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DYNAMICAL SYSTEM FOR GLUCOSE - INSULIN SPACE IN DIFFERENT ORGANS OF DIABETICS

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Abstract. Long persistence of diabetes affect the functioning of major organs of the human body. An attempt has been made to capture the changes in glucose - insulin dynamics of central nervous system, liver and kidney which are severely affected by diabetes through mathematical modeling and simulation. The numerical simulation of the mathematical models explains that decreased volume of glucose and insulin space may be one of the possible reasons behind the prolonged raised glucose level in the central nervous system, liver and kidney of the diabetic people.

Keywords: Central nervous system; liver; kidney; modeling; simulation; diabetes; glucose; insulin.

2010 AMS Subject Classification: 34C60, 34D20, 92B05.

1. Introduction

Globally, as of 2013, an estimated 382 million people have diabetes worldwide, with type 2 diabetes making up about 90 % of the cases [1]. Diabetes overall at least doubles the risk of death [2]. The number of people with diabetes is expected to rise to 592 million by 2035 [3]. The economic costs of diabetes in the United States in 2012 at $ 245 billion [4] and globally was estimated in 2013 at $ 548 billion [5]. Diabetes affects our blood vessels and nerves and therefore can affect any part of the body. Diabetes, if uncontrolled, can affect both the

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nervous system and circulatory system if persists long. As these two systems involved in almost all body functions resulting diabetes leads to many health related complications and sometimes leads to failure of the multiple organs. However, certain organs of our body are affected more than other organs for e.g brain, heart, kidney, liver and pancreas.

It is clinically proved that type 2 diabetes may increase the risk of failure of many major organs in the body, directly and indirectly. The following parts of the body which may be affected by the diabetes depends upon the severity of the disease : eye, heart, kidney, liver, nervous system and the reproduction system. In diabetes, nervous system fails first and later all other systems. It motivates us to find the possible reasons behind the raised glucose concentration in the respective organs whose functioning are impaired by the diabetes.

Diabetes affect the CNS in several ways. Diabetes increases the stroke risk and overdose with insulin or oral intake can permanently damage the brain. Diabetes changes brain transport, blood flow and metabolism [6]. The brain system fails first which puts pressure on the islet system, causing further decomposition in the brain system that ends in type 2 diabetes. The vessels in the brain can also become damaged by hyperglycemia, and there is evidence that this damage contributes to a progressive decline in brain function [7,8]. Frequent exposure to high glucose levels likely diminishes mental capacity, as higher HbA1C levels have been associated with a greater degree of brain shrinkage [9].

Continued excessive sugar levels in the kidney affect the glomeruli, or the blood filtering units of the kidneys. In diabetes, the flow of blood through the kidneys increases and the glomeruli have to work harder resulting the kidneys get larger in size than normal. Diabetes is among the leading causes of kidney failure [10]. Nearly one third of kidney failure patients are diabetics.

Liver plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production and detoxification [11]. Several roles are played by liver like carbohydrate metabolism, formation of glycogen, breakdown of glycogen, synthesis of glucose from certain amino acids and many more. In diabetics, fat is accumulated in the liver resulting excess deposition of fat in the liver and decreased removal of fat increase the size of liver. An enlarged liver and enzyme abnormalities are characteristics of fatty liver. The National Institute of Diabetes and Digestive and kidney disease reports that 10 to 20% of Americans have fatty liver [12].

The whole body models provide very important quantitative information about the glucose - insulin dynamics, since it is important but at the same time remarkably difficult, to measure the physiological changes in the glucose - insulin dynamics at the organ level. Here, for all the three: CNS, kidney and liver, mathematical models have been developed for each organ, to analyze the effect of volume of glucose and insulin space on the glucose - insulin dynamics of diabetic people. The mathematical model is checked for its stability properties, positive and bounded solutions of the system are also discussed in further section of the paper.

It can be concluded from the results obtained from numerical simulation of the mathematical model that decreased volume for glucose and insulin space (plasma and remote compartments) may be one of the major reason for the raised glucose level in type 2 diabetics. Other possible reasons together with the decreased volume of glucose and insulin space for the raised glucose concentration (hyperglycemia) in each organ of the body are discussed at the end of each section.

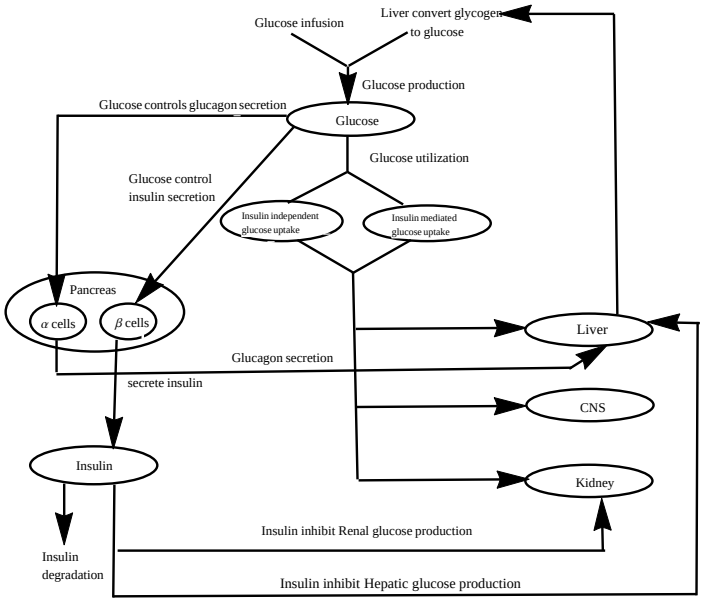


FIGURE 1. Glucose - Insulin dynamics of the human body

2. Model derivation

Insulin and glucose are the two main factors in the glucose - insulin endocrine metabolic regulatory system. The glucose - insulin dynamics of the body is shown graphically in Figure 1. By applying law of conservation of mass, we attempt to model the glucose - insulin dynamics of the organs (CNS, Kidney and Liver) which are severely affected by the long term persistence of diabetes in body. Let G(t) and I(t) are the glucose and insulin concentration at time $t \geq 0$, then

$$\frac{dG}{dt} = \text{Glucose production - Glucose utilization}$$

$$\frac{dI}{dt} = \text{Insulin production - Insulin utilization}$$

On the basis of conservation law, we discuss the mathematical models to capture the physiological changes of the glucose - insulin dynamics in various organs of the body.

