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Article *in* International Journal of Diabetes in Developing Countries · March 2016

DOI: 10.1007/s13410-016-0475-8

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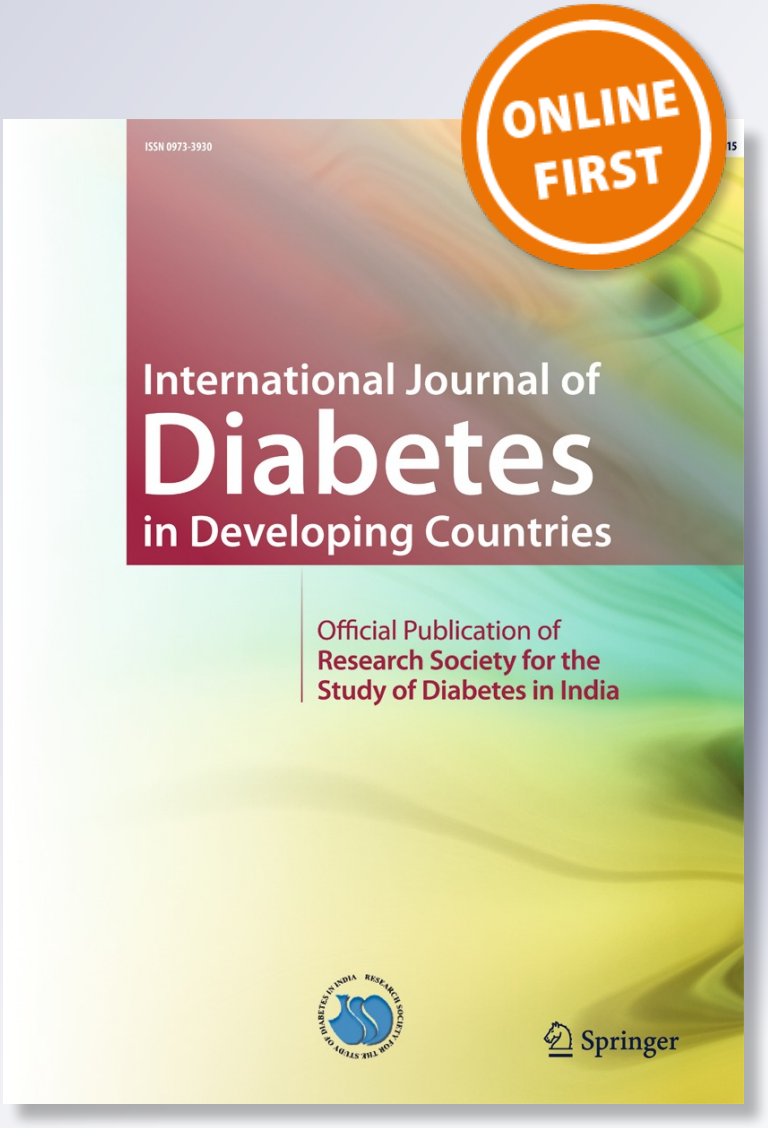
International Journal of Diabetes in Developing Countries
Incorporating Diabetes Bulletin

ISSN 0973-3930

Int J Diabetes Dev Ctries
DOI 10.1007/s13410-016-0475-8



Springer

Int J Diabetes Dev Ctries
DOI 10.1007/s13410-016-0475-8

REVIEW ARTICLE

ODE models for the management of diabetes: A review

Saloni Rathee[1] · **Nilam**[1]

Received: 14 October 2015 / Accepted: 17 February 2016

Abstract Diabetes also known as diabetes mellitus is a chronic and complex metabolic disease due to the persistent raised blood glucose concentration for long duration. The mechanism behind the disturbed glucose-insulin dynamics is still not fully understood. The mathematical models which describe the glucose homeostasis, different aspects of diabetes and its consequences are growing rapidly, provide new insights into the biological mechanism involved and help in the management of diabetes. Here, contribution of diabetic's modelling using ordinary differential equations over the past five decades is discussed. Some parameter estimation techniques, softwares involved and some computational results are also presented.

Keywords Diabetes · Glucose-insulin · ODE models · Softwares · Parameter estimation techniques

Introduction

Diabetes is a disease of the glucose-insulin regulatory system. It is classified into three main categories: type 1 diabetes, type 2 diabetes and gestational diabetes. Type 1 diabetes is considered to be the result of an immunological destruction of the insulin-producing β cells [1]. Type 2 diabetes is the result of insulin resistance which increases resistance of the body to the effects of insulin on glucose uptake, metabolism or storage due to excessive hepatic glucose production and defective β cell function [2].

Diabetes is a condition in which high blood glucose concentration persists for long duration due to the disturbed insulin-glucose-glucagon dynamics in the body. Glucagon and insulin are two hormones secreted by α and β cells of the pancreas which take part to maintain the glucose level in normal range. In normal individual, blood glucose level is maintained in the physiological range (70-110 mg/dl) as the glucose-insulin regulatory system works properly. After glucose infusion (food intake, oral ingestion), raised blood glucose level triggers the pancreas to release insulin which helps the body cells (muscles and skeletal) to take up glucose. In case of low blood glucose concentration, glucagon helps the liver to break glycogen into glucose as shown in Fig. 1a. In diabetic individual, the glucose-insulin dynamics is disrupted resulting to persistent high blood glucose level as shown in Fig. 1b. Long-term persistence of diabetes affects the major organs of the body like the liver, kidney, eyes, nervous system and reproductive system and causes multiple organ failure [3].

A large number of research articles are published on diabetes, its types and related complications during the last decades [4–8]. Many mathematical models were developed and successfully captured the physiological changes occurring in the human body with or without diabetes [9–15]. Out of many, few mathematical models proved a milestone in the pathogenetic and physiological studies of diabetes [9, 13, 15]. Previously developed mathematical models are still used by researchers with suitable and significant modifications. The literature deals with different mathematical models and simulation of different aspects of diabetes is abundant. Several reviews based on the different mathematical models, tools and softwares are timely published and have proven to be useful for the academicians and researchers [16–18].

