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A systems modelling approach for the prevention and treatment of diabetic retinopathy

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Abstract

Diabetic patients may suffer from a number of long-term complications. One such complication is the onset of diabetic retinopathy, which damages the eyes and can lead to blindness. We describe the use of a systems modelling approach for the progression of diabetic retinopathy that has been used for cost-effectiveness evaluations of various prevention and patient care options. The adopted framework incorporates retinopathy risk groupings, created using classification and regression tree (CART) analysis, which are then fed into a developed simulation model, at the level of individual diabetic patients. A multidisciplinary task group, comprising of clinicians and health care modellers, guided the necessary modular development involving the definition of risk groups in the community, natural history of diabetic retinopathy, and options for early detection and treatment. Data has been taken from a prospective Wellcome Diabetes Study at the Diabetes Unit, King Edward Memorial Hospital, Pune, India. India has the highest number of diabetic patients in any one country, approximately 25 million in 2000, and this number is predicted to rise to 57 million by the year 2025.

Keywords: Health services; Diabetic retinopathy; Risk grouping; CART analysis; Simulation modelling

1. Introduction

Diabetes mellitus is a disorder of carbohydrate metabolism characterised by high levels of blood glucose resulting from insufficient insulin secretion, insulin action, or both. Excess glucose is passed out of the body in the urine. Over time, this excess glucose circulating through the body in the bloodstream can lead to a number of long-term complications including kidney failure, blindness, amputations and heart problems [1,2].

By 2010 the world's diabetic population is estimated to double from 110 million in 1994 to 221 million [3]. Prevalence varies widely by ethnic group and country with adult rates ranging from less than 2% in rural Bantu people in Tanzania to nearly 50% in US Pima Indians and South Pacific Naurauns. India has the highest number of diabetic patients in any one country, approximately 25 million in 2000, and this number is predicted to

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rise to 57 million by the year 2025 [4]. Rates are also relatively high in "transplanted populations", such as Asians in Europe [5] and African Americans [6]. The projected increase in rates, however, is universal. Diabetes causes a great deal of suffering in the community and the costs for the necessary health services are high.

Diabetes can remain undiagnosed for many years and this delay in the detection of diabetes has many serious consequences. One such complication is the onset of diabetic retinopathy which involves damage to the retina of the eyes and can lead to blindness [7]. Blindness is a major cause for concern in many developing countries, such as India [8], where much of the working population find employment in the labour/manufacturing industries. Hence without their sight, a person can expect to be out of work and also unable to attend the fields in order to provide their family with income and food. Detection and treatment of diabetes is an involved process and in developing countries with resource constraints, there are more undiagnosed than diagnosed cases.

Care of people with diabetes requires a multidisciplinary team with an active participation of the patients. In this paper a systems level approach is used to model the care of people with diabetes in a community. The approach combines statistically and clinically meaningful risk groups with a simulation model that captures the natural history of the onset of diabetic retinopathy. The integrated system ensures that the developed model describes the community through the assignment of individuals to defined risk groups. These individuals are then simulated as they progress through the retinopathy natural history. Transition times and transition probabilities are used to capture the variability between risk groups, and intervention and treatment programmes are modelled through changes to the nature of these parameters. For example, a particular treatment might delay the onset of retinopathy, modelled by increasing the individual's dwelling times in natural history states or by changing their transition probabilities.

Since the natural history of diabetic retinopathy is well known, the model presented here could be applied to any community of diabetic patients through suitable definition of risk groupings that capture the local diabetic population. We illustrate the approach using data from a prospective Wellcome Diabetes Study at the Diabetes Unit, King Edward Memorial Hospital, Pune, India. India has the highest number of diabetic patients in any one country and the evaluation of various intervention and treatment programmes provided the emphasis for this work.

Computer simulation is widely used for modelling diseases and their complications, including discrete event models for screening services for diabetic retinopathy [9]. Our work differs from published work in this area since it incorporates a systems modelling approach, using patient classification techniques coupled with discrete event simulation, which has worked well for modelling the onset of retinopathy. The approach lends itself well to disease modelling incorporating different prevention and treatment strategies targeted at different risk groups within the population.