3. Mathematical Model

The mathematical model for glucose - insulin dynamics of the whole body [13] is given as :

$$\frac{dG}{dt} = G_{in} - f_2(G(t)) - f_3(G(t))f_4(I(t)) + f_5(I(t)) \tag{1}$$

$$\frac{dI}{dt} = f_1(G(t)) - d_i I(t) \tag{2}$$

with the initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G(t)$ and $I(t)$ represent the glucose concentration and insulin concentration at time t.

- G_{in} is glucose infusion rate.
- $f_1(G(t))$ represents the insulin secretion.
- $f_2(G(t))$ represents the glucose utilization independent of insulin.
- $f_3(G(t))f_4(I(t))$ represents the insulin mediated glucose utilization.
- $f_5(I(t))$ represents the total glucose production.
- d_i is insulin degradation rate.

The functions f_i, i = 1, 2, 3, 4, 5 are given below [13] :

$$f_1(G) = \frac{Rm}{1 + exp((C_1 - G/V_1)/a_1)}$$

$$f_2(G) = U_b(1 - exp(-G/(C_2V_1)))$$

$$f_3(G) = \frac{G}{C_3V_1}$$

$$f_4(I) = U_0 + \frac{(U_m - U_0)}{1 + exp(-\beta log(I/C_4(1/V_2 + 1/Et_i)))}$$

$$f_5(I) = \frac{Rg}{(1 + exp(\alpha(I/V_3 - C_5)))}$$

where,

- V_1 represents the volume of glucose space.
- V_2 represents the volume of remote insulin compartment.
- V_3 represents the volume of plasma insulin compartment.
- t_i is time constant for remote insulin degradation.
- E is the rate constant for exchange of insulin between plasma and remote compartment.

4. Mathematical Model for Central Nervous System (CNS)

Brain controls and governs the action of all parts of the body and approximately 25 % of total body glucose is required for the proper functioning of the brain. Brain also maintains the glucose homeostasis. Normal glucose regulation in the body depends upon the link between insulin produced by β cells and signal in hypothalamus.

Initially, the brain was considered to be an insulin-insensitive tissue, and the uptake of glucose was an insulin-independent process [14]. However, subsequent studies demonstrated the existence of Insulin Receptors in the brain [15]. Type 2 diabetes appears to be the result of failure of both brain centered system and pancreatic islet system. The magnitude of the glucose utilization dependent on insulin may not seems large, but it is because it is superimposed on background of insulin independent glucose uptake. A 15 % increase in brain glucose uptake secondary to insulin stimulation may have clinical significance [16].

In model (1-2), the functions f_i, i = 1,2,3,4,5 represents the physiological changes occurred in the glucose - insulin dynamics of the human body. The functions which are included in the mathematical model for CNS are given as :

- $f_1(G_B(t))$ represents the insulin secretion but there is no significant production of insulin takes place in CNS hence not considered in the CNS model.
- $f_2(G_B(t))$ represents the glucose utilization independent of insulin and according to the literature available almost glucose uptake in brain is non insulin mediated [14], hence the function is included in the model.
- $f_3(G_B(t))f_4(I_B(t))$ represents the insulin mediated glucose utilization, it has been demonstrated that insulin mediated glucose uptake take place in brain, hence the functions are considered for the CNS model.
- $f_5(I_B(t))$ represents the glucose production and there is no direct glucose production in the brain, hence the function is not included in the model.
- $V_1^{'}$ represents the volume of glucose space in CNS.
- $V_2^{'}$ represents the volume of remote insulin compartment.
- γ denotes the insulin concentration in the brain.

Rosenzweig in 1980 demonstrated the presence of insulin in the brain of rat and human in higher concentration than in plasma [17]. In 1986, Darrel illustrated that insulin is produced within the CNS, specifically by neurons within the CNS of rats [18]. Insulin in the brain has been found at level higher level than plasma. It has been reported that high concentration of insulin are maintained in the CNS compartment compared to plasma level and the CNS insulin concentration are not affected by alternations in plasma insulin concentration [19]. Due to the above evidences, γ has been introduced in eqn.(4) of the model (3-4).

The glucose - insulin regulatory system for the Central Nervous System is

$$\frac{dG_B}{dt} = G_{in} - f_2(G_B(t)) - f_3(G_B(t))f_4(I_B(t)) \tag{3}$$

$$\frac{dI_B}{dt} = -d_i I_B(t) + \gamma \tag{4}$$

with the initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$. $G_B(t)$ represents the glucose concentration in the brain, $I_B(t)$ represents the insulin concentration in the CNS at time t. The functions f_i, i = 2,3,4 are described below :

$$f_2(G_B) = U_b^{'}(1 - exp(-G_B/(C_2V_1^{'})))$$

$$f_3(G_B) = G_B/(C_3V_1^{'})$$

$$f_4(I_B) = U_0^{'} + \frac{(U_m - U_0^{'})}{1 + exp(-\beta log(I/C_4(1/V_2^{'} + 1/Et_i)))}$$

5. Mathematical Model for Liver

Liver plays an important role to maintain the homeostasis of glucose level in the body for the normal subjects. But for the diabetic people, α and β cells are impaired in action and hence the working of liver is also disturbed due to which glucose absorption and production from the liver is also disturbed and resulting the glucose level either lowers down or raised very much leads to hypoglycemia or hyperglycemia respectively. In type 2 diabetes, increased level of insulin resistance leads to increase hepatic glucose production [20].