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Published online: 03 March 2016

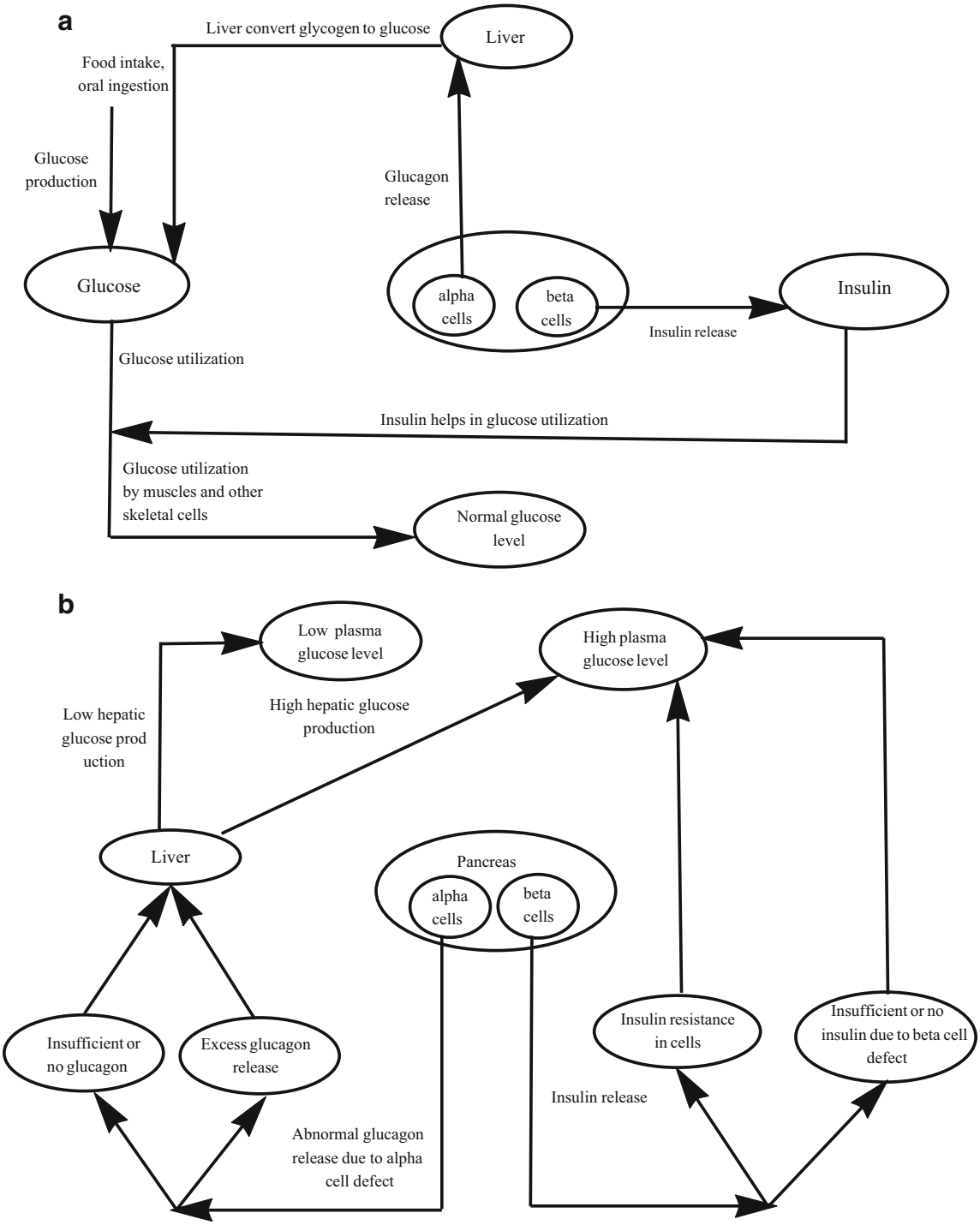

Fig. 1 Glucose-insulin dynamics under normal and diabetic condition. **a** In normal condition, β cells of the pancreas release insulin, which helps muscles and skeletal cells to take up glucose and maintain the normal glucose level. Also, the glucagon secreted by α cells of pancreas helps the liver to convert glycogen into glucose. **b** In diabetic condition, the glucose-insulin dynamics is disrupted and insufficient or no insulin is secreted from the β cells due to β cell defect which leads to high glucose level. Also, the glucagon secretion from α cells is disturbed, resulting in excess glucagon or insufficient glucagon release leading to high glucose level or low glucose level

The mathematical models may be simple/complex, deterministic/stochastic, continuous/discrete using ODE (ordinary differential equations), PDE (partial differential equations), DDE (delay differential equations), statistical differential equations (SDE), integral equations and many more. Mathematical models presented to the time can be classified into different categories based upon the physiology involved, complexity level of model and which type of data is used in the models. The models further can be classified according to the biological processes involved and also the motive for

