A MATHEMATICAL STUDY ON BEHAVIOR OF EPINEPHRINE IN GLUCOSE TOLERANCE TEST

Ashwini M Rao, Associate Professor, Department of Mathematics, Bapuji Institute of Engineering and Technology, Davanagere, Karnataka, India.
Sathisha A B, Assistant Professor, Department of PG Studies in Mathematics, Government Science College, Chitradurga, Karnataka, India.
K S Basavarajappa, Professor, Department of Mathematics, Bapuji Institute of Engineering and Technology, Davanagere, Karnataka, India.

Abstract:

Mathematical modeling on behavior of epinephrine in diabetic patients has been discussed in the paper. Epinephrine is the “fight or flight” hormone that gives a quick boost of extra energy overcome of low blood glucose. When blood glucose levels drop too low, the adrenal glands secrete epinephrine (also called adrenaline), causing the liver to convert stored glycogen to glucose and release it, raising blood glucose levels. Epinephrine also causes many of the symptoms associated with low blood glucose, including rapid heart rate, sweating, and shakiness. The epinephrine response spurs the liver to correct low blood glucose or at least raise blood glucose levels long enough for a person to consume carbohydrates. Our findings suggest that epinephrine is an important contributor to stress-induced hyperglycemia and the susceptibility of diabetics to the adverse metabolic effects of stress. Numerical method is employed to analyze the effect of epinephrine in diabetic patients.

Keywords: Epinephrine, Blood, Glucose, Diabetes, glycogen.

Introduction:

Diabetes is classified into two main categories: Type 1 diabetes, juvenile onset and insulin-dependent, and type 2 diabetes, adult onset and insulin-independent. Complications of the disease may include retinopathy, nephropathy, peripheral neuropathy and blindness. There are many diabetic patients in the world and diabetes mellitus is becoming one of the diseases with respect to the size of the affected population. This motivates many researchers to study the glucose-insulin endocrine regulatory system.

Epinephrine causes a prompt increase in blood glucose concentration in the postabsorptive state. This effect is mediated by a transient increase in hepatic glucose production and an inhibition of glucose disposal by insulin-dependent tissues. Epinephrine augments hepatic glucose production by stimulating glycogenolysis and gluconeogenesis. Although its effect on glycogenolysis rapidly wanes, hyperglycemia continues because the effects of epinephrine on gluconeogenesis and glucose disposal persist. Epinephrine-induced hyperglycemia is markedly accentuated by concomitant elevations of glucagon and cortisol or in patients with diabetes. In both cases, the effect of epinephrine on hepatic glucose production is converted from a transient to a sustained response, thereby accounting for the exaggerated hyperglycemia. During glucose feeding, mild elevations of epinephrine that have little effect on fasting glucose levels cause marked glucose intolerance. This exquisite sensitivity to the diabetogenic effects of epinephrine is accounted for by its capacity to interfere with each of the components of the glucoregulatory response, i.e., stimulation of splanchnic and peripheral glucose uptake and suppression of hepatic glucose production. Our findings suggest that epinephrine is an important contributor to stress-induced hyperglycemia and the susceptibility of diabetics to the adverse metabolic effects of stress. The majority of mathematical models were devoted to the dynamics of glucose-insulin, including Intra Venous Glucose Tolerance Test (IVGTT), Oral Glucose Tolerance Test (OGTT) and Frequently Sampled Intra Venous Glucose Tolerance Test (FSIVGTT). So far, all the existing models were based on two variables only: glucose and insulin. In the GTT, an individual comes to the hospital after an overnight fast and is given a large dose of glucose (sugar in the form in which it

usually appears in the blood-stream). During the next three to five hours several measurements are made on the concentration of glucose in the patient's blood and these measurements are used in the diagnosis of diabetes Mellitus. Important effects of epinephrine includes increased glucose production from glycogen breakdown, increased glucose production from lactate and amino acids, increased fat mobilization by stimulation of hormone sensitive lipase and small net stimulation of insulin secretion from pancreatic cells

