International Research Journal of Mathematics, Engineering and IT
ISSN: (2349-0322)
Impact Factor- 5.489, Volume 5, Issue 6, June 2018
Website- www.aarf.asia, **Email** : editor@aarf.asia , editoraarf@gmail.com

A

STUDY ON MATHEMATICAL MODELS OF PROGRESSION

Raviraj Sureshchandra Katare

Assistant Professor

MSS'S Arts Science and Commerce College , Ambad. Dist-Jalna. Maharashtra, India.

ABSTRACT

This study presents a pancreatic islet compensation model, provides an explanation of its physiological assumptions, describes the numerical values assigned to its parameters (including those derived from available cross-sectional epidemiologic data), and finally simulates the model's lifetime performance under a variety of conditions, including increasing insulin resistance and primary replication defects. It also discusses in detail the numerical values assigned to its parameters. The compensatory mechanisms of the glucose-insulin system evolve in both healthy and diabetic individuals, and this model of diabetes development offers a more plausible and persuasive explanation of this process. For the aim of this comparison, we examine it in relation to two distinct hypotheses that seek to explain the development of diabetes. By going to the website of the authors and following the link, you will be able to view the model simulations.

Keywords: - *Glucose, mathematical models, beta cell mass, Diabetes Mellitus..*

INTRODUCTION

A negative feedback loop is responsible for the regulation of glucose and insulin levels in the immediate time frame, which spans from minutes to hours. This loop involves the stimulation of β−cell glucose uptake by insulin, as well as the enhancement of tissue glucose uptake mediated by insulin, and the reduction of hepatic gluconeogenesis and glycogenolysis. In addition, studies conducted on rats have shown that prolonged exposure to high blood sugar levels might have a detrimental impact by increasing the total rate of beta cell replication. This refers to the process of beta cell replication or differentiation from progenitor ductal cells, without taking into account the process of beta cell death. In spite of the fact that it has been shown that very high blood sugar levels over an extended period of time might lead to a reduction in the rate at which beta cells replicate, perhaps as a consequence of glucose toxicity, this happens.

In the process of developing Type 2 Diabetes Mellitus (T2DM), the relationship between insulin sensitivity, pancreatic β−cell responsiveness, and the dynamics of the β−cell population is the fundamental fundamental factor. It is expected that a gradual increase in glycemia will be determined by insulin resistance in the liver and peripheral tissues, as well as the inability of the pancreas to adjust by raising the concentration of circulating insulin. This is the case regardless of whether environmental or hereditary variables are involved. This phenomenon seems to be the basis for the development of pre-diabetic states, such as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), and ultimately, full-blown type 2 diabetes mellitus (T2DM) in populations. When comparing people with type 2 diabetes to those who are lean or obese and do not have diabetes, it is seen that there is a large increase in the mass of β-cells in individuals who are normoglycemic and have obesity-induced insulin resistance. On the other hand, there is a drop in the mass of β-cells in individuals who have type 2 diabetes.

When considering the majority of instances of type 2 diabetes, it seems that insulin resistance, in conjunction with a relative decrease in β-cell mass and/or activity, is the primary mechanism responsible for the condition. As a matter of fact, severe hyperglycemia is not often brought about by isolated insulin resistance, which is shown in individuals who are very obese and pregnant women, or by decreased β-cell mass, which is observed in pre-clinical cases of Type 1 Diabetes Mellitus (T1DM) and in animals that have had pancreatectomy after receiving an islet transplant. In order to get a quantitative grasp of the dynamic relationship that exists between the many elements that have an effect on the regulation of glycemia, mathematical models have been used. In most cases, these models illustrate the rapid changes in glycemia and insulinemia that take place during perturbation studies. Some examples of these experiments are the Intra-Venous Glucose Tolerance Test (IVGTT), the Oral Glucose Tolerance Test (OGTT), and the Euglycemic Hyperinsulinemic Clamp (EHC). At this stage, we are able to identify the insulin resistance or beta cell activity of the person at a certain moment in time by statistically estimating the model parameters based on the concentrations that were acquired via experimentation.

