RESEARCH ARTICLE

MEDICATION-FREE MANAGEMENT OFTYPE 2 DIABETESMELLITUS: EMPIRICAL AND MODELING-BASED CASE STUDY

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Manuscript Info	*Abstract*
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This study addresses the possibility of medication-freemanagement of type 2 diabetesmellitus (DM). Typical glucose values, in terms of hemoglobin A1C (HbA1C) test resultsof less than6.0%, could be attained by consuming low carbohydrate meals and participating in physical exercises without pharmaceutical adjuncts. Four to six meals should be consumed in 12 hours, preferably during the day's activities between six in the morning and six in the evening. It is important to walk for about one hour after the main meal, although a better practice is to wait two to three hours after the main meal before doing so. Such an approach assures low glucose levels at night. When possible, lifting weights to develop muscles can help regulate sugar levels in the blood and maintain homeostasis. There are empirical findings that HbA1C values could be reduced by 0.5 in 23 days. These findings were supported by simulation results based on Bergman's minimal model ofblood glucose control. The minimal model is modified to address the role of low-carb meals and physical exercises by simulation and is used to study the effects of different model parametersthat represent the liver and muscles. Simulation-based sensitivity analysis is presented, showing positive results toward mitigating type 2 DM.

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Introduction:-

Diabetes mellitus (DM), often simply called diabetes [1-34], is a chronic metabolic disorder in the human body. It is diagnosed as a state of low insulin sensitivity or an insulin-resistant state. The main characteristic of DM is hyperglycemia due to dysfunction of insulin secretion, insulin influence, or both [1]. Usually, DM is classified into type1 and type 2 [2-4].Type 1 DM, also known aschildhood diabetes, generally arisesfromthe destruction of pancreatic beta cells, leading to a state of insulin deficiency or absence [5].Type 2 DM, which has usually been associated with adults, has recently gained another name—adolescent diabetes—because of its presence in an increasing number of patients in their late adolescence. It is diagnosed as a state of low insulin sensitivity or aninsulin-resistant state. The causes of type 1 DM include autoimmune processes or are due to unknown causes of destruction of pancreatic beta cells.The causes of type 2 DM includefactors significantly more focused on lifestyle and genetics [4,6-7]. However, despite the wealth of experience and knowledge concerning the epidemiology, pathophysiology, and medical management of type 2 diabetes in adults, we know little about the disease in children [34].

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According to their study [8], DM, especially type 2, is increasing steadily worldwide. The number of affected people is expected to double in the next decade due to increases in the aging population [4]. In 2017, the number of people with DM worldwide was estimated to be 451 million. The expectation is thatDM will increase to 552 million by 2030 [4] and to 993 million by 2045 [8].

Conditions of hyperglycemia are associated with symptoms such as frequent urination, thirst, blurred vision, and fatigue [9]. The incentive of lowering glucose levels is linked to reducing or removing health risks and increasing the quality of life of the person with DM [9], without medical treatment for or management of DM, the person with DM will be subject to severe health risks. Some examples of such risks include long-term damage, dysfunction, and failure of different organs, especially those within the vision, urinary, nervous, and circulatory systems. The complications of DM might eventually lead to loss of extremities and, finally, to death. Diabetes mellitus is one of the reasons for the high morbidity rate and mortality [4].In 2017, 5 million deaths worldwide were attributable to DM in people aged 20 and above [8].

People with DM should consult with their physicians for help and guidance in reducing the levels of blood glucose concentration as they seek a better health status and an improved quality of life. Usually, treatment of type 2 DM includes medication and changes of habit and lifestyle. As was reported by[10], there are different medication treatments, either oral or injectable. It is important to highlight and stress that the responsibility and decision-making for the type of the medicationare those of the physician, in consultation with the patient or the patient's guardian or parent. As was pointed out by their research [10], not only are medication treatments essential, but lifestyle changes, as well, are beneficial in type 2 DMmanagement.

Changing eating and sports habits are two important examples of lifestyle changes.Studies by [11-13] found that a low carbohydrate diet reduced glucose concentration. Thus, people with DM might substantially improve their quality of life and reduce health risk factors by seeking a similarly healthy diet. In addition to seeking to maintain a healthy diet, [14-18] found physical activity to be an important factor for managing type 2 DM. Activities such as aerobic exercises, resistance exercises, or both improve glycemic control and reduce health risks.

As pointed out in [18], the type 2 DM condition is highly linked to weight and the inability to control blood sugar levels. This condition forcespeople with type2 DM to inject themselves with insulin doses when needed. The insulinhormone regulates and facilitates the movement of sugar into the liver, muscle, and fat cells. As suggested by their study [18], careful scheduling of meals mitigates the need to use insulinand other DMmedications. Scheduling could be accomplished by consuminga starch-rich breakfast early in the morning, coupled with a small dinner in the evening.

Diagnostic tools are essential for DM treatment and management. In the following paragraphs, a concise review is given regarding the glucose tolerance test and mathematical modeling.

Mathematical modeling [19 − 33] of glucose homeostasis, insulin-controlled, glucagon-controlled, and insulin-glucagon-controlled systems forpeople with DM to understand their conditions and associated complications is rapidly growing. When mathematical models are used as diagnostic and treatment tools the understandings, they provide grant new insights into the underlying mechanisms involved.

In [10], the intravenous glucose tolerance test (IVGTT) is a standarddiagnostic tool used to assess pre-diabetic and diabetic conditions by measuring blood glucose and insulin changes after exposure to a large bolus of glucose.

Mathematical models [22, 26, 28] widely accompany the analysis of IVGTT results and are used to improve the understanding of blood glucose regulation, offering insights into the relationships between key components such as the dynamics of the relationship between glucose-insulin dynamics and speculation about the effects of different parametersand activities on DM conditions.Similar studies, such as [29], have consideredthe glucose-insulin-glucagon dynamics.

In the review by [27], based on wisdom gained in the five past decades of modeling in the field, the aims of developing DM models are to understand the dynamics of the glucose levels in the blood and identify potential therapeutic targets for its control and treatment.

Another study highlights the motivation of using mathematical modeling. As was given by [30], mathematical modeling of glucose metabolism has a longstanding tradition. Models have been used for indirectly calculating parameters of physiological interest from experimental data, providing unambiguous quantitative representationsof pathophysiological mechanisms, to determiningindices of clinical usefulness from simple and practicaltests.

In their study [31], the power and strength of mathematical models are demonstrated by analyzingthe static and dynamical properties of the proposed models. These models are capable of representing different types of diabetes and other dysfunction in the insulin-glucose system.

Mathematical models can seek good practices. As was shown in [32], the power of a mathematical model was demonstrated by getting good dietary advice such as a daily value of exogenous glucose intake to keep blood glucose within a reasonable range for everyone.

As stated by [33], mathematical modeling can significantly impact our understanding of metabolic regulation. Bergman's minimal model [21, 24, 33] is a part of an extensive number of mathematical models that have enabled the scientific community to understand metabolic physiology, predict the temporalcourse of metabolic disease development, and design devices to regulate blood sugar more effectively.

In summary, it is possible to conclude that thebody of researchhad gained substantial knowledge regarding type 2 DM and the steadily increasing number of people with DM.

This manuscript highlights and readdresses the risks of type 2 DM and suggests a management method without consuming any medications.

The following hypothesis is raised to seek good results and sustainable diabetes-free conditions: every person with DM can naturally control their blood glucose levels. The means for achieving this goal are threefold: (1) every person with DM should follow a personal schedule of free or low-carb meals; (2) every person with DM should follow a sports plan (walking and muscle building); (3) every person with DM should find the best synchronization between meals and sports.

The wisdom gained is supported empirically by addressing medication-freeglucose management for more than 11 years. The study's subject is a person with DM who used lifestyle changes, including general time scheduling and specific types and timing of meals and avoiding all glucose-management pharmaceuticals during the entire study period.The empirical findings were supported by performing sensitivity studies using Bergmann's minimal model for glucose control.

The suggested plan ofaction includes three steps: (1) a suggestion of a working procedurefor type 2 DM management; (2) an explanation of how does the procedure works and; (3) a means of motivating self-discipline and adopting responsibility for acting in a waythat enables the person with DM to regulate glucose levels without medication.Consultation with the physician is always essential and mandatory.

The manuscript is arranged as follows: materials and methods are addressed in section 2, the self-managing procedure of type 2 DM is given in section 3, simulations by the minimal model of glucose dynamics are given in section 4, numerical examples are given in section 5 and finally, summary and conclusions are given in section 6.

Materials and Methods:-
This study aims to address the need to increase awareness among people with type 2 DM and motivate them to use self-regulation and self-management of their hyperglycemia without pharmaceutical medications,to reduce their blood glucose levels.As mentioned in the introduction, type 2 DM is recognized as a growing global problem. The health risks that the disease posesreduce thequality of life of the person with DM.

Hypothesis:
The central hypothesis of this study is to ensure that, by increasing awareness and changing lifestyle and habits without consuming medications, it is possible to reach normal glucose levels and thus eliminate significant DM-related health risk factors. We hypothesize that it is possible to reduce blood glucose concentration without

medication. If the person with DM follows the suggested procedure, glucose levels below 126 mg/dl, or HbA1C values below 6.0%, could be achieved.

Research question:
How can the hypothesized low glucose levels be achieved?

The current research indicates that thetargeted objective of self-regulation of glucose levelscould be achieved by changing habits, specifically, by adopting personal low-carb meals and by participating in sports.

Methods:-
The answer to the research question is achieved by following two paths: The first is theexperimental-based case study, where empirical wisdom is gained by evaluating a case study of a person with type 2 DM. The second path follows a simulation-based sensitivity study. With the aid of local health services, datafor the projectwere collected and analyzed over more than 11years.The study's conclusions, obtained by analyzing collected data, are supported by conducting simulations and performing sensitivity studies based on Bergman's minimal model.

As previously stated, data were collected from the local health services for more than eleven years. The data specificallyincluded two variables—body weight in kilograms (kg)and the percentage of HbA1C in blood. Following the suggested plan of action, conclusionswere extracted from the data based on interpreting the changes of the variables concerning time. The data is presented graphically and is arranged in tables.

The sensitivity studies,conductedusing Bergmann's minimal model, address the effects of consuming low carbohydrates meals and participating in sports on the dynamics of glucose and insulin and their interaction. The results of the simulations are presented for blood glucose concentration and plasma insulin versus time and their relative integrated effect as a result of ±20% change in the model parameters. The simulation predictions were interpreted, and conclusionswere drawn while relating them to the experimental results.

Self-managingprocedure for type 2 diabetesmellitus - a case study
This section considers a case study to demonstrate medication-free self-managing glucoselevels. It is shown that blood glucose levels bel1ow 126 mg/dl are achieved by changing lifestyle habits,including two main activities: 1) consuming low-carb meals; 2) adopting sports activities scheduled between two and three hours after the main meal.

Observations:-
Atthe beginning of 2010,the subject, a 51-year-old, 189 cm high male who weighed 102 kg,discovered by accident that the glucose level in his blood was 500 mg/dl. This shocking high measure of glucose levelled to a panic state characterized by fasting until thefollowing day. After approximately 12 hours,his glucose level had decreased to a value of 250 mg/dl. The new measure gave a hint of what should be done. A decision was made that included two modes of action: changinghis eating habits and adopting sports activities.

