRS severity level 20-47A, visual acuity ≥75 ETDRS letters, and no previous laser treatment)	Ruboxistaurin (32md/d)	3 y	No significant effect on progression to sight-threatening DME or need for focal laser treatment	Variation in application of focal laser between centers Ruboxistaurin reduced progression of DME vs placebo in secondary analysis (P = .054, unadjusted)

JAMA, August 22/29, 2007-vol 298, No 8

Effect of Ruboxistaurin on Visual Loss in Patients with Diabetic Retinopathy

PKC-DRS2 Group*

Objective: To evaluate the effect of ruboxistaurin, an orally administered protein kinase C β (PKC β) isozyme-selective inhibitor, on vision loss in patients with diabetes.

Design: Thirty-six-month, randomized, double-masked, placebo-controlled, parallel, multicenter trial.

Participants: Six hundred eighty-five patients randomized at 70 clinical sites.

Methods: Ophthalmologic examination was performed at screening and at each 3-month visit. Retinopathy status was assessed every 6 months with Early Treatment Diabetic Retinopathy Study (ETDRS) standard 7-field 30° color stereoscopic fundus photography. Levels of diabetic retinopathy and diabetic macular edema were determined by 2 independent graders masked to site and treatment assignment, with additional independent adjudication as required. Eligible patients had a best-corrected visual acuity (VA) score of ≥45 letters, retinopathy level ≥ 47A and ≤ 53E, and no prior panretinal photocoagulation in at least one eye.

Main Outcome Measure: Effect of oral ruboxistaurin (32 mg/day) on reduction of sustained moderate visual loss (≥15-letter decrease in ETDRS VA score maintained ≥ 6 months) in patients with moderately severe to very severe nonproliferative diabetic retinopathy.

Results: Sustained moderate visual loss occurred in 9.1% of placebo-treated patients versus 5.5% of ruboxistaurin-treated patients (40% risk reduction, $P = 0.034$). Mean VA was better in the ruboxistaurin-treated patients after 12 months. Baseline–to–end point visual improvement of ≥15 letters was more frequent (4.9% vs. 2.4%) and ≥15-letter worsening was less frequent (6.7% vs. 9.9%) in ruboxistaurin-treated patients relative to placebo ($P = 0.005$). When clinically significant macular edema was >100 μm from the center of the macula at baseline, ruboxistaurin treatment was associated with less frequent progression of edema to within 100 μm (68% vs. 50%, $P = 0.003$). Initial laser treatment for macular edema was 26% less frequent in eyes of ruboxistaurin-treated patients ($P = 0.008$).

Conclusion: Oral ruboxistaurin treatment reduced vision loss, need for laser treatment, and macular edema progression, while increasing occurrence of visual improvement in patients with nonproliferative retinopathy.

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Ophthalmology 2006;113:2221–2230

Effect of Ruboxistaurin in Patients With Diabetic Macular Edema

Thirty-Month Results of the Randomized PKC-DMES Clinical Trial

*The PKC-DMES Study Group**

Objective: To evaluate the safety and efficacy of orally administered ruboxistaurin (RBX) as a mesylate salt in patients with diabetic macular edema (DME).

Design: Multicenter, double-masked, randomized, placebo-controlled study of 686 patients receiving placebo or RBX orally (4, 16, or 32 mg/d) for 30 months. At baseline, patients had DME farther than 300 µm from the center of the macula, an Early Treatment Diabetic Retinopathy Study retinopathy severity level from 20 to 47A without prior photocoagulation, and an Early Treatment Diabetic Retinopathy Study visual acuity of 75 or more letters in the study eye. The primary study outcome was progression to sight-threatening DME or application of focal/grid photocoagulation for DME.

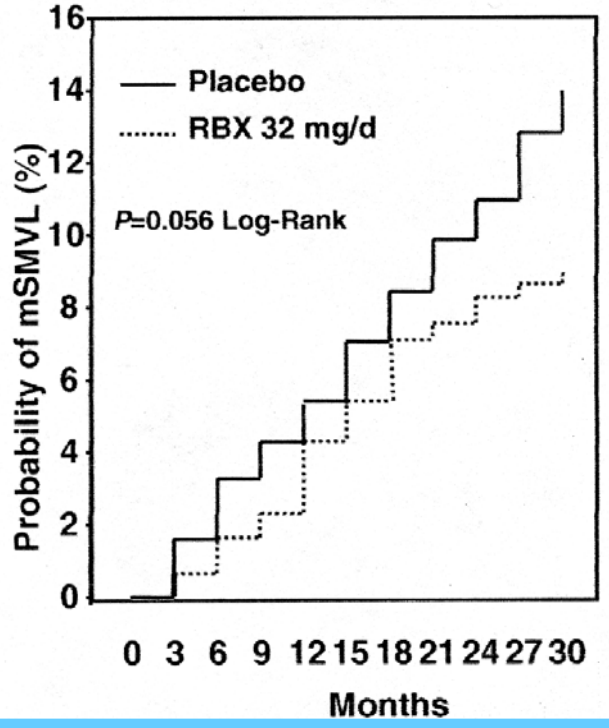
Main Out
scopic func

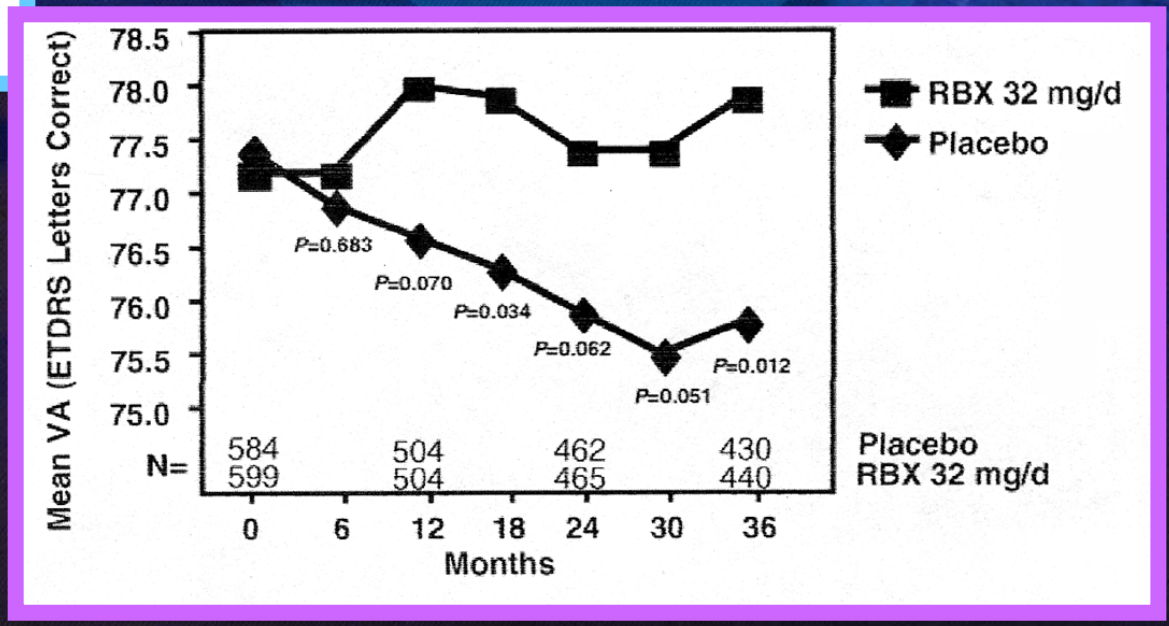
Results: The delay in progression to the primary outcome was not statistically significant (32 mg of RBX vs placebo, $P=.14$ [unadjusted]; Cox proportional hazards model adjusted for covariates, hazards ratio=0.73; 95% confidence interval, 0.53-1.0; $P=.06$). However, application of focal/grid photocoagulation prior to progression to sight-threatening DME varied by site, and a secondary analysis of progression to sight-threatening DME alone showed that 32 mg of RBX per day reduced progression, compared with placebo ($P=.054$ [unadjusted]; Cox proportional hazards model, hazards ratio=0.66; 95% confidence interval, 0.47-0.93; $P=.02$).

Conclusions: Although progression to the primary outcome was not delayed, daily oral administration of RBX may delay progression of DME to a sight-threatening stage.

Conclusions: Although progression to the primary outcome was not delayed, daily oral administration of RBX may delay progression of DME to a sight-threatening stage. Ruboxistaurin was well tolerated in this study.

RBX 32 mg/d


Placebo
RBX 32 mg/d
P=0.056 Log-Rank
Probability of mSMVL (%)
16
14
12
10
8
6
4
2
0
0 3 6 9 12 15 18 21 24 27 30
Months


Mean VA (ETDRS Letters Correct)
78.5
78.0
77.5
77.0
76.5
76.0
75.5
75.0
P=0.683
P=0.070
P=0.034
P=0.062
P=0.012
P=0.051
N=
584
599
504
504
462
465
430
440
0 6 12 18 24 30 36
Months
RBX 32 mg/d
Placebo
Placebo
RBX 32 mg/d

Σχόλια για τις μελέτες RBX

- Ασφαλής και καλός ανεκτός ειδικός αναστολέας PKCβ
- Η RBX δε μεταβάλλει τον κίνδυνο εξέλιξης της μέτριας ή βαρείας ΜΠΔΑ σε ΠΔΑ, άρα δεν ελαττώνει τη νεοαγγείωση
- Χρειάζονται τουλάχιστον 18 μήνες θεραπείας για να διαπιστωθεί κάποιο αρχικό όφελος, συνεπώς η μακροχρόνια χορήγηση είναι απαραίτητη
- Ο χρόνος οφέλους κρίνεται σχετικά βραχύς συγκριτικά με άλλες μελέτες (DCCT~3 έτη, DRS~1 έτος)
- Στις 18/8/2006 η E. Lilly έλαβε επιστολή αποδοχής από το FDA, αλλά στη συνέχεια ζητήθηκαν περισσότερες τριετείς κλινικές δοκιμές φάσης 3, με αποτέλεσμα την ακύρωση πολλών ελπίδων και επενδύσεων, τόσο επιστημονικών όσο και οικονομικών

Η δυσλειτουργία των μιτοχονδρίων αφετηρία της ΔΑ

Mary Ann Liebert, Inc. - Antioxidants & Redox Signaling - 7(11-12):1581

ANTIOXIDANTS & REDOX SIGNALING
Volume 7, Numbers 11 & 12, 2005

Forum Review

Diabetic Retinopathy: Mitochondrial Dysfunction and Retinal Capillary Cell Death

RENU A. KOWLURU

Oxidative stress is increased in proteins are elevated, and antio the retina, and the mitochondri cytosol into the mitochondria, increased retinal capillary cell early signs of retinopathy in an induced mitochondrial dysfun models, long-term administra retinopathy via inhibition of a apoptosis in the retina. Unders should help identify therapies the development of retinopathy

INTRODUC

RETINOPATHY, A PROGRESSIVE D debilitating complications of cause of acquired blindness among countries. Animal models have sh induced abnormalities in retinal m vated polyol pathway activity (44 glycation (56), oxidative stress (6, ity (34, 59), and the expressior growth factor (VEGF) (1, 40), evid velopment of microangiopathy. Be recognize which abnormalities are rationale for possible therapies lim