Furthermore, mathematical models that incorporate the interaction of β−cell population, Fasting Plasma Glucose (FPG), and Fasting Serum Insulin (FSI) over time have been proposed for the purpose of depicting the progression of type 2 diabetes mellitus (T2DM) or as discrete-state dynamical systems with transition probabilities among states that are dependent on covariates. These models have been suggested for use in depicting the progression of T2DM. Because of the time-scale over which type 2 diabetes develops and the practical difficulties of continually monitoring the expansion of the β−cell population, the possibility of properly estimating the relevant parameters from observations in this situation is very greatly reduced. For the purpose of gaining an understanding of the progression of illnesses, we depend primarily on research that is cross-sectional and acceptable extrapolations of limited experimental data. Mathematical modeling provides a precise method for methodically integrating different data sets in order to approximate the basic structure of the phenomena. This method is especially helpful in situations when long-term longitudinal studies are not accessible.

Due to the slow time scale of the process, which is described by, for example, FPG, FSI, or Glycosylated Hemoglobin (HbA1C), as well as the absence of reliable early (surrogate) biomarkers for the development of type 2 diabetes, it is imperative that the mathematical structure of the proposed model in question be understood and verified. Considering the limits that are imposed by the short amount of time that is available for data gathering, it becomes very challenging to produce even a reasonable approximation of the curves that have been seen. Furthermore, any assumptions that are made result in projections for the future that are unduly optimistic. A basic model that assumed a linear rise of glycemia at rates observed early in the prediabetic stage would likely not be able to accurately forecast the state of the majority of individuals who actually develop type 2 diabetes. This is an extreme case. For this reason, it is of the utmost importance to verify that the assumptions of the model correspond to the explanatory power that it is intended to have, that the non-estimable parameters are evaluated with the utmost precision (either by consulting the relevant literature or by reaching a consensus among experts), that the confidence regions are evaluated in order to provide a range of credible predictions, and that the mathematically derived qualitative properties of the model correspond to the accepted physiology.

OBJECTIVE

1. To use modelling to create a new mathematical theory or technique.
2. To use their knowledge of mathematics and statistics to interpret current data

RESEARCH METHODOLOGY

Model Structure

The equations of the model that is being considered are as follows (for the derivation of the model and the relevance of the suffix "slow":

$$\frac{dB}{dt} = \lambda B \ , \quad B(t_0) = B_0$$

$$\frac{d\eta}{dt} = -K_{\eta G}\, G\, \eta + T_\eta \ , \quad \eta(t_0) = \eta_0$$

$$G = \frac{\gamma}{\rho + I}$$

$$I = h(G)\, I_{max B}\, B$$

$$h(G) = \frac{(G/G_h)^{\nu_h}}{1 + (G/G_h)^{\nu_h}} = \frac{G^{\nu_h}}{\alpha_h + G^{\nu_h}} \ , \text{ letting } \alpha_h = (G_h)^{\nu_h}$$

As we begin our examination of the model, it becomes evident that equations 3 and 4 merely demonstrate that the current glycemias are inversely related to the current insulinemias. Furthermore, it is evident that the current insulinemias are directly related to the current glycemias, available β−cell mass, and secretory capacity, all of which are directly related to the current insulinemias.

At each given moment in time throughout history, the levels of glycemia and insulinemia will be representative of a point of equilibrium between these two tendencies. In this step, we will examine the model's many equations one by one, dissecting the assumptions that were used in its formation while doing so.

To put it in a straightforward manner, the model makes the assumption that the change in β-cell mass B (equation 1) is equivalent to the current mass multiplied by a constant λ that represents the net growth rate. In accordance with the principles of population dynamics, a negative value signifies the net mortality of the population.

Equation 6 demonstrates that the value of λ is contingent upon the concentrations of glucose that are present. Because of this, it is possible for it to vary from a negative minimum value (λmin) to a positive maximum value (λmax), which is influenced by both the pancreatic reserve (λmax = λmin+η) and the glucose level (λ = λmin when G = 0 and λmax as G approaches infinity).

The Hill function is normalized, which means that it becomes a function of x rather than G, at the glycemia value Gλ. This is done to guarantee that the Hill function has the maximum slope possible. It is a valid assumption that the regulatory mechanisms of the pancreas work most effectively in close proximity to the goal fasting glycemia, provided that Gλ is relatively near to the normal fasting glycemia, for instance, about 5 mM.

