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MATLAB Design for Solving a Mathematical Model of Insulin Dynamic

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Abstract: *This paper intended to solve an insulin mathematical model for determining the response of body's organs to the insulin action and to assess the possible effects of Type 2 diabetes risk on insulin secretion. A mathematical model governed by non-linear ordinary differential equations is presented. The numerical resolution of these equations is done by using Matlab packages. The discussed results show the curves of the model variables against time identifying the variation of insulin concentration in human body adjusted for a diabetic person.*

Keywords: *Insulin failures, Diabetes, Ordinary differential equations, Numerical simulation*

1. INTRODUCTION

Insulin is a hormone secreted by the pancreas responsible for the regulation of glucose level in the blood plasma. It also intervenes in the cell glucose uptake and may be used to convert the glucose in glycogen as a kind of energy mostly used by the brain in memory development [1].

Since insulin controls the central metabolic processes, failure of insulin production leads to a condition called Type 2 diabetes which is a metabolic disorder characterized by chronic hyperglycemia with disturbances in fat and protein metabolism [2]. The two major pathophysiological defects in Type 2 diabetes are impaired insulin secretion resulting in insulin deficiency production and insulin resistance where cells fail to respond to insulin action. These metabolic abnormalities lead to long-term damage of various organs, causing their dysfunction and failure.

Untreated, diabetes can cause many complications like macro- vascular defects responsible for the majority of new cases of blindness and kidney failure. These complications are among the leading causes of mortality worldwide, and cause a significant decrease in the life expectancy of diabetic patients.

Type 2 diabetes appears as terrible disorder with potentially destroying defects that affects all age groups in almost all countries. The International Diabetes Organization estimates that in 1985, 30 million people around the world were diagnosed with diabetes; in 2000, that figure rose to over 150 million, and it is projected to rise further to 380 million by 2025 [3]. Billions of people are suffering from Type 2 diabetes throughout the world. Hence it is a subject of interest for scientists and care providers.

A considerable number of studies have been carried out to investigate the mechanisms leading to diabetes, and the genetic background of this disease. Mathematical models quantifying insulin action has been developed by Sorensen [4]. The role of pancreas in insulin release and the effects of fats in insulin resistance leading to the obesity have not been considered in the development of diabetes. The present thesis focus on this subject where the mathematical model is modified by Alvehag [5] by including the pancreas as a compartment, considering the adipose tissue as a separate compartment and including incretin effects on insulin under meal consumption. This is

an attempt to adapt the model to include insulin resistance effect on glucose regulation under fat effects either due to obesity or genetic dysfunction.

The remaining part of this paper is organized as follows. The section 1 presents mathematical model equations. Numerical approach is presented in section 2. The section 3 deals with simulation results while concluding remarks are discussed in section 4.

2. MATHEMATICAL MODEL EQUATIONS

The model of insulin action in normal body which is used in this paper is based on initial work of Sorensen [4] mathematical model and revisions made by Alvehag [5]. The proposed model following the whole body approach is divided into a number of individual compartments: brain, liver, heart and lungs, adipose tissue, periphery, gut, kidney and pancreas to describe the physiological behavior of a healthy human subject; 70 kg man, plasma glucose regulation. The adapted model considers the pancreas as a metabolic source of insulin inputted directly into the liver. The model also takes adipose tissue as a separate compartment to take into consideration the effects of fats in the development of Type 2 diabetes throughout the obesity.

A schematic diagram of insulin compartmental model is depicted in the figure 1 and this diagram explains well how pancreas secretes insulin which is captured by certain organs like the liver, kidney, and peripheries to be used in the take up of glucose into the cell.

