

A Model of Diabetic Eye Disease

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Abstract

We use algebraic and calculus-based equations that incorporate the risk factors of duration of diabetes, glycemia, blood pressure, lipids and diabetes type (1 or 2) to represent the physiological development of non-proliferative diabetic retinopathy, macular edema, and proliferative diabetic retinopathy. For patients with proliferative diabetic retinopathy, we assess the probability of progression to legal blindness.

Introduction

- Eye disease is a common, serious complication of diabetes. Typically, 15% to 20% of patients have already developed some form of diabetic retinopathy (DR) at the time of diabetes diagnosis, and approximately 75% will have retinopathy after twenty years.
- Patients first develop non-proliferative diabetic retinopathy (NPDR) characterized by swelling, bleeding and blocking of retinal blood vessels. Although damage is occurring to the retina, many patients feel no symptoms.
- The eye may respond to NPDR by growing new vessels. When this neovascularization occurs, the disease has progressed to a more serious second stage: proliferative diabetic retinopathy (PDR). The new vessels are fragile, bleed easily and often die leading to scarring of the retina. The fibrous tissue may then pull away from the back of the eye resulting in a retinal detachment.
- If neovascularization is not halted by medical treatment (laser photocoagulation), a patient with PDR has about a 50% chance of going blind in four years.
- New vessels may also grow into the vitreous gel, the liquid that occupies most of the space of the eye. If these vessels then leak, clouding of the vitreous occurs. If severe, a vitrectomy may be needed to replace the opaque vitreous by a clear fluid.
- In either the NPDR or PDR stage, fluids may accumulate causing swelling. If this edema happens in the central region of the retina (the macula), vision reduction occurs. Ophthalmologists often treat macular edema (ME) with focal laser coagulation.

Context of the Research

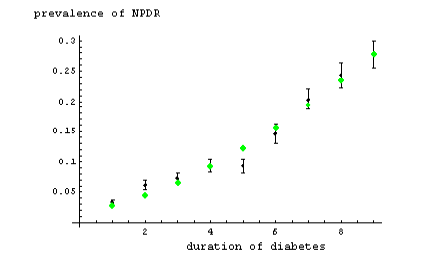
- Archimedes is a mathematical model of human physiology, diseases, and healthcare systems. It is used by researchers to design clinical trials, by health plans and providers to optimize care delivery, and by voluntary health organizations to evaluate policies, set standards and help patients. As an example of the latter, Archimedes is the engine for the American Diabetes Association's online risk assessment tool Diabetes PHD.
- As a major complication of diabetes, retinopathy and accurately modelling it are important.
- We developed our model of diabetic retinopathy for inclusion in Archimedes to improve its eye-disease predictions.

Methods

- Our literature review identified more than 130 references which were used to build the DR model. Major contributing studies were the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), the Early Treatment Diabetes Retinopathy Study (ETDRS), the United Kingdom Prospective Diabetes Study (UKPDS), the Diabetes Control and Complications Trial (DCCT), the Kaiser Permanente Study, the Epidemiology and Prevention of Diabetes (EURODIAB), the New Jersey 725, the Barbados Eye Studies, the Diabetes Retinopathy Study (DRS), the Taiwan Diabetes Study, the Diabetes Incidence Study in Sweden (DISS), and the Helsingborg Study.
- The major risk factors for DR were identified as glycemia (as measured by HbA1c), systolic blood pressure, duration of diabetes and diabetes type (1 or 2). For ME, dyslipidemia (as indicated by LDL cholesterol) was also a risk factor.
- We used the information from certain references (typically involving the largest cohorts) to construct incident rates for the four outcomes NPDR, PDR, ME and legal blindness.
- Other references were set aside for validation purposes. There were 12 validations involving outcomes versus duration of diabetes and 39 for outcomes of fixed duration.
- We also constructed a model of NPDR levels. It allows one to compute 2-step and 3-step progressions, level distributions and transition probabilities between levels. It had its own set of validations in table and matrix form.

