A DYNAMIC SIMULATION MODEL FOR INSULIN RESISTANCE AND TYPE II DIABETES IN THE CONTEXT OF OBESITY

ABSTRACT

Type 2 diabetes, is a frequently seen endocrinological disease leading to other serious health problems such as heart disease and kidney dysfunction that may eventually lead to a premature death. Insulin resistance is seen as the starting point of this disorder. Obesity, hyperglycemia (high blood sugar), hyperinsulinemia (excess levels of insulin in the blood) are the main reasons for developing insulin resistance and type 2 diabetes, ultimately. Other factors are indicated as age, gender and genetic factors. The aim of this study is to construct a dynamic simulation model that can realistically reproduce the long term behavior of developing insulin resistance and type 2 diabetes related to obesity. For this purpose, a model which shows the relationship between body weight and glucose-insulin mechanism for a healthy body is generated. In the validation part, the effect of obesity on glucose regulation is demonstrated. According to the available research on this topic, doing exercise and changes in the diet may reduce the severity of insulin resistance or even eliminate this disorder completely. Simulation experiments with the model show that different physical activity levels and dietary intakes have impact on developing insulin resistance. Yet in the long run, insulin secretion level and beta-cell dysfunctionality play a more significant role for developing type II diabetes. In conclusion, the obesity factor on insulin resistance and type II diabetes is demonstrated in the model in a major scope, by using available information and data in the literature.

Key Words: insulin resistance, obesity, type II diabetes, medical modeling.

1. INTRODUCTION

Diabetes mellitus is a condition that shows a significant problem in glucose and insulin regulation because of an impaired carbohydrate, fat and protein metabolism, which causes an inadequate secretion of insulin, or a reduction in insulin sensitivity of the target tissues for insulin hormone. There are mainly two cases for this condition, type I diabetes (insulin-dependent diabetes mellitus) and type II diabetes (Guyton, 2006).

Type II diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM), is one of the most common endocrine disorders, which causes serious physiological problems, leading to premature death. About 80-95% of the diabetic patients have type II diabetes (Sizer and Whitney, 2010). In the United States, the fourth leading cause of death by disease is diabetes, as it causes major damage in the cardiovascular system (Tortura and Grabowski, 2004). 11.3% of the U.S. population (about 25.6 million people), who are 20 years or older, have diabetes (NIDDK, 2011). According to the statistical results done by World Health Organization, there are approximately 310 million patients who have type II diabetes in the world (WHO, 2011).

Type II diabetes occurs when the sensitivity of body tissues, such as muscle and liver, decreases and cannot respond adequately to the effect of insulin hormone (Guyton, 2006). This disease is mostly seen in obese individuals who are generally middle aged (older than 30 years). Insulin resistance is indicated as one of the most significant causes for this disorder. Insulin resistance is the inappropriate response to insulin in insulin receptors and target tissues (Tortura and Grabowski, 2004). Besides insulin resistance, there are several risk factors of type II diabetes,

which are obesity, hyperglycemia, genetic factors, age and gender. In this study, the effects of obesity factor on developing hyperglycemia and insulin resistance, and ultimately type II diabetes is taken into consideration.

Obesity is one of the most important factors in developing insulin resistance, and ultimately having type II diabetes. It occurs when there is an imbalance between energy intake and energy expenditure of the body in the long term. In order to prevent this condition, the factors that cause the imbalance should be well-understood, and necessary precautions have to be taken with respect to the related circumstances (Abdel-Hamid, 2002). Currently, obesity has become one of the most prevalent "disorders" in the world. According to the statistics in Turkey; the prevalence of obesity is 32% of total population, and the prevalence of diabetes is 13.7% of the total population based on the 2010 census. When it is compared with the previous study TURDEP-conducted in 1998, it is found that the prevalence of obesity and diabetes has increased by 44% and 90% in the last 12 years, respectively (TURDEP-II, 2010).

To supply sufficient energy for the body, a person needs to get nutrients according to his resting metabolic rate, which is affected by the factors of age, gender, weight and height. Furthermore, the composition of dietary intake is also important, because the energy-yielding nutrients which are fat, protein and carbohydrate give different amounts of energy, and can be converted to each other. When an individual takes one of these nutrients in excess, it is stored as fat in the body. A healthy person can lose fat (and consequently, lose weight) by doing exercise, which is a process governed by a negative feedback mechanism. Therefore, the relationship between food intake and gaining/losing weight is constructed in the model by using the components of energy intake and energy expenditure, which also includes doing physical activity and muscle build up.

On the other hand, fat storage level affects glucose and insulin regulation in the body, which constitute several negative feedback loops. The link between obesity and insulin resistance is represented with this relation. Due to the complexity of human nature, some simplifying assumptions are made for these mechanisms. The key factor of inducing disorder of glucose homeostasis is known as non-esterified fatty acids (free fatty acids), which is a product of fat breakdown. Furthermore, the functionality of beta-cells is also essential in developing type II diabetes, ultimately. Beta-cells are responsible for regulating insulin release, from the pancreas. Therefore, a dysfunction of beta-cells will induce an inadequate response to glucose stimulation by secreting inadequate insulin, which also works in a negative feedback mechanism.

In this study, a dynamic simulation model of developing insulin resistance and Type II diabetes in obese people will be constructed. The aim of the study is to observe the long term behavior of developing insulin resistance when the obesity factor is considered. In Section 2, the macro view of the model is introduced. Section 3 looks at the model in detail. In Section 4, the equilibrium behavior and base behavior of the model are introduced. Validity tests are shown in Section 5. In Section 6, one scenario analysis is conducted. Section 7 summarizes our findings in this study.

2. OVERVIEW OF THE MODEL

The main focus of the model is the body weight maintenance and its properties. Depending on food intake and physical activity, the body weight can be kept at its baseline level. In order to find these, energy levels can be observed. If the energy intake and energy expenditure are equal, then there will be no change in the body weight. However, if energy intake is greater than energy expenditure, the difference which is not used in the body is converted to fat as an energy reserve,

and stored in the fat depot, leading to weight gain. Similarly, if energy intake is lower than energy expenditure, then fat in the storage will break down to meet the energy requirement of the body, which leads to lose weight. Furthermore, doing exercise will help to regulate the body weight, by increasing the level of energy expenditure. If the person continues to gain weight, he ultimately will become obese. In this case, the glucose and insulin regulation metabolism will change with respect to the severity of obesity.

On the other hand, the glucose regulation system in the body is also integrated in the model, and the consequences of impaired glucose metabolism, which is directly related with the diabetes, are discussed in this study. Even though the feedback mechanism of the glucose-insulin regulatory system in the body occurs in a very short span of time, main variables related with the disorder are constructed within the scope of the cause-and-effect relationships. According to fat mass in the body and physical activity endurance, glucose and insulin production and their functionality may be disrupted. Moreover, the insulin secretion from beta-cells, and glucose release and uptake by liver has a significant impact on maintaining glucose homeostasis in the body. Therefore, these variables and their effects are also considered during the model construction step.

The overall causal-loop diagram is given in Figure 1, in order to demonstrate the general mechanism of the system. Since the mechanisms in human body are very complex, this study concentrates only on the long term effects of the main components. Thus, some variables in the mechanism are considered as constants for making simplification in the model. For instance, the glucagon hormone, which increases plasma glucose concentration, and also secreted by pancreas, is not considered in the model. Besides, other hormones, such as leptin and adiponectin, which play important roles in regulation of energy metabolism, and cytokines such as TNF-α, IL-2 and IL-6, which play key roles in the regulation of immune system, are also not shown in the model. On the other hand, the individual in the model is considered as an average male, who has almost sedentary lifestyle, and the reference values are used for this assumption. Furthermore, the values of bone mass and extracellular water mass (ECW) are assumed to be constant for all experiments.

The 1st loop represents the negative feedback mechanism on energy balance-body weight axis. The 2nd loop demonstrates that there is a positive feedback mechanism on energy balance-physical activity-body weight axis. In addition, the 3rd loop displays the glucose transport rate-physical activity feedback mechanism for carbohydrate and body weight. The 4th loop represents the feedback effect of essential protein on body weight change. The 5th loop represents the delayed feedback effect between the physical activity level and muscle mass in the related axis. The 6th and 7th loops demonstrate short-term hormone control mechanisms for glucose and insulin regulation in the body. In addition to the short term effects, delayed effects between insulin secretion and the beta-cell functionality are observed in the 8th negative feedback mechanism.
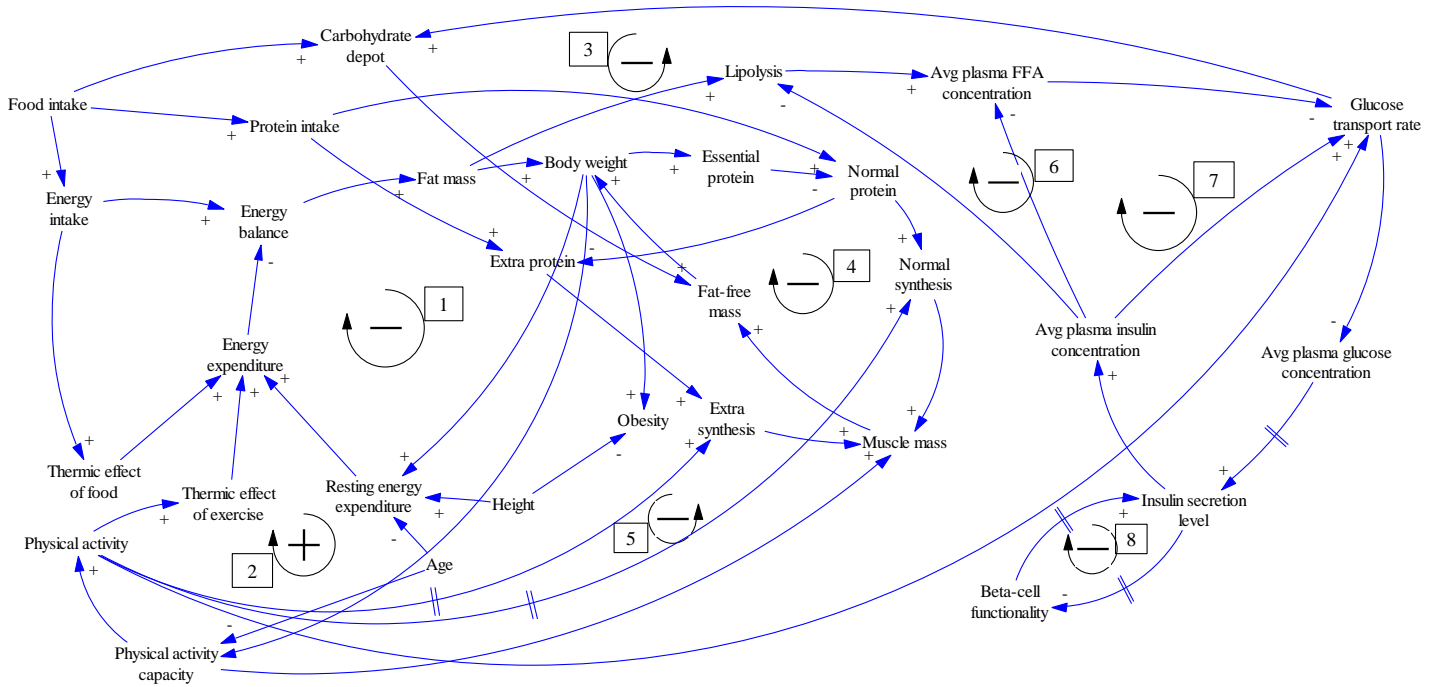
Figure 1. The cause-and-effect diagram of the model

3. DESCRIPTION OF THE MODEL

As discussed previously, obesity is the leading factor on developing insulin resistance. Therefore, the starting point for building the model is constructing the body weight dynamics. The main issues considered in this part are food intake and energy expenditure. Energy expenditure contains three different components which are known as resting energy expenditure (REE), thermic effect of exercise (TEE), and thermic effect of food (TEF). Resting energy expenditure refers to the minimum energy requirement that maintains the functions of the body at awake and resting state, which is measured by three standardized conditions: body weight, age and height (McArdle *et al.*, 2010). This value also differs according to the gender; however, in the model, the individual is assumed as male. Thermic effect of exercise refers to the energy expenditure by doing physical activity, which is also indirectly related to the body weight. Furthermore, thermic effect of food which is also known as diet-induced thermogenesis refers to the energy expenditure for breaking down the food, digestion, transform and absorption of them (Yamada, 2009).