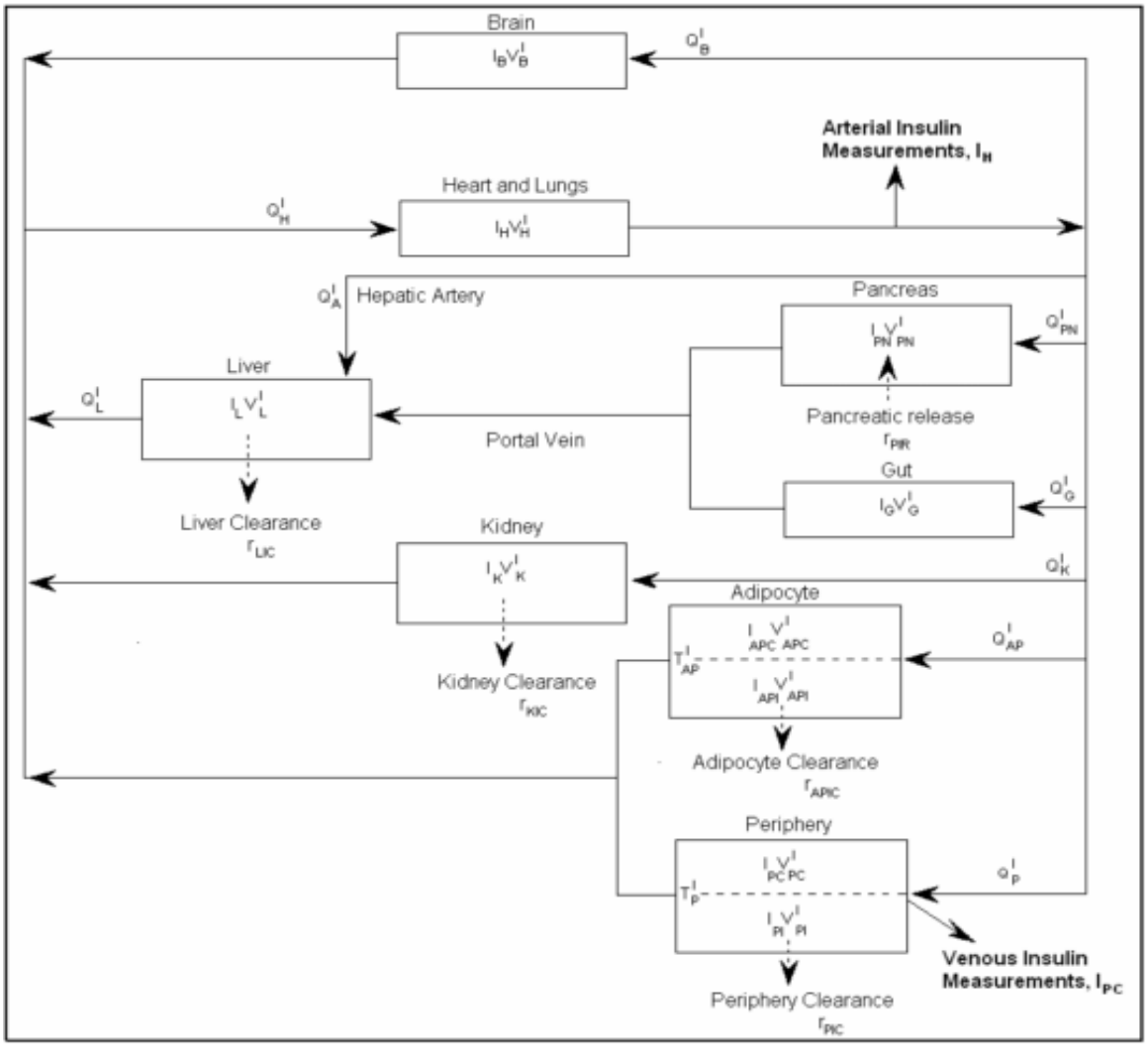

Figure 1: *Diagram of insulin model representation*

The arrows show the blood direction and the rectangular blocks represent the compartment. Muscles and body tissues are represented as the periphery. The stomach and intestine are lumped into the gut compartment. From this diagram, mass balance equations for the model are written as follows:

$$
\begin{cases}
\text{Brain :} & V_B^I \dfrac{dI_B}{dt} = Q_B^I (I_H - I_B) \\
\text{Heart and lungs :} & V_H^I \dfrac{dI_H}{dt} = Q_B^I I_B + Q_L^I I_L + Q_K^I I_K + Q_P^I I_{PC} + Q_{AP}^I I_{APC} - Q_H^I I_H \\
\text{Gut :} & V_G^I \dfrac{dI_G}{dt} = Q_G^I (I_H - I_G) \\
\text{Liver :} & V_L^I \dfrac{dI_L}{dt} = Q_A^I I_H + Q_G^I I_G + Q_{PN}^I I_{PN} - Q_L^I I_L - r_{LIC} \\
\text{Kidney :} & V_K^I \dfrac{dI_K}{dt} = Q_K^I (I_H - I_K) - r_{KIC} \\
\text{Periphery:} & V_{PC}^I \dfrac{dI_{PC}}{dt} = Q_P^I (I_H - I_{PC}) - \dfrac{V_{PI}^I}{T_P^I} (I_{PC} - I_{PI}) \\
 & V_{PI}^I \dfrac{dI_{PI}}{dt} = \dfrac{V_{PI}^I}{T_P^I} (I_{PC} - I_{PI}) - r_{PIC} \\
\text{Adipocyte :} & V_{APC}^I \dfrac{dI_{APC}}{dt} = Q_{AP}^I (I_H - I_{APC}) - \dfrac{V_{API}^I}{T_{API}^I} (I_{APC} - I_{API}) \\
 & V_{APC}^I \dfrac{dI_{API}}{dt} = \dfrac{V_{PI}^I}{T_{AP}^I} (I_{APC} - I_{API}) - r_{APIC} \\
\text{Pancreas :} & V_{PN}^I \dfrac{dI_{PN}}{dt} = Q_{PN}^I (I_H - I_{PN}) + r_{PIR},
\end{cases}
\tag{1}
$$

with the following additional expression;

$$
\begin{aligned}
r_{LIC} &= F_{LIC} \; Q_A^I I_H + Q_G^I I_G + Q_{PN}^I I_{PN} \\
r_{KIC} &= F_{KIC} Q_K^I I_H \\
r_{PIC} &= F_{PIC} Q_K^I I_H \\
r_{APIC} &= F_{APIC} Q_{AP}^I I_H \\
r_{PIR} &= \frac{S\ G_H, \gamma}{S\ G_H^B, \gamma} r_{PIR}^B,
\end{aligned}
\tag{2}
$$

where $S\ G_H, \gamma$ is the insulin secretion rate depending on glucose concentration G_H in heart and incretins concentration above normal levels γ, $S\ G_H^B, \gamma^B$ is the secretion rate depending on basal glucose concentration G_H^B in heart and basal incretins concentration γ^B and r_{PIR}^B is the basal insulin release rate. In addition, the presence of two equations for muscles and adipocyte represents the capillary and interstitial blood space in order to incorporate the effects of capillary wall resistance. The description of variables and parameters used for designing the model equations (1) are presented in the Table 1.

Table 1: *Variables and parameters for insulin dynamic model*

Variables	Description	Unit
I_B	Insulin concentration in Brain	mU/l
I_G	Insulin concentration in Gut	mU/l
I_K	Insulin concentration in Kidney	mU/l
I_H	Insulin concentration in Heart and Lungs	mU/l
I_L	Insulin concentration in Liver	mU/l
I_{PN}	Insulin concentration in Pancreas	mU/l
I_{PC}	Insulin concentration for Periphery capillary	mU/l

I_{API}	Insulin concentration for Adipocyte Interstitial	mU/l
I_{APC}	Insulin concentration for Adipocyte capillary	mU/l
I_{PI}	Insulin concentration for Periphery interstitial	mU/l
R	Metabolic sink or source	mU/min
Parameters	**Description**	**Unit**
V^I	Volume of insulin	L
Q^I	Interstitial vascular blood flow	l/min
T^I	Interstitial transcapillary diffusion time	Min
F	Fractional clearance	

