MATHEMATICAL MODEL ON THE BLOOD GLUCOSE/INSULIN CONCENTRATIONS IN AN INSULIN- DEPENDENT DIABETIC PATIENT: CASE OF A PATIENT WITH VARIABLE PANCREATIC INSULIN RELEASE.

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ABSTRACT

The generalized model of the blood glucose/insulin concentration in an insulin-dependent diabetic patient where the patient has variable pancreatic response to glucose level was considered. It was shown that greater response of the pancreas to glucose concentration leads to quicker clearance of excess glucose in the blood. Also, the greatest quantity of glucose to be found at any time when the response is high is less when compared with that of lower response of the pancreas to the glucose level. Another disturbing result is the fact that if the pancreatic response to glucose level (and thus level of insulin release) is non-steady, we then have dual or multiple peak of insulin level, which present variable insulin production for those with higher pancreatic response. This results to problem as regards the conversion mode of the glucose to glycogen. The consequence of this is that the patient might be exposed to such situations like low blood glucose level and might then suffer hypoglycemia if proper diagnosis was not made to determine the exact diabetic level or severity.

The conclusion derivable here therefore is that appropriate control of the blood glucose level will not be possible by insulin infusion since the correct blood insulin level
can not be accurately estimated at any time.

KEYWORDS: Mathematical model, Blood, Glucose, Insulin, Pancreas, Diabetic Patient.

INTRODUCTION

Diabetes mellitus is a disease characterized by chronic high blood plasma glucose concentration and other disturbances of carbohydrate and lipid metabolism in man. Depending on the level of severity of this disease, the plasma glucose concentration can be as high as 200 mg/100 cc or even more as against the normal plasma glucose level of between 70 – 115 mg/100 cc in an overnight fasting, (Ellenberg and Rifkin, 1983). This high plasma glucose concentration usually results to micro-vascular complications of which the most importantly affected parts of the human system are the eyes and the kidney, (Czech and Massagnes, 1982 ; Vallence-Owen, 1975).

There are various causes of diabetes mellitus though they are put into two broad forms: insulin –dependent and the non-insulin –dependent. Of particular interest in this work is the insulin-dependent form. The insulin-dependent diabetes mellitus is a type of disease caused by low insulin concentration in the blood plasma of which the simplest approach to treatment is the insulin infusion or administration. Insulin is a hormone secreted by the islet of langerhans of the pancreas. It has wide spectrum of activities among, which is the enhancement of the cell conversion of the excess glucose in the plasma to glycogen, which is the storable form of glucose in the body organs and cells (Mbah, 1998). It is this particular attribute of the insulin that is usually lacking in an insulin-dependent diabetic patient. In normal persons, carbohydrate taken as food is digested in the alimentary canal from where the glucose and other monosacharides are absorbed into the blood. From the blood, they diffuse into the extra-cellular fluids. By facilitated-mediated transport process, this glucose is taken to the cell plasma membrane by the carrier proteins called glucose transporters (Simpson and Cushman, 1985). About six of such glucose transporters have been identified (Bell et al, 1989). The cell membrane structure shows that the outer surface of the plasma membrane is lined with evenly distribution protein receptors for hormones and other chemical messengers (Czech and Massagnes,1982, Gavin et al , 1974, Kosmokos and Roth, 1980, Lorinth and Smith, 1983). This makes the plasma membrane a signal –receiving device for the detection of chemical signals that regulate the cell activities. It is at this membrane that the insulin performs its function by binding with these receptor proteins either in phosphorylated or unphosphorylated forms. It is this autophosphorylation action of the insulin that causes the aggregation of the protein receptors at the plasma membrane (Quon and Campfield , 1985). This reduces the inhibitory action of these proteins to the entry of glucose into the cells. Although the exact mechanism of glucose entry into the cells is not clearly known, it is thought that the glucose, through the facilitated-mediated transport, gets to the plasma membrane where they bind with the appropriate carrier proteins leading to conformal changes in the carrier molecules that will now allow the passage of the glucose. Though this is what happens in the blood/ cells of a normal person, it is not exactly the same in an insulin-dependent diabetic patient. In this case, there is usually low concentration of insulin in the plasma. This affects the proper functioning of the insulin with particular reference to the plasma glucose regulation, (Bute, 1982). Usually the low plasma insulin concentration is occasioned by reduced response of the pancreatic cells to produce/release insulin when stimulated by high plasma glucose concentration. This action leads to reduced interaction of the plasma glucose and insulin and thus the high plasma concentration of the glucose.