Furthermore, the importance of nutrition intake in weight management is taken into consideration for constructing the model in this study. When the recommendations concerning macronutrients, which are carbohydrates, fats and proteins, are considered, different energy-yielding food intakes will change the fat mass, muscle mass and body weight, consequently.

In the long term, it can be considered that there are mainly two relationships between energy expenditure and body weight. Since body weight has two main components in the model, one of the relationships can be shown between energy expenditure and muscle mass, through fat-free mass, which is constructed via the link of physical activity level. Besides, the other relationship is modeled between energy expenditure and fat mass by using energy balance effect on fat synthesis / breakdown.

On the other hand, when glucose and insulin regulation mechanism is considered, there are several key variables which should be taken into consideration. In this part, average plasma FFA

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concentration level refers to average free fatty acid concentration in blood, in units of *mEq/L*. Since this level changes in minutes (especially after food intake), we take weekly average value for this variable. Similarly, average plasma glucose concentration level and average plasma insulin concentration level are also taken as their weekly average values in blood. Besides, insulin secretion level refers to the amount of insulin release from pancreas (β-cells) in a week which changes according to the plasma glucose concentration level in order to decrease and keep it in the normal values. Secretion from pancreas is triggered when the blood glucose concentration is greater than *70 mg/dL* (Li *et al.*, 2006). In healthy subjects; when insulin hormone is released to blood, insulin receptors play an important role of transporting glucose from blood to the target tissues such as adipose tissue, liver and muscle. Beta-cell functionality refers to the ability of reaction for the rise of the blood glucose level. In healthy subjects, beta-cells respond to the level of glucose concentration in a normal way. However, in obese individuals, beta-cell dysfunction may be present which leads to type II diabetes, as the extreme condition. HOMA-IR index refers to "Homeostatic Model Assessment" of insulin and glucose regulation, and used for quantifying insulin resistance (Matthews *et al.*, 1985).

3.1. Assumptions and Detailed Description of the Model

There are three main stocks in this model. Fat stock refers to the total fat mass in the body. Carbohydrate stock refers to the total glycogen store in muscles and liver. Muscle stock refers to the total muscle mass in the body which changes with respect to muscle protein synthesis and degradation rates. Besides, there are five stocks of first-order information delay in the model, two of them are related with the body weight management part: "delayed effect of physical activity on normal synthesis" and "delayed effect of physical activity on extra synthesis", which indicate the delay physical activity effect on the muscle protein synthesis. Other stocks of first-order information delay are related with the glucose-insulin regulation mechanism: "delayed effect of glucose concentration on insulin secretion", "delayed effect of insulin secretion on beta-cell functionality", and "delayed effect of beta-cell functionality on insulin secretion".

In the model, a different approach is applied in this part of formulation. The inflow of *Muscle* stock "Muscle protein synthesis" is considered in two different components, named as *normal synthesis* and *extra synthesis*. The reason behind this assumption is that muscle protein synthesis is possible if both physical activity and sufficient amount of protein exist in the system at the same time. Thus, the inflow with regard to the stock of muscle mass is implied as follows:

Muscle protein synthesis = Normal synthesis + Extra synthesis

The equations of the components in muscle protein synthesis are shown as follows. The equations of relevant variables can be seen from Appendix A.

Normal synthesis=Delayed eff of PA on normal muscle synthesis*Normal protein

Extra synthesis = Extra protein*Delayed eff of PA on extra muscle synthesis

Muscle protein synthesis rate cannot change instantaneously after the physical activity. Therefore, the time lag associated with the physical activity effect and developing muscle mass is considered in this model. It is shown by using the first-order information delay structures for both parts of syntheses, with a delay time of 8 weeks for normal synthesis and 6 weeks for extra synthesis. The graphical functions regarding normal and extra protein syntheses are shown in Figure 2 and 3, respectively.
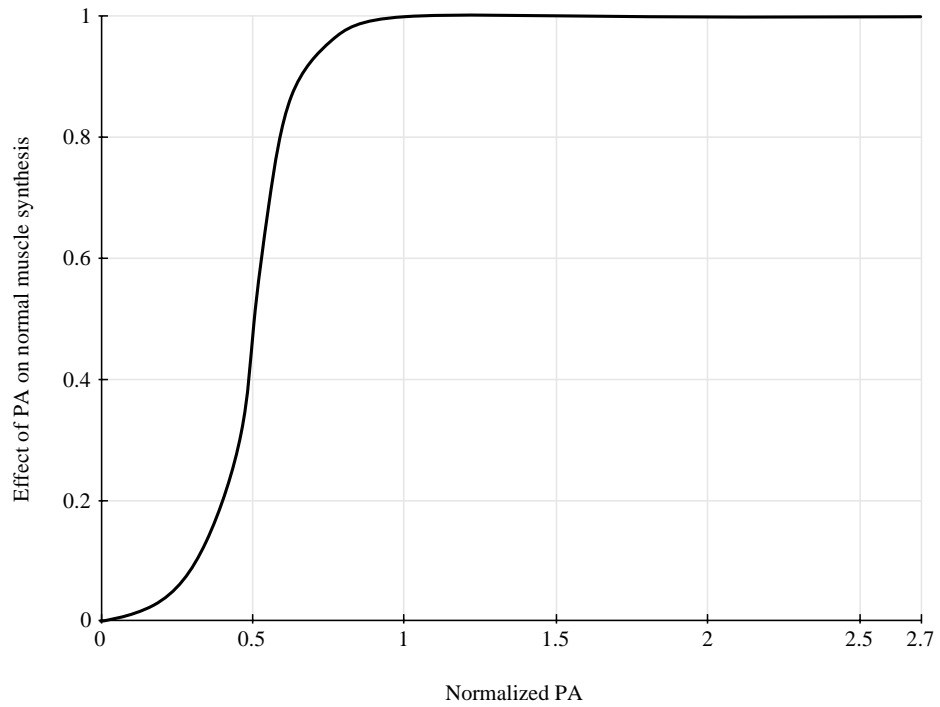
Figure 2. Graphical function for the effect of physical activity on normal muscle synthesis
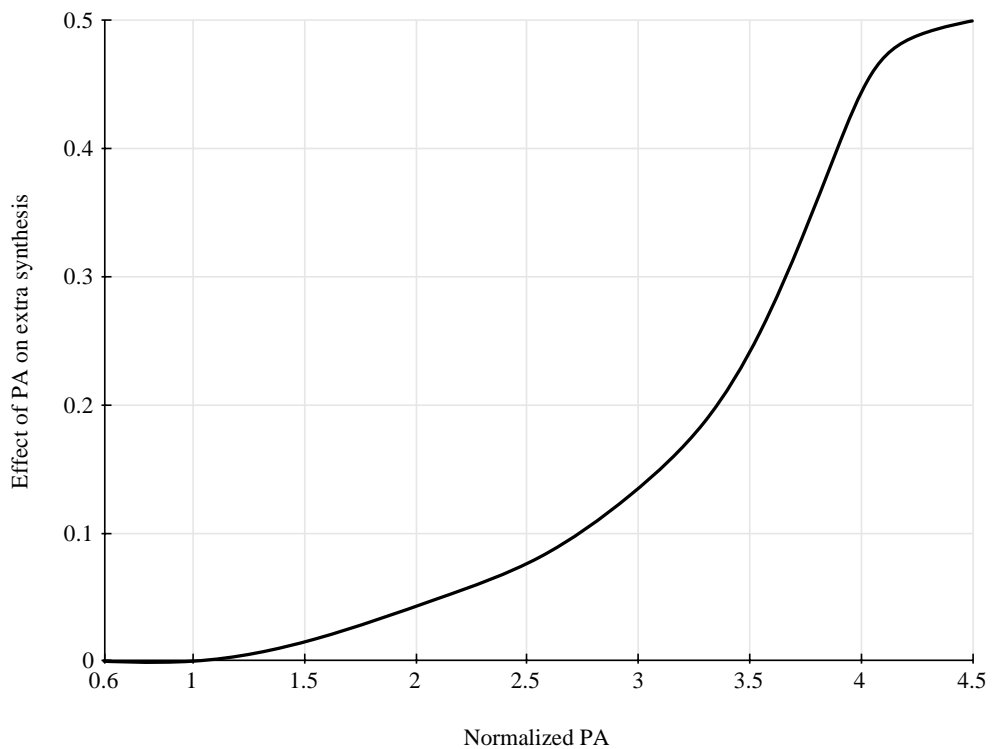

Figure 3. Graphical function for the effect of physical activity on extra muscle synthesis

In the model, physical activity capacity is defined as a variable, PA, which is altered with respect to the changes in one's body weight and age. Therefore, PA factor refers to the coefficient of doing physical activity, according to one's activeness for a long period. There are various definitions and formulations regarding this factor; however, it is considered as an effect on the capacity of physical activity performance in this model, and it can be changed according to the lifestyle of the individual. The relevant equation is given as follows:

*Physical activity = PA factor * Physical activity capacity*

In addition, regarding the "lifestyle", there are five main levels of doing activity during the lifetime. The minimal physical exertion is defined as the sedentary lifestyle. "Sedentary" means that the person does not exercise at all, and the PA factor is assumed to be 0.6 in the model, as given in Table 1. "Lightly active" means that a person engages in light exercise or sports 1-3 days per week, which corresponds to approximately 4130 kcal/week. "Moderately active" means that an individual exercises at least half an hour per day, five days per week, coincides with about 6090 kcal/week. "Very active" means that the person engages in fairly strenuous exercise or sports 6-7 days a week, expends about 8050 kcal/week. Lastly, "extra active" means that the person has a physical job where he is very active throughout a day, which corresponds to approximately 11060 kcal/week (Velardo and Ducelay, 2012).