It was found in the study that hepatic glucose production in obese type 2 diabetic patients may be increased by 12% compared to healthy people. The reason for including the insulin production function in the second differential equation of the model is that insulin is able to suppress hepatic glucose production down to about 25% of the values measured at fasting insulin concentration in the morning both in the healthy and in type 2 diabetic subjects [21]. The liver seems to be very sensitive and important organ to insulin in both normal and T2D subjects because maximal suppression is obtained at insulin values of about 30 to 50 $\mu U/min$. Endogenous glucose production can be considered as sum of all the glucose production by kidney, intestines, liver, glucose intake and even muscles, and here hepatic glucose production is used synonymous with total endogenous glucose production. Hepatic glucose production was found more in type 2 diabetics due to a reduced insulin sensitivity of the liver cells. Increased amount of hepatic glucose production add to the degree of hyperglycemia in diabetic people [21]. Splanchnic glucose production was higher in diabetic than in the non diabetic people. Thus, excessive insulin induced suppression of splanchnic glucose release is also impaired [22].

The functions which are included in the mathematical model of Liver are given as :

- $f_1(G_L(t))$ represents the insulin secretion and almost glucose utilization in the liver is insulin mediated, hence the function is included in the model.
- $f_2(G_L(t))$ represents the glucose utilization independent of insulin and some amount of glucose uptake in the liver is also non insulin mediated, hence included in the model.
- $f_3(G_L(t))f_4(I_L(t))$ represents the insulin mediated glucose utilization, hence incorporated in the model.

- $f_5(I_L(t))$ represents the hepatic glucose production.
- $V_1^{''}$ represents the volume of glucose space in liver.
- $V_2^{'}$ represents the volume of remote insulin compartment.
- $V_3^{'}$ represents the volume of plasma insulin compartment.
- $R_m^{'}$ represents the rate of insulin secretion.
- $R_g^{'}$ represents the rate of hepatic glucose production.

The glucose - insulin regulatory system for liver is :

$$\frac{dG_L}{dt} = G_{in} - f_2(G_L(t)) - f_3(G_L(t))f_4(I_L(t)) + f_5(I_L(t)) \tag{5}$$

$$\frac{dI_L}{dt} = f_1(G_L(t)) - d_i I_L(t) \tag{6}$$

with the initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G_L(t)$ represents the glucose concentration in liver and $I_L(t)$ represents the insulin production in liver at time t. And the functions f_i, i = 1,2,3,4,5 are given as :

$$f_1(G_L) = \frac{R_m^{'}}{1 + exp((C_1 - G_L/V_1^{''})/a_1)}$$

$$f_2(G_L) = U_b(1 - exp(-G_L/144V_1^{''}))$$

$$f_3(G_L) = G_L/(C_3 V_1^{''})$$

$$f_4(I_L) = U_0 + \frac{U_m - U_0}{1 + exp(-\beta log(I_L/C_4(1/V_2^{'} + 1/Et_i)))}$$

$$f_5(I_L) = \frac{R_g^{'}}{(1 + exp(\alpha(I_L/V_3^{'} - C_5)))}$$

6. Mathematical Model for Kidney

Besides the liver, kidney is the only organ capable of generating sufficient glucose (gluconeogenesis) to release in the blood, and is reabsorption and excretion of glucose [23,24,25]. The kidneys are designed to filter plasma, reabsorb glucose and excrete substances that must be eliminated from the body. The basic functions of the kidney is regulation of fluid, body fluid osmolality, excretion of metabolic waste, hormone secretion and maintain glucose balance [26,27]. The primary mechanism of the kidney include release of glucose into the circulation via gluconeogenesis, glucose uptake from the circulation to satisfy the kidney's energy needs and reabsorption of glucose at the level of the proximal tubule [26]. Diabetes is characterized by increased rate of glucose turnover (Glucose production - Glucose utilization) in the human body. Increased glucogenesis is considered to be one of the major reason of overproduction of glucose in type 2 diabetics [28,29]. It was observed approximately 25 % of systemic glucose production is contributed by renal glucose production and renal glucose uptake accounts for 20 % of systemic glucose removal indicate an important role of the human kidney to maintain the glucose homeostasis [30].

The observation also provide a possible explanation that why people with renal failure are more prone to develop hypoglycemia [31,32]. In case of type 2 diabetic people, renal glucose release is inscribed in both the postprandial and post absorptive states, implies the kidney's distribution to the hyperglycemia [25]. A 3 -fold increase in renal glucose release was observed in patients with diabetes verses normal [33], while as hepatic glucose release increased by only 30% in the diabetic state. During hypoglycemia, the twofold increase in renal glucose production rates in normal subjects, was not observed in patients with diabetes [34].

Renal glucose reabsorption tends to increase with plasma glucose levels, upto plasma concentration of 180 mg/dl to 200 mg/dl [26]. In patients with diabetes, the kidneys may be susceptible to the effects of hyperglycemia, as kidney cells are unable to decrease glucose transport rates to prevent intracellular hyperglycemia in states of increased glucose concentration [35]. The possible reason behind is that may be insulin fails to suppress renal glucose production in diabetic patients. Diabetic kidney diseases more common in type 2 diabetic people and is the reason for kidney failure.

The functions which are included in the mathematical model for kidney are given as :

- $f_1(G_K(t))$ represents the insulin secretion and glucose utilization is controlled by the insulin hence incorporated in the model.
- $f_2(G_K(t))$ represents the glucose utilization independent of insulin and some glucose uptake in the kidney is also non insulin mediated, hence the function is included in the model.
- $f_3(G_K(t))f_4(I_K(t))$ represents the insulin mediated glucose utilization, hence incorporated in the model.
- $f_5(I_K(t))$ represents the renal glucose production.
- $V_1^{''}$ represents the volume of glucose space in kidney.
- $R_m^{''}$ represents the rate of insulin secretion.
- $R_g^{''}$ represents the rate of renal glucose production.