In the following section we discuss the different types of diabetes and the clinical compilations that arise. Details of the Wellcome Diabetes Study is presented in Section 3 and this is followed by retinopathy data analysis and risk grouping in Section 4. The resulting risk groups are then used within a developed operational model, as discussed in detail in Section 5. Intervention cases studies are presented in Section 6 and a section on policy implications concludes the paper.

2. Types of diabetes and diabetic complications

There are two main types of diabetes: type 1 diabetes also known as insulin dependent diabetes mellitus (IDDM), and type 2 diabetes also known as non-insulin dependent diabetes mellitus (NIDDM) [10]. In type 1 diabetes, there is very little or no production of insulin in the body and therefore insulin must be injected (it cannot be ingested as it would be digested by the body). Type 2 patients can produce some insulin themselves and their diabetes is controlled by diet or drugs. The commonest form of diabetes in a community is usually type 2 diabetes. Other forms of diabetes are Gestational Diabetes, which appears during pregnancy, and impaired glucose tolerance (IGT)

Table 1
Summary of type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes
Other names	IDDM	NIDDM
Age of onset	Usually less than 30 years	Usually over 40 years
Weight	Usually normal or underweight	Usually over-weight
Onset	Usually over weeks	Often over months or years

which may be thought of as a mild condition where the patient shows slightly higher than normal levels of glucose. Table 1 gives a summary of type 1 and type 2 diabetes patients.

Diabetic patients may suffer from a number of long-term complications. Over time, the excess levels of glucose in the bloodstream can damage the nervous system as well as damaging small blood vessels in the eyes and kidneys. Three of the main diabetic complications can be summarised as:

- *Retinopathy*—involves damage to the retina of the eyes and can lead to blindness [7,10]. It can be treated successfully if detected in time. Around 20% newly diagnosed type 2 diabetic patients have retinopathy (background retinopathy). Average time to develop background retinopathy is 6–7 years from the diagnosis of type 2 diabetes [1].
- *Neuropathy*—damage to the nerves. Nerve damage can eventually lead to foot ulceration and amputation. Around 15% of all people with diabetes eventually develop foot ulcers [1,2,10].
- *Nephropathy*—complications with the kidneys. Damage to the small blood vessels in the kidneys can eventually lead to the renal failure [1,10].

In addition there are many other complications, not specific to diabetes, where the risk of developing them increases if diabetes is present. Such complications include cardiovascular disease, cerebrovascular disease and peripheral vascular disease. In this paper we concentrate on retinopathy, a complication that has particular importance since it leads to blindness.

India is currently witnessing a rapidly escalating epidemic of type 2 diabetes. The prevalence has increased in adult urban Indians from less than 3% in early 1970s to over 13% in a recent survey in six major cities [8,11]. The rapid rise is ascribed to changes in life style: altered food habits, reduced physical activity and psychosocial stress. Migrant Indians also show a higher prevalence of diabetes compared to local populations.

Indian type 2 diabetic patients are usually younger at the time of diagnosis than their western counterparts and are thinner by the body mass index (BMI) criteria, but may possess excess body fat percent and are centrally obese. In addition, Indians are more insulin resistant than their western counterparts. Insulin resistance in Indians is associated with high blood pressure and abnormal circulating lipid concentrations, suggesting the existence of an insulin resistance syndrome [12,13].

There is little prospective data on the predictors of diabetic tissue damage in Indians and most of the available data is cross sectional. In the Wellcome Diabetes Study, an ongoing study at the KEM Hospital, Pune, India, doctors have serially followed newly diagnosed diabetic patients for more than 10 years. In this paper we analyse the predictors of diabetic retinopathy in Indian type 2 diabetic patients. We also discuss an operational model for the cost-effectiveness evaluation of various interventions and patient care options.

3. Patients and methods

The design of Wellcome Diabetes Study has been described earlier [14,15]. As part of the study, 189 newly diagnosed NIDDM patients, 79 IGT patients and 133 normal glucose tolerance (NGT) patients were enrolled from outpatients and wards of the King Edward Memorial Hospital, Pune, India between February 1987 and December 1989. Patients were prospectively followed for 10 years and were studied at enrolment and 1, 5 and 10 years later. A number of variables were recorded at each follow-up, and included clinical history, height, weight, waist and hip circumferences, biomedical data, toescore measurements and markers of tissue damage [16].

