Understanding adult blood glucose homeostasis.
A System Dynamics approach.

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Abstract

Blood glucose homeostasis is the processes of bringing blood glucose concentration within a normal blood glucose range through effective and complex contribution of different body organs, tissues, hormones, enzymes, and others in a human body when there is an imbalance condition happened between glucose oxidation as energy source for the body and carbohydrate intake as a daily diet, glucose and fat serve as a fuel to produce energy for the human body. During the process of blood glucose homeostasis, excess glucose that are not used by the body gets transported and stored as glycogen in liver and muscle tissues by the help of hormone insulin, but further conversion of glucose to fat happens when muscle glucose storage is full. Excess fat in the body due to imbalance glucose and fat intake induces communication failure between the hormone insulin and insulin induced glucose transporter (GLUT4) on muscle and adipose tissue cells during glucose oxidation, hormone insulin failure to produce enough glucose transporter has given name of a disease insulin resistance (Type II NIDDM). Unsuccessful glucose oxidation on adipose and muscle tissue let blood glucose concentration to be above the normal range and in lifelong develops complication on pancreas to be totally unable to produce insulin (Type I IDDM), heart, kidney, eye, and the others.

Given that the human anatomy and physiology are an integrated complex system of organs, cells, hormones, enzymes and others, a System Dynamics approach is a relevant and effective way to investigate the underlying causes and dynamic mechanisms influencing insulin resistance and to identify and test feasible solutions. By modelling and simulating the represented organ and system in the blood glucose homeostasis process, these possible solutions targeted on weight reduction (BMI) specifically excess fat in the body. Weight reduction as a treatment of insulin resistance gives a significant change on glucose oxidation in adipose tissue, glucose oxidation in muscle tissue, blood glucose concentration and unnecessary production of hormone insulin in the body. Therefore, a planned daily diet, using body fat as direct source of energy and as a source of blood glucose in the process of gluconeogenesis, and daily physical activity that contributes to energy expenditure; are the most effective strategies found in this study to reach body weight (BMI) goal since excess fat hinders glucose oxidation in the muscle and adipose tissue.

The System Dynamics simulation model presented in this thesis can contribute to a better understanding of the factors driving increasing trends of serious diseases, such as diabetes mellitus, across populations and detect and test in future scenarios, potential prevention and treatment policies and interventions to help reduce these trends.

Key words: Blood glucose concentration, daily diet, body hormones, NIDDM (Insulin Resistance), physical activity, System dynamics.

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Etaba…

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Nomenclature.

BGH: Blood glucose homeostasis.

CICC: Carbohydrate intake calibration coefficient.

CLD: Closed loop diagram.

DM: Diabetes mellitus.

GIT: Gastrointestinal tract.

GLUT: Glucose transporter.

GLUT4: Glucose transporter 4.

IAF: Intra-abdominal fat.

IDDM: Insulin dependent diabetes mellitus.

SAT: Subcutaneous Adipose tissue.

SD: System Dynamics.

SFD: Stock and flow diagram.

SGLTS: Sodium glucose linked transporters.

VAT: Visceral Adipose Tissue.

Chapter 1 . Introduction

1.1. Background.

The anatomy and physiology of a human being is described as one of the widest and complex systems which shows the structure of the human organ from the small level to the biggest including its function to perform a specific task (Cobelli & Carson, 2019), the organs have its own main function or helping the other organs function either locally or in a general system level to keep alive the life of the human beings (Wingerd & Taylor, 2020).

Organs and the system developed based on the organs that are found in human body works dependently to each other, this interconnection is grouped in a system level like lymphatic system, nervous system, urinary system, blood circulatory system, skeletal system, muscular system, endocrine system, vascular system, system in the respiratory organ, system in the digestive organ, and system in the reproductive organ (Cohen & Hull, 2020). All the systems that are described above working together according to both the internal and external factors to regulate the parameters found in the human body through metabolism (Castillo-Armengol et al., 2019; Solomon, 2015), Homeostasis is one of the mechanisms that keep the parameters within a normal range when unbalanced intake and usage of glucose by the organs to benefit the whole organs in the body to keep going normal and to provide its service effectively (Coad et al., 2019).

Studies showed and defined blood glucose homeostasis as holding the parameter blood glucose concentration from 3.9-7.1 mmol/l (Shah & Wondisford, 2020), during any internal or external glucose related influences are applied on human body. For instance, after a meal blood glucose level rise to be above the normal limit (hyperglycemia), then the body organizes all the responsible systems to transport excess glucose to be stored as glycogen (Adeva-Andany et al., 2016) and convert excess glucose to fat (Fialkowski Revilla et al., 2018), in the other way during starvation(fasting) or when the blood glucose level is below (hypoglycemia) our body reuses the stored glucose by converting glycogen to glucose or by converting noncarbohydrate (proteins and fats) to glucose in order to increase blood glucose concentration level by using different hormones and enzymes in the body (Kim et al., 2020).

Organs and organ-based systems that are found in human body needs sufficient amount of energy to accomplish their own function from minimum which is basal up to the highest energy demanding activity in our daily life cycle (Laughlin, 2001). The fundamental nutrients that are important and useful as a source of energy for our body are glucose and fats (Pang et al., 2014), glucose is a monosaccharide carbohydrate which can absorbed easily in the gastrointestinal tract and it is the only source of energy as a fuel in normal condition for brain but brain uses ketones from fat as energy source when shortage of glucose happens in the body (Kroemer et al., 2018).

Blood glucose in human body is exogenously influenced by the external factors, those factors which elevates or decreases the blood glucose level are the daily meal intake as an input and the physical status (physical activity level) from the rest state to the high energy demanding physical activity level as an output, but the endogenous factors regulates and brings back the extreme blood glucose level to the normal state by using different hormones and metabolism processes as far as blood glucose homeostasis is concerned , the processes are classified as follows (Fialkowski Revilla et al., 2018).

1. By converting glucose to other forms of carbohydrate(glycogen) and storing in different organs through the process of glycogenesis to keep euglycemia from hyperglycemia.
2. By synthesizing fat from blood glucose to keep euglycemia from hyperglycemia.
3. By synthesizing glucose from noncarbohydrate (fats and proteins) nutrients to keep euglycemia from hypoglycemia through the process of gluconeogenesis.
4. By converting the stored form of glucose (glycogen) to glucose through the process of glycogenolysis to keep euglycemia from hypoglycemia.
5. By excreting excess glucose together with urine from the body by the organ Kidney.

Basically, the relation between daily meal intake and daily utilized nutrients in the cell shows how blood glucose homeostasis goes in the human body. All the physiological processes that are involved in blood glucose homeostasis forced to have a dynamic behavior, this dynamic behavior is manifested by the glucose storage and the accumulation of unnecessary fat (Sears & Perry, 2015). Fat accumulation in the body (adipose tissue) exposes organ cells to suffer in a disease insulin resistance (Donath & Shoelson, 2011; Jensen et al., 2011; Sears & Perry, 2015) and for a long run, probability of facing further complications due to insulin resistance is high (Kahn, 1998). Insulin resistance defined as the falling of organ cells response (tissues especially muscle and adipose) to insulin during glucose uptake, insulin is an endocrine hormone secreted by pancreas β-cells (Yaribeygi et al., 2019).

Since the blood glucose level relies on both internal and external factors, its variation detected by the human body organ pancreases, the hormones that are secreted by the alpha and beta cells of the pancreases to lower or increase the blood glucose level are Insulin and glucagon (Gowd et al., 2017).

The hormones insulin and glucagon applied on the conversion of glucose by up taking glucose or by releasing glucose according to the blood glucose level but on the other side this hormone has role on the concentration of free fatty acids in the blood and triglycerides in the adipose tissue since both free fatty acids and triglycerides are products for each other through active interventions of the hormones Insulin and Glucagon (Fujikawa, 2021). According to Americans diabetic association lack of hormones that are involved in the glucose conversion process are the main possible cause for a diseases Diabetics Mellitus (Association, 2014).

As far as blood glucose homeostasis is concerned, blood glucose concentration varies with in the limit for normal healthy persons. In this thesis, the author is using a healthy person's blood glucose concentration as a reference, the study was applied on twenty-four nondiabetic adult volunteers living in normal condition by using 50-gram glucose intake as a diet three times a day for one day duration (Figure 1-1.) (Freckmann et al., 2007).

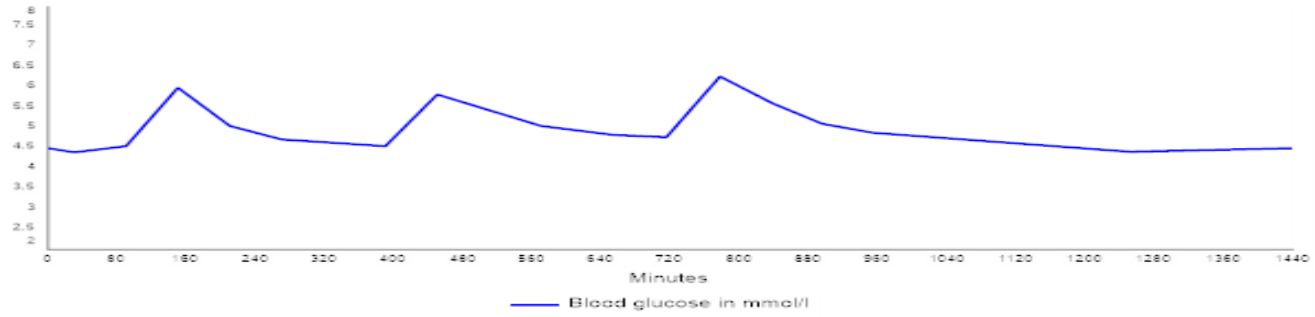

Figure 1-1. Normal Blood glucose level as a reference mode.

1.2. History and Types of Diabetics Mellitus.

The name Diabetics Mellitus is derived from a Greek word having a meaning of “pass through” for Diabetes and “sweet” for mellitus, this implies the meaning resembles to the availability of glucose in urine (Lakhtakia, 2013; Zajac et al., 2010).

Out of 10 popular leading to death diseases in the world, Diabetes Mellitus is included in the group and it is also one of the top 4 non communicable diseases that has complications in human body which can be an immediate cause for mortality (Oguntibeju, 2019). Diabetes Mellitus is very well-known health problem progressing every year (Glovaci et al., 2019).

Metabolic disorders specifically Diabetics mellitus is manifested by the increasing of blood glucose concentration (hyperglycemia) relative to the normal range, the possible cause of diabetic’s mellitus to attain hyperglycemia is caused by interruption of insulin production on pancreas beta cell, cell response reduction for insulin and due to the existence of both problems at the same time (Yaribeygi et al., 2019).

Hyperglycemia has a long-term complication on human organs, gradual loss of organ functionality is a complication of diabetic induced hyperglycemia which is more observable on the organs heart, kidney, eye and the others (Ahmad et al., 2021).

Enormous research classified Diabetic Mellitus based on the problems related to Insulin action and Insulin production as follows.

1.Type I (Insulin Dependent Diabetes Mellitus) is developing due to malfunction of insulin production on β-cells in the human organ Pancreases that leads to inadequacy of Insulin in the body (Paschou et al., 2018).

2.Type II (Non-Insulin Dependent Diabetes Mellitus) is developing due to decreasing response of cells to hormone insulin (insensitive to insulin) but sometimes decreasing of insulin production and less sensitivity of cells to insulin happens together (Han Wu et al., 2018).

3.Gestetional Diabetes Mellitus

Repeated increasing of morning blood glucose level during pregnancy diagnoses Gestational diabetes mellitus, early treatment by doing daily activity can prevent further complication (McIntyre et al., 2019).Diseases related to Cardiovascular and diabetes mellitus are complications for the mother and complications on the infant happens at birth, history of diabetes in the family and obesity are the risk groups (Plows et al., 2018).

1.3. Problem Identification Statement.

Insulin Resistance.

Regular homeostasis effectiveness assures the health status of human body (Abdel-Hamid, 2003), any abnormal weight change especially fat in the body exposes human beings to fall on a risk of diseases (Manuel-y-Keenoy & Perez-Gallardo, 2012).

Insulin resistance and other cardiovascular diseases are considered as epidemic in the world due to its annual increasing rate of new patients, insulin resistance is one of the outcomes of a disease developed due to obesity (Ghadimi et al., 2021; Huaizhu Wu & Ballantyne, 2020).

Glucose up taking during the process of metabolism in the cell needs hormone insulin as a stimulator, the action of the hormone insulin in human body especially muscle and adipose tissue cell of insulin stimulated glucose transporter GLUT4 varies according to the level of cell tissue inflammation induced by the excess accumulated fat on the process of insulin signaling (Zatterale et al., 2020).

This abnormal communication between stimulator insulin and the expected amount of glucose to be used by the cell leads the blood glucose concentration keep higher and pancreas forced to secrete more insulin to metabolize glucose in the cell, this continuous request of insulin production(hyperinsulinemia) from beta cells of the pancreas due to hyperglycemia overload the beta cells and beta cells gets production imbalance then the organ will face insulin production problem(diabetics mellitus) in addition to glucose utilization problem (Schinner et al., 2005). Gradual uprising of diabetic's mellitus complication appears as macrovascular diseases by affecting the heart and as microvascular disease by affecting kidney, eye, and nerve system (J. B. Cole & Florez, 2020).

In general, Insulin resistance refers resisting or decreasing glucose uptake of muscle and adipose tissue cells in response to the hormone insulin when the human body is under the process of anabolism and catabolism due to less number production of insulin stimulated glucose transporter (GLUT4) in a single cell. This implies as the number of glucose transporters decreases relative to the normal production, enough glucose will not reach inside the cell to be oxidized.

Additional scientific research show that investigation focuses on the cause-and-effect relation between insulin resistance and diseases developed because of insulin resistance as follows.

Unplanned diet habit as an energy intake without taking physical activity as energy expenditure into consideration worsen the situation in a long-time basis due to overfeeding and conversion of unused carbohydrates to fat in the body in addition to our daily fat intake (Fialkowski Revilla et al., 2018; Houghton et al., 2019), this indicates the major excess fat accumulation in adipose tissue found in visceral and muscle.

As a result of increasing the number of adipocytes due to excess accumulation of fat in the body the hormone adipokines production will increase (Zorena et al., 2020), rising adipokines in the body together with fat induced low density lipoproteins and reduction of fat induced high density lipoproteins become the dominant cause for the complications developed on cardiovascular and metabolism (Su & Peng, 2020).

Studies for the past decades shows that the excess accumulation of fat from direct diet of fat and ingestion as carbohydrate through conversion to fat has effect on our body mass index, BMI classified in a group of normal, overweight, and Obese based on body mass index. Normal body mass index is less than 25 kg/m^2 and Obese group shows BMI is greater than 30 kg/m^2 whereas overweight is in between 25 and 30 kg/m^2 (Hasan et al., 2021; Martinez et al., 2017), degree of fat accumulated in the body in both groups of obesity and overweight has a significant factor to be a risk group for the development of Insulin resistance.

In this thesis, the author is trying to take as a reference of insulin resistance in the modelling process as a problem which is studied on eight obese volunteers with

Average BMI of 34.4 ± 1.8 kg/m^2

Average body weight of 102.9 ± 5.1 kg

And with a medical history of non-insulin dependent diabetic mellitus without any health abnormality issues (there is no additional health problem identified during recruitment) (Henry et al., 1986).

During the study on Insulin resistance patients by Henry et al. (1986), the process had separate phases.

1. Preparation phase: is a period for all the voluntary to have medical check-up until having stable body weight, it took 2 months.
2. Weight reduction period is the main part of the research which was conducted in the hospital and at home ranging from 60 to 380 days.

Before all the volunteers following the treatment as an outpatient from home, they were admitted in the hospital from 10 to 40 days.

3. Weight maintenance period is a 3-week period.

during this research, long term morning blood sugar level was considered as one of the signs of Insulin resistance, blood sugar early in the morning was taken at 7:00 A.M and all the volunteers took 75-gram carbohydrate in liquid form prepared for this purpose then began to measure blood glucose level for 3 hours, the same procedure had been taken after weight reduction with good improvement result of morning blood glucose level (see figure 1-2).

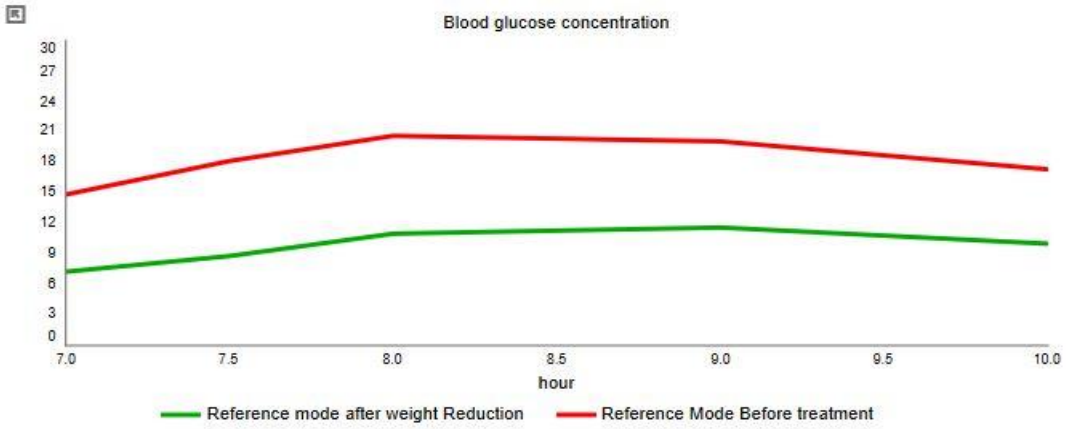

Figure 1-2. Blood glucose level for non-insulin dependent diabetics mellitus (Insulin Resistance) before and after weight reduction as a reference mode.

Based on the average blood glucose concentration sample took from the voluntaries in the morning, the value was 14.85149 mmol/l which is too high relative to the normal human expected fasting blood glucose concentration level and can fulfil the requirement for Insulin resistance with fasting blood glucose concentration level ≥ 7.0 mmol/l (Martinez et al., 2017; Tang et al., 2019) whereas the initial point for the green line (7.26 mmol/l) indicates the treatment was effective and shows a 50% progress on the fasting blood glucose concentration level.

1.4. Thesis justification.

Insulin resistance is a complex problem with many interrelated variables and interactions involved, that can lead to serious diseases on organs and systems such as Type I Diabetes Mellitus, cardiovascular, Kidney and eye. SD is a tool that allows to understand and analyses complex problems like this one and provides a way to test and assess interventions to reduce and prevent this problem.

In this thesis, the author intends to investigate how blood glucose homeostasis can be understood by different stakeholders such as medical experts, health decisionmakers and the public in general, and it can be used as a starting point for more in-depth studies on how to help reduce diseases that affect populations world-wide.

1.5. Objectives of the Research

Human physiology in blood glucose homeostasis process has dynamics due to the presence of natural interactions in and out of the cell, those normal and abnormal dynamic interactions in the body needs to have a detail analysis to investigate the cause for the problem, the solution as a management of the problem and cause and effect relation(physiology) of cells, tissues, organs, and systems in the body. In general, the objective of this thesis marked as follows.

1.To explore the main underlying dynamic interactions among variables (hormone, cell, organ, and nutrients) and feedback processes involved during blood glucose homeostasis.

2. To analyze dynamic effect of body hormones especially insulin on glucose metabolic process since less quantity (unproportionable) production of insulin in the body is an indication to the disease Diabetics mellitus.

3. To study the dynamic implication of insulin resistance development in the body and to investigate potential management mechanisms to address insulin resistance (type 2 diabetics mellitus) due to excess accumulation of fat (BMI based) in the body through daily diet relative to daily activity by using system dynamics feedback mechanism.

Chapter 2 . Literature Review

In this chapter the author reviews blood glucose homeostasis related to Insulin resistance literature undertaken in system dynamic approach and other study methodologies, the ultimate goal is to get updated understanding on the solutions and on the main cause of insulin resistance during the process of blood glucose homeostasis to achieve efficient solution for the diseases and its complications by applying additional features during the study, making easily understandable physiology of blood glucose homeostasis in system dynamic approach is also included as a goal.

Computer based automated technologies on human physiologies for the purpose of medical treatment is not that much developed relative to automation on the other sectors, complex system induce blood glucose controlling application is one of the automated technologies and insulin resistance is one of the cause for blood glucose to be high (Chase et al., 2019).

Studies that are found during literature review labeled as follows.

Model-based studies on insulin resistance.

The model designed and studied by Pielmeier et al. (2010) concludes that understanding the amount and the effect of insulin in the body on insulin resistance patients by the help of models prevents the prevalence of excess insulin in the body, excess insulin in the body exposes the patient to fall in the condition of hypoglycemia. For the purpose of controlling glucose in the blood, a normal Physiology based compiled metabolic model studies glucose absorption in the gut and insulin action on the organs to see how far organs response for insulin to reach its maximum level. The compiled model contains endogenously influenced blood glucose dynamics, insulin, and assimilation of glucose from the diet. Insulin and glucose intake administered externally to control the blood glucose in addition to the normal anatomy and physiology.

Systems thinking and System Dynamics literature.

System thinking on the developed complex system is the base to analyze the behavior of the system, reason out how the feedback loop is part of it. Representing blood glucose homeostasis by the help of closed loop diagram to give insight and to have better mental model for the students about anatomy and physiology of blood glucose is studied by (Wellmanns & Schmiemann), feedback reasoning skill on the behavior of complex blood glucose level helps to investigate the cause and effect relation of hormones, organs and blood glucose level. Reasoning the regulatory system of feedback loop includes the hormones of insulin and glucagon, both hormones play its specific role on the conversion of glucose to glycogen and vice versa. Analyzing the feedback loop shows the dynamic of blood glucose during internal and external influences occur on the body, external influences include food as diet and glucose as a source of energy.

Abdel-Hamid (2003) studied obesity treatment through exercise and diet by using system dynamics approach to get understanding on the relation between diet and exercise with weight change, weight change is exempted a dynamic behavior due to the systems. In the model building, the author shows the interdependency of hormones and different organs during the process of metabolism. Finally, the simulation result shows that more weight is lost due to diet than moderate exercise in a daily life due to exercise effect on fat mass. On the other experiment, moderate to high level exercise is more

effective way of reducing weight but better weight reduction is recorded by increasing carbohydrate portion with increasing exercise intensity.