When the glucose-insulin regulation is considered, there are three stocks, which are shown in the first-order information delay structure. According to the level of insulin concentration in the blood, glucose concentration level changes, and vice versa. In order to specify this negative feedback mechanism, a first-order information delay between these two concentrations has been defined in the model. It means that when plasma glucose concentration increases, it will take some time to trigger the pancreas, and to release the hormone into the bloodstream. However, in this model, this effect is considered as a long term effect. Thus, the effect formulation is obtained by using a first-order delay structure with delay time 10 weeks. The graphical function is shown in Figure 4.
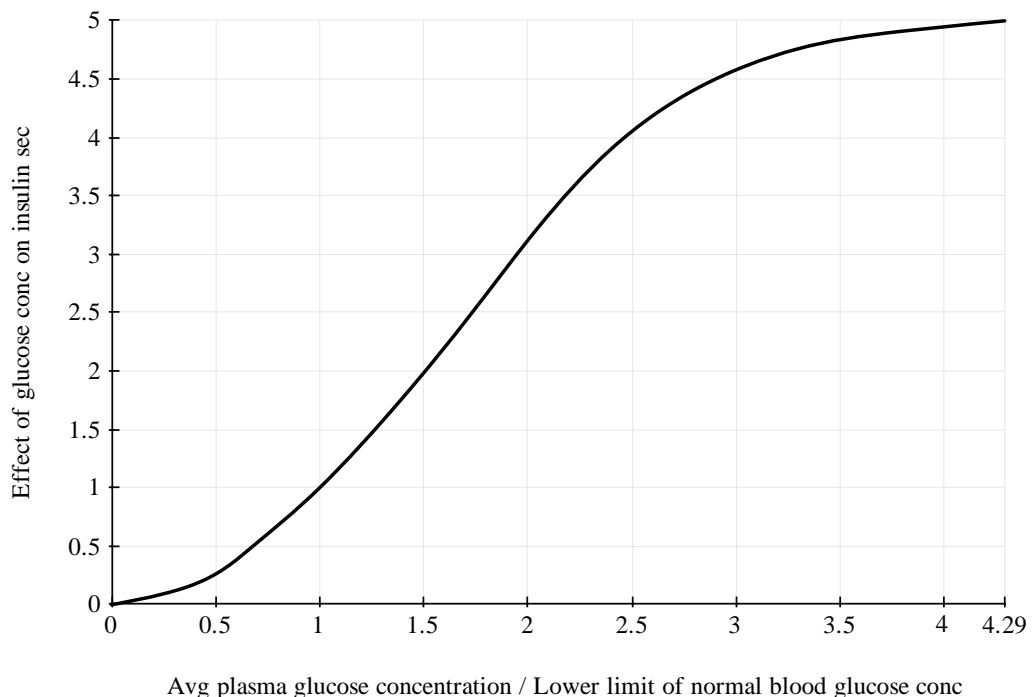

Figure 4. Graphical function for the effect of average plasma glucose concentration on insulin secretion.

Furthermore, according to the level of insulin secretion, beta-cells may lose their functionality with some percentage. When the individual develops hyperglycemia, then pancreas is stimulated to secrete more insulin into the bloodstream; therefore, beta-cell functionality decreases to 25% of its healthy capacity (Kahn *et al.*, 2006). The effect of insulin secretion level is smoothed with a first-order information delay structure with a delay time of 15 weeks.

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Nevertheless, the other way around of this process is also considered in the model. There is a first-order information delay structure between beta-cell functionality and the units of insulin secretion. It will take some time to induce beta-cell dysfunction according to the level of stimulation and secretion of insulin. The delay time for the effect of beta-cell functionality on insulin secretion is assumed as 12 weeks. These graphical functions are shown in Figure 5 and 6, respectively.
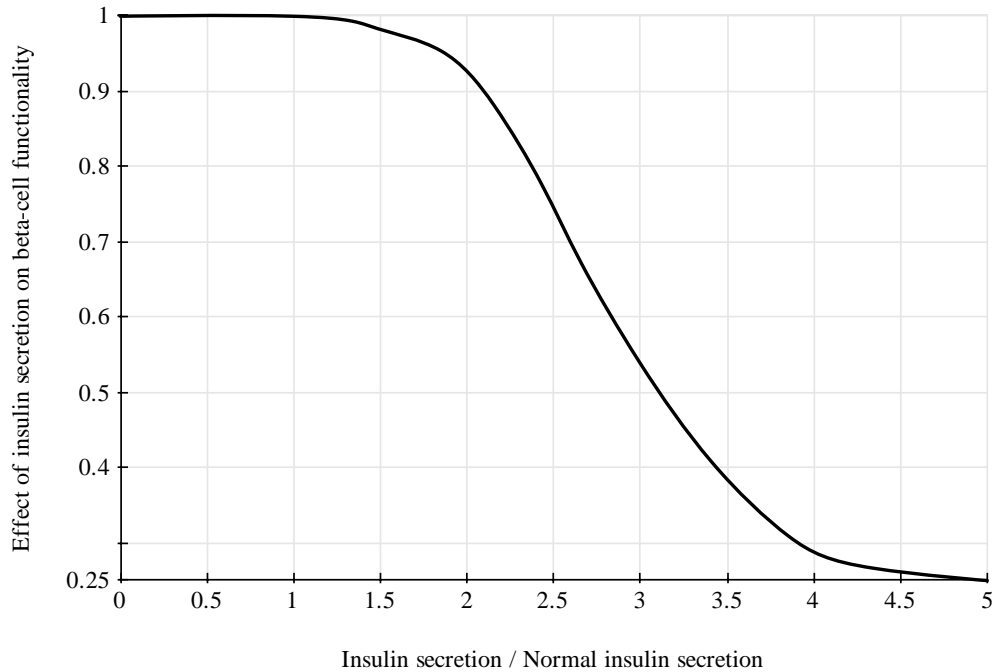

Figure 5.Graphical function for the effect of insulin secretion on beta-cell functionality

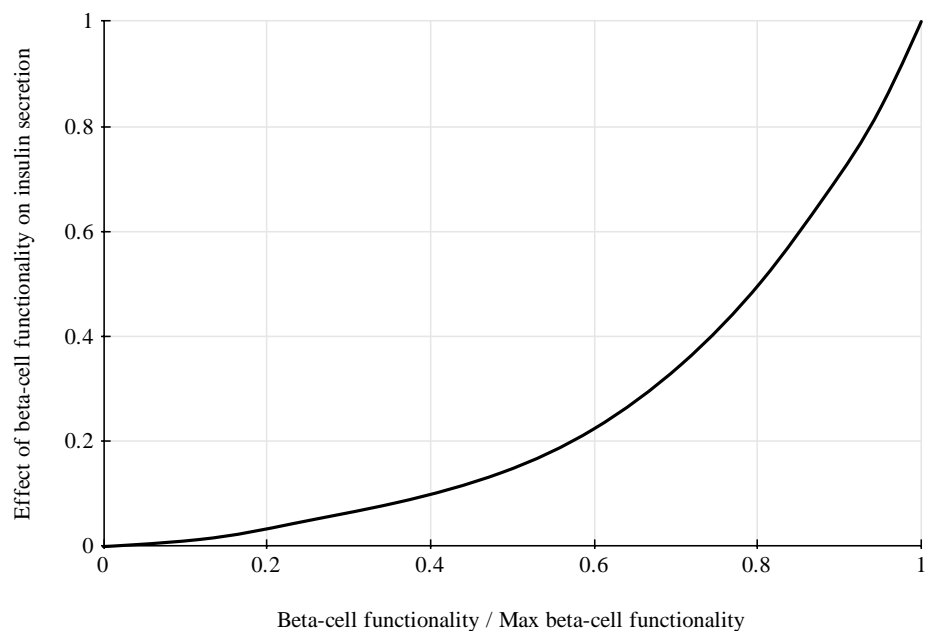Figure 6.Graphical function for the effect of beta-cell functionality on insulin secretion
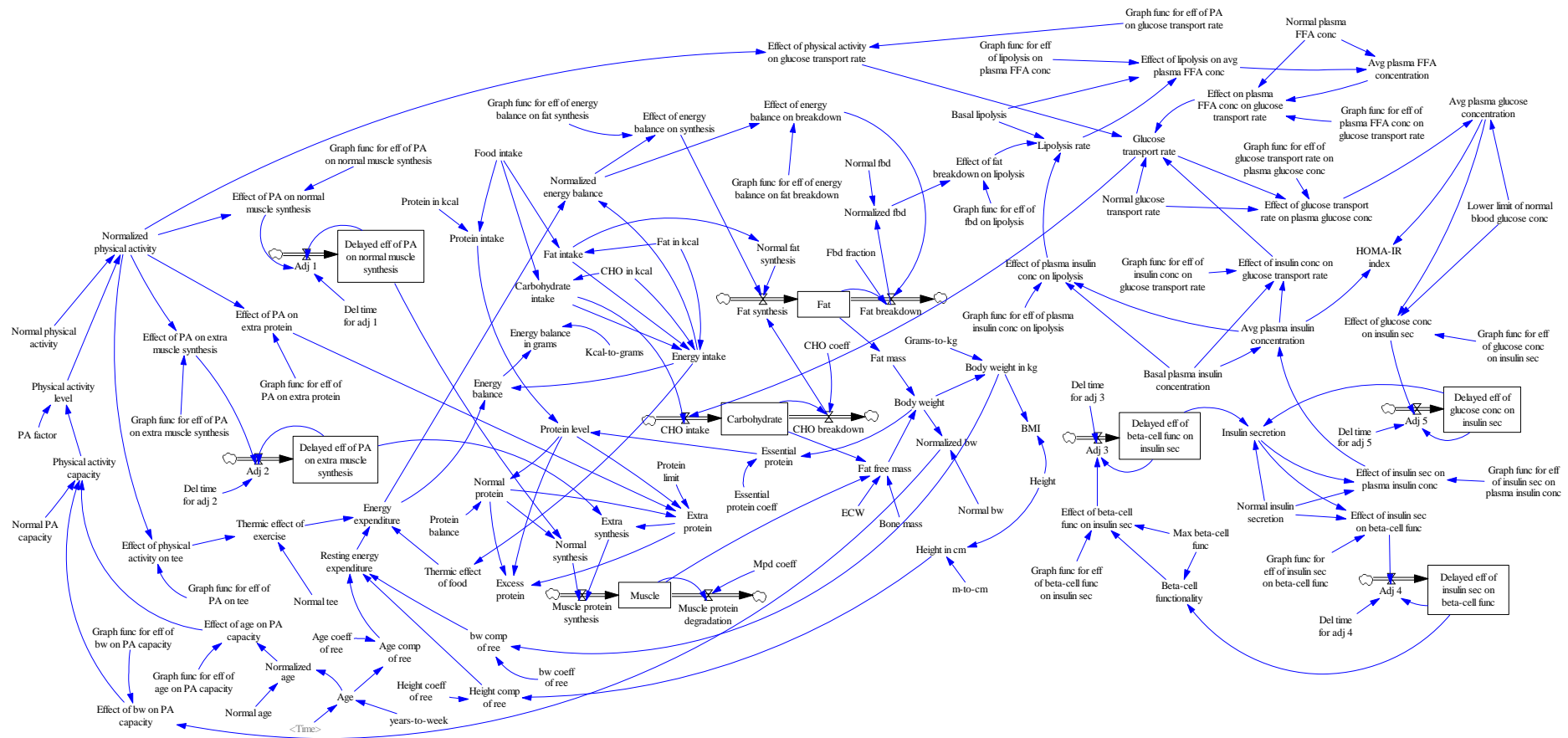
Figure 7. The stock-flow diagram of the whole model

The initial values of the stocks and the values of the variables at equilibrium are given in Table 1. In order to observe the changes in the stocks and other relevant variables such as average plasma glucose and insulin concentrations, different physical activity levels and dietary intakes are selected.

Table 1. Variables and initial values in the model.

Variable Name	Initial Value	Unit	Reference
Carbohydrate	500	Grams	(McArdle *et al.*, 2010)
Fat	12500	Grams	(Sizer and Whitney, 2010)
Muscle	31500	Grams	(Sizer and Whitney, 2010)
PA factor	0.6	Dimensionless	Assumption
Food intake	20000	Kcal/Week	(Hargrove, 1998)

The dynamic behaviors of body weight with respect to the changes in food intake (when physical activity level is kept as its baseline value), and the different physical activity levels (when food intake is considered as in Table 1) are shown in Figure 8.

In the run, named as *DoubledFoodIntake*, food intake is doubled, 40000 kcal/Week, and in the run *ExcessFoodIntake*, the amount of food intake is taken as 30000 kcal/Week, for determining the dynamic behavior of fat storage level. In the runs, named as *InsufficientFoodIntake* and *HalfFoodIntake*, decreased amount of food intake is observed. For these two runs, weekly food intake is given as 15000 kcal and 10000 kcal, respectively.