The clinical tests performed by the local health services showed a glucose level value of 9.0%, measured in terms of HbA1C (see Table 1). This state was characterized and classified by the physician as type 2 DM. The doctor suggested a treatment regimen that included one tablet of metformin per day,to be taken immediately after the subject ate a meal. The subject, however, refused any treatment based on medication and wished to adopt a medicine-free treatment.

The subject's usual daily behavior before making changes included two meals every day. In the early morning, he had breakfast that included a cup of instant coffee with milk (250 cc). At around 19:00, he had dinner that included a plate full of meat (300g), rice (150 g), bread (4 slices), and a cup of soup. Besides those two meals, the subject could eat fruits, cakes, or other sweets, without obstacles or constraints. In short, the subject hadpoor or no control of his eating habits. Further, because of his work obligations, sportsactivities were not an option.

The treatment procedure included three phases that were adopted and modified by trial and error, based on experiencegained.

First treatment phase:
after consulting with a dietitian, the subject changed his eating habits and sports activities as follows:

Schedule for atypical day:
A) meals - The day's first meal began at 08:00. The meal included three slices of rice chips with three spoons of cheese cream and one tomato. At 11:00, a second meal provided two eggs, a salad or a tomato, and a banana. At 14:00, the main course wasscheduled and included either a meatsteak, a breast of chicken, or fish (300 g), with low-carb vegetables like zucchini, pumpkin, or squash (300 g), and an apple or an orange. The final meal was scheduled at 19:00 and was based on the subject's perception of hunger, with no other constraints placed on consumption; B) sports activity consisting of one hour of walking every morning.

A blood test collected one year later showed that the subject'sHbA1C % level had decreased to 6.4 (see Table 1). The treatment included no medications at all. The time variations of HbA1C for the period 2010-2021 are shown in Table 1. Unfortunately, the values of glucosebegan to increase during the 2016 to 2018 period. Possible explanations of the increase may have been related to a shift of elements of the treatment procedure, breaking the specified habits of low-carb meals,or a decreased sense of obligation to continue sports activities. The increased values in the HbA1C % level alerted that something was not proper in the schedule.

One day, after eating dinner, a dish full of green wheat caused the subject fell asleep for two hours while experiencing profuse perspiration. A home glucosetest set determined that the subject's glucose level was 190 mg/dl two hours after the meal.Again, this was alarming and made mandatory the second change in behavior.

Second treatmentphase:
This phase waslike the first, with two modifications.The first change was to remove the 19:00 meal (dinner) or replace it with a tomato salad with 300g of yogurt. The second change replaced the previously scheduled one hour morning with one hour evening walkwhich started two to three-hours after the 14:00 meal. Good results were achieved in 2019 (see Tables 1 and2).

In early 2020, however, SARS-CoV-2 (the official name of the virus that causes COVID-19) changed the face of the world.In March 2020,the Israeli government closed the country. This closure, or lockdown, dictated the need for a new procedure to treat DM.

Third treatmentphase:
This phase was like phase two, except walking was not allowed. Instead of walking, a 2kg setof weights (see Figure 1) strengthened and built arm muscles. After half a year, the weight of the set was increased to 4 kg.

Figure 1:- 2 kgpracticing set, extracted from https://www.amazon.co.uk/Generic-Dumbell-Weights-Dumbbell-Dumbbells/dp/B07MFZNSGR.

As mentioned earlier, local health service personnel performed periodic blood tests on the subject. Values of the HbA1c are given in Table 1.

Table 1:- Values of HbA1C versus date between the years 2010 and 2021.

Date	HbA1C %
04/03/2010	9.0
10/03/2011	6.4
27/10/2011	6.6
09/06/2013	6.6
30/11/2014	6.4
30/04/2015	6.2
09/05/2016	7.0
01/06/2017	7.0
30/08/2018	7.9
18/06/2019	7.1
11/07/2019	6.6
02/10/2019	5.8
09/01/2020	6.1
25/06/2020	6.0
22/10/2020	6.0
03/08/2021	6.5

Similarly,subject's body weight values are given in Table 2.

Table 2:- Values of body weight versus date between the years 2010 and 2021.

Date	Weight (kg)
04/03/2010	101.8
04/03/2012	97
01/06/2013	94
30/11/2014	102
30/12/2014	100
09/05/2016	103
01/06/2017	101
01/10/2019	98
22/10/2020	92
23/08/2021	98

Body weight values are plotted against dates and given in Figure 2.
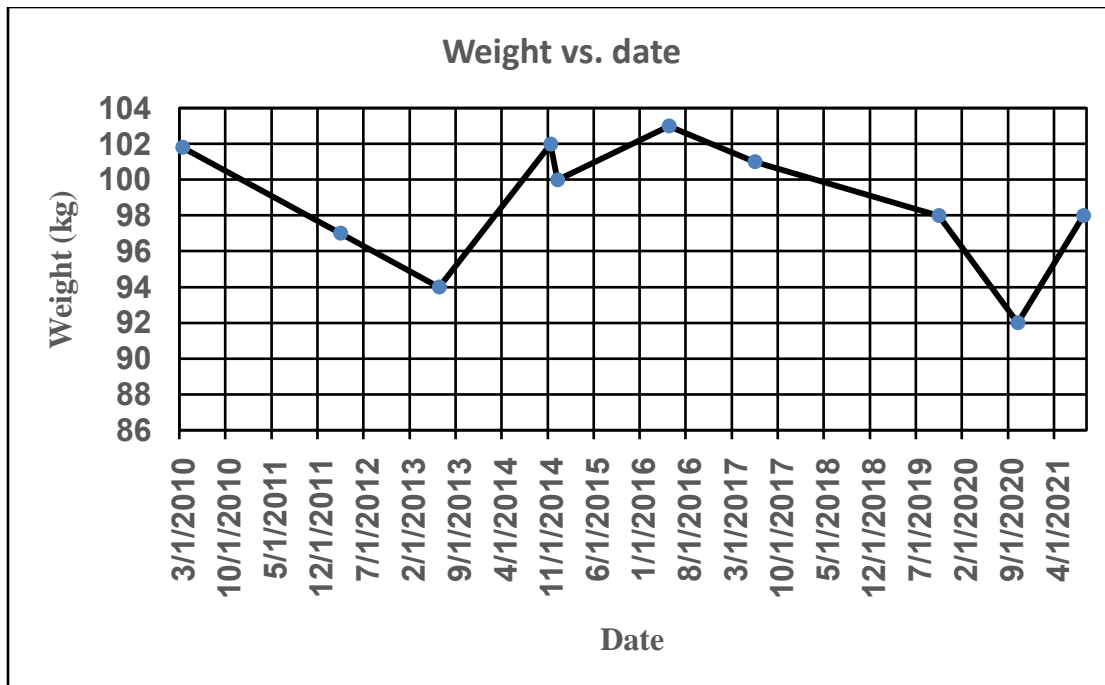
Figure 2:- Body weight versus date for the period 2010 – 2021. See Table 2 for tabulated values.

Figure 2demonstrates the changes in the subject's body weight that were attained following the suggested plan. Body weight values were reduced from 102 kg in 2010 to 94 kg in 2013. Then body weight increased and reached values of 102 kgin 2014 and 103 kg in 2016. By 2020 body weight decreased again, to 92 kg. These values corresponded to the three phases of treatment.

Similarly, Figure 3 demonstrates the changes in HbA1C.
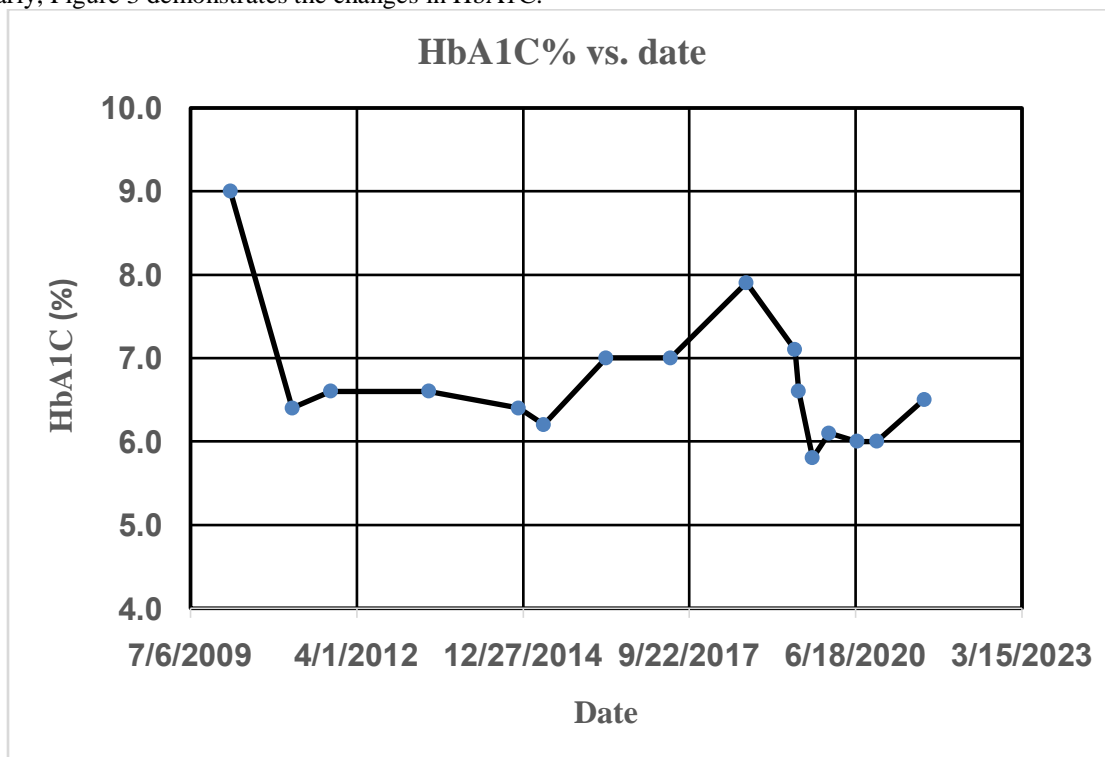
Figure 3:- Values of HbA1C% versus date for the period 2010 – 2021. See Table 1 for tabulated values.

Figure 3 demonstrates the changes in HbA1C attained following the suggested plan. The HbA1C values decreased from 9.0 % to 6.4% at the end of the first year of lifestyle habit changes. These values stayed at values slightly above 6% until 2015. These value changes are most likely related to the subject's loss of discipline and patience and are less likely to a decrease of the subject's obligation to the action plan. However,although by 2018, the values of HbA1Chad increased and reached 7.9%. This increased value motivated the subject to return to stricter adherence to the action plan.

Here comes the great discovery of what should be done (see phase two of treatment). The importance of walking after the main meal was under focus. Blood tests were collected three weeks after phase two was implemented. Those test results were used to determine the effect of delaying the walking time until two to three hours after the main meal. On June 18, 2019,HbA1C% was 7.1, resulting in phase 2 schedule changes. Approximately three weeks later, on July 11, 2019, the HbA1C%value decreased to 6.6, a0.5 reduction (difference between the consecutive values) in 23 days. Eventually, the HbA1C%value reached 5.8by October 2, 2019.