Modeling glucose homeostasis by using system dynamic methodology undertaken to understand the phenomena included in the model as organ, the study concludes that the secretion dynamic behavior of insulin is determined by the duration of infused glucose and further when the amount of glucose in the blood increases nervous system glucose utilization increases but in adipose and muscle tissue, insulin is the additional requirement for glucose utilization. the study also focused on to see how the blood glucose homeostasis goes when the connection between glucose level and insulin secretion is interrupted by some factors to see how diabetics looks like during less insulin production (Foster et al., 1973).

The above model-based literatures do not have complete anatomy and physiology on insulin resistance that the author studies right now, instead the above study focuses on part of the authors model, relation between blood glucose and insulin can be example for the literature found during reviewing literature.

Therefore, in this study, the author shows blood glucose homeostasis on the diseases of Insulin resistance by including more organs, tissues, and systems in the model.

Chapter 3 . Methodology

System dynamics (SD) is a methodology and works as a basic tool to understand the complex dynamic behavior developed by the structure, understanding the complex dynamic behavior favor the reader or the researcher to have a good insight during identifying the right problem, hypothesize and analyzing by the help of computer simulation to make reliable policy before implementation (Sterman, 2000).

The research objectives in this thesis regarding excess fat induced Insulin resistance as a problem has given attention to answer in detail by using system dynamic approach as a relevant and optimal way of studying broadly blood glucose homeostasis to investigate the main cause of the problem since in human anatomy and physiology, blood glucose homeostasis with problems related to it like Insulin resistance is one of the complex systems encapsulated in human body.

Using System dynamics approach to study problematic issue relies on the feedback relation in the system between two or more variables included in the structure, variables are directly or indirectly responsible for the generated dynamic behavior in a complex system since a collection of variables in the system are the foundation of the structure but share of variable effect on the generated dynamic behavior differs accordingly.

Feedback relation implies that the effect of one variable as a cause for the next variable forward any signal to the next and receive any signal back from previously influenced variable or literally it is the result of action and reaction between two or more variables in a complete loop, those feedback relations represented by Balancing (B) and Reinforcing (R) loops (Lin et al., 2020).

Dynamic behavior is developed due to the interaction of balancing and reinforcing loops in the system, balancing loops rises from the opposite interaction of variables in the loop whereas reinforcing refers transferring by amplifying received signal to the next (Mohammadi et al., 2018).

According to Sterman (2000), causal loop diagrams are tools that helps to have a good image on the system developed by the feedback structure whereas stock and flow diagrams shows the right structure and mathematical relations in between, stocks are the accumulated result of the rated flow.

A CLD aids in synthesizing key factors generating a problem and identifying the relationships among these factors; and is then used by stakeholders and practitioners to investigate the cause of the problem (El-Sayed & Galea, 2017).

Example: figure 2-1 shows the population growth by taking birth and death into consideration, both reinforcing and balancing loops are developed due to the cause-and-effect relation between birth rate with total population and death rate with total population.

Reinforcing loop.
In the Figure 2-1, the arrow from birth rate to total population indicates that birth rate influences total population and the (+) sign indicates when birth rate increases total population also increases, and total population has also the same effect on birth rate back through the other arrow. Therefore, the relation between birth rate and total population are positive and at every cycle the number of birth rate and total population increases, this implies reinforcing is developed in the closed loop.

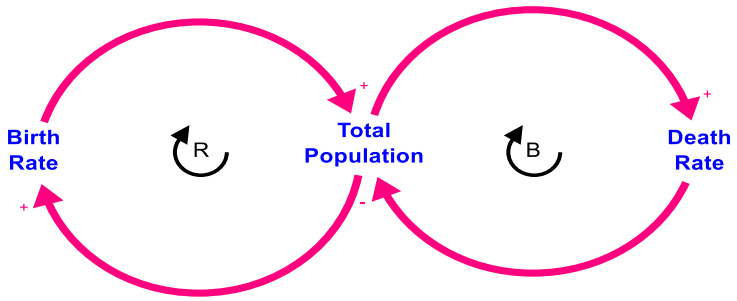

Figure 3-1. Example of casual loop diagram for population growth.

Balancing Loop.
In the figure 2-1, when total population increases death rate also increases because the arrow from total population to death rate is positive but when death rate increases total population decreases because the (-) sign indicates that there is opposite relation. Therefore, total population and death rate has a counteracting relation, this implies that balancing loop is developed in the system between total population and death rate.

CLD is a straightforward way description which can introduce how the cause-and-effect relation goes based on the type of response on hormones, organs or in system level. In the CLD of figure 3-1, (+) indicates both cause and effect go in the same direction but (-) indicates cause and effect goes in opposite direction.
Note. Total number of (-) in a single loop determines the feedback loop behavior, if the number of (-) s are even the loop becomes reinforcing but if it is odd the loop becomes balancing (Inghels, 2020).

According to Abdel-Hamid (2003), human anatomy and physiology holds both reinforcing and balancing loops, balancing feedback loops are more dominant on the homeostasis process especially the effect of hormones. Missing insulin sensitivity by the organ's attacks back the feedback systems and develops a consequence on other organs or systems like blood glucose concentration due to less capacity of glucose uptake by the cell (Chase et al., 2019).

Ethics
The increased use of computer technologies and modelling techniques addressing complex problems raises many ethical questions such as: What is the proper relationship between the model builder and the model user? Should the model builder assume professional responsibility for the result of their models? (Wallace, 1994), these questions were taken into account by the author during the development of this thesis. Ethical evaluation is important to apply on the modelling process, using professional guidelines to follow ethical research procedures and standards during the modelling work (Pruyt & Kwakkel, 2007; Saltelli, 2020). Models' assumptions and limitations must be appraised openly and honestly(Saltelli et al., 2020). Hence, this thesis provides complete model documentation for model replication, described all assumptions made during the modelling process, and defined model boundary.

In this thesis, there was no primary data collection involved, therefore, ethical considerations related to the treatment of research participants is not applicable in this work.

Chapter 4 . Model description

In this chapter the author shows the structure representing tissues, organs and systems that are involved in blood glucose homeostasis by using stock and flow diagram (SFD) and then theory of human anatomy and physiology function described in a cause-and-effect relation by using feedback loops on the developed CLD.

4.1. Structure of blood glucose homeostasis by using SFD.

Constructing well functioned model is the result of good scientific reasoning of how each organ, system or hormone in the body interlinked and influencing each other in a cause-and-effect relation. The conceptual model in figure 4-1 represents the main constructed model structure that generates a dynamic behavior of both problematic for insulin resistance and a normal behavior that develops after the treatment described in the introduction part since conceptual model helps us to easily understand the physiology of the organs in the body, but detail anatomy and physiology is described on the actual model.

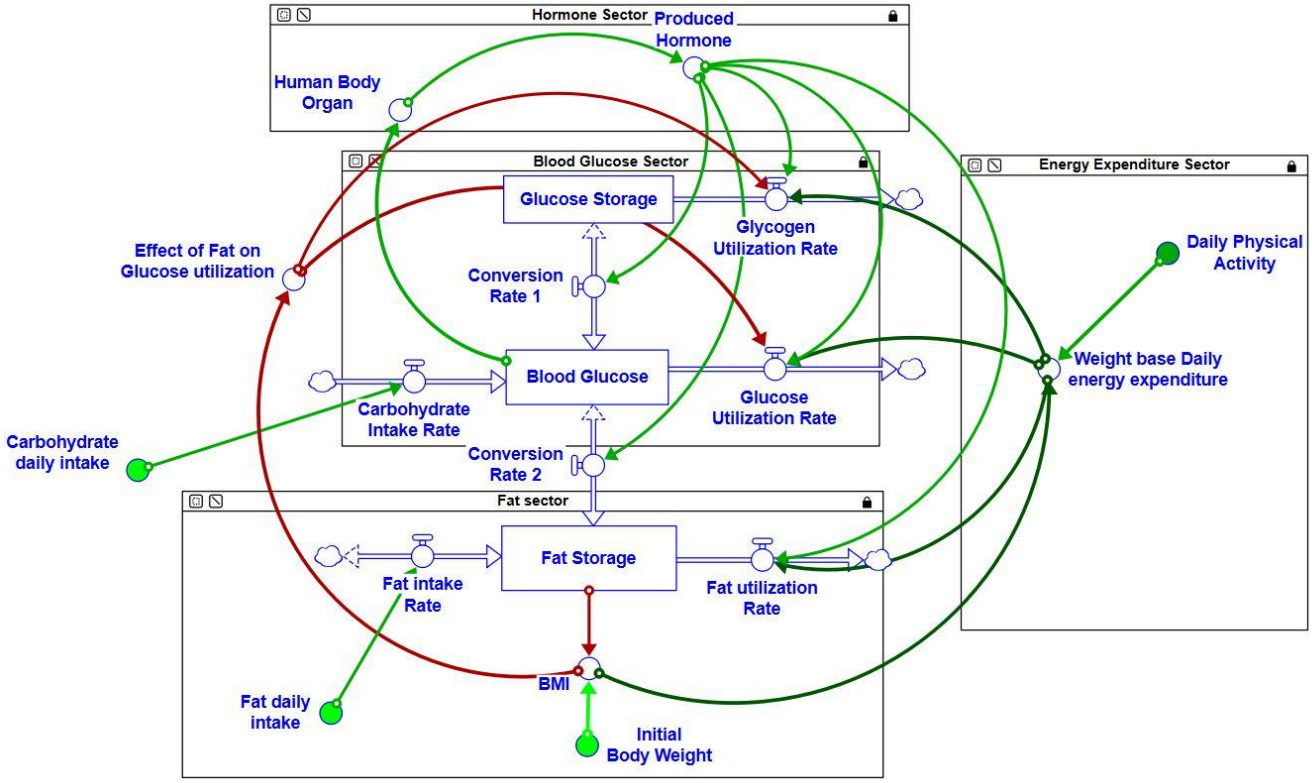

Figure 4-1. Conceptual model for blood glucose homeostasis.

The model has 4 sectors and represented by the conceptual model on figure 4-1, the sector is described as follows.

1. Blood glucose sector.
   In the actual model of blood glucose sector on figure 4-2, the main organs or tissues involved in the processes of metabolism are listed below.

Daily carbohydrate intake as an exogenous factor through the process of glucose absorption from GIT is followed by storing excess blood glucose in liver and muscle through the process of glycogenesis, excess glucose further converted to fat when muscle glycogen is full.

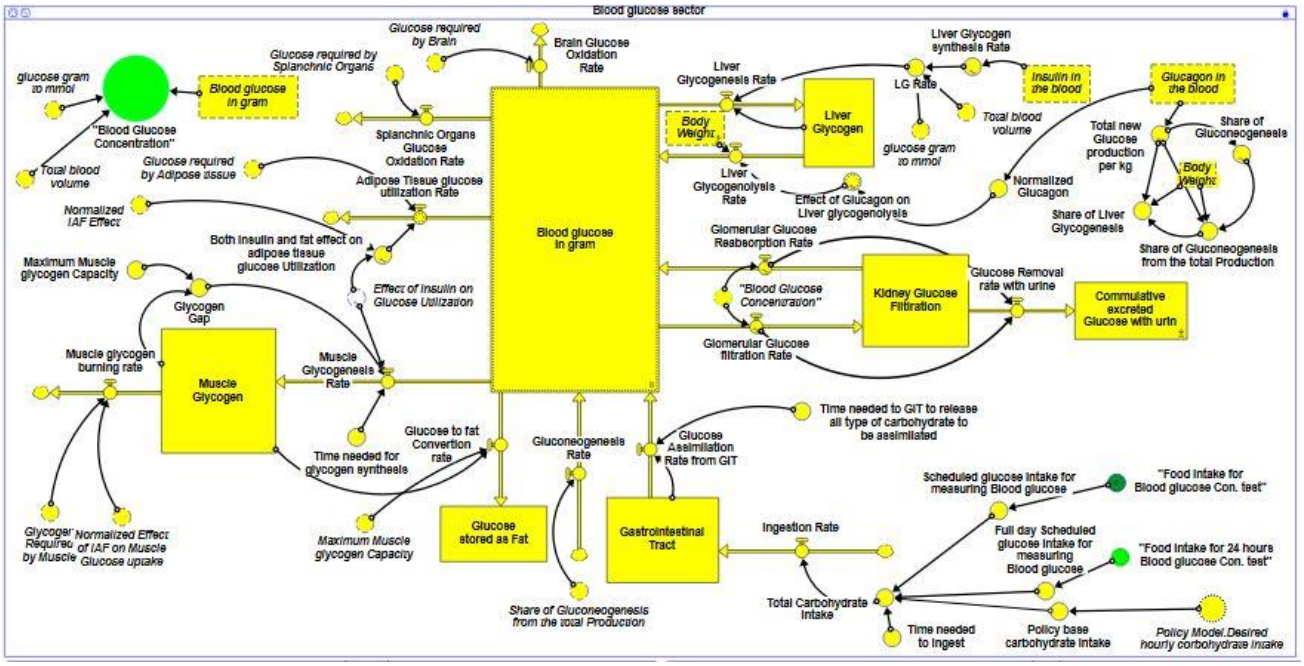

Figure 4-2. Blood glucose sector of actual model structure.

Converting the stored glucose(glycogen) in liver to glucose during shortage of blood glucose happens in the blood vessel through the process of glycogenolysis, non-carbohydrate nutrients (fat and protein) from the body converted to glucose through the process of gluconeogenesis when glycogen in the liver reduced. Kidney is involved in the process of blood glucose filtration and re-absorption; its rate is relay on blood glucose concentration level.

Glucose utilization or oxidation on the process of glycolysis in the cell of the body is grouped in to four (Brain Glucose oxidation, Splanchnic organs glucose oxidation rate, adipose tissue glucose utilization rate and muscle glycogen burning rate), all oxidation rate on the model release energy for the body during the process of burning glucose.

2. Hormonal Sector.

   Pancreases is the organ that detects the level of blood glucose level and produces the hormone insulin and glucagon accordingly, insulin is responsible to stimulate the processes listed above on blood glucose sector (glycogenesis and glycolysis).

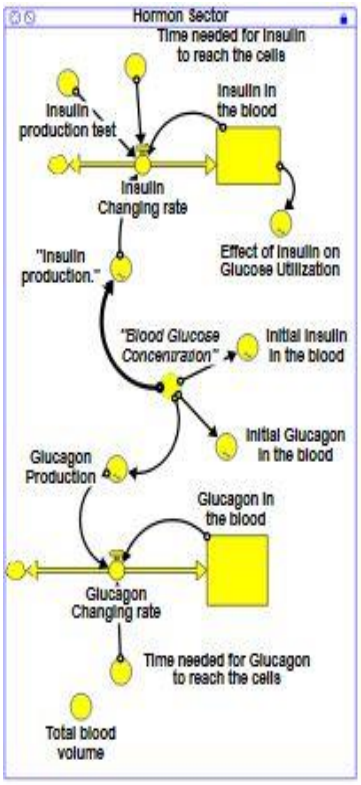

Figure 4-3. Hormonal sector of model structure.

Glucagon is involved on the process opposite to insulin, the process of glycogenolysis and gluconeogenesis are stimulated by the hormone glucagon when blood glucose level is below the normal level.

3. Fat Sector

   Fat daily intake and fat from glucose are the only source of fat but total fat is the sum of both three (total daily fat intake, body fat and fat stored from glucose). Fat is one of the continuous sources of energy during body metabolism through the process of fat oxidation and fat could be the source of glucose through the process of gluconeogenesis when blood glucose is below the normal level.

   Excess fat found in the body through the effect of BMI controls blood glucose utilization in adipose and muscle tissues, the variation of fat in the body varies BMI of the body.

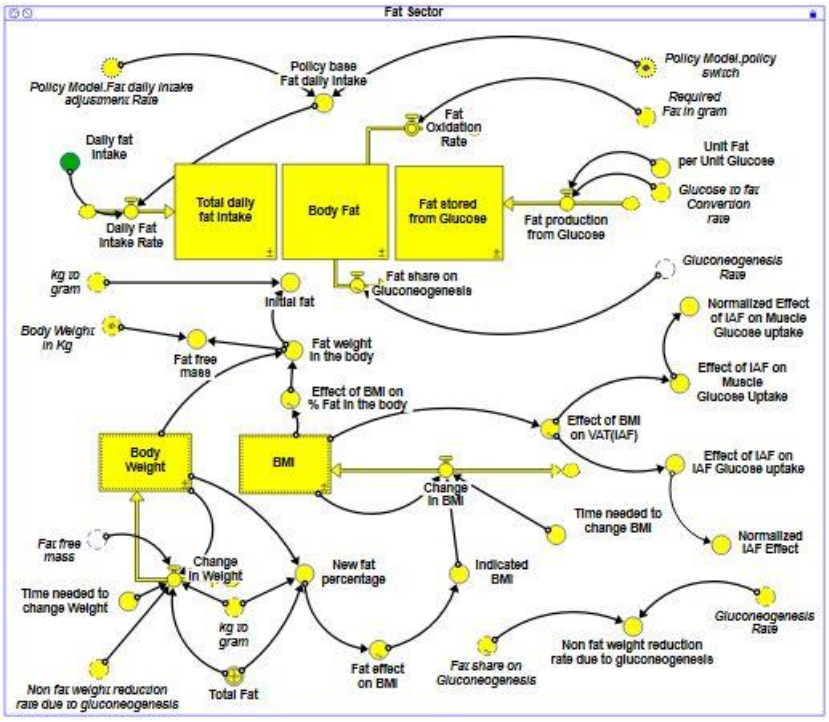

Figure 4-4. Fat sector of model structure.

4. Energy Expenditure Sector

   Energy sector highly concerned on the amount of energy needed by the body, the amount of energy needed by the body relies on the weight and the daily physical activity of the body. Weight of the body varies every time according to the amount of fat in the body since fat uses as a source of energy in the body.

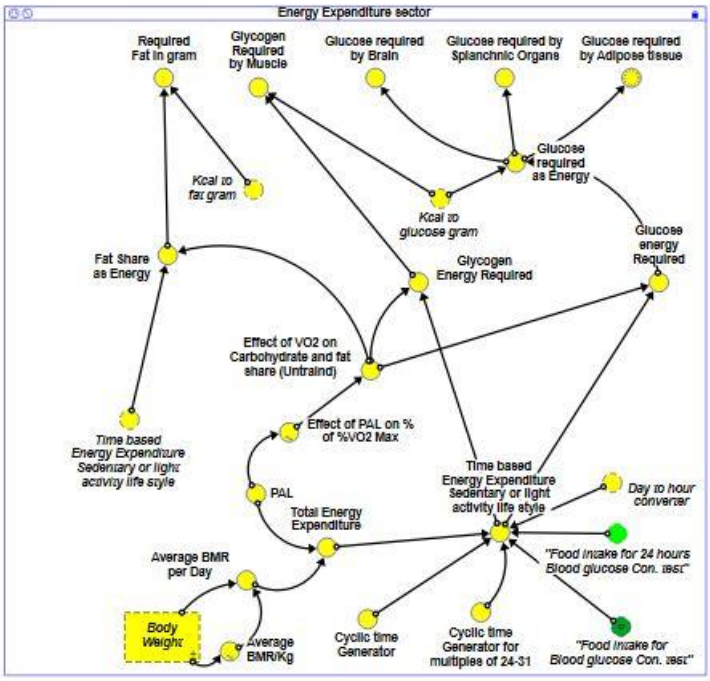

Figure 4-5. Energy expenditure sector of model structure.

Weight base hourly energy expenditure of the body uses fat and glucose as a source of energy, the required energy is grouped in the body in to four main tissues or organ groups (glycogen required by muscle, glucose required by brain, glucose required by splanchnic organs and glucose required by adipose tissue).

4.2. Dynamic hypothesis and main feedback loops.

In addition to the conceptual and actual model described above, the author shows how blood glucose concentration level influences and gets influenced by the other hormones, organs, and system in detail by using a CLD (See figure 4-6).

System dynamics classified the factors that influence the dynamic behavior in to two.

- Daily Carbohydrate intake as a meal, Daily fat intake as a meal, Physical activity level, Weight, and height are the exogenous factors that influences the system without any feedback on it (See figure 4-6).
- Endogenously engaged variables in the model controls the system by influencing its next parameter in the loop and influenced back the system by another parameter, endogenous parameters in this model explained in detail based on the loop grouped in the CLD of figure 4-6.

4.2.1. External source influencing the physiology of the body (Exogenous Factors).

I. Carbohydrate.

Carbohydrate in human daily diet covers 50% of nutrients needed for daily energy requirement since it is the main source of energy relative to proteins and fat (Shan et al., 2020).

Carbohydrate in the form of glucose taken as a diet in human body to achieve daily need for the organ cells, brain and some of the cells found in human body uses glucose as source of energy in normal condition since glucose has a capacity to pass blood brain barrier to reach the cells of brain (Koepsell, 2020).

Carbohydrate is water soluble containing elements carbon, hydrogen, and oxygen but the ratio varies according to the type of carbohydrate in the subgroup, the carbohydrate group that our body uses as a source of energy contains 6 elements of carbon,12 elements of hydrogen and 6 elements of oxygen. as a source (Stick & Williams, 2010).

Carbohydrate is classified in a subgroup of simple and complex based on how the structure of each element is bind together to get separately as an energy source, simple carbohydrates have a behavior of releasing quickly during digestion whereas slowly digestible carbohydrates are complex but both of them synthesized in animals and plants (Siva et al., 2019).

Based on the contents in, carbohydrate classified as monosaccharides, disaccharides and polysaccharides (L. A. Cole & Kramer, 2015). Simple carbohydrates are the group name given for both monosaccharides and disaccharides, monosaccharides are Glucose, Fructose and Galactose but Maltose, Lactose and Sucrose are simple disaccharides carbohydrates (Blanco & Blanco, 2017). Polysaccharides under the complex carbohydrates, are formed by making a long chain of monosaccharides, Starch and Glycogen as a Polysaccharides can be synthesized from monosaccharides on the process of dehydration (Muhamad et al., 2017).

