Deteriorating beta-cell function in type 2 diabetes: a long-term model

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Summary

Background: Type 2 diabetes is characterized by insulin resistance and the progressive loss of islet beta-cell function. Although the former is already established at diagnosis and changes little thereafter, beta-cell function continues to decline, leading to secondary failure of anti-hyperglycaemic therapies.

Aim: To develop a quantitative model of the process of beta-cell function decay over time, using trial data.

Design: Re-analysis of published data.

Methods: The results of the Belfast Diet Study were re-analysed. Assuming patients are diagnosed at different stages in the disease process, time displacement of data was used to obtain a bi-partite spline model describing loss of insulin secretion over a 6-year period.

Results: The model was developed combining two phases, in which a long slow gradual loss of beta-cell function leads to a crisis in metabolic regulation, precipitating a much more rapid decay phase. This paradigm was consistent with a previous non-linear model of beta-cell mass regulation.

Discussion: This model may have important implications for targeting appropriate therapy to patients in each phase: delaying or avoiding full clinical type 2 diabetes in the first phase; and preventing the development of diabetic complications in the second phase.

Introduction

Several authors have recently reviewed the long-running debate on the relative contributions of beta-cell dysfunction and tissue insulin insensitivity to the development and progression of type 2 diabetes.[1–5] There is consensus on the primary role of secretory dysfunction from the time that hyperglycaemia is established. Several trials have now chronicled continuing loss of effective beta-cell function as the key determinant of deteriorating glycaemic control and progressive failure of all types of therapy.[6–9] It is also recognized that for the great majority of patients, substantial loss of insulin sensitivity is well-established at the time of diagnosis.[10]

Despite remaining aetiological uncertainties, in part attributable to the heterogeneous nature of type 2 diabetes, it is important that these insights into the natural history of the condition should be factored into the formulation of recommended therapeutic strategies. To achieve this, medium- and long-term quantified predictions of clinical variables and underlying drivers of disease progression need to be available for both individual patients and typical cohorts.

Mathematical and economic modelling of long-term outcomes in type 2 diabetes began with the publication in 1997 by Eastman[11,12] of a model developed from previous modelling of the cost-effectiveness of intensive insulin therapy in DCCT for type 1 diabetes. Subsequent models, though employing different architectures, have drawn on

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similar assumptions and data sources,[13–15] and share a common descriptive paradigm, relying heavily on epidemiological evidence from observational and long-term cohort studies to provide a description of future incidence and progression of complications. This approach is useful for broad scoping of public policy and estimating burden of disease. However, it is inadequate for predicting the impact of novel treatment strategies for which accumulated empirical evidence does not exist, especially when new agents are used with only short-duration evidence of efficacy.

We have developed a new type of model (the subject of a separate paper) to predict long-term changes in metabolic variables based on evidence of the underlying natural history of type 2 diabetes. This model is then used to generate future estimates of changes in key clinical indicators of glycaemic control and in risk factors for the progression of micro- and macrovascular disease, to replace static epidemiological estimates in our established economic model.[15]

Since it is generally agreed that insulin resistance varies little in patients diagnosed with type 2 diabetes, the principal challenge in modelling is to characterize secular change in insulin secretory potential. This is particularly difficult in the post-UKPDS era, since early and aggressive anti-hyperglycaemic therapy is now established as the norm, and empirical evidence of treatment-naïve disease progression over periods of 5 years or more is consequently scarce. A search of the literature revealed only one study in which natural history was studied in a controlled manner in a substantial group of patients without pharmacological interventions—the Belfast Diet Study (BDS). In this paper we report the findings of a secondary analysis of results published in 1998 of 10-years follow-up of BDS patients,[16] describing the derivation of a mathematical model of the beta-cell function decay process, and discussing its relation to the dynamics of beta cell mass regulation.

Belfast Diet Study

The BDS[6,17] was designed to test the effects of intensive dietary management on blood glucose control, lipid abnormalities, morbidity and mortality in newly presenting patients with type 2 diabetes. A secondary objective was to determine the natural history of the condition over an extended period. Newly-diagnosed, untreated and symptomatic subjects at the Royal Victoria Hospital clinic, aged 40–69 years, were recruited from 1972 to 1980 and prescribed an energy-restricted low-sucrose diet adapted individually to normalize body weight. A total of 432 patients were enrolled and were followed closely for 6 years (monthly for 6 months, then quarterly) and annually to 10 years. Regular measurements of fasting plasma glucose and insulin concentrations were converted to HOMA estimates[18,19] of beta-cell function (%B) and insulin sensitivity (%S).