Furthermore, in the run that is named as "Light", the individual is "lightly active", who spends about 4130 kcal in a week. In the run named as "Moderate", the person is "moderately active" who spends around 6090 kcal per week, which let us take PA factor as 1.475. Similarly, in the run named "Active", it is supposed that the energy expenditure by exercising is nearly 8050 kcal/week as being "very active" and PA factor is about 1.98. In the run named "Strenuous", the person is doing vigorous physical exercise, also known as being "extra active", and spending nearly 11060 kcal/week, that PA factor is taken as 2.67.
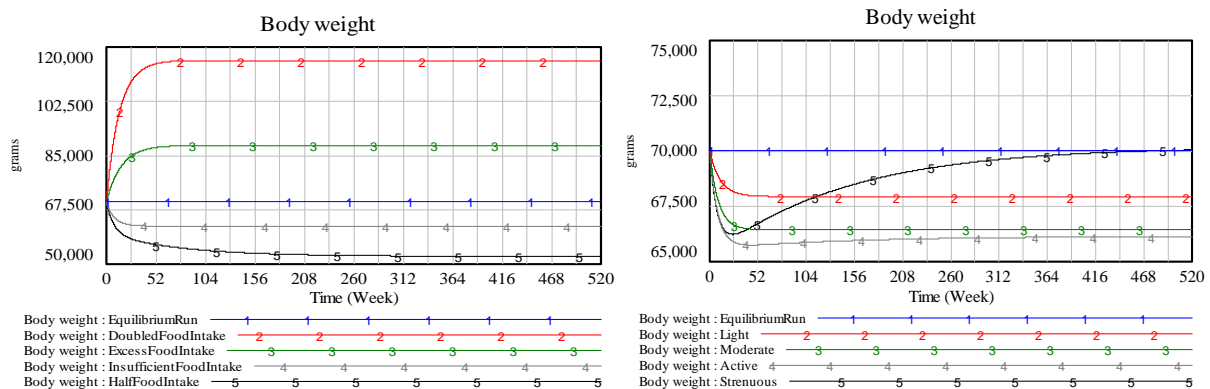
Figure 8. Dynamics of body weight with respect to changes in food intake and exercise levels.

The dynamic behavior is obtained according to different amount of dietary intakes, while keeping the proportions of food composition intact. As it can be seen from Figure 8, there is a change observed in the body weight with respect to the modification only in the amount of food intake, and physical activity level is kept as the same as its baseline value, which shows that the individual is almost sedentary. When the amount of food intake is increased, fat mass also increases according to the level of increase. Similarly, when the amount is decreased, fat mass

decreases, and fat stock reaches equilibrium about in approximately one year, which is an expected result of negative feedback effect of the as it is shown in the first loop, in Figure 1.

As it can be seen from the second behavior in Figure 8, body weight decreases according to the increase in the level of physical activity. When an individual increases his muscular activity, fat storage will start to decrease after some time. Since more glucose is necessary for a higher level of exercise, rate of fat breakdown will increase. Fat will be converted to carbohydrate, to be used for maintaining the requirement of the exercise. Therefore, if the "lifestyle" requires more physical activity, then fat mass will decrease, and muscle mass will increase. Since the individual we consider in the model is lean, he will not be able to lose too much fat, even he does strenuous exercise. However, muscle mass will increase because of sufficient protein and a very high level of exercise.

When age effect is also taken into consideration, the dynamic behaviors of body weight, fat mass and muscle mass with respect to the changes in PA factor are constructed in Figure 8 and 9, respectively. Related literature states that both physical activity capacity and resting energy expenditure decrease, when the individual gets older (McArdle *et al.*, 2010). Therefore, when a person keeps his food intake and physical activity as his baseline values, he will gain some fat. Since muscle mass decreases more than the increase in fat, he will eventually lose weight just because of aging (see Figure 9). When both age and PA factor are considered, an individual will again lose some weight, because he performs some physical activity. Thus, the individual will start to lose weight in the long term, because of losing physical activity capacity, and muscle mass will also decrease, which is an expected consequence.
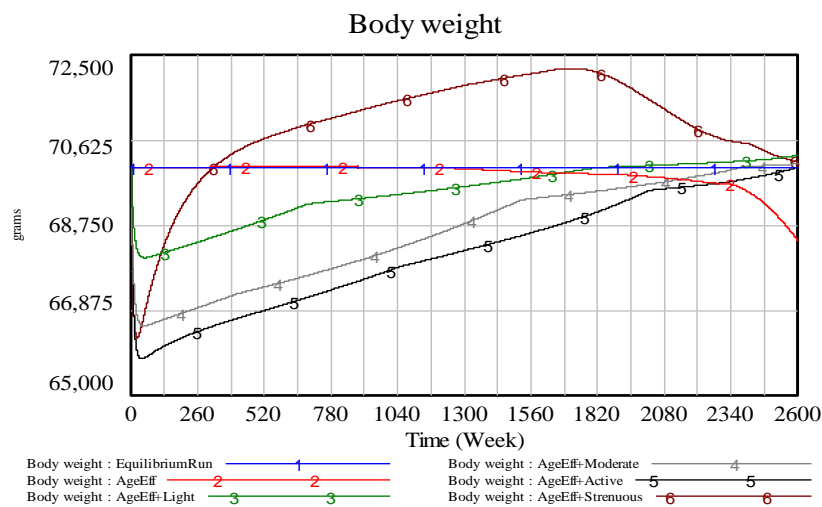

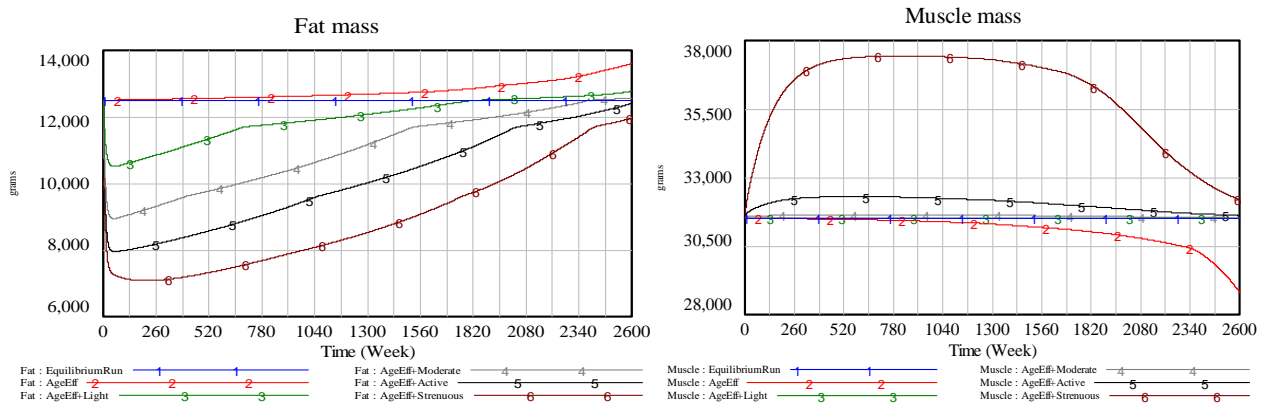Figure 8. Dynamics of body weight with respect to the changes in PA factor and aging.

Figure 9. Dynamics of fat mass, muscle mass with respect to the changes in PA factor and aging.

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Furthermore, it should also be discussed on the change in muscle mass according to the change in PA factor. In this experiment, both PA factor and age effect on the behavior of muscle mass are observed, which is shown in Figure 9. According to the graph, it is seen that the most increase in muscle mass is observed in strenuous exercise. On the contrary, the most decrease in muscle mass is observed in sedentary lifestyle, which is an expected result when energy expenditures of each physical activity and effects of muscle building are considered.

When age effect and changes in physical activity level are considered, it is observed from the dynamic behavior of fat mass that his fat mass decreases according to the increase in PA factor, because the person increases his physical activity performance. Thus, the most decrease is observed when the person does strenuous physical activity. In Figure 10, the graph shows the changes in body weight and fat mass by aging (Goodman, 2009), which is similar to the dynamic behaviors obtained in Figure 8 and 9.
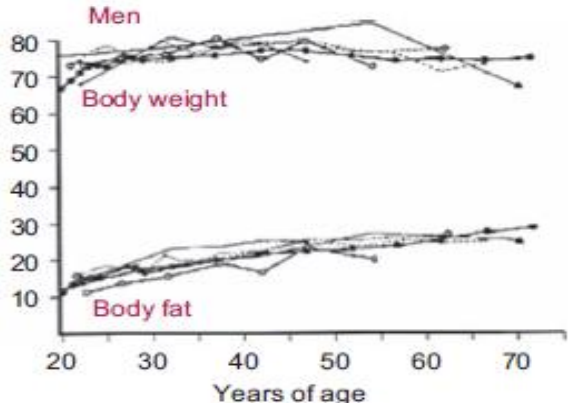

Figure 10. Data showing changes in body weight and fat content with aging(Goodman, 2009).

4. BASE BEHAVIOUR OF THE MODEL

The start of the simulation for the equilibrium runs, week zero, represents an average, 30-year old male, who is healthy and almost sedentary individual, also has not experienced any diabetic problems, which means that plasma glucose and insulin concentrations are in the normal ranges. The simulation ends after about 10 years, which is sufficient to observe the maintenance of body weight with performing physical activity, and taking adequate amount of food according to reference values for that individual. The parameters in the equilibrium are selected as it is given in Appendix A.

When all the variables are initially set to their equilibrium (normal) levels, all concentration levels and body weight components stay constant at their equilibrium values, as expected, which can be seen in the figures as below:
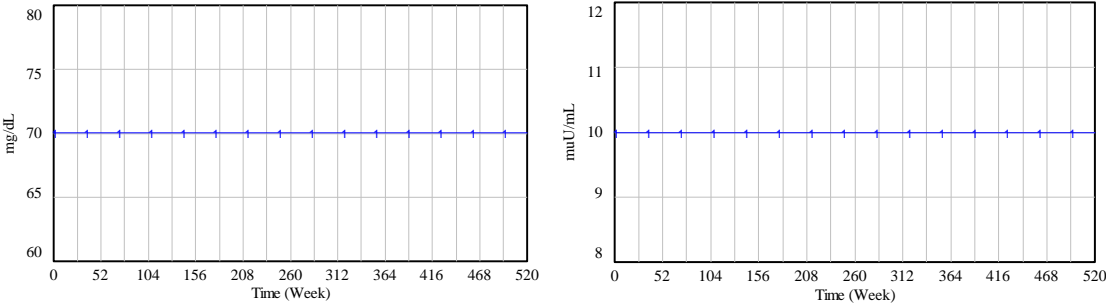

Figure 11. Average plasma glucose and insulin concentrations at equilibrium.
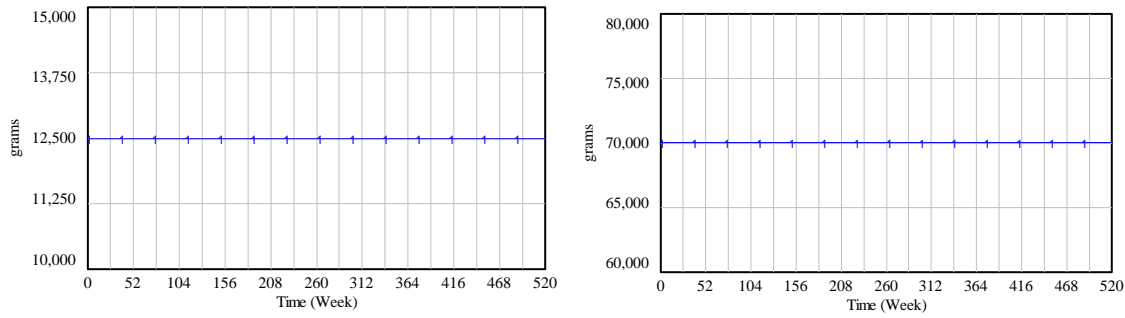
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Figure 12. Fat and body weight at equilibrium.