Over the past years, mathematics has been used to understand and predict the spread of diseases, relating important public health questions to basic infection parameters. Diabetes Mellitus is a disease which is characterized by too high sugar levels in the blood and urine. It is usually diagnosed by means of a glucose tolerance test (GTT). Suad Efendic et al [1] characterised major impairment of insulin release and another with marked decrease in insulin sensitivity as a principal derangement. Mary M. Tai [2] determined total area under a curve with precision, calculated area with varied shapes that may or may not intercept on one or both *X/Y* axes, estimated total area under a curve plotted against varied time intervals (abscissas), whereas other formulas only allow the same time interval and compared total areas of metabolic curves produced by different studies. Andrea De Gaetano et al [3] concluded that a global unified model is both theoretically desirable and practically usable, and that any such model ought to undergo formal analysis to establish its appropriateness and to exclude conflicts with accepted physiological notions. Jiaxu Li et al [4] generalized the dynamical model to allow more general functions and an alternative way of incorporating time delay. Bo Ahren et al [5] established the hyperbolic relationship between insulin sensitivity and insulin secretion in humans. F. Di Nardo et al [6] appears a potentially useful tool to estimate insulin sensitivity and the rate constant of systemic glucose absorption from reduced oral glucose tests. A Boutayeb and A Chetouani [7] proposed a global overview of mathematical models dealing with many aspects of diabetes and using various tools. The review includes, side by side, models which are simple and/or comprehensive; deterministic and/or stochastic; continuous and/or discrete; using ordinary differential equations, partial differential equations, optimal control theory, integral equations, matrix analysis and computer algorithms. Yesenia Cruz Rosado [8] we develop a graphical user interface to facilitate the entering of the patient's data and the visualization of the results. Christian Anderwald et al [9] created three novel methods including a new mathematical model, which account for the main processes to control blood glucose during the OGTT. B Kwach et al [10] presents a new mathematical model for blood glucose regulatory system which includes epinephrine as a third variable in the form y'=AY. Sandhya et al [11] proposed a new mathematical model for the study of diabetes mellitus and the model takes into account all plasma glucose concentration, generalized insulin and plasma insulin concentration. I Ajmera et al [12] discussed contributions to the diabetes modeling field over the past five decades, highlighting the areas where more focused research is required. Jamal Hussain et al [13] presented a mathematical model of diabetes mellitus, which is a metabolic disease concerned with the regulation process of glucose in the body by the pancreatic insulin. Neeru Gupta et al [14] observed that prevalence rate of type 2 diabetes mellitus in rural areas can be estimated by using non-invasive tests such as Urine Benedict's test that provides same estimated prevalence as true prevalence measured by blood test by using a mathematical formula. Usha Rani et al [15] aimed of study can be concluded that the optimal value of $g_0, \beta, w_0, \alpha, \delta$ can be calculated in Blood Glucose regulatory system to a Glucose Tolerance Test. Venkatesha et al [16] presents a model for detecting diabetes Mellitus in the blood described by equation and epinephrine has been successfully incorporated as a third variable. Sukriti Sudhakar [17] showed the difference of glucose-insulin regulatory system, between a normal person and diabetic person and the glucose concentration of diabetic patient does not come down after a certain time which shows the evidence that the person suffer from diabetes. Dr. P.K. Dwivedi et al [18] presented a new Mathematical model to detect the diabetes in human being and their statistical Analysis. The model takes into account all plasma glucose concentration, generalized insulin and plasma insulin concentration. Nelida Elizabeth Lopez-Palau et al [19] concluded that the model emulates with acceptable precision what is reported in

the clinical data for PGIGI, and OGTT. However, this model considers only the carbohydrate metabolism but not fat, and protein metabolism. Wellars Banzi [20] compared our results with results obtained from a simulation of the mathematical model for healthy subjects and proposed mathematical model allows further investigation of the dynamic behavior of glucose, insulin, glucagon, stored insulin, and labile insulin in different organs for type 2 diabetic patients.

In this paper, we present how ephinephrine secretion is important during metabolism in diabetic patients. Ephinephrine relaxes the smooth muscle of bronchi and iris and is a histamine antagonist, rendering it useful in treating the manifestations of allergic reactions and associated conditions. Numerical technique is employed to study the nature of ephinephrine during the metabolism in diabetic patients.

