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MATHEMATICAL MODELLING APPROACH TO THE TREATMENT OF INSULIN-DEPENDENT DIABETES DISEASE

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ABSTRACT

Medical scientists have various ways of handling cases of insulin-dependent diabetes diseases of which one of the most popularly used methods is carrying out experiments on the patient. However, each time a case is presented, the need for fresh experiment to determine the treatment procedure will arise. To therefore reduce the time in experimentation as well as to save life of the patient by using accurate information of the patient's state of health, the need for mathematical model arises. A mathematical model that can be used to estimate the level of the plasma insulin and glucose levels at all times is presented. The required insulin dose to be given to the patient so as to correct the disease with the subsequent doses of glucose intake without necessarily arousing the disease again is also determined using this model.

The effect of the pancreatic release of the insulin and the peripheral response of the cells to the available insulin were demonstrated. Also it was shown that the reduction in body cell usage of plasma glucose results mainly to the increase in time of clearance of glucose in the blood plasma. Equally demonstrated is the consequence of improper diagnosis of the level of severity of the disease before recommending certain dose of the insulin to be given to the patient as a corrective measure. Solutions to the modeled equations were obtained by linearising the non-linear equations and then solving analytically.

Keyword: Mathematical modelling, Treatment of Diabetes Disease.

INTRODUCTION

Insulin-dependent diabetes mellitus is a disease caused by low plasma insulin concentration resulting in high plasma glucose concentration. This high plasma glucose concentration causes Osmotic diuresis in the Kidney, loss of glucose in urine, excessive urination and thirst, excessive hunger and weight loss, Vallence-Owen (1975), Ellenberg and Rifkin (1983). The low concentration of insulin in the plasma affects the amount of glucose that enters the cells. The insulin binding membrane proteins, which are found evenly distributed at the plasma membrane surface of the cells, mainly inhibit glucose transport into the cells under low physiological levels of insulin, Czech and Massagne (1982), Butte (1992). Insulin therefore functions primarily to aggregate this inhibitory system. Clinically, it has been known that the simplest method for the control and treatment of this disease is by insulin infusion/administration into the patient.

It is this clinical method of control and or treatment that is demonstrated by use of mathematical models. A mathematical model that determines the level of glucose and insulin in the plasma at all times is built and solved by analytical approach after linearising, rather than the numerical approach used by many authors, Mbah (1998), Mbah (2000). The resulting solutions are used in the subsequent analysis and prediction of the possible consequences of wrong clinical approach to treatment of the disease. The effect of the doses of the insulin administered to the patient is demonstrated and it is shown that the dose has to be a function of the level of severity of the disease. In the same way, the dose also determines the pattern of feeding and even the quantity of food (in terms of glucose value) to be taken, Townsend (1980). The severity of the disease is known by carrying out accurate diagnostic work on the patient. It has also to be said that the severity report is method-dependent as well as the type of blood sample used. Sometimes even the location of the part from where the blood sample is drawn for the diagnosis contributes to the glucose concentration value, Vallence-Owen (1975).

THE MATHEMATICAL MODEL

Glucose is a product of digestion of carbohydrates in the alimentary canal. It readily gets absorbed into the blood from where it diffuses into the extra-cellular fluid. Much of the glucose absorbed is usually

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taken to the liver where the storage of the excess glucose takes place. The insulin, which is produced in the pancreas, is also taken to this liver to enhance the storage of the excess glucose.