In 1998, Levy and colleagues[16] reported on the final 10-year follow-up from the BDS, stratifying patients into four subgroups according to the time from diagnosis at which additional non-dietary interventions became necessary. This allowed clinical variables to be compared between semi-homogeneous populations, over 6–10 years. They reported that all variables were subject to change during the first 6 months, due to the introduction of the intensive dietary regimen. Our analysis is directed at identifying secular changes attributable to natural disease progression, and we therefore excluded values prior to the 6-month review.

Secondary analysis and long-term modelling

Figure 1 (adapted with permission from Figure 1(d) of Levy's paper[16]) indicates clearly that insulin resistance is well established at diagnosis in all groups, and there is no evidence of temporal trends over the following 6 years. On this basis, the secondary analysis proceeded by considering only changes in HOMA beta-cell function (%B). By contrast, Figure 2 (adapted with permission from Figure 1(c) of Levy's paper[16]) shows no consistency between the four subgroups, except that all experience a steady decline in %B for the duration of the study.

In search of a single conceptual framework for modelling these patterns, we hypothesized that the subgroups might be following similar trajectories, but displaced in time, i.e. that diagnosis occurred at different times in relation to the underlying stage of disease progression. A similar technique has recently been used to analyse UKPDS fasting plasma glucose data.[20] To test this, we explored a range of possible displacements and concluded that the three subgroups suffering failure of dietary regimen within the study could be closely aligned by suitable choice of displacements, but that the remaining subgroup (those continuing on diet only at 10 years) remained distinct. Taking the former groups together, a simple exponential model was found to provide an acceptable description of the study data (see Figure 3). However, several early results in the group failing dietary therapy in years
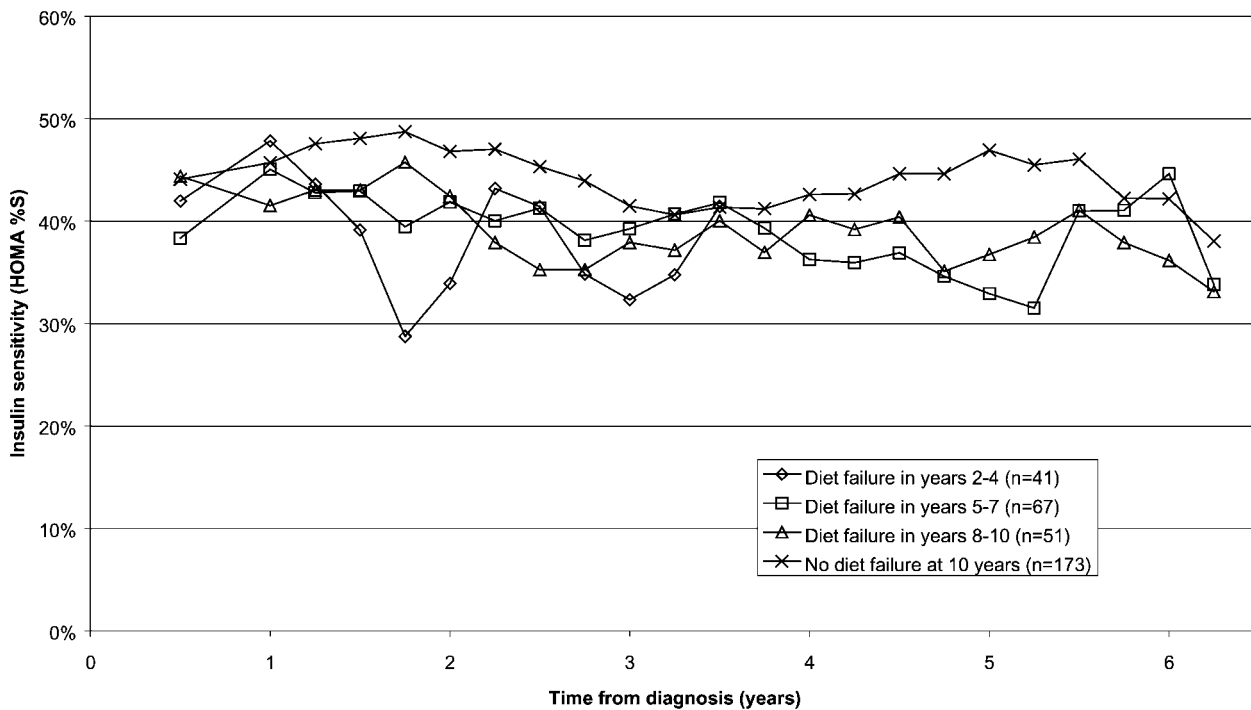
Figure 1. Mean HOMA estimated insulin sensitivity (%S) by dietary failure subgroups in the Belfast Diet Study. Adapted with permission from reference 16.
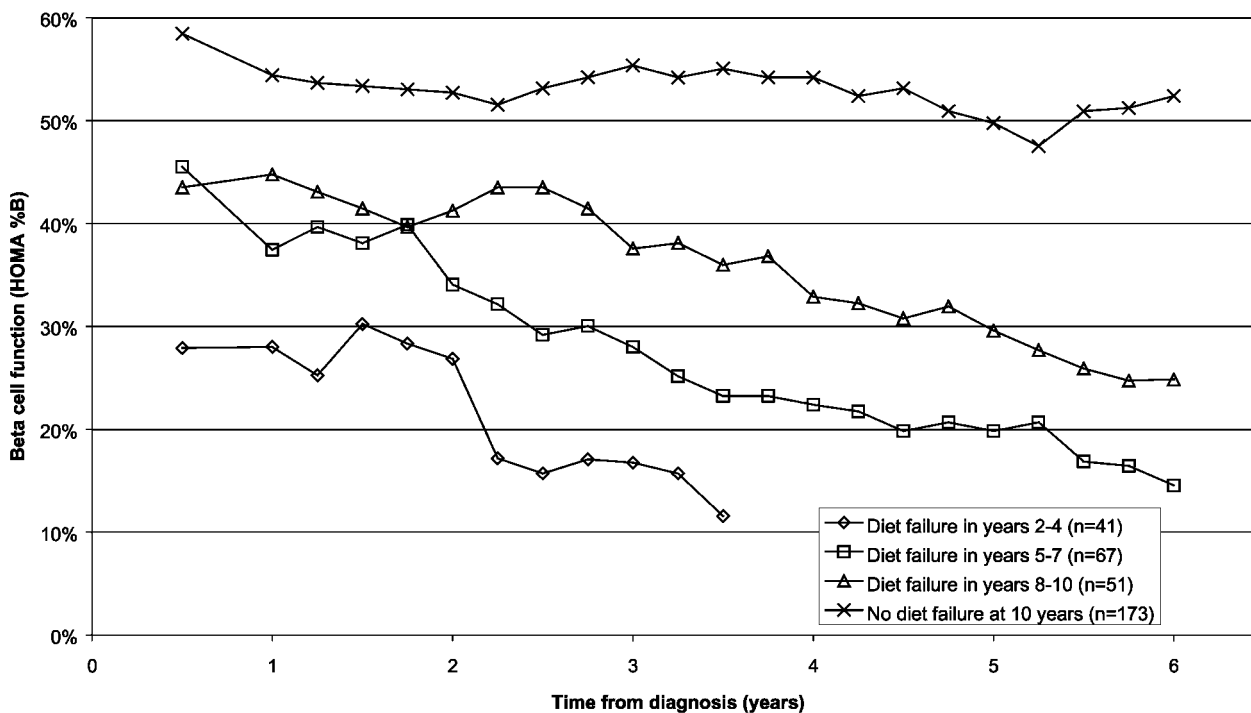

Figure 2. Mean HOMA estimated beta-cell function (%B) by dietary failure subgroups in the Belfast Diet Study. Adapted with permission from reference 16.

8–10 (marked with solid triangles) did not conform to the general pattern.