The encouraging test results for HbA1Cchanges continued to deliver results at a 6.0% level, even when virus-imposed restrictions had a chilling effect on worldwide behavior. Phase three treatment, which included muscle-building of the subject's arms, showed that it is possible to practice sports at home even when restrictions deterred prolonged walking.

Weight and HbA1C values were extracted from Tables 1 and 2, then arranged in Table 3 for the convenience of the reader.

Table 3:- Values of body weight and HbA1C during the 2010-2021 period.

| Year	Weight	HbA1C
2010	101.8	9
2013	94	6.6
2014	102	6.4
2016	103	7
2017	101	7
2019	98	5.8
2020	92	6
2021	98.5	6.5

These values are plotted and presented in Figure 4.
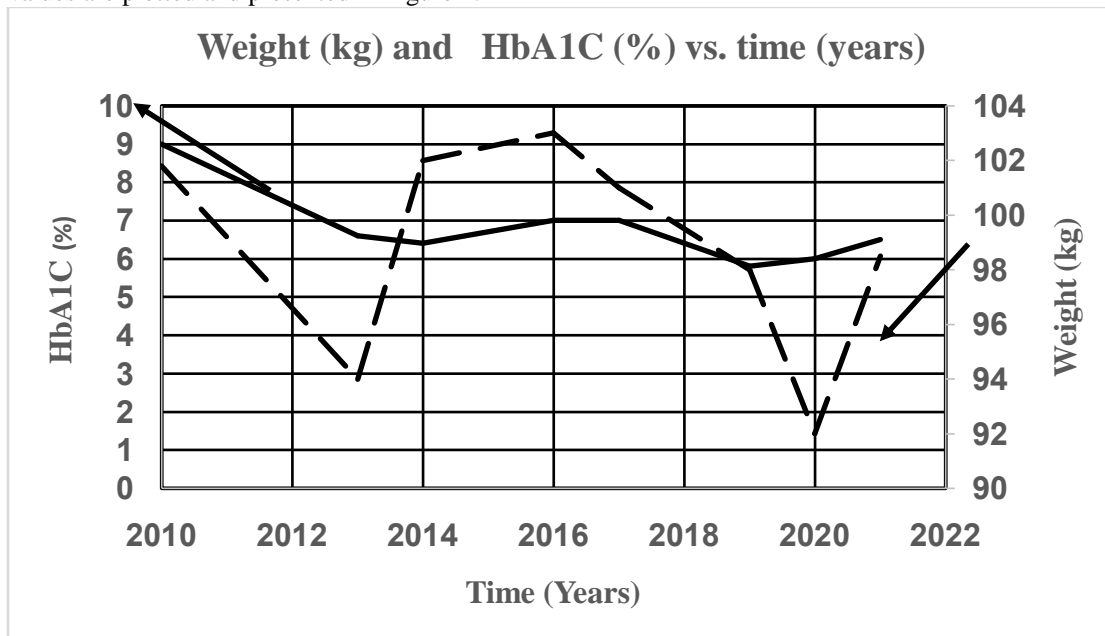
Figure 4:- HbA1C (% - left axis) and body weight (kg – right axis) versus date. (SeeTable 3 for tabulated values).

Figure 4 shows values of HbA1C and body weight versus date. A correlation between the two variables is demonstratedin the figure(e.g., both either decrease or increase). This correlation could be explicitly shown as it is in Figure 5.
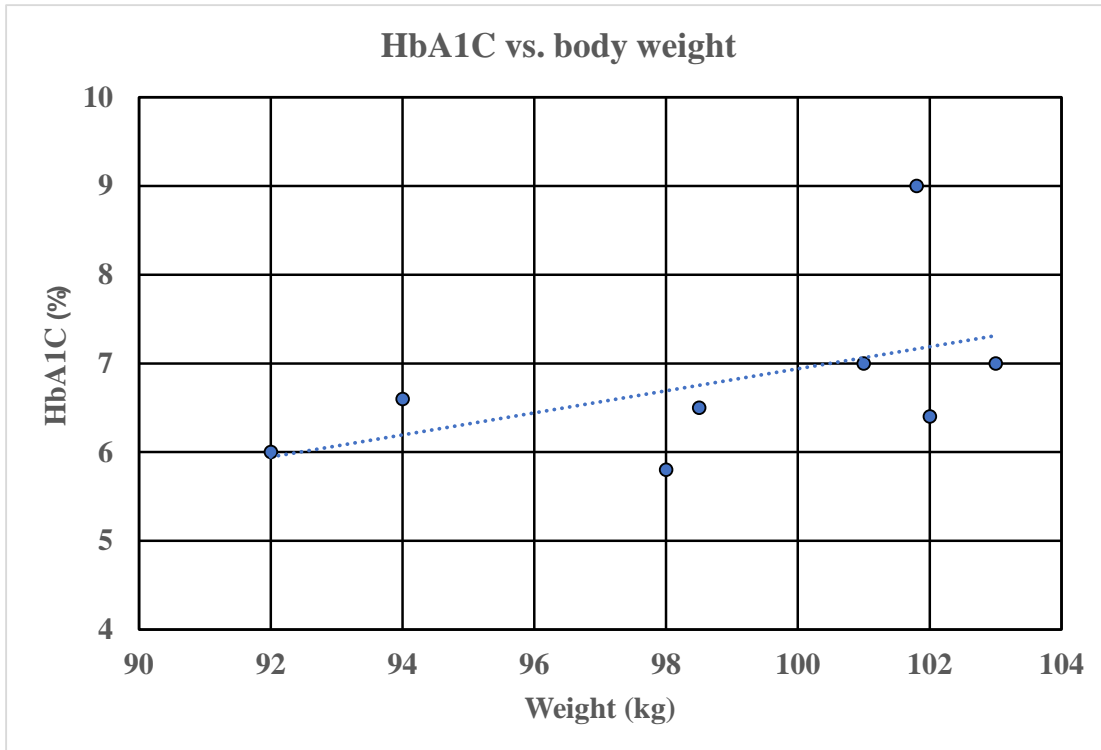
Figure 5:- Values for HbA1Cversus body weight in the year range 2010 – 2021. (See Table 3 for tabulated data).

Figure 5 demonstrates the correlation between HbA1C and body weight. Although the R^2 value is low, the direction of the correlated line (dotted line) is clear.

In summary, the suggested procedure for changing lifestyle or habits, of eating and doing sports, either by walking or by practicing muscle building,can control body weight and HbA1C, and a state of desired values is reached. It is essential to note that thepatience and self-disciplineof a person with DM could control the specified state variables (body weight and HbA1C) by adopting this procedure. While doing that, consultation with the physician and local health services representatives is mandatory.

Simulations by a minimal model of glucosedynamics
Glucose homeostasis and its importance
The human body requiresa stable and continuous flow ofglucoseto maintain its normal behavior. Steady glucose supply comes from the intrinsic hormonal-based control system and the consuming and producing organs of the human body.

Glucose is essential for living cells, and its level should be in a narrow range of 70 – 100 mg/100ml for arisk-free experience [1]. After a rich dose of carbohydrates, the glucose is absorbed from the intestine into the circulating blood in normal subjects. The elevated glucose levels trigger the control system, and the insulin hormone is secreted from the pancreas. This action, in turn, reduces the glucose level as a means of maintaining homeostasis. The glucose is used for fatty acid synthesis, storage as glycogen, protein synthesis, and adenosine triphosphate (ATP)formation.

Insulin lowers blood glucose by increasing glucose uptake in muscle and adipose tissue and promoting glycolysis and glycogenesis in the liver and muscle. Figure 6[1] summarizes a few of the insulin functions towards reducing the high glucose level in the blood.
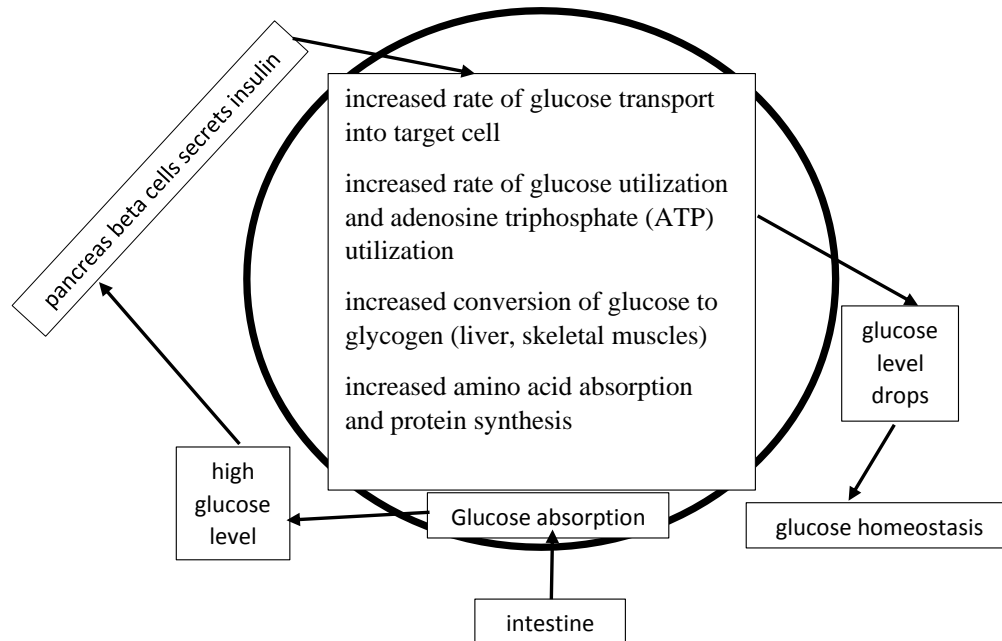
Figure 6:- Schematics of a glucose control system in the human body.

With lower glucose levels, the pancreas releases the glucagon hormone, which has the opposite effect of insulin. As a result of its action,glucose is released from the liver by breaking down glycogen.

In type 2 DM, glucose homeostasis is more complicated, and medical intervention is required. Mathematical models enhance understanding of the effects of several parameters by simulation and design better experiments and controllers (artificial pancreas).

This section reviews Bergman's minimal model [21, 23, 24, 33], using the same notations. The dynamics of the state variables are evaluated concerning their baseline values.Our study uses the minimal model to perform sensitivity analyses, which simulate different processes and actions that a person with DM subject could perform.

Bergman's minimal model
In their study [21], the researchers introduced and applied the minimal model approach as a toolfor evaluating glucose tolerance in humans. The purpose of their study was to determine the specific contributions of pancreatic responsiveness and insulin sensitivity to normal and low glucose tolerance in lean and obese subjects.

In this article, the minimal model is used as a tool for sensitivity studies and evaluation of the model's response to ±20% changes in the model's parameters.

Bergman's minimal model of glucose control includesthe three interacting compartments of glucose, remote insulin, and plasma insulin. At the detection of increased glucose levels, the beta cells of the pancreas release insulin into the blood, which enters the interstitial fluid (the remote insulin compartment). This entry of insulin into the interstitial fluid causes a delayed effect on plasma insulin.

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[1]Figure 6 is based on "Essentials of Anatomy & Physiology", 4th Edition Martini /Bartholome, Copyright © 2007 Pearson Education, Inc., publishing as Benjamin Cummings.PowerPoint ® Lecture Outlines prepared by Alan Magid, Duke University.