According to the dynamic behaviors shown in Figure 11 and 12, if an average male individual takes the adequate amount of food which is determined for his body, and expends energy as being about sedentary person, then his plasma concentration levels will stay at their initial values (small changes can be ignored for a long term). Therefore, a healthy person will not develop insulin resistance and type 2 diabetes, because all of the values are in the range of normal levels at the equilibrium.

In order to observe the base dynamics of the model, the amount of food intake is increased to 40000 kcal/week at time t = 52, and all other parameters are selected as in the equilibrium run. As it can be seen in Figure 4, fat storage and body weight increase, and reach equilibrium at a higher level than their initial values. Since the individual performs a lower level of physical activity, muscle mass will decrease and reach equilibrium at a smaller level than its initial value.
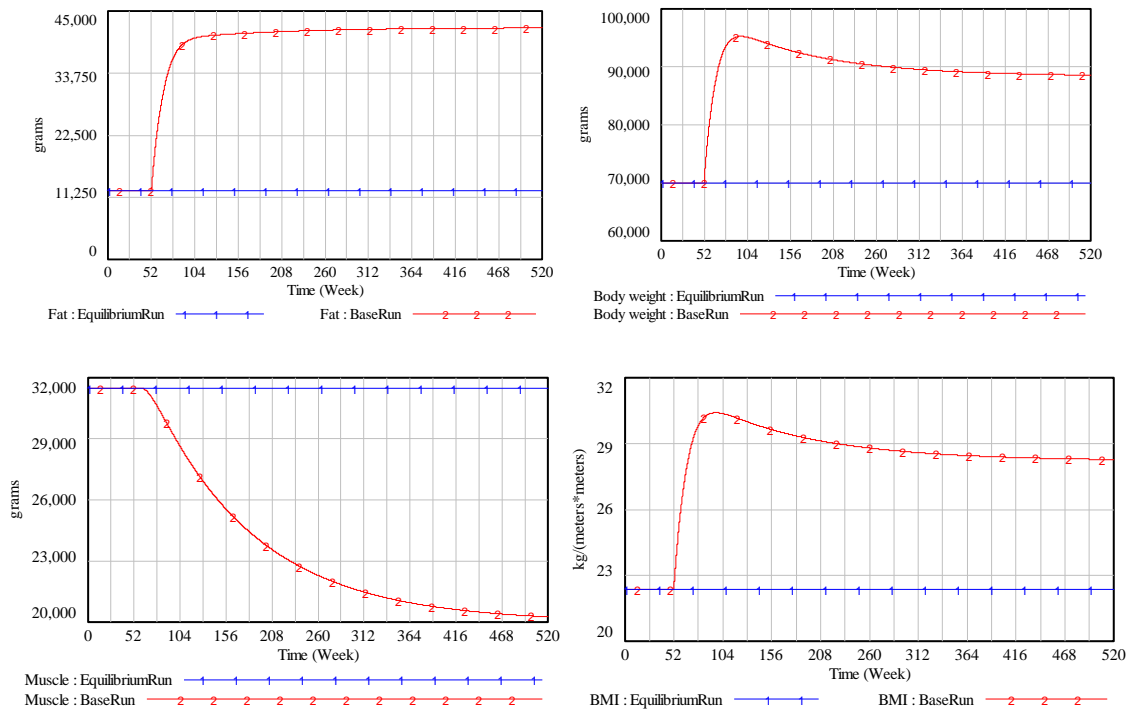

Figure 13. Fat, body weight, muscle mass and body mass index (BMI) in the base run.

In order to check whether the individual becomes obese or not, one of the most frequently used measurements is body mass index (BMI). Therefore, for the base run, BMI shows that the individual becomes overweight after the change in t = 52 (see Table 2). A classification of obesity

has been demonstrated according to the body mass index by World Health Organization (WHO), which is shown in Table 2 (McArdle *et al.*, 2010).

Table 2. Classification of obesity with respect to the body mass index.

BMI	Classification
< 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Class I obesity
35.0-39.9	Class II obesity
$\geq$ 40.0	Class III obesity

Besides, when the changes in average plasma concentrations of the individual are observed in Figure 14, it is obtained that plasma glucose and insulin concentration levels are above the upper limit of the normal ranges. Furthermore, the changes in HOMA-IR index, which also is a measurement for determining the insulin resistance, can be observed. Since the limit value of HOMA-IR index for insulin resistance is 2.7, it can be said that the individual becomes insulin resistant after t = 52, as a result of increase in obesity level of that individual. Therefore, we can say that these results support our hypothesis: the individual develops insulin resistance, and ultimately type II diabetes by the effect of obesity factor, in the long term.
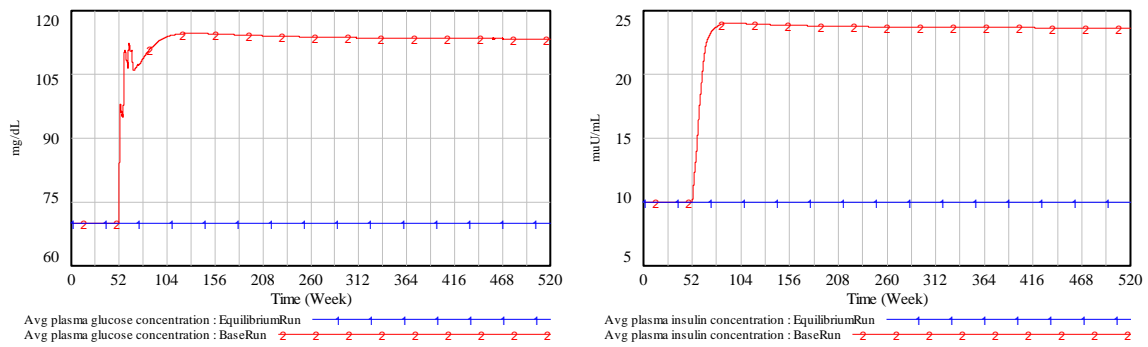

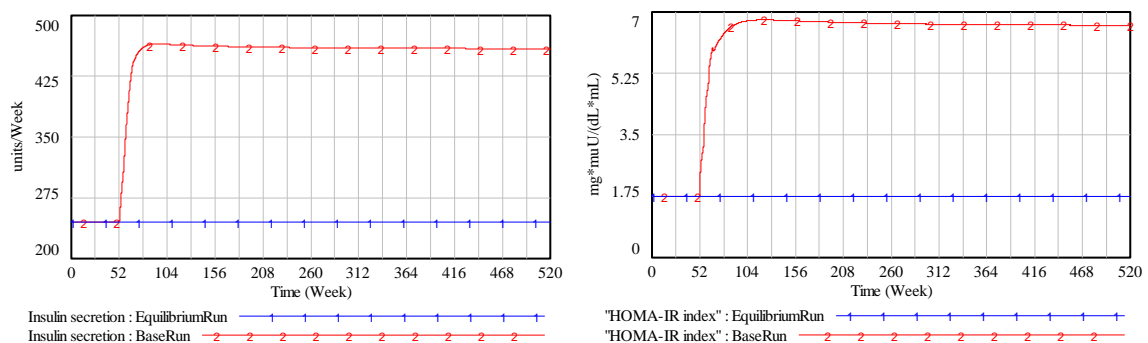Figure 14. Dynamics of average plasma glucose and insulin concentrations in the base run.

Figure 15. Dynamics of insulin secretion and HOMA-IR index in the base run.

Furthermore, the changes in beta-cell functionality are vital in order to determine if the individual may develop type II diabetes, ultimately. As it can be seen in Figure 16, there is a decrease observed in beta-cell functionality. Since only the amount of food intake is changed in the base run, and other factors which play a significant role in this disorder are not considered, beta-cell functionality does not decrease as it is expected. However, it can be said that the individual is a possible candidate for being a diabetic patient, when other factors which are assumed to be constant in the model.
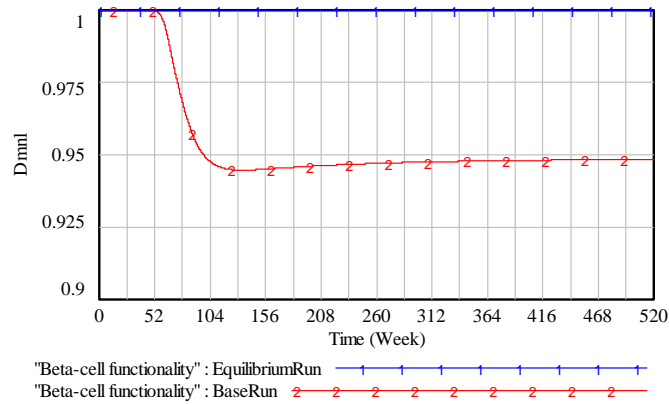
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Figure 16. Dynamics of beta-cell functionality in the base run.

5. MODEL VALIDITY

In this part, validation tests of the model will be conducted by using the relevant literature. The model is simulated by using Vensim 5.9c software, and the simulation time unit is chosen as one week, in order to monitor the long term behavior of developing insulin resistance and type II diabetes. Therefore, most of the runs are conducted for 520 weeks (10 years), only the runs which are testing the aging effect are demonstrated for 2600 weeks. Moreover, time step (DT) is chosen as 0.0078125 (1/128) that is considered as sufficiently small for the simulation.

In order to illustrate validation analysis of the model, two different tests should be conducted, which are known as structural and behavior tests. In structural tests, the robustness of the model is shown under extreme conditions, for indicating that the real problem has the similar relationships as shown in the model. Besides, in behavior tests, the dynamic behaviors of different variables in the model are demonstrated in order to show that the real behaviors give the similar patterns with the hypothetical behaviors (Barlas, 1999; Barlas, 2002).

In the research of Anderson *et al.*, the effect of weight management for diabetic individuals on plasma glucose concentration levels is investigated. It is shown that if the individuals lose weight, plasma glucose concentrations will decrease accordingly. This research is conducted for 48 weeks in total, and the values are measured in every 6 weeks (Anderson *et al.*, 2003).
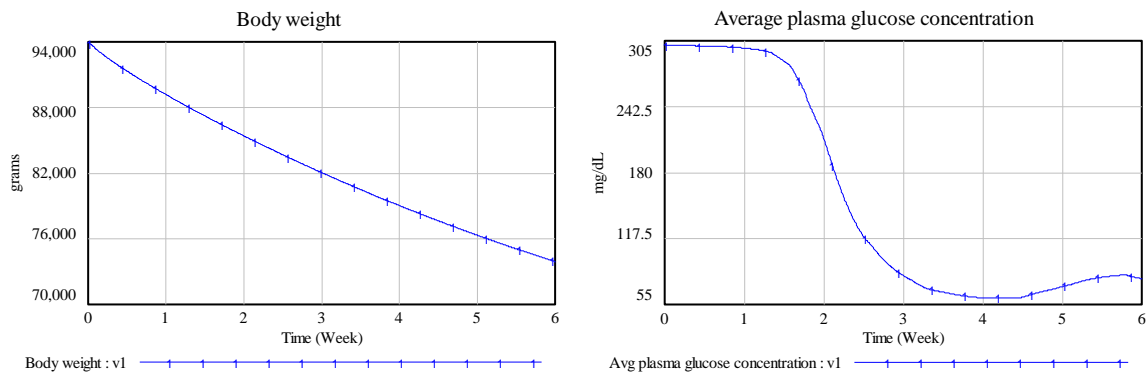

Figure 17. Dynamics of body weight and average plasma glucose concentration.