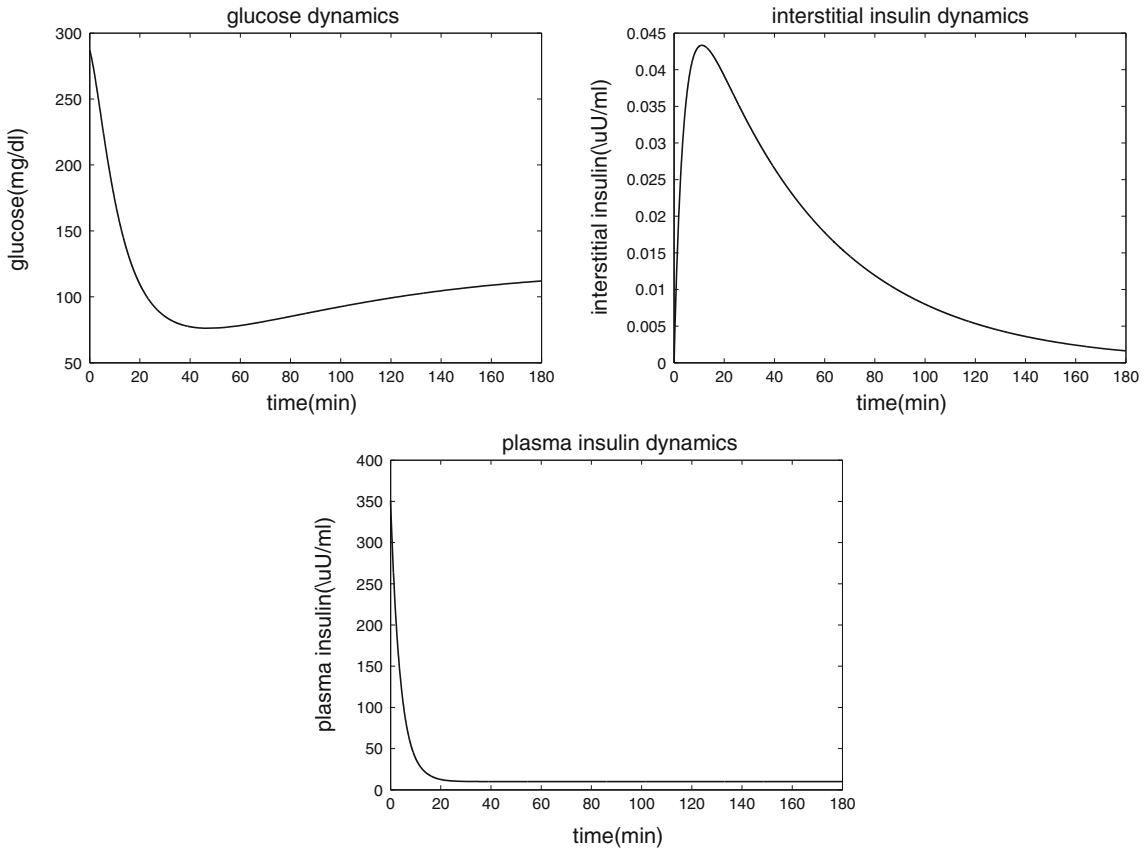

Fig. 2 Glucose, plasma insulin and interstitial insulin concentration levels are obtained using ODE45

which the models were proposed. Many attempts have been made to address the complexity behind the mechanism of the disease, but still an imbalance exists between the information obtained from the experimental theory and their mathematical representation.

Most of the ODE models were developed to evaluate the diagnostic tests such as intravenous glucose tolerance test (IVGTT), oral glucose tolerance test (OGTT) and meal glucose tolerance test (MGTT). The aim of these tests were to estimate the insulin sensitivity (S_I), glucose effectiveness (S_G), disposition index (DI), insulin secretion, insulin action and β cell function. To include all the mathematical models published so far in one review paper is difficult, but we tried our best to include the important mathematical models based on ordinary differential equations, which were used to manage the level and complexity of the disease.

To discuss the mathematical models of diabetes, it is necessary to get the knowledge of all the basic terms and definitions which are frequently used in the physiological and clinical study of diabetes. Some important basic terms and definitions which will be used in the paper are as follows:

- S_I (insulin sensitivity): effect of insulin to catalyse the glucose disappearance from the plasma [19]
- S_G (glucose effectiveness): ability of glucose to enhance its own disappearance independent of insulin presence [19]
- $\mathrm{AIR}_{\mathrm{glucose}}$: first-phase insulin response [19]
- DI (disposition index): ability of pancreatic β cells to compensate for insulin resistance [19]
- φ_1: first-phase pancreatic responsivity [6]
- φ_2: second-phase pancreatic responsivity [6]
- IVGTT (intravenous glucose tolerance test): a test in which glucose is injected intravenously and blood samples are collected following the glucose injection [5]
- OGTT (oral glucose tolerance test): a test in which glucose is given orally and blood samples are collected over 2 h following the glucose infusion [20]
- FSIGT (frequently sampled intravenous glucose tolerance test): a test to measure the blood glucose level in which nothing (drink and eat) is given for 8 to 12 h before the test

Ordinary differential equation models

To study the glucose-insulin regulatory system in the human body, many mathematical models were found in the literature. Out of those, mathematical models containing ordinary

differential equations are abundant, and approximately more than 500 papers can be found in the literature based on the ODE models [16]. Here, we tried to give the overview of the papers which consider ODE model to discuss different aspects of diabetes and its consequences.

Bolie [4] is considered as the pioneer in introducing the ODE mathematical model to capture the physiological changes in the glucose-insulin dynamics.

•In 1961, Bolie [4] developed a minimal model to evaluate the coefficients of normal blood glucose regulation.

The differential equations for glucose-insulin regulatory system are written as

$$\frac{dx(t)}{dt} = p - \alpha x + \beta y \tag{1}$$

$$\frac{dy(t)}{dt} = q - \gamma x - \delta y \tag{2}$$

Where x represents the deviation in insulin concentration from their mean physiological value, y represents the deviation in glucose concentration from their mean physiological value, p is the intravenous injection functions I divided by extracellular compartment value, q is the intravenous injection functions $\dot{G}$ divided by extracellular compartment value, α denotes the sensitivity of insulinase activity to elevate insulin concentration, β denotes the sensitivity of pancreatic insulin to elevate glucose concentration, γ represents the combined sensitivity of liver glycogen storage and tissue glucose utilization to elevate insulin concentration and δ represents the combined sensitivity of liver glycogen storage and tissue glucose utilization to elevate glucose concentration [4].

Results By the help of several assumptions like liver, pancreas and peripheral tissues were considered to communicate with each other in a single compartment, the values of four coefficients (α, β, γ, δ) and their biological variations were evaluated and used for managing the diabetes.

In 1964, Ackerman et al. [20] reviewed a model to predict the blood glucose level by simulating the behaviour of human regulating system. He compared the predictions made during OGTT to regulate the blood glucose and blood insulin concentration.