As described by their study [21], the minimal model accounts for glucose return to the basal value after injection. A critical experimental discovery was that the effect of insulin needed to be delayed; in fact, insulinslowly leaks into the blood plasma to enter the interstitial fluid before acting on skeletal muscle.
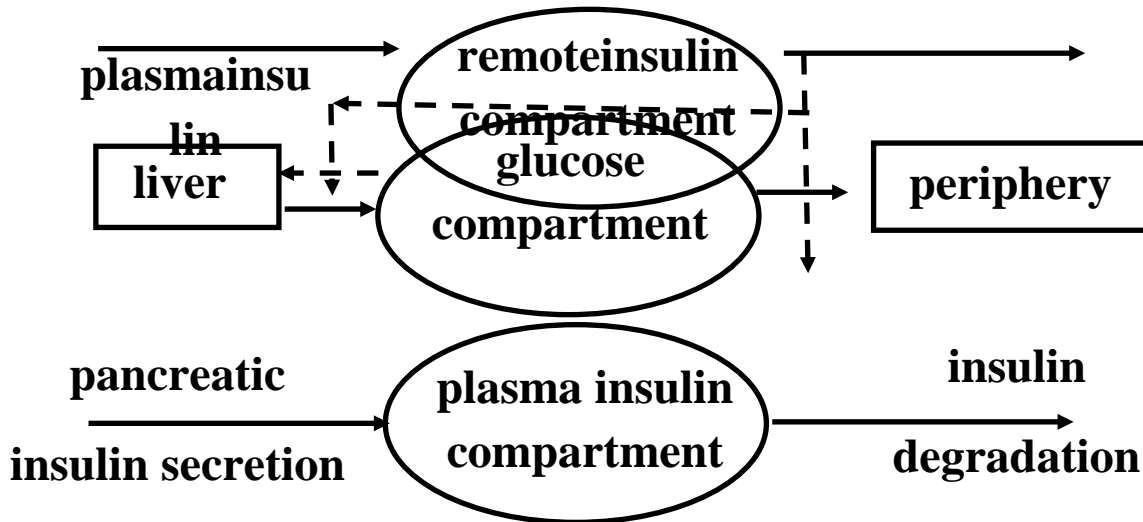

Figure 7:- Schematics of Bergman's minimal model.

Each compartment (see Figure 7) accounts for one variable degraded exponentially, based on its value. The remaining equations account for the rate of substance accumulations in the compartment, which is affected by the input and output rates.The equations of the different compartments are given in the following subsections.

Glucose compartment
While above baseline level, plasma glucose is reduced by its uptake in the liver and peripheral tissues, which are activated by the uptake ability X due to the action of insulin in the remote compartment. The time rate change of glucose is given by:

$$\frac{dG}{dt} = -p_1(G - G_b) - plXG, \tag{1}$$

where G is the plasma glucose concentration in mg/100ml (or mg/dl), p_1 is the non-insulin-dependent rate constant of tissue glucose uptake in 1/min, G_b is the basal glucose concentration in mg/dl, plis the sensitivity factor(introduced in the study – to account for liver function),and Xis the insulin-dependent uptake ability (remote insulin) in 1/min.The initial glucose condition is given by:

G(t=0) =Gi   (2)

Remote insulin compartment
Uptake ability Xincreases with the plasma insulin concentration and is degraded proportionally to its value.The time rate change of X is given by:

$$\frac{dX}{dt} = -p_2X + p_3(I - I_b), \tag{3}$$

where p_2, is the relaxation constant of the uptake ability by remote insulin, in 1/min, p_3, is the uptake ability constant contributed by plasma insulin, in ml/μU·min^2, Iis plasma insulin, in μU/ml, and $I_b$isthe insulin baseline concentration, in μU/ml.Theinitial condition of X is given by:

X(t=0) =Xi = 0   (4)

Plasma Insulin compartment
The plasma insulin concentration is increased by secretion from the pancreas and decreased by decay in the plasma.The time rate change of plasma insulin is given by:

$$\frac{dI}{dt} = -n(I - I_b) + \gamma[G - h]^+t, \tag{5}$$

where n is the decay constant of plasma insulin in 1/min, γ is the rate constant of pancreatic release in 1/min, h is a glucose threshold for which the insulin increase is proportional to glucose level for the specified time interval when G>h.

Equation (5) could be written more explicitly as follows:

$$\frac{dI}{dt} = \begin{pmatrix} -n\,(I - I_b) + \gamma\,(G - h)t\,when\,G > h \\ -n\,(I - I_b)\,when\,G \leq h \end{pmatrix} \tag{6}$$

The initial condition of plasma insulin is given by:

I(t=0) =Ii   (7)

Minimal model-based sensitivitystudies
As one could quickly note, equations (1) – (7) include several parameters that enable the ability to conduct sensitivity analyses. The numerical solution of these equations is done by using the VBA programming language ofthe Microsoft Excel application. The first-order differential equations are solved by the Runge-Kutta 4th order method (see appendix 1).

The sensitivity study based on the minimal model is performed as follows:The baseline case is arbitrarily taken as the lean subject number 1 [21] for each of the parameters given in the following subsections, which are changed by ±20%. Using the simulation program (see appendix 1), the integrated insulin and glucose concentrations over 120 min are calculated and compared to thosecalculated for the baseline case. The integral of the glucose values $A_G$over a period$\tau$is given by:

$$A_G(\tau, \alpha p) = \int_0^\tau G(t, \alpha p)\,dt, \tag{8}$$

where p is the sensitivity parameter, and α takes the values 1, 0.8, and 1.2 to account for the ±20% change in each parameter. The relative change of integrated glucose concentration is calculated as follows:

$$RA_G(\alpha) = \left(\frac{A_G(\tau, \alpha p) - A_G(\tau, p)}{A_G(\tau, p)}\right) \cdot 100\% \tag{9}$$

Similarly, the integral of the insulin values A_I over a periodτ is given by:

$$A_I(\tau, \alpha p) = \int_0^\tau I(t, \alpha p)\,dt, \tag{10}$$

where p is the sensitivity parameter, and α takes the values 1, 0.8, and 1.2 to account for ±20% change in each parameter. The relative change of integrated insulin concentration is calculated as follows:

$$RA_I(\alpha) = \left(\frac{A_I(\tau, \alpha p) - A_I(\tau, p)}{A_I(\tau, p)}\right) \cdot 100\% \tag{11}$$

The parameters studied are summarized in Table 4.

Table 4:- Attributes of model parameters-name, units, and definition.

Parameter number#	Name	Units	Definition
1	p_1	1/min	glucose clearance rate independent of insulin
2	p_2	1/min	rate of clearance of remote insulin
3	p_3	$ml/\mu U \cdot min^2$	increase in uptake ability caused by insulin
4	n	1/min	rate of blood insulin decay
5	γ	$\dfrac{\mu U}{mgmin^2}$	rate of pancreatic release after glucose bolus
6	l	Sensitivity factor	increase or decrease factor multiplying the term XG in equation (1)

Numerical examples
In this section, we consider numerical experiments. Data were extracted from reference [21]. For the reader's convenience,these data are given in the following tables. (Bergman's minimal model parameters and their initial and base values – see Tables 5 and 6).

Table 5:- Model parameters extracted from [21].

#	$p_1.10^2$	$p_2.10^2$	$p_3.10^6$	$\gamma.10^3$	h	N
1	2.96	1.86	6.51	5.36	90.9	0.23
6	1.36	3.41	17.30	0.89	90.9	0.22
9	4.00	0.42	2.56	3.72	154	0.22
12	1.80	1.08	2.29	3.42	153	0.13

Table 6:- Initial and base values of glucose(mg/100ml) and insulin (µU/ml),extracted from [21].

#	G_i	I_i	G_b	I_b
1 lean good tolerance	298	333	94	17
6 lean low tolerance	296	50	98	4
9 obese good tolerance	297	209	100	8
12 obese good tolerance	256	99	110	26

A typical response of the minimal model is given in Figures 8 and 9, which illustrate the behavior of glucose and insulin concentrations versus time,based on the numerical simulation of the model.

The glucose concentrations for the subjects considered in this study are given in Figure 8.
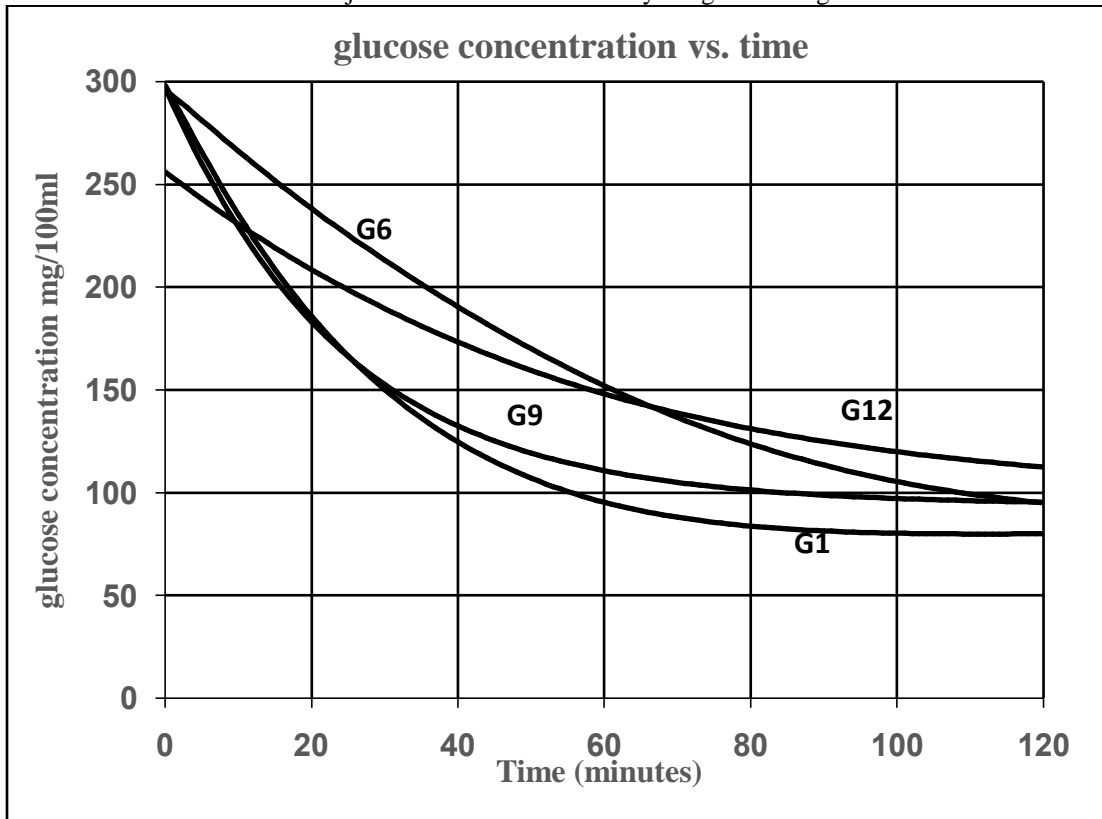
Figure 8:- Glucose concentrations (G1, G6, G9, G12)are plotted versus time for four subjects (1, 6, 9, 12) whose data are given in [21].