The glucose - insulin regulatory system for kidney is :

$$\frac{dG_K}{dt} = G_{in} - f_2(G_K(t)) - f_3(G_K(t))f_4(I_K(t)) + f_5(I_K(t)) \tag{7}$$

$$\frac{dI_K}{dt} = f_1(G_K(t)) - d_i I_K(t) \tag{8}$$

with the initial conditions $I(0) = I_0 \geq 0$, $G(0) = G_0 \geq 0$, $G_K(t)$ represent the glucose concentration in kidney and $I_K(t)$ represent the insulin concentration in kidney at time t. And the functions f_i, i = 1,2,3,4,5 are given below :

$$f_1(G_K) = \frac{R_m^{''}}{1 + exp((C_1 - G_K/V_1^{''})/a_1)}$$

$$f_2(G_K) = U_b(1 - exp(-G_K/144V_1^{''}))$$

$$f_3(G_K) = G_K/(C_3V_1^{''})$$

$$f_4(I_K) = U_0 + \frac{U_m - U_0}{1 + exp(-\beta log(I_K/C_4(1/V_2^{'} + 1/Et_i)))}$$

$$f_5(I_K) = \frac{R_g^{''}}{(1 + exp(\alpha(I_K/V_3^{'} - C_5)))}$$

7. Stability analysis of the mathematical model

To discuss the stability analysis of the model (1-2), we assume that all the functions f_i, i = 1,2,3,4,5 satisfies the following conditions [36] :

(i) β cells of the pancreas secrete insulin to control the glucose concentration level and since pancreas stop releasing insulin when the glucose concentration is abundant, hence $f_1(x) > 0$ and $f_1^{'}(x) < 0$ for $x > 0$. Since the highly raised glucose concentration saturate the secretion of insulin, hence the amount of insulin secreted by pancreas is finite and so we take $\lim_{x\to\infty} f_1(x) = K_1$ for $x > 0$. Some amount of insulin can also be secreted by pancreas without the glucose stimulation, hence we assume $f_1(0) = k_1 > 0$.

(ii) The function $f_2(x)$ represents the insulin - independent glucose utilization, it is clear that $f_2(0) = 0$, $f_2(x) > 0$ and $f_2^{'}(x) > 0$ for $x > 0$. Also the utilization of glucose is limited, we assume that $\lim_{x\to\infty} f_2(x) = K_2$ and $f_2^{'}(x) < K_2^{'}$ for $x > 0$.

(iii) The insulin - dependent utilization of glucose in the body is represented by the function $f_3(G(t))f_4(I(t))$, so it can be written as $f_3(0) = 0$, $f_3^{'}(x) > 0$, $f_4(0) = k_4 > 0$, $f_4(x) > 0$, and $f_4^{'}(x) > 0$ for $x > 0$. From [36], we assume that there exists constants $k_3 > 0$, $K_4 > 0$ and $K_4^{'} > 0$ such that $0 < f_3(x) \leq k_3 x$, $\lim_{x\to\infty} f_4(x) = K_4$, and $f_4^{'}(x) < K_4^{'}$ for $x > 0$.

(iv) f_5 denotes the total glucose production and since liver stops releasing glucose when the insulin concentration is abundant, hence $f_5(x) > 0$, and $f_5^{'}(x) < 0$ for $x > 0$, and $\lim_{x\to\infty} f_5(x) = 0$. Amount of glucose produced by liver is small and it takes some time also, so there exists K_5, $K_5^{'} > 0$ such that $f_5(x) \leq K_5$ and $\mid f_5(x) \mid \leq K_5^{'}$ for $x > 0$, and $f_5(0) = k_5$.

Consider the linearized system of model (1-2) about the steady point (G^*, I^*):

$$\frac{dG}{dt} = -AG(t) - BI(t) \tag{9}$$

$$\frac{dI}{dt} = CG(t) - d_i I(t) \tag{10}$$

where, A= $f_2^{'}(G^*)$ + $f_3^{'}(G^*)f_4(I^*)$, B = $f_3(G^*)f_4^{'}(I^*)$ - $f_5^{'}(I^*)$, C = $f_1^{'}(G^*)$

The characteristic equation is given as :

$$\lambda^2 + a\lambda + b = 0$$

in which, a = A + d_i, b = Ad_i - BC.

Apply Routh - Hurwitz Criterian on the characteristics polynomial to prove the system as stable and for that we need to show the following conditions :

(i) a = A + d_i >0

(ii) b = Ad_i - BC >0

(iii) A > 0

(i) $a = f_2^{'}(x) + f_3^{'}(x)f_4(x) + d_i$, since $f_2^{'}(x) > 0$, $f_3^{'}(x) > 0$, $f_4(x) > 0$ and $d_i > 0$ implies a > 0.

(ii) $b = (f_2^{'}(x) + f_3^{'}(x)f_4(x))d_i$ - $(f_3(x)f_4^{'}(x)$ - $f_5^{'}(x))f_1^{'}(x)$, since $f_2^{'}(x) > 0$, $f_3^{'}(x) > 0$, $f_4(x) > 0$, $f_5^{'}(x) < 0$, $d_i >$ 0, $f_4(x) > 0$, $f_4^{'}(x) > 0$ and $f_1^{'}(x) < 0$ implies b > 0.

(iii) A > 0, as we can see from the part (i) that all the terms of A are > 0.

Hence it is concluded that the mathematical model (1-2) which represents the glucose - insulin dynamics for normal people is stable. To avoid the repetition, the stability analysis of the remaining mathematical models are not discussed.

8. Positive and bounded solution of the mathematical model

The solution of model (1-2) with given initial condition exists and is unique for all $t \geq 0$. If there exists a $t_0 > 0$ such that $G(t_0) = 0$ and $G(t) > 0$ for $0 < t < t_0$, then $G^{'}(t_0) \leq 0$. So we have

$$\begin{aligned} 0 \geq G^{'}(t_0) &= G_{in} - f_2(G(t_0)) - f_3(G(t_0))f_4(I(t_0)) + f_5(I(t_0)) \\ &= G_{in} - f_2(0) - f_3(0)f_4(I(t_0)) + f_5(I(t_0)) \\ &= G_{in} + f_5(I(t_0)) > 0 \end{aligned}$$

A contradiction, hence implies $G(t) > 0$ for all $t > 0$.