A second hypothesis was proposed to account for this apparent anomaly, and at the same time encompass the fourth (non-failing) subgroup within the same conceptual framework: that β-cell function decay may be characterized by a bi-partite function involving an initial slow rate of %B loss,
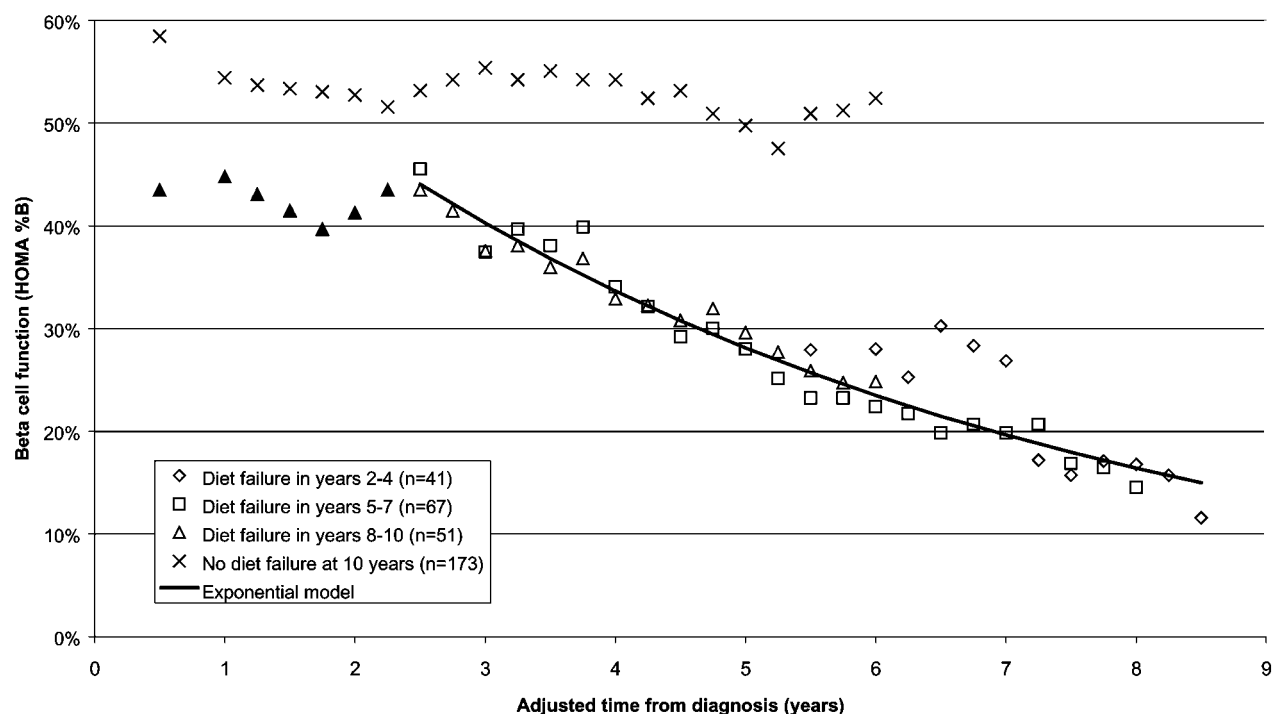
Figure 3. Mean HOMA estimated β-cell function (%B) by dietary failure subgroups, time-displaced to show common decay pattern in three diet failure groups. Solid triangles denote points not conforming to exponential model.