The complexity of this insulin model is exhibited in the non-linear behavior of insulin release. The model for this insulin release was initially proposed by Landahl [6] and modified for human by Sorensen [4] to account for the effects of pancreas in the secretion of insulin. Hence the pancreatic insulin release rate r_{PIR} is given by the following relation

$$r_{PIR} = \frac{S\ G_H, \gamma}{S\ G_H^B, \gamma} r_{PIR}^B \tag{3}$$

To get r_{PIR}, we need to calculate the rate of insulin secretion *(S)* depending on heart glucose concentration G_H, the amount of labile insulin I_l, the concentration of incretins above normal levels γ and the difference in the instantaneous excitation factor *X* and its inhibitor *I*;

$$S = \left[M_1 Y + M_2\ \ X\ \ G_H\ \ - I\ \ + \varphi_2 \gamma \right] I_l\ , \tag{4}$$

with

$$X = \frac{G_H^{3.27}}{132^{3.27} + 5.93\ \ G_H}^{3.02}, and$$

$$Y = X^{1.11} + \varphi_1 \gamma,$$

with M_1, M_2 φ_1 and φ_2 constants.

As we see the equation (4) combines the effects of pancreas and incretins and their models help us to compute the values *I*, and I_l as follows

$$\begin{cases} V^{\gamma} \dfrac{d\gamma}{dt} = \dfrac{\gamma_G}{\tau_{\nu}} - r_{M\gamma C}\gamma \\ \dfrac{dP}{dt} = \alpha\ \ X^{1.11} - \varphi_1 \gamma\ \ - P \\ \dfrac{dI_l}{dt} = K\ \ I_{l0} - I_l\ \ + \psi, P - S \\ \dfrac{dI}{dt} = \beta\ \ X - I\ \ , \end{cases} \tag{5}$$

with γ_G the quantity of incretins in gut above normal levels, *P* is glucose-stimulated factor and parameters α , β , δ , ψ, K , V^{γ}, $r_{M\gamma C}$ and $OGCs$ are constants.

As indicated in previous sections, the model has many parameters which can be adjusted to represent the behavior of a Type 2 diabetic person. The non- linearity of equations, the presence of ten variables and many parameters for the mathematical model deprive us solving it analytically. Since solutions to non-trivial problems are non- analytic, they must be approximated by numerical schemes. Thus, we need to solve the problem presented by the system given in (1) using the Matlab packages [7].

The numerical resolution of the system (5) by the help of a Matlab function Ode45 with the parameter values in the Table 2 gives us the values of I, and I_l which are replaced in the relation (4) to get S, hence, to obtain the value of r_{PIR} .

3. NUMERICAL APPROACH

The resolution of the system () can be determined in several platform. The implementation of the solution is made using MATLAB packages where we use one of its solvers for ordinary differential equations [7]. A MaTlaB function ode45 is used for solving the state system. For the use of the function ode45 it is required to write the state system (1) or (5) in the following form

$$\dot{x(t)} = f(t, x(t))$$

Given a positive integer N we define a time grid points on the interval $(0,T)$ using the following MaTlaB line

>> TT = 0: T/N: T;

Let us consider the vector $Q \in \mathbb{R}^{2(N+1)}$ whose components are defined by the vector $x(t_0),...,x(t_N);v(t_0),...,x(t_N)^T$ where $t_i = iT/N$. Considering Q as a global variable, we implement the second hand side of the system (5) by the following code:

```
function F=second_member1(t,x)
global psi OGCs taugamma Vgamma rMgammaC alpha
phai1 phai2
global K IL0 fi beta GH M1 M2
F1= psi*OGCs-x(1)/taugamma;
F2=(x(1)/taugamma-rMgammaC*x(2))/Vgamma;
X= (GH) ^3.27/ ((132^3.27) +5.93*(GH) ^3.02);
F3=alpha*(X^1.11+phai1*x (2))-x (3);
Y=X^1.11+phai1*x(2);
S= [M1*Y+M2*(X-x(5)) +phai2*x(2)]*x(4);
F4=K*(IL0-x (4)) +fi*x (3)-S;
F5=beta*(X-x (5));
F= [F1; F2; F3; F4; F5];
```

Then, the solution of the system () is computed via a single of MaTlaB line using the ode45 function. This is done by the command line:

>> [TDATA, X] =ode45 ('second_member1', [0:300], Y0)
where Y0 denotes the initial values given by
$Y0 = (12.7, 22.8, 5, 10; 7.9)^T$.