Prior to assimilation of carbohydrate from GIT, disaccharides and polysaccharides need to be converted to monosaccharide through the process of digestion, digestion of carbohydrates starting from the mouse by the help of salivary amylase (Lunn & Buttriss, 2007).

Stomach is the organ next to esophagus that chemical reaction and digestion are performed due to production of different enzymes based on the type of food intake available in the stomach, the acidity in the stomach deactivates the action of salivary amylase through the process of chyme formation prior to digestion in the small intestine, in the small intestine by using hormones pancreatic amylase, maltase and sucrase involved in the process of converting polysaccharides and disaccharides to monosaccharides where monosaccharides are absorbable form of carbohydrates at intestinal villi (Walther et al., 2019).

Monosaccharides from the small intestine absorbed from the intestine and transported in to the blood circulation by sodium dependent transporters(SGLT1) and other non-sodium dependent transporters (GLUT 2 and GLUT 5) (Hinsberger & Sandhu, 2004).

The importance of glucose as a source of energy for most cells in the body required to have a transporter that helps glucose to be easily reachable when there is in need of it, Sodium glucose linked transporters(SGLTS) and Glucose transporters (GLUT) are the main carrier of glucose, Glucose transporters described in detail as follows in table 7-1(Appendix) since the cause of insulin resistance is Physiological communication failure between hormone insulin through the insulin receptor and availability of GLUT4 on the wall of the cell (Navale & Paranjape, 2016).

II. Fat daily intake.

According to Hamosh (2020), Fat in human beings is essential for body growth, development, and an energy source. Gastric lipase is the second enzyme secreted in stomach next to Lingual lipase which is produced in the mouth that emulsifies and helps digestion of fat, digestion of fat helps to isolate fats in the form of fatty acids and watery compounds.

lipids are the complex form of fats and fatty acids are the simplest form (Zárate et al., 2017).

Further digestion and absorption of lipids in the small intestine supported by the hormone produced by liver and stored in a gallbladder. Pancreatic lipase is an enzyme synthesized in the pancreases and involved in the conversion of triglycerides into fatty acids and glycerol's in small intestine, absorption of digested fat in the small intestine through microvilli (Goodman, 2010).

The assimilated fat products used as energy source during energy in need but excess fat available in the blood vessel transported to adipose tissue for storage, triglycerides in the adipose tissue convert back to fatty acids and glycerol during energy need as fat (fatty acids) and can also be the source during gluconeogenesis(glycerol).

Absorption rate and the process of making free fatty acids and monoglycerides ready for absorption in the GIT is controlled by the availability of digestive enzymes, pancreatic and gastric lipase has a role for hydrolyzing the fats during digestion and absorption (Joyce et al., 2020).

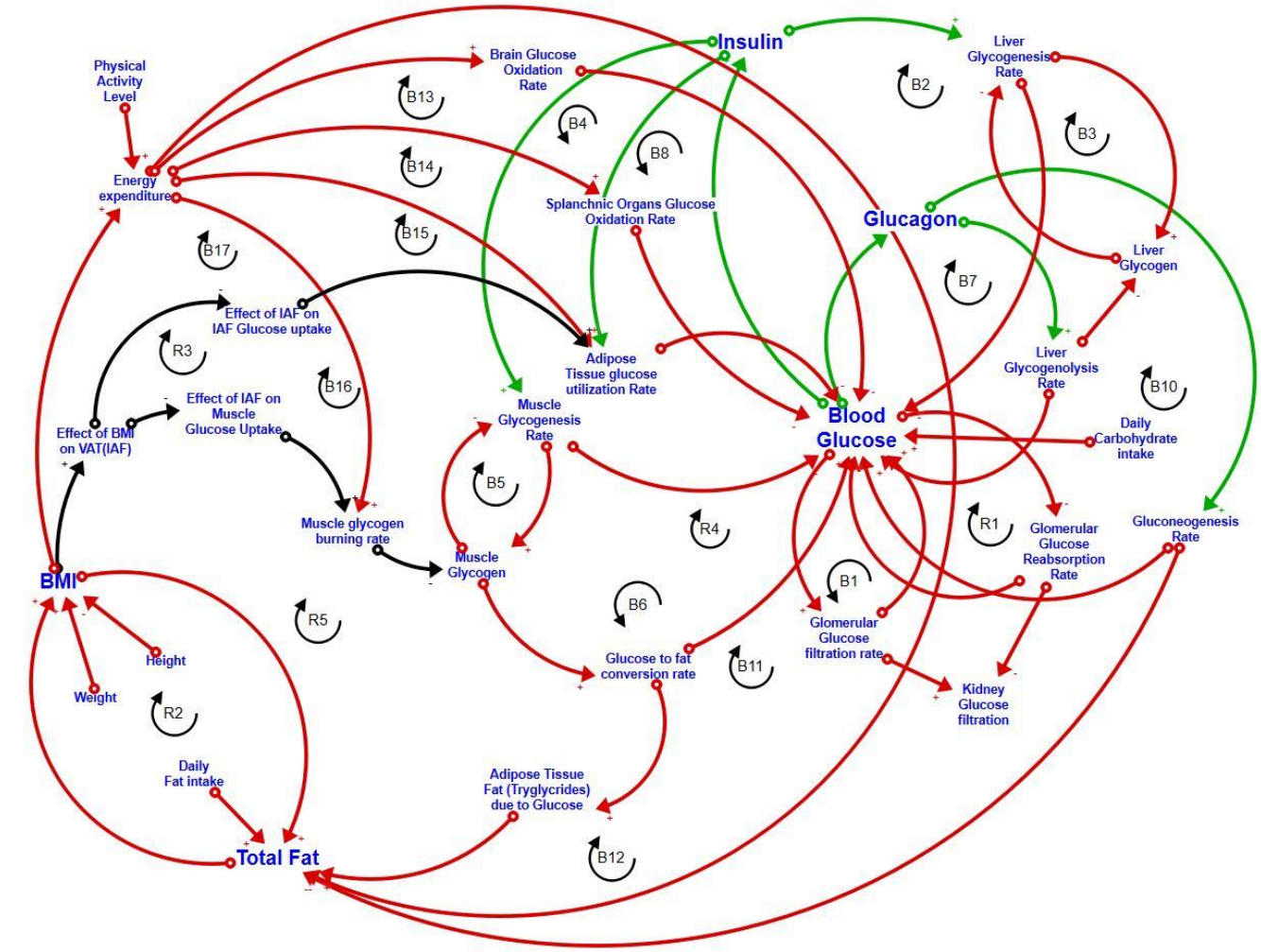

Figure 4-6. Adult blood glucose homeostasis CLD, green color is for hormonal sector and the black connector shows the relation of BMI on adipose and muscle glucose utilization.

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Table 4-1. Assigned loops from the CLD with description.

No	Loop	Given name of the Loop	Description
1	B1	Kidney glucose filtration.	Glucose involved on the process of filtration by Kidney.
2	R1	Kidney glucose reabsorption.	Glucose reabsorption in the kidney during filtration.
3	B2	Liver Glycogenesis.	The Process of converting Glucose to glycogen in the liver stimulated by hormone insulin.
4	B3	Liver storage capacity.	Liver glycogen holding capacity controls glycogenesis rate when it reaches maximum.
5	B4	Insulin Muscle Glycogenesis.	Insulin mediated glucose to glycogen conversion in the liver.

6	B5	Muscle storage capacity.	Muscle glycogen holding capacity controls glycogenesis rate when it reaches maximum.
7	B6	Insulin glucose fat conversion.	Condition for glucose to fat conversion begins when insulin mediated glucose to glycogen conversion in the muscle reaches its maximum capacity.
8	B7	Liver Glycogenolysis.	Glucagon mediated glycogen to glucose conversion in the liver.
9	B8	Insulin Adipose Tissue.	Insulin stimulated glucose utilization.
10	B10	Gluconeogenesis.	Glucagon stimulated gluconeogenesis.
11	B11	Gluconeogenesis on glucose to fat conversion.	Effect of gluconeogenesis on glucose to fat conversion through muscle glycogen.
12	B12	Fat energy expenditure	The relation between fat as a source of fuel and fat as part of weight with energy expenditure.
13	B13	Non-insulin dependent organ energy expenditure	Gluconeogenesis effect on non-insulin dependent organs glucose utilization through energy expenditure.
14	B14	Splanchnic organs energy expenditure	Gluconeogenesis effect on Splanchnic organs glucose utilization through energy expenditure
15	B15	Adipose tissue energy expenditure	Gluconeogenesis effect on adipose tissue glucose utilization through energy expenditure
16	B16	Muscle glycogen energy expenditure 1	Gluconeogenesis effect on muscle glycogen glucose utilization through energy expenditure further controls glucose to fat conversion.
17	B17	Muscle glycogen energy expenditure 2	Gluconeogenesis effect on muscle glycogen glucose utilization through energy expenditure further controls how fast glucose to glycogen conversion since glycogenesis rate is dependent on the level of muscle glycogen.
18	R2	Fat BMI	The relation between total fat of a body and body mass index
19	R3	BMI adipose tissue	Gluconeogenesis effect on adipose tissue glucose utilization through BMI
20	R4	BMI Muscle Glycogenesis	Gluconeogenesis effect on muscle glycogen glucose utilization through BMI further controls how fast glucose to glycogen conversion since glycogenesis rate is dependent on the level of muscle glycogen.
21	R5	BMI Glucose to fat conversion.	Total fat effect on glucose to fat conversion through BMI effect on muscle glucose utilization.

III. Physical Activity level (PAL).

Physical activity level refers how strong is our physical status from the minimum energy demand metabolic rate up to the maximum energy demand of human energy metabolism during our daily

physical activity, its unitless numerical value is the quotient of our total daily energy expenditure with the body basal metabolic rate (Westerterp, 2013).

According to the joint report of FAO/WHO/UNU (Food and Agriculture Organization/World Health Organization/ United Nations University) Joint (2004), physical activity level varies in the society since physical activity differs between sedentary/Light activity, moderately active/Active and vigorously active lifestyles.

A. Light activity Lifestyle (Sedentary).

The physical activity level in this group is between 1.4 and 1.69 because in this group they are not regularly doing physical exercises, mostly the daily life including daily work of this group does not need physical demand, for example using private car instead of using a collective transport or walk as a hobby, etc.

B. Moderately active life

Reference to the name given, the people in this group engaged on physical demanding activities throughout their life.

Physical Activity Level is between 1.7 and 1.99 because all the daily physical activities require more energy source, mostly the people in this group doing energy demanding exercise.

Cycling regularly, walking regularly could be high energy demanding daily exercise.

C. Vigorously active lifestyle.

The lifestyle in Vigorously active group is engaged on high energy demanding and time taking daily activities like swimming, walking, and running…etc. more than two hours per day. Athlete could be included in this group and the physical activity level is between 2 and 2.4.

Oxygen consumption during any physical movement relies on our physical activity level (Burton et al., 2004) and it shifts the share of human body energy sources especially share of fats and carbohydrates, this carbohydrate or fat metabolization share vary according to the percentage of the maximum oxygen consumption Vo2 Max % (Holloszy et al., 1998). In general, increasing physical activity level from mild to moderate increases usage of glucose as a source of energy (Heinonen et al., 2014), but increasing the duration of physical movement increases fat utilization (Jeukendrup, 2003).

4.2.2. Endogenous factors: Blood glucose concentration through feedback relation with other organs or systems in the body.

I. Kidney

Minerals, electrolytes, and blood glucose…etc. in human body is filtered, reabsorbed, and excreted through the organ kidney (Miyoshi et al., 2020).

Sodium glucose co-transporters (SGLTs) in the Kidney reabsorbs blood glucose back to the blood vessels with a reabsorption rate of linearly increasing until it reaches a maximum rate as blood glucose concentration increases(R1) whereas the blood glucose filtration rate (average 180 liter of blood per day)increases linearly as blood glucose concentration increases, linearly increasing of glucose filtration rate decreases the blood glucose concentration which is represented by a balancing loop of B1(Poudel, 2013).

II. Liver and muscle.

Due to rising of blood glucose concentration above the normal range during postprandial condition, glucose is transported and involved on the process to be stored as glycogen highly in human organs of Liver(normal range is between 0-160 gram, ~80 gram) and Muscle(normal range is between 300-700 gram ,~500 gram), the other glycogen storage sites that have a storage capacity of approximately 100 times less than the capacity muscle glycogen are brain, heart, kidney and red blood cells (Murray & Rosenbloom, 2018).

The name glycogenosis refers to the formation of glycogen from glucose through the hormone insulin and glycogenosis rate refers how fast the conversion of glucose to glycogen goes in order to reach maximum liver glycogen capacity with a balancing loop of B2, further level of the liver storage controls back the conversion rate through the balancing loop of B3 because of limited storage capacity of the liver.

Insulin is one of the hormones and its production relies on the amount of glucose in the blood vessel, the production of insulin also further determines how fast the conversion of glycogen from glucose in the liver and in the muscle by stimulating different hormones that are responsible during conversion process (Blanco & Blanco, 2017; Chadt & Al-Hasani, 2020; Vargas et al., 2020) (See Appendix figure 7-4).

Liver glycogenesis rate and muscle glycogenesis rate variation due to insulin concentration in the blood regulate further concentration of blood glucose through the loop B2 and B4, respectively.

Muscle glycogenesis rate is the main gate controlling the storage of glucose as glycogen in the muscle and the level of glycogen back determines how fast muscle glycogenesis rate through the balancing relation of the storage and the rate (B5). According to (Fialkowski Revilla et al., 2018), fat conversion from excess blood glucose after a carbohydrate diet begins when muscle glycogen storage is full, and further manages the level of blood glucose concentration through the loop B6.

On the other hand, liver is the only organ that supplies back to the blood vessels from the storage of glucose as glycogen when blood glucose concentration is below the normal range because muscle has no glucose-6-phosphate to change glycogen to glucose but it involves during gluconeogenesis as a source of lactate even if muscle glycogen has no that much significant role during starvation/fasting in order to keep blood glucose concentration in the normal range (Jensen et al., 2011). Liver supplies glucose from the storage continuously through the hormonal influence of glucagon on Liver glycogenolysis rate and takes blood glucose from the blood vessel continuously until equilibrium is reach between glycogenolysis and glycogenesis (Blanco & Blanco, 2017).

Blood glucose concentration has an increasing and decreasing dynamics following the daily meal. During falling phase, the hormone glucagon secretion increases and stimulates different hormones to convert glycogen to glucose, the converted glucose enters to the blood vessels and raise the glucose concentration through the loop B7 described on figure 4-6 (Adeva-Andany et al., 2019).

III. Carbohydrate Utilization.

Glucose is the fuel that is oxidized by body cell as a source of energy (Tunduguru & Thurmond, 2017). In the process of glycolysis, glucose enters into the cell by the glucose transporter and end up

to Pyruvate after several steps of reaction, pyruvate goes further to powerhouse of the cell mitochondria (Hall & Hall, 2020).

Inside mitochondria, pyruvate get in to the Krebs cycle as acetyl CoA and then involved in the oxidation process to get energy, Co2 and H2O but when the cell is exposed to the condition where there is absence or shortage of oxygen in cells of skeletal muscle, lactate will be the product (Kumari, 2017) (see Appendix figure 7-2).

Utilization of glucose in human body facilitated with and without the hormone insulin depends on which glucose transporters are the carrier to deliver the required glucose for the specific tissue cell, adipose and muscle tissue glucose transportation is mediated by the hormone insulin (Navale & Paranjape, 2016).

- Effect of Insulin on Adipose Tissue glucose utilization.

The collection of adipose cells in human body forms adipose tissue. Adipose tissues classified as white and brown adipose tissues; white adipose tissues are the main site for energy storage whereas the brown adipose tissues are responsible for body heat source (Bano, 2013).

Glucose utilization in adipose tissues is regulated by insulin in the blood vessel since GLUT4 activated by insulin has a transportation role in the delivery of glucose to the adipose tissue cell during catabolism. The effect of blood glucose back on it through the above physiology develops a balancing loop of B8 in figure 4-6.

IV. Gluconeogenesis.

Gluconeogenesis is a metabolic process of getting glucose as from non-carbohydrate substrates in the body during shortage of glucose in human body to fulfil the energy demand for those human organs that are using glucose exclusively as the only source of energy like brain and eye, the main non-carbohydrate sources that are available in human body are proteins and fats (Melkonian et al., 2020) (see Appendix figure 7-3).

Lactate, glycerol, alanine, and glutamine are non-carbohydrate sources during gluconeogenesis (Hatting et al., 2018), the organs/tissues/cells that are involved in the process of gluconeogenesis are Liver, Kidney, brain, and erythrocytes (Melkonian et al., 2020).

Based on the CLD on figure 4-6, gluconeogenesis rate activity is highly dependent on blood glucagon concentration but additional exogenous hormones which is not included in this paper has a potential to activate gluconeogenesis (growth hormone, epinephrine, and cortisol) (Dashty, 2013), the hormone glucagon managing gluconeogenesis rate directly when there are enough non carbohydrate sources are available during the conversion process (Adeva-Andany et al., 2019).

The human physiology above classifies the effect of blood glucose on gluconeogenesis through the hormone glucagon in two paths, now let us see how the effect of gluconeogenesis on blood glucose concentration.

- Direct effect on blood glucose concentration as a supplier of blood glucose.
- Indirect effect on blood glucose concentration through body weight or body fat as a user since body weight variation has effect on energy expenditure.

A. Direct effect of Gluconeogenesis on blood glucose concentration.

Based on the physiology of gluconeogenesis, the conversion of non-carbohydrate to glucose increases the level of blood glucose concentration by using glucagon hormone as an initiator of enzyme reaction for the sake of glucose production, all those action and reaction processes connected through blood glucose concentration builds a balancing loop of B10 since hormone glycogen is inversely related to blood glucose concentration.

B. Indirect effect of gluconeogenesis on blood glucose concentration through body weight or body fat as energy user.

According to Eckel (2018), adipose cells in adipose tissue found in visceral and subcutaneous tissues for the storage purpose of triglycerides. Triglycerides decomposes to glycerol and fatty acids, glycerol's are the only source of fat used for synthesis of glucose in the process of gluconeogenesis (Melkonian et al., 2020).This implies that, gluconeogenesis from fat as glycerol has effect on body weight since fat as glycerol is part of the body weight, body weight and body mass index are proportional.

Body mass index (BMI) (previously the name was Quetelet index) is calculated by considering weight in kg and height in meter with a unit of kg/m2, it is a good indication of fat in the body (Nadeem et al., 2018).

The variation of Body mass index in human body determines energy requirement for metabolism, visceral adiposity (VAT) and the total body weight, the relation is described as follows.

- Effect of BMI on Body weight (Total fat).

Body mass index has effect on total body weight since body weight is proportional to total body fat (Nadeem et al., 2018), the relation between body mass index and total body weight engaged in a reinforcing loop of R2(figure 4-6).

- Effect of BMI on visceral adiposity.

Fat composition in human body is mainly grouped in to two types based on the place where it founds anatomically, those are subcutaneous Adipose Tissue (SAT) and visceral adipose tissue (VAT).

Reference to Shuster et al. (2012), visceral adiposity is the prevalence of excess fat in adipose tissue around the abdomen and inside the abdomen as ectopic fat which surrounds the organs inside abdominal cavity. Adipose tissue is originally from lipoblasts and visceral adiposity, abdominal obesity has a significant complication in human physiology than subcutaneous obesity, impaired glucose utilization is one of the problems when there is change on visceral adipose tissue (Lim et al., 2020).Impaired glucose utilization effect is further entrenched on muscle and adipose tissues as follows.

i. Effect of Visceral adipose tissue (intra-abdominal fat) on adipose tissue glucose utilization.

Adipose tissue expansion during weight gain conditions shows change on the adipose cell size(hypertrophy) or on the number of adipose cells (hyperplasia) (Tandon et al., 2018).

The enlargement of adipose tissue above the cell limit develops poor sensitivity of the cell for insulin during burning of glucose in the cell, reduction of insulin sensitivity and expansion of the cell above the limit aggravate inflammation of the cell and gets more worse on glucose metabolism on adipose cells (Longo et al., 2019). In general reduction of glucose metabolism in the adipose cell decrease blood glucose drainage by adipose cells, this implies blood glucose concentration do not decrease as expected.

The influence of visceral adipose tissue through adipose tissue glucose utilization on blood glucose concentration and the effect of blood glucose concentration on visceral adipose tissue through gluconeogenesis based on the physiological explanation above concludes the inter relation of all the organs/hormones/cells engaged in the line as a loop have a reinforcing behavior and represented in the diagram as R3.

ii. Effect of Visceral adipose tissue (intra-abdominal fat) on Muscle tissue glucose utilization.

There are three types of muscle tissues that are found in human body for generating physical power and supporting organ function (Dong et al., 2020), skeletal muscles are voluntary that supports skeletal bone whereas cardiac and smooth muscles are involuntary and additionally can give response for hormones (Migliozzi, 2016).

Insulin stimulated glucose metabolism in skeletal muscle decreases as insulin sensitivity decreases because of visceral tissue induce sensitivity of muscular response on glucose utilization (Ferrannini et al., 2008).

As muscle glucose utilization effectiveness relies on existence of the visceral adipose tissue, muscle glycogen storage will face a problem to reach its maximum capacity and the case further influence blood glucose concentration.

1. Directly through muscle glycogenesis rate by making a closed reinforcing loop of R4 through hormone glucagon.

2. Through the fat formation from glucose since formation of fat from glucose begins to be processed when muscle glycogen storage is full (Fialkowski Revilla et al., 2018; Hall & Hall, 2020; Jensen et al., 2011). This human physiology condition influences

Total fat in the body back and makes reinforcing loop of R5 since it increases the total fat of the body when there a possibility of glucose to fat conversion.

Blood glucose concentration by developing inter relational effect on one to the other in a balancing loop of B11 due to the blood glucose base glucagon production on the process of gluconeogenesis, gluconeogenesis further influences total fat.

- Effect of BMI on Energy expenditure

Reference to the joint report of FAO/WHO/UNE Joint (2004), total energy expenditure of human beings can be formulated based on age and weight (BMI=Weight per height2), this report shows weight variation is one of the primary parameters which determines how much energy is needed for human beings in daily life basis.