The solid lines in Figure 8 show simulation results of Bergman's minimal model for the specified subjects. Similarly, the insulin concentrations for the subjects considered in this study are given in Figure 9.
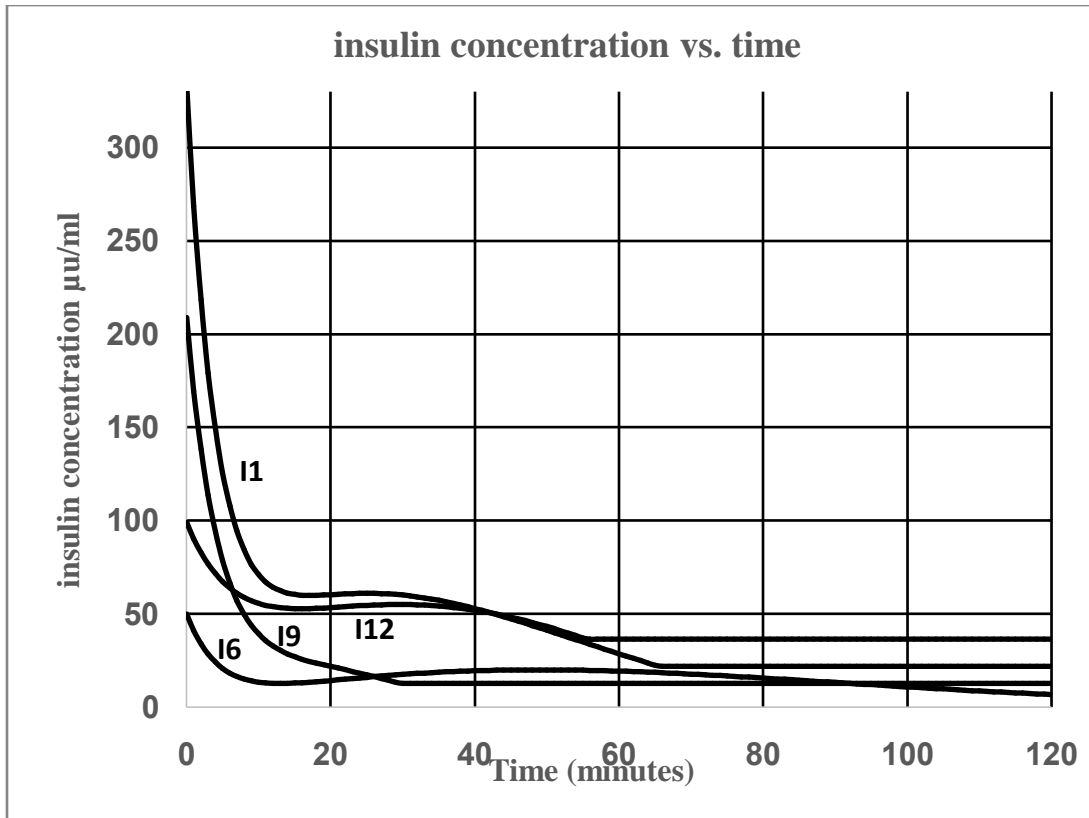
Figure 9:- Insulinconcentrations(I1, I6, I9, I12) are plotted versus time for four subjects (1, 6, 9, 12) whose data are given in [21].

The solid lines in Figure 9 show simulation results of Bergman's minimal model for the specified subjects.

In the remainder of this section, we report the results of the sensitivity analyses we performed. The response times (120 minutes range) of the glucose and insulinconcentration variables are calculated for three values of each parameter considered in the model (1±20%), as was described in the previous section.The calculated results are plotted and shown in Figures 10-21.

Sensitivity of parameter p_1 to ±20%
The results of ±20% changes in p_1 values are given in figure 10 (glucose concentration) and figure 11 (insulin concentration).
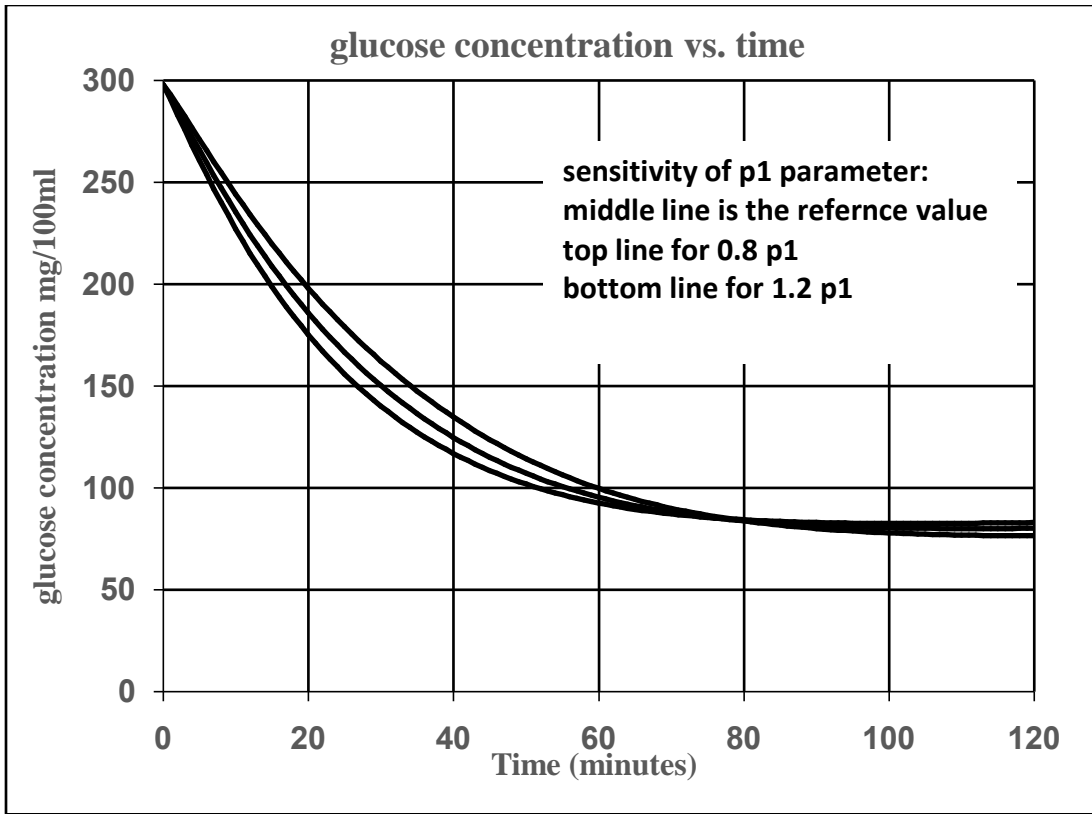
Figure 10:- Glucose concentrationG1is plotted versus time for three values of p_1.

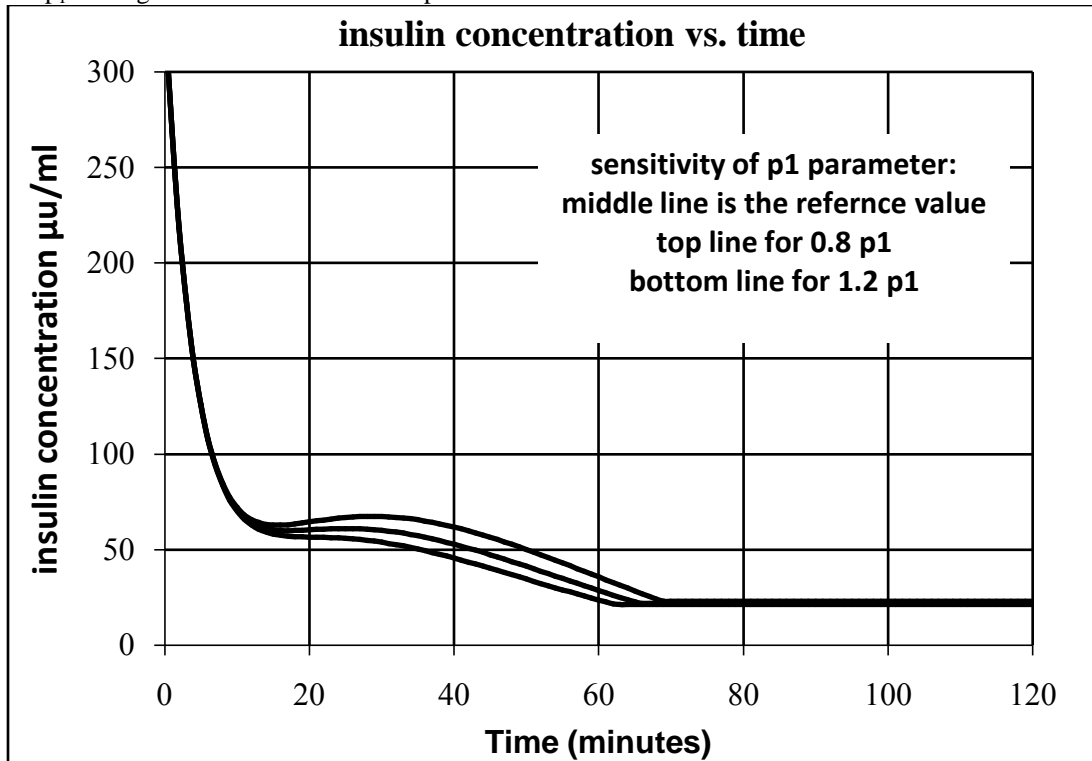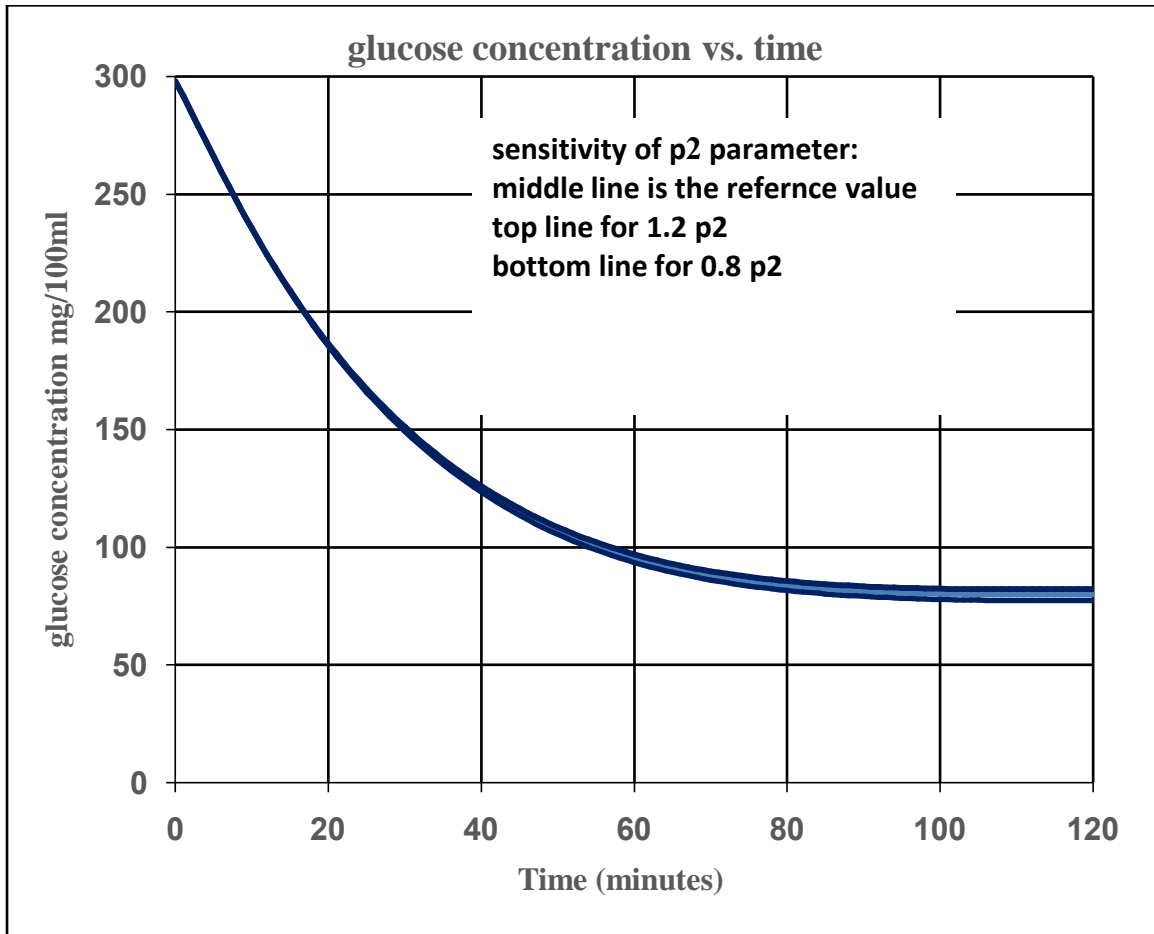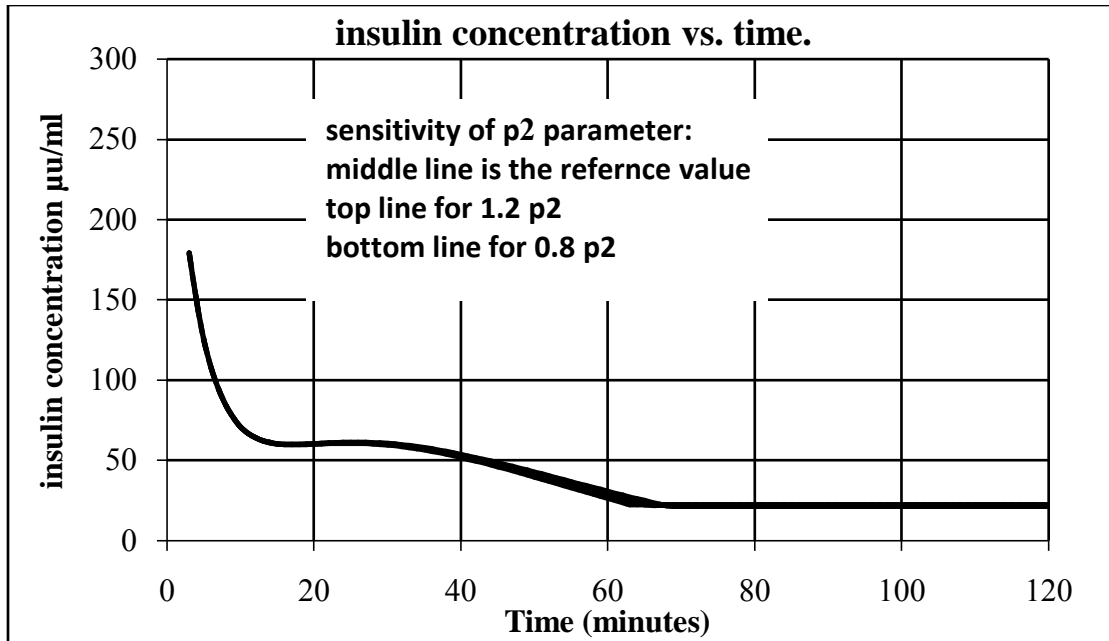Parameter p_1 is the glucose clearance rate independent of insulin.