Next, the solution of (5) is used for computing the solutions of the system of (1). The MaTlaB routine defined below described the second hand side of this system.

```
function F=second_member(t,x)
global VIB QIB VIH QIL QIK QIP QIAP QIH VIG QIG VIL QIA QIPN FLIC
global VIK FKIC VIPC VIPI TIP FPIC VIAPC VIAPI TIAP FAPIC VIPN
load InsuinDA TDATA gammaG gamma P IL
gammaint=interp1(TDATA,gamma,t,'cubic');
gammaGint=interp1(TDATA,gammaG,t,'cubic');
Pint=interp1(TDATA,P,t,'cubic');
ILint=interp1(TDATA,IL,t,'cubic');
Iint=interp1(TDATA,I,t,'cubic');
GH=100;
BGH=91.5;
rBPIR=1/16;
M1=0.00797;
```

```
M2=0.136;
phai1=0.003;
phai2=0.0001;
XGH=(GH)^3.27/((132^3.27)+5.93*(GH)^3.02);
XBGH=(BGH)^3.27/((132^3.27)+5.93*(BGH)^3.02);
YGH=(XGH)^1.11+phai1*gammaint;
YBGH=(XBGH)^1.11+phai1*gammaGint;
SGH=(M1*YGH+M2*(XGH-Iint)+phai2*gammaint)*ILint;
SBGH=(M1*YBGH+M2*(XBGH-Iint)+phai2*gammaGint)*ILint;
F1=QIB*(x(2)-x(1))/VIB;
F2=(QIB*x(1)+QIL*x(4)+QIK*x(5)+QIP*x(6)+QIAP*x(8)-QIH*x(2))/VIH;
F3=QIG*(x(2)-x(3))/VIG;
rLIC=FLIC*(QIA*x(2)+QIG*x(3)+QIPN*x(10));
F4=(QIA*x(2)+QIG*x(3)+QIPN*x(10)-QIL*x(4)-rLIC)/VIL;
rKIC=FKIC*QIK*x(2);
F5=(QIK*(x(2)-x(5))-rKIC)/VIK;
F6=(QIP*(x(2)-x(6))-(VIPI/TIP)*(x(6)-x(7)))/VIPC;
rPIC=FPIC*QIP*x(2);
F7=((VIPI/TIP)*(x(6)-x(7))-rPIC)/VIPI;
F8=(QIAP*(x(2)-x(8))-(VIAPI/TIAP)*(x(8)- x(9)))/VIAPC;
rAPIC=FAPIC*QIAP*x(2);
F9=((VIPI/TIAP)*(x(8)-x(9))-rAPIC)/VIAPI;
rPIR=(SGH/SBGH)*rBPIR;
F10=(QIPN*(x(2)-x(10))+rPIR)/VIPN;
F=[F1;F2;F3;F4;F5;F6;F7;F8;F9;F10];
```

Finally, the solution of the global system (1) is obtained by the following code function solution

```
[T,X]=ode45('second_member',[0:12],X0);
```

where X0 is vector of initial values for variables as presented in the table 4.

Table 2: *Initial values for solving the system of equations in (1)*

Variable	I_B	I_H	I_G	I_L	I_K	I_{PC}	I_{PI}	I_{APC}	I_{API}	I_{PN}
Initial value	2.06	8.2	4.56	9.54	7.96	5.16	3.19	3.16	2.9	6.5

The numerical resolution of the system (5) using the parameter values in the table gives us the values of I , γ and I_l which are replaced in the relation (4) to get S . Therefore this allows us to obtain the value of r_{PIR}.