followed by a second stage with a much steeper decay curve. To explore this model, an integrated analysis was undertaken of all data points to fit a spline function, simultaneously optimizing three time-displacement parameters and two exponential decay function parameters to minimize least-squares deviations. The result is displayed in Figure 4, and involves displacing the 2–4 and 5–7 year failure groups by +4.2 and +2.0 years, respectively, whilst displacing the 'no failure'
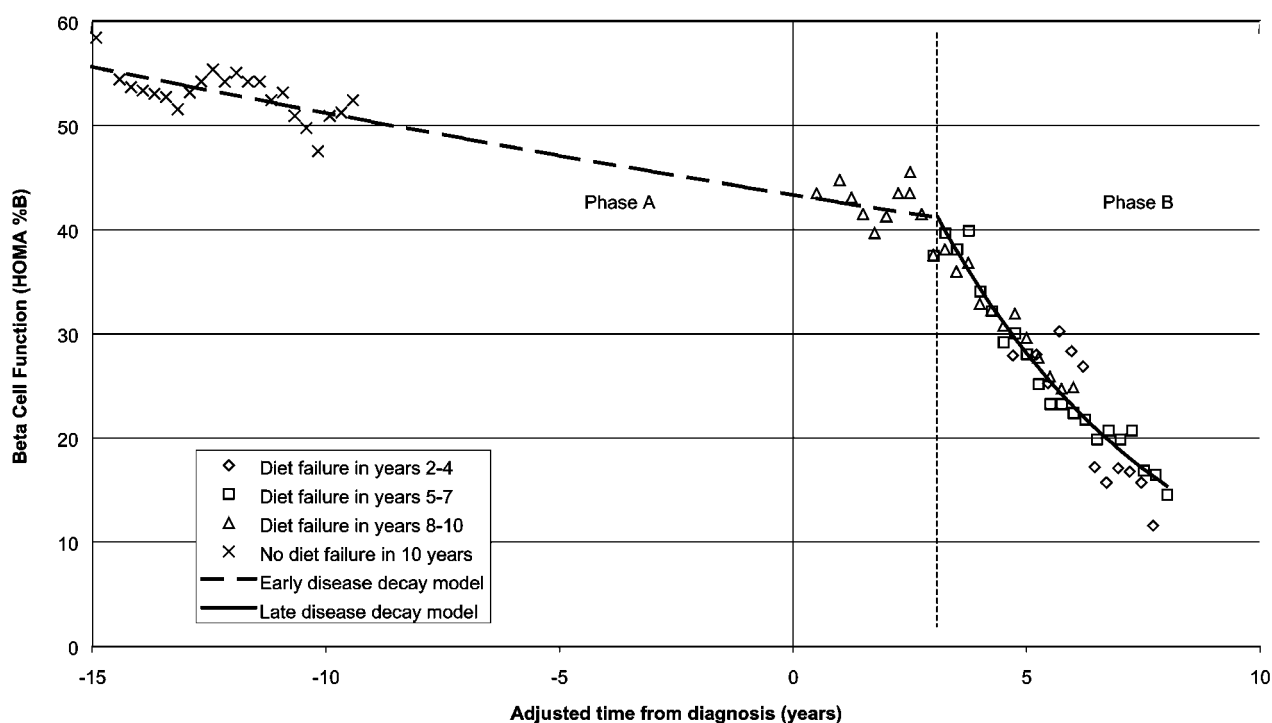

Figure 4. Final spline function model fitted to Belfast Diet Study results, showing two phases of beta-cell function decay.

group by −15.4 years. The estimated annual rates of beta-cell function decay are 1.7% in the initial Phase A, followed by 18.2% in the latter Phase B.

Comparison to other studies

Although the methodology of the BDS has not been reproduced in any other studies (and indeed would not receive ethical approval following the compelling evidence from UKPDS in favour of early intensive intervention), it is important to consider whether the model developed here is compatible with data on the progression of beta-cell function loss obtained in other studies. However, comparable long-term studies are scarce, and the best figures available are from two papers[1,7] reporting UKPDS interim results after 6 years for patients initially randomized to sulphonylurea monotherapy. These show geometric mean beta-cell function declining at 9.5% per annum between years 1 and 6, midway between the Phase A and Phase B estimates derived from BDS. Matthews[1] also shows Kaplan-Meier curves for the proportion of patients failing initial sulphonylurea therapy, stratified into three groups by beta-cell function at randomization. If this is seen as a proxy measure for beta-cell function loss, then we estimate decay rates ranging from 5.8% to 12.6% per annum for patients with best and worst initial %B values. This is consistent with the three groups comprising Phase A and Phase B patients in the ratios 75%/25%, 56%/44% and 34%/66%, respectively. Thus, UKPDS data is compatible with increasing numbers of patients moving over time from Phase A into Phase B as anticipated in the bi-partite model.

In prospective studies and when modelling a typical mixed incident cohort, the observed trend in beta cell function represents a smoothed average of the rates applicable to the two disease phases. Therefore, we would predict that the beta-cell function loss gradient should steadily accelerate as an increasing proportion of patients move into phase B, and this is consistent with UKPDS trial findings.[7]

Summary

The findings of this analysis can be summarized in the form of three hypotheses. (i) That beta-cell function decay proceeds by processes resulting in a simple exponential loss function (i.e. secretory capacity is at constant risk per unit of time). (ii) That beta-cell function decay is a two-phase process, with a critical point in disease progression at which the behaviour of the metabolic system changes from a very slow rate of loss to a much more rapid decline. (iii) That the clinical diagnosis of type 2 diabetes does not occur at a consistent point in disease progression, but may occur at any time over a very long period, resulting in non-homogeneous mixed cohorts if type 2 diabetes is defined by date of clinical diagnosis.