In the analyses, it is indicated that the individuals who are obese and diagnosed with type II diabetes, are treated in a weight management program, with a very-low-energy diets. In the

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practice, their energy intake is between 800-1200 kcal/day. At t=0, their average body weight is about 93.8 kg, and baseline fasting plasma glucose value is 15.9 mmol/L (286.2 mg/dL). Therefore, the dynamic behaviours are obtained, which is shown in Figure 17, according to the information in the study.
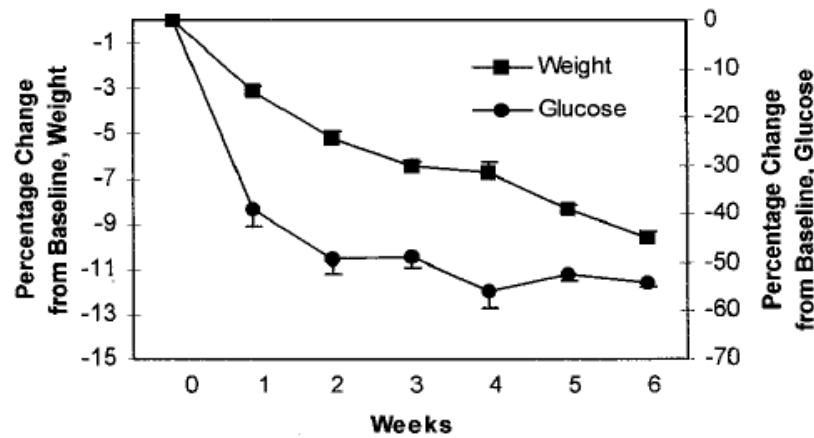

Figure 18. Effects of weight loss on plasma glucose concentration values of obese patients with type II diabetes (Anderson *et al.*, 2003).

Since the other factors, such as physical activity level, age, percentage of lean mass, are not totally clarified in the study, the changes in body weight and plasma glucose concentration values are not totally matched by the value, but the sudden decrease is observed in plasma glucose concentration during the first 6 weeks, and there is a small decrease in body weight, observed in the model result.

6. SCENARIO ANALYSIS

In this part, an average man who has prevalence of diabetes will be tested. As it is discussed previously, genetic factors for this disease are ignored in the model. With respect to genetic factors, there is a possibility that some people may not develop this disorder, because of no dysfunctionality in beta-cells, even he becomes obese. Therefore, it is assumed that if the individual we consider in this study already developed insulin resistance and type II diabetes, eventually, and it is likely to decrease the resistance by exercising and diet. The simulation starts with a 30-year-old adult, healthy male in both scenarios. In the other experiment, the simulation starts with an adult, who is an insulin-resistant man, and tested whether the insulin resistance disappears or not, by the treatment.

The scenario tests the effects of diet and exercise on obesity and the development of insulin resistance and type II diabetes. Thus, several variables are taken into consideration for this experiment: food intake, physical activity level, body weight and body mass index (from the body weight sector), average plasma glucose, FFA and insulin concentrations, and HOMA-IR index (from the glucose-insulin regulation sector).

In the Da Qing Study, if these interventions (diet and exercise) are applied to the patients who are diagnosed type II diabetes, the incidence of diabetes significantly decreases according to the results obtained in 6-years study (Pan *et al.*, 1997). Since there were differences between the values, such as glucose concentrations, age and BMI, of the patients in the study, a general case will be applied in the scenario.

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Firstly, an individual is assumed to be sedentary, and have a high level of BMI, who is also getting high amount of energy from nutrients. Therefore, at t = 0, food intake is assumed to be 25000 kcal/week, PA factor is 0.6, and body weight is 95000 grams, which results his BMI is about 30.3 kg/m^2.

With regard to this classification, in this scenario, the individual is assumed to be class-I obese (see Table 2).

In order to show the effects of diet and exercise, PA factor will be increased at every 52 week, according to the different levels of physical activity as it is discussed previously. Besides, food intake will be decreased 500 kcal at every 52 week, and the simulation will be conducted for a time horizon of 520 weeks. Therefore, according to the assumptions, the dynamic behavior of body weight is obtained as shown in Figure 19.
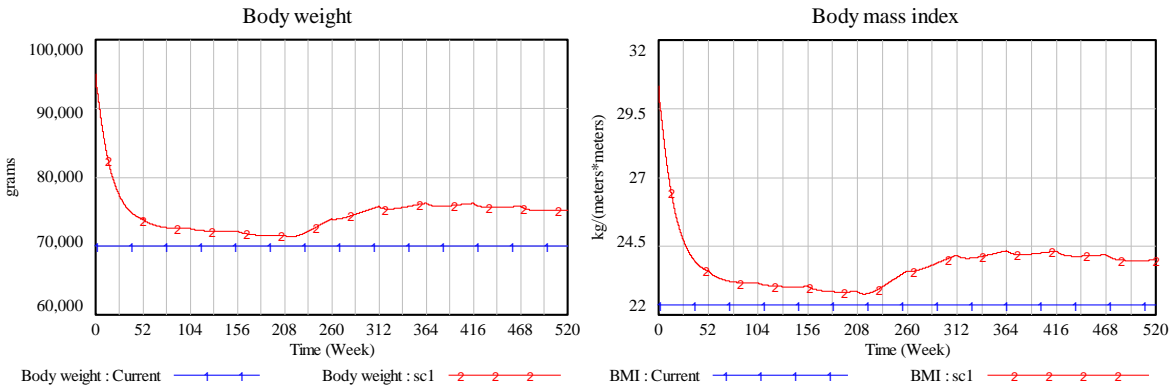

Figure 19. Dynamics of body weight and BMI according to the first scenario.

According to the interventions which are mentioned above, body weight decreases because of doing more physical activity, and the decrease in food intake. However, since the amount of food intake is higher than the protein balance, body starts to synthesize muscle proteins, and consequently, muscle mass increases. Therefore, in a longer term, body weight starts to increase gradually. With respect to the changes in the body weight, a similar behavior can be observed in BMI, which is also shown in Figure 19.

Besides, the dynamic behaviors of average plasma glucose, FFA and insulin concentrations are shown in Figure 20, 21 and 22, respectively. As it can be observed from Figure 20, at the beginning of the simulation, plasma glucose concentration is above the normal range, even at a critical value. However, with the effects of both decreasing food intake and increasing muscular activity, this level reaches equilibrium at a point which is approximately 70 mg/dL.
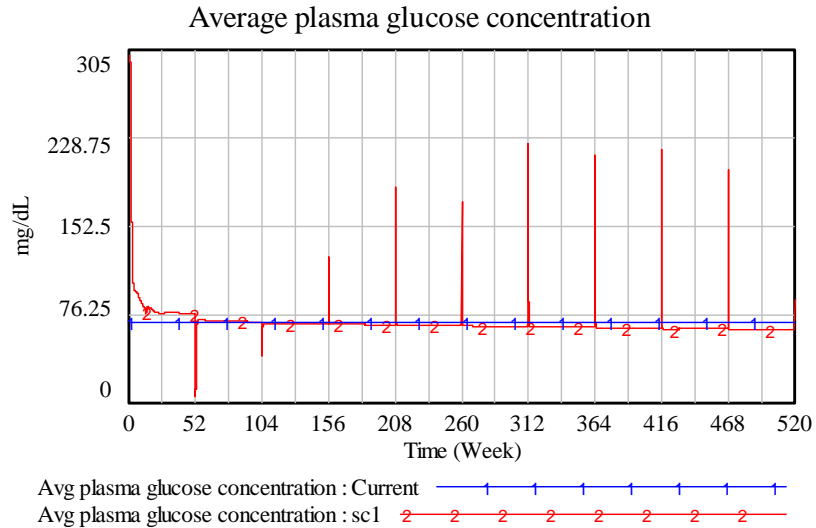
Average plasma glucose concentration

Figure 20. Dynamics of plasma glucose concentration according to the scenario.

Since plasma glucose concentration decreases in the long term, FFA concentration will also decrease according to this level. However, with respect to the rise in physical activity, the glucose level will not be sufficient in order to provide necessary glucose uptake for the muscles. Therefore, FFA concentration increases in blood to be used in giving energy to the muscles, as a substitution of glucose.

Average plasma FFA concentration
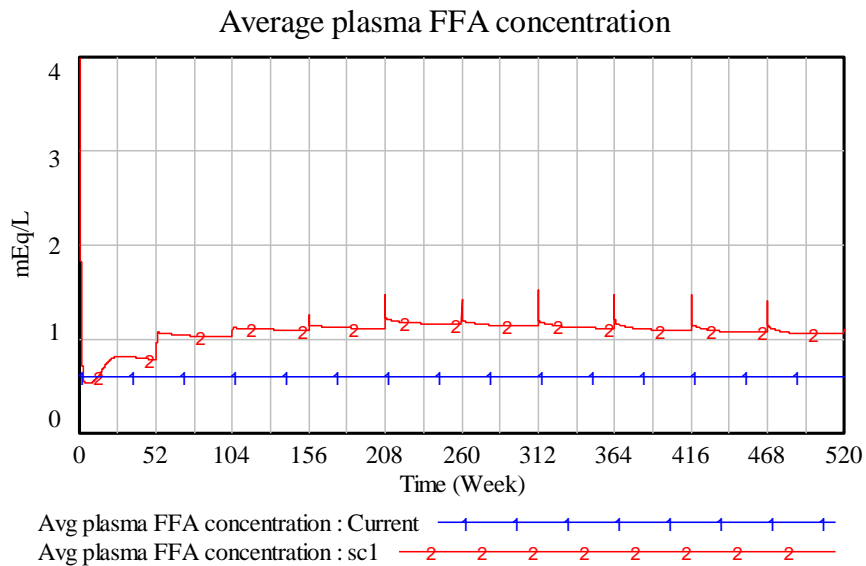
Figure 21. Dynamics of plasma FFA concentration according to the scenario.

With respect to the changes in glucose concentration in blood, insulin hormone will be secreted in order to regulate the metabolism. Therefore, as it is observed in Figure 22, insulin concentration is above the normal range, similar to the glucose and FFA concentrations at the beginning, and then this level decreases according to the effects of physical activity and diet levels.

Besides, the change in HOMA-IR index is also shown in Figure 23. As it is discussed in the literature survey, if the limit for this index is 2.7, which shows that the individual develops insulin resistance. According to the dynamic behavior of HOMA-IR index, one can observe that insulin resistance can disappear with the effects of physical activity and decrease in food intake level.

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In the Da Qing Study, these levels are not shown in details, but it is declared that the incidence of diabetes decreases by the help of doing more physical activity and changing the diet (Pan *et al.*, 1997).