Table 2
Patient status at the 10 year follow-up

	NGT	IGT	NIDDM
Initially enrolled (*n*)	133	79	189
Studied at 10 year follow-up (*n*)	94	60	143
Dead (*n*)	7	4	22
Lost to follow-up (*n*)	32	15	24
Followed-up (%)	76	81	87
Diabetic retinopathy (*n*)	0	0	43

All patients received appropriate treatment, including advice on diet, exercise and oral hypoglycaemic agents or insulin as appropriate. Table 2 gives the follow-up status of the Wellcome Diabetes Study after 10 years. It helps to show the high prevalence of diabetic retinopathy among NIDDM patients (43 followed-up patients had onset of retinopathy within 10 years of being diagnosed with diabetes).

4. Data analysis and retinopathy risk groupings

The initial phase of the analysis attempted to classify patients into risk groups for progression of diabetic retinopathy in India. Quantitative measures of the risk of suffering from diabetic complication can help in the care of people with diabetes.

The Wellcome study data was analysed using a multivariate statistical technique called classification and regression tree (CART) analysis. CART has proved to be a highly useful tool in the work of the Institute of Modelling for Healthcare, University of Southampton UK, and in the work of many other people [17–19]. Depending on the problem, the basic purpose of the CART analysis is to either produce an accurate classifier or to uncover the predictive structure in the available data. The CART algorithm [20] incorporates a binary splitting system that attempts to create groups of patients such that patients within the same group are as closely related as possible and statistically different from the other groups (a variance reduction algorithm is incorporated). The resulting *tree* clearly shows each risk group, and how it was formed, and can be easily interpreted by clinicians.

The dependent variable was a nominal 0–1 variable, clinically defining the presence and absence of retinopathy at 10 year follow-up. The list of independent variables included age, sex, BMI, waist to hip ratio, supscapular skinfold, triceps skinfold, mean toescore, systolic blood pressure, diastolic blood pressure, circulating concentrations of fasting glucose, two hour glucose, fasting insulin, two hour insulin, glycated haemoglobin (HbA_{1C}) and cholesterol levels. All of the independent variables are measured at enrolment. Fig. 1 shows the resulting classification tree. Table 3 gives a summary of the data for the patients in the various *nodes* of the tree. The probability of retinopathy for each group is calculated as the percentage of patients within that group who were diagnosed with retinopathy at the 10 year follow-up. For numerical independent variables, the minimum and maximum values are presented to indicate classification rules for forming these nodes. The final risk groupings are found as *terminal nodes* (nodes from which there are no further binary splits—type 2 final groups are highlighted in Table 3).

From the node tree and node summary table, it is apparent that overall 22.7% of type 2 diabetic patients (NIDDM) had developed diabetic retinopathy by the 10 year follow-up (node 3). No NGT and IGT patients had retinopathy (node 2). The most important predictor of retinopathy for type 2 diabetics is the sex of the patient, as indi-

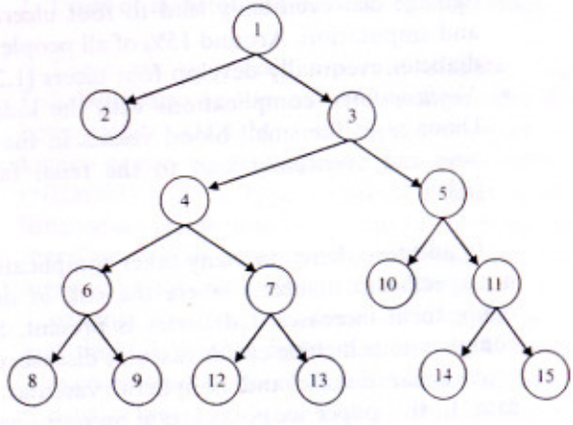

Fig. 1. Risk groups for diabetic retinopathy.