In 1970, Segre et al. [21] considered a two-compartment model and applied to the analysis of glucose and insulin control mechanism in 26 normal, 16 diabetic and 8 obese subjects. Glucose level for all the three groups were determined by infusing glucose (0.5 g/min for about 300 min).

Results A discriminant analysis for two groups gave a statistically significant separation between normal and diabetic subjects (with infused or impulsive glucose) and between normal and obese subjects (with infused glucose).

In 1978, Ruby et al. [22] presented a model which indicates the roles of both insulin and glucagon as regulators of blood glucose. The model simulations suggest that insulin plays the most important role in the control of hyperglycaemia, and glucagon is an important regulatory hormone under conditions of hypoglycaemia when the blood glucose value falls below 50 mg/dl.

In 1979, Bergman et al. [23] discussed the studies which led to definition and measurement of the characteristic parameters of metabolic regulation. They attempted to show that the parameter presents a novel and powerful way to conceive of metabolic regulation, which provides an improved means for investigating the environmental, dietary and activity-related factors which alter the regulation of metabolism in mammalian species.

In 1979, Bergman and Cobelli [5] estimated the insulin sensitivity after evaluating a mathematical model of glucose disappearance. Seven mathematical models of glucose uptake were compared to find the glucose disappearance. The parameter of the model was estimated from a single IVGTT to estimate the insulin sensitivity.

Limitations The study was for the animals, and experimental studies were required whether insulin sensitivity was estimated also for humans.

In 1980, Toffolo et al. [24] proposed the minimal model for the insulin kinetics in dog. The proposed minimal model was used for the physiological studies of insulin secretary function in dog by using IVGTT and proposed the idea to also apply the model for the pathophysiological studies in humans. Toffolo et al. compared six mathematical models to study the insulin kinetics and found that the model, given below, is superior in explaining insulin dynamics with respect to all aspects.

$$\frac{dI(t)}{dt} = -\gamma(G(t) - h)t, \text{ if } G(t) \geq h \tag{3}$$

$$= 0, \text{ if } G(t) \leq h \tag{4}$$

In 1981, Bergman et al. [6] introduced two separate mathematical models: one for glucose kinetics and another for insulin kinetics. Insulin model produce the parameters: φ_1, φ_2, responsivity of β cells to glucose, whereas glucose model produce the insulin sensitivity (S_I) parameter during IVGTT.

The minimal model for the glucose-insulin regulatory system is as follows:

$$\frac{dG(t)}{dt} = -X(t)G(t) - p_1(G(t) - G_b) \tag{5}$$

$$\frac{dX(t)}{dt} = p_2 X(t) + p_3 I(t) \tag{6}$$

$$\frac{dI(t)}{dt} = -nI(t) + \gamma(G(t) - G_c)^+ t \tag{7}$$

Where $G(t)$ (mg/dl) represents glucose concentration, $X(t)$ (min^{-1}) represents remote insulin concentration, $I(t)$ (μU/ml) represents the interstitial insulin, G_b (mg/dl) represents the basal glucose level, h (mg/dl) represents the threshold glucose level of glucose above which the endogenous insulin secretion will be stimulated, p_1 represents glucose effectiveness, p_2 is the fractional rate of insulin appearance in interstitial compartment, p_3 represents contribution of plasma insulin to the remote compartment from interstitial compartment, n represents the rate of plasma insulin clearance and γ is the degree by which glucose exceeds threshold or baseline glucose level.

Results The aim of the study was to determine the quantitative contributions of pancreatic responsiveness and insulin sensitivity to glucose tolerance by using "minimal model technique".

Limitations The results were limited to evaluation of IVGTT only. It remained to prove whether the model and the parameters are applicable on other dose such as OGTT and other stimulus pattern.

In 1984, Defronzo et al. [25] examined the tissue sensitivity to insulin in 36 control subjects and 19 insulin-dependent diabetics using insulin clamp technique. Following hyperinsulinaemia, suppression of hepatic glucose production was ~95 % in both diabetics and controls, suggesting that peripheral tissues are primarily responsible for observed impairment in insulin-mediated glucose uptake.

Results The result indicates that impaired insulin action is a common feature of insulin-dependent diabetics, despite daily insulin requirements that would not clinically characterize them as insulin resistant.

In 1985, Bergman et al. [7] examined the different approaches introduced by researchers for the evaluation of insulin sensitivity. He reviewed pancreatic suppression test ([26–28]), glucose clamp ([27, 28]) and minimal model approach ([6, 8]) to find the effect of closed loop feedback relation between insulin action and insulin secretion.

In 1986, Pacini and Bergman [9] proposed a mathematical model for measuring two main factors—insulin sensitivity and pancreatic responsivity—to control glucose tolerance. Bergman proposed MINMOD (minimal modelling approach)—a computer program to identify the model parameters S_G, S_I, φ_1 and φ_2 and analyse FSIGTT data.

The selected mathematical model is given as

1. For glucose disappearance

$$\frac{dG(t)}{dt} = -(p_1 + X(t))G(t) + p_1 G_b, G(0) = G_0 \tag{8}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3(I(t) - I_b), X(0) = 0 \tag{9}$$

2. For insulin kinetics

$$\frac{dI(t)}{dt} = p_5(G(t) - h)^{+} t - n(I(t) - I_b), I(0) = I_0 \tag{10}$$

Results Program MINMOD successfully calculated S_G, S_I, φ_1 and φ_2 which represent an integrated metabolic portrait of any individual and help in managing diabetes.

Limitations

1. Insulin concentration and glucose concentration were treated as input data to derive the parameters of the equations.
2. Equilibrium does not exist and the solutions of the minimal model may not be bounded.
3. The variable $X(t)$ was introduced to consider the delay in action of insulin to stimulate glucose uptake.

In 1990, Welch et al. [10] determined the exogenous infusion of insulin in the minimal model FSIGTT analysis. He also extracted the information about insulin-mediated glucose uptake and noninsulin-mediated glucose uptake, insulin sensitivity and insulin secretion.