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A mathematical model showing the variation in the level of the glucose or insulin in the blood of an insulin-dependent diabetic patient was presented (Mbah, 1998).   In summarized form we state the factors that affect the levels of glucose and insulin in the blood at all times. We have that for the blood glucose level, the factors that determines it are:

the quantity of food taken,

glucose/insulin interaction (in other words the glucose conversion to glycogen

due to peripheral cell response),

the amount of this glucose being converted to energy and finally

the release of the stored glycogen by the liver for a long period of no food intake.

For the insulin level, we see that the factors are the pancreatic cell response to the level of glucose in the blood, the insulin usage and the insulin infusion because the patient is diabetic.

Detailed study on the derivation of the mathematical models can be obtained in Mbah (1998), Mbah (2001). The resulting mathematical models are:

$$\frac{dx}{dt} = a_1 z(t) - a_2 xy - a_3 x + ax(x_0 - x) ------------(1)$$

$$\frac{dy}{dt} = b_1 x - b_2 y + b_3 w(t) --------------------(2)$$

where x = glucose level

y = insulin level

$$z(t) = Q e^{-k(t-t_0)} \qquad and$$

$$w(t) = \begin{cases} \dfrac{w_0(t-t_0)}{\bar{t}-t_0}, & t_0 < t \le \bar{t} \\ \dfrac{-w_0(t-(2\bar{t}-t_0))}{\bar{t}-t_0}, & \bar{t} \le t \le 2\bar{t}-t_0 \\ 0 & \text{elsewhere.} \end{cases} = \gamma t + \delta$$

The constants a_1, a_2, a_3, a_4 and b_1, b_2, b_3, δ, γ are associated with the behaviour of the glucose and insulin to the system of the individual concerned respectively.

Equation (1) as presented is a general case but we shall assume that the patient is not starving so that $a_4 (x_0 - x)$ will be neglected. Thus our equations of interest will be

$$\frac{dx}{dt} = a_1 z(t) - a_2 xy - a_3 x ----------------------------(3)$$

$$\frac{dy}{dt} = b_1 x - b_2 y + b_3 w(t) ------------------------------(4)$$

Now a look at equation (3) shows that it is non-linear. However, since the patient is not starving meaning that there is always enough glucose in the blood to be converted to glycogen in the presence of insulin, we may linearize the term xy to $\bar{x}y$ where $\bar{x}$ is now a constant. With this, equation (3) now becomes a linear differential equation and given as:

$$\frac{dx}{dt} = a_1 z(t) - a_2 \bar{x}y - a_3 x ------------------------(5)$$

Method of solution

The equations (4) and (5) are first order differential equations and are to be solved simultaneously. Substituting as given above, we have

$$\frac{dx}{dt} = a_1 Q e^{-k(t-t_0)} - a_2 \bar{x}y - a_3 x \qquad (6)$$

$$\frac{dy}{dt} = b_1 x - b_2 y + b_3 (\gamma t + \delta). \qquad (7)$$

In equations (6) and (7), a_2 and b_1 measures the glucose and insulin interaction and the pancreatic response to the glucose stimulation respectively. Hence, the severity of the patient's diabetes depends principally on how small the value of b_1 is and also on the value of a_2. These two equations are solved simultaneously by finding their complementary and particular solutions which when added up give their solutions. Suppose the complementary solutions $(x,y) = (x_c, y_c)$ to the homogenous equations.

$$\frac{dx}{dt} = -a_2\bar{x}y - a_3x \tag{8}$$

$$\frac{dy}{dt} = b_1x - b_2y \tag{9}$$

is given by

$$\begin{pmatrix} x_c \\ y_c \end{pmatrix} = \begin{pmatrix} \xi_1 \\ \eta_2 \end{pmatrix}e^{\lambda_1 t} + \begin{pmatrix} \xi_2 \\ \eta_2 \end{pmatrix}e^{\lambda_2 t} \tag{10}$$

From equations (8) and (9) we have the matrix of coefficients as

$$T = \begin{pmatrix} -a_3 & -a_2\bar{x} \\ b_1 & -b_2 \end{pmatrix} \tag{11}$$

The eigen-values λ_1 and λ_2 of matrix T are got by solving for λ in the determinantal equation

$$\begin{vmatrix} -a_3 - \lambda & -a_2\bar{x} \\ b_1 & -b_2 - \lambda \end{vmatrix} = 0.$$

Hence, we have

$$\lambda_{1,2} = \frac{1}{2}\left[-(a_3 + b_2) \pm \left\{(a_3 + b_2)^2 - 4(a_3b_2 + a_2b_1\bar{x})\right\}^{\frac{1}{2}} \right] \tag{12}$$