Claim 8.1. The solution $G(t)$ is bounded for t > 0.

Proof. If $\lim_{t\to\infty} \sup G(t) = \infty$, then there exist a sequence $\{t_n\}_{n=1}^{\infty} \uparrow \infty$ such that $\lim_{n\to\infty} G(t_n) = \infty$ and $G(t_n^{'}) \geq$ 0. Thus $0 < G^{'}(t_n) = G_{in} - f_2(G(t_n)) - f_3(G(t_n))f_4(I(t_n)) + f_5(I(t_n)) \leq G_{in} - f_2(G(t_n)) - k_4 f_3(G(t_n)) + K_5$, and therefore

$$\begin{aligned} 0 \leq \lim_{n\to\infty} G^{'}(t_n) &\leq G_{in} - \lim_{n\to\infty} f_2(G(t_n)) - k_4 \lim_{n\to\infty} f_3(G(t_n)) + K_5 \\ &\leq G_{in} - K_2 - k_4 \lim_{x\to\infty} f_3(x) + K_5 < 0 \end{aligned}$$

(The steady state of the system (1-2) is unique, hence

$$\lim_{x\to\infty} f_3(x) > (G_{in} - K_2 + K_5)/k_4).$$

This contradiction shows that there exist a $K_G > 0$ such that $G(t) < K_G$ for all $t > 0$ implies $G(t)$ is bounded above.

Claim 8.2 The solution I(t) is positive and bounded for t > 0.

Proof. Eqn.(4) can be written as

$$\begin{aligned} \frac{dI}{dt} &= f_1(G(t)) - d_i I(t) \\ \frac{dI(t)}{dt} + d_i I(t) &= f_1(G(t)) \end{aligned}$$

The solution is given by

$$\begin{aligned} I(t)e^{d_i t} &= I(0) + \int_0^t f_1(G(t))e^{d_i t}dt \\ I(t) &= I(0)e^{-d_i t} + e^{-d_i t}\int_0^t f_1(G(t))e^{d_i t}dt \end{aligned}$$

which implies, I(t) $\geq$ I(0)$e^{-d_i t}$, At $t \to \infty$, I(t) > 0, implies I(t) is positive.

At steady point, I(t) = $d_i^{-1} f_1(x)$, Since $|f_1(x)| \leq K_1$, therefore I(t) $\leq d_i^{-1} K_1$ = K, hence I(t) is bounded.

Hence the solution $(G(t), I(t))$ of the model (1-2) are positive and bounded.

9. Numerical simulation

We used Matlab 2012b to simulate the mathematical models numerically. The results of our simulation reveals the possible reasons behind the raised glucose concentration in CNS, liver and kidney which are severely affected by the diabetes, if it persists long in the human body.

The total glucose space for the severe diabetic people is 124.47 ml/kg or 9.68775 l [37]. Out of which 1.04 % *i.e* 0.8112 l of body weight is taken for the CNS and 11.41 % *i.e* 8.8765 l of the total body weight is taken for the remaining compartments (liver and kidney). The total volume space for the insulin is 10.92 l or 14.04 % of the body weight, out of which 3.131 l is for the plasma insulin compartment and 7.800 l is for the remote insulin compartment [38]. The average weight of the human body is assumed to be 77.8 kg throughout the paper.

9.1 Normal

Mathematical model (1-2) is numerically simulated to observe the glucose and insulin concentration in the normal body. The values of the parameters which are taken in the numerical simulation are given in Table 1. The glucose concentration approaches to 110 mg/dl in 3 hours after glucose infusion, which lies in the normal physiological range (70 - 110 mg/dl) as shown in the Figure 2.

9.2 Central Nervous System

(i) To find the direct impact of volume of glucose and insulin space on the glucose - insulin dynamics in CNS for diabetic people, the parameters $V_1^{'}$ and $V_2^{'}$ are taken and are given in Table 2. Since glucose uptake and glucose production are impaired in diabetics, the effected glucose concentration level are shown with the help of graphs after numerical simulation of the mathematical model (3-4).

It can be seen from the Figure 3(a) that after a initial dip in starting, glucose concentration starts increasing and after approximately 1.5 hrs, glucose concentration crossed the normal glucose level. It approaches to 190 mg/dl within 3 hrs of glucose infusion, which explains the condition of hyperglycemia in and near the CNS compartment of the diabetic people. Our simulation shows that decreased volume of glucose and insulin space may be one of the major reason for raised glucose concentration in the CNS. The other possible reasons together with the decreased volume of glucose and insulin space are discussed further.

(ii) The glucose concentration is already raised in the diabetic people as the glucose utilization is impaired in the diabetic people. The parameter $U_b^{'}$ denotes the rate of glucose utilization with respect to glucose concentration *i.e* non insulin mediated glucose uptake. The parameter $U_0^{'}$ denotes the glucose utilization rate with respect to plasma insulin *i.e* insulin mediated glucose uptake in the CNS.

The value of U_b is 72 $mgmin^{-1}$ for normal people [13]. Since the rate of glucose utilization is lower in diabetics than normal person, hence three smaller values of $U_b^{'}$ are taken (60 $mgmin^{-1}$, 50 $mgmin^{-1}$, 40 $mgmin^{-1}$) to discuss the glucose - insulin dynamics in CNS of diabetics as shown in the Figure 4. Figure 4(a) shows that glucose concentration level in the CNS compartment of a diabetic people may acquire a blood sugar concentration over 200 mg/dl and reached nearly 230 mg/dl if the value of $U_b^{'}$ decreases and value of $U_0^{'}$ kept fixed. The glucose concentration continuously increases as the rate of glucose utilization decreases (depend upon the severity of disease) and may leads to diabetic comma sometimes, but never exceeds the glucose infusion value even for $U_b^{'}$ tends to zero.