In 1991, Sturis et al. [13] developed a six-dimensional ODE model. Tolic et al. [29] simplified the model, and the model has been the basis of many DDE models [15, 30–33].

$$\frac{dG(t)}{dt} = G_{in} - f_2(G(t)) - f_3(G(t) f_4(I_i(t)) + f_5(x_3(t))$$

$$\frac{dI_p(t)}{dt} = f_1(G(t)) - E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_p}$$

$$\frac{dI_i(t)}{dt} = E\left(\frac{I_p(t)}{V_p} - \frac{I_i(t)}{V_i}\right) - \frac{I_p(t)}{t_i}$$

$$\frac{dx_1(t)}{dt} = \frac{3}{t_d}\left(I_p(t) - x_1(t)\right)$$

$$\frac{dx_2(t)}{dt} = \frac{3}{t_d}\left(x_1(t) - x_2(t)\right)$$

$$\frac{dx_3(t)}{dt} = \frac{3}{t_d}\left(x_2(t) - x_3(t)\right)$$

Where $G(t)$ is mass of glucose; $I_p(t)$ and $I_i(t)$ are the mass of insulin in the plasma and intercellular space; V_p is the plasma insulin distribution volume; V_i is the volume of intercellular space; E is the diffusion transfer rate; t_p and t_i are insulin degradation time constants in plasma and intercellular space; G_{in} is glucose supply rate to the plasma and $x_1(t)$, $x_2(t)$ and $x_3(t)$ are the three additional variables associated with certain delays of the insulin effect on HGP with total time delay t_d.

The function $f_1(G)$ represent the pancreatic insulin secretion; f_2, f_3, f_4 represent the glucose utilization in the body (brain (f_2), muscles and fat cells (f_3, f_4) and f_5 represents HGP) [29].

Results The occurrence of sustained insulin and glucose oscillations was found to be dependent on two essential features, a time delay of 30–45 min for the effect of insulin on glucose production and a sluggish effect of insulin on glucose utilization.

In 1991, Fisher [34] presented a mathematical model for glucose insulin interaction in the blood system. Mathematical optimization techniques are applied to mathematical model to derive insulin infusion program. A semi-closed algorithm is proposed for continuous insulin delivery to diabetic patients.

Results Insulin infusion program which incorporates an injection to coincide with the meal succeeds in achieving the most effective short-term control.

In 1995, Coates et al. [35] studied the minimal model (MINMOD) analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT) which depends on an adequate insulin response to the glucose load. Subjects with an insulin-dependent diabetes mellitus (NIDDM) was not included in MINMOD. Hence, in the paper, the technique has been modified by using intravenous bolus of insulin. They compared estimates of insulin sensitivity derived from minimal modelling of a 4-h insulin-modified FSIVGTT and the glucose clamp in subjects with NIDDM.

Results MINMOD analysis of the insulin-modified FSIVGTT provides a valid measure of insulin sensitivity in subjects with NIDDM.

In 1997, Vicini et al. [11] shows that 2CMM (two-compartment minimal model) provides indexes of glucose effectiveness (S_G), insulin sensitivity (S_I) and plasma clearance rate (PCR) and also overcomes the limitation of one-compartment minimal model [12] by providing the plausible profile of endogenous glucose production.

The 2CMM for the glucose-insulin regulatory system is as follows:

$$\dot{q}_1(t) = -\left[k_p + \frac{R_{d,0}}{Q_1(t)} + k_{21}\right] q_1(t) + k_{12}(t) q_2(t), q_1(0) = d \quad (11)$$

$$\dot{q}_2(t) = k_{21} q_1(t) - [k_{02} + x(t) + k_{12}] q_2(t), q_2(0) = 0 \quad (12)$$

$$\dot{x}(t) = -p_2 x(t) - s_k [I(t) - I_b], x(0) = 0 \quad (13)$$

$$g(t) = \frac{q_1(t)}{V_1}$$

Where q_1 and q_2 denote hot glucose masses in the first (accessible pool) and second (slowly equilibrating) compartments; $x(t)$ is insulin action; $I(t)$ and I_b are the plasma and basal insulin; $Q_1(t)$ is cold glucose mass in the accessible pool (mg/kg); $g(t)$ is plasma hot glucose concentration (mg/dl), d is the hot glucose dose (mg/kg); V_1 is the volume of the accessible pool (ml/kg); $R_{d,0}$ (mg kg^{-1} min^{-1}) is the constant component of glucose disposal; k_p (min^{-1}), k_{21} (min^{-1}), k_{12} (min^{-1}) and k_{02} (min^{-1}) are the parameters of glucose kinetics and p_2 and s_k (ml μU^{-1} min^{-1}) are the parameters describing insulin action.

Limitations

1. Effect of glucose on insulin-independent glucose uptake takes negative values.
2. Precision of 2CMM parameters estimation was not satisfactory every time.

In 2000, Topp et al. [14] developed a βIG model for β cell mass, insulin and glucose kinetics for diabetes.

The mathematical model for the glucose-insulin regulatory system is as follows:

$$\frac{dG(t)}{dt} = a - (b + cI)G \quad (14)$$

$$\frac{dI(t)}{dt} = \frac{d\beta G^2}{e + G^2} - fI \quad (15)$$

$$\frac{d\beta(t)}{dt} = \left(-g + hG - iG^2\right)\beta \quad (16)$$

Where a denotes hepatic glucose production, b is the rate of insulin-independent glucose utilization, c is the rate of insulin mediated glucose utilization, d denotes rate of insulin secretion by β cells, e determines inflection point of sigmoidal function, f denotes rate of insulin clearance, g is β cell natural death rate, h determines β cell glucose tolerance range, G is the blood glucose concentration (mg/dl), I is the blood insulin concentration (μU/ml) and β is the β cell mass (mg).

Results The model predicts three distinct pathways into diabetes: regulated hyperglycaemia, bifurcation and dynamical hyperglycaemia.