Formulation:

If G is taken to be excess glucose concentration and H is excess insulin concentration at time t, then at equilibrium, $G = H = 0$; positive value of G or H corresponds to concentrations greater than the equilibrium values while negative values corresponds to concentrations less than equilibrium values. If either Gor $H$is a non-zero value then the body tries to restore the equilibrium. It is assumed that the rate of change of these quantities depend only on the values of $G$and H. If there is an internal rate at which the blood glucose concentration is being increased, epinephrine is included as a separate variable in this model of blood glucose regulatory system. It is assumed that there is no recent digestion.
The system of differential equations is:

$$\frac{dG}{dt} = -aG - bH + fE \quad (1)$$

$$\frac{dH}{dt} = cG - dH + kE \quad (2)$$

$$\frac{dE}{dt} = -lG - mH + nE \quad (3)$$

where E represents ephinephrine.
Thus, a, b, c, d, f, k, l, m and n are constants.

Analysis:

Epinephrine has been successfully incorporated as a third variable in this model of blood glucose regulatory system (BGRS). The importance of this third variable lies in its ability to help in conducting a reliable test for detecting diabetes in the blood. This leads to a system of linear homogenous equations, which are expressed in the form $Y' = AY$ and whose solution provides the blood glucose concentrations for diabetics and non-diabetics. This shows that the glucose concentration returns to normal level within a shorter time. The model developed in this study considers internal rate at which the blood glucose concentration is being increased. Future research may take into consideration an external rate at which the blood glucose concentration is being increased.

The model predicts that oscillations occur if there is sufficient diffusion to create adequate concentrations mixing in the reacting layers of the cells. With insufficient such mixing, the oscillations are inhibited. Numerical method is employed to observe the nature of epinephrine secretion in diabetic patients.
The following are the observations obtained.

	$t = 0$	0.5	1	1.5	2	2.5	3
G	26	1.613	-22.774	-8.1635	6.447	1.5875	-3.2721
H	6.8	4.2014	1.6028	1.5918	1.58097	1.9287	2.2765
E	3.0634	-70381	-17.8245	-2.756	12.3116	7.798	3.2846

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Results and discussion:

The results show that the ephnephrine produces an increase in blood sugar and increases glycogenolysis in the liver. Through its action on adrenergic receptors, ephinephrine leads to bronchial smooth muscle relaxation that helps to relieve bronchospasm, wheezing and dyspinea that may occur during anaphylasis. Our study shows that the glucose concentration returns to normal level within a shorter time. This study considered an internal rate at which the blood glucose concentration is being increased. Epinephrine causes a prompt increase in blood glucose concentration in the postabsorptive state. This effect is mediated by a transient increase in hepatic glucose production and an inhibition of glucose disposal by insulin-dependent tissues. Epinephrine augments hepatic glucose production by stimulating glycogenolysis and gluconeogenesis. Although its effect on glycogenolysis rapidly wanes, hyperglycemia continues because the effects of epinephrine on gluconeogenesis and glucose disposal persist. Epinephrine-induced hyperglycemia is markedly accentuated by concomitant elevations of glucagon and cortisol or in patients with diabetes. In both cases, the effect of epinephrine on hepatic glucose production is converted from a transient to a sustained response, thereby accounting for the exaggerated hyperglycemia. During glucose feeding, mild elevations of epinephrine that have little effect on fasting glucose levels cause marked glucose intolerance. Our findings suggest that epinephrine is an important contributor to stress-induced hyperglycemia and the susceptibility of diabetics to the adverse metabolic effects of stress.