We must find the particular solutions for the equations in terms of $z(t)$ and $\omega(t)$ respectively. Let these particular solutions be denoted by

$$\begin{pmatrix} x_z \\ y_z \end{pmatrix} and \begin{pmatrix} x_w \\ y_w \end{pmatrix}$$

Thus, for z (t), we solve to get the particular solution as:

$$\begin{pmatrix} x_z \\ y_z \end{pmatrix} = \frac{1}{D}\begin{pmatrix} a_1Q(b_2 - k) \\ a_1b_1Q \end{pmatrix}e^{-k(t-t_0)} \tag{13}$$

$$\text{where} \quad D = k^2 - (a_3 + b_3)k + a_3b_2 + a_2b_1\bar{x}.$$

For w(t), we also solve to get the particular solution as

$$\begin{pmatrix} x_w \\ y_w \end{pmatrix} = \frac{1}{m}\begin{pmatrix} -a_2\bar{x} \\ a_3 \end{pmatrix}\gamma t + \begin{pmatrix} \dfrac{a_2\bar{x}\gamma(b_2a_3 + a_3^2)}{a_3m^2} - \dfrac{a_2\bar{x}\delta}{m} \\ \dfrac{\delta a_3}{m} - \dfrac{\gamma}{m}(a_3^2 - a_2b_1\bar{x}) \end{pmatrix} \tag{14}$$

$$\text{where } m = a_3b_2 + a_2b_1\bar{x}$$

In general therefore, the solution to the equation is

When equations (10),(13) and (14) are substituted into equation (15) we have

$$x = \varepsilon_1 e^{\lambda_1 t} + \varepsilon_2 e^{\lambda_2 t} + a_1 Q \frac{(b_2 - k)e^{-k(t-t_0)}}{z} - b_3 \frac{(a_2 \bar{x} \eta)}{m}$$

$$+ \frac{b_3 a_2 \bar{x} \gamma (b_2 a_3 + a_3^2)}{a_3 m^2} - \frac{b_3 a_2 \bar{x} \delta}{m}$$

$$y = -\frac{(\lambda_1 + a_3)\varepsilon_1 e^{\lambda_1 t}}{a_2 \bar{x}} - \frac{(\lambda_2 + a_3)\varepsilon_2 e^{\lambda_2 t}}{a_2 \bar{x}} + \frac{a_1 b_1 Q e^{-k(t-t_0)}}{z}$$

$$+ \frac{b_3 a_3 \eta}{m} + \frac{b_3 \delta a_3}{m} - \frac{b_3 \gamma (a_3^2 - a_2 b_1 \bar{x})}{m^2}$$

where $\quad z = k^2 - (b_2 + a_3)k + a_3 b_3 + a_2 b_1 \bar{x}$

$$m = b_2 a_3 + a_2 b_1 \bar{x}$$

$$\lambda_1 = 0.5\left[-(a_3 + b_2) + \left\{(a_3 + b_2)^2 - 4(a_3 b_2 + a_2 b_1 \bar{x})\right\}^{\frac{1}{2}} \right]$$

$$\lambda_2 = 0.5\left[-(a_3 + b_2) - \left\{(a_3 + b_2)^2 - 4(a_3 b_2 + a_2 b_1 \bar{x})\right\}^{\frac{1}{2}} \right]$$

$$\varepsilon_1 = \frac{(\lambda_2 + a_3)}{\lambda_1 - \lambda_2} e^{-\lambda_1 t^*} \left[\frac{a_1 Q(b_2 - k)}{z} e^{-k(t^* - t_0)} - \frac{b_2 a_2 \eta^*}{m} + \frac{b_3 a_2 \bar{x} \gamma (b_2 a_3 + a_3^2)}{a_3 m^2} - \frac{b_3 a_2 \bar{x} \delta}{m} - x^* \right]$$

$$+ \frac{(a_2 \bar{x} e^{-\lambda_2 t^*})}{\lambda_1 - \lambda_2} \left[\frac{a_1 b_1 Q e^{-k(t^* - t_0)}}{z} + \frac{b_3 a_3 \eta^*}{m} + \frac{a_3 b_3 \delta}{m} - \frac{b_3 \gamma (a_3^2 - a_2 b_1 \bar{x})}{m^2} - Y^* \right]$$