Table 3
Node summary for diabetic retinopathy

Node	n	Field name	Minimum	Maximum	Probability of retinopathy
1	401	All patients	–	–	0.107
2	212	NGT and IGT	–	–	0.000
3	189	NIDDM	–	–	0.227
4	123	Sex (male)	–	–	0.262
6	59	Mean toescore	0	0	0.100
8	25	Fasting insulin	0	14	0.800
9	34	Fasting insulin	15	54	0.130
7	64	Mean toescore	1	27	0.250
12	32	HbA_{1C}	0	62	0.031
13	32	HbA_{1C}	63	107	0.470
5	66	Sex (female)	–	–	0.170
10	22	Mean toescore	0	0	0.140
11	44	Mean toescore	1	26	0.160
14	23	120 Min insulin	0	62	0.300
15	21	120 Min insulin	63	300	0.000

cated by the first binary split below node 3. For men the prevalence of retinopathy is 26.2% while among women it falls to 17.5%. The next most important determinant of retinopathy among men is the mean toescore. This finding is clinically meaningful since it shows that the patients with higher toescores, and hence with greater damage to their nervous system, are also at high risk of developing diabetic retinopathy. Neuropathy is generally easy to diagnose in clinical practice. Retinopathy is however more difficult to diagnose. Thus the advantage of incorporating toescore as a predictor means that we can more readily identify those at risk of developing diabetic retinopathy. The patient's fasting insulin, glycated haemoglobin (HbA_{1C}) and two hour insulin levels are all shown to be predictive variables in the subsequent binary splits.

Our findings compare well with other studies of retinopathy predictor variables. In recent published papers [21,22] sex, glucose levels (HbA_{1C}) and insulin levels were found to be important predictors for the onset of retinopathy. Results from the CART analysis reinforce these findings. Furthermore, the CART analysis has indicated that toescore, used to measure the risk of diabetic neuropathy, is also a useful predictor for diabetic retinopathy. This is clinically helpful since toescore is relatively easy to measure, particularly in a resource-poor developing country such as India.

From an overall prevalence of 22.7% the CART algorithm has found seven risk groups (terminal nodes) with prevalence of retinopathy varying from 0%, where nobody in the group has developed retinopathy, to a group where 80% of patients have developed the complication. This information alone is of practical help to clinicians in India in helping them to identify patients who are at increased risk of developing retinopathy. For example, a high-risk patient (node 9) satisfies the following classification rules (path to node 9 via nodes 3, 4 and 7): NIDDM, male, mean toescore between 1 and 27, and glucose (HbA_{1C}) level greater than 63. Furthermore, this information has been used in the development of a cost-effectiveness tool for the evaluation of different interventions, for example through the use of drugs or through changing a patient's diet.

5. A cost-effectiveness simulation model for diabetic retinopathy

An operational model for the patients with type 2 diabetes has been developed. This detailed simulation tool, at the level of indiviual patients, has been designed for use by clinicians for cost-effectiveness evaluations of various intervention and patient care options. The approach taken ensures that the model incorporates the evolved risk groups

in the community (using the CART analysis), together with the natural history of retinopathy and options for early detection and treatment of patients. The model was built using SIMUL8 (Visual Thinking Ltd.) and enhanced with an MS-Excel front and back-end interface. Fig. 2 illustrates the progression (natural history) of patients with diabetic retinopathy, as captured within the simulation model.

The simulation model of the natural history incorporates seven retinopathy risk groups (as defined by the final nodes in the CART analysis, Table 3), transition times and transition probabilities among the different states of Fig. 2, intervention options and the costs of the interventions. Information on transition time and the probability of transition for the different risk groups has been obtained from the Wellcome diabetes study. There is no clear record in the Wellcome diabetes study, however, about the cost of the different treatment options for a given risk group, and so this information has been obtained using clinician's expert opinion at KEM Hospital.

The model takes a cohort of type 2 diabetic patients through time. Both the cohort size and time horizon are user-defined. The transition from *no retinopathy* to *background retinopathy* is governed by each risk group's associated probability of developing retinopathy (from the CART analysis, Table 3). Once a patient has made this initial transition, the patient enters the natural history model and is simulated to progress through the states (blindness is the final state they can reach). Dwelling times in each state are sampled from the appropriate statistical distributions, as fitted to the Wellcome study data and expert clinical opinion, as shown in Table 4. For example, the time from background retinopathy to maculopathy (in years) follows a Weibull distribution with parameters $\alpha = 1.76$ and $\beta = 0.63$. Movement among states is governed by user-defined probabilities.