Limitations The model did not incorporate effects of hyperglycaemia on neogenesis, insulin sensitivity, insulin secretion rates and β cell heterogeneity. Also, the model does not incorporate the effects of insulin and incretin hormones on β cell mass dynamics.

In 2001, Ryan et al. [36] modified the mathematical model of β cell mass, insulin and glucose kinetics for diabetes developed by Topp et al. [14] by including the effects of insulin receptor dynamics which was important in the pathogenesis of diabetes and showed that insulin sensitivity can be increased by 36 % due to exercise, and required insulin level can also be decreased to maintain the glucose concentration. Also, the system of equations improves the quantitative prediction of β cell mass values and provides a theoretical justification for the fact.

Limitations The dimension of the mathematical model can be extended by incorporating other hormone secreting cells in the islets of Langerhans and incorporating the insulin sensitivity dynamics in the model.

In 2000, Gaetano and Arino [37] proposed another model known as "dynamical model" in order to overcome the limitations and drawbacks of the coupled minimal model.

The dynamical model for the glucose-insulin system is as follows:

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7 \tag{17}$$

$$G(t) = G_b \forall t \in [-b_5, 0], G(0) = G_b + b_0$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s)ds, I(0) = b_5 + b_3 b_0 \tag{18}$$

Where, b_0 (mg/dl) is the increase in plasma glucose concentration over basal glucose concentration at time zero after instantaneous administration of the i.v. glucose bolus; b_1 (min^{-1}) is the glucose disappearance rate constant, b_2 (min^{-1}) is the insulin disappearance rate constant, b_3 (pM $(mg/dl)^{-1}$) is the first-phase insulin concentration increase per (mg/dl) increase in the concentration of glucose at time zero due to the injected bolus; b_4 ($min^{-1}(pM)^{-1}$) is the constant amount of insulin-dependent glucose disappearance rate constant per pM of plasma insulin concentration; b_5 (min) is the length of the past period whose plasma glucose concentrations influence the current pancreatic insulin secretion; b_6 (min^{-1} pM $(mg/dl)^{-1}$) is the constant amount of second-phase insulin release rate per mg/dl of average plasma glucose concentration throughout the previous b_5 minutes; b_7 ((mg/dl) min^{-1}) is the constant increase in plasma glucose concentration due to constant baseline liver glucose release [37].

Results The original minimal model [9] was developed to cope for first 3 h after glucose infusion while the present dynamic model deals with many hours after the administration of glucose bolus and also prevailing a few minutes before glucose infusion. The model admits only one equilibrium point; the model is stable around that equilibrium point and the solutions are positive and bounded.

Limitations The assumptions taken in the paper might not be realistic, and the way in which the delay term was introduced was too restrictive based on the fact that pancreatic insulin secretion at time t was proportional to the average value of glucose concentration in b_5 min preceding time t.

Gaetano and Arino [37] reported that unstable steady state does not exist for the model while Li et al. [38] found that these models can posses unstable positive steady states producing oscillatory solutions.

In 2001, Li and Kuang [38] generalized the Arino's paper [37] to find an alternative way of incorporating time delay.

The mathematical model for the glucose-insulin regulatory system is as follows:

$$\frac{dG(t)}{dt} = -b_1 G(t) - \frac{b_4 I(t) G(t)}{\alpha G(t) + 1} + b_7 \tag{19}$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{-b_5}^{0} G(t+\theta)d\theta \tag{20}$$

With initial conditions, $G(0) = G_b + b_0$, $I(0) = I_b + b_3 b_0$, $G(t) \equiv G_b$ for $t \in [-b_5, 0]$, where $G_t(\theta) = G(t + \theta)$, $t > 0$, $\theta \in [-b_5, 0]$. The parameters b_0, b_3, b_5 and b_7 are the same as in model (17-18).

Results Sustainable oscillatory solutions (G and I) of mathematical model obtained for ($\tau > 60$ min) and no oscillations exist for ($\tau < 60$ min). The solution may converge to the steady state in an oscillatory way even the delay was small. Better ways of delivering insulin and timings of the intake of glucose were found. Also, they found that generalized dynamic model can produce oscillatory solutions without hepatic glucose production.

Limitations The obtained results were on the basis of only two subjects (1 male, 1 female). Insulin influenced on the hepatic glucose production were not taken and kept open for further studies.

In 2002, Cobelli et al. [39] proposed a new approach to estimate insulin sensitivity from an OGTT using an "integral equation". Three different model to determine R_a (rate of appearance of oral glucose in plasma) were presented in the paper: piecewise linear (P), spline (S) and dynamic (D). All the three models estimated the insulin sensitivity.

Limitations

1. The time course of (R_a) does not disclose explicitly in model.
2. It does not provide the recision with which S_I^I (I denoted integral) is estimated.
3. It assumed glucose and insulin concentration has returned to basal level at the end of the test to calculate the area under the curve correctly.

In 2002, Derouich and Boutayeb [40] introduced the effect of physical activities and exercise via parameters in a mathematical model given by Bergman et al. [6] and compared the behaviour of normal, NIDD and IDD people. The new added parameters demonstrated the effect of physical exercise on the diabetic body.

In 2002, Mari et al. [41] investigated β cell function and its relationship to insulin sensitivity by choosing 17 normal

volunteers. Insulin secretion and insulin sensitivity were measured by applying mathematical model on meal test (MT) and oral glucose tolerance test (OGTT) with the help of euglycaemic insulin clamp technique.

In 2003, Toffolo and Cobelli [42] introduced a new improved version of two-compartment minimal model (2CMM) [11]. The new improved version of 2CMM, proved a more reliable and precise parameter of glucose metabolism during an IVGTT.

In 2004, Dellaman et al. [43] used the reference method tracer two-step method and compared the results on database of 88 subjects. The method was compared with the homeostasis model assessment (HOMA) [44, 45], the quantitative insulin sensitivity (QUICK) [46] and MATSUDA-De Fronzo [47] to measure the insulin sensitivity during an OGTT. The results confirm that the OMM estimates the rate of appearance of glucose absorption and insulin sensitivity accurately.