It can be concluded from the results that decreased volume of glucose and insulin space together with the decreased rate of glucose utilization (independent of presence of insulin) may affect the glucose concentration in the CNS compartment and hence can be considered as one of the reason for hyperglycemia in the CNS.

Similarly Figure 5(a) demonstrate the glucose concentration level in the CNS compartment when the value of $U_0^{'}$ varies with fixed value of $U_b^{'}$. The glucose concentration in this case is nearly 270 mg/dl which clearly indicates that hyperglycemia exists and impaired the functioning of CNS. Also, it can be concluded that since both the uptakes (insulin mediated and non insulin mediated) affect the glucose concentration but decreased rate of insulin mediated glucose uptake has more impact than non insulin mediated glucose uptake in keeping the raised glucose concentration in the CNS.

9.3 Liver

Liver plays a major role in maintaining the glucose - insulin dynamics of the body. To the time non suppressed hepatic glucose production is considered as one of the main reason behind the raised glucose concentration in the body. Figure 6(a) shows the glucose concentration level in liver for different values of $R_m^{'}$ (20 $\mu Umin^{-1}$, 15 $\mu Umin^{-1}$, 10 $\mu Umin^{-1}$) with fixed value (200 $mgmin^{-1}$) of the parameter $R_g^{'}$. The reason for taking the value of $R_m^{'}$ very less compared to normal people is that since maximum suppression of hepatic glucose production was observed at insulin level of about 30 $\mu Umin^{-1}$ to 50 $\mu Umin^{-1}$ and it fails to do so in diabetic people hence a value near to 20 $\mu Umin^{-1}$ is considered. The value of the parameter $R_g^{'}$ in case of type 2 diabetics is taken as 200 $mgmin^{-1}$ (12 % more than that of normal) [21], as hepatic glucose production is increased in type 2 diabetics due to the increased insulin resistance. The glucose level goes up and a risk of diabetic comma may be occurred if the value of $R_m^{'}$ reduced further as shown in Figure 6(a). It is concluded from the simulation that impaired insulin production from the pancreas together with the decreased volume of glucose and insulin space may be the possible reasons for the raised glucose concentration in the liver. Figure 6(b) demonstrate the insulin concentration level in the liver. The values of the parameters taken to discuss the glucose - insulin dynamics in liver are given in Table 3.

9.4 Kidney

Stumvoll in [30] shows the renal glucose production (RGP) and hepatic glucose production (HGP) in the basal state and the graphs for both production are similar in shape, only the concentration differs. Infact glucose concentration produced by renal is approximately half of the glucose concentration produced by liver. Hence the value of $R_g^{''}$ is taken as 90 $mgmin^{-1}$ for kidney.

In the diabetic people, insulin mediated glucose uptake and glucose production are disturbed due to the insulin resistance of the body and hence the raised glucose concentration in the kidney can be seen in the Figure 7(a) for three different values (15 $\mu Umin^{-1}$, 10 $\mu Umin^{-1}$, 5 $\mu Umin^{-1}$) of $R_m^{''}$. To the time, insulin resistance and non suppressed renal glucose production were supposed to be the reason of hyperglycemia but through this study, it can be concluded clearly that decreased volume of distribution of glucose and insulin space may be one of the major reason together with the impaired rate of insulin production for raised glucose concentration in the diabetic people. Figure 7(b) demonstrate the insulin concentration level in the kidney. The values of the parameters taken to discuss the glucose - insulin dynamics for kidney are given in Table 4.

Parameters	Units	Values	Parameters	Units	Values
R_m	$mUmin^{-1}$	210	V_3	l	3
R_g	$mgmin^{-1}$	180	V_2	l	11
U_m	$mgmin^{-1}$	940	V_1	l	10
U_0	$mgmin^{-1}$	40	t_i	min	100
U_b	$mgmin^{-1}$	72	a_1	mgl^{-1}	300
C_1	mgl^{-1}	2000	α	$lmin^{-1}$	0.29
C_2	mgl^{-1}	144	E	$lmin^{-1}$	0.2
C_3	mgl^{-1}	1000	β		1.77
C_4	mUl^{-1}	80	C_5	mUl^{-1}	26

TABLE 1. The values of parameters for normal case [13].

Parameters	Units	Values	Parameters	Units	Values
$V_1^{'}$	l	0.8112	$V_2^{'}$	l	7.800

TABLE 2. The values of the parameters for CNS

Parameters	Units	Values	Parameters	Units	Values
$V_1^{''}$	l	8.8765	$V_2^{'}$	l	7.800
$V_3^{'}$	l	3.131	$R_g^{'}$	$mUmin^{-1}$	200

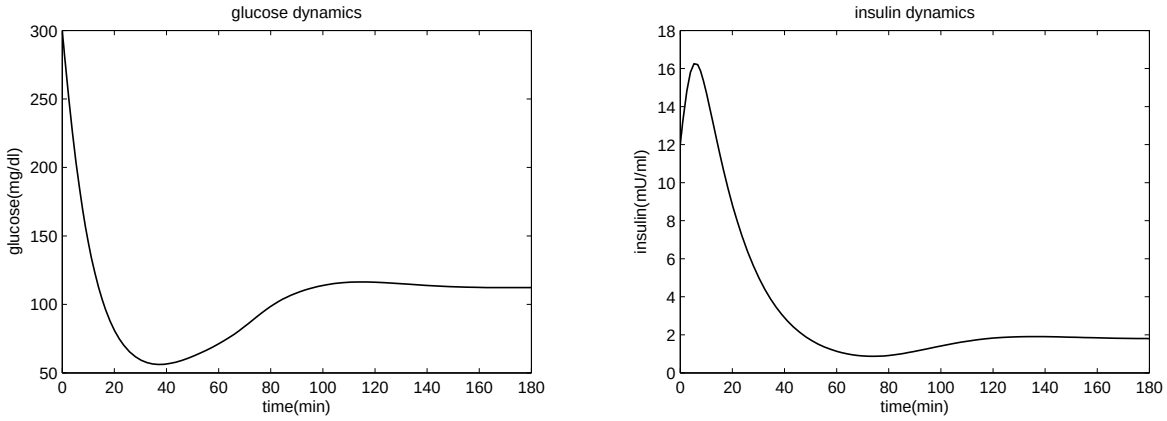
TABLE 3. The values of the parameters for liver