The glucose in the extra-cellular fluid is then taken to the plasma membrane of the cells by mediated-facilitated transport means. In the absence of insulin, only very low quantity of this glucose gets into the cell since even though glucose transporters, which are carrier proteins, are responsible for glucose entry into the cell, some of them are non-insulin responsive. About six of such glucose transporters have been identified, **Bell et al., (1989).** Since low plasma insulin level affects the amount of glucose that enters the cells, the model is expected to show how pancreatic response to glucose stimulation leads to the low plasma insulin level. It will also show how this low plasma insulin level contributes to the high plasma glucose level. Also the low plasma insulin level affects the plasma membrane response to glucose and this action is expressed mathematically as an interaction between the plasma glucose and insulin. **Porte and Pupo (1969), Grodsky (1972),** have shown that this interaction is non-linear in nature since the rate of increase in insulin level to plasma glucose increase is not linear. This relationship was further demonstrated by **Track (1977)** as he showed that when the pancreas is stimulated with glucose, the stored insulin in the granules are released while further production of insulin continues by the continued production and conversion of pro-insulin. This pro-insulin gets converted to insulin and for a prolonged stimulation, the rate of production and or conversion to insulin gets reduced. This is because the β-cells have some maximal capacity of pro-insulin production and or conversion to insulin for a given period of stimulation. In this model, it is shown that the cells utilization of glucose for energy production affect the plasma glucose level so that failure of the cells to use the glucose contributes to the high plasma glucose concentration. In designing the model, **Mbah (1998),** the effect of the basal level of glucose to the subsequent glucose and insulin levels in the plasma was taken into account. Therefore, considering an insulin-dependent diabetic patient who feeds well and with twice insulin administration at breakfast and dinner times, a comparison of the clinical treatment analysis and mathematical analysis are made for the same level of severity of the disease.

The mathematical models that are used in the determination of the plasma glucose and insulin concentrations at all times are given as:

$$\frac{dX}{dt} = a_1 Q e^{-k(t-t)} - a_2 XY - a_3 X \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

$$\frac{dY}{dt} = b_1 X - b_2 Y + b_3 \omega(t) \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

where

$$\omega(t) = \begin{cases} \dfrac{\omega(t-t)}{t-t}, & t < t \leq t \\ -\dfrac{\omega(t-(2t-t))}{t-t}, & t < t \leq 2t-t \\ 0 \quad \text{elsewhere.} \end{cases}$$

$$\omega(t) = \gamma t + \delta \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

where γ and δ are constants.

Here X is the glucose level, Y is the insulin level, Q is the food quantity(in terms of glucos concentration), $\omega(t)$ is the dose of insulin administered while $a_1, a_2, a_3, b_1, b_2, b_3$ and k are all constants, measures the half-life of the administered insulin while t_0 is the initial time of the study or the time th insulin was administered.

SOLUTION

The method of solution of these equations was shown in the work of Mbah (1998) and Mbah (2000) where the non-linear term was linearised first by writing XY as XY where X = X(t), the plasma glucos

level at the beginning of the study. We now therefore re-write the model equations as:

$$\frac{dX}{dt} = a_1 Q e^{-k(t-t)} - a_2 XY - a_3 X \qquad \text{.......... (4)}$$

$$\frac{dY}{dt} = b_1 X - b_2 Y + \gamma t + \delta \qquad \text{.......... (5)}$$

In equations (4) and (5), a_2 measures the rate of interaction of the glucose and the insulin while b_1 measures the pancreatic response in insulin release due to glucose stimulation, a_3 measures the rate of the body cell utilization of the glucose and b_2 measures the rate of insulin degradation. We solved these equations simultaneously by finding the complementary function and the particular solution to get:

$$X = \xi_1 e^{\lambda t} + \xi_2 e^{\lambda t} + \frac{a_1 Q}{Z}(b_2 - k) e^{-k(t-t)} - \frac{a_2 X\gamma t}{m} + \frac{a_2 X\gamma(b_2 a_3 + a_3^2)}{a_3 m^2} - \frac{a_2 X\delta}{m} \qquad \text{.......... (6)}$$

$$Y = -\frac{\lambda_1 + a_3}{a_2 X}\xi_1 e^{\lambda t} - \frac{\lambda_2 + a_3}{a_2 X}\xi_2 e^{\lambda t} + \frac{a_1 b_1 Q}{Z} e^{-k(t-t)} + \frac{a_3 \gamma t}{m} + \frac{\delta a_3}{m} - \frac{\gamma}{m^2}(a_3^2 - a_2 b_1 X) \qquad \text{......... (7)}$$

where $\lambda_{1,2} = \frac{-(a_3 + b_2) \pm \{(a_3 + b_2)^2 - 4(a_3 b_2 + a_2 b_1 X)\}^{1/2}}{2}$