The model allows for the evaluation of clinical interventions (treatment) to patients within *proliferative retinopathy* and/or *maculopathy* states [7]. The effects of these interventions are modelled through changes to the transition probabilities and dwelling times in each stage. For example, a proliferative retinopathy patient receiving treatment might subsequently stay within *Treated Proliferative* for the remainder of their life, thus avoiding the transition to blindness. Associated costs of interventions are defined as the costs per patient per year (in rupees) and the model calculates the corresponding health care costs for each intervention programme.

Non-clinical interventions, such as changes to the patient's diet, can be evaluated by changing the distribution of numbers of patients across the risk groups. For example, an education programme aimed at type 2 diabetics on decreasing the risks of developing retinopathy through improved diet and exercise, would have the effect of moving patients from a high risk group (80% prevalence) to a lower risk group. The movement of people among

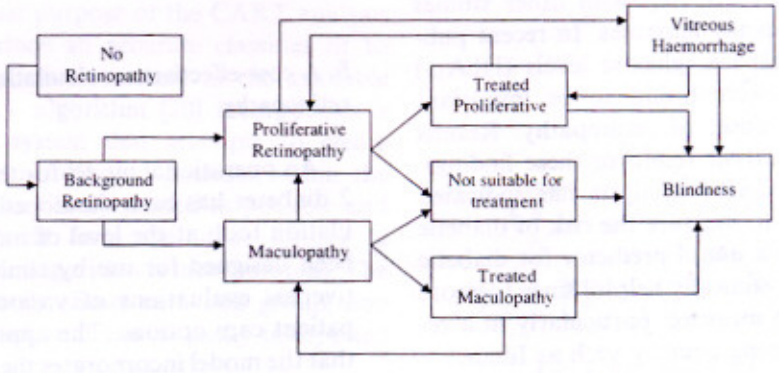

Fig. 2. A natural history for the progression of patients with diabetic retinopathy.

Table 4
Natural history transition times and probabilities

To		From				
		No retinopathy	Background retinopathy	Maculopathy	Proliferative retinopathy	Vitreous haemorrhage
Background retinopathy	%					
	α	7.2				
	β	6.9				
Maculopathy	%		90			
	α		1.8			
	β		0.6			
Proliferative retinopathy	%		10	85		
	α		3.9	4.5		
	β		0.9	3.4		
Vitraeous haemorrhage	%				85	
	α				1.5	
	β				1.0	
Blindness	%			15	15	100
	α			2.6	2.6	2.8
	β			1.7	1.7	2.3

Percentage indicates probability of transition with dwelling times (in years) sampled from Weibull (α, β).

groups can be quantified using the CART analysis, shown in Fig. 1, and the associated classification rules, shown in Table 3.

Fig. 3 shows the MS-Excel front-end screen used to define the diabetic type 2 risk groups and any associated interventions. The user is allowed to change any of the following parameters: percentage of patients in each risk group, percentage from each group likely to develop retinopathy, percentage of patients from each group receiving treatment in proliferative retinopathy and maculopathy states and associated costs per patient for treatment (in rupees). The flexibility of the developed tool allows clinicians to evaluate different treatment options targeted at different risk groups.

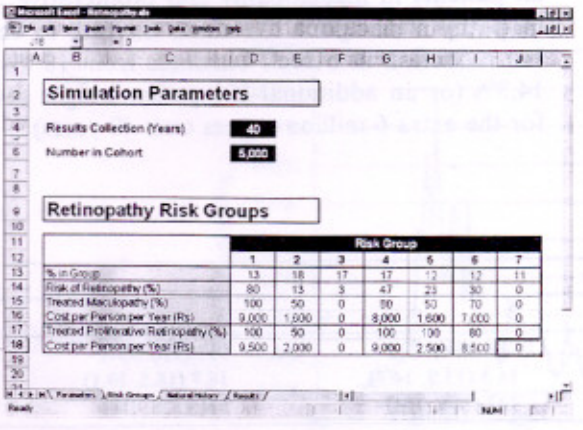

Fig. 3. Defining intervention strategies: the model front-end.