In 2005, DallaMan et al. [48] presented a labelled oral minimal model (OMM*) in which a tracer was added to the oral dose and S_I (labelled insulin sensitivity) was determined. OMM* not only estimates the R_a (labelled rate of appearance of oral glucose in plasma) but also accurately measures S_I^*.

In 2005, Bergman [19] considered the minimal model and showed that insulin sensitivity or insulin sensitivity index (S_I) can be calculated from parameters of minimal model by

1. performing frequently sampled IVGTT
2. measuring glucose and insulin
3. fitting the data to the minimal model
4. calculating insulin sensitivity

Also, he showed that product of insulin sensitivity and insulin secretion would be approximately constant, i.e. insulin sensitivity × insulin secretion = disposition index($S_I \times \mathrm{AIR}_{\mathrm{glucose}} = \mathrm{DI}$).

In 2006, Boutayeb et al. [49] presented a mathematical model of the size of a population of diabetes mellitus. The nonlinear case was discussed and critical values of the population were analysed for stability.

The nonlinear ODE mathematical model is as follows:

$$\frac{dD}{dt} = I - (\lambda + \mu)D(t) + \gamma C(t)$$

$$\frac{dC}{dt} = \lambda \mathrm{D}(t) - (\gamma + \mu + \nu + \delta)C(t)$$

Since $N(t) = D(t) + C(t)$ gives rise to initial value problem (IVP).

$$\frac{dC}{dt} = -(\lambda + \theta)C(t) + \lambda N(t), t > 0, C(0) = C_0 \quad (21)$$

$$\frac{dN}{dt} = I - (\nu + \delta)C(t) - \mu \mathrm{N}(t), t > 0, N(0) = N_0 \quad (22)$$

Where $\theta = \gamma + \mu + \nu + \delta$ and C_0 and N_0 are the initial case of $C(t)$ and $N(t)$.

$C(t)$ is the number of diabetics with complications, $D(t)$ is the number of diabetics without complications and $N(t)$ denotes the size of population of diabetics at time t.

Results The result obtained estimates the size of the population of diabetics and the numbers with complications.

In 2006, Bergman et al. [50] performed dimensional analysis of MINMOD and found that with nondimensionalization, pathological DI is naturally defined in the model and it has the meaning of insulin sensitivity at unit first-phase pancreatic response. Using simulated data and human FSIVGTT data, they found the new approach which gives highly correlative parameter estimates to the original dimensional formulation.

In 2006, Wang et al. [51] formulated a mathematical model to deal with the question about heterogeneity between young- and adult-onset type 1 diabetes. It was found that if autoimmunity is initiated, then the turnover is slow, and a stable steady state can exist with the β cell turnover being rapid. Also, the model analysis pointed that pathway regulating β cell turnover can be a new target to interfere with the disease process of T1D.

In 2007, Silber et al. [52] developed an integrated model for healthy and type 2 diabetic patients to regulate the glucose and insulin concentration by using IVGTT data form 30 healthy and 42 diabetic individuals. Analysis of all the data by nonlinear mixed effect modelling was performed in NONEM.

Results The model could be used to analyse the effects of antidiabetic drugs on a physiological system and can be used to predict and stimulate data for different types of IVGTT in healthy and diabetic patients.

Limitations The design which were used to study glucose-insulin regulatory system seems very time consuming and expensive in sampling.

In 2007, Silber et al. [53] extended the previously developed integrated model [52] for glucose-insulin regulatory system by including the OGTT in healthy volunteers by simulation and bootstrap of the model. The base on which the new model developed was the incretin effect (i.e. oral glucose provocations results in stronger insulin response compared to intravenous provocations).

Results Glucose homeostasis parameters can be derived from the glucose provocations by the help of present model, which was most commonly used in the early stage of clinical drug development.

In 2007, Roy and Parker [54] extended the minimal model [6] and included the major effects of exercise on plasma glucose and insulin concentration level in the body.

In 2008, Gaetano et al. [55] made an attempt to discuss the progression of type 2 diabetes through a mathematical model. A model of the pancreatic islet compensation was formulated by the help of some physiological assumptions. The mathematical model was compared with the model developed by Topp et al. [14] and found to be more robust and useful for clinical purpose through assessment of the related parameters.

In 2008, Stahl and Johansson [56] made an attempt to show how system identification and control may be used to estimate predictive quantitative models to be used in design of optimal insulin regimens.

In 2008, Periwal et al. [57] examined a variety of mathematical models analogues to the minimal model of glucose disposal (MMG). To quantify the combined influence of insulin on lipolysis and glucose disposal during an insulin-modified frequently sampled intravenous glucose tolerance tests (FSIGT). The tested models contain compartments of plasma free fatty acids (FFA), glucose and insulin. Out of 23 models, they select the best fitted model by using Bayesian model comparison method which minimized model complexity. In the best model, insulin suppressed lipolysis via a Hill function through a remote compartment that acted both on FFA and glucose simultaneously, and glucose dynamics obeyed the classic MMG.

In 2010, Pacini et al. [58] compared the insulin sensitivity index (S_I) and glucose effectiveness (S_G) obtained in 16 normal subjects with two tests. The common protocol are regular (rFSIGT) and an insulin-modified test (mFSIGT), with an additional insulin administration at 20 min. Both FSIGTs with minimal model analysis provide the same S_I, which was a very robust index. S_G was different by 28 %, and the reason behind may be the relationship between S_G and the amount of circulatory insulin.

In 2011, Javier et al. [59] extended the model of Topp et al. [14] by proposing two models: one to show the adipose tissue effects on insulin sensitivity and another to show the effect of fat accumulation on the regulatory system. He discussed three different formulations for fat accumulation: a linear case and two nonlinear cases where the relationship between fat accumulation, insulin and glucose was discussed.