Remark that all problem constants are defined as global variables. These constants should be introduced by a function which we have called pardef.
As in many software environments, typical problems in MaTlaB are solved interactively and the results displayed graphically. Here is an example of MaTlaB command lines for plotting the problem solution.

```
>> pardef,[tt,X]=solution;
>> plot(tt,X(:,1))
```

4. SIMULATION RESULTS

For our simulations we have considered parameters presented in the tables 3 and 4.

Table 3: *Values of parameters for pancreas-incretins model presented by the system (5)*

Parameters [units]	**Parameters [units]**
G_H^B =91.5 mg/dl	r_{PIR}^B =4 mU/min
G_H =100 mg/dl	V^γ =9.93 l

M_1 =1.00797 min^{-1}	I_{l0} =6.33 U
M_2 =0.136 min^{-1}	$OGCs$ =0
φ_1 =0.003 l/pmol	δ =0.009 pmol/min
φ_2 =0.0001 l/pmol	$r_{M\gamma C}$ =0.14 l/min
α =0.998 min^{-1}	τ_ν =25 min
β =0.931 min^{-1}	ψ =0.575 U/min
K =0.00794 min^{-1}	

Table 4: *Values of parameters for insulin model*

Vascular volume [l]	Blood flow rate [l/min]	Fractional clearance/ Time [min]
V_B^I =0.265	Q_B^I =0.45	F_{LIC} =0.4
V_H^I =0.985	Q_H^I =3.12	F_{KIC} =0.3
V_G^I =1.07	Q_G^I =0.684	F_{PIC} =0.148
V_L^I =0.945	Q_L^I =0.9	F_{APIC} =0.02
V_K^I =0.505	Q_K^I =0.72	T_P^I =20
V_{PI}^I =6.3	Q_A^I =0.18	T_{AP}^I =20
V_{PN}^I =0.998	Q_P^I =1.05	
V_{PC}^I =0.44	Q_{AP}^I =0.36	
V_{API}^I =0.411	Q_{PN}^I =0.036	
V_{APC}^I =0.07		

The physiological effects of organs to the response of insulin actions are presented in the figures 2, 3, 4 , 5 , and 6.