Basal metabolic rate is the minimum daily energy metabolic rate to ensure vital human organs working properly which is calculated from the total energy expenditure, estimated basal metabolic rate for adult human beings at specific weight takes 35 to 70 % of the total energy expenditure (Kliemann et al., 2020).

- Energy expenditure

Resting metabolism which is the minimum energy demanding uses dominantly fat but share of glucose increases linearly for both trained and untrained human beings when energy demand increases because of change of physical activity (Burton et al., 2004).

Fat in adipose tissue is source of energy during fat metabolism, share of fat in the body as a source of fuel is share of body weight, this implies the weight of a body directly controls the energy required by the body and the effect further influences the weight of the body through total fat by developing of balancing relation in the loop of B12.

As far as metabolic rate of a human being is concerned, metabolism occurs in different tissue cells by using glucose or fat as a source of energy as follows.

1. Brain Glucose Utilization.

Brain and nerves system are the major organs/system that are not using insulin because glucose is transported to the organs by using non-insulin dependent glucose transporter (Bano, 2013). In addition to physical activity level, body weight is the only factor that determines how many grams of glucose is going to burn to get enough amount of energy to assure maximal well-functioning of brain and nerves system in human body (Pellerin & Magistretti, 2003).

The body weight is varying according to the fat that human body uses as glucose during starvation in the process of gluconeogenesis, gluconeogenesis relies on the concentration of glucagon available in the blood stream (see gluconeogenesis part above).

From the above explanation, the loop that explains in detail about the connection of glucagon through gluconeogenesis is represented by a closed balancing loop B13.

2. Splanchnic Organs glucose utilization (Other's insulin independent organs).

Splanchnic organs are a collection of vital organs found in the cavity of abdomen, some of the organs in this group are intestine, liver, kidney (Tappy, 2020).

Energy expenditure on the share of glucose for splanchnic organs have an indirect relation with the blood glucose concentration as follows. The body weight is varying according to the fat that human body uses as a glucose during starvation in the process of gluconeogenesis, gluconeogenesis relies on the concentration of glucagon in the blood vessel (see gluconeogenesis).

From the above explanation, the influence of blood glucose concentration back on itself through the other organs/hormones/cells described by a closed balancing loop of B14, the loop is developed due to direct involvement of the hormone glucagon on the process of gluconeogenesis since glucagon is produced due to less blood glucose. Total fat of the body is part of the body weight and controlled by gluconeogenesis and further influences the amount of glucose used by the splanchnic organ's cells.

3. Adipose Tissue glucose utilization.

The collection of adipose cells in human body forms adipose tissue (Chait & den Hartigh, 2020). Adipose tissues classified as white and brown adipose tissues; white adipose tissues are the main site for energy storage whereas the brown adipose tissues are responsible for body heat source (Bano, 2013).

Energy expenditure on the share of glucose for adipose tissue has an indirect relation with the blood glucose concentration as follows.

The body weight is varying according to the fat that human body uses as a glucose during starvation in the process of gluconeogenesis, gluconeogenesis relies on the concentration of glucagon in the blood stream (see gluconeogenesis).

From the above explanation, the influence of blood glucose concentration back on itself through the other organs/hormones/cells described by a closed balancing loop of B15, the loop is developed due to direct involvement of the hormone glucagon on the process of gluconeogenesis since glucagon secretion is relied on the level of blood glucose. Total fat of the body is part of the body weight and controlled by gluconeogenesis and further influences the amount of glucose used by the adipose tissue cells.

4. Muscle tissue glucose utilization.

Human body physical movement is supported by musculoskeletal systems, muscle and skeleton align together by tendons (Dave et al., 2020).

Glucose metabolism in skeletal muscle takes the highest share of total glucose next to brain (Bano, 2013), the amount of muscle glucose utilization indirectly influences the blood glucose concentration through.

a. Muscle glycogenesis.

When glucose utilization varies, muscle glycogenesis also follows the dynamics of the utilization to fill up the gap in muscle glycogen due to oxidized glucose on the muscle. Rate of muscle glycogenesis directly controls the blood glucose concentration; the effect further determines the existence of gluconeogenesis through the hormone glucagon. The closed loop that is generated due to the physiological relationship of the organs/hormones/cells is well described by a balancing loop of B17.

b. Glucose to Fat conversion.

Formation of fat from excess blood glucose is dependent on the amount of glycogen stored in the muscle, the conversion begins when the muscle glycogen storage holds its maximum capacity (Fialkowski Revilla et al., 2018). The physiology that described above develops a closed balancing loop of B16.

4.2.3. Endogenous hormones in the process of blood glucose Homeostasis.

Blood glucose homeostasis largely regulated by the hormones produced in the body, insulin and glucagon are the most dominant hormones that produced from the alpha and beta cells of the organ

pancreas to facilitate glucose metabolism and working to elevate blood glucose concentration respectively, the amount of the hormones produced in the pancreas relies on the concentration of glucose in the blood vessel.

4.3.1. Insulin.

Insulin is an endocrine hormone of 51-amino acid secreted from pancreas of beta cells in islet of Langerhans (Ojha et al., 2019). Insulin production in human body is stimulated by the presence of non-nutrients(hormones) and nutrients (Wilcox, 2005).

Insulin production in beta cells of the pancreas allows glucose into the cell by the help of glucose transporters (GLUT) and going through different reactions by the main mediator of enzymes in the cell until the release of insulin (Yaribeygi et al., 2019)(see Appendix Figure 7-4).

Secreted insulin from the pancreas of beta cells regulates blood glucose concentration during metabolism on insulin sensitive tissues of muscle, adipose tissue and liver (Petersen & Shulman, 2018), fatty acids and glycerol release as a product of triglycerides disintegration suppressed by insulin (Czech, 2020).

Normal physiology of glucose uptake in muscle and adipose tissue cells are regulated by insulin since production of glucose transporters (GLUT4) inside the cell that allows glucose to get into the cell is dependent on insulin through insulin receptor located at the cell membrane of the cell (Leto & Saltiel, 2012).

Glucose is water soluble nutrient which can float over the outer part of a cell instead of getting into or diffuse in the cell because the outer part of a cell (cell membrane) with a thickness of 7-9 nm is made up of phospholipids (Navale & Paranjape, 2016; Wallig et al., 2017).

The interaction of insulin receptor and insulin develops further molecular reactions inside the cell, after some steps of molecular interaction inside the cell Glucose transporter (GLUT 4) activated and make a tunnel on the cell membrane to let glucose in to the cytoplasm of the cell (Hoeg-Jensen, 2021) (See appendix figure 7-5).

4.3.2. Glucagon.

Glucagon is a hormone of 29-amino acid peptide and secreted from the alpha cell in islet of Langerhans of the organ pancreas due to the condition of low blood glucose concentration happens in the blood vessels (Rix et al., 2015).

Hepatic glucose production during hypoglycemia is stimulated by glucagon (Galsgaard et al., 2019), production of glucose pass through the process of both glycogenolysis and gluconeogenesis (Hayashi, 2020).

Chapter 5 . Model Analysis

5.1. Insulin Resistance.

5.1.1. Model Setting

The model needs to set different variables by taking the health status of the person with insulin resistance and with normal health condition under consideration since the model considers all adults with and without a sign of morning high blood glucose level but in this part the author considers the volunteers with a high blood glucose level in case of insulin resistance (Henry et al., 1986).

Table 5-1. Model setting for Insulin resistance before treatment.

Variable	Description
Start time	The model starts to simulate at 7 Since the first sample took at 7 A.M from those volunteers with a problem of Insulin resistance.
Stop time	the model ends at 10 since the last sample took from the reference was at 10 A.M
Initial Blood glucose in gram	Blood concentration in the model initialize with 14.9 mmol/l (13.5 gram) since morning blood concentration was 14.9mmol/l.
Average Body weight	103 kg
Average height	1.74 m
Energy Expenditure during the test	Energy expenditure is set (PAL=1.4) by considering the volunteers are admitted just to take the samples
Physical Activity level	Physical activity level is set at the basal level (PAL=1.4) since participants are at rest condition while they gave blood sample.
Time units	Hour
Sim duration	1.5 minutes
Integration Method	Euler
Delta time	0.1
software	Stella architecture 2.1 version software.
Food intake for Blood glucose Con. test	75gm since participants took 75mg during blood glucose concentration test.

5.1.2. Simulated Behavior Analysis.

Blood glucose concentration normally expected to increase and decrease when there a difference between daily carbohydrate intake and glucose utilization, the simulated results on figure 5-1 indicates blood glucose concentration of insulin resistance voluntaries have increasing and decreasing patterns within three hours.

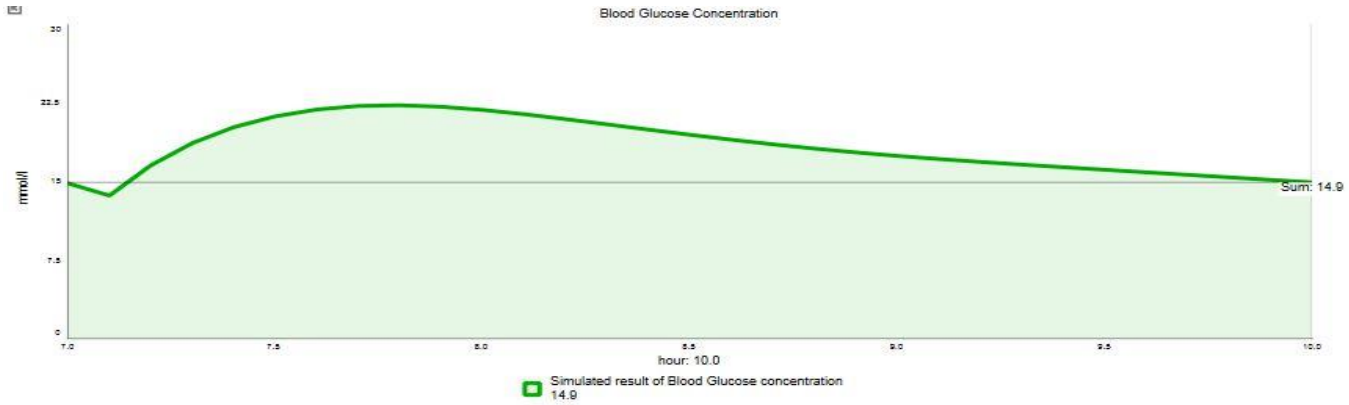

Figure 5-1. Simulated Blood glucose concentration result for insulin resistance patients before treatment.

Reference to the figure 5-1, blood glucose concentration level fall linearly for 6 minutes (0.1 hour) by following a gradual raise until it reaches its maximum point within 36 minutes (0.6 hour), and then it goes down slowly for a longer period relative to the time has taken to reach the maximum level. The unequal increasing or decreasing rate of blood glucose concentration during the specified period needs further time-based analysis to see how the physiology of organs and its contribution regarding blood glucose concentration clarified as follows**.**

<u>At 7 A.M.</u>

The simulated result of blood glucose concentration initialized with 14.9 mmol/l (13.5 gram) since the sample of blood glucose concentration took from the volunteers participated in the research.

<u>From 7A.M to 7:06 A.M(7.1).</u>

Linearly decreasing of Blood glucose concentration from 14.9 mmol/l to 13.7 mmol/l indicates that there is a higher drainage of blood glucose relative to glucose entering to the blood vessel, organs or cells in the body using blood glucose from capillaries of the blood vessel as a source of energy and organs that supplies glucose to the blood vessel are classified to give a detail time base analysis as follows.

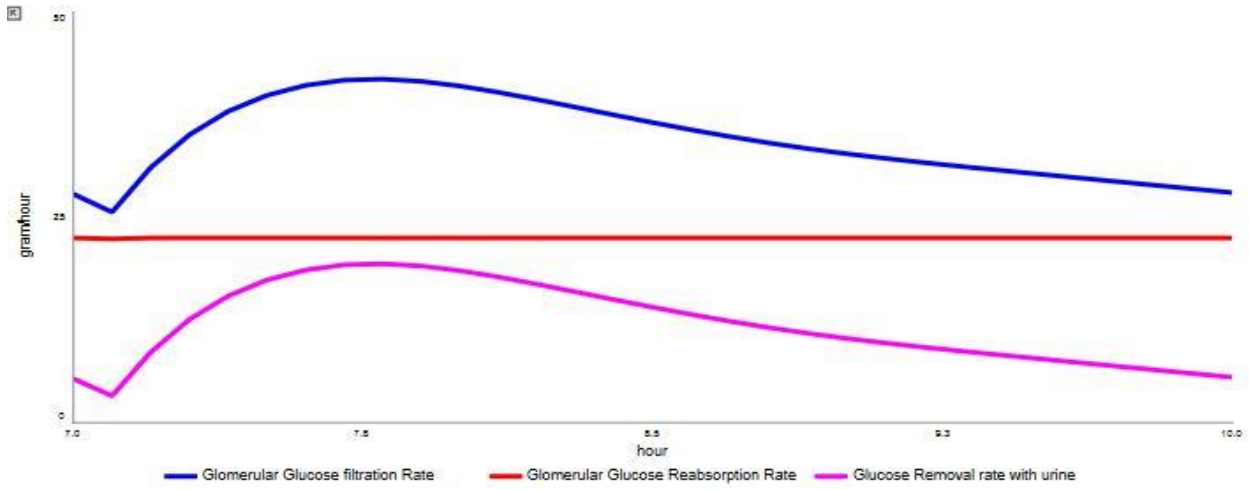

Figure 5-2. Simulated graph of the role of kidney on glucose filtration and reabsorption.

i. Kidney in the process of glucose Filtration

Blood glucose going through the process of filtration decreases linearly even the effect decreases the blood glucose concentration through the balancing loop of B1 but the capacity of kidney to reabsorb the glucose under filtration reaches its maximum level and adds more glucose to the blood vessel through the reinforcing loop of R1 since glucose reabsorption rate is constant.

Based on the physiology and the analysis above, the rate difference between kidney glucose filtration and reabsorption, kidney forced to excrete excess glucose with urine(glucosuria) with a removal rate of the name given Glucose removal rate through urine (see Figure 5-2).

Consequently, the leading role of kidney in this specific time is removing excess glucose because the filtration rate through the balancing loop B1 is dominating over the reinforcing loop (R1) of reabsorption rate.

ii. Muscle, Liver and Adipose tissue as a storage.

Continuous conversion of glucose to glycogen (glycogenesis) in the liver and muscle takes insulin as a stimulator, the amount of glucose in the blood vessel and liver storage/muscle storage level into consideration but in case of the reverse process(glycogenolysis) in liver hormone glucagon stimulates the process instead of insulin.

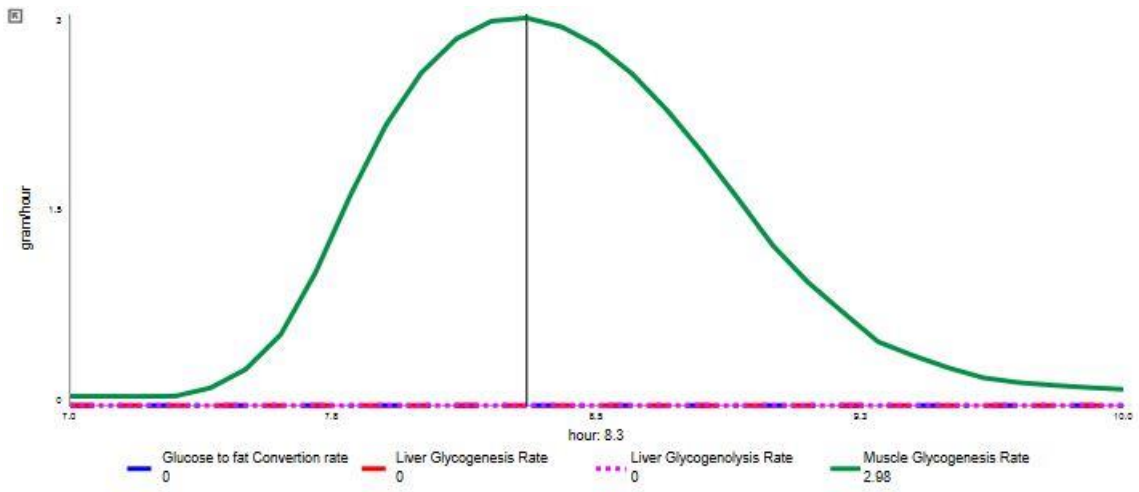

Figure 5-3. Simulated results for liver, muscle, and adipose tissue glucose conversion rate through the process of glycogenesis, glycogenolysis and glucose to fat conversion, respectively.

Reference to the simulated result in Figure 5-3, contribution of liver on the process of converting glucose to glycogen (glycogenesis) is zero because liver storage has no free space to store more glucose, so the closed balancing loop(B3) dominates the effect of insulin on liver glycogenesis through the loop(B2). Liver as a glucose supplier due to liver glycogenolysis is zero since glucagon hormone production is less in the body to convert glycogen to glucose.

Muscle glycogenesis rate is small because the muscle needs to have enough amount of insulin (B4) to overcome the effect of excess fat on the muscle glycogenesis through the loop R5, then the effect further limits the conversion of glucose to fat in adipose tissue.

Therefore, the role of liver as a user in the process of glycogenesis and as a supplier in the process of glycogenolysis has no contribution but muscle has a little contribution as a user of blood glucose to compensate the muscle glycogen used by the body for 6 minutes.

iii. Glucose utilization in the organs or cells.

Total body weight base energy requirement for the organs takes glucose into consideration as a source, simulated results of glucose oxidation in Figure 5-4 shows in detail.

Glucose oxidation in the body is expected to be constant since the volunteers participated in this research has constant physical activity level during blood glucose assessment.

Based on the simulated result in Figure 5-4, Brain burns highest amount of glucose because glucose is the only source of energy for brain in normal condition and splanchnic organs are the second one that uses glucose as an energy source.

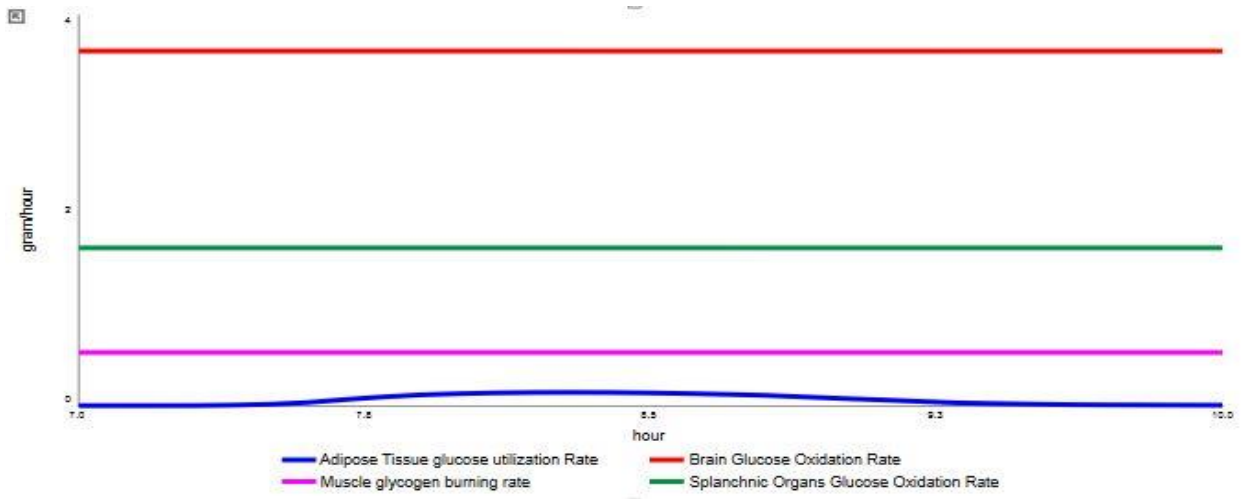

Figure 5-4. Simulated results of glucose oxidation rate in the body.

iv. Blood glucose suppliers.

Assimilation of glucose as daily intake through GIT and gluconeogenesis through the organ liver and kidney from non-carbohydrate sources are the only supplier of glucose to the blood vessel.

Based on the simulation result on Figure 5-5, gluconeogenesis rate is zero since there is no enough glucagon production in the body to convert non carbohydrate nutrients into glucose but carbohydrate intake through GIT increases linearly from 0 to 34.9 gram per hour. As a glucose provider, glucose from GIT is dominant over gluconeogenesis to provide glucose for blood vessel.

Conclusion: Blood glucose concentration linearly decreases for the first 6 minutes due to the dominant effect of Brain using glucose as a source of energy through the balancing loop of B13 over the rest of the body.

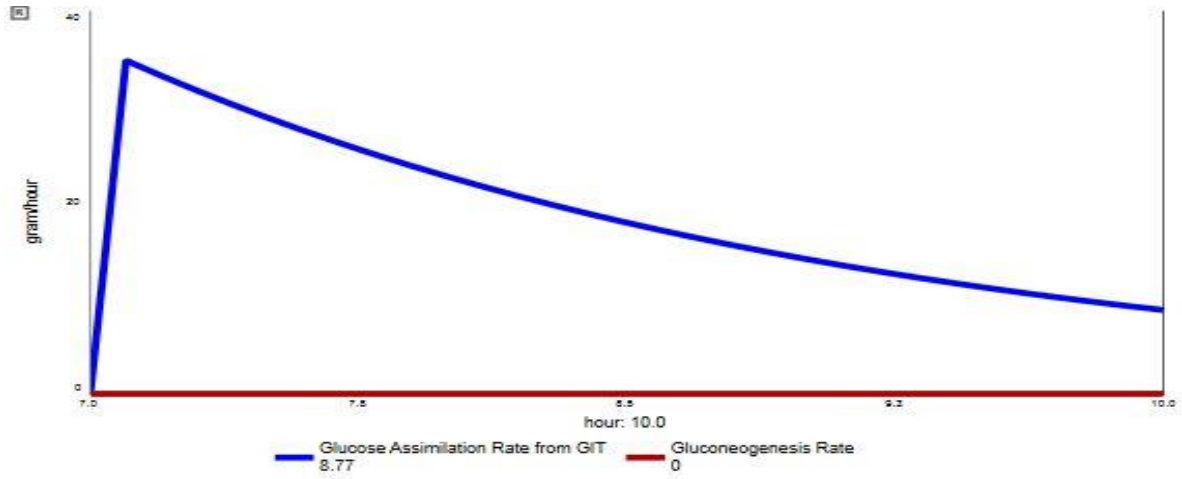

Figure 5-5. Simulated result of glucose providers to blood vessel.