Parameters	Units	Values	Parameters	Units	Values
$V_1^{''}$	l	8.8765	$V_2^{'}$	l	7.800
$V_3^{'}$	l	3.131	$R_g^{''}$	$mUmin^{-1}$	90

TABLE 4. The values of the parameters for kidney

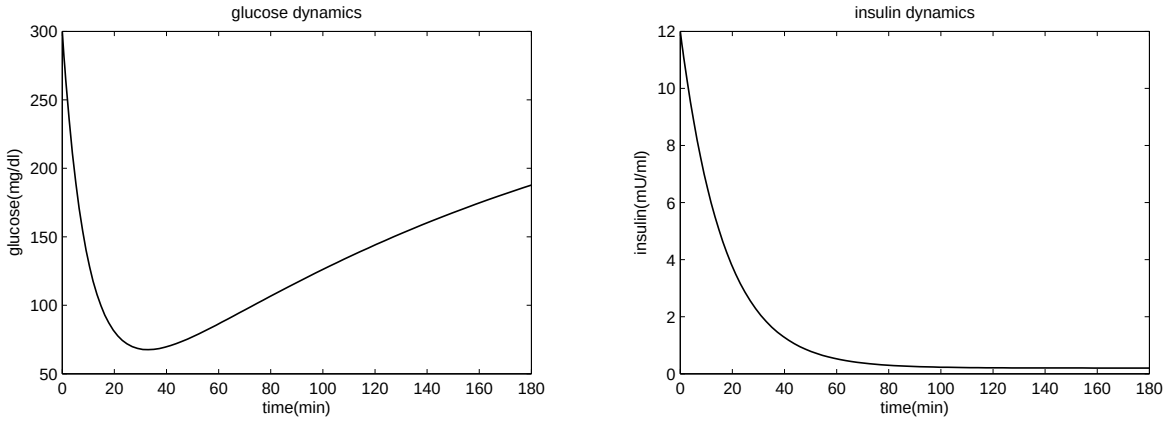
10. Discussion

All the mathematical models are simulated analytically and numerically for the transient behavior of glucose and insulin profiles. The figures illustrate the curves of glucose and insulin concentration level in CNS, kidney and liver, corresponding to the changed value of volume of glucose space and insulin space in the organs.



(A) (B)

FIGURE 2. Glucose - Insulin dynamics for Normal case

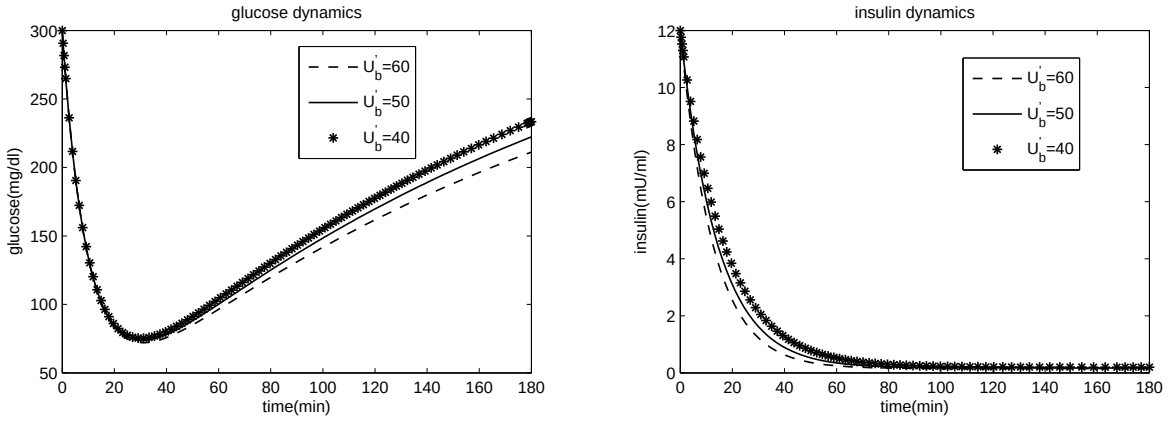


(A) (B)

FIGURE 3. Glucose - Insulin dynamics of CNS for diabetic people with changed volume of glucose and insulin space.

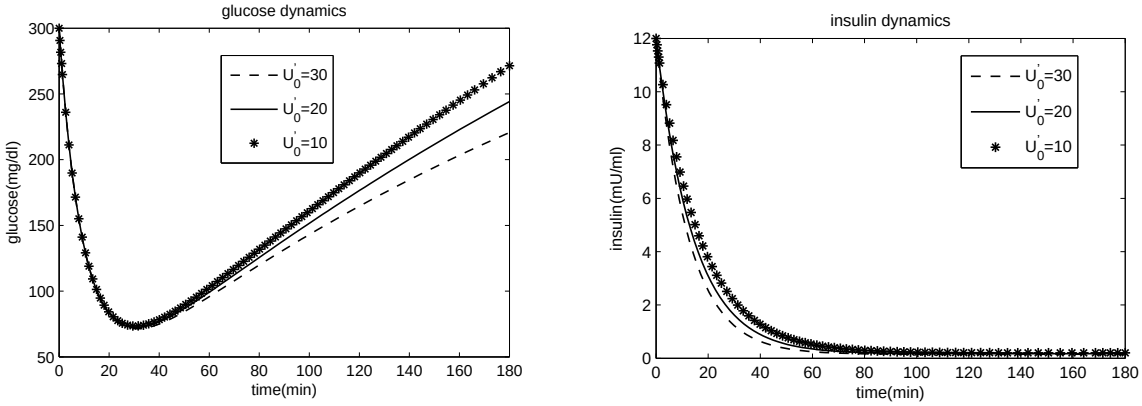
Compared with the observations obtained by many biologists and researchers, the results obtained confirms most of the known observations and also reveals additional insightful information for type 2 diabetics. The results are concluded in the form of list given below :

(i) In section 9.2, Figure 3 reveals that decreased volume of glucose and insulin space for diabetic people affect the CNS and may be considered as one of the possible many causes of raised glucose level which may lead to diabetic comma.