OXIDATIVE STRESS

Diabetes increases oxidative str ulatory role in the development o

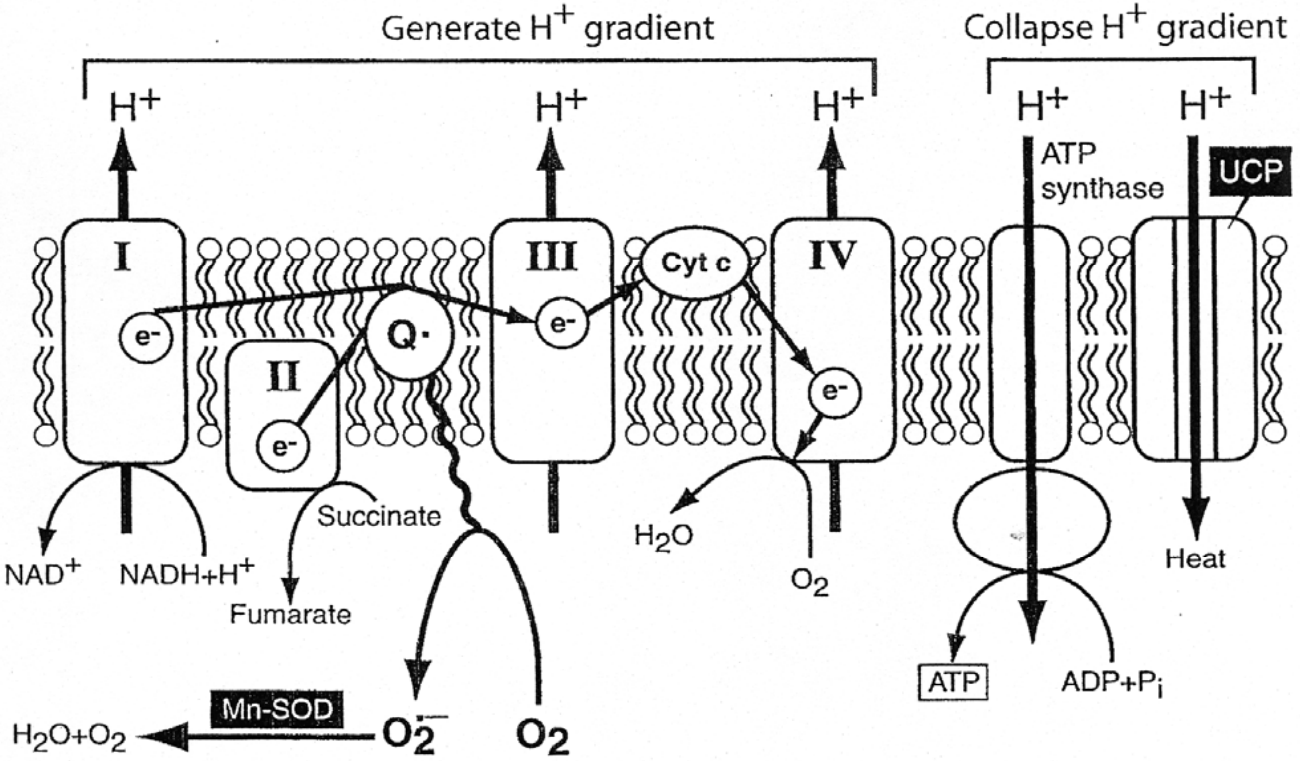
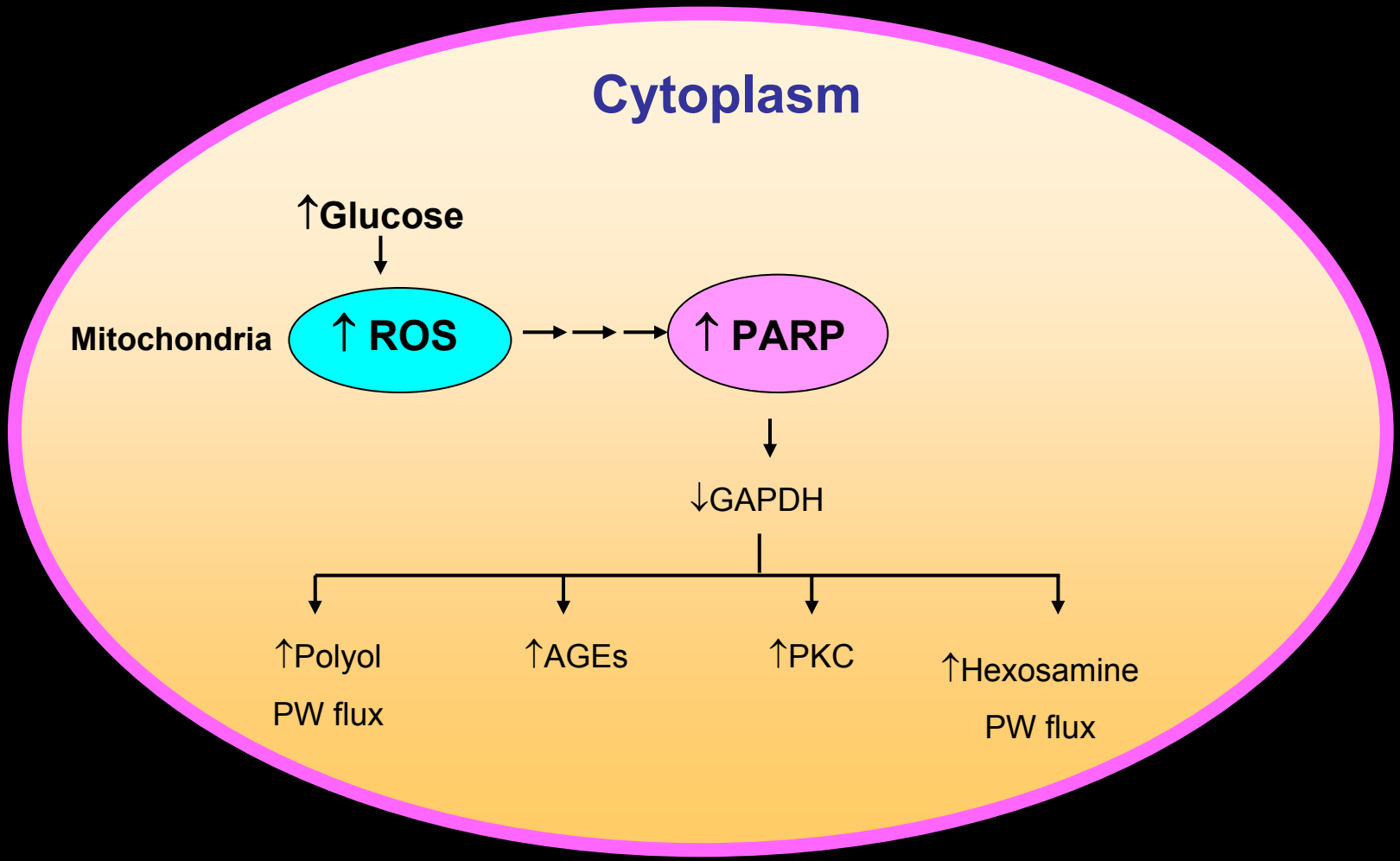
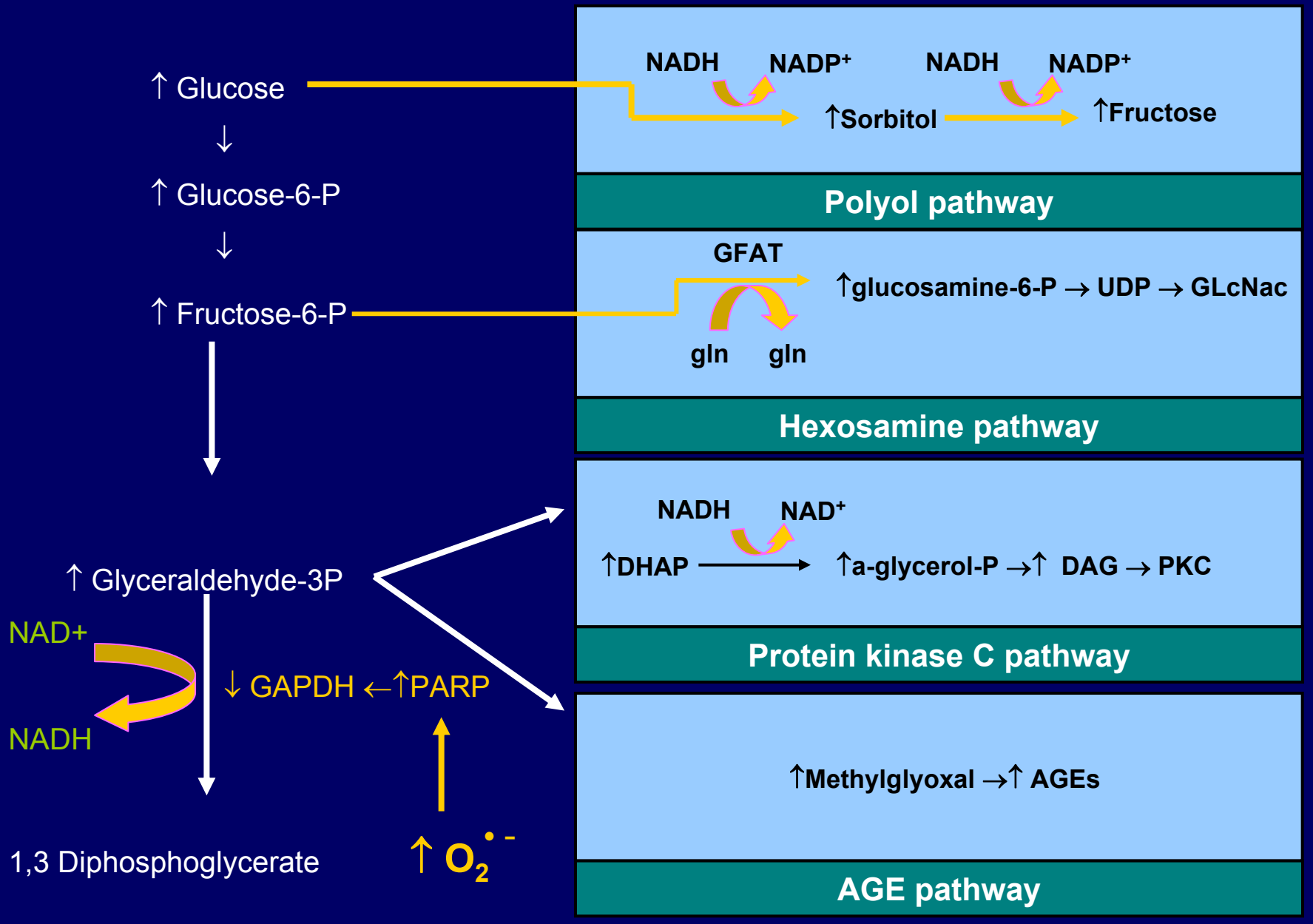


FIG. 6. Hyperglycemia-induced production of superoxide by the mitochondrial electron transport chain.

The unifying mechanism of hyperglycemia-induced cellular damage



Η δυσλειτουργία του μιτοχονδρίου οδηγεί μέσω ROS σε δυσλειτουργία του ενδοθηλίου



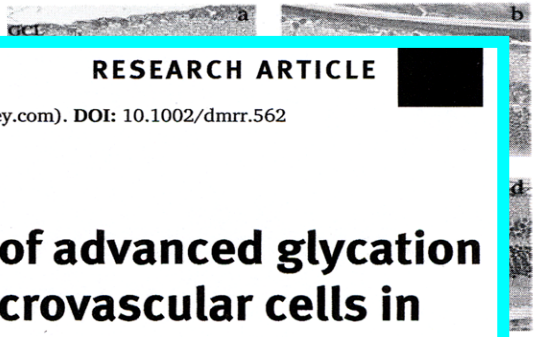
Mitochondrial overproduction of superoxide activates four major pathways of hyperglycemic damage by inhibiting GAPDH. From Brownlee M.: Biochemistry and molecular cell biology of diabetic complications Nature 414: 813-820, 2001.

DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2006; **22**: 38–45.
Published online 12 May 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/dmrr.562

RESEARCH ARTICLE

Antioxidants and an inhibitor of advanced glycation ameliorate death of retinal microvascular cells in diabetic retinopathy

Αντιοξειδωτικά και αναστολείς AGEs στη ΔΑ



AGE-like immunoreactivity (brown) in the inner segment of the photoreceptor layer (PRL) was not found in the Control group. It was found much in the Diabetic group and less in the Vit. C + E and in the AGE-I group than in the Diabetic group (original magnification, ×400)

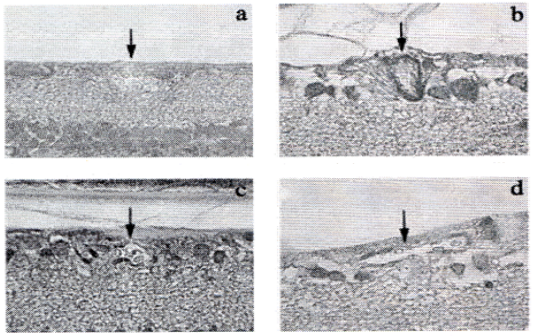


Figure 5. Immunohistochemical staining of AGE in retinal vascular walls. Figures (a), (b),(c), and (d) represent retinal blood vessels of the GCL in the Control, the Diabetic, the Vit. C + E, and the AGE-I groups respectively. AGE-like immunoreactivity of retinal vascular walls in the Diabetic group was found more than that in the Control, whereas that in the Vit. C + E and the AGE-I groups was less than that in the Diabetic group (original magnification, ×1000)

lead to apoptosis of RMCs and shows that it was not caused by streptozotocin or alloxan.

Our data shows that the evaluation of apoptosis of RMCs is a good marker of diabetic retinopathy in animal models because the amount of apoptosis, as well as the number of acellular capillaries, increased in the diabetic rats more than in the control, and the difference in the amount of apoptosis between the diabetic GK rats and the controls was large. A cellular capillaries and pericyte ghosts are well known as early histological changes of diabetic retinopathy, and these changes mean that the nuclei of RMCs have disappeared from capillaries. An acellular capillary is a capillary from which all endothelial cells and all pericytes have disappeared, and a pericyte ghost is an empty pocket in the basement membrane from which a pericyte nucleus has disappeared. Because cells in which apoptosis has started will soon die and disappear, we presume that these two changes appear as a result of apoptosis of RMCs. The evaluation of apoptosis shows how many RMCs are dying now, and the evaluation of the two morphological changes show how many RMCs have died so far. Because the evaluation of apoptosis predicts prospective histological changes, it is useful as well as the evaluation of morphological changes.

Because it has been known that TUNEL labeling is not an apoptosis-exclusive assay, our data cannot suggest that apoptosis is the only way in which vascular cells die during diabetes. However, it suggested that it was a useful evaluation method of diabetic retinopathy to count TUNEL-positive cells, which are dying mainly through apoptosis presumably.

Another of the novel findings in our study is that antioxidants (Vitamin C and E) and an AGE inhibitor (OPB-9195) ameliorated the increase of apoptosis of RMCs and acellular capillaries in diabetic GK rats. Vitamin C is water soluble and one of the most powerful natural antioxidants [12]. It scavenges reactive oxygen species in aqueous phase (plasma, cytoplasm, and so on). Moreover, there is evidence from *in vitro* studies that it is capable of regenerating tocopherol from the tocopheroxyl radical that is formed upon the inhibition of lipid peroxidation by vitamin E. Vitamin E is lipophilic, operating in membranes or lipoprotein particles. It scavenges lipid peroxyl radicals and inhibits lipid peroxidation. It was reported that, in the lipid phase, it might be the most efficient of lipophilic antioxidants [25]. Therefore, a combination of vitamins C and E is thought to work as a powerful antioxidant in aqueous and lipid phases.

Our data demonstrated that the combination of vitamins C and E reduced apoptosis of RMCs and acellular capillaries in diabetic rats and suggested that the combination of vitamins C and E might inhibit the progression of early retinopathy in diabetic patients.

Brownlee M *et al.* reported [26] that high concentrations of glucose increased the production of reactive oxygen species (ROS) in endothelial cells, and inhibition of mitochondrial ROS production prevented high glucose-induced activation of PKC, formation of AGE, sorbitol accumulation, and NFκB activation. This means oxidative stress though mitochondrial ROS production should be the most important cause of diabetic endothelial dysfunction and inhibition of mitochondrial ROS production or elimination of intracellular excess ROS will be a effective and reasonable therapeutic approach to prevent diabetic complications.

A couple of recent articles studied whether a combination of vitamins C and E can improve diabetic retinopathy in diabetic rats. One of them [27] reported that a combination of vitamins C (10 g/kg diet) and E (1 g/kg diet) inhibited 50% of acellular capillaries

Νεότερα αντιοξειδωτικά παράγωγα

χαμηλό μοριακό βάρος

μιμητικά SOD / καταλάσης

καρνιτίνη, λιποϊκό οξύ

θειαμίνη, μπενφοτιαμίνη

στατίνες, α-MEA, ARBs, κ.ά.

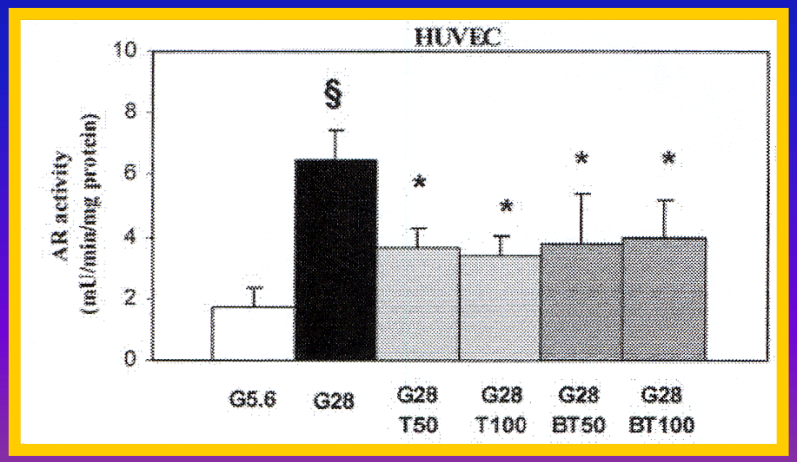
βελτιώνουν τη μιτοχονδριακή λειτουργία

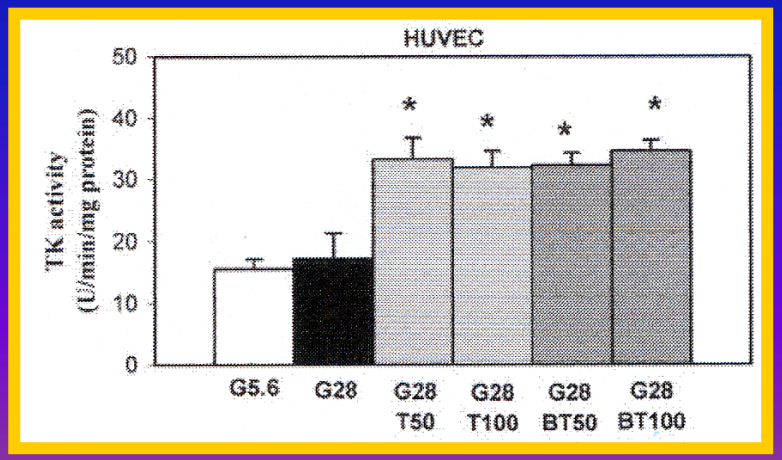
και μειώνουν βλάβες του DNA

σε πρώιμα στάδια ΔΑ

Thiamine, Benfotiamine

↓ έκφραση mRNA AR, ↓ δραστικότητα AR
↓ ενδοκυττάριο φορτίο σορβιτόλης και γλυκόζης
↑ έκφραση mRNA TK, ↑ δραστικότητα TK
ενίσχυση και επιτάχυνση γλυκόλυσης
↓ AGEs, ↓ PKC, ↓ οδός εξοζαμίνης, ↓ ROS
αναστολή ΠΔΑ και πειραματικής ΔΑ και νεφροπάθειας
προσιτή, οικονομική και αποτελεσματική επιλογή





Efficacy of Calcium Dobesilate (Doxium®) on the Blood–Retinal Barrier Permeability in Early Diabetic Retinopathy: a Double–Blind Study.

M.L. Ribeiro[1], P. Caillon[2], G. Gamba[3], J. Cunha–Vaz[1] and DX–retinopathy study group

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[2] OM PHARMA, Meyrin, Geneva, Switzerland
[3] Biometrix SA, Gland, Switzerland

Commercial Relationships: M.L. Ribeiro, OM PHARMA F; **P. Caillon**, OM PHARMA E; **G. Gamba**, OM PHARMA R; **J. Cunha–Vaz**, OM PHARMA R.

Grant Identification: none

Abstract

Objective: Doxium® (DX, Calcium dobesilate) has been shown to reduce retinal vessel hyperpermeability and leakage from vascular lesions. The aim of this study is to confirm the efficacy of DX on the Blood–Retinal Barrier (BRB) permeability.

Methods: Adult patients, aged 35 to 70, with type 2 diabetes an
confirmed by stereoscopic fundus photography (up to level 47
fluorophotometry were enrolled in this double–blind, placebo–
regimen was 4x500 mg (2g) daily during 24 months. The evolu
Penetration Ratio (PVPR) of the eye defined as "worst" at basel
fluorophotometry (Ocumetrics Fluorotron Master) performed at
fundus photography and fluorescein angiography were carried
evaluations were performed at 3–month intervals. 194 patients
137 completed the study period (69 DX and 68 PL).

Results: PVPR global evolution, analysed by ANCOVA of leas
significant superiority of DX over PL (p=0.0378) with mean slo
0.050) and +0.010 (SE 0.052). Moreover, mean PVPR (differen
lower at the end of treatment period in DX group (–3.87 (SD 12
12.86)), Δ=–5.91 (95%CI –10.20 –1.62, p=0.0016).

Conclusions: Treatment with DX 2g per day during 24 months had a significant effect on the evolution of the BRB permeability with placebo showing an increase in retinal leakage. Tolerance was very good and similar for both treatment groups.

Key Words: diabetes • diabetic retinopathy • clinical (human) or epidemiologic

Doxium
στη ΔΑ

Ανεξάρτητα από τη ρύθμιση του Διαβήτη
η θεραπεία με DX
(Doxium, Calcium Dobesilate)
σε δόση 2 g/ημ. επί 24 μήνες
είχε προστατευτική επίδραση
στον αιματο-αμφιβληστροειδικό φραγμό
Η ανοχή ήταν πολύ καλή

Hypophysectomy for Diabetic Retinopathy

Diabetes which is resistant to diet and insulin therapy is often easier to control—and retinal deterioration slowed—if certain pituitary hormones are prevented from being excreted by destruction of the pituitary gland.

SHARON M. STOWE

For a few patients with diabetic retinopathy, hypophysectomy, or removal of the pituitary gland, is the palliative procedure of choice to slow or halt their progressive blindness(1).

Four of the anterior pituitary hormones — corticotropin, thyrotropin, luteotropin, and growth—have, in susceptible patients, a diabetogenic effect. Interrupting the production and dissemination of these hormones, by hypophysectomy, and replacing them with chemical substitutes in controlled amounts have arrested some patients retinal damage and made their diabetes easier to control (2).

Ms. R., a 19-year-old, single, Puerto Rican girl, was one of my patients who had an hypophysectomy. She had a history of repeated retinal hemorrhages, progressive loss of vision for two years prior to admission, and diabetes which was refractory to a well-supervised and frequently adjusted regimen of diet and insulin. She was a good candidate for hypophysectomy because her renal and cardiac functions were within normal limits and because she wanted very much to live a more normal life and preserve her remaining vision.