In the event that the concentration of glucose in the surrounding environment is sufficiently elevated, the pancreas has the capability to increase its β−cell proliferation rate, which is represented by the symbol η. On the other hand, pancreatic reserve is not a property that remains unchanged over time (equation 2), but rather a quantity that changes over time with a consistent tendency to return to a steady state. This balance represents the stable state of both forces, and it is possible for the pancreas to either repair on its own or endure a shrinking as a result of glucose poisoning. There is an inverse relationship between the pancreatic reserve of an individual and their blood sugar levels. To rephrase, equation 6 indicates that hyperglycemia will always lead to an increase in the replication of pancreatic β−cells, but only up to the limit that is imposed by the current pancreatic reserve level. On the other hand, equation 2 indicates that chronic hyperglycemia, when prolonged, will cause the pancreatic reserve to approach zero. It is important to note that, regardless of the present glucose content, the β-cell population would decline in the absence of therapy if the pancreatic reserve is considerably damaged, which is denoted by the symbol η -λmin.

The'slow' model takes into consideration changes that occur over a period of months or years; hence, equations 3slow and 4slow are derived from the equilibrium conditions for glycemia and insulinemia, respectively. It is generally accepted that our glucose and insulin systems, which are both quite active, are in a state of equilibrium at every single moment in slow time. According to one interpretation, this equilibrium may be seen as the average blood sugar level that is the consequence of the average insulin levels and the current degree of insulin sensitivity. On the other hand, the predominant glycemias, the available β-cell mass, and a coefficient of insulin production at maximal stimulation per β-cell mass unit are the factors that determine the average insulinemia. Because we only need indicator data for the system's prevailing state over the course of a day or a week, fasting glucose and insulin concentrations and average glucose and insulin concentrations are conceptually comparable to one another.

We had to stipulate that, as recorded in the literature, the apparent first order rate constant of insulin elimination from plasma decreases with age. This was necessary in order for the model to be able to represent the known loss in insulin secretory function that occurs with age. Insulin resistance is represented by the variable γ, which is the inverse of KxgI. This variable is the concentration at which glucose stabilizes for each pM of insulin concentration.

RESULT DISCUSSION

Mathematical Analysis

Following this, we will provide a series of assertions about the qualitative characteristics of the model. These assertions are either proved in or directly follow from the proofs in traditional calculations.

Model behavior.

The proposed model's qualitative behavior is similar to that of the current model. Under the given assumptions, there could be three possible equilibrium points in the βGI-system and the current model. One is a physiological steady-state with normal basal values of glycemia and insulinemia (Gb and Ib), which is locally asymptotically stable. The other is a pathological steady-state with zero levels of β−cell mass and insulinemia, which is also locally asymptotically stable. In this state, hyperglycemia (Gh > Gb) is associated. Finally, there is an unstable saddle point with intermediate glycemia (Gb<Gs<Gh). Consistent with physiological assumptions, the proposed model displays dynamic changes. When blood sugar levels are low (G(t) < Gb) or moderately high (Gb < G(t) < Gs), the normal range for plasma glycemia is G(t) → Gb. When insulin sensitivity is impaired or when there is a moderate rise in blood sugar levels, the number of beta cells increases and insulinemia develops. However, when the saddle point is reached, when glucose toxicity sets in and beta cell mass eventually drops to zero, the body enters a pathological steady state where insulin production stops altogether.

Given that the glucose effectiveness at zero insulin (Kxg) is strictly positive, the same pathological steady-state exists in both Topp(61) and the current model, mathematically speaking: B = 0, which is a trivial equilibrium point for the β−cell mass dynamics, corresponds to I = 0, and a positive finite hyperglycemia. The zeroes of a certain function of G define the other two equilibrium points, the physiological steady-state and the saddle point. According to Topp(61), this kind of function is a second-order polynomial with a negative second-order coefficient, a negative value for the zero-order coefficient at G = 0, and a positive first derivative at G = 0. So, it's possible for it to have two zeros: one for the physiological steady-state and another for the saddle point, provided that the lesser of the two numbers is less than Gs. A nonlinear function χ(G), representing the asymptotic λ at a given level of glycemia, is constructed from the slow dynamics in this study. Like Topp's second order function, this one allows a negative value for λmin at G = 0, grows monotonically for G > 0 until it reaches its unique maximum, and then falls monotonically, getting asymptotically closer to the same negative value at G = 0. Later on, it is possible to generate two zeroes, one representing the physiological steady-state and the other the saddle point (if the sum of the two is smaller than Gs). In contrast to the parabolic function in Topp, which may achieve unrealistically huge negative values for high G, the pre-specified limitations on the net rate of βcell replication limit χ(G) for every non-negative G. This is the fundamental mathematical difference between the two functions.

Parameter sensitivity analysis.