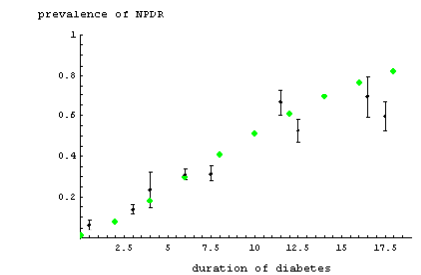
Results

- NPDR: The dependence on duration of type 2 diabetes was fixed as the best overall fit to the baseline data of two references.^{1,2} Here is the comparison for the Kaiser Permanente Study¹, which involved about 7000 patients:

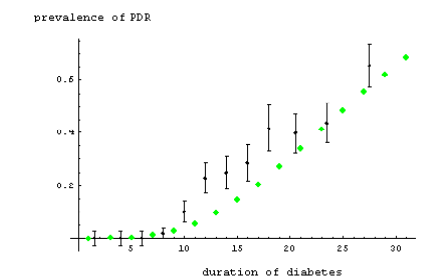


Here and in the next two figures, data of a study are in black; green points are the results of the DR model, and error bars represent one standard error.

- A validation involves using the model's formulas to predict the results of a publication that has not been used to build the model. Here is the example for NPDR involving the Barbados Eye Study³:



- This figure is the validation of PDR for type 1 diabetes in the New Jersey 725 Study⁴:

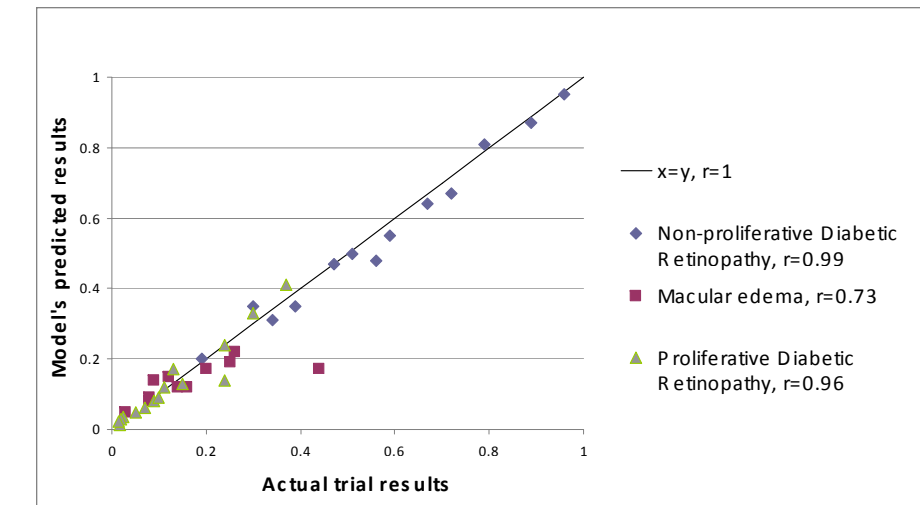


- Building a model for blindness involved considerable uncertainty because of rare events: Studies typically only report a dozen or so cases. Here are the validations for the incidence of legal blindness among type 1 patients:

Study	Model	Study Time	Source
0.04	0.02	baseline	reference 5
0.02	0.01	4 years	reference 6
0.02	0.03	10 years	reference 7
0.03	0.03	14 years	reference 8
0.00	0.01	3 years	reference 9

- When the validations for legal blindness among type 2 patients were performed, the results for the model were systematically low. A fit to all sources was performed. Hence, there is no independent validation for this case.

- The following figure summarizes the 39 fixed-duration validations for cumulative incidence of NPDR, ME and PDR:



The correlation coefficient for actual trial results compared with the model's predicted results is 0.99 for NPDR, 0.73 for ME, and 0.96 for PDR. One validation of ME failed and the removal of this single outlier improves the correlation coefficient for ME to 0.92.

Conclusions

- We have developed an evidence-based, physiological model of diabetic retinopathy.
- Numerous independent validations indicate that the model produces accurate predictions for diabetic retinopathy. Based on these validations, we believe, given the essential bio-medical information for an individual, such as duration of diabetes, HbA1c, etc., that the model can predict the chances of patients developing NPDR to an accuracy of better than 10% up to 20 years into the future. For PDR, ME and legal blindness, the corresponding figures are respectively 25%, 25% and 40%, also based on these independent validations.
- For patients who have developed NPDR, the model provides the state of the disease, namely whether the retina of a patient is likely to have only microaneurysms, or to be mildly hemorrhaging, or to have more serious problems.
- When this upgrade to the existing retinopathy model is incorporated into Archimedes [which, as of June 2008, is close to being completed], virtual patients will continue to respond to eye-disease related symptoms (such as cloudy vision) and schedule visits with virtual ophthalmologists, who will, in turn, assess the damage to the eye and perform the appropriate medical treatment (such as vitrectomy) if needed. At this point, the upgraded DR pathophysiology model will be functioning not in isolation but within a health care system, thereby leading to even more realistic predictions.

References

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