(A) (B)

FIGURE 4. Glucose - Insulin dynamics of CNS for diabetic people in which value of parameter $U_b^{'}$ varies.

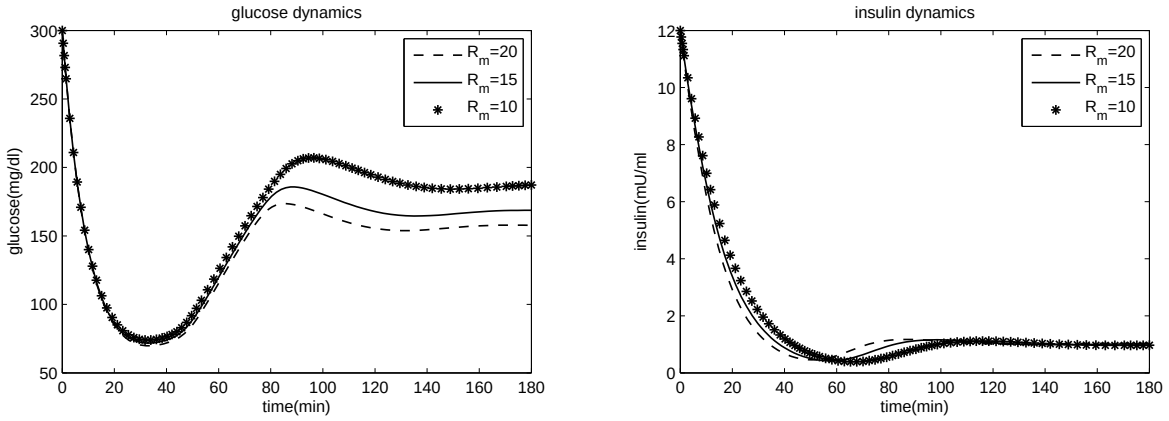


(A) (B)

FIGURE 5. Glucose - Insulin dynamics of CNS for diabetic people in which value of parameter $U_0^{'}$ varies.

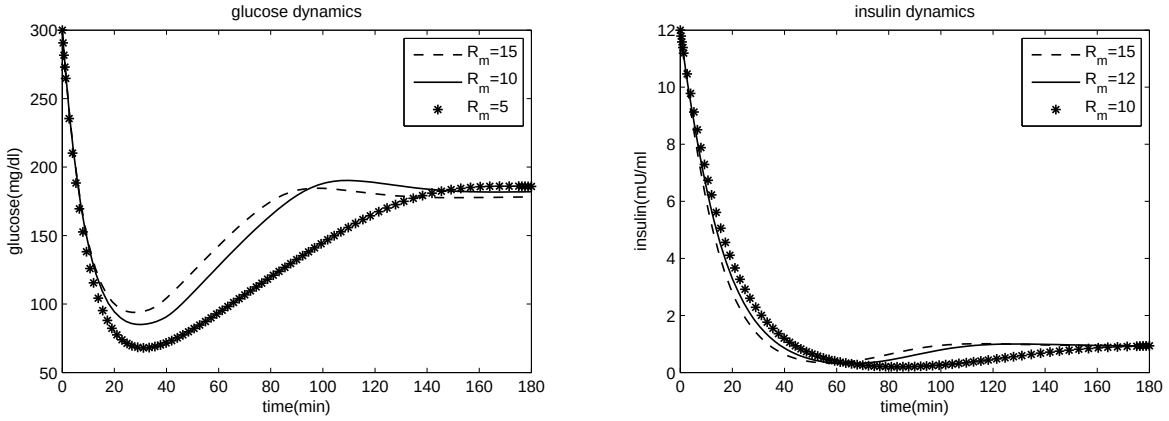
(ii) Figure 4 and Figure 5 shows that decreased volume of glucose and insulin space with decreased rate of glucose uptake (insulin mediated and non insulin mediated) also intimidate continuous raised blood glucose concentration in CNS. Such condition may sometime leads to brain damage and some other brain related diseases.

(iii) Figure 6 reveals that in liver raised glucose concentration are caused by impaired insulin production from the pancreas together with the decreased volume of glucose and insulin space.



(A) (B)

FIGURE 6. Glucose - Insulin dynamics of Liver



(A) (B)

FIGURE 7. Glucose - Insulin dynamics of Kidney

(iv) Figure 7 depicts that impaired insulin production and decreased volume of glucose and insulin space together raised the glucose concentration and leads to many diseases related to kidney and sometimes leads to kidney failure.

11. Conclusion

An attempt has been made to capture the behavior of glucose - insulin dynamics in CNS, liver and kidney as different organs have different functions to perform and hence their need of glucose is also different. Separate mathematical models have been developed for CNS, liver and kidney depending on their response towards glucose

and insulin dynamics. It is concluded that decreased volume of glucose and insulin space may be one of the major possible reason for the prolonged raised glucose concentration in CNS, liver and kidney of type 2 diabetics. Other reasons behind the raised glucose concentration may vary according to the behavior and physiology of affected organs as discussed in the paper. We hope the results obtained from the analytical and numerical study of the mathematical models will be the base to explore the role of volume of glucose and insulin space on diabetes.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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