Given that the glucose effectiveness at zero insulin (Kxg) is strictly positive, the same pathological steady-state exists in both Topp and the current model, mathematically speaking: B = 0, which is a trivial equilibrium point for the β−cell mass dynamics, corresponds to I = 0, and a positive finite hyperglycemia. The zeroes of a certain function of G define the other two equilibrium points, the physiological steady-state and the saddle point. According to Topp, this kind of function is a second-order polynomial with a negative second-order coefficient, a negative value for the zero-order coefficient at G = 0, and a positive first derivative at G = 0. So, it's possible for it to have two zeros: one for the physiological steady-state and another for the saddle point, provided that the lesser of the two numbers is less than Gs. A nonlinear function χ(G), representing the asymptotic λ at a given level of glycemia, is constructed from the slow dynamics in this study. Like Topp's second order function (61), this one allows a negative value for λmin at G = 0, grows monotonically for G > 0 until it reaches its unique maximum, and then falls monotonically, getting asymptotically closer to the same negative value at G = 0. Later on, it is possible to generate two zeroes, one representing the physiological steady-state and the other the saddle point (if the sum of the two is smaller than Gs). In contrast to the parabolic function in Topp, which may achieve unrealistically huge negative values for high G, the pre-specified limitations on the net rate of βcell replication limit χ(G) for every non-negative G. This is the fundamental mathematical difference between the two functions.

In light of the fact that the glucose effectiveness at zero insulin (Kxg) is a strictly positive value, the same pathological steady-state occurs in both Topp and the present model, mathematically speaking: The value of B equals zero, which is a point of equilibrium for the dynamics of the β-cell mass, corresponds to the value of I equal to zero and a positive hyperglycemia that is finite. The physiological steady-state and the saddle point are the other two equilibrium points that are defined by the zeroes of a particular function of G. As stated by Topp, this particular kind of function is a polynomial of the second order, with a negative value for the second-order coefficient, a negative value for the zero-order coefficient at G = 0, and a positive first derivative at G = 0. This means that it is feasible for it to have two zeros: one for the physiological steady-state and another for the saddle point, provided that the value that is lower of the two is lower than Gs. The slow dynamics in this work are used to generate a nonlinear function $\chi(G)$, which represents the asymptotic λ at a certain level of glycemia. In the same way as Topp's second order function, this particular function permits a negative value for λmin at G = 0. It then increases monotonically for G > 0 until it hits its one-of-a-kind maximum, and then it declines monotonically, moving asymptotically closer to the same negative value at G = 0. At a later point in time, it is feasible to create two zeroes, one of which represents the physiological steady-state, and the other of which represents the saddle point (provided that the total of the two is less than Gs). The pre-specified constraints on the net rate of βcell replication limit $\chi(G)$ for any non-negative G, in contrast to the parabolic function in Topp, which has the potential to obtain negative values that are unreasonably large for high G. The difference between the two functions may be summed up in one basic mathematical distinction.

Regarding the parameters that have the same meaning in terms of the affects that altering the parameters has on the behavior of the model, the present model is pretty comparable to the Topp model. This is significant since the parameters have the same meaning. The following is something that both models need to take into consideration with regard to these parameters.

A decrease in insulin sensitivity does not have any impact on the relative equilibrium glycemias, as well as the existence or absence of the three equilibrium points. The converse is true when insulin sensitivity declines; this therefore leads to an increase in both the mass of equilibrium β-cells and the quantity of insulin that is needed to keep the same level of blood sugar maintained.

Regardless of the rise in glucose production (R0 in Tgl here), the three equilibrium points continue to exist (and continue to maintain their stability characteristics). In the physiological steady-state, the glycemia is maintained by the increased β-cell mass and insulinemia. Therefore, an increase in glucose production does not result in an increase in the glycemia amount. However, it does produce an increase in the pathological glycemia that is associated with diabetes, which is a result of the absence of β-cells because to insulinemia. In a manner that is analogous to the way in which an increase in glucose synthesis Tgl influences the equilibrium, a decrease in glucose effectiveness at zero-glycemia Kxg performs the same function.

When the insulin clearance rate is raised, the existence of the three equilibria, as well as the stability characteristics of each of them, do not alter. Physiological and saddle points both keep

blood sugar levels constant at elevated β-cell mass and insulinemia, but there is no impact at pathological steady state levels (clearly, since no insulin has to be cleared).