$m = a_3 b_2 + a_2 b_1 X$

$S = k^2 - (a_3 + b_2)k + a_3 b_2 + a_2 b_1 X$

$$\xi_1 = \left(\frac{\lambda_2 + a_3}{\lambda_1 - \lambda_2}\right) e^{-\lambda t}\left\{\frac{a_1 Q}{S}(b_2 - k) e^{-k(t-t)} - \frac{a_2 X\gamma t^*}{m} + \frac{a_2 X\gamma(b_2 a_3 + a_3^2)}{a_3 m^2} - \frac{a_2 X\delta}{m} - X^*\right\} +$$
$$\left(\frac{a_2 X}{\lambda_1 - \lambda_2}\right) e^{-\lambda t}\left\{\frac{a_1 b_1 Q}{S} e^{-k(t-t)} + \frac{a_3 \gamma t^*}{m} + \frac{\delta a_3}{m} - \frac{\gamma}{m^2}(a_3^2 - a_2 b_1 X) - Y^*\right\} \qquad \text{.......... (8)}$$

$$\xi_2 = \left(\frac{\lambda_1 + a_3}{\lambda_2 - \lambda_1}\right) e^{-\lambda t}\left\{\frac{a_1 Q}{S}(b_2 - k) e^{-k(t-t)} - \frac{a_2 X\gamma t^*}{m} + \frac{a_2 X\gamma(b_2 a_3 + a_3^2)}{a_3 m^2} - \frac{a_2 X\delta}{m} - X^*\right\} +$$
$$\left(\frac{a_2 X}{\lambda_2 - \lambda_1}\right) e^{-\lambda t}\left\{\frac{a_1 b_1 Q}{S} e^{-k(t-t)} + \frac{a_3 \gamma t^*}{m} + \frac{\delta a_3}{m} - \frac{\gamma}{m^2}(a_3^2 - a_2 b_1 X) - Y^*\right\} \qquad \text{.......... (9)}$$

The time t^* represents the times of interest in the course of this analysis such as the initial time t_0. At each time t^*, we have corresponding values of X and Y which we denote as X^* and Y^*. Also ξ_1 and ξ_2 are determined at such times with the values of X^* and Y^* being used.

ANALYSIS

In a normal person, the values of these constants are higher than what obtains in a diabetic case. For a norm al person, we have the values for some of these constants as:
$a_1 = 4.0$, $a_2 = 0.05$, $a_3 = 0.03$, $b_1 = 0.5$, $b_2 = 2.0$ and $b_3 = 1.0$. Since we are considering a diabetic patient whose liver is not functioning properly, we expect these constants to have smaller values so that we may choose these constants as: $a_2 = 0.03$, $a_3 = 0.03$, $b_1 = 0.05$ & 0.10, while retaining others as usual since they are not affected by liver's function. Various forms of analysis are considered by varying the constants to see their effect on the glucose and insulin concentrations in the blood. Also

considered is the treatment of this insulin-dependent diabetes by insulin administration. The effect of various doses of this infused insulin is equally considered. The effect of the quantity of food taken for the given dose of insulin, the pattern of intake of food and the timing of the insulin infusion into the blood are clearly demonstrated. Since the site of injection of the insulin has effect on the quantity of insulin that eventually gets into the blood, this has been taken care of in the model in the form of expression for $\omega(t)$. It may however be stated that unless by intra-venous injection, the amount of this injection that eventually get into the blood is also dependent on the level of severity of the diabetes.