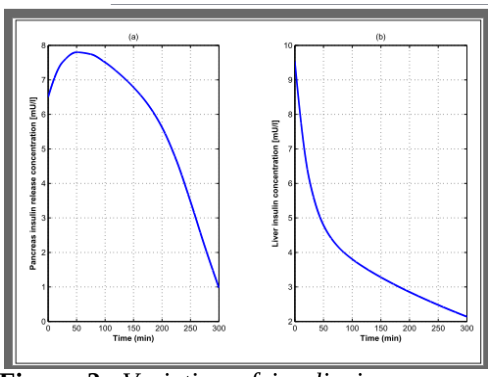

Figure 2: *Variation of insulin in pancreas (a) and liver (b) compartments*

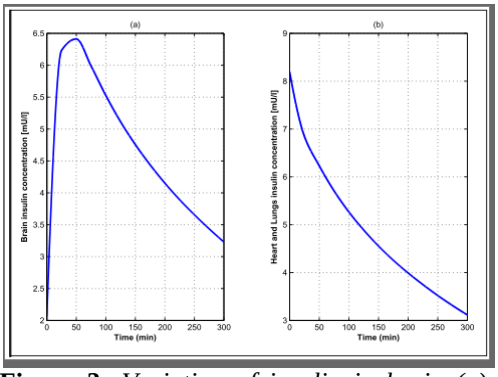

Figure 3: *Variation of insulin in brain (a) and heart (b) compartments*

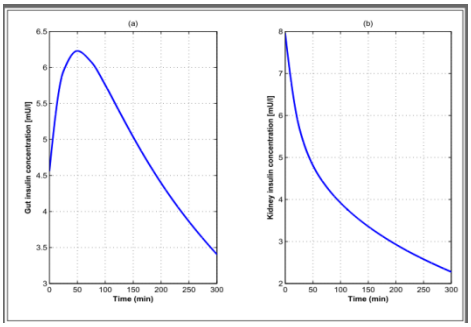

Figure 4: *Variation of insulin in gut (a) and kidney (b) compartments*

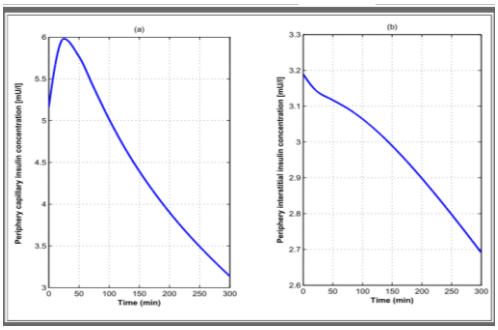

Figure 5: *Variation of insulin in capillary (a)and interstitial (b) periphery compartment*

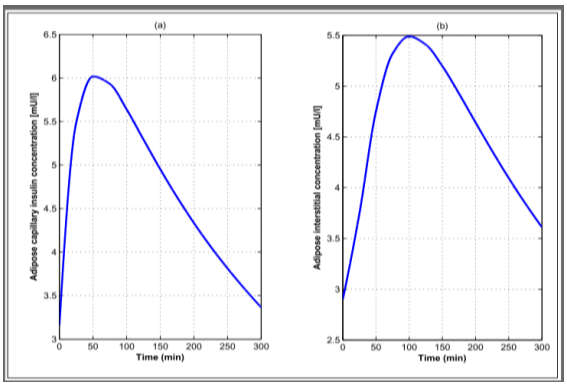

Figure 6: *Variation of insulin in capillary (a) and interstitial (b) adipocyte compartment*

The results are presented in 5 different figures. Each figure contains 2 graphs representing 2 organs or tissues grouped due to their physiological functions.

Actually a person develops Type 2 diabetes when there is no control of blood sugar levels in his body through a decreased sensitivity to insulin which results in plasma high glucose level concentration. This makes the pancreas regulate that disturbance by secreting insulin. The figure 2(a) shows a decrease of insulin concentration in the pancreas against the time. The pancreas secretes insulin to regulate the presence of high glucose concentration in the blood plasma. Once insulin reaches the plasma, it is used by the major target organs for insulin action specialized for fats breakdown and energy storage; liver, muscles and adipose tissue, hence, the decrease of this insulin concentration as shown in the figures (b),5 and 6 . In addition the rest of organs such as brain, heart gut and kidney. The figure 3 expresses the decrease in insulin concentration in the brain and heart because insulin helps neurons in promoting and using glucose in areas involved in improving memories and participate in the glucose uptake and the regulation of substrate utilization such as myocardial energy metabolism and protein synthesis. The figure 4 shows how insulin decreases in gut and kidney by helping the cells in glucose and fats uptake after nutrients absorption. After entering the renal tubule lumen, more than 99% of the filtered insulin is reabsorbed by tubule cells in degradation process and relatively little insulin is ultimately excreted in urine.

5. CONCLUDING REMARKS

In present work, we have shown the impact of insulin hormone failure effects in the development of Type 2 diabetes during its circulation into the blood. The pancreas releases insulin at a high concentration and this insulin quantity is captured by some target organs such as the liver, heart, kidney to respond to the high glucose level, to participate in the energy storage because a person with this diabetes, his body is not able to respond to the insulin secretion. The decrease of this insulin concentration in all of those organs specifies the reaction of a diabetic patient body because his organs try to use the quantity received in the regulation of glucose level concentration as the patient is suffering from Type 2 diabetes.

The findings of our studies contribute new knowledge on the pathophysiology of Type 2 diabetes. Further progress in this field could provide much information enabling better lifestyle modification programs to prevent Type 2 diabetes.

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