$$\varepsilon_2 = \frac{\lambda_2 + a_3}{\lambda_2 - \lambda_1} e^{-\lambda_1 t^*} \left[\frac{a_1 Q(b_2 - k)}{z} e^{-k(t^* - t_0)} - \frac{b_3 a_2 \bar{x} \eta^*}{m} + \frac{b_3 a_2 \bar{x} \gamma (b_2 a_3 + a_3^2)}{a_3 m^2} - \frac{b_3 a_2 \bar{x} \delta}{m} - x^* \right]$$

$$+ \frac{a_2 \bar{x} e^{-\lambda_2 t^*}}{\lambda_2 - \lambda_1} \left[\frac{a_1 b_1 Q e^{-k(t^* - t_0)}}{z} + \frac{b_3 a_3 \eta^*}{m} + \frac{a_3 b_3 \delta}{m} - \frac{b_3 \gamma (a_3^2 - a_2 b_1 \bar{x})}{m^2} - Y^* \right]$$

Here, t^* represents the time of interest and can assume various values as we may desire such as $t^* = t_0$ which in this case will mean wishing to know what happens to the glucose and insulin levels at the beginning of the experiment denoted by t_0. The essence of the time t^* other than t_0 is that ε_1 and ε_2 are to be determined at times other than t_0 most especially as we now have insulin infusion to determine the plasma glucose and insulin levels. Recall from the expression for the $\omega(t)$ that insulin has a $t_{\frac{1}{2}}$ value that presents different glucose response to the levels of the insulin at such a time. The x^* and y^* stands for the amount of glucose and insulin in the plasma at such a time t^* respectively. The change in x^* and y^* have the same importance as stated in the case of t^*.

ANALYSIS

In the analysis here, we wish to see what happens for a case where the pancreatic insulin release varies. By this, it can be likened to looking at the blood glucose/insulin levels of diabetic patients of different levels of severity that are being fed similarly with similar insulin infusion. It can also be likened to a diabetic patient whose insulin release is not steady but varies at different times within the same period of feeding. Theoretically, we know that if two patients of different levels of severity are fed with the same quantity of food (same glucose worth) and treated with equal quantity of insulin; they will present reactions to this and will have different levels of glucose/insulin, differing clearance time of the glucose etc.

Using the model and the resulting solution, we tried to replicate this result. In figure (1), we considered a case where b_2, b_3, a_2 and a_3 are constant while b_1 varies. The values of a_2, a_3, b_2, b_3 are given: From the graph, we can see that for b_1 = 0.05, 0.1, 0.2 and 0.25, we can see that both the glucose levels and the clearance time varied. For b_1 = 0.25,