Figure 11:- Insulin concentrationI1 is plotted versus time for three values of p_1.

When $p_1$was increased, the glucose concentration decreased relative to its reference value (see Figure 10). This effect leads to a reduction in insulin values (see Figure 11). The opposite occurred when p_1 had been lowered. The same effect could be achieved by consuming low-carbs meals or by participating in sports.

Sensitivity of parameter p_2 to ±20%
The results of ±20% changes in p_2 values are given in figure 12 (glucose concentration) and figure 13 (insulin concentration).

glucose concentration vs. time

sensitivity of p2 parameter:
middle line is the refernce value
top line for 1.2 p2
bottom line for 0.8 p2

Figure 12:- Glucose concentrationG1 is plotted versus time for three values of p_2.

Figure 13:- Insulin concentrationI1 is plotted versus time for three values of p_2.

Parameter p_2 is the rate of clearance of remote insulin. When p_2 was increased, the glucose concentration increased relative to its reference value. This effect leads to a reduction in insulin values. The opposite occurred when p_2 was lowered. (See Figures 12 and 13).

5.3Sensitivity of parameter p_3 to ±20%
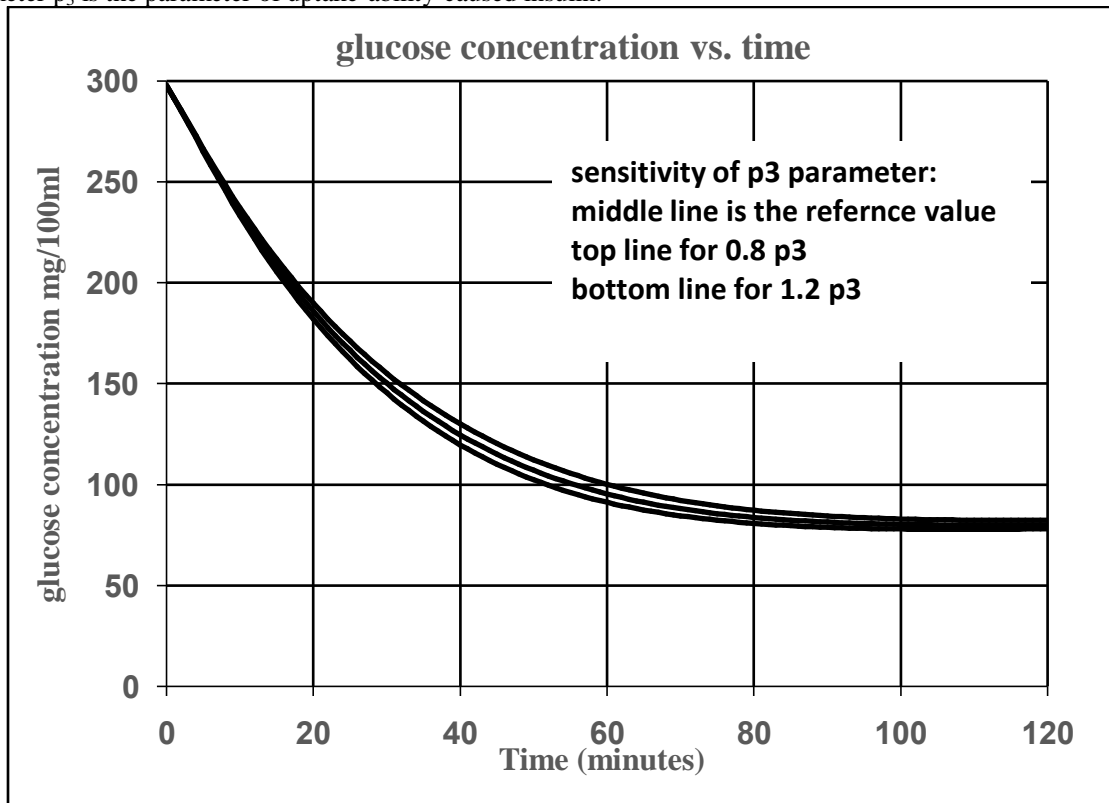Parameter p_3 is the parameter of uptake-ability-caused insulin.

Figure 14:- Glucose concentrationG1 is plotted versus time for three values of p_3.
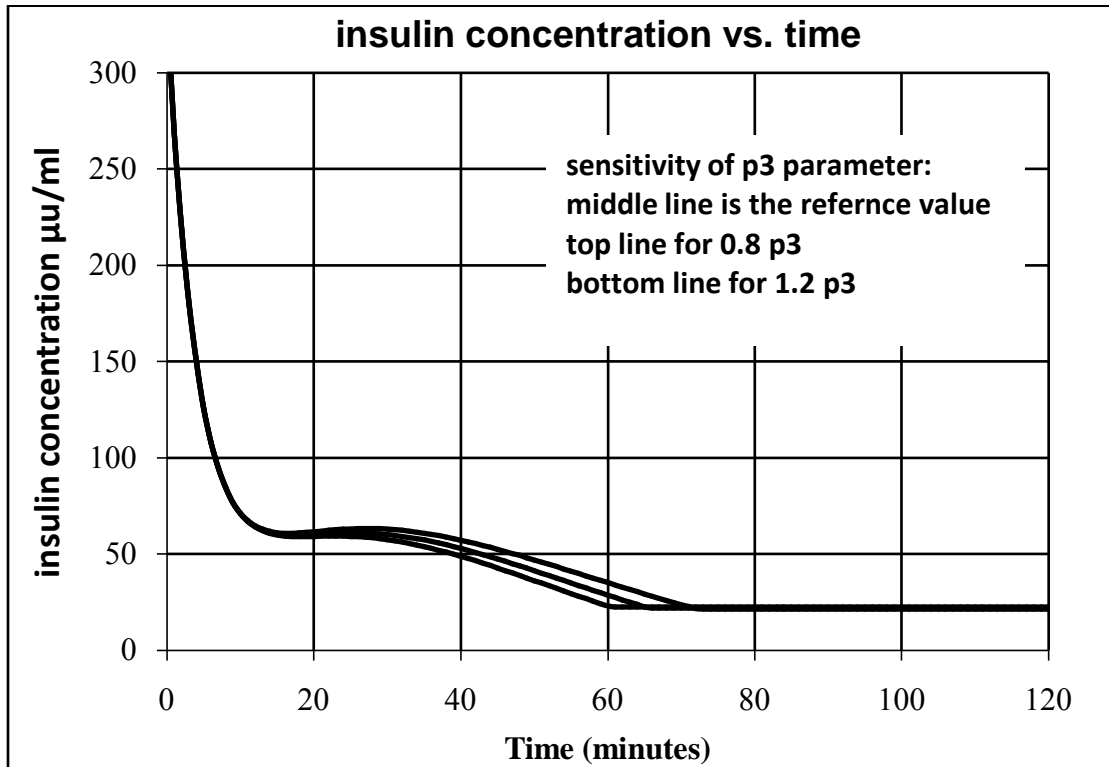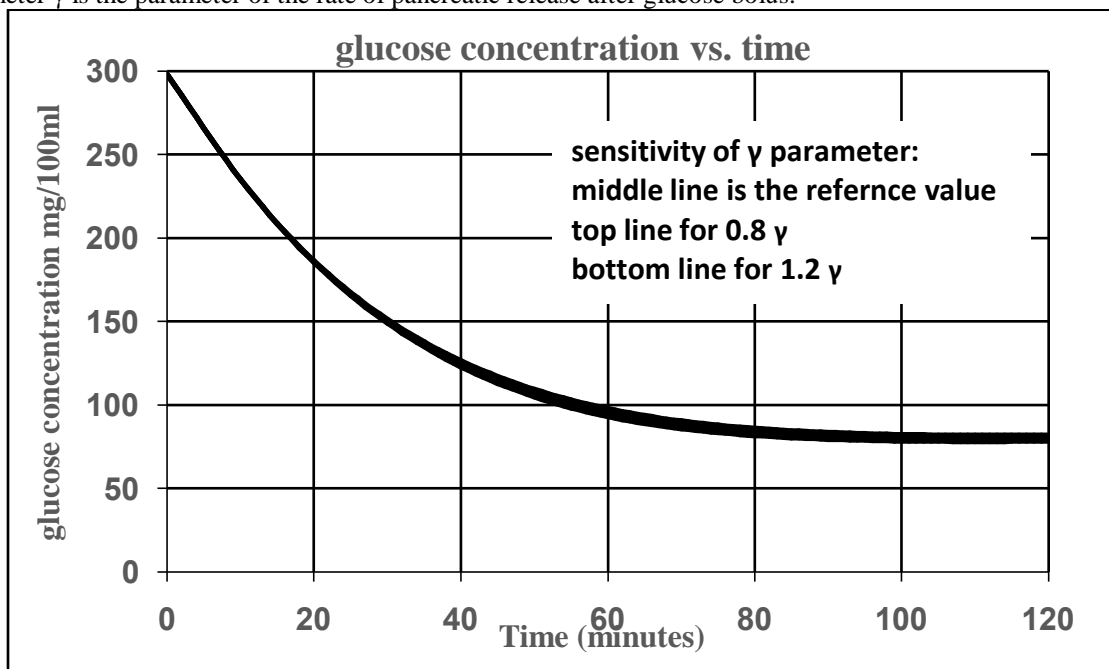
Figure 15:- Insulin concentrationI1 is plotted versus time for three values of p_3.