From 7:06(7.1) A.M to 7:48 A.M(7.8).

Blood glucose concentration increases decreasingly from initial level of 13.7 mmol/l to its highest concentration of 22.3 mmol/l for 42 minutes stay since the hourly carbohydrate intake is greater than the total amount of glucose drained by different organs/tissues/cells out from the blood vessel according to the anatomy and physiology of the body, glucose providers/users to/from the blood vessel can be classified as follows.

i. Kidney for filtration.

Kidney filtration rate increases decreasingly, and the reabsorption rate reaches its maximum capacity and becomes constant, rate difference between kidney glucose filtration and reabsorption determines the amount of glucose excreted as excess through urination, excretion rate increases decreasingly by following the filtration rate since reabsorption is constant (See Figure 5-2).

In this period glucose removed from the whole body through urine (Glucosuria), the existence of glucose in the urine can be considered as one of sign of increasing blood glucose concentration.

Therefore, the net role of kidney in this specific period is excretion of glucose from the whole body together with urine since the loop developed due to filtration rate B1 is dominant over the closed loop developed due to reabsorption rate R1.

ii. Muscle, Liver and Adipose tissue as a storage.

During the process of Glycogenesis in the muscle and in the liver, glucose transported from the blood vessel to be stored as glycogen but in the process of glycogenolysis in liver, glucose delivered back to the blood vessel from glycogen storage in the liver.

Reference to the simulated result in Figure 5-3, liver contribution on draining glucose from blood vessel (glycogenesis) or as a glucose supplier due to glycogenolysis is almost negligible since liver glycogenolysis become active when blood glucose concentration is lower than the normal range and glucagon is enough in the blood. Muscle glycogenesis begins to increase increasingly by following increase decreasingly until it reaches its maximum level since the effect of insulin on muscle glycogenesis become stronger through the balancing loop of B4. Comparative limitation of muscle

glycogenesis rate with muscle glycogen burning rate, allows to have more free storage place in the muscle and then further hinders the conversion of glucose to fat.

Therefore, the role of liver as a glucose storage does not use glucose from the blood vessels or does not supply glucose from the storage but muscle shows improvement on the conversion of glucose to glycogen whereas conversion of glucose to fat is zero.

iii. Glucose utilization in the organs or cells.

Total body weight base energy requirement for the organs uses glucose and fat as a source, simulated results of glucose oxidation in figure 5-4 shows in detail.

Glucose oxidation in the body is expected to be constant since the volunteers participated in this research has constant physical activity level during blood glucose assessment.

Based on the simulated result on figure 5-4, Brain burns highest amount of glucose because glucose is the only source of energy in normal condition and splanchnic organs are the second one that uses glucose as an energy source.

Muscle and adipose tissues use less amount of glucose during this period, the glucose utilization on adipose tissue begins to increase slowly because adipose tissue needs insulin to oxidize glucose (B8), and with the same physiology the effect of insulin on muscle is described on muscle glycogenesis.

Therefore, glucose oxidation in the brain cell keeps being dominant over the other tissues, but adipose tissue due to increasing of insulin in the blood shows an improvement to nourish adipose tissues cell.

iv. Blood glucose suppliers.

Assimilation of glucose as daily intake through GIT and gluconeogenesis through the organ liver and kidney from non-carbohydrate sources are the only supplier of glucose to the blood vessel.

Based on the simulation result on figure 5-5, gluconeogenesis rate is remaining zero since there is no enough glucagon production in the body to convert non carbohydrate nutrients into glucose but glucose intake through the GIT as a dominant supplier provides glucose to the blood vessel even if glucose intake decreases decreasingly.

From 7:36(7.8) A.M to 10:00 A.M.

Blood glucose concentration decreases decreasingly from its uppermost value of 22.3 mmol/l to 14.9 mmol/l until 10 o'clock. The blood glucose dynamics shows that the organs or cells that are using blood glucose as energy source oxidizes more glucose than the organs supplying glucose to the blood vessel. providing to or using blood glucose from blood vessels varies according to the organs glucose requirement and organs capacity to glucose oxidation, based on the simulated results the author shows in detail as follows,

i. Kidney in the process of glucose filtration.

Reference to the simulated result in Figure 5-2, the removal of glucose through urinary tract with urine decreases decreasingly by following the filtration rate pattern of the kidney because kidney still have a capacity limitation on the reabsorption process even less glucose is removed from the body relative to the increasing phase.

Therefore, the net role of kidney in this period is excretion of glucose from the whole body through urinary tract with urine since the loop developed due kidney filtration rate B1 is dominant over the closed loop through reabsorption rate R1 but the dominancy difference getting closer relative to the previous period described in between 7:06 and 7:48 o'clock.

ii. Muscle, Liver and Adipose tissue as a storage.

Using glycogen from the storage as a source of energy allows glycogen synthesis from glucose through B5 in the process of muscle glycogenesis, synthesis of glycogen needs insulin through the balancing loop of B4. Based on the simulated result on Figure 5-3, muscle glycogenesis rate decreases to fill up glycogen in the muscle by following availability of insulin through B4 because when accessibility of insulin in the blood decreases muscle glycogenesis decreases even if there is available place in the muscle to store glycogen (figure 5-6 and figure 5-7), the presence of free storage place in the muscle prevents glucose to fat conversion.

Glycogenesis in the liver has no contribution for this specific period (see figure 5-3).

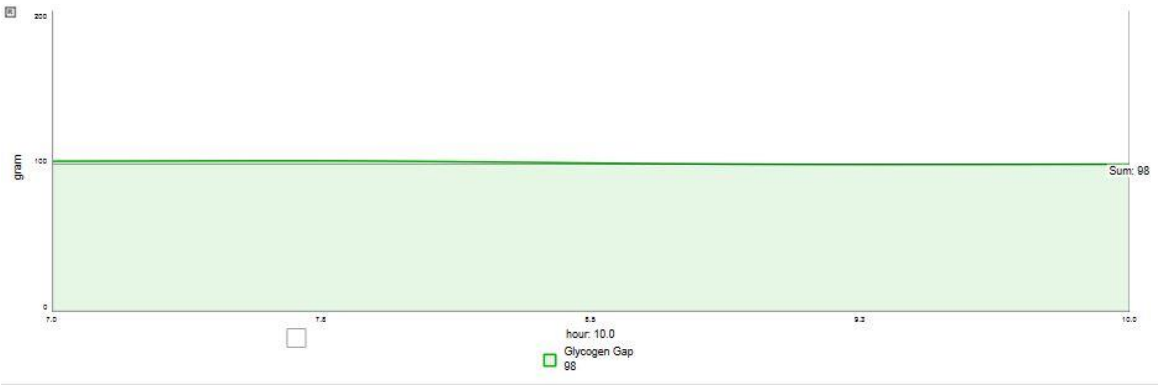

Figure 5-6. Remaining free place for glycogen storage in muscle.

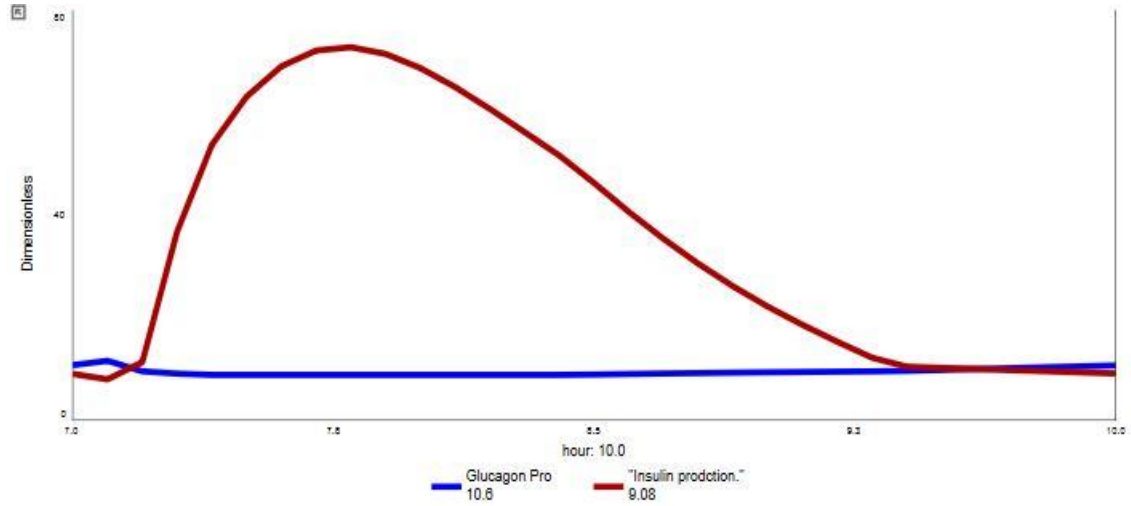

Figure 5-7. Simulated result of hormone Insulin and Glucagon production in the blood vessel.

iii. Glucose utilization in the organs or cells.

Reference to the simulated result in figure 5-4, brain burns highest amount of glucose because glucose is the only source of energy in normal condition and splanchnic organs are the second one that uses glucose as an energy source.

Muscle and adipose tissues use less amount of glucose during this period, glucose utilization on adipose tissue decreases due to decreasing of insulin in adipose tissue to oxidize glucose (B8), and with the same physiology the effect of insulin on muscle is described on muscle glycogenesis.

Therefore, glucose oxidation in the brain cell keeps being dominant over the other tissues, but adipose tissue due to dependence on insulin decreases blood glucose oxidation rate.

iv. Blood glucose suppliers.

As a provider of Glucose through GIT and through gluconeogenesis, gluconeogenesis has no contribution on the blood glucose concentration but daily glucose intake through carbohydrate assimilation in the intestine has a dominant role over gluconeogenesis even it is decreasing gradually (see figure 5-5).

Summary of required blood glucose as energy source and oxidized blood glucose by the organ cells.

The simulated and calculated results in figure 5-8 and Table 5-2 shows that splanchnic organs glucose usage as a source of fuel is the second one next to brain glucose oxidation , both organs cells have got enough energy from glucose since required glucose is equal to the oxidized glucose (100%) but in case of muscle and adipose tissue, still there is a higher requirement of glucose as energy relative to the glucose oxidized in the muscle and adipose tissue cell even if there is an improvement on adipose tissue glucose oxidation between 7.8 to 8.8 hour.

Table 5-2. Comparison table for oxidized and required glucose in Organ cell.

Required vs Oxidized Glucose				
Organ/Tissue/Cell	Duration (From-To)	Glucose Required	Oxidized Glucose	% Of glucose used by the cell
Brain	7-7.1	3.63	3.63	100
	7.1-7.8	3.63	3.63	100
	7.8-10	3.63	3.63	100
Splanchnic Organs	7-7.1	1.62	1.62	100
	7.1-7.8	1.62	1.62	100
	7.8-10	1.62	1.62	100
Adipose tissue	7-7.1	0.196	0.00466	2.37755102
	7.1-7.8	0.196	0.0938	47.8571429
	7.8-10	0.196	0.0485	24.744898
Muscle Tissue	7-7.1	1.16	0.548	47.2413793
	7.1-7.8	1.16	0.548	47.2413793
	7.8-10	1.16	0.548	47.2413793

In Muscle tissue, 47% of glucose as energy required by the cell oxidized but the rest 53% glucose oxidation is trapped by intra-abdominal fat (IAF) through the reinforcing loop R3 and further the conversion of glucose to fat is not activated since muscle glycogenesis due to B4 and B5 dominates over B6.

In adipose tissue, there is glucose oxidation improvement from 2% to 47% because of the increment of insulin through the loop B8 but still there is a dominant effect from intra-abdominal fat (IAF) through (R3) that averts the adipose tissue to use glucose properly based on the required glucose as energy.

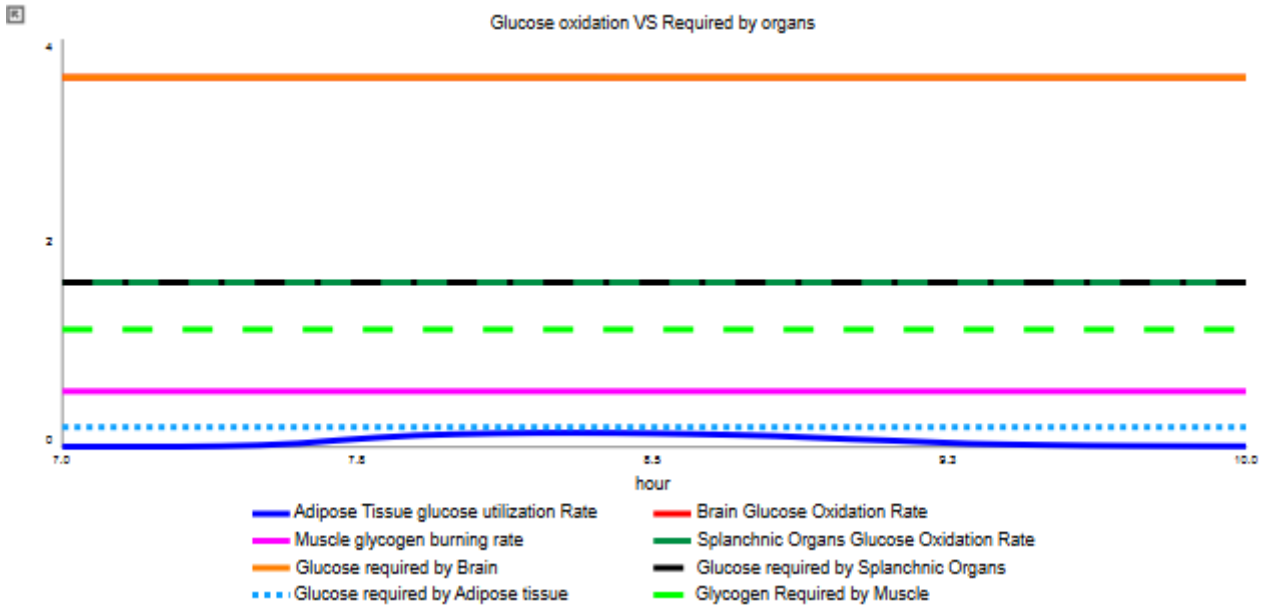

Figure 5-8. Simulated result of required energy by the organ cell and the oxidized glucose on the organ cell.

Glucose utilization percentage indicates that the cell in the adipose tissue has no full access to oxidize glucose, the highly controlling effect of Intra-abdominal fat through the reinforcing loop R3 together with the effect of less insulin production through B8 leads glucose utilization on adipose tissue to be less.

Muscle tissue too has the same glucose utilization deficiency even if the percentage of glucose utilization is more than the Adipose tissue since muscle can burn the stored glycogen without using insulin, Muscle glucose utilization is less than the required amount of glucose in the cell by ~ 53 % since the effect of intra-abdominal fat (IAF) through the reinforcing loop of R5 deters muscle glucose utilization.

5.2. Insulin Production variation role on glucose metabolism.

As an objective of the thesis, the author wants to study the effect of insulin on glucose metabolism since production level of insulin in the body helps to differentiate the type of diabetic's mellitus.

Table 5-3. Model setting for Insulin production test.

Variable	Description
Start time	The model starts to simulate at 7.
Stop time	The model ends at 12.
Initial Blood glucose in gram	Blood concentration in the model initialize with 14.9 mmol/l (13.5 gram) since morning blood concentration was 14.9 mmol/l.
Average Body weight	70 kg since normal BMI is less than 25, now let us take BMI =23
Average height	1.74 m
Energy Expenditure during the test	Energy expenditure is set (PAL=1.4) by considering the volunteers are admitted just to take the samples
Physical Activity level	Physical Activity level: physical activity level is set at the basal level (PAL=1.4) since participants are at rest condition while they gave blood sample.
Time units	Hour
Sim duration	1.5 minutes
Integration Method	Euler
Delta time	0.1
software	Stella architecture 2.1 version software.
Food intake for Blood glucose Con. test	75gm since 75 gram is for testing purpose.
Insulin Production test	Varies from 0 to 1 to specify insulin production from 0% to 100 % respectively.

According to figure 5-9, the simulated result on figure 5-10 and 5-11, adipose tissue glucose utilization rate and muscle glycogenesis are highly relying on the hormone insulin production. Adipose tissue and muscle tissue reaches its maximum after 1 hour because of the initial insulin in the blood, but the rate varies according to the production of insulin.

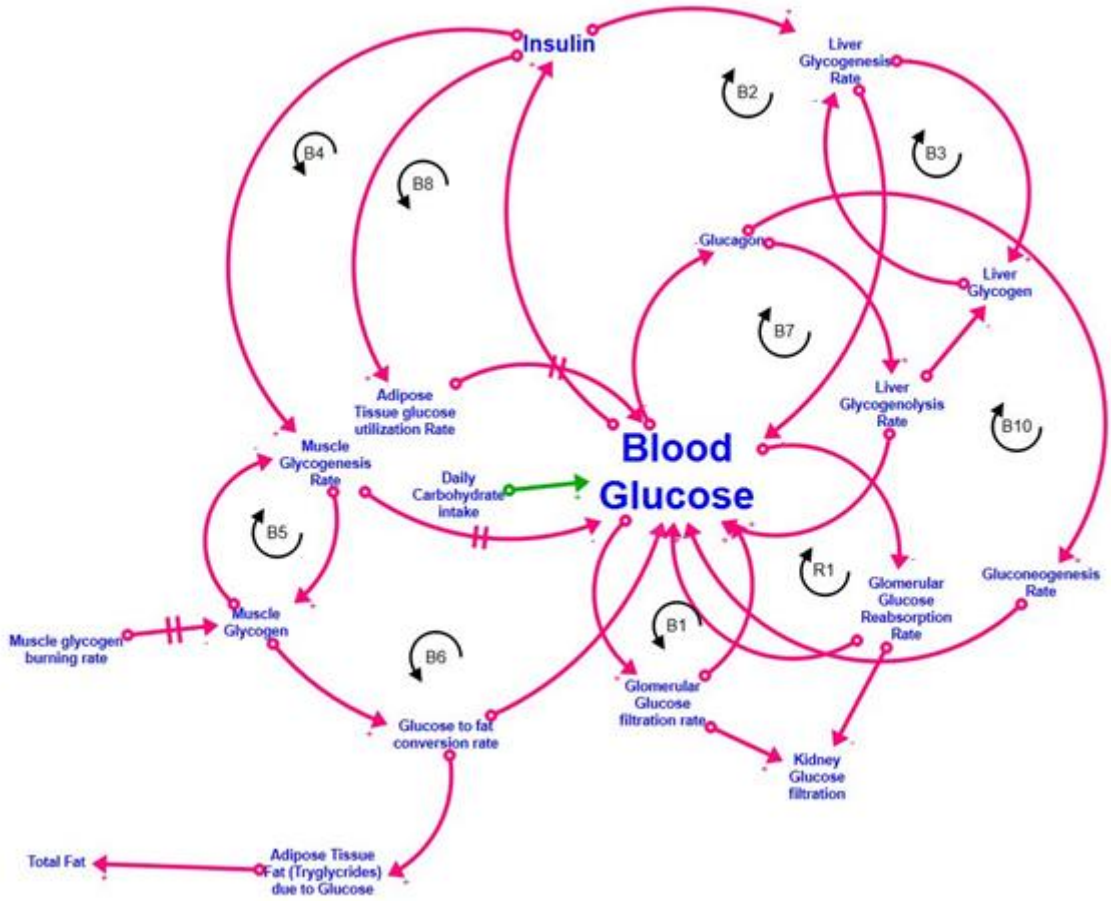

Figure 5-9. CLD Relation between hormones and blood glucose concentration.

Adipose tissue utilizes glucose at maximum rate of 0.141 gram per hour for normal production of insulin but for those who has no insulin production, adipose tissue uses the initial insulin and becomes 0.0025 gram per hour, this implies that glucose utilization decreases to 0.00201/0.141=1.4 %. therefore, almost all the cells have no enough energy during metabolism.

Muscle glycogenesis also face the same problem with adipose tissue, but the magnitude differs accordingly.

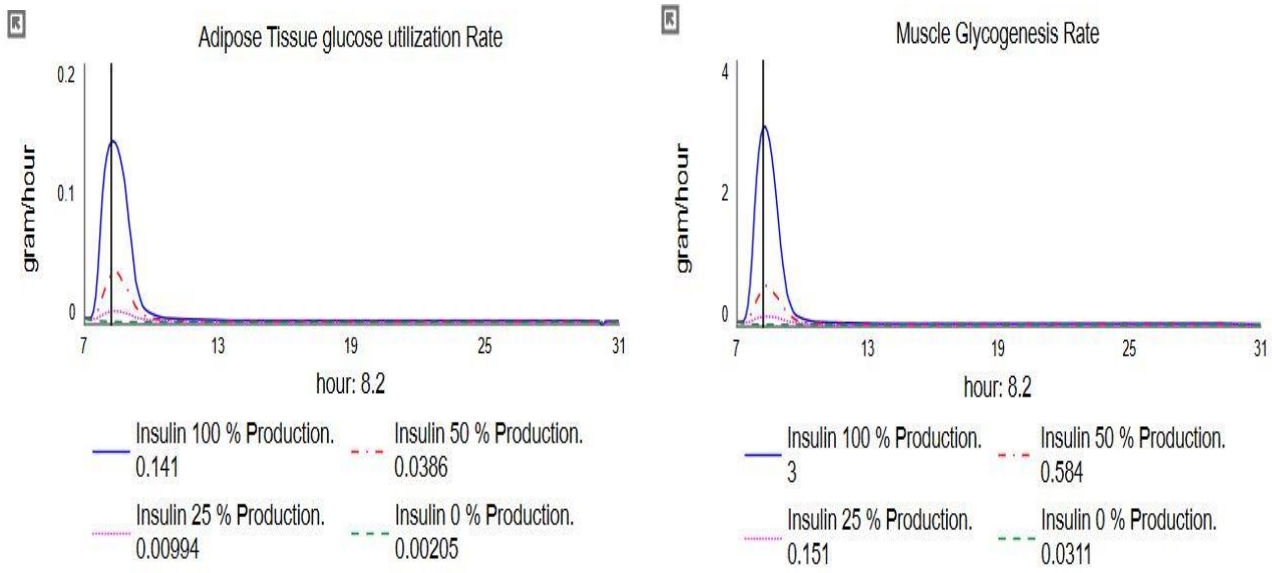

Figure 5-10. Simulated result for adipose tissue glucose utilization rate and muscle glycogenesis rate.