To plan and carry out the best possible care for Ms. R., I needed to know the cause of diabetic ret-

MS. STOWE, who is a clinical nurse specialist in neurology and neurosurgery at the Veterans Administration Hospital, Bronx, N.Y., is a graduate of the Kaiser Foundation School of Nursing, Oakland, Calif. She earned a B.S. degree at the University of Washington, Seattle, and an M.A. degree in nursing education at New York University, N.Y. She wishes to express appreciation to Dr. Ved Sechder of Mount Sinai Hospital, New York, for review of the paper.

direct is unknown at present. The pituitary is centrally located under the frontal lobe of the brain, within the sella turcica under the branches of the optic chiasm. The hypophyseal

parathyroid, and pancreatic glands. Whether the effect is direct or in-

ly retaining electrolytes.

In diabetes insipidus, a condition

TREATMENT - RETINOPATHY

IGF-1 Antagonists in Diabetic retinopathy

- Pituitary infarction and hypophysectomy benefit PDR
- DR also seen after treatment with GH in non diabetics
- What about somatostatin and it's analogues ? (Anti GH and IGF-1
- IGF-1 increases VEGF by retinal pigmented cells
- Will it reduce retinal neo vascularization ?

Progression of Retinopathy in Insulin-Treated Type 2 Diabetic Patients

MARIANNE HENRICSSON, MD, PHD[1]
KERSTIN BERNTORP, MD, PHD[2]
PER FERNLUND, MD, PHD[3]
GÖRAN SUNDKVIST, MD, PHD[2]

OBJECTIVE — To study the progression of retinopathy 3 years after initiation of insulin therapy.

RESEARCH DESIGN AND METHODS — In a prospective, observational case-control study, 42 type 2 diabetic patients were examined at baseline and 1, 3, 6, 12, 24, and 36 months after change to insulin therapy. Retinopathy was graded based on fundus photographs using the Wisconsin scale; HbA_{1c} and IGF-1 were measured.

RESULTS — During the observation period of 3 years, 26 patients progressed in the ... athy scale; 11 patients progressed at least three levels. After 3 years of insulin thera... IGF-1 were significantly lower than at baseline. Progression of retinopathy ... to three levels was related to high IGF-1 levels.

CONCLUSIONS — A relationship was found betw... progression of retinopathy in type 2 diabetic pati...

In diabetic ret... illaries ... was ...tinal neo- ...tic patient was ...ter postpartum pitu- ...(12). Subsequent controlled ...trials showed that pituitary abla- ...on could improve DR (13). Many mito- genic effects of GH are mediated by IGF-1 (14). Merimee et al. (15) found increased serum IGF-1 levels in patients with rapidly accelerating DR, and Chantelau et al. (16,17) reported a relationship between upregulation of IGF-1 and progression of retinopathy in Mauriac's syndrome and in type 1 diabetes.

...Con- ...CCT) (8) In ... relationship be- ...improvement in HbA_{1c} ...sion of retinopathy 2 years after ...art of insulin therapy in type 2 diabetic patients (9).

In a randomized controlled study, Grant et al. (18) showed that the progression to high-risk proliferative diabetic retinopathy (PDR) was diminished in patients treated with ocreotide, a somatostatin analog decreasing the secretion of GH.

We have now followed the ... abetic patients of our pr... study regarding the ... nopathy. In th... study, w... ...ars of age ...dy when they, ...y metabolic control, ...to the Diabetic Day Care ...the Department of Endocrinology ...Malmö, Sweden, to be changed to insulin therapy (Table 1). Patients with severe concomitant diseases preventing follow-up, patients with severe nonproliferative retinopathy or proliferative retinopathy, and patients with cataracts, making retinal photography impossible, were excluded from the study.

The patients were examined at baseline, before the introduction of insulin therapy, and at follow-up after 1, 3, 6, 12, 24, and 36 months. Fundus photography including visual acuity testing was performed, and blood samples for HbA_{1c} and IGF-1 were collected during all examinations. At baseline, a simple neurological examination was performed; tendon reflexes and vibratory sensory thresholds were assessed using a biothesiometer at the ankle region (Bio-thesiometer; Bio-Medical Instrument, Newbury, OH). Patients were asked about smoking and current antihypertensive treatment. Blood pressure was measured in each patient in the supine position after 5 min rest. Hypertension was considered

From the Department of [1]Ophthalmology, University Hospital, Malmö, Sweden; the [2]Department of Endocrinology, University Hospital, Malmö, Sweden; and the [3]Department of Clinical Chemistry, University Hospital, Malmö, Sweden.

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Received for publication 13 June 2001 and accepted in revised form 16 October 2001.

Abbreviations: DR, diabetic retinopathy; GH, growth hormone; PDR, proliferative diabetic retinopathy.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

CONCLUSIONS — A relationship was found between high IGF-1 levels at 3 years and progression of retinopathy in type 2 diabetic patients.

Diabetes Care 25:381–385, 2002

IGF-1 και ΔΑ

ΜΠΔΑ: ↑ IGF-1 ορού, ΠΔΑ: ↑ IGF-1 υαλοειδούς

Συνέργεια IGF-1 με VEGF στη νεοαγγείωση

Ήβη και κύηση: ↑ IGF-1 ⇒ επιδείνωση ΔΑ

Σωματοστατίνη: φυσικός αναστολέας άξονα GF/IGF-1.

Τα ανάλογα σωματοστατίνης -με κύριο εκπρόσωπο το οκτρεοτίδιο- εφαρμόζονται στη θεραπεία της μεγαλακρίας, καρκινοειδών όγκων και VIPωμάτων

Αναστέλλουν την έκκριση γαστρίνης, χολοκυστοκινίνης, γκρελίνης, σεκρετίνης, VIP, γλυκαγόνης, GH, IGF-1, κ.ά.

Topics in Diabetic Retinopathy CME/CE

Disclosures

Hans-Peter Hammes, MD, PhD

The symposium entitled "Diabetic Retinopathy -- Diagnostic and Treatment Novelties[1]" centered on 2 important areas of research: (1) the retina as an additional independent risk indicator of cardiovascular morbidity and mortality and (2) clinical treatments.

Insulin-like Growth Factor-1 Antagonists in the Treatment of Retinopathy

Maria Grant, MD,[2] University o
in which patients with preexistin
(IGF) antagonist. With the repor
pituitary gland experienced resc
experimental and clinical studie
in the initiation and/or progressi
(1) patients with diabetic retinop
diabetic retinopathy had elevate
other important retinal growth fa
neovascularizations.

Experimental inhibition of the GI
new vessel formation, and smal
the administration of the somato
frequent administration of the dr
a long-acting release form of oc
established for larger clinical tria

Dr. Grant reported the results of
802 study, 61 centers in 15 Euro
nonproliferative to non-high-risk
Retinopathy Study [ETDRS] lev
effect of 2 doses of octreotide lo
the progression of preexisting d
ETDRS retinopathy scale or a m
endpoints were the time to deve
tolerability also were assessed.

In the 804 study, 313 patients fr
octreotide long-acting release in
study. (Patient characteristics w
finding was the significant delay
of octreotide in the 804 study (h
acuity and progression to macul
studies, the most frequent side effects being diarrhea, development of cholelithiasis, and mild

Η πειραματική αναστολή του άξονα GH/IGF-1 σε μοντέλο οξείας ΠΔΑ ανέστειλε περαιτέρω νεοαγγείωση
Αρκετές μικρές κλινικές δοκιμές στις ΗΠΑ και Ευρώπη είχαν δείξει ότι **η χρήση του οκτρεοτιδίου ήταν ευεργετική**.
Όμως, η ανάγκη για συχνή υποδόρια χορήγηση εμπόδιζε την ευρύτερη θεραπευτική του εφαρμογή. Με την ανάπτυξη οκτρεοτιδίου μακράς δράσης (Sandostatin LAR, Novartis) στο προηγούμενο ερευνητικό υπόβαθρο οικοδομήθηκαν μεγαλύτερες κλινικές μελέτες.
2006, 66η Συνάντηση ADA, Dr Grant (Florida): 2 μεγάλες κλινικές δοκιμές, όπου ασθενείς με προϋπάρχουσα ΔΑ αντιμετωπίσθηκαν με οκτρεοτίδιο. Οι **μελέτες** αυτές είναι γνωστές ως **802** και **804**.

Μελέτη 804

313 ασθενείς από ΗΠΑ, Καναδά και Βραζιλία, ETDRS 47-61

οκτρεοτίδιο 30 mg, 1 φορά/μήνα I.M.

Σημαντική επιβράδυνση επιδείνωσης ΔΑ
(9% εξέλιξη σε υψηλού κινδύνου ΠΔΑ
έναντι 42% με συμβατική θεραπεία)

Καλή ανοχή και ασφάλεια

Διάρροια, χολολιθίαση και ήπιες υπογλυκαιμίες

Συγκριτικά με την 802 είχε καλύτερη οργάνωση και συμμόρφωση με αποτέλεσμα μεγαλύτερη καταστολή του άξονα GH/IGF-1 (↓IGF-1)

Μελέτη 802

585 ασθενείς από 61 κέντρα σε 15 ευρωπαϊκές χώρες

Μελετήθηκαν 2 δόσεις οκτρεοτιδίου, 20 και 30 mg 1 φορά/μήνα I.M.

Δεν επιβεβαιώθηκαν τα αποτελέσματα της 804

Dev Ophthalmol. 2007;39:111-21.

Use of long-acting somatostatin analogue treatment
diabetic retinopathy

Boehm BO.

Division of Endocrinology and Diabetes, Department of Me
Ulm University, Ulm, Germany. berhard.boehm@uniklinik-

The diabetes epidemic continues unabated, leading to an increasing number of acute and chronic complications, including sight-threatening proliferative diabetic retinopathy. Currently, there is no accepted pharmaceutical therapy for diabetic retinopathy besides nearnormal glycemia, treatment of hypertension, and dyslipidemia. For an effective treatment of retinopathy, one would recommend a concept leading to the downregulation of endogenous angiogenic stimulators and the upregulation of endogenous angiogenic inhibitors, resulting in a restoration of the balance in angiogenic control. The naturally occurring growth hormone inhibitor, somatostatin, has been suggested as candidate for developing novel therapies. Somatostatin may exert its antiangiogenic effects, both through antagonism of the growth hormone axis and through direct antiproliferative and apoptotic effects on endothelial cells. Therefore, the use of long-acting somatostatin analogues will lead to an upregulation of antiangiogenic signaling. Use of long-acting somatostatin analogues in diabetic retinopathy would be an important extension of the initial concept somatostatin is a regulator of growth hormone secreti only. Currently available analogues have already allow to modulate the expression of diabetic retinopathy at various disease stages. Somatostatin analogues remai the only nondestructive therapeutic alternative to patients with proliferative diabetic retinopathy who have failed to respond to panretinal photocoagulation.

PMID: 17245082 [PubMed - indexed for MEDLINE]

Η σωματοστατίνη, φυσικός αναστολέας του άξονα GH/IGF-1, ενισχύει ενδογενείς αναστολείς και καταστέλλει ενδογενείς διεγέρτες αγγειογένεσης συμβάλλοντας στη διατήρηση της ισορροπία τους

Προτείνεται ως ασφαλής εναλλακτική θεραπεία επίμονης ΔΠΑ που δεν ανταποκρίθηκε σε παναμφιβληστροειδική φωτοπηξία

Εντατική ινσουλινοθεραπεία ΣΔΤ1

μετά παρατεταμένη φτωχή ρύθμιση

↓HbA_1c

διέγερση άξονα GH/IGF-1

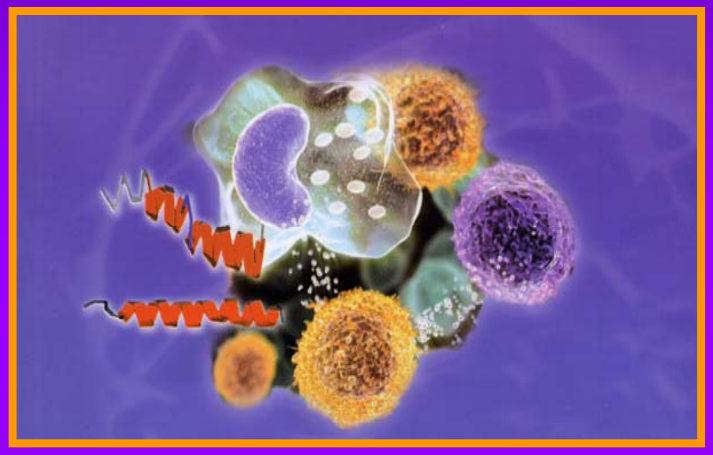
⇓

επιδείνωση προϋπάρχουσας ΔΑ
("florid" retinopathy)
οίδημα ωχράς, νεοαγγείωση

Τα μακροπρόθεσμα οφέλη της εντατικής ινσουλινοθεραπείας υπερκαλύπτουν την ενδεχόμενη βραχυπρόθεσμη επιδείνωση.