DISCUSSION

Substituting the given values of the constants into the solutions we obtain the following results We found that decrease in the pancreatic response to glucose stimulation (denoted by reduction in the value of b_1) results to low plasma insulin level. This result goes to confirm in the first case that decreased response of the pancreas to glucose stimulation can lead to diabetes. As known below, we therefore agree that this equally result to low rate of glucose conversion to glycogen. We show this in form of a graph as fig:1 :

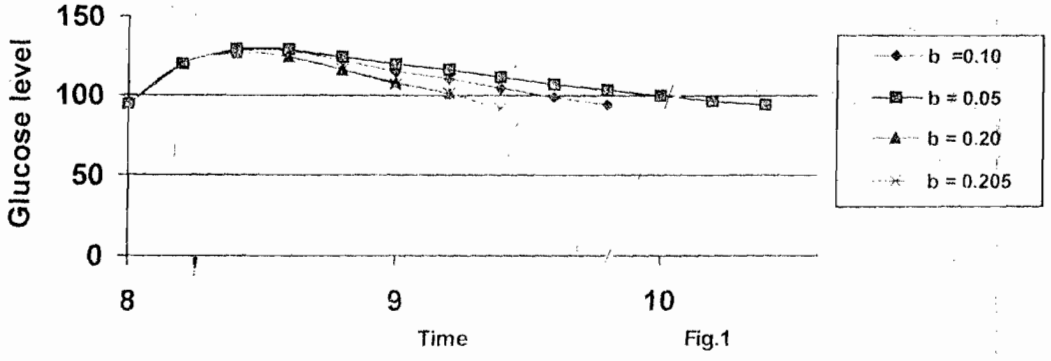

Fig.1

Effect of variation of b on the blood glucose level

We can show the corresponding insulin levels for the various levels of b_1 as:

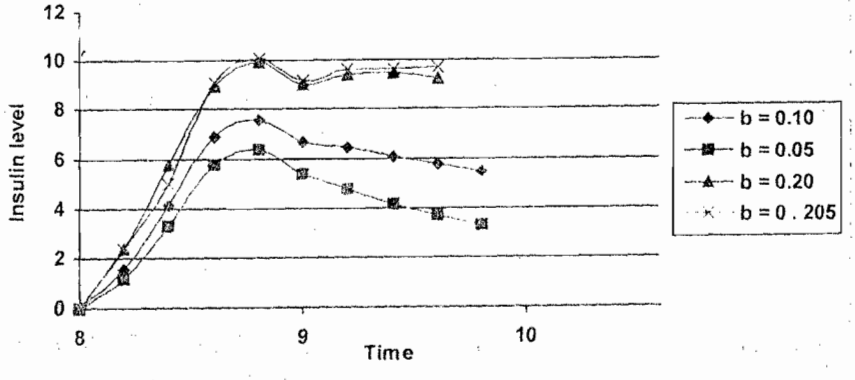

Fig.2 Effect of variation of b on the blood insulin levels

From our analysis also we found that reduction in the binding rate of the insulin with the receptor proteins at the cell membranes as well as the reduction in the rate of release of the insulin by the pancreas leads to an increase in the plasma glucose level. We equally noticed that when there is high plasma glucose concentration but with reduced binding rate of the insulin with the receptor proteins at the cell membrane, then the length of time taken to reduce the glucose and even the insulin to the basal levels will increase. As much as we believe that the binding action of the insulin on the cell affects the plasma glucose level, this action is found to affect largely the length of time required to reduce the plasma glucose level to the basal level. From this therefore, we conclude that what actually determines the plasma glucose level in an insulin-dependent diabetic patient is the response of the pancreas to glucose

stimulation. Thus the severity of the diabetes in a patient is a function of the response of the pancreas to glucose stimulation. We show this finding in the form of graph as in fig.3 :

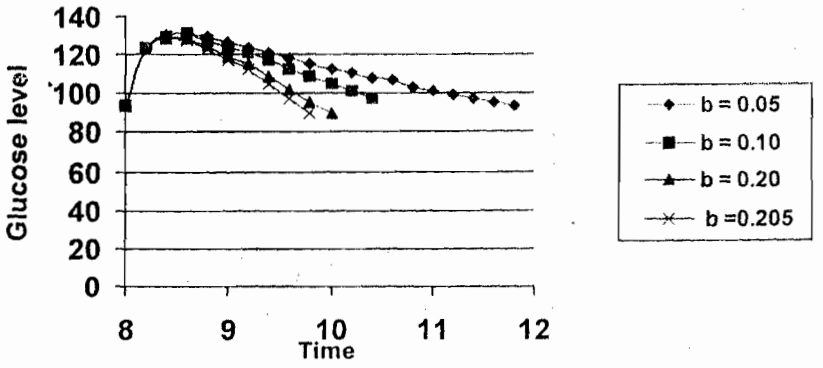

Fig. 3 Effect of reduced response of the pancreas to glucose stimulation and insulin respose to the receptor proteins on the blood glucose level