Discussion

Plausibility of hypotheses

Though interesting as a *post hoc* exploration of empirical data, this analysis requires theoretical support if it is to have any credibility as a basis for further research or for interpreting clinical evidence. This is provided in a paper published by Topp and colleagues in the Journal of Theoretical Biology.[20] They describe a non-linear model based on laboratory relationships between cell death and replication rates and glucose concentrations, to predict short- and long-term behaviour of glucose metabolism. In Figure 5 (reproduced with permission from Topp's Figure 2), three zones of behaviour are delineated by reference to increasing glycaemia. With sub-normal glucose concentrations (Zone I), the beta-cell death rate is accelerated and the replication rate suppressed, leading to a net reduction in beta-cell mass and consequent regulation of glycaemia toward the normal balance at P. Conversely, in Zone II, the beta-cell death rate is reduced and the replication rate enhanced resulting in a net increase in beta-cell mass, also regulating glycaemia toward P. However, if blood glucose levels increase beyond the second intersection point S, the combined effect of steadily increasing death rates and reducing replication rates is an accelerating loss of beta cell mass, further increasing glycaemia in a vicious spiral, which leads eventually to the complete elimination of pancreatic insulin production.

Topp's model describes a dynamic system operating in two distinct modes, linked by a critical point at which system behaviour changes abruptly, corresponding closely to the pattern observed in our analysis of the BDS findings. The right-hand portion of Topp's Zone II is then equivalent to our Phase A, and Zone III to Phase B.

Individuals in Phase A would be subject to one or more pathological processes operating to increase glycaemia, but these would be opposed by the gradually weakening system regulation process attempting to restore normoglycaemia through
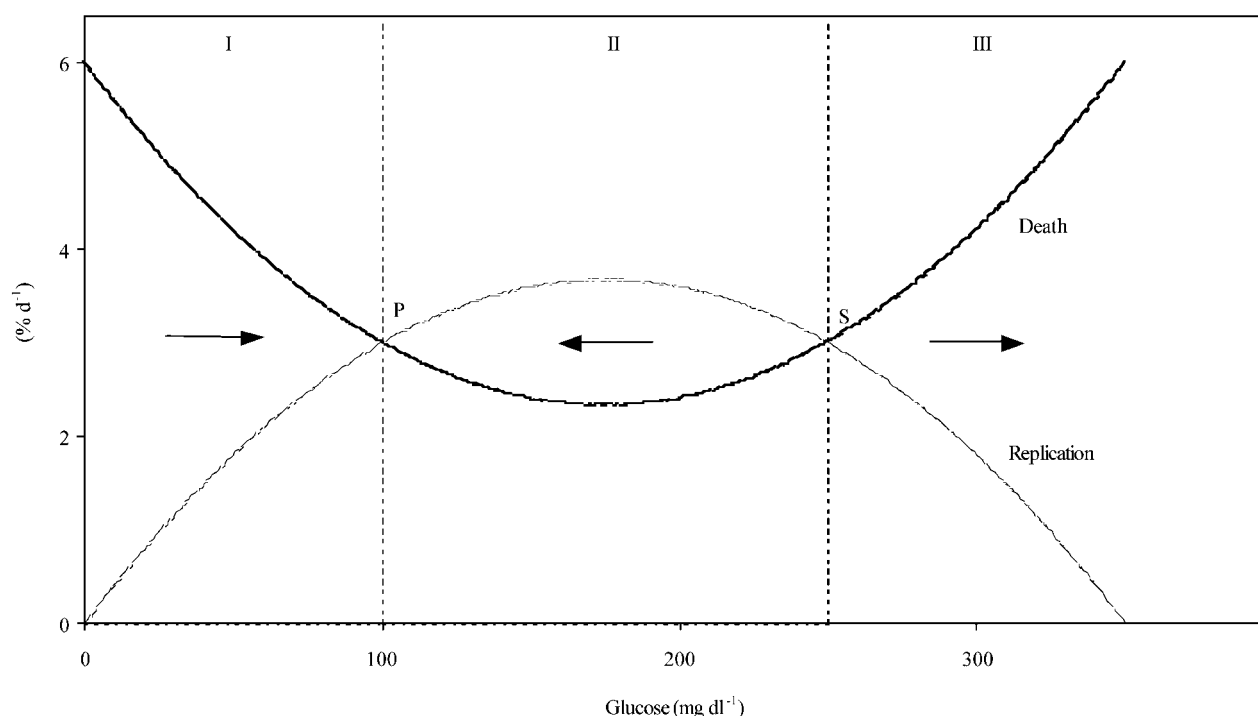
Figure 5. Representation of non-linear beta-cell mass regulation model, showing physiological balance point (P), unstable saddle point (S) and three regulatory behaviour zones. Reproduced with permission from reference 20.