Έχει προταθεί αντιμετώπιση με **οκτρεοτίδιο**
(ίσως και σε συνδυασμό με ελαφρά μείωση των δόσεων ινσουλίνης)

Τα προσεχή χρόνια
θα είναι διαθέσιμες αρκετές
νέες, αποτελεσματικές φαρμακευτικές θεραπείες
για τη διαβητική αμφιβληστρειδοπάθεια.



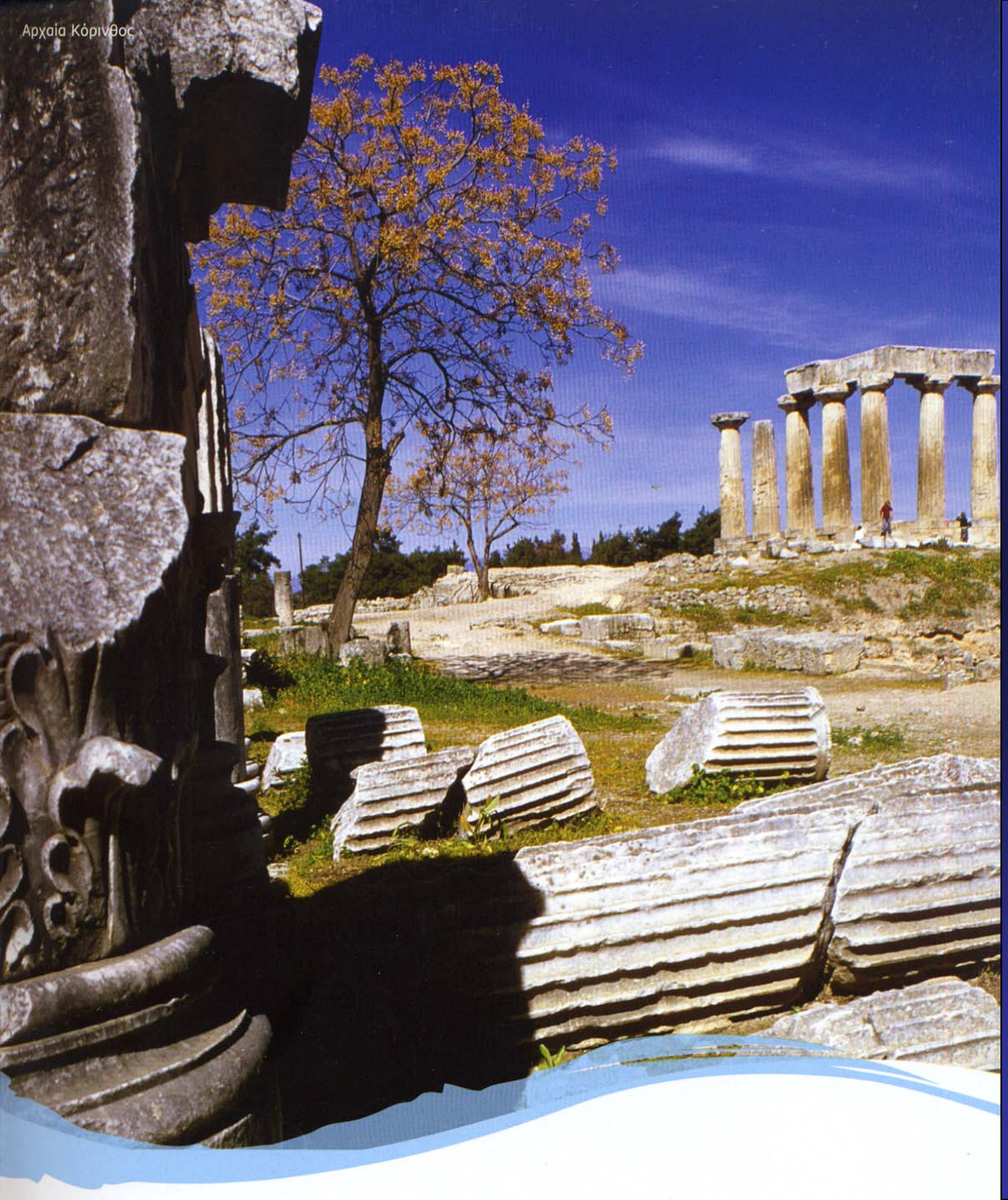
Οι πιθανές ενδείξεις τους θα είναι:

• η σοβαρή ΜΠΔΑ • η ΠΔΑ

• το κλινικά σημαντικό οίδημα της ωχράς

Θα λειτουργούν ως συμπληρώματα της φωτοπηξίας,
σε αποτυχία της ή σε αντένδειξή της

Ελπίδες και φόβοι



Σταθερές αξίες

Ανατροπές

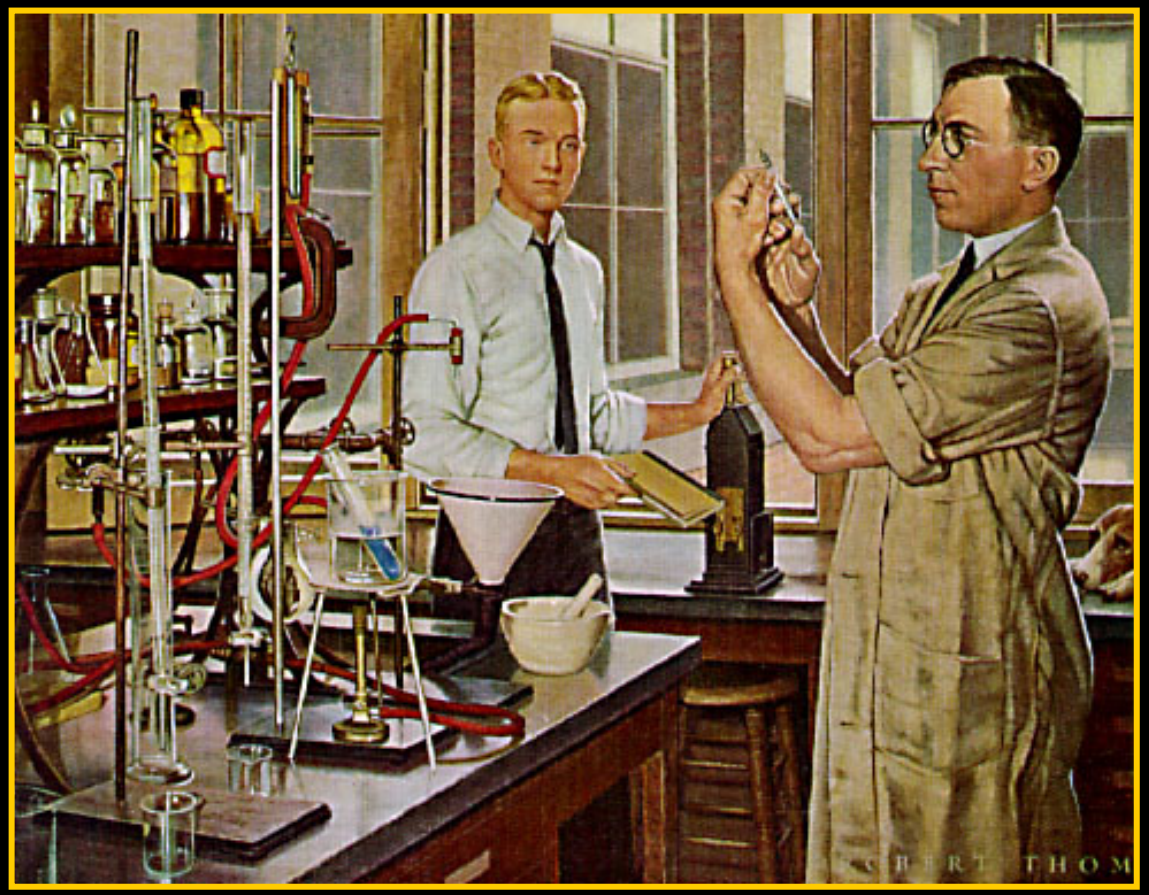
Μια σταθερή αξία, ο Ιπποκράτης, έγραψε ότι
ο καλός γιατρός πρέπει να θεραπεύει με βάση
τα αποτελέσματα της παρατήρησης
και όχι της συλλογιστικής.

Η τοποθέτησή του αυτή ήταν η αρχή της Ιατρικής που βασίζεται σε τεκμήρια (Evidence Based Medicine – EBM)

Η θεραπευτική πρέπει να στηρίζεται στα ευρήματα μεγάλων προοπτικών, πολυκεντρικών, τυχαιοποιημένων διπλών – τυφλών μελετών, ικανών να υπαγορεύουν κατευθυντήριες οδηγίες (guidelines)

Παραδείγματα: η Αμερικανική DCCT (Diabetes Control and Complication Trial) και η Βρεττανική UKPDS (United Kingdom Prospective Diabetes Study)

DCCT



Ινσουλινοθεραπεία

χθες και σήμερα...

DCCT: Intensive Glucose Control in Type 1 diabetes mellitus

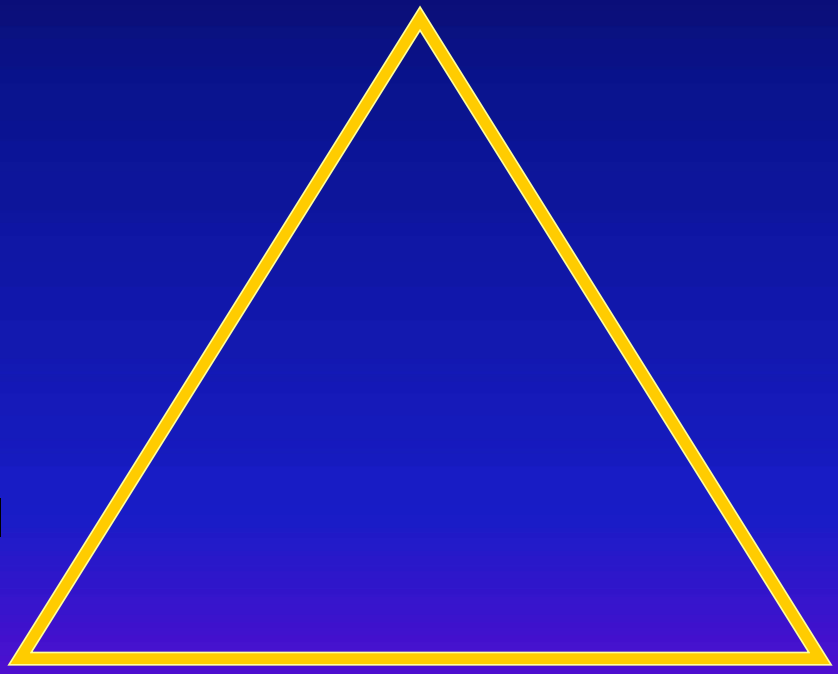
Compared to conventional insulin therapy, intensive insulin therapy reduced the risk of development and progression of:

	Risk Reduction*
Retinopathy	63%
Nephropathy†	54%
Neuropathy	60%

*Compared with conventional treatment
†Urinary albumin excretion ≥ 300 mg/24 h

Adapted from DCCT Research Group. *N Engl J Med*. 1993;329:977-986.