Other approaches

Other type of equations which are widely used in the mathematical models are the following: partial differential equations (PDE), stochastic differential equations (SDE), delay differential equations (DDE) and integral differential equations (IDE).

Parameter estimation techniques

- Bayesian parameter estimation technique to estimate the parameters of mathematical model [37, 60–63].
- Nonparametric stochastic deconvolution estimation technique [64–66].
- Pancreatic suppression test (PET) [67–69] and glucose clamp technique (GCT) used to evaluate the insulin resistance.
- Parameter estimation was performed on a digital computer (IBM 370/168, IBM corp.) using a nonlinear least square technique [70].
- Nonlinear mixed effects modelling using NONEM VI and the first-order conditional estimation method (FOCE) was used for data analysis [71, 72, 52, 53].

Software tools for numerical simulation

- Monte Carlo simulation are a broad class of computational algorithm to obtain numerical results [73].
- SAAM II software: Simulation, Analysis and Modelling software is widely used for tracer and pharmacokinetic studies [74, 75].
- Several physiology-based paradigm models are available for diagnosis like HOMA [44, 45], QUICKI [46] and MATSUDA [47].
- ODESOLVE is a MATLAB program for solving ordinary differential equations and described in the third edition of ordinary differential equations using MATLAB.
- MATCONT is a software for numerical bifurcation analysis of ordinary differential equations in MATLAB [76, 77].
- WinSAAM is a program used to model all types of biological systems [78].
- ODE23 and ODE45 are the tools used to solve ordinary differential equations in MATLAB and can be found in http://in.mathworks.com/help/matlab/ref/ode23.html and http://in.mathworks.com/help/matlab/ref/ode45.html.
- WINSTODEC is a stochastic deconvolution interactive program used for physiological and pharmacokinetic systems [66, 79].
- XPPAUT (XPP) is a tool for solving ordinary differential equations (ODE), difference equations (DE), delay differential equations (DDE), functional equations, boundary value problems and stochastic equations [80].

Computational results

Numerical simulation has been done for many mathematical models in the research papers. To include all the

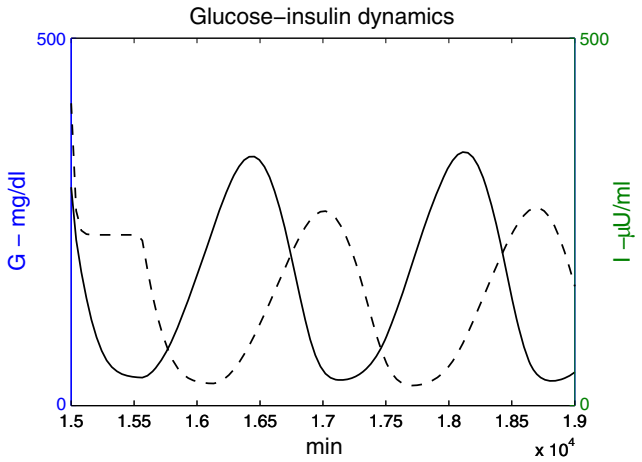

Fig. 3 DDE23 shows the sustained oscillations at $\tau = 550$ min

computational simulation in one paper is difficult or probably an impossible task. Here, we tried to give some computational results of few mathematical model.

Consider the Bergman model (8-10) [9], by using ODE45 tool in MATLAB 2012b, we plotted the glucose-insulin concentration level as shown in Fig. 2 and the steady point is taken as (G^*, X^*, I^*). Using ODE45 tool, it is easy to solve the mathematical model and helps to detect the glucose concentration, plasma insulin concentration and interstitial insulin concentration.

Consider a IVGTT model (19-20) [38], by using DDE23 tool in MATLAB 2012b, we can plot the glucose and insulin sustained oscillations for subject 6. The data has been taken from [37] having (G^*, I^*) as the equilibrium point. The tool DDE23 helps to detect the value of delay term τ at which sustained oscillations occur. The periodic and sustained oscillations at time delay $\tau = 550$ min is shown in the Fig. 3. No sustained and periodic oscillations obtained for $\tau < 550$ min.

Discussion

Mathematical models provide new insights for better understanding of the physiology involved in the disease for better management of the disease. They provide a justification of the theory; provide new information and software tools; help in estimating parameters and most importantly simulate the simple and complex mechanism involved in occurrence of any disease. Literature deals with many mathematical models (ODE, DDE, PDE, SE and IE models), and they are proven to be very informative for better understanding of the disease. In the present review paper, our motive was to give an overview of ODE models which deal with different aspects, diagnosis, care, cure and complications of diabetes. We indent to discuss the purpose behind every paper which deals with mathematical models. We discussed the theoretical, analytical and numerical results and also the limitations of every paper. The limitations of a previous paper motivate the occurrence of the next paper, and in this way, improved mathematical models were developed and presented which confirm the clinical and nonclinical results of the diabetes.

For example, Javier et al. [59] included the assumption of adipose tissue in the model of Topp et al. [14] to describe the effects of fat accumulation in diabetes. Similarly researchers may relax or include more assumptions in the model to describe more complex dynamics involved in the disease, which may throw light in the direction of controlling the disease.

In the three sections before the "Discussion section", a list of parameter estimation techniques, computer softwares and some computational results are presented in the paper.

Conclusion

During the last five decades, many research articles were published on different mathematical models and the computer algorithms. Besides the fact that many models were presented, still the exact mechanism involved in the physiology of the diabetes is not fully understood. The reason for the long persistence of hyperglycaemia acting differently in different individuals is not known. Here, we tried to present a panorama of all ODE models according to their year-wise publication so that it provides new insight to the researchers to think for further development in the diabetes research.

Acknowledgments The authors are thankful to Delhi Technological University, Delhi for the financial support.

Authors' contribution Ms. Saloni Rathee has contributed to the study design, numerical analysis and manuscript preparation. Ms. Nilam has contributed to the manuscript editing and review. Both have made equal contribution in the literature search.

Compliance with ethical standards This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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