stimulating additional secretory capability. This accounts for an extended period of very gradual decline in effective beta-cell function. However, once the unstable saddle point is reached, only a very modest event (such as an acute infection, or a period of festive over-indulgence) may be sufficient to propel the patient into Phase B with a sudden acceleration of disease progression.

Thus re-analysis of BDS results appears to offer compelling empirical support to the Topp model. Indeed it implies that regardless of the particular aetiology of a patient's metabolic dysfunction (whether from genetic predisposition, dietary excess, or other causes), once insulin insensitivity is established, a common bio-regulatory dysfunction may be responsible for precipitating the fully developed stage of type 2 diabetes mellitus, characterized by rapid and apparently irreversible loss of pancreatic insulin production capacity.

Implications for research and clinical practice

If confirmed by other studies, the natural history of progressive beta-cell dysfunction leading to type 2 diabetes described here poses at least three important questions to the clinical research community. (i) Are existing diagnostics (preferably those accessible to the general practitioner) able easily and reliably to identify at what point on the pathway from Phase A to Phase B a newly-presenting patient is located? (ii) If patients are identified as being located in Phase A, are current interventions (lifestyle, educational or pharmacological) able to prevent, or even significantly delay, progression to Phase B? (iii) If patients are identified as being located in Phase B, are there any interventions that could reverse the condition of patients to such an extent that they could be returned to the pre-crisis system behaviour of Phase A?

If we are able to answer 'yes' to both of the first two questions, then a clear basis exists for primary prevention of the full-blown type 2 diabetes syndrome. The estimated long-term decline in beta-cell function in Phase A based on the BDS (1.7% per annum) is only slightly greater than the normal age-related loss rate of 1% per annum observed in normal glucose-tolerant people.[21] Thus, only modest changes may be required to yield good results for suitable patients, and evidence recently published of reduced progression to diabetes with troglitazone therapy in women with a previous history of gestational diabetes is encouraging.

If we can answer 'yes' to the first and third questions, then there are grounds for testing the potential of 'rescue' interventions to recover failing beta-cell function at the earliest opportunity. Even if a patient in Phase B can never be restored to Phase A, reliable confirmation of their status provides

information to support more effective targeting of traditional anti-hyperglycaemic therapies for secondary prevention of complications.[22]

Thus, there are important potential benefits if these hypotheses can be validated. However, direct verification is now ethically difficult through traditional observational studies. Early work by Lyons and colleagues[23] used simple criteria to predict patients requiring insulin therapy, and more recently Taverna[24] has demonstrated the use of HOMA estimates to predict secondary sulphonylurea therapy failure. These encourage us to believe that a reliable method can be found from normal clinical evidence at, or soon after, diagnosis to assign patients to Phase A or B, thus providing a basis for setting appropriate therapeutic objectives. We plan to carry out further analysis on the BDS dataset for this purpose, with the support and assistance of BDS researchers.

The spline model fitted to BDS data suggests that patients newly-diagnosed with type 2 diabetes are very far from being a homogeneous group. The displacement parameter value estimated for the group successfully treated on diet alone throughout the study (-15.4 years) is the least reliable aspect of the fitted model and may be varied by $+/- 5$ years without materially impairing the fit of the model to the data available. Nonetheless, it is broadly compatible with back-projections made by Harris *et al.*[25] from observations of retinopathy in Wisconsin and Western Australia, that detectable retinopathy was present 4–7 years prior to diagnosis and the onset of diabetes may have occurred a further 5 years earlier.

The extremely varied condition of patients presenting with clinical diabetes implied by this analysis suggests that caution should be exercised in the application of standard treatment protocols. Clinically similar appearances may mask dramatically different prognoses, such that one patient may require early insulin treatment, and another may thrive for years with a modified lifestyle and diet alone. More rigorous initial investigation, and closer supervision of patients over the first few months of treatment may be indicated to ensure that treatment is appropriate to a patient's current stage of disease progression as shown by metabolic markers and early evidence of developing complications.

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