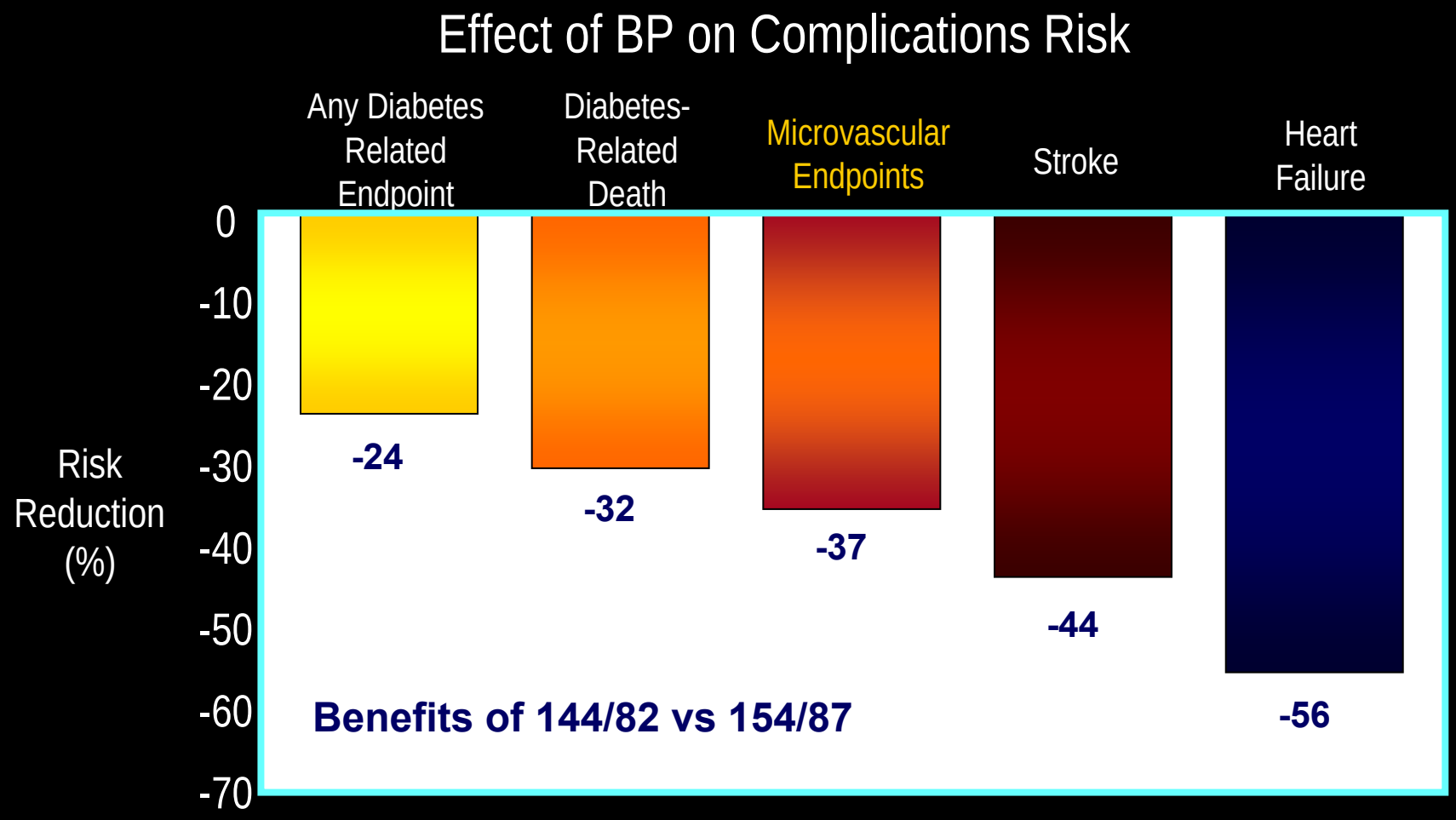
Components of Glycemic Control



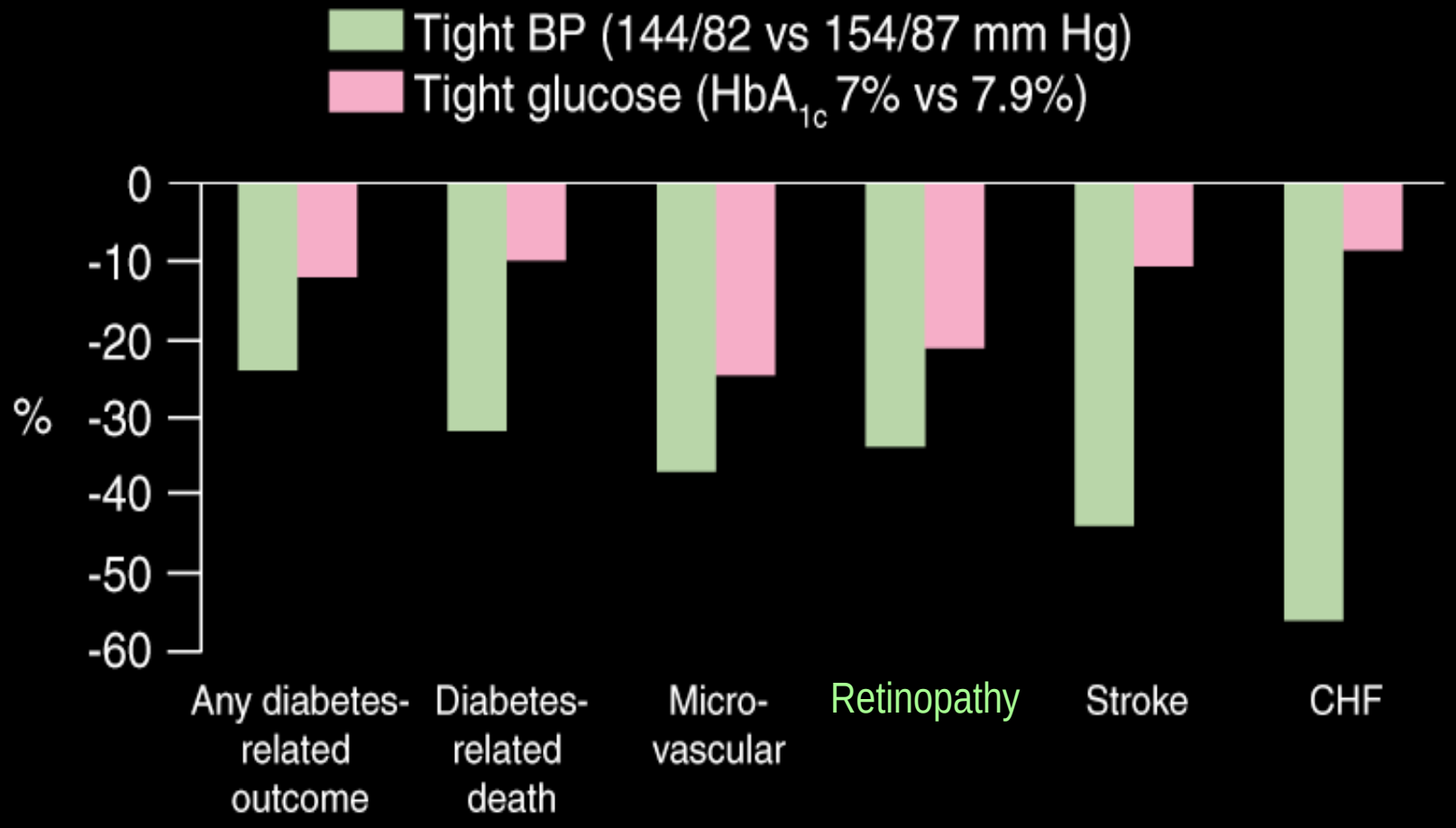
*If can be achieved safely

UKPDS: BP Control Study

in Type 2 Diabetes



UKPDS: Comparison between tight control of BP and glycemia on risk of diabetes complications



UKPDS Group. *Lancet*. 1998;352:837-853.
UKPDS Group. *BMJ*. 1998;317:703-713.

Tight Blood Pressure Control in Diabetes

- UKPDS- tight control defined as <150/85
  - Actual average blood pressures were 144/82 vs 154/87
  - Associated with lower stroke, retinopathy and Diabetic related deaths
- HOT study-diastolic BP goal of 80
  - Resulted in lower cardiovascular deaths and events compared with goal of 90.
- ABCD trial-**128/75** achieved BP
  - Tight BP control associated with lower overall mortality 5.5% vs 10.7% for “moderate control” (137/81)

Role of Serum Lipids in DR

- Elevated serum lipids are associated with increased risk of retinal hard exudates
- Increased amounts of hard exudates are associated with increased risk of visual impairment
- Elevated lipids, most notably triglycerides, are a risk factor for development of high-risk PDR

ETDRS Report # 18 and 22

Lipids and Retinopathy

There is an ongoing debate about whether elevated lipids are important in the pathogenesis of diabetic retinopathy. Several historical anecdotal reports have shown that diabetic patients with elevated lipids were more prone to diabetic macular edema, and that treatment with lipid-lowering drugs resolved these deposits. Because elevated lipids are involved in atherosclerosis and vessel stenosis, including stenosis of the carotid artery, an indirect relationship may exist between hyperlipidemia and diabetic retinopathy, given that moderate carotid artery stenosis protects from diabetic retinopathy, whereas more severe stenosis leads to ischemic retinopathy. The Atherosclerosis Risk in Communities (ARIC) study showed a weak but significant correlation between thickening of the carotid artery intima-media wall and diabetic retinopathy.[4] In that light, Paul Dodson, MBBS, MD, FRCP, FRCOphth,[5] Birmingham Heartlands Hospital, Birmingham, United Kingdom, summarized studies on the effect of statins and fibrates in the treatment of diabetic retinopathy.

In the Collaborative Atorvastatin Diabetes Study (CARDS),[6] approximately 1400 patients with type 2 diabetes received 10 mg of atorvastatin for primary prevention of coronary heart disease, which resulted in a 26% drop in total cholesterol and a 40% drop in low-density lipoprotein (LDL) cholesterol. Treatment duration was 4-4.5 years. At baseline and at annual follow-up, the investigators reported whether any fundal examination record from the previous year showed "no retinopathy," "nonproliferative retinopathy," "preproliferative retinopathy," or "proliferative retinopathy." Whether the patient had received photocoagulation in the past year was also noted, but the type or purpose of any photocoagulation was not recorded. Retinal photographs were not obtained. The investigators used accelerated failure time models with interval censoring to examine whether there was any treatment effect on retinopathy over a median 4-year follow-up.

The study's main problem was that there were considerable data missing, both at baseline and during follow-up. Of 2838 patients enrolled in CARDS, only 65% had retinopathy status recorded at baseline, and 39% of these patients had some retinopathy. There was no effect of treatment on progression of retinopathy severity by at least 1 step (6% lower rate in the atorvastatin group; $P = .5$). At least 1 follow-up recording of photocoagulation status was available in 2298 (81%) participants. Baseline status was available in just 1729 of these (61% overall). The incidence of photocoagulation was 6.03/100 person-years at risk (95% confidence interval [CI]: 5.28, 6.90) in the placebo group and 5.50/100 person-years at risk (95% CI: 4.81, 6.30) in the atorvastatin group. This 13% reduction in coagulation with atorvastatin treatment ($P = .4$) increased to a 21% reduction on adjusting for baseline status but remained nonsignificant ($P = .1$).

Firm conclusions about the effect of atorvastatin on retinal outcomes in CARDS are hindered by the lack of photographs and considerable missing data. Although there was no clear evidence of a treatment effect, the results, although nonsignificant, are consistent with some protective effect.