6. Intervention case studies

6.1. Laser photocoagulation treatment

For the treatment of both maculopathy and proliferative retinopathy, patients at KEM Hospital are treated with laser photocoagulation [7, 10]. Indian consultants were able to provide estimates on the amount of laser photocoagulation, and associated costs, for different risk groups. For example, a severe case requires 10–12 sessions of laser photocoagulation and a mild case for only one or two sessions. Each session costs approximately 800 Indian rupees. This information was used in the model to help evaluate the cost-effectiveness of laser photocoagulation treatment. An

important consideration of any retinopathy intervention programme is the effectiveness of the treatment, measured here by the prevention of blindness, versus the total cost of resources, which is particularly relevant to India.

To illustrate the cost-effectiveness tool, the model was used to simulate a cohort of 5000 diabetic patients over a period of 40 years. Data on transition times and movement through the retinopathy natural history (Fig. 2) was obtained from the Wellcome Study and expert clinical opinion (Table 4). The effect of the laser photocoagulation treatment is modelled through changes to the transition probabilities and dwelling times for maculopathy and proliferative retinopathy states, shown in Table 5. The risk groups used were those defined in the classification analysis. Three illustrative scenarios were chosen:

1. No intervention.
2. Laser photocoagulation treatment for all patients (100% coverage).
3. Laser photocoagulation treatment for all patients in high-risk groups only (defined to be groups 1 and 4, with 80% and 47% retinopathy prevalence respectively).

The following response variables were recorded for each scenario: the total costs of the intervention program, and the number of patients who lost their sight over the 40 years. Table 6 gives the model predictions. 95% confidence intervals are displayed.

Table 6 helps to show the cost effectiveness of the laser photocoagulation treatment in helping to preventing blindness. Left untreated, retinopathy would cause blindness in 27% of the population over the 40 years. Treatment of all patients in maculopathy and proliferative retinopathy states of the natural history reduces this to 14.3%. Within a cohort of 5000 patients this equates to saving the sight of 653 patients. By only treating the two high-risk groups, 18.7% of the cohort develop blindness. The corresponding costs of treatment, however, are also an important consideration in India. The difference in costs between treating all patients and only high-risk is marginal (142 million rupees over the 40 years compared to 136 million rupees respectively). High-risk groups require intensive treatment and have high associated costs. There appears to be a benefit in treating all patients in maculopathy and proliferative retinopathy states given the small increase in costs but reduction in overall blindness from 18.7% to 14.3% (or an additional 221 patient's sight saved for the extra 6 million rupees over 40 years).

Table 5
Effect of laser photocoagulation treatment on transition times and probabilities

To		From	
		Maculopathy	Proliferative retinopathy
Maculopathy	%	50	
	α		
	β		
Proliferative retinopathy	%	45	50
	α	8.9	
	β	3.5	
Vitraeous haemorrhage	%		45
	α		5.6
	β		2.3
Blindness	%	5	5
	α	4.4	4.4
	β	3.4	3.4

Percentage indicates probability of transition (or remaining in state) with dwelling times (in years) sampled from Weibull (α, β).

Table 6
Intervention programme predictions

	Intervention programme		
	1	2	3
Number of blind patients	1369 (1349, 1397)	716 (696, 736)	937 (916, 957)
Percentage of cohort losing sight	27.4 (27.0, 27.9)	14.3 (13.9, 14.7)	18.7 (18.3. 19.1)
Costs (millions of rupees)	0 (0, 0)	142 (134, 154)	136 (128, 144)

6.2. Reduced glucose levels through improved diet

Educating society on the importance of a healthy and balanced diet can help to reduce obesity and glucose levels. In the classification analysis of the Wellcome study data, glucose levels (as measured by HbA_{1C}) has been shown to an important variable in the prediction of diabetic retinopathy. A high glucose level increases a patient's likelihood of developing retinopathy. Hence an education programme aimed at increasing the awareness of the importance of good diet among type 2 diabetics may help in reducing retinopathy prevalence. Non-clinical interventions, such as changes to the patient's diet, correspond to changing the distribution of numbers of patients across the risk groups. To help illustrate this aspect of the developed model, we consider an education intervention programme to reduce glucose levels of type 2 diabetics from their current levels by 10%, 20% and 30%. The probability density function of HbA_{1C} levels over the population of patients in the Wellcome study is shown in Fig. 4.