Fig. 1
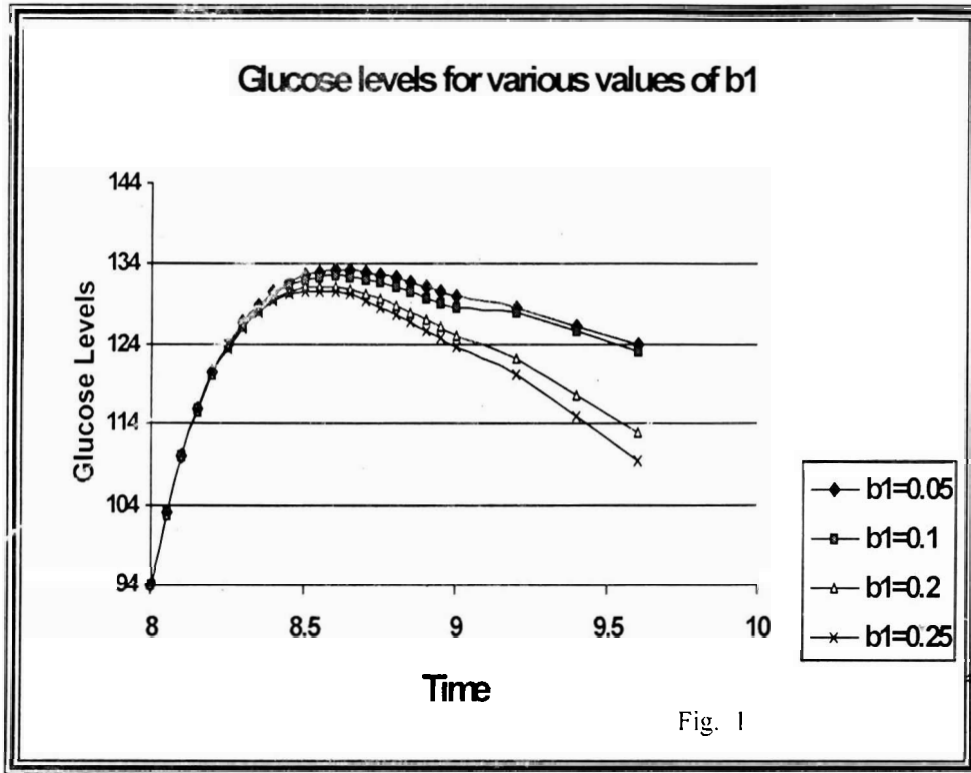
meaning greater pancreatic response to presence of glucose, the glucose level in the blood is lower than the case where b_1 = 0.05. This is because greater response of the pancreas means more release of insulin to the blood and therefore more interaction of the glucose with the insulin. This greater interaction means greater reduction in the quantity of glucose in the blood by conversion into glycogen. The converse is the case in the case of b_1 = 0.05. We can equally see that the clearance time of the entire glucose from the blood is larger in value for the case of b_1 =0.05 than in b_1 = 0.25 because less quantity of insulin is in the blood and thus less interaction with glucose which subsequently leads to longer time of clearance.
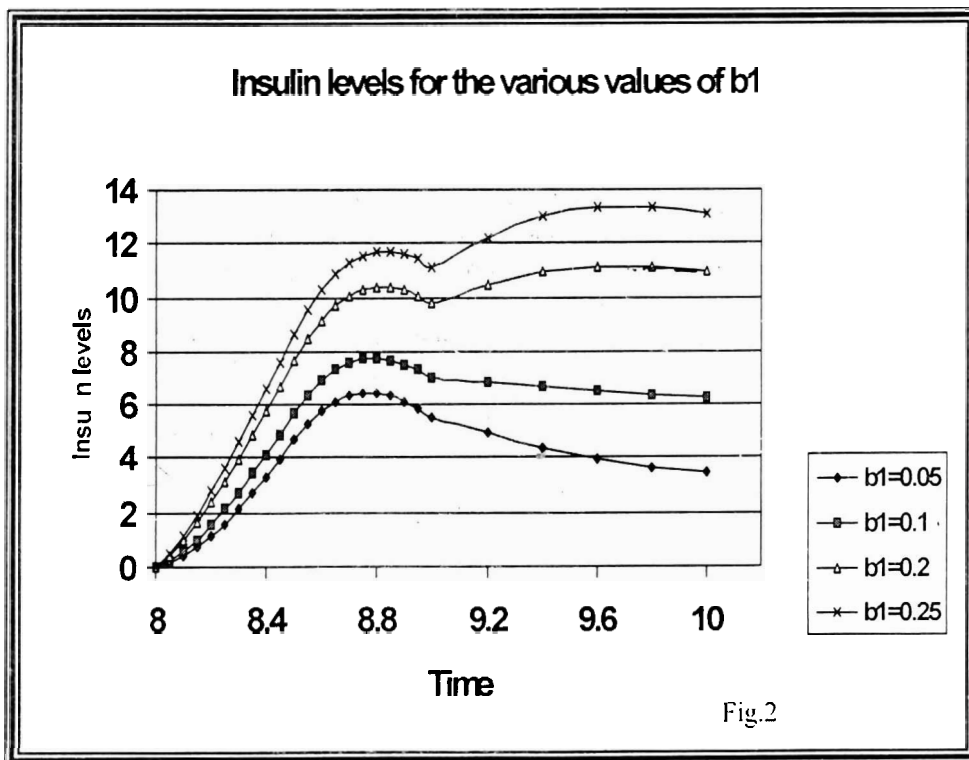
Fig.2

In fig. (2), we show the corresponding insulin level in the blood for the value of b_1 and a_2, a_2, b_2, b_3 as used above. We can see from this graph that for $b_1 > 0.1$, the resulting curves became crooked. What this means is that at this level of diabetes, the pancreas has the capacity to produce insulin and this capacity has to be respected in trying to treat such diabetic patient by insulin infusion. Because of the infused insulin the pancreas insulin release is inhibited until this infused one is exhausted and the pancreas will then start to release insulin because of the demand for more insulin due to the level of excess glucose in the blood that is not yet converted.

The biological implication of varied pancreatic response to glucose level in the blood is that we will not be sure of the state of health of the patient. If enough quantity of food is not taken by such a patient and insulin is infused, such a patient might suffer hypoglycemia as the subsequent released insulin will reduce the blood glucose level to such a low level. Therefore, we may conclude that for such a patient, it will be very difficult to control the blood glucose level since the insulin release and thus its level in the blood cannot be correctly predicted. Even the quantity of the insulin to be infused cannot also be correctly measured. Pancreatic varied insulin release should therefore be considered and handled with all sense of seriousness wherever and whenever it is noticed in any patient

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