Average plasma insulin concentration
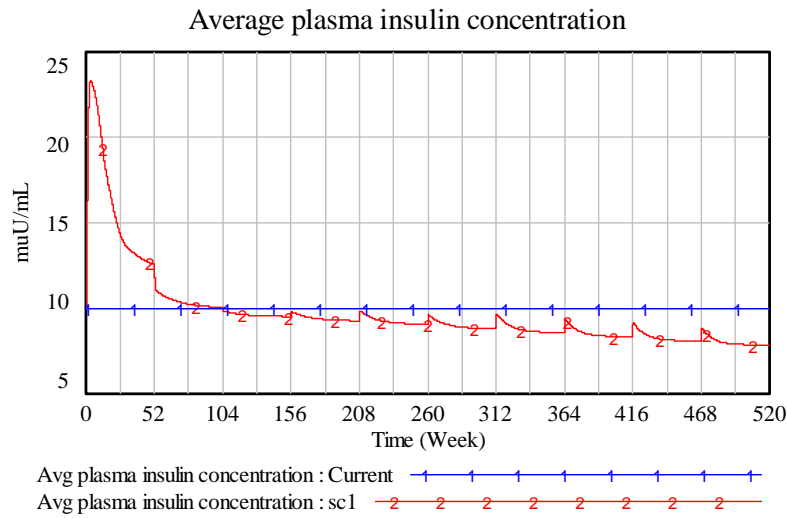
Figure 22. Dynamics of plasma insulin concentration according to the scenario.
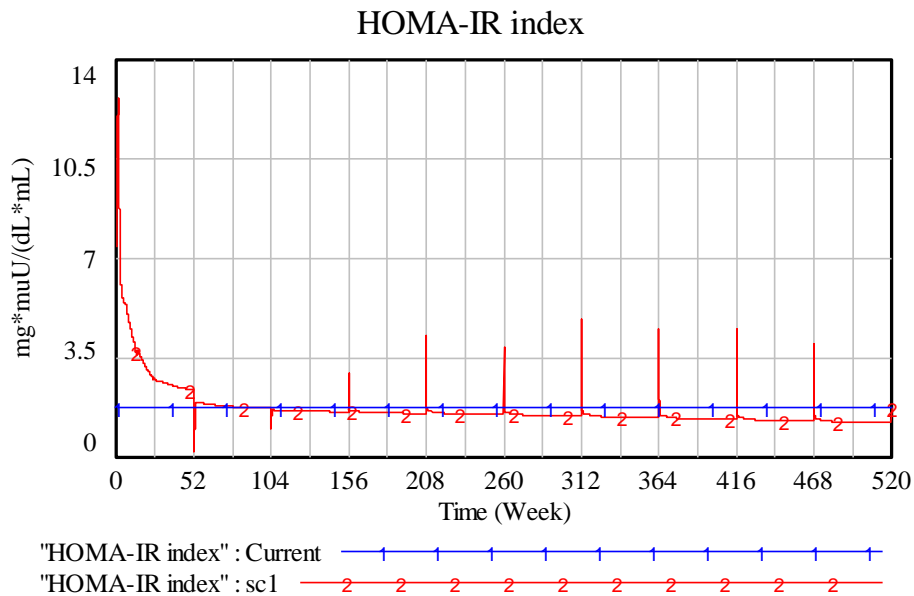
HOMA-IR index

Figure 23. Dynamics of HOMA-IR index according to the scenario.

7. CONCLUSION AND FUTURE RESEARCH

Obesity is shown one of the leading causes for insulin resistance and type II diabetes. In this study, the problem we considered is the dynamics of developing insulin resistance and type II diabetes, ultimately, assuming that a person has prevalence for obesity. In order to show that, a dynamic model which includes both body weight metabolism and glucose-insulin metabolism are constructed for an average man. In body weight metabolism, energy-yielding macronutrients, main body weight stocks and effect of physical activity are indicated in order to show the balance between energy intake and expenditure. In glucose-insulin regulation metabolism, only the main

variables and the relationships between them in the system are shown, since the model is constructed for the long term.

The aim of the study is to construct a long term dynamic model which demonstrates the dynamics of developing insulin resistance and type II diabetes which specifically focuses on obesity. Therefore, different experiments which test the effects of aging, changes in diet and different physical activity levels are conducted in this study.

In the equilibrium runs, the dynamics of the regulation in glucose-insulin metabolism by considering body weight components of an average man in the equilibrium state are shown. In the validation analysis of the model, one case related with type II diabetic patients are conducted. In the scenario analysis, typical interventions which make the insulin resistance and type II diabetes to disappear, by decreasing glucose and insulin concentrations, and keeping them in the normal ranges. These interventions include the effect of diet management and doing physical activity.

As it is discussed previously, type 2 diabetes may induce numerous physiological disorders in the body, such as kidney failure, atherosclerosis, and other cardiovascular problems. However, detailed analyses and the consequences related with that topic are not demonstrated in this study. Thus, modeling of physiological disorders related with type II diabetes can be a further research topic.

On the other hand, the model is demonstrated only for 10 years (520 weeks), which can be considered as a sufficient time for determining insulin resistance, but not a very long time for developing type II diabetes. In order to show the results for developing type II diabetes, a dynamic model which includes other factors that affect developing type II diabetes by conducting the simulation for a long time (30-50 years) can be demonstrated as a further research.

Furthermore, all of the values of the parameters in the model are set according to the reference values of an average male individual in the literature. In order to make experiments for another individual who is not in the average, the parameters should be changed manually for that specific person. Therefore, constructing a dynamic model of developing insulin resistance and type II diabetes which allows automatic changes according to the specific values for any type of individual can also be a further research topic.

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APPENDIX: LIST OF EQUATIONS

Stocks:
Carbohydrate= INTEG (CHO intake-CHO breakdown, 500) {grams}

"Delayed eff of beta-cell func on insulin sec"= INTEG (Adj 3, 1) {Dmnl}

Delayed eff of glucose conc on insulin sec = INTEG (Adj 5, 1) {Dmnl}

"Delayed eff of insulin sec on beta-cell func"= INTEG (Adj 4, 1) {Dmnl}

Delayed eff of PA on extra muscle synthesis = INTEG (Adj 2, 1) {Dmnl}

Delayed eff of PA on normal muscle synthesis = INTEG (Adj 1, 1) {Dmnl}

Fat= INTEG (Fat synthesis-Fat breakdown, 12500) {grams}

Muscle= INTEG (Muscle protein synthesis-Muscle protein degradation, 31500) {grams}

Flows:
Adj 1 = (Effect of PA on normal muscle synthesis-Delayed eff of PA on normal muscle synthesis)/Del time for adj 1 {Dmnl/Week}

Adj 2 = (Effect of PA on extra muscle synthesis − Delayed eff of PA on extra muscle synthesis)/Del time for adj 2 {Dmnl/Week}

Adj 3 = ("Effect of beta-cell func on insulin sec" − "Delayed eff of beta-cell func on insulin sec")/Del time for adj 3 {Dmnl/Week}

Adj 4 = ("Effect of insulin sec on beta-cell func" − "Delayed eff of insulin sec on beta-cell func")/Del time for adj 4 {Dmnl/Week}

Adj 5 = (Effect of glucose conc on insulin sec − Delayed eff of glucose conc on insulin sec)/Del time for adj 5 {Dmnl/Week}

CHO intake = Carbohydrate intake * Glucose transport {grams/Week}

CHO breakdown = Carbohydrate*CHO coeff {grams/Week}

Fat synthesis = (Effect of energy balance on synthesis*Normal fat synthesis)+IF THEN ELSE(CHO breakdown>3750, CHO breakdown-3750, 0) {grams/Week}

Fat breakdown = (Fat*Fbd fraction)*Effect of energy balance on breakdown {grams/Week}

Muscle protein synthesis = Normal synthesis + Extra synthesis {grams/Week}

Muscle protein degradation = Mpd coeff*Muscle {grams/Week}

Auxiliary variables:
Age = 30 + (Time/"years-to-week") {year}

Age coeff of ree = 6.8*7 {kcal/Week/year}

Age comp of ree = Age*Age coeff of ree {kcal/Week}

Avg plasma FFA concentration = Effect of lipolysis on avg plasma FFA conc*Normal plasma FFA conc {mEq/L}

Avg plasma glucose concentration = Lower limit of normal blood glucose conc*Effect of glucose transport rate on plasma glucose conc {mg/dL}

Avg plasma insulin concentration = Basal plasma insulin concentration*Effect of insulin sec on plasma insulin conc {muU/mL}

Basal lipolysis = 980 {grams/Week}

Basal plasma insulin concentration = 12 {muU/mL}

"Beta-cell functionality" = "Delayed eff of insulin sec on beta-cell func"*"Max beta-cell func" {Dmnl}

BMI = Body weight in kg/(Height*Height) {kg/(meters*meters)}

Body weight = Fat free mass + Fat mass {grams}

Body weight in kg = Body weight*"Grams-to-kg" {kg}

Bone mass = 70000*0.15 {grams}

bw coeff of ree = 13.7*7 {kcal/Week/kg}

bw comp of ree = Body weight in kg*bw coeff of ree {kcal/Week}

Carbohydrate intake = (Food intake*0.45/CHO in kcal) {grams/Week}

CHO coeff = 4.39 {1/Week}

CHO in kcal = 4.1 {kcal/grams}

Del time for adj 1 = 6 {Week}

Del time for adj 2 = 12 {Week}

Del time for adj 3 = 12 {Week}

Del time for adj 4 = 15 {Week}

Del time for adj 5 = 10 {Week}

ECW = 15000 {grams}

Effect of age on PA capacity = LOOKUP EXTRAPOLATE(Graph func for eff of age on PA capacity, Normalized age) {Dmnl}

"Effect of beta-cell func on insulin sec" = LOOKUP EXTRAPOLATE("Graph func for eff of beta-cell func on insulin sec", "Beta-cell functionality"/"Max beta-cell func") {Dmnl}

Effect of bw on PA capacity = LOOKUP EXTRAPOLATE(Graph func for eff of bw on PA capacity, Normalized bw) {Dmnl}

Effect of energy balance on breakdown = LOOKUP EXTRAPOLATE(Graph func for eff of energy balance on fat breakdown, Normalized energy balance) {Dmnl}

Effect of energy balance on synthesis = LOOKUP EXTRAPOLATE(Graph func for eff of energy balance on fat synthesis, Normalized energy balance) {Dmnl}

Effect of fat breakdown on lipolysis = LOOKUP EXTRAPOLATE(Graph func for eff of fbd on lipolysis, Normalized fbd) {Dmnl}

Effect of glucose conc on insulin sec = LOOKUP EXTRAPOLATE(Graph func for eff of glucose conc on insulin sec, (Avg plasma glucose concentration/Lower limit of normal blood glucose conc)) {Dmnl}

Effect of glucose transport rate on plasma glucose conc = LOOKUP EXTRAPOLATE (Graph func for eff of glucose transport rate on plasma glucose conc, (Glucose transport rate/Normal glucose transport rate)) {Dmnl}

"Effect of insulin sec on beta-cell func" = LOOKUP EXTRAPOLATE("Graph func for eff of insulin sec on beta-cell func", (Insulin secretion/Normal insulin secretion)) {Dmnl}

Effect of insulin sec on plasma insulin conc = LOOKUP EXTRAPOLATE(Graph func for eff of insulin sec on plasma insulin conc, (Insulin secretion/Normal insulin secretion)) {Dmnl}

Effect of lipolysis on avg plasma FFA conc = LOOKUP EXTRAPOLATE(Graph func for eff of lipolysis on plasma FFA conc, (Lipolysis rate/Basal lipolysis)) {Dmnl}

Effect of PA on extra muscle synthesis = LOOKUP EXTRAPOLATE(Graph func for eff of PA on extra muscle synthesis, Normalized physical activity) {Dmnl}

Effect of PA on extra protein = LOOKUP EXTRAPOLATE(Graph func for eff of PA on extra protein, Normalized physical activity) {Dmnl}

Effect of PA on normal muscle synthesis = LOOKUP EXTRAPOLATE(Graph func for eff of PA on normal muscle synthesis, Normalized physical activity) {Dmnl}

Effect of physical activity on glucose transport rate = LOOKUP EXTRAPOLATE(Graph func for eff of PA on glucose transport rate, Normalized physical activity) {Dmnl}

Effect of physical activity on tee = LOOKUP EXTRAPOLATE(Graph func for eff of PA on tee, Normalized physical activity) {Dmnl}

Effect of plasma insulin conc on glucose transport rate = LOOKUP EXTRAPOLATE(Graph func for eff of plasma insulin conc on glucose transport rate, (Avg plasma insulin concentration/Basal plasma insulin concentration)) {Dmnl}

Effect of plasma insulin conc on lipolysis = LOOKUP EXTRAPOLATE(Graph func for eff of plasma insulin conc on lipolysis, (Avg plasma insulin concentration/Basal plasma insulin concentration)) {Dmnl}

Effect on plasma FFA conc on glucose transport rate = LOOKUP EXTRAPOLATE(Graph func for eff of plasma FFA conc on glucose transport rate, (Avg plasma FFA concentration/Normal plasma FFA conc)) {Dmnl}

Energy balance = Energy intake-Energy expenditure {kcal/Week}

Energy balance in grams = Energy balance*"Kcal-to-grams" {grams/Week}

Energy expenditure = Resting energy expenditure + Thermic effect of food + Thermic effect of exercise {kcal/Week}

Energy intake = (Fat in kcal*Fat intake) + (CHO in kcal*Carbohydrate intake) {kcal/Week}

Essential protein = Body weight*Essential protein coeff/1000 {grams/Week}

Essential protein coeff = 0.8*7 {1/Week}

Excess protein = MAX (Protein level-Normal protein-Extra protein, 0) {grams/Week}

Extra protein = IF THEN ELSE (Protein level - Normal protein > Protein limit, Protein limit, Protein level-Normal protein)*Effect of PA on extra protein {grams/Week}

Extra synthesis = Extra protein*Delayed eff of PA on extra muscle synthesis {grams/Week}

Fat free mass = ECW + Bone mass + Muscle + Carbohydrate {grams}

Fat in kcal = 9.3 {kcal/grams}

Fat intake = (Food intake*0.35/Fat in kcal) {grams/Week}

Fat mass = Fat {grams}

Fbd fraction = 752.68/12500 {1/Week}

FINAL TIME = 520 {Week}
The final time for the simulation.