Insulin production gets maximum when pancreas works well but when the production rate decreases, tissues use all insulin initially found in the blood and become zero after some hour.

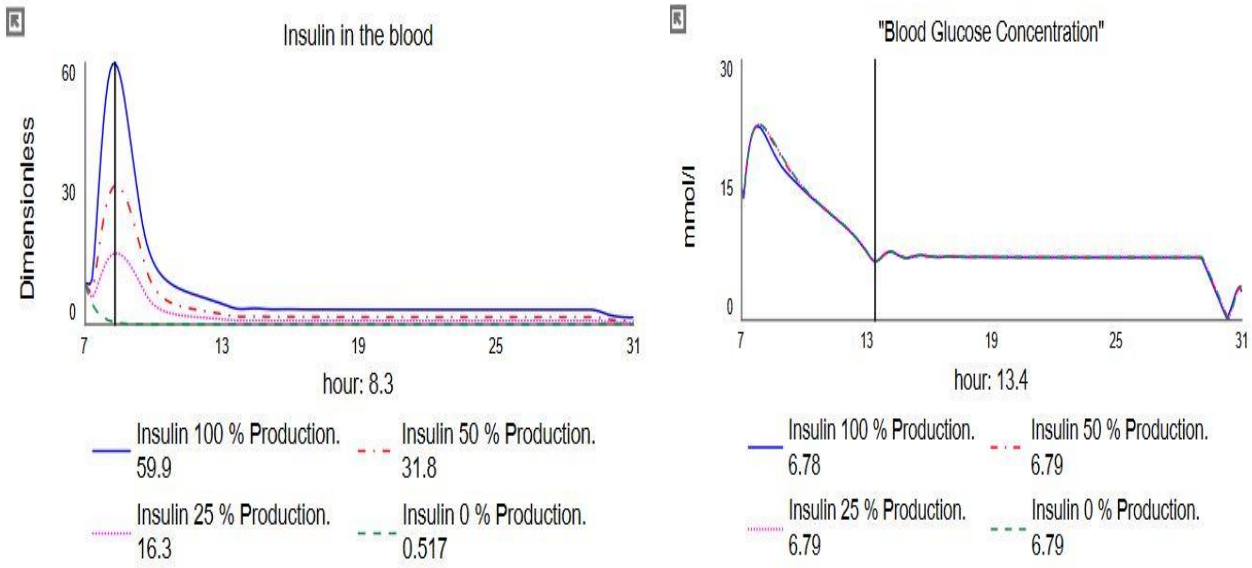

Figure 5-11. Simulated result for insulin in the blood and blood glucose concentration.

Blood glucose concentration with 100 % production is less than the rest of the insulin production scenarios between 8 -10 hour because insulin production was enough to burn glucose in the adipose and in muscle tissues but for the other scenarios blood glucose concentration keep higher due to less insulin in the blood to stimulate glucose utilization.

Table 5-4. Summary for insulin production variation and its effect on tissue glucose utilization.

Insulin Production (%)	Adipose tissue glucose utilization (%)	Muscle Glycogenosis (%)	Blood glucose concentration @ 8.8 hr. (%)	Remark
100	100	100	100	Has taken as a reference since it is normal production.
50	28.8	20.3	105.5	Both in Adipose and muscle tissue rate decreases, but in case of blood glucose concentration, blood glucose become overloaded.
25	7.1	5.06	106.6	
0	1.4	1	107.1	

5.3. Model Validation Testing.

Based on the validation guidelines developed by (Barlas, 1994; Senge & Forrester, 1980; Sterman, 2000), there are different types of testing with different procedures based on the purpose of the test. In the following section, those tests are described and conducted in an iterative manner to build and increase confidence in the model.

5.3.1. Model Boundary test.

Building a model boundary chart for the purpose of model boundary test is useful to summarize the boundary of the model by differentiating and listing the variables that already comprised in the model and the variables that are not included, such kind of illustration further helps to easily modify the model when model improvement is in need.

Table 5-5. Model boundary description table.

Model Boundary		
Endogenous Variables	Exogenous Variables	Excluded Variables
See CLD on figure 4-6.	See CLD on figure 4-6.	Effect of Protein on Insulin Production
		Effect of Fat on Insulin Production
		Adrenalin, Epinephrine, cortisol, and growth Hormone
		Hormone Somatostatin
		Hormone incretins
		Hormone amylin

5.3.2 Integration Error.

Table 5-6. Integration error description table.

	DT=0.1	DT=0.05	Comment
Euler	Scenario 1	Scenario 5	Based on the simulated result all scenarios show the same but there is 12.7 % maximum difference at 7.1 between RK2 at DT=0.1 and Euler at DT=0.1(Euler at DT=0.1= Cycle time at DT=0.1) See figure 5-12.
RK2	Scenario 2	Scenario 6	
Cycle Time	Scenario 3	Scenario 7	
RK4	Scenario 4	Scenario 8	

Based on the scenario-based blood glucose concentration simulation result in fig 5-12, there is no that much big difference for all scenarios except at the beginning for 6 minutes (0.1hour).

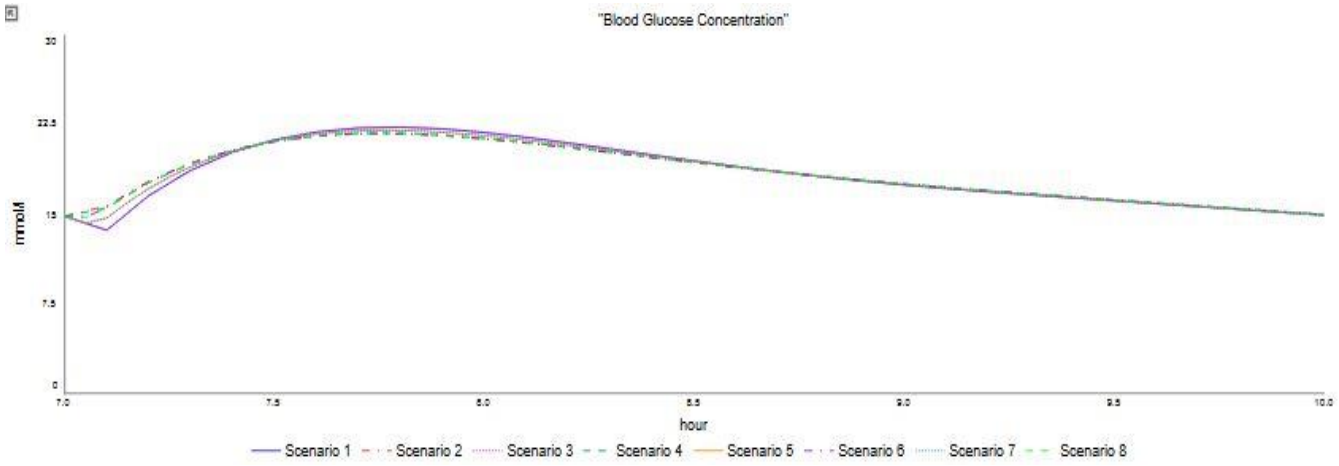

Figure 5-12. Simulated result of blood glucose concentration during Integration Error.

5.3.3. Structure assessment.

Structure assessment test requires consistency of the model respond to the real conditions by considering the purpose of the model. In this model testing stage blood glucose concentration should be always greater than or equal zero when there is no carbohydrate ingestion, this implies the model does not violate the physical low.

Based on the simulated result of figure 5-14, blood glucose concentration is greater than 0 when glucose intake =0

5.3.4. Dimensional Consistency.

Dimensional consistency of the model tests the consistency of variables equation and its units without any additional unit modifications in the equation, equations with units should be meaningful. In this model, stella architecture automatically check the validity of the equations and its units, and the model runs without any error.

5.3.5. Extreme condition Test.

Extreme condition test is useful to see how the model responds when exposed to different combined input conditions, testing the model ability is by considering the variable maximum and minimum extreme points based on the concept of (high. high, high. low, low. high and low. low).

Additional Setting.

Table 5-7. Scenario setting and result table for Extreme condition test.

Simulation run for 1 day (7-31). H =High and L=Low. PAL High =1.69 and PAL Low =1.4 since the model considers only sedentary life. Glucose intake Low =0 gram and H=500. Weight High =120 Kg and Weight Low =40 kg.				
	PAL	Glucose Intake	Weight	Result
Scenario 1	H	H	H	The simulated result shows blood glucose concentration increases during high glucose intake but varies according to weight and physical activity level whereas for low glucose intake gluconeogenesis keep the blood glucose from falling to zero. See simulated result down on figure 5-13.
Scenario 2	H	H	L	
Scenario 3	H	L	H	
Scenario 4	H	L	L	
Scenario 5	L	H	H	
Scenario 6	L	H	L	
Scenario 7	L	L	H	
Scenario 8	L	L	L	

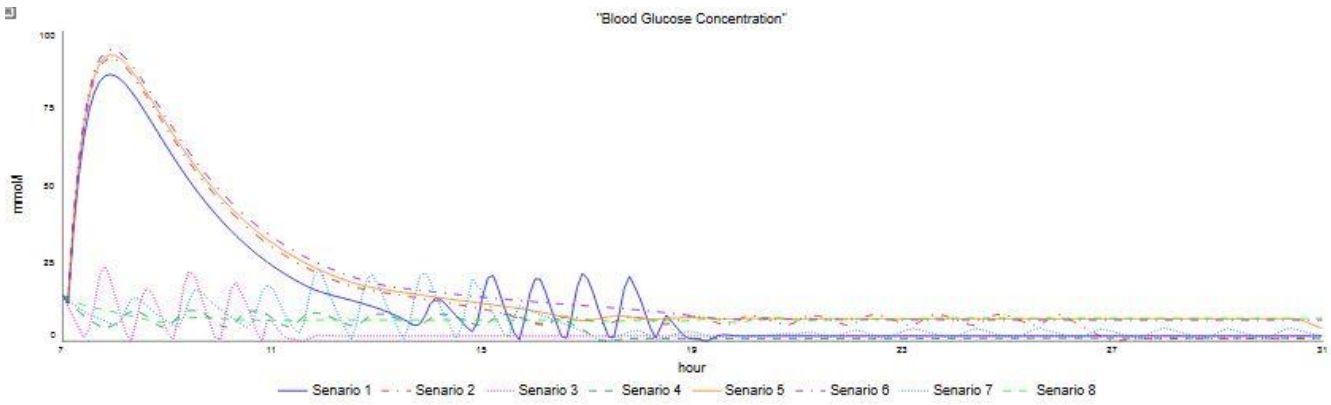

Figure 5-13. Simulated result Blood glucose concentration during extreme test.

From scenario base simulation result of blood glucose concentration, the model works well in all scenarios as expected.

5.3.6. Sensitivity Analysis.

Additional Setting

Table 5-8. Setting and result table for sensitivity analysis.

Simulation run for 1 day (7-31). H =High and L=Low. PAL High =1.69 and PAL Low =1.4 since the model considers only sedentary life. Glucose intake Low =0 gram and H=500. Weight High =120 Kg and Weight Low =40 kg.	
Parameter	Result and conclusion.
PAL	Based on the simulation result on Figure 5-14, 5-15 and 5-16, Blood Glucose concentration is more sensitive on glucose intake than the other parameters.
Glucose Intake	
Weight	

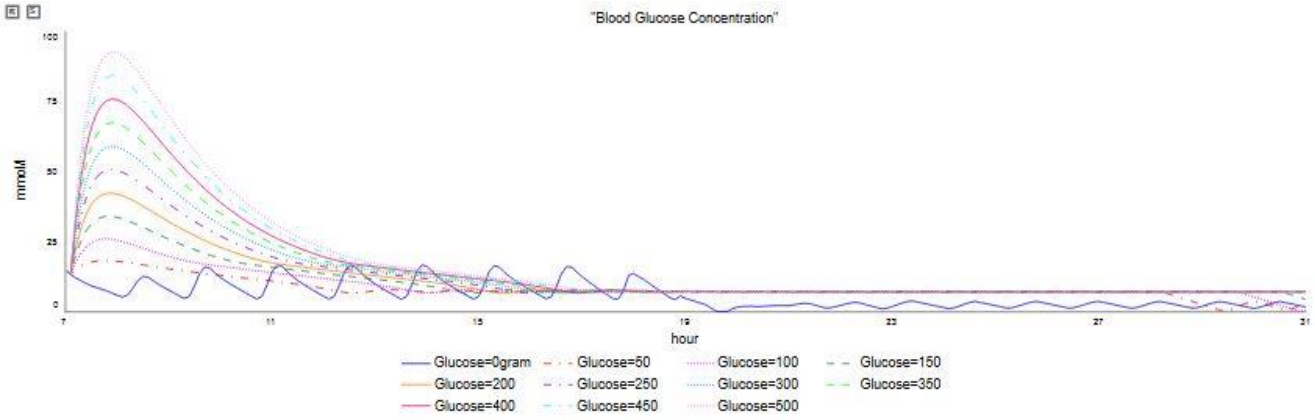

Figure 5-14. Simulated sensitivity result of blood glucose concentration based on glucose intake**.**

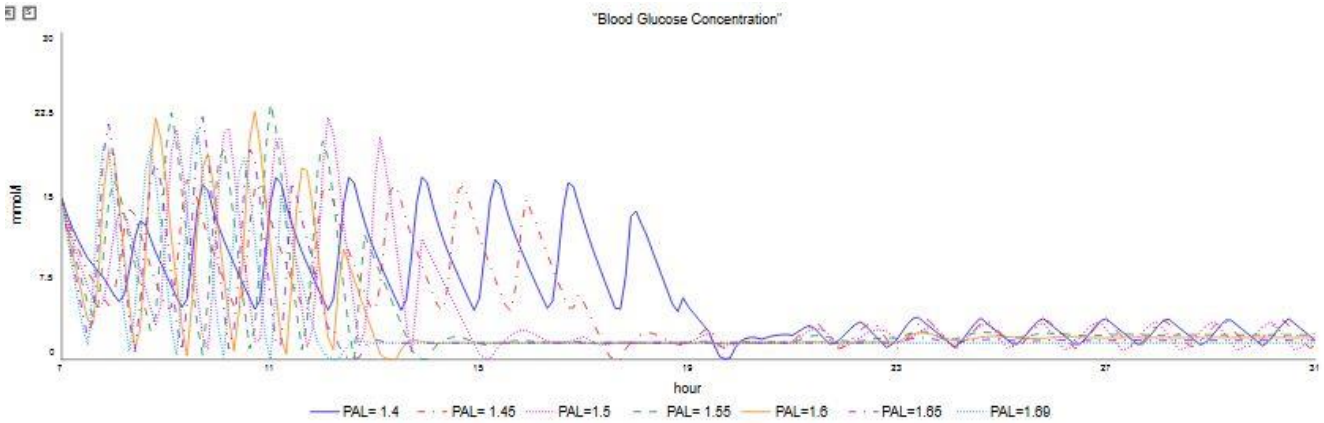

Figure 5-15. Simulated sensitivity result of blood glucose concentration based on PAL.

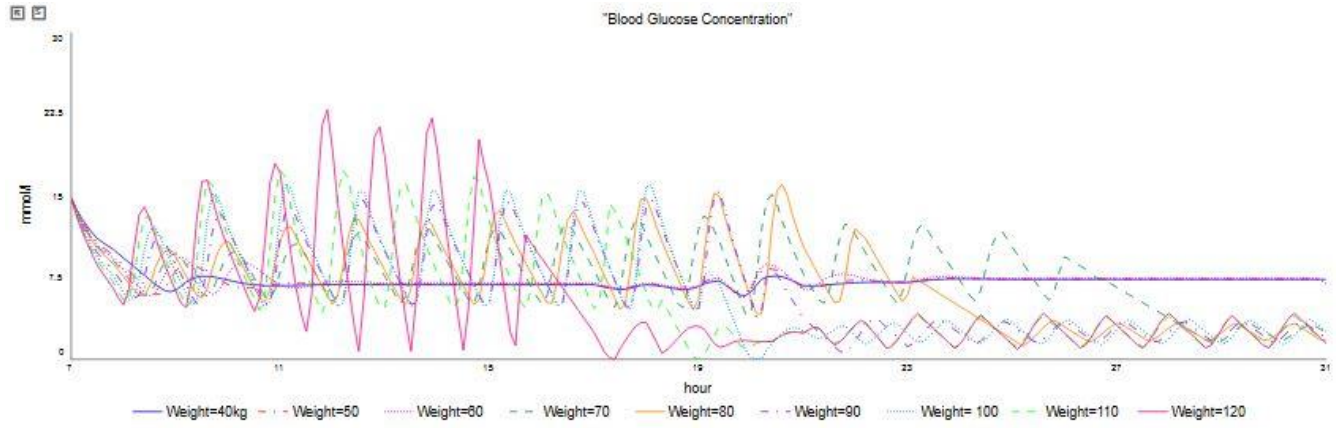

Figure 5-16. Simulated sensitivity result of blood glucose concentration based on Body weight.

5.3.7. Family Member.

Based on Sterman (2000), procedure to perform family member test, sample took from the volunteers considered as a reference as follows.

The model needs to set different variables by taking the health status of the volunteers under consideration since the model considers all normal participants without any health problem and taken as a reference for normal blood glucose level (Freckmann et al., 2007).

Table 5-9. Model setting for normal volunteers as a reference mode.

Variable	Description
Start time	The model starts to simulate at 7 Since the first sample took at 7 A.M from normal volunteers.
Stop time	The model ends at 31(one day duration).
Initial Blood glucose in gram	Blood concentration in the model initialize with 4.29 mmol/l (3.9 gram) since morning blood concentration was 4.29 mmol/l.
Average Body weight	70 kg (calculated from the given BMI of 23kg/m^2).
Average height	1.74 m (not given, assumed based on the given BMI).
Energy Expenditure during the test	Energy expenditure is set (PAL=1.4) by considering the volunteers are admitted just to take the samples
Physical Activity level	Physical activity level is set at the basal level (PAL=1.4) since participants are at rest condition while they gave blood sample.
Time units	Hour.
Sim duration	1.5 minutes.
Integration Method	Euler.
Delta time	0.1.
software	Stella architecture 2.1 version software.
24 hours Food intake for Blood glucose Con. test	50gm.

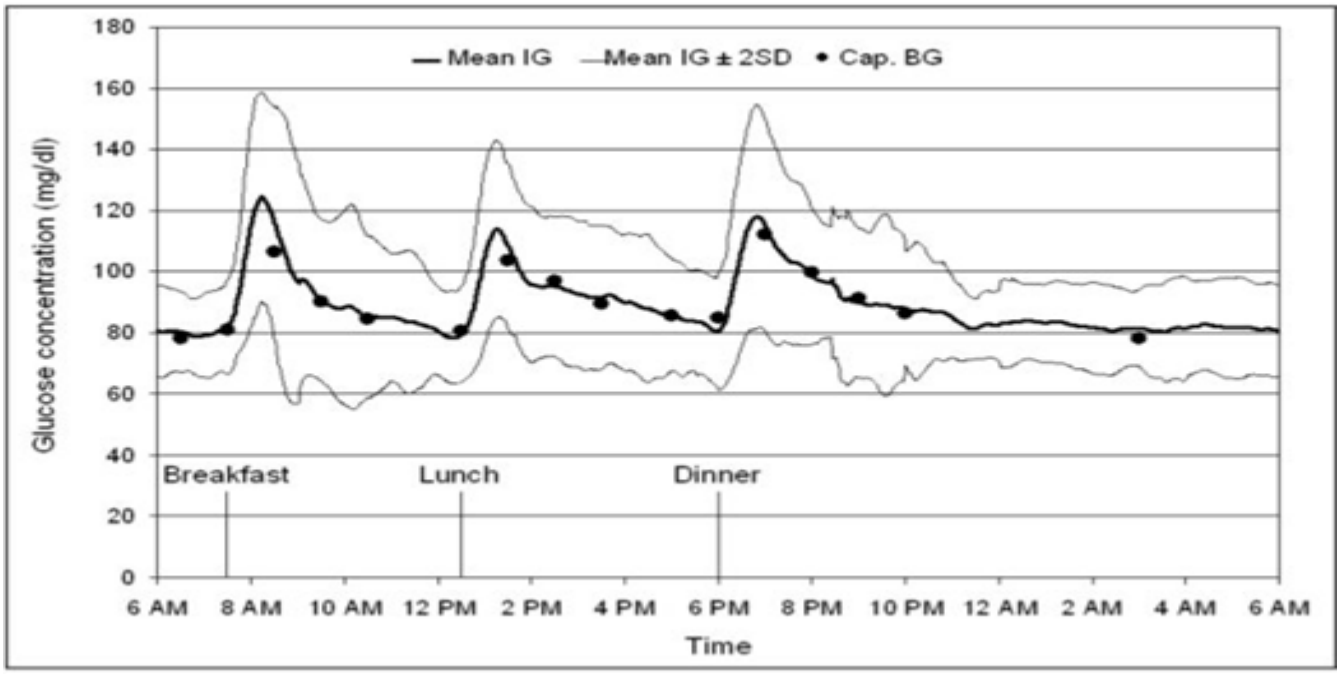

Figure 5-17. Reference mode of a normal blood glucose concentration adapted from (Freckmann et al., 2007).