CONCLUSION

A mathematical model that illustrates the course of diabetes over an extended period of time is presented and justified by the current study, which concludes that the research presented and provided support for the model. The idea that is now being pursued is better than the one that was being pursued before. A model that is immediately applicable to clinical conditions is generated as a consequence of meticulously studying the relevant components. This model is immediately applicable. As a result of the fact that we now possess a trustworthy quantitative account of the progression of type 2 diabetes mellitus over time, we are in a position to adjust our experimental questions in order to make them more precise and easier to assess. In addition to this, we are able to better concentrate our efforts in order to determine the replies that are the most suitable.

REFERENCES

1. Bergman RN, Ider YZ, Bowden CR and Cobelli C. Quantitative estimation of insulin sensitivity. Am J Physiol 236: E667-E677, 1979.
2. Bernard C, Berthault MF, Saulnier C and Ktorza A. Neogenesis vs. apoptosis As main components of pancreatic beta cell ass changes in glucose-infused normal and mildly diabetic adult rats. FASEB J 13: 1195-1205, 1999.
3. Bernard C, Thibault C, Berthault MF, Magnan C, Saulnier C, Portha B, Pralong WF, Penicaud L and Ktorza A. Pancreatic beta-cell regeneration after 48-h glucose infusion in mildly diabetic rats is not correlated with functional improvement. Diabetes 47: 1058-1065, 1998. 8.
4. Bolie VW. Coefficients of normal blood glucose regulation. J Appl Physiol 16: 783-788, 1961.
5. Bonner-Weir S, Deery D, Leahy JL and Weir GC. Compensatory growth of pancreatic beta-cells in adult rats after short-term glucose infusion. Diabetes 38: 49-53, 1989.
6. Boutayeb A and Chetouani A. A critical review of mathematical models and data used in diabetology. Biomed Eng Online 5: 43, 2006.
7. Bouwens L, Lu WG and De Krijger R. Proliferation and differentiation in the human fetal endocrine pancreas. Diabetologia 40: 398-404, 1997.
8. Bouwens L and Pipeleers DG. Extra-insular beta cells associated with ductules are frequent in adult human pancreas. Diabetologia 41: 629-633, 1998.
9. Breda E, Toffolo G, Polonsky KS and Cobelli C. Insulin release in impaired glucose tolerance: oral minimal model predicts normal sensitivity to glucose but defective response times. Diabetes 51 Suppl 1: S227-S233, 2002.
10. Brissova M, Fowler MJ, Nicholson WE, Chu A, Hirshberg B, Harlan DM and Powers AC. Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy. J Histochem Cytochem 53: 1087-1097, 2005.

11. Bunn H, Haney D, Kamin S, Gabbay K and Gallop P. The biosynthesis of human hemoglobin A1c. J Clin Invest 57: 1652-1659, 1976.
12. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA and Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. Diabetes 52: 102- 110, 2003.
13. Cao Minh, L., Galasso, R., Gurlo, T., Basu, R., Rizza, R. A., and Butler, P. Three Fold Increase in Beta Cell Mass in Twenty Weeks in Human Pregnancy. 68th American Diabetes Association Meeting 18-B Islet Biology - Beta Cell Growth and Differentiation, 4-OR. 2008. San Francisco.
14. Clausen JO, Borch-Johnsen K, Ibsen H, Bergman RN, Hougaard P, Winther K and Pedersen O. Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians. Analysis of the impact of gender, body fat, physical fitness, and life-style factors. J Clin Invest 98: 1195-1209, 1996.
15. de Winter W, DeJongh J, Post T, Ploeger B, Urquhart R, Moules I, Eckland D and Danhof M. A mechanism-based disease progression model for comparison of long-term effects of pioglitazone, metformin and gliclazide on disease processes underlying Type 2 Diabetes Mellitus. J Pharmacokinet Pharmacodyn 33: 313-343, 2006.
16. de Winter, W., Post, T., DeJongh, J., Moules, I., Urquhart, J., Eckland, D., and Danhof, M. A mechanistic disease progression model for Type 2 Diabetes Mellitus and Pioglitazone treatment effects. PAGE 2004 Meeting Poster, 17. 2004.
17. Defronzo R.A. The triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 37, 37: 667, 1988.
18. Eddy DM and Schlessinger L. Validation of the archimedes diabetes model. Diabetes Care 26: 3102-3110, 2003.
19. Efanova IB, Zaitsev SV, Zhivotovsky B, Kohler M, Efendic S, Orrenius S and Berggren PO. Glucose and tolbutamide induce apoptosis in pancreatic beta-cells. A process dependent on intracellular Ca2+ concentration. J Biol Chem 273: 33501-33507, 1998.
20. Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. N Engl J Med 314: 1360-1368, 1986.