Μελέτη CARDS

Η ατορβαστατίνη δεν αποδείχθηκε αποτελεσματική στην εξέλιξη της ΔΑ

Μελέτη FIELD

Η φενοφιμπράτη σε Σ.Δ. Τ 2 μειώνει την ανάγκη για φωτοπηξία με άγνωστο μηχανισμό

PPAR-alpha?

Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial

A C Keech, P Mitchell, P A Summanen, J O'Day, T M E Davis, M S Moffitt, M-R Taskinen, R J Simes, D Tse, E Williamson, A Merrifield, L T Laatikainen, M C d'Emden, D C Crimet, R L O'Connell, P G Colman, for the FIELD study investigators*

Summary

Background Laser treatment for diabetic retinopathy is often associated with visual field reduction and other ocular side-effects. Our aim was to assess whether long-term lipid-lowering therapy with fenofibrate could reduce the progression of retinopathy and the need for laser treatment in patients with type 2 diabetes mellitus.

Methods The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multinational randomised trial of 9795 patients aged 50–75 years with type 2 diabetes mellitus. Eligible patients were randomly assigned to receive fenofibrate 200 mg/day (n=4895) or matching placebo (n=4900). At each clinic visit, information concerning laser treatment for diabetic retinopathy—a prespecified tertiary endpoint of the main study—was gathered. Adjudication by ophthalmologists masked to treatment allocation defined instances of laser treatment for macular oedema, proliferative retinopathy, or other eye conditions. In a substudy of 1012 patients, standardised retinal photography was done and photographs graded with Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of diabetic retinopathy and its component lesions. Analyses were by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN64783481.

Findings Laser treatment was needed more frequently in participants with poorer glycaemic or blood pressure control than in those with good control of these factors, and in those with a greater burden of clinical microvascular disease, but the need for such treatment was not affected by plasma lipid concentrations. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (164 [3·4%] patients on fenofibrate *vs* 238 [4·9%] on placebo; hazard ratio [HR] 0·69, 95% CI 0·56–0·84; p=0·0002; absolute risk reduction 1·5% [0·7–2·3]). In the ophthalmology substudy, the primary endpoint of 2-step progression of retinopathy grade did not differ significantly between the two groups overall (46 [9·6%] patients on fenofibrate *vs* 57 [12·3%] on placebo; p=0·19) or in the subset of patients without pre-existing retinopathy (43 [11·4%] *vs* 43 [11·7%]; p=0·87). By contrast, in patients with pre-existing retinopathy, significantly fewer patients on fenofibrate had a 2-step progression than did those on placebo (three [3·1%] patients *vs* 14 [14·6%]; p=0·004). An exploratory composite endpoint of 2-step progression of retinopathy grade, macular oedema, or laser treatments was significantly lower in the fenofibrate group than in the placebo group (HR 0·66, 95% CI 0·47–0·94; p=0·022).

Interpretation Treatment with fenofibrate in individuals with type 2 diabetes mellitus reduces the need for laser treatment for diabetic retinopathy, although the mechanism of this effect does not seem to be related to plasma concentrations of lipids.

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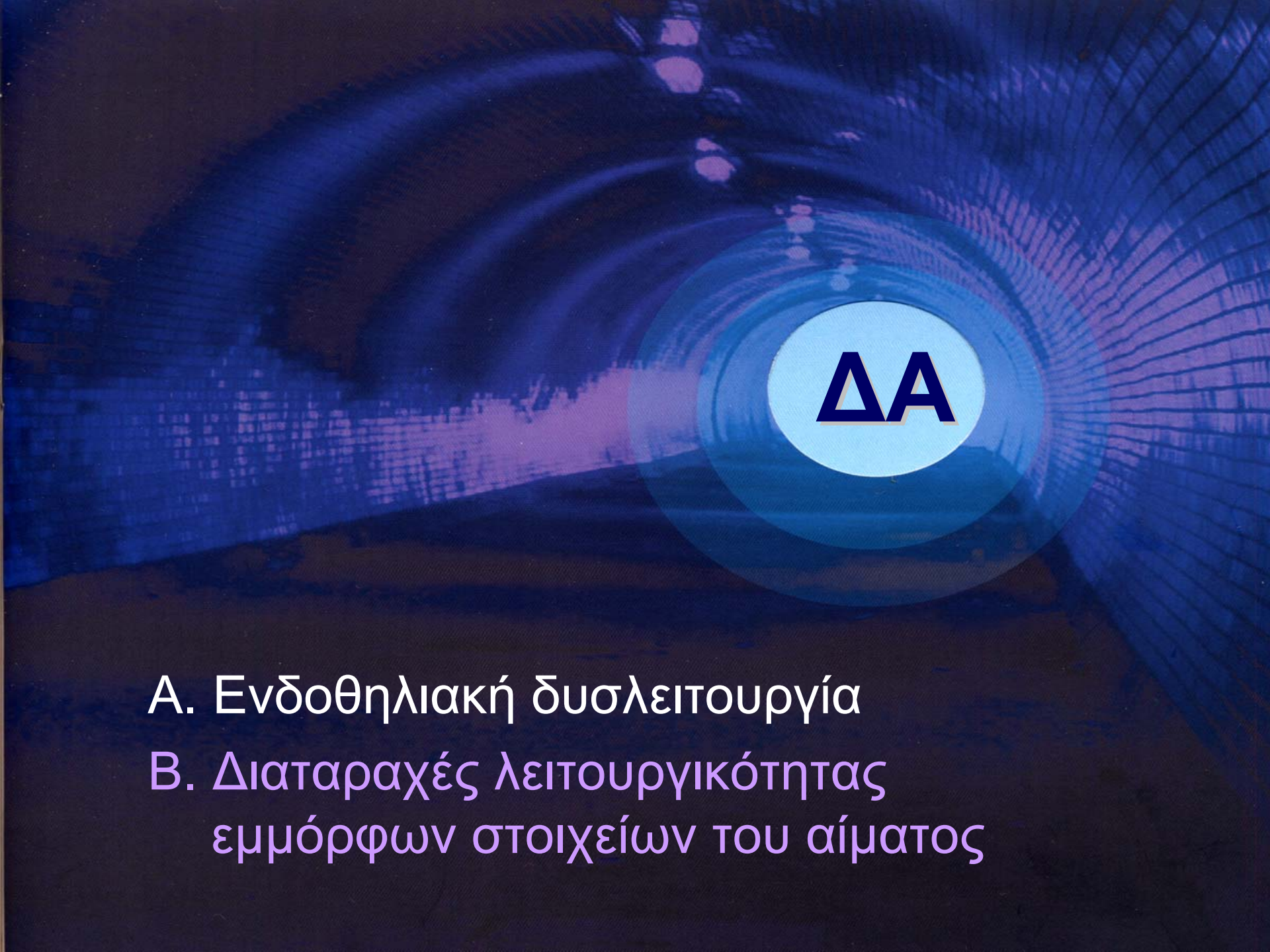
Introduction

Diabetic retinopathy has become the leading cause of vision loss and blindness in working-age adults in both developed and developing countries.[1,2] Visual loss results mainly from central macular oedema, and less frequently from proliferative diabetic retinopathy. The onset of diabetic retinopathy is characterised by vasodilation and hyperperfusion, followed by capillary loss and ischaemia. Leakage of protein and fluid from damaged capillaries leads to oedema at the macula, the focal centre of the retina, together with lipid and protein deposits termed hard exudates. The development of these pathological changes is strongly related to hyperglycaemia in type 2 diabetes.[3,4]

Laser treatment to photocoagulate ischaemic retina and leaking microaneurysms has been proven in clinical trials to slow or prevent further vision loss from diabetic retinopathy.[2,5,6] Although successful, laser treatment is frequently associated with visual field reduction and other ocular side-effects,[7] and so any treatment that could reduce the need for the use of lasers would be an important advance. Medical management of risk factors associated with diabetic retinopathy is also important in slowing the progression of retinal disease.[8–10] Although there is clear evidence of an association between diabetic retinopathy and glycaemia, duration of diabetes, raised blood pressure, and microalbuminuria, neither control of glycaemia nor blood pressure has fully prevented the progression of diabetic retinopathy, underscoring the importance of also assessing the management of other potential risk factors.

Raised serum cholesterol and triglyceride concentrations have been reported to be associated with both the



Α. Ενδοθηλιακή δυσλειτουργία

Β. Διαταραχές λειτουργικότητας εμμόρφων στοιχείων του αίματος

Β. ΑΙΜΑΤΟΛΟΓΙΚΕΣ ΔΙΑΤΑΡΑΧΕΣ ΣΤΟ ΔΙΑΒΗΤΗ

α. Λειτουργικές διαταραχές αιμοπεταλίων:

αυτόματη συσσώρευση
↓ ευαισθησία σε PGI_2 και NO
⇓
↑↑ συσσώρευση

β. Διαταραχές πήξης – ινωδόλυσης

↑ ινωδογόνο
↓ πρωτεΐνης C
↓ ινωδολυτική δραστηριότητα (↓tPA και ↑PAI-1)

γ. αύξηση προσκόλλησης και συσσώρευσης ερυθροκυττάρων και λευκοκυττάρων στο ενδοθήλιο

Απαντούν και στους δύο τύπους διαβήτη και είναι συχνά αναστρέψιμες μετά από χρήση ινσουλίνης

Αντιθρομβωτικά φάρμακα και ΔΑ

Ασπιρίνη

?

Table 3. Randomized Controlled Trials of Medical Interventions in Diabetic Retinopathy

Source	No.	Diagnosis	Intervention	Follow-up	Outcome	Comments
ETDRS,[65] 1991 Chew et al,[66] 1995	3711	Mild to severe NPDR or early PDR	Aspirin (650 mg/d) vs placebo	3 y	Vitreous hemorrhage in 32% vs 30% ($P = .48$) No difference in the severity of vitreous/preretinal hemorrhages ($P = .11$) or rate of resolution ($P = .86$)	Aspirin had no effect on DR incidence/progression, vitreous hemorrhage, or need for vitrectomy
DAMAD,[67] 1989	475	Early diabetic retinopathy (type 1 and type 2 DM)	Aspirin (330 mg 3 times/d) alone vs aspirin + dipyridamole (75 mg 3 times/d) vs placebo	3 y	With aspirin alone and aspirin + dipyridamole, decreased mean yearly increases in microaneurysms on FFA (aspirin alone, 0.69 [SD, 5.1]; aspirin + dipyridamole, 0.34 [SD, 3.0]; placebo, 1.44 [SD, 4.5]) ($P = .02$)	Loss to follow-up in 10% of patients
TIMAD,[68] 1990	435	NPDR	Ticlopidine hydrochloride (antiplatelet agent) vs placebo	3 y	Decreased yearly microaneurysm progression on FFA (0.23 [SD, 6.66] vs 1.57 [SD, 5.29]; $P = .03$) and decreased progression to PDR ($P = .056$)	Adverse reactions included neutropenia (severe in 1 case), diarrhea, and rash

Κατευθυντήριες οδηγίες για πρωτογενή και δευτερογενή αντιμετώπιση ΔΑ

Table 6. Summary of Clinical Recommendations for Primary and Secondary Interventions for Diabetic Retinopathy