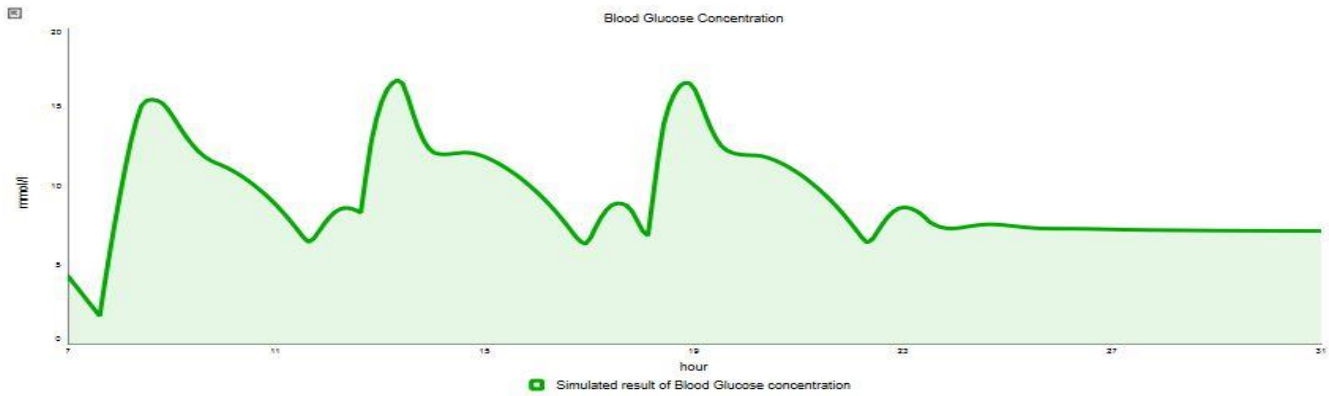

Figure 5-18. Simulated result of normal human volunteer's blood glucose concentration.

Figure 5-17 and figure 5-18 shows similarities on the behavior but there is a magnitude difference, this implies the model also works for other groups in addition to insulin resistance patients.

5.3.8. Behavior Anomaly Test.

Behavior anomaly test is useful to know how the selected loop or variable is important for the model. By doing analysis on the knockout loop and its effect on the behavior of the main stock, it becomes easy to conclude how the importance of the specific loop on the model.

For example, it is clear to see the effect of insulin on the blood glucose concentration and other tissues by knock out the insulin loop (see figure 5-10 and 5-11), knock out insulin loop means consider insulin production is zero.

5.3.9. Behavior Reproduction Test.

Behavior reproduction test is one of the methods that shows the ability of the model in replicating the real reference mode by measuring, calculating the simulated and the main reference data. The degree of accuracy indicates how the whole model is working well, this approach can be calculated by using Mean absolute Error (MAE), Mean absolute percent error (MAPE) and Root Mean square error (RMSE).

Table 5-10. Blood glucose concentration behavior reproduction test.

Behavior Reproduction Test					
Time	Reference Mode	Simulated Data	Mean absolute Error (MAE)	Mean absolute percent error (MAPE) %	Root Mean square error (RMSE)
7	14.9	14.9	1.8	10	2.1
7.5	18.1518152	21.3			
8	20.6270627	21.9			
9	20.0770077	17.5			
10	17.3267327	14.9			

Behavior reproduction test indicates that the dynamics of both the reference and the simulated data have the same pattern, and both are in phase, table 5-10 above shows in detail to decide how much the model is representing adult blood glucose homeostasis.

The dynamics of both the reference mode and the simulated result have the same pattern (see figure 5-19 below).

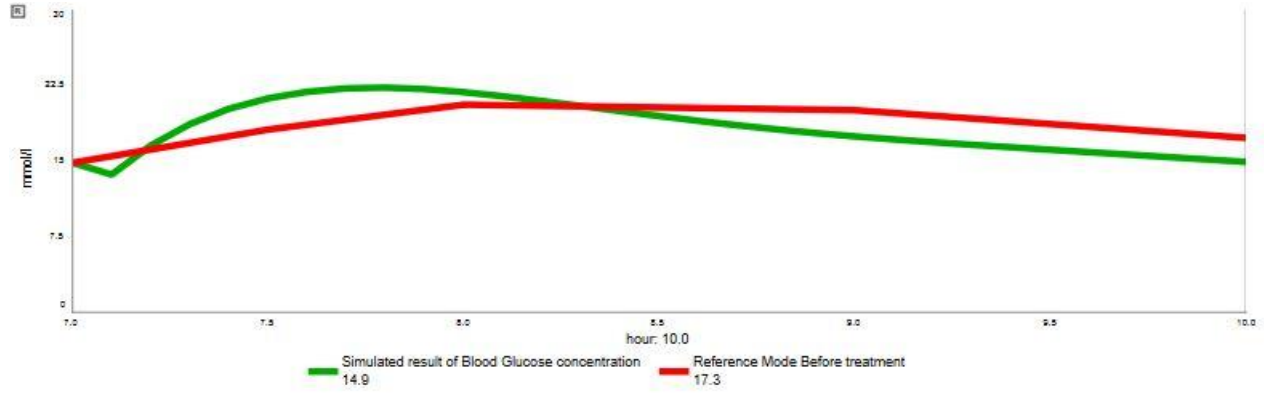

Figure 5-19. Blood glucose concentration for both reference mode and simulated result.

5.3.10. Summary of Model test.

Generally, reference to the guidelines and procedures of testing a model by (Sterman, 2000), summary of test types with comments as follows.

Table 5-11. Summary of results for the specific type of test.

Type of Test	Result	Remark
Boundary Test	valid	Based on boundary test guideline, some of the parameters listed excluded as exogenous; parameters will be under consideration during upgrading the model (future work).
Structure assessment	valid	Published sources are the foundation of the structure; structure improvement during model upgrading on future work.
Dimensional Consistency	valid	Equations and units in the model are consistent.
Behavior Anomaly Test	valid	Specific loop importance detected: importance of insulin as an example is detected by the behavior anomaly test.
Extreme Condition test	valid	Model is working well during extreme test
Integration Error Test	valid	All types of integration methods are almost the same.
Behavior Reproduction	valid	There is quantitative difference but have the same pattern.
Sensitivity Analysis	valid	Blood glucose concentration shows sensitivity for some of the parameters, glucose daily intake could be example.
Family member	valid	Additionally, Model can generate well for other conditions but there is magnitude difference between the reference mode and the simulated result.

Chapter 6 . Policy and Policy implementation.

6.1. Proposed Policy.

The coherence of a system dynamic approach helps us to easily investigate the main cause of the problem by following a detailed analysis, based on the analysis at the behavior of blood glucose concentration for participants who is considered as a reference mode of the problem with insulin resistance in the previous chapter, the author designs efficient policy as a treatment of insulin resistance by using modeling software which is applicable in system dynamic approach to get rid of the main cause of the problem before aggravating the diseases.

The author focuses to lower the morning blood glucose concentration level less than 7 mmol/l(Tang et al., 2019) as a treatment of insulin resistance by making a policy of considering the main cause of elevated morning blood glucose level since elevation of morning blood glucose level greater than 7 mmol/l has long run complications on cardiovascular, kidney, pancreas, eye…etc. if not treated early, and also rising of morning blood glucose level indicates shortage of glucose utilization on muscle and adipose tissues, shortage of glucose utilization also has a complication by following inflammation on the tissues.

The aim of the policy is to achieve the goal through direct and indirect controlling mechanisms, setting a goal and controlling body fat is the first direct fat controlling way of the human physiology and then body weight controlling mechanism indirectly controls blood glucose concentration.

The policy application throughout the policy time horizon described in detail as follows.

1. Proposing an improvement on adipose and muscle tissue glucose utilization through body fat reduction by setting body fat goal, proposed body fat goal has a minimum effect on glucose utilization in those specific tissues because fat in adipose and muscle tissues limits glucose utilization.

   Fat reduction is applied on excess fat beyond body fat goal by controlling fat and glucose daily intake since excess glucose has a possibility to be converted to fat.

2. By following body fat reduction, proposing daily net glucose in the body to be zero by using daily carbohydrate intake based on the total daily energy expenditure (Daily carbohydrate intake = total daily glucose oxidation), balancing daily intake and usage of glucose in the body become useful for human body due to the following benefits.
   - To have enough glucose in the blood vessel and prevents the blood glucose concentration level above the normal range since blood glucose concentration above the normal has long run complications on the vital organs and tissues.
   - It prevents conversion of excess glucose to fat.
   - Prevents shortage of glucose in the body.

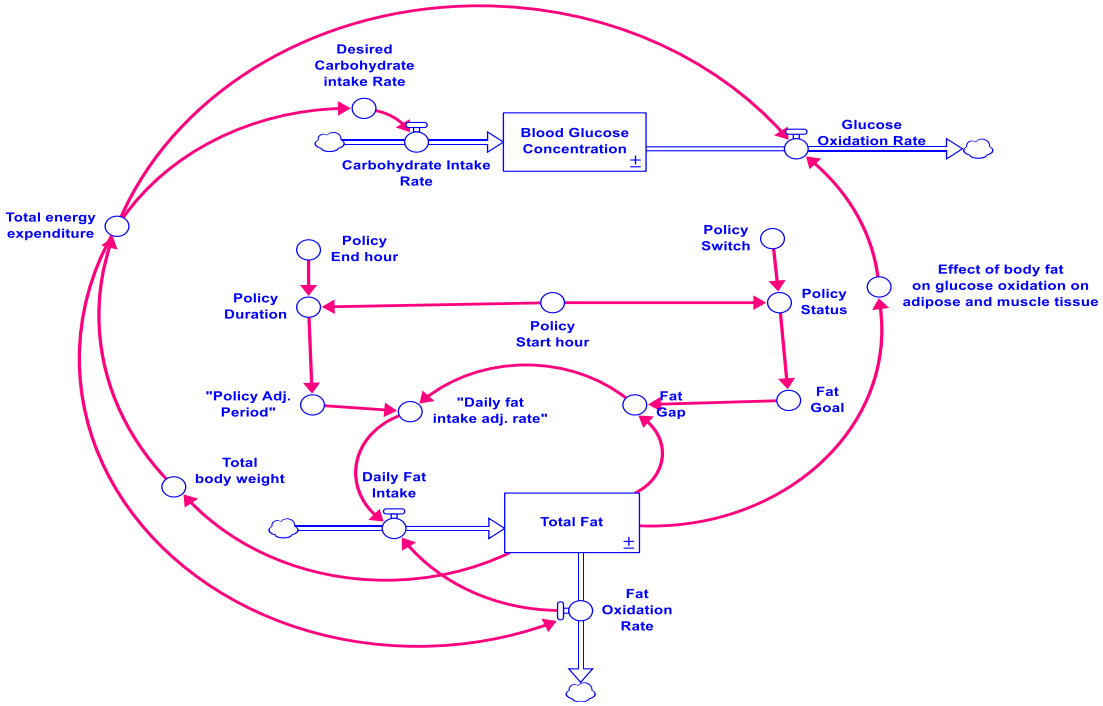

Figure 6-1. Proposed policy structure.

In the figure 6-1 above, policy starts at 7 o'clock after initializing blood glucose concentration from the volunteers participated in and ends after 2167 hours (about 3 months) since blood glucose concentration has taken from the participants when they were average weight of 103 Kg, 2167 hours means 3 months at the last day of treatment at 7 o'clock in the morning (7 o'clock considered as a morning blood glucose concentration after the policy). During this treatment period (see treatment phase on 6.3.1) the difference between the desired and the actual fat in the body decreases gradually, but policy adjustment period determines how fast the current fat reaches the desired body fat weight.

6.2. Policy Hypothesis.

During the treatment period of 3 months, fat weight in the body reaches to its desired goal through the process of oxidation of fats but compensation of fat by using a daily intake of fat through the balancing loop of B18 keep on filling up the gap between the desired and the current fat weight in the body (see figure 6-2).

Oxidation of fat in the figure 6-2 shows that controlled by body weight through energy expenditure (B12 in figure 6-3), the variation of weight due to the goal indirectly influences the current weight of the body by taking compensation of fat as daily fat intake and oxidation of fat into consideration until it reaches its desired goal.

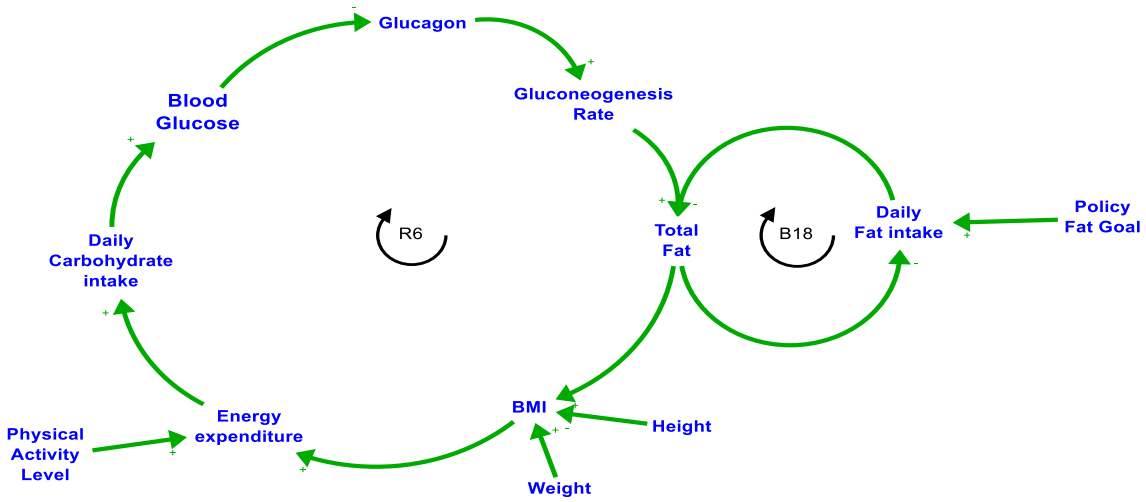

Figure 6-2. Policy closed loop diagram.

A gradual decreasing of body weight decreases a daily intake of carbohydrate through the reinforcing loop of R6 since carbohydrate daily intake is calculated based on the participants daily energy expenditure of the body.

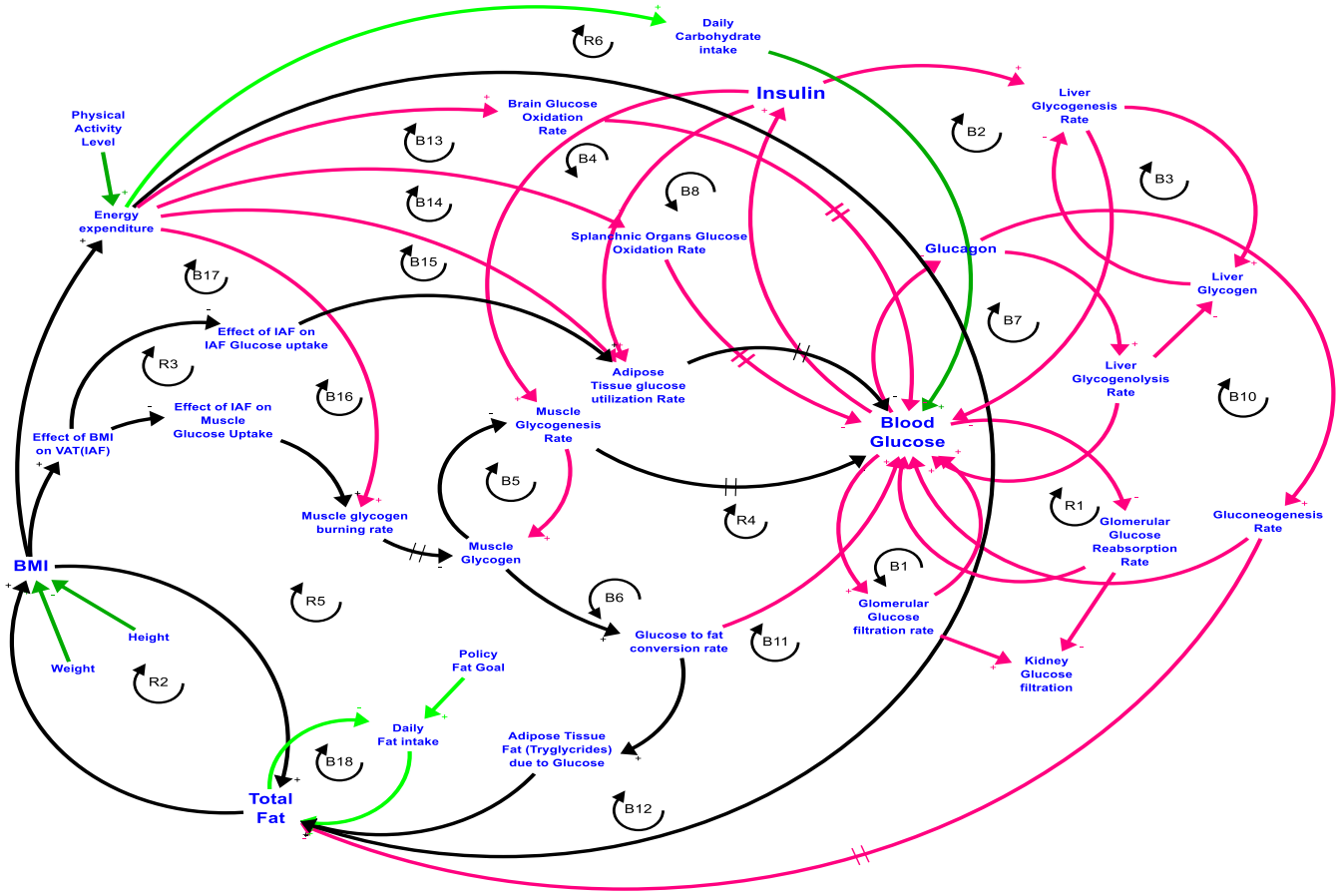

Figure 6-3. Policy included closed loop diagram for blood glucose homeostasis.

6.3. Policy Analysis.

Investigating the proposed policy in detail shows how the body responds to the proposed policy in order to reach the goal as a treatment of insulin resistance, this policy can be grouped and analyzed in to two sub phases, the first phase is the treatment phase and testing is the second phase.

6.3.1. Treatment Phase.

Treatment phase runs for 2160 hours from 7 o'clock to 3rd month morning 7 o'clock (2167) by taking the participants real average data as an input for the simulation result.

Model Setting:

Table 6-1. Model setting during treatment phase.

Variable	Description
Start time	The model starts to simulate at 7 Since the first sample took at 7 A.M from those volunteers with a problem of Insulin resistance.
Stop time	The model ends at 2167 hour.
Initial Blood glucose in gram	First day morning 7 o'clock Blood glucose in gram =13.5 g Since blood glucose concentration =14.9 mmol/l =270mg/dl=13.5 g.
Average Body weight	103 kg
Average height	1.74 m
Total fat goal	BMI goal =25 kg/m^2 => Total fat goal = 30.4 Kg
Physical Activity level	Physical activity level is set at the basal level (PAL=1.4).
Time units	Hour
Sim duration	1.5 minutes
Integration Method	Euler
Delta time	0.1
software	Stella architecture 2.1 version software
Policy energy expenditure	Policy energy expenditure during the treatment phase is based on a daily scheduled activity for sedentary lifestyle (see table 6-2)

Table 6-2. Hourly activity of sedentary life adapted from Joint FAO/WHO/UNU report(Joint, 2004).

Sedentary or light activity lifestyle			
Main daily activity	Energy cost PAR	Time Energy Cost	Total Hour/day
Sleeping	1	8	8
Personal care (dressing, showering	2.3	2.3	1
Eating	1.5	1.5	1
Cooking	2.1	2.1	1
Sitting (Office work, selling, produce, tending shop)	1.5	12	8
General household work	2.8	2.8	1

Driving car to/from work	2	2	1
Walking at varying paces without a load	3.2	3.2	1
Light leisure activities (watching TV, chatting)	1.4	2.6	2
		36.5	24

There are two main types of treatment policy, those two main policies are designed based on how many grams of carbohydrate eat per day with and without using non carbohydrate (fat and protein) sources from our body.

6.3.1.1 Policy A.

Only daily carbohydrate intake is a source for blood glucose.

In this policy type, blood glucose is supplied by daily carbohydrate intake, daily carbohydrate intake could be calculated based on total energy expenditure as follows.

Daily carbohydrate intake= (Carbohydrate intake calibration coefficient) * (Total daily energy expenditure)

where, Carbohydrate intake calibration coefficient shows how much (percentage or it can be between 0 and 1) is the daily carbohydrate intake relative to total daily energy expenditure.

Let Carbohydrate intake calibration coefficient as CICC.

i) At CICC =1, implies Daily carbohydrate =total daily energy expenditure.

Simulated result

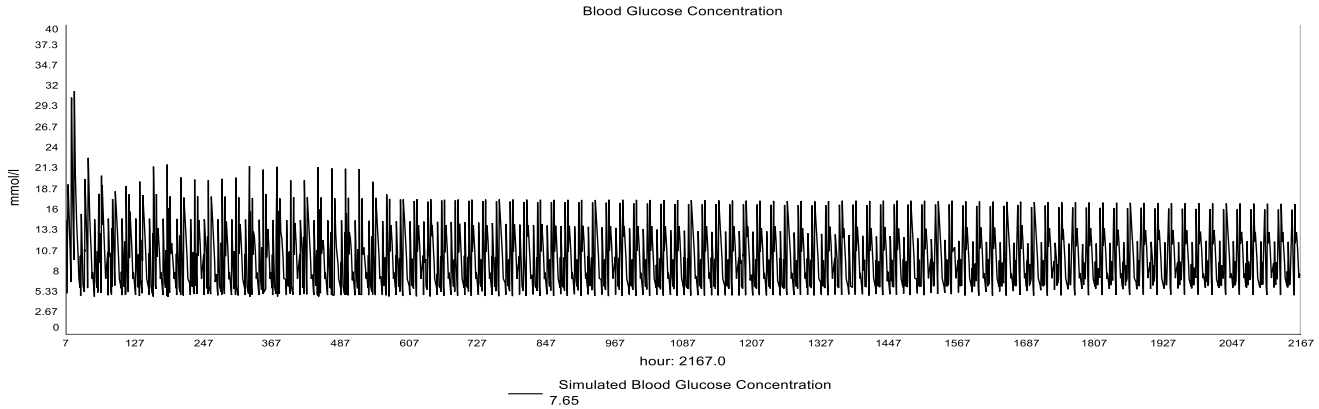

Figure 6-4. Simulated result of blood glucose concentration under policy A and CICC =1.