We simulate a reduction in glucose levels by reducing individual patient's glucose levels by 10%, 20% and 30% and re-plotting the HbA_{1C} probability density function. The corresponding new distributions are then used in the CART analysis, and using the defined classification rules, the proportion of patients in each of the seven risk groups may be recalculated. The new risk group data may then be run through the simulation model.

This analysis has shown that the overall risk of 22.7% of developing retinopathy decreases to 22.0%, 21.1% and 20.0% with reductions in glucose levels in the population of type 2 diabetics of 10%, 20% and 30% respectively. With a cohort of 5000 diabetic patients, this equates to further preventing 35, 80 and 135 patients from developing retinopathy, respectively. In turn, the simulation model predicts that, with a 30% glucose level reduction, a further 40 patients in the cohort may be saved from blindness with a saving of 6.3 million rupees for treatment over 40 years. Clearly there are many advantages, as quantified in the analysis, of educating the population on the importance of a good diet and regular excise. Such a programme will cost money to the hospital, but if this were less than 6.2 million rupees over 40 years, or 155,000 rupees per year, then the programme would be cost-effective.

7. Conclusions and policy implications

This paper has demonstrated the value of a multidisciplinary study of the care of people with diabetic retinopathy. The systems modelling approach adopts appropriate databases, multivariate statistical analysis including CART analysis,

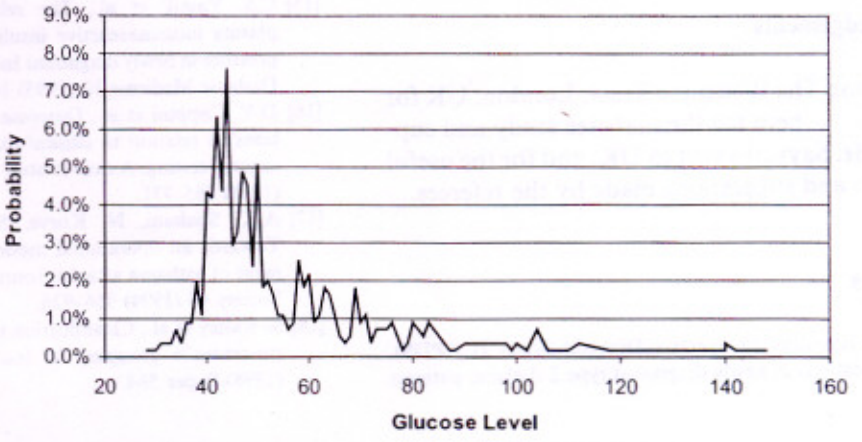

Fig. 4. Probability density function of HbA1C (glucose).

mathematical modelling, together with the development of easy to use models on personal computers.

India currently has the highest number of diabetic patients in any one country and so there is a need to prevent retinopathy, a complication that has particular importance in India since it leads to blindness. Blindness is a major concern in developing countries. Data for this work was taken from a Wellcome Diabetes study at King Edward Memorial Hospital, Pune, India. As part of the study newly diagnosed type 2 diabetic patients were prospectively followed for 10 years. The initial phase of the analysis classified patients into risk groups for prediction of retinopathy. Quantitative measures of the risk of suffering from diabetic complication can help in the care of people with diabetes. From an overall prevalence of 22.7% the CART algorithm found seven risk groups with prevalence of retinopathy varying from 0%, where nobody in the group developed retinopathy, to a group where 80% of patients developed the complication.

Retinopathy risk groups are then fed into a developed simulation model, at the level of individual diabetic patients, for cost-effectiveness evaluations of various intervention and patient care options. The approach taken ensures that the model incorporates the evolved risk groups in the community, together with the natural history of retinopathy and options for early detection and treatment of patients. Case studies demonstrate how the model may be used to evaluate different interventions and patient care options.

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