The effect of insulin infusion when there is reduced response of the pancreas to glucose stimulation along with varied insulin binding rate on the blood insulin level is that there is the possibility of having double peak in the insulin concentration. This was found to be possible if correct diagnosis was not carried out to determine the severity of the disease before administering the insulin. This claim is supported by fact that for a case where there is severe diabetes, insulin infusion did not lead to double peaked concentration of the insulin in the blood. We show this result as in fig. 4:

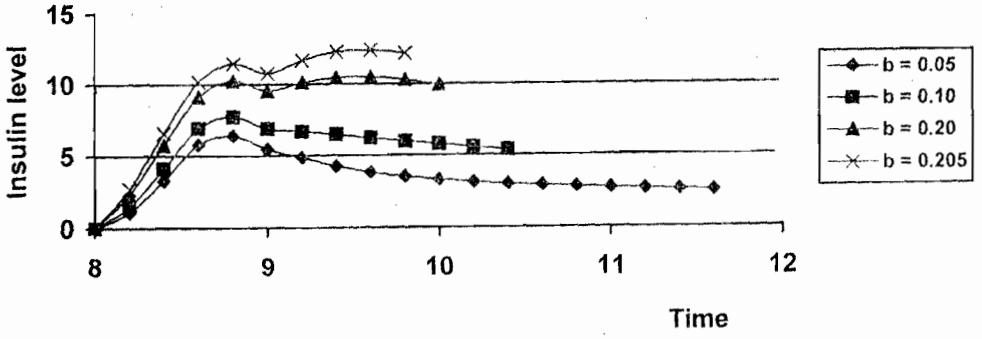

Fig. 4 Effect of varied b and a on the blood insulin level

On the effect of the cell utilization of glucose on the blood glucose level, it was found that this affects the blood glucose level both for the diabetic and the non-diabetic patient. However, cell utilization of glucose has no appreciable effect on the blood insulin level. Having convinced ourselves that low presence of insulin in the blood due to poor response of the pancreas to glucose stimulation results to high blood glucose level, we now looked at how this abnormally high glucose level can be corrected. For the disease to be controlled effectively, proper diagnosis has to be conducted to know the level of severity of the disease. After the determination of the level of severity, the first task is to bring down the blood glucose level to the normal level by injecting appropriate doses of the insulin. Following this later will be the maintenance of this level of glucose so that the patient will be healthy by consistent but correctly administering the effective doses of the insulin and the glucose (food). To demonstrate this corrective approach, moderately and severely diabetic patients whose blood (plasma) glucose levels were 175mg/100cc and 200mg/100cc were considered. At this we took $a_2 = 0.03$ and $b_1 = 0.05$. We administered 50mg of glucose (food) at about 8:00 hours with 20 units of the insulin injected at the same time to the patient. It was seen that the blood glucose level was normal until 13:00 hours and a lunch of another 50mg was taken but with no further injection of the insulin. At about

17:00 hours, the plasma glucose level started plunging below the basal level. A snack worth 10mg of glucose was taken to avoid this situation and to sustain the patient till dinner. We had to do this because of the possibility of the patient suffering Hypoglycemia, which is a disease associated with very low glucose level in the blood. At dinner by 18:00 hours, a heavier meal of about 100mg of glucose was taken but with lower dose of insulin injected. The higher dose of the glucose and lower dose of insulin injected was to take care of the length of time involved, from 18:00 hours to 8:00 hours the following morning. The dose of insulin given now is half of the former or even less. However, since the interval is quite large, and insulin dose was administered, we require another meal of 50mg – 100mg worth of glucose to be taken at about 22:00 hours but with no further insulin injection. This is shown in fig. 5 as:

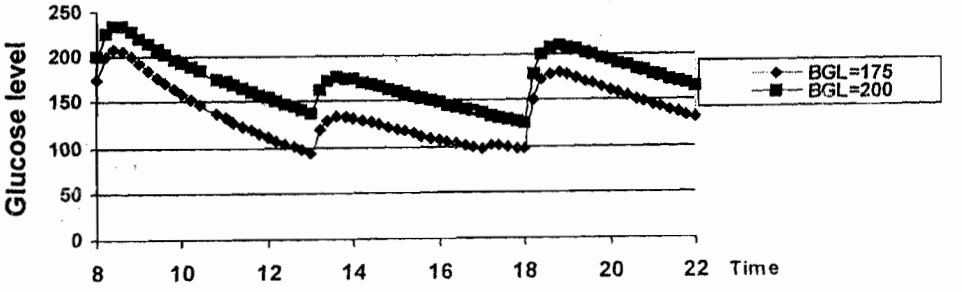

Fig. 5 Comparison of blood glucose levels (BGL) for two levels of diabetisms but with the same pattern of feeding and insulin injection.

Here we compared the treatment of two diabetic patients with different levels of severity of the disease but given the same quantity of food and insulin injection. From this fig.5, we can see that the level of severity of the disease must be known if we wish to correctly and effectively control this disease. To now maintain the blood glucose level as if the patient is normal, it was seen that if the patient is such that his pancreatic response to glucose stimulation is denoted by $b_1 = 0.10$, then at 8:00 hours, he should be given 50mg worth of glucose with insulin dose of 20 units injected at the same time. To avoid plunging of the glucose level, the patient should always take a snack of 25mg worth of glucose at 100:00 hours. This sustains him till at least 12:00 hours when he can take his lunch of about 50mg worth of glucose. During dinner he should, he should take 100mg worth of glucose but with another dose of insulin injection of about10 units. Because of this insulin injection, the patient needs another meal, 50mg worth of glucose, at about 22:00 hours. This will sustain the blood glucose level of the patient to at least the basal level till the following morning when he will take his breakfast. We demonstrate this by the use of fig. 6 as:

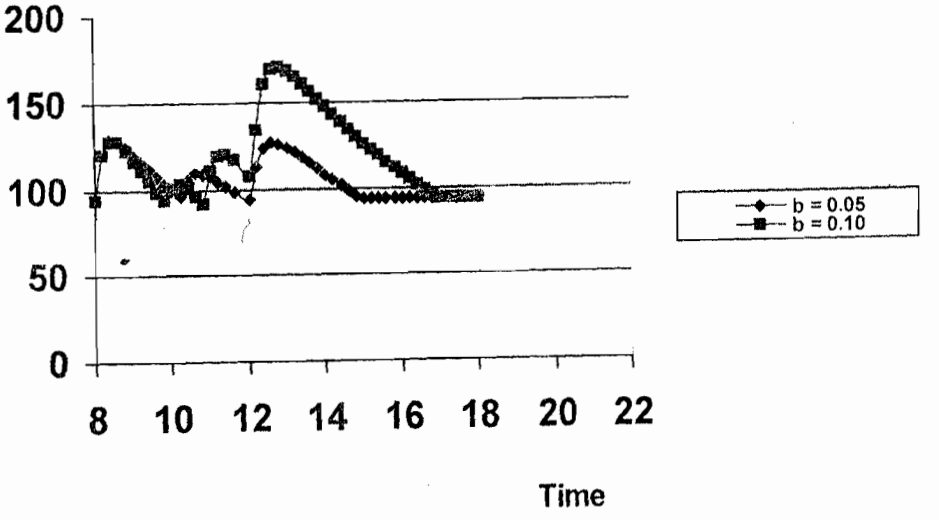

Fig 6. **Comparison of blood glucose levels (BGL) for two levels of diabetisms but with the different pattern of feeding and insulin injection after the disease has been brought under control.**

CONCLUSION

From all these analysis therefore, we can conclude that these models and the procedure discussed can useful if correct diagnosis of the level of severity is carried out. Also, these models and the resulting solutions can be effectively used in controlling diabetes if applied under the conditions it was modeled and applied for the control of the disease as demonstrated.

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