When p_3 was increased, the glucose concentration decreased relative to its reference value. This effect leads to a reduction in insulin values. The opposite occurred when p_3 was lowered. (See Figures 14 and 15).

Sensitivity of parameter γ to ±20%
Parameter γ is the parameter of the rate of pancreatic release after glucose bolus.

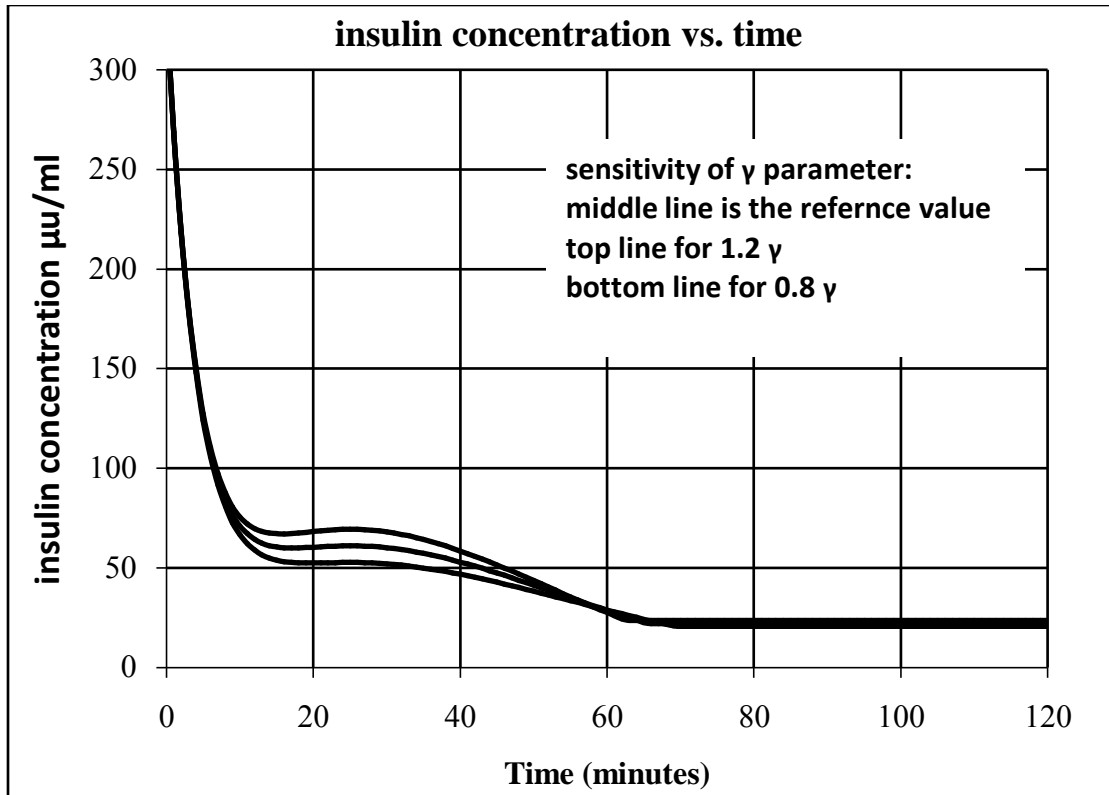**Figure 16:-** Glucose concentrationG1 is plotted versus time for three values of γ.

Figure 17:- Insulin concentrationI1 is plotted versus time for three values of γ.

When γwas increased, the glucose concentration decreased relative to its reference value. This effect leads to an increase in insulin values. The opposite occurred when γ was lowered. (See Figures 16 and 17).

Sensitivity of parameter n to ±20%
Parameter n is the parameter of the decay rate of blood insulin.

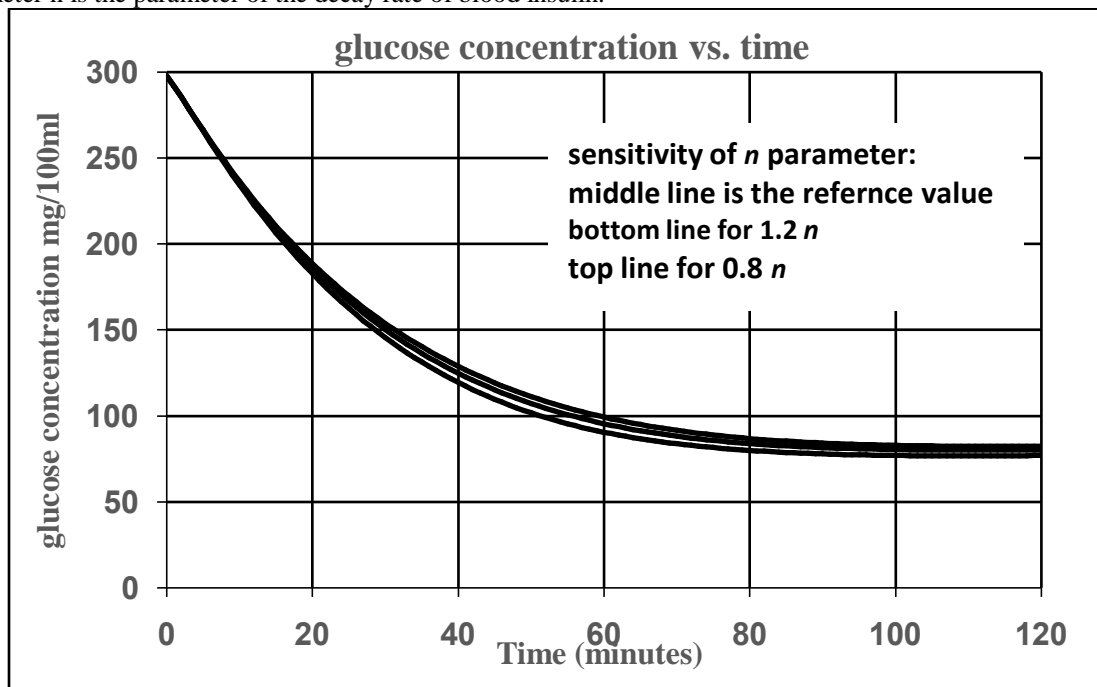**Figure 18:-** Glucose concentrationG1 is plotted versus time for three values of n.
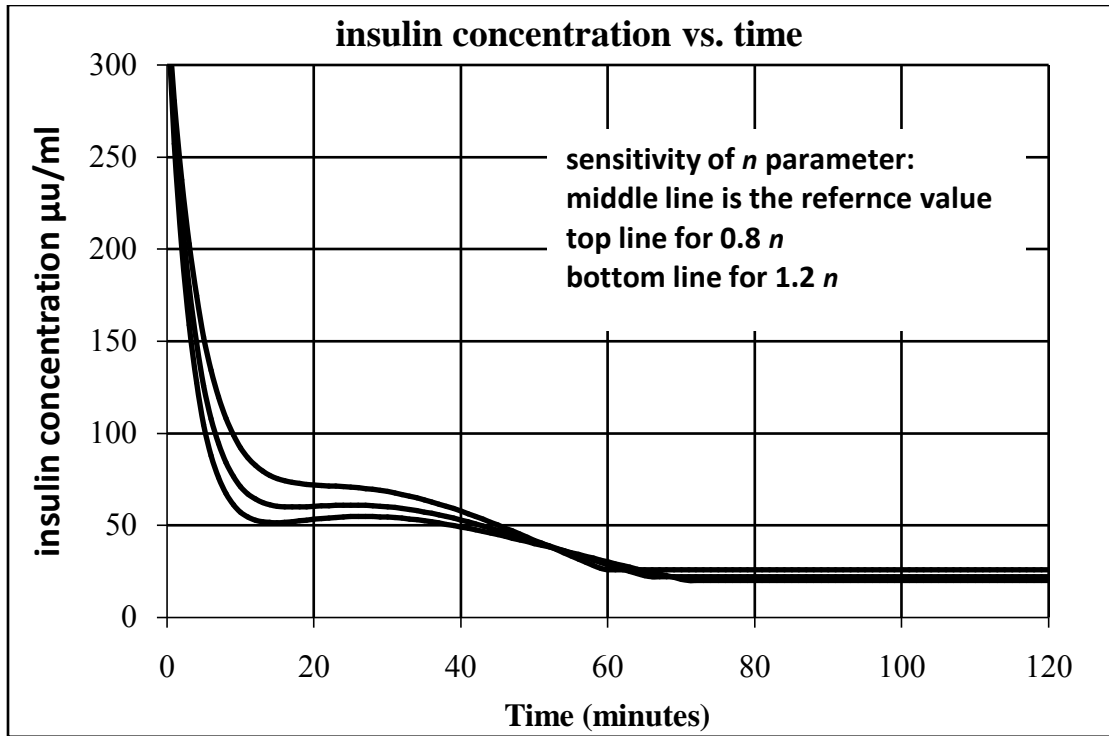
Figure 19:- Insulin concentrationI1 is plotted versus time for three values of n.

When nwas increased, the glucose concentration increased relative to its reference value. This effect leads to a decrease in insulin values. The opposite occurred when n was lowered. (See Figures 18 and 19).