Intervention	Evidence Level[a]	Recommendation
Glycemic control	A, I	Any lowering of HbA_{1c} level advantageous in reducing development of new or progression of existing DR In patients with DR, HbA_{1c} level <7% is ideal
BP control	A, I	Any lowering of systolic and/or diastolic BP is advantageous in reducing development and progression of DR
Lipid-lowering therapy	A, II	Lowering of LDL-C levels reduces macrovascular complications of diabetes and may be advantageous in DME
		present
	A, II	Early PDR with less severe PDR (flat new vessels elsewhere and no high-risk features) and severe NPDR may be observed closely, but treatment recommended if any difficulty or delay in follow-up is anticipated or there are associated risk factors or signs of progression, especially in patients with type 2 diabetes
Aspirin and other medical treatment	C, I	Aspirin does not reduce risk of developing DR or increase the incidence of retinal or vitreous hemorrhage
	C, II/III	Currently, there is insufficient evidence to recommend routine use of PKC inhibitors, GH antagonists, and other treatments, but they may have a role in some patients
		Vitrectomy should be considered in eyes with severe PDR not responsive to extensive PRP, associated with traction involving the macula, or both
	B, III	Vitrectomy may be advantageous in selected cases of diffuse severe DME not responsive to other therapies, especially in presence of vitreomacular traction
Intravitreal steroids	B, II	Intravitreal triamcinolone may have a role in diffuse DME unresponsive to focal laser

C, II/III Currently, there is insufficient evidence to recommend routine use of PKC inhibitors, GH antagonists, and other treatments, but they may have a role in some patients

Aspirin and other medical treatment | C, I | Aspirin does not reduce risk of developing DR or increase the incidence of retinal or vitreous hemorrhage

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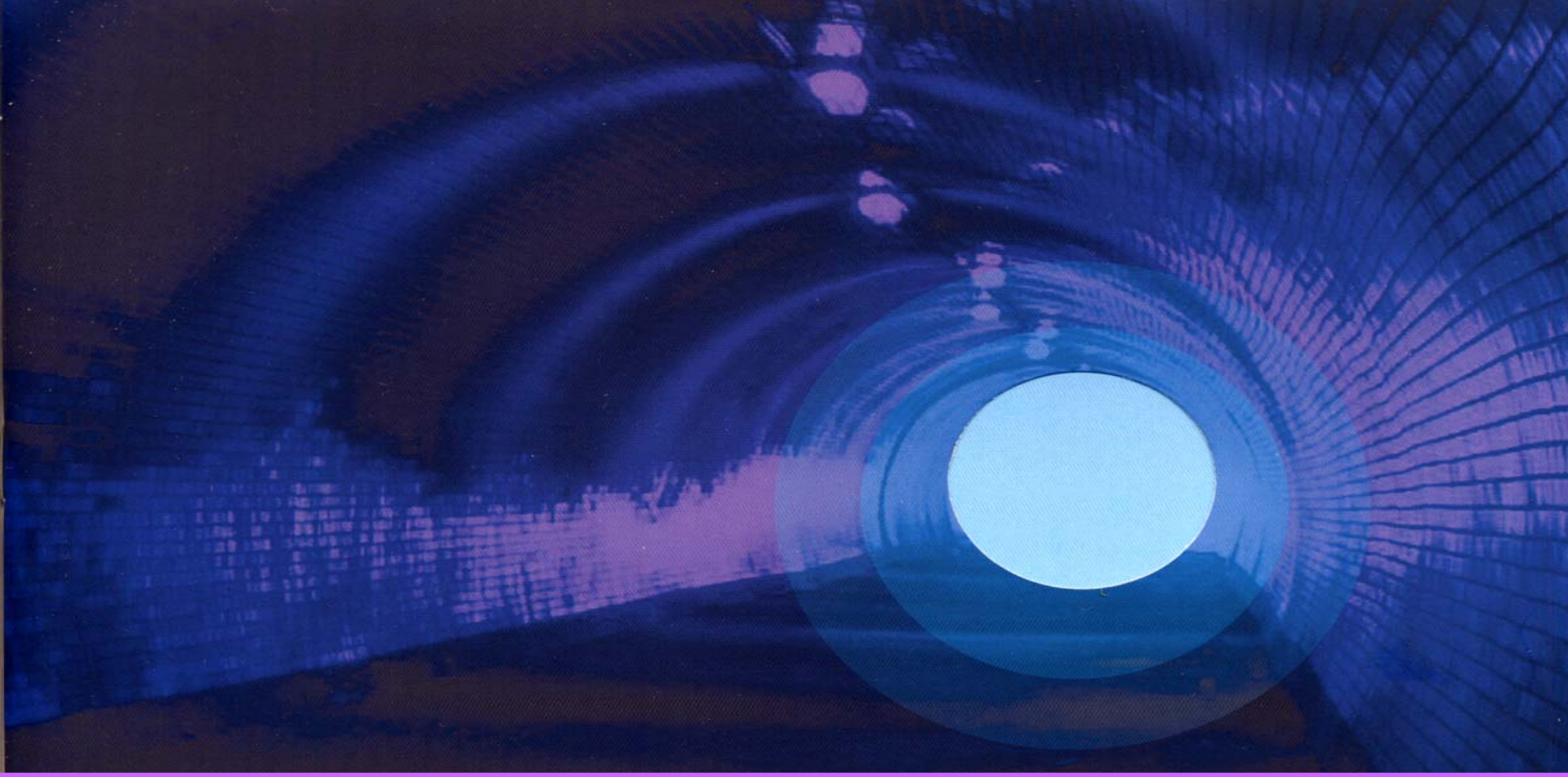
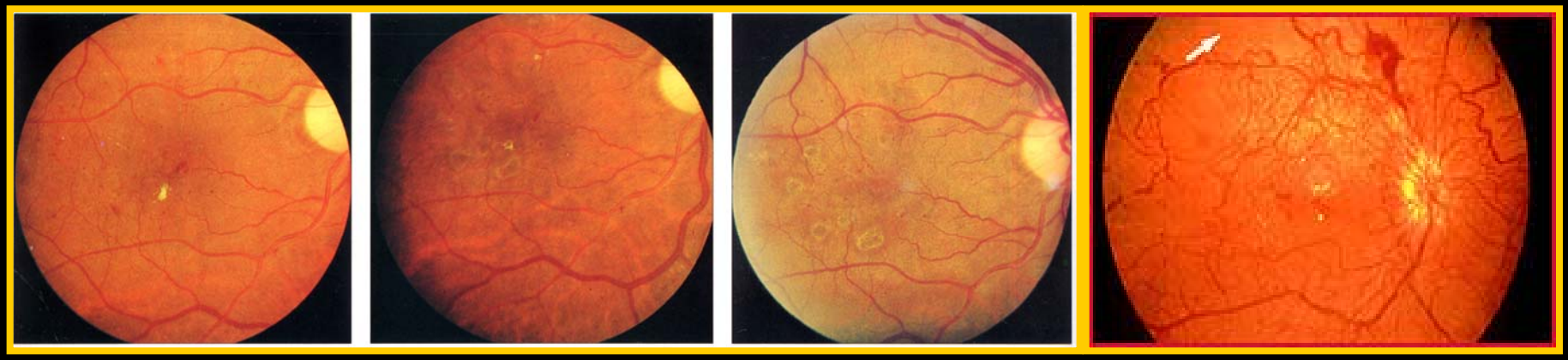


C, II/III	Currently, there is insufficient evidence to recommend routine use of PKC inhibitors, GH antagonists, and other treatments, but they may have a role in some patients

Θεραπευτικοί προορισμοί



Προθάλαμος του χειρουργείου ή της απώλειας όρασης από ΔΑ είναι συχνά ένα ιατρείο με χαλαρούς στόχους ή -σπανιότερα- με φιλόδοξους στόχους αλλά φτωχά αποτελέσματα

Χρειάζεται τόσο η συμμόρφωση των γιατρών
προς τις κατευθυντήριες οδηγίες όσο και των ασθενών
προς τις ιατρικές οδηγίες

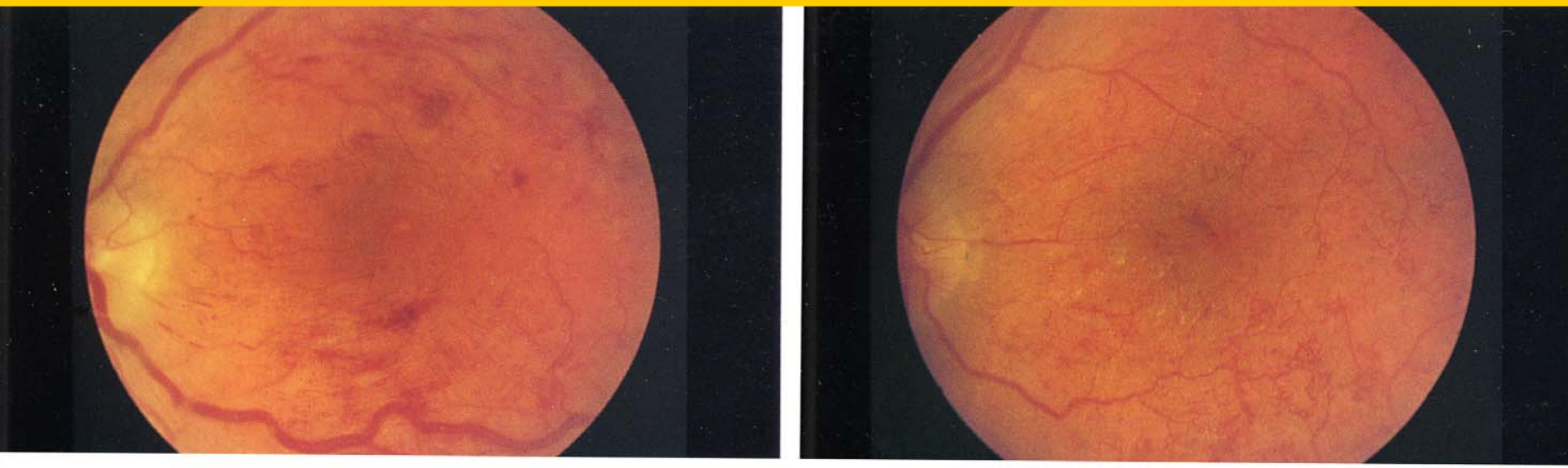
Προϋπόθεση της συμμόρφωσης είναι η εκπαίδευση
και η «μύηση» στις αξίες και τα οφέλη της ιδανικής ρύθμισης.

Απαραίτητη η εξέταση από οφθαλμίατρο τουλάχιστον 1 φορά ετησίως για πρώιμη ανίχνευση και έγκαιρη αντιμετώπιση της ΔΑ

Role of Renal Disease in DME

- Gross proteinuria associated with 95% increased risk of DME (WESDR)
- Case reports of reduction of diabetic macular edema after dialysis
- Type 1 DM patients with microalbuminuria have three-fold risk of PDR compared to those with normal levels

ΕΝΔΕΧΟΜΕΝΗ ΕΠΙΔΕΙΝΩΣΗ ΔΑ ΣΕ ΚΥΣΗ



Εικόνα 15.16 Η διαβητική αμφιβληστροειδοπάθεια μπορεί να χειροτερεύει πολύ κατά τη διάρκεια της κύησης και οι ασθενείς να αναπτύξουν ωχροπάθεια ή παραγωγική βλάβη. Η ασθενής αυτή είχε αμφιβληστροειδοπάθεια υποστρώματος πριν την κύηση αλλά ανέπτυξε εμφανές οίδημα ωχράς την 36η εβδομάδα και στον τοκετό η οπτική οξύτητα έπεσε σε 20/80. Τρεις βδομάδες μετά τον τοκετό το οίδημα αυτόματα λύθηκε και η οπτική οξύτητα βελτιώθηκε σε 20/30.

Κλινική Οφθαλμολογία, David J Spalton, Roger A. Hitchings, Paul A. Hunter, Β΄Έκδοση

Έλεγχος για ΔΑ αναγκαίος μετά την επιβεβαίωση κύησης και κάθε 2 μήνες σε απουσία ΔΑ ή κάθε μήνα σε παρουσία ΔΑ

Πρωτογενής & Δευτερογενής Αντιμετώπιση ΔΑ

Καλύτερος **τρόπος**
είναι
ο κατάλληλος **χρόνος**
παρέμβασης !

Σας ευχαριστώ θερμά!