Food intake = 20000 {kcal/Week}

Glucose transport rate = Effect on plasma FFA conc on glucose transport rate*Effect of physical activity on glucose transport rate*Normal glucose transport rate {Dmnl}

"Grams-to-kg" = 1/1000 {kg/grams}

Graph func for eff of age on PA capacity([(1,0.6)-(2.7,1)],(1,1),(1.205,0.995),(1.38991,0.99), (1.58226,0.98),(1.75,0.963),(1.96697,0.931579),(2.16453,0.889474),(2.32049,0.835088), (2.48685,0.757895),(2.61162,0.677193),(2.7,0.6)) {Dmnl}

"Graph func for eff of beta-cell func on insulin sec"([(0,0)-(1,1)],(0,0),(0.116208,0.0131579),(0.232416,0.0438596),(0.357798,0.0833333),(0.486239,0.140351),(0.599388,0.223684),(0.706422,0.346491),(0.804281,0.504386),(0.883792,0.671053),(0.95107,0.837719),(1,1)) {Dmnl}

Graph func for eff of bw on PA capacity([(1,0.545)-(1.3,1)],(1,1),(1.03394,0.996009),(1.06055,0.988026),(1.08624,0.96807),(1.10917,0.932149),(1.12844,0.858311),(1.14771,0.778487),(1.16697,0.706645),(1.18991,0.642785),(1.21835,0.592895),(1.25413,0.554978),(1.3,0.545)) {Dmnl}

Graph func for eff of energy balance on fat breakdown([(0,0)-(2,2)],(0,2),(0.269113,1.97368),(0.489297,1.89474),(0.66055,1.74561),(0.819572,1.51754),(0.929664,1.24561), (1,1),(1.5,1),(2,1)) {Dmnl}

Graph func for eff of energy balance on fat synthesis([(0,0)-(2,2)],(0,1),(1,1),(1.08869,1.31579),(1.24159,1.57018),(1.3945,1.77193),(1.55963,1.89474),(1.737,1.95614),(2,2)) {Dmnl}

Graph func for eff of fbd on lipolysis([(0,0)-(4,3.1)],(0,0),(0.366972,0.326316),(0.672783,0.652632),(1,1),(1.34557,1.42763),(1.71254,1.88991),(2.07951,2.35219),(2.37309,2.65132),(2.72783,2.86886),(3.08257,3.01842),(3.5107,3.05921),(4,3.1)) {Dmnl}

Graph func for eff of glucose conc on insulin sec([(0,0)-(4.29,5)],(0,0),(0.367339,0.153509),(0.682202,0.504386),(1,1),(1.39064,1.75439),(1.73174,2.5),(2.04661,3.22368),(2.40083,3.90351),(2.82064,4.42982),(3.29294,4.75877),(3.80459,4.91228),(4.29,5)) {Dmnl}

Graph func for eff of glucose transport rate on plasma glucose conc([(0,0)-(1.8,4.29)],(0,4.29),(0.247706,4.19592),(0.412844,4.04539),(0.550459,3.68789),(0.666055,3.12342),(0.770642,2.42724),(0.880734,1.69342),(1,1),(1.10092,0.639737),(1.22202,0.338684),(1.38165,0.131711),(1.57431,0.0564474),(1.8,0)) {Dmnl}

"Graph func for eff of insulin sec on beta-cell func"([(0,0.25)-(5,1)],(0,1),(1,1),(1.48318,0.983553),(1.85015,0.953947),(2.15596,0.881579),(2.43119,0.776316),(2.66055,0.671053),(2.99694,0.539474),(3.40979,0.407895),(3.85321,0.309211),(4.34251,0.266447),(5,0.25)) {Dmnl}

Graph func for eff of insulin sec on plasma insulin conc([(0,0)-(5,5)],(0,0),(0.336391,0.175439),(0.672783,0.526316),(1,1),(1.46789,1.71053),(1.95719,2.5),(2.35474,3.20175),(2.81346,3.94737),(3.25688,4.47368),(3.77676,4.80263),(4.40367,4.93421),(5,5)) {Dmnl}

Graph func for eff of lipolysis on plasma FFA conc([(0,0)-(3.1,6.67)],(0,0),(0.379205,0.146272),(0.692049,0.46807),(1,1),(1.2893,1.69675),(1.5263,2.60364),(1.73486,3.71531),(1.9055,4.6807),(2.07615,5.52908),(2.28471,6.20193),(2.55963,6.49447),(2.85352,6.61149),(3.1,6.67)) {Dmnl}

Graph func for eff of PA on extra muscle synthesis([(0.6,0)-(4.5,0.5)],(0.6,0),(1,0),(1.55413,0.0175439),(2.09083,0.0482456),(2.55596,0.0811404),(2.96147,0.129386),(3.29541,0.186404),(3.54587,0.256579),(3.7367,0.33114),(3.89174,0.399123),(4.04679,0.458333),(4.26147,0.489035),(4.5,0.5) {Dmnl}

Graph func for eff of PA on extra protein[(0.6,0)-(4.5,0.5)],(0.6,0),(1,0),(1.55413,0.0175439),(2.09083,0.0482456),(2.55596,0.0811404),(2.96147,0.129386),(3.29541,0.186404),(3.54587,0.256579),(3.7367,0.33114),(3.89174,0.399123),(4.04679,0.458333),(4.26147,0.489035),(4.5,0.5) {Dmnl}

Graph func for eff of PA on glucose transport rate([(0,0)-(2.7,1.8)],(0,0),(0.222936,0.228947),(0.462385,0.473684),(0.710092,0.726316),(1,1),(1.29633,1.27105),(1.65963,1.52368),(1.98165,1.68947),(2.3367,1.76053),(2.7,1.8)) {Dmnl}

Graph func for eff of PA on normal muscle synthesis([(0,0)-(2.7,1)],(0,0),(0.181651,0.0131579),(0.429358,0.0789474),(0.594495,0.184211),(0.734862,0.350877),(0.833945,0.557018),(0.916514,0.754386),(1,1),(1.33761,1),(2.02294,1),(2.7,1)) {Dmnl}

Graph func for eff of PA on tee([(0,0)-(1,1)],(0,0),(0.107034, 0.153509),(0.211009,0.324561), (0.318043,0.508772),(0.428135,0.679825),(0.562691,0.872807),(0.703364,0.960526),(0.862385,0 .991228),(1,1)) {Dmnl}

Graph func for eff of plasma FFA conc on glucose transport rate([(0,0)-(6.67,1.8)],(0,1.8), (0.244771,1.53158),(0.591529,1.26316),(1,1),(1.48902,0.757895),(1.99896,0.513158),(2.65168,0. 331579),(3.3044,0.205263),(4.07951,0.126316),(4.87502,0.0710526),(5.79291,0.0236842),(6.67, 0)) {Dmnl}

Graph func for eff of plasma insulin conc on glucose transport rate[(0,0)- (5,1.8)],(0,0),(0.244648,0.260526),(0.489297,0.505263),(0.703364,0.73421),(1,1),(1.37615,1.247 37),(1.85015,1.43684),(2.4159,1.57105),(3.02752,1.67368),(3.70031,1.73684),(4.37309,1.76842), (5,1.8)) {Dmnl}

Graph func for eff of plasma insulin conc on lipolysis([(0,0)-(5,3.1)],(0,3.1),(0.142,2.52), (0.338,1.97),(0.611621,1.48202),(1,1),(1.39144,0.652632),(1.88073,0.435088),(2.47706,0.299123),(3.04281,0.203947),(3.63914,0.122368),(4.26606,0.054386),(5,0)) {Dmnl}

Height = 1.77 {meters}

Height coeff of ree = 35 {kcal/Week/cm}

Height comp of ree = Height coeff of ree*Height in cm {kcal/Week}

Height in cm = Height*"m-to-cm" {cm}

"HOMA-IR index" = Avg plasma glucose concentration*(Avg plasma insulin concentration/18)/22.5 {(mg*muU)/(dL*mL)}

INITIAL TIME = 0 {Week}
The initial time for the simulation.

Insulin secretion = "Delayed eff of beta-cell func on insulin sec"*Delayed eff of glucose conc on insulin sec*Normal insulin secretion {units/Week}

"Kcal-to-grams" = 1/7.7 {grams/kcal}

Lipolysis rate = Effect of fat breakdown on lipolysis*Effect of plasma insulin conc on lipolysis*Basal lipolysis {grams/Week}

Lower limit of normal blood glucose conc = 70 {mg/dL}

"m-to-cm" = 100 {cm/meters}

"Max beta-cell func" = 1 {Dmnl}

Mpd coeff=220.5/31500 {1/Week}

Normal age = 30 {year}

Normal bw = 70000 {grams}

Normal fat synthesis = Fat intake {grams/Week}

Normal fbd = 752.68 {grams/Week}

Normal glucose transport rate = 1 {Dmnl}

Normal insulin secretion = 245 {units/Week}

Normal PA capacity = 4130 {kcal/Week}

Normal physical activity = 2478 {kcal/Week}

Normal plasma FFA conc = 0.6 {mEq/L}

Normal protein = IF THEN ELSE(Protein level > Protein balance, Protein balance, Protein level) {grams/Week}

Normal synthesis = Delayed eff of PA on normal muscle synthesis*Normal protein {grams/Week}

Normal tee = 2458 {kcal/Week}

Normalized age = Age/Normal age {Dmnl}

Normalized bw = Body weight/Normal bw {Dmnl}

Normalized energy balance = (Energy intake/Energy expenditure) {Dmnl}

Normalized fbd = Fat breakdown/Normal fbd {Dmnl}

Normalized physical activity = Physical activity level/Normal physical activity {Dmnl}

PA factor = 0.6 {Dmnl}

Physical activity capacity = Effect of age on PA capacity*Effect of bw on PA capacity * Normal PA capacity {kcal/Week}

Physical activity level = PA factor*Physical activity capacity {kcal/Week}

Protein balance = 0.45*7*70 {grams/Week}

Protein in kcal = 4.35 {kcal/grams}

Protein intake = (0.2*Food intake/Protein in kcal) {grams/Week}

Protein level = MAX (Protein intake-Essential protein, 0) {grams/Week}

Protein limit = 150 {grams/Week}

Resting energy expenditure = (66*7) + bw comp of ree + Height comp of ree − Age comp of ree {kcal/Week}

SAVEPER = TIME STEP {Week [0,?]}
The frequency with which output is stored.

Thermic effect of exercise = Normal tee*Effect of physical activity on tee {kcal/Week}

Thermic effect of food = Energy intake*0.1 {kcal/Week}

TIME STEP = 0.0078125 {Week [0,?]}
The time step for the simulation.

"years-to-week" = 52 {Week/year}