Sensitivity of parameter pl to ±20%
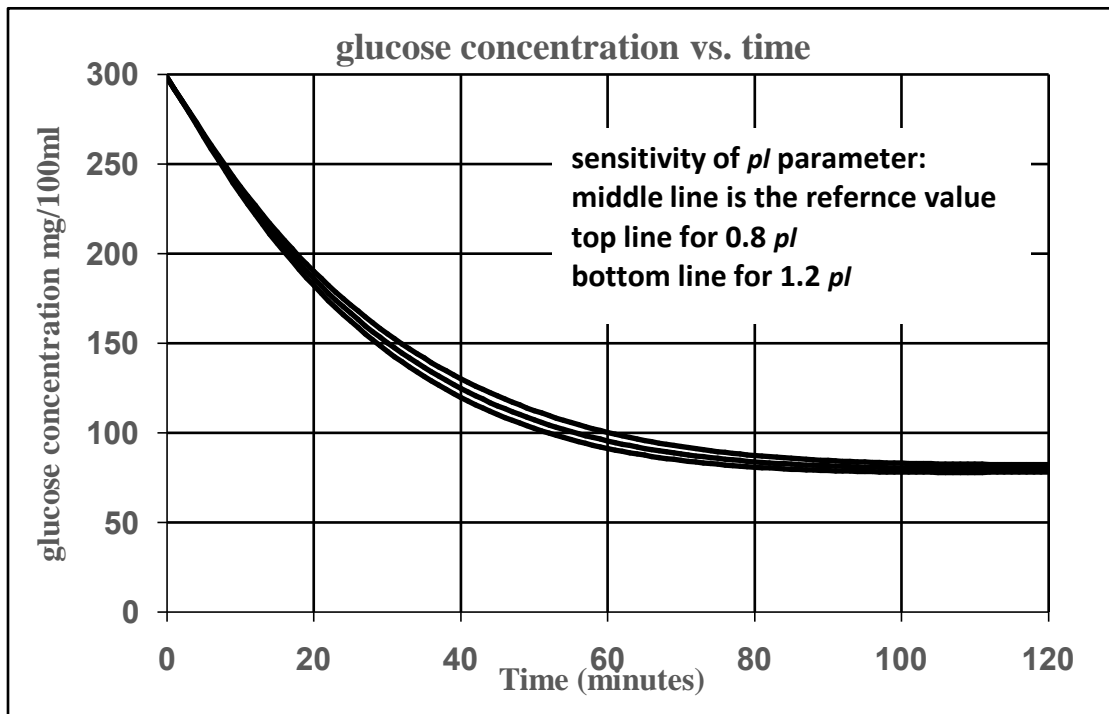Parameter pl is introduced in this study to model liver activity (release or store).

Figure 20:- Glucose concentrationG1, is plotted versus time for three values of pl.
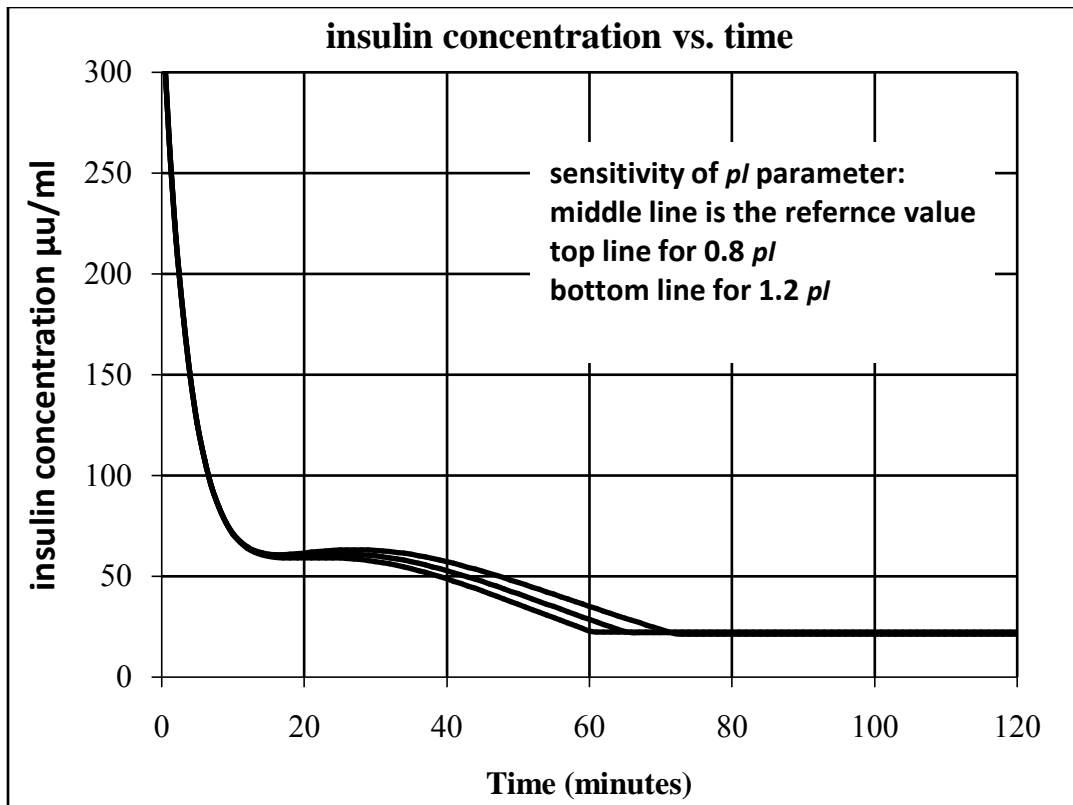
Figure 21:- Insulin concentrationI1 is plotted versus time for three values of pl.

When plwas increased, the glucose concentration decreased relative to its reference value. This effect leads to a decrease in insulin values. The opposite occurred when pl was lowered. (See Figures 20 and 21).

Figures 10-21 illustrated the variations of glucose and insulin concentrations with respect to time, visually.

The integrated relative changes of glucose and insulin (Equations 9 and 11) are summarized in Table 7.

Table 7:- Integrated relative changes of glucose and insulin calculated usingEquations 9 and 11.

Parameter Sensitivity value ±20%	Integrated glucose relative change %		Integrated insulin relative change %	
	-20%	+20%	-20%	+20%
p_1	3.2	-2.6	8	-6.2
p_2	-1.3	1.1	-0.5	0.5
p_3	2.9	-2.6	3.7	-2.8
γ	1.3	-1.2	-6.7	6.6
n	-3	2.2	13.9	-8.8
p_l	2.9	-2.6	3.7	-2.8

Table 7 quantitively demonstrate the sensitivity effects of the various parameters. These effects fall in the range 0 – 10%.

Section 6: Summary and Conclusions:-

This study sought to suggest a treatment procedure to manage type 2 DM without medications. A case study was considered, and an approach to control blood glucose levels was described. The treatment procedure included three phases that were adopted by a trial and error process that was modified according to life constraints and the quality of achieved results. Data were collected during 11 years of treatment. Results included a reduction inHbA1Cvalues from 9.0% to a minimum of 5.8%. This result was achieved by a low-carb diet and by adopting asportsregimen that encompassed walking or lifting small weights to strengthen arm musculature or both.

A sensitivity study based on Bergman's minimal model was introduced to support the experimental findings. It was shown that by changing the parameters of the minimal model, the model variables responded accordingly.Numerical examples were given in section 5.

It is important to stress that there were no prescription medications in the treatment procedure and that the subject remained medication-free throughout treatment. Eating foods with low carbohydrate content will reduce glucose levels in the blood, especially when coupled with participating in sports.These effects could be found in the minimal model while considering the insulin-independent terms, including p_1, pl,and γ (see Table 7 for numerical values).

In conclusion, if desired blood glucose levels could be achieved by changing lifestyle and habits and by adopting a proper treatment procedure, then medications are unnecessary. Most importantly,the subject must act under the umbrella of local health services and the family physician.

The findings outlined herein motivate the need to continue this research protocol,consider more cases to classify the personal needs for each case, and study the complexity of the problem. Such an investigation could be continued at centers where the primary focus is directed to treating and counseling people with DM.

Data Availability
The data used to support the findings of this study are included in the article.

Conflicts of Interest
The author declares that he has no conflicts of interest.

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Appendix 1
VBA code

```
Dim p1, p2, p3, gamma, n, h, i0, g0, gb, ib, al, el As Double

Function f1(t, y1, y2, y3) As Double

f1 = -p1 * (y1 - gb) - al * y1 * y2 - 0.00001 * el * (y1 - 94#) * y3
End Function
Function f2(t, y1, y2, y3) As Double
f2 = -p2 * y2 + p3 * (y3 - ib)
End Function
Function f3(t, y1, y2, y3) As Double
If ((y1 - h) > 0) Then
f3 = gamma * maxm((y1 - h), 0) * t - n * (y3 - ib)
Else
f3 = 0
End If
End Function
Function maxm(a, b) As Double
If (a > 0) Then
maxm = a
Else
maxm = b
End If
End Function
Sub rk4()
Dim y1, y2, y3, t As Double
p1 = 0.0296 * 0.8
p2 = 0.0186 * 1#
p3 = 0.00000651 * 1# * 1#
gamma = 0.00536 * 1#
h = 90.9
n = 0.23 * 1#
al = 1#
el = 0#
gb = 94#
ib = 17#
sumg = 0#
sumi = 0
'tine initial
```

```
t = 0
g0 = 298#
i0 = 333# * 1#
y1 = g0
y2 = 0.0001
y3 = i0
dt = 0.1
For i = 0 To 1200
If (Int(i / 10) * 10 = i) Then
Cells(i / 10 + 2, 1) = t
Cells(i / 10 + 2, 2) = y1
Cells(i / 10 + 2, 3) = y3
Cells(i / 10 + 2, 4) = y2
End If
ga = y1
ia = y3
k1 = dt * f1(t, y1, y2, y3)
l1 = dt * f2(t, y1, y2, y3)
m1 = dt * f3(t, y1, y2, y3)
k2 = dt * f1(t + dt / 2, y1 + k1 / 2, y2 + l1 / 2, y3 + m1 / 2)
l2 = dt * f2(t + dt / 2, y1 + k1 / 2, y2 + l1 / 2, y3 + m1 / 2)
m2 = dt * f3(t + dt / 2, y1 + k1 / 2, y2 + l1 / 2, y3 + m1 / 2)
k3 = dt * f1(t + dt / 2, y1 + k2 / 2, y2 + l2 / 2, y3 + m2 / 2)
l3 = dt * f2(t + dt / 2, y1 + k2 / 2, y2 + l2 / 2, y3 + m2 / 2)
m3 = dt * f3(t + dt / 2, y1 + k2 / 2, y2 + l2 / 2, y3 + m2 / 2)
k4 = dt * f1(t + dt, y1 + k3, yy + l3, y3 + m3)
l4 = dt * f2(t + dt, y1 + k3, yy + l3, y3 + m3)
m4 = dt * f3(t + dt, y1 + k3, y2 + l3, y3 + m3)
y1 = y1 + (k1 + 2 * k2 + 2 * k3 + k4) / 6
y2 = y2 + (l1 + 2 * l2 + 2 * l3 + l4) / 6
y3 = y3 + (m1 + 2 * m2 + 2 * m3 + m4) / 6
t = t + dt
sumg = sumg + (ga + y1) / 2 * dt
sumi = sumi + (ia + y3) / 2 * dt

Next i
Cells(1, 5) = sumg
Cells(2, 5) = sumi
Cells(3, 5) = sumg / sumi
End Sub
```