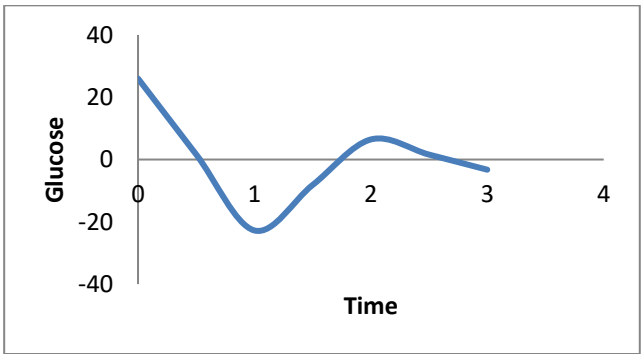

Fig 1: Glucose concentration v/s Time

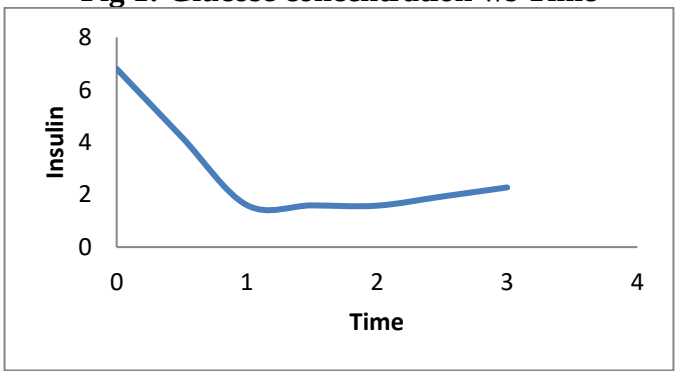

Fig 2: Insulin concentration v/s Time

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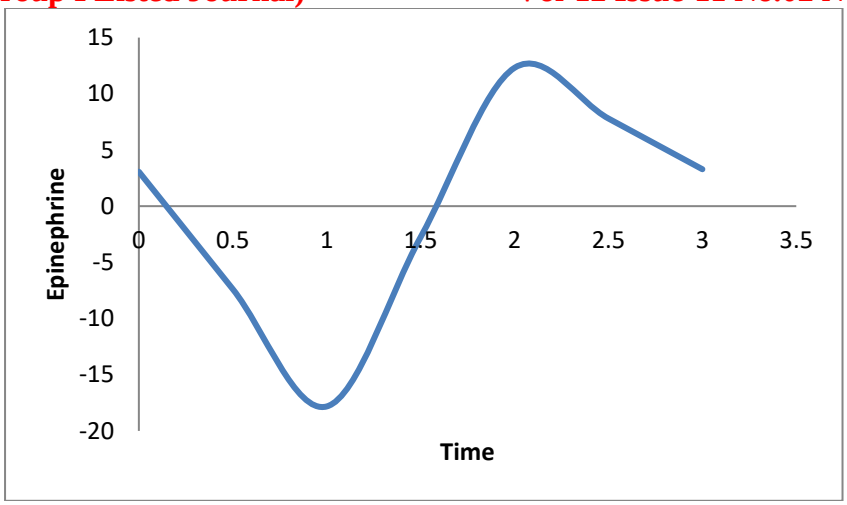

Fig 3: Ephinephrine concentration v/s Time

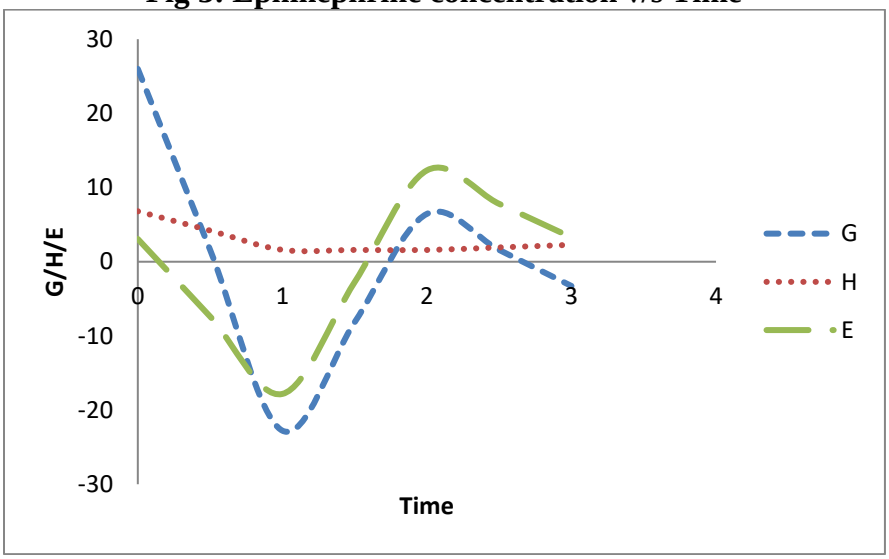

Fig 4: G/H/E concentration v/s Time

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