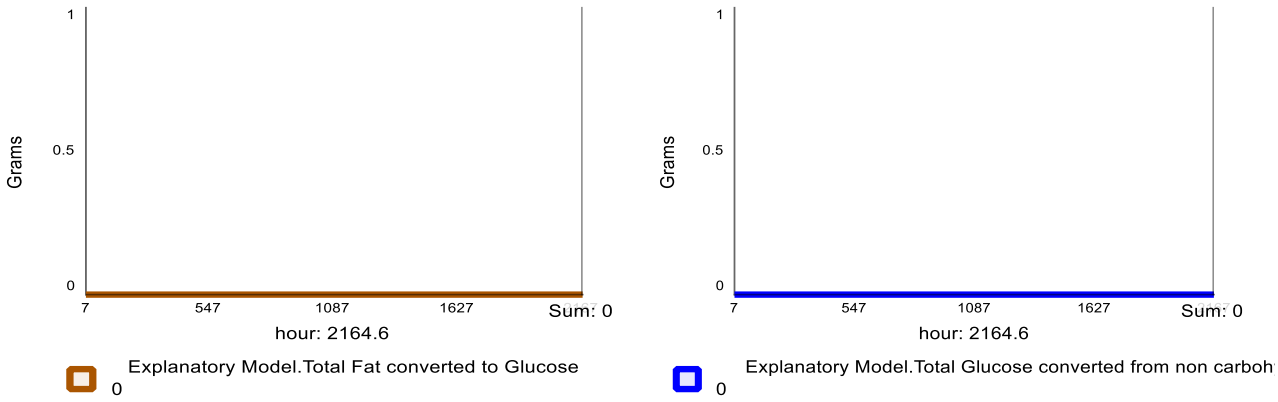

Figure 6-5. Simulated result of fat converted to glucose and glucose from non-carbohydrate nutrients from the body under policy A and CICC =1

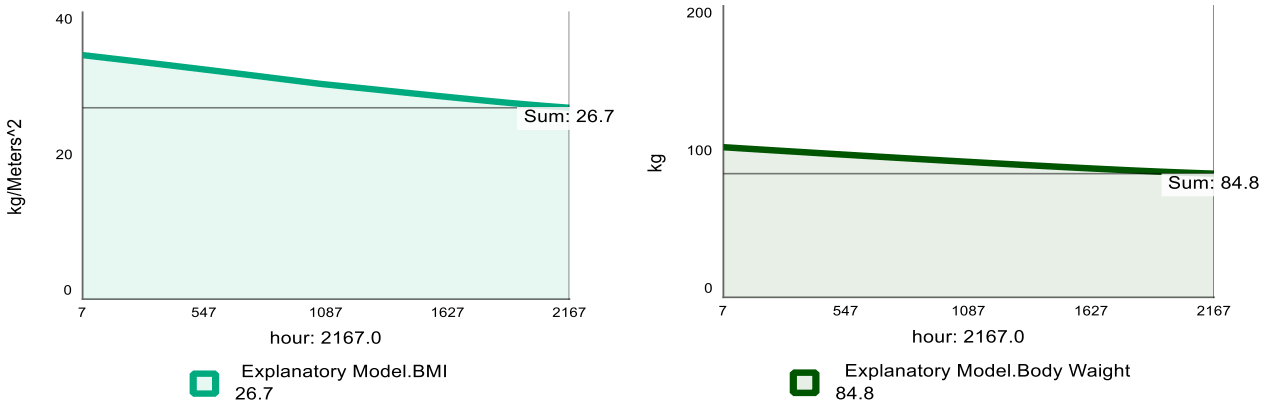

Figure 6-6. Simulated result of BMI and Body weight under policy A and CICC =1.

ii) At ACCI=0.94, implies Daily carbohydrate intake = 94 % of total daily energy expenditure

Simulated Results

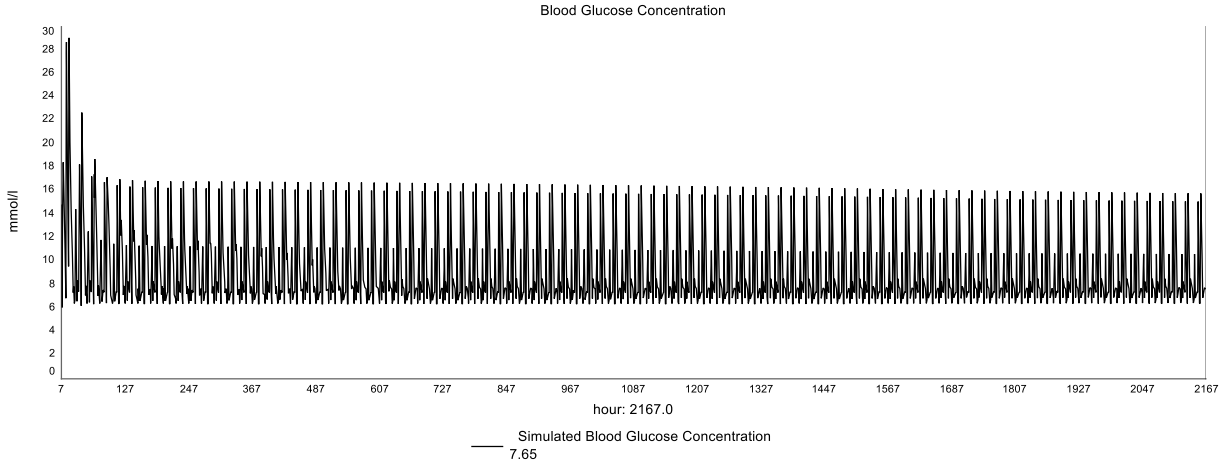

Figure 6-7. Simulated result of blood glucose concentration under policy A and CICC =0.94.

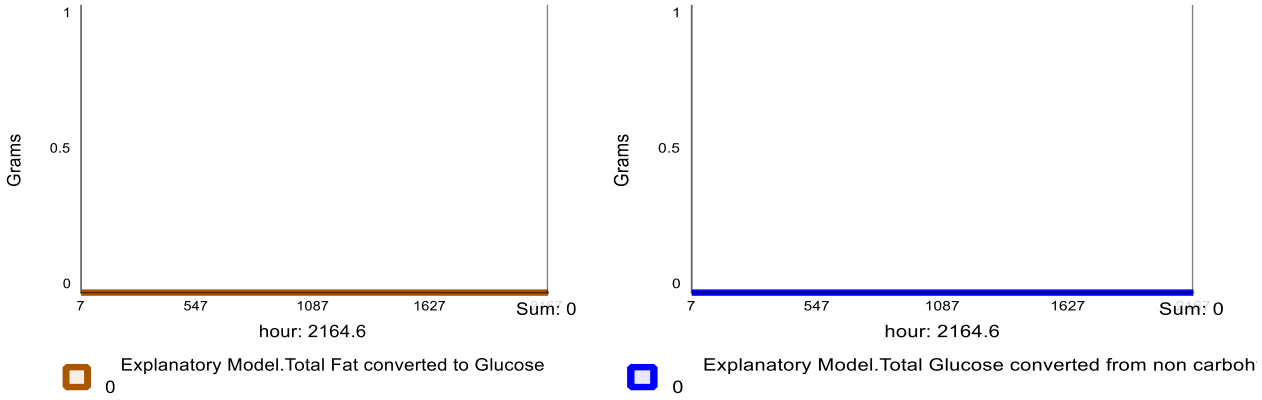

Figure 6-8. Simulated result of fat converted to glucose and glucose from non-carbohydrate nutrients from the body under policy A and CICC =0.94.

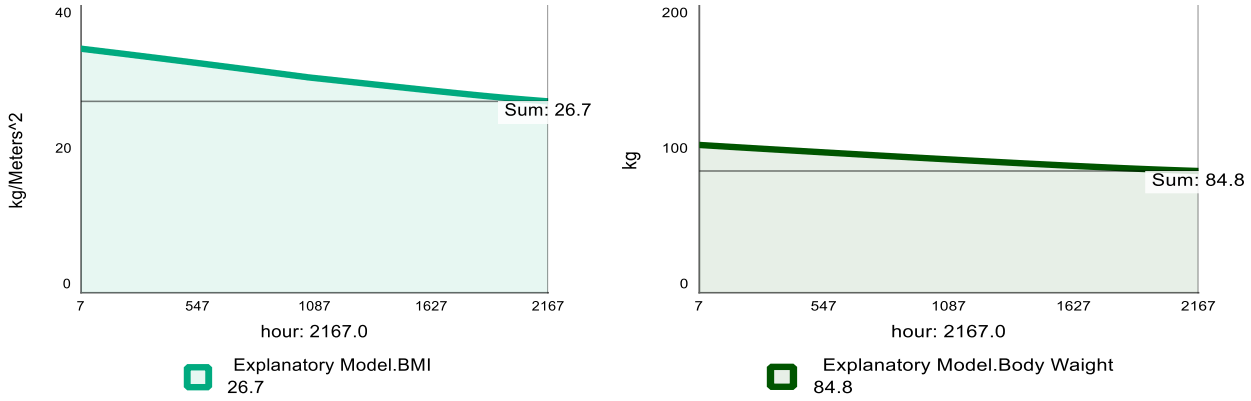

Figure 6-9. Simulated result of BMI and Body weight under policy A and CICC =0.94.

6.3.1.2 Policy B.

Both daily carbohydrate intake and body fat are a source for blood glucose.

In this policy type, blood glucose is supplied by daily carbohydrate intake and fat from the body through the process of gluconeogenesis (see B10 on CLD). Dual use of body fat as a source of glucose through the process of gluconeogenesis and fat as a source of energy for fat utilization (see B10 and B12 Figure 6-3) become more effective in this type of treatment.

i) At ACCI=0.93, implies Daily carbohydrate intake = 93 % of total daily energy expenditure and the rest blood glucose for glucose utilization is covered by the conversion of non-carbohydrate (fat and protein) to blood glucose from the body.

Simulated Results

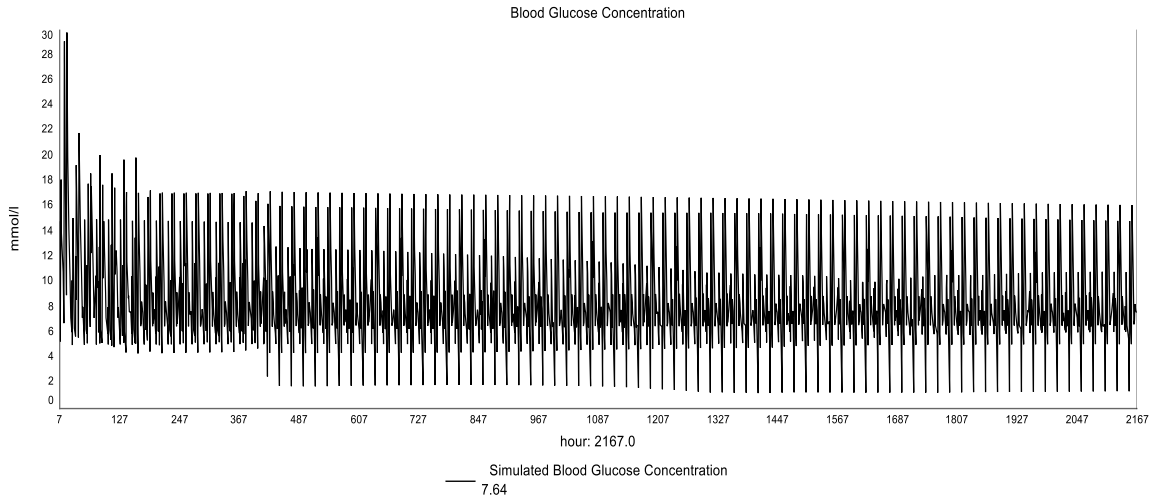

Figure 6-10. Simulated result of blood glucose concentration under policy A and CICC =0.93.

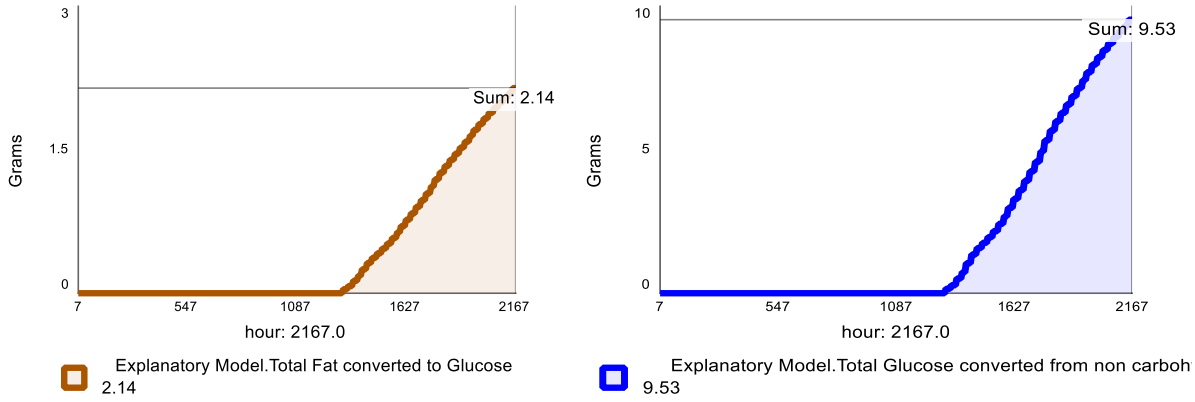

Figure 6-11. Simulated result of fat converted to glucose and glucose from non-carbohydrate nutrients from the body under policy A and CICC =0.93.

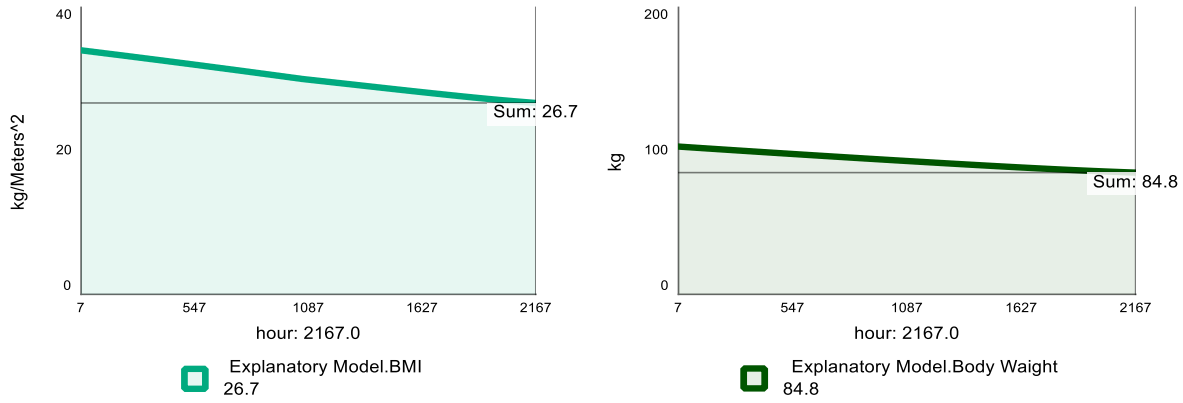

Figure 6-12. Simulated result of BMI and Body weight under policy A and CICC =0.93.

ii) At ACCI=0.90, implies Daily carbohydrate intake = 90 % of total daily energy expenditure and the rest blood glucose for glucose utilization is covered by the conversion of non-carbohydrate (fat and protein) to blood glucose from the body.

Simulated Results

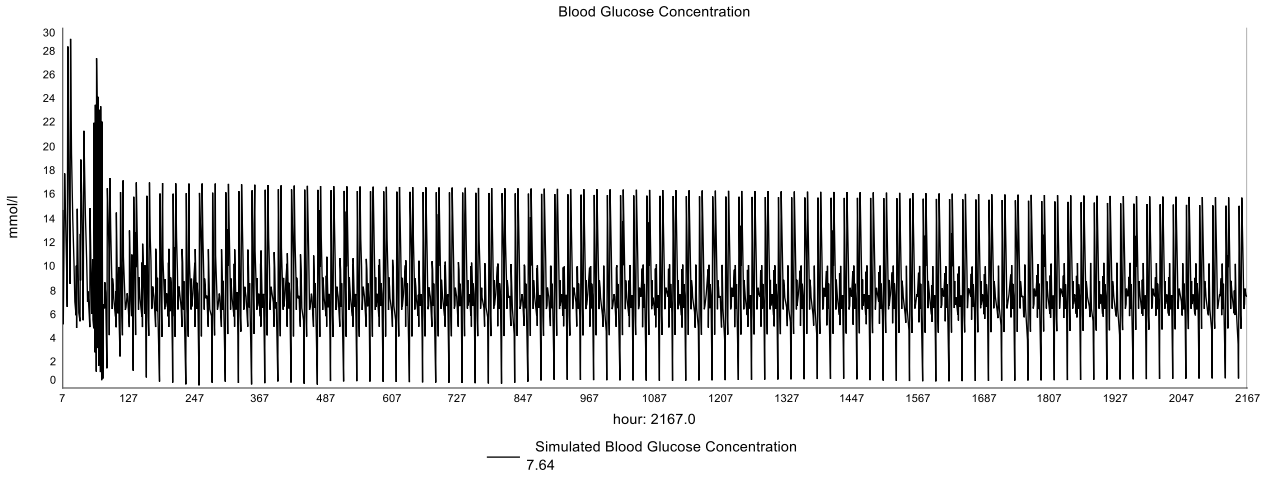

Figure 6-13. Simulated result of blood glucose concentration under policy A and CICC =0.9.

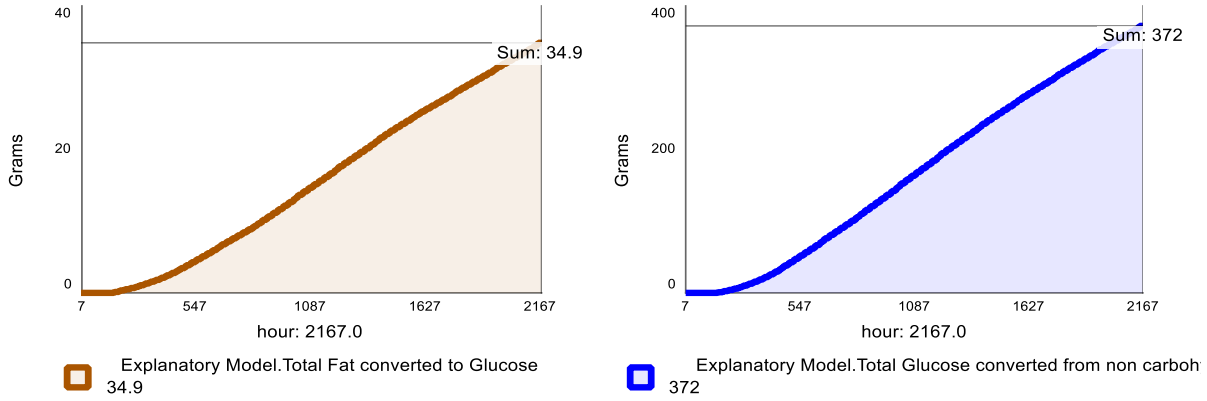

Figure 6-14. Simulated result of fat converted to glucose and glucose from non-carbohydrate nutrients from the body under policy A and CICC =0.9.

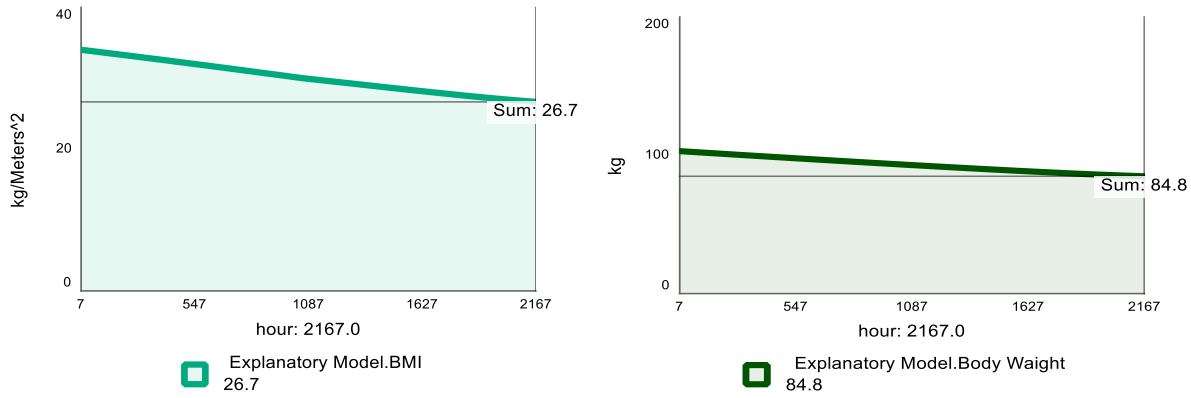

Figure 6-15. Simulated result of BMI and Body weight under policy A and CICC =0.9.

6.3.1.3 Summary for simulated results of both treatments.

Table 6-3. Simulated policy result comparison table.

Parameter	Policy A		Policy B	
	ACCI=1.00	ACCI=0.94	ACCI=0.93	ACCI=0.90
Last day Morning Blood Glucose Concentration(mmol/l)	7.65	7.65	7.64	7.64
Total Fat Converted to Glucose(gram)	0	0	2.14	34.9
Total non-Carbohydrate converted to Glucose(gram)	0	0	9.53	372
Last day BMI(Kg/m^2)	26.7	26.7	26.7	26.7
Last day Body weight (Kg)	84.8	84.8	84.8	84.8

6.3.1.4 General treatment phase result analysis.

Total fat goal is calculated from BMI goal since fat is directly proportional to BMI.

Reference to the simulated result of total fat, fat goal (figure 6-16) and BMI (table 6-4), total fat in the body decreases linearly and decreases decreasingly at the end until it reaches fat mass of 34.1 kg because daily fat intake rate for 2166 hours as a supplier of fat increases gradually from zero and approaches to fat oxidation rate as a source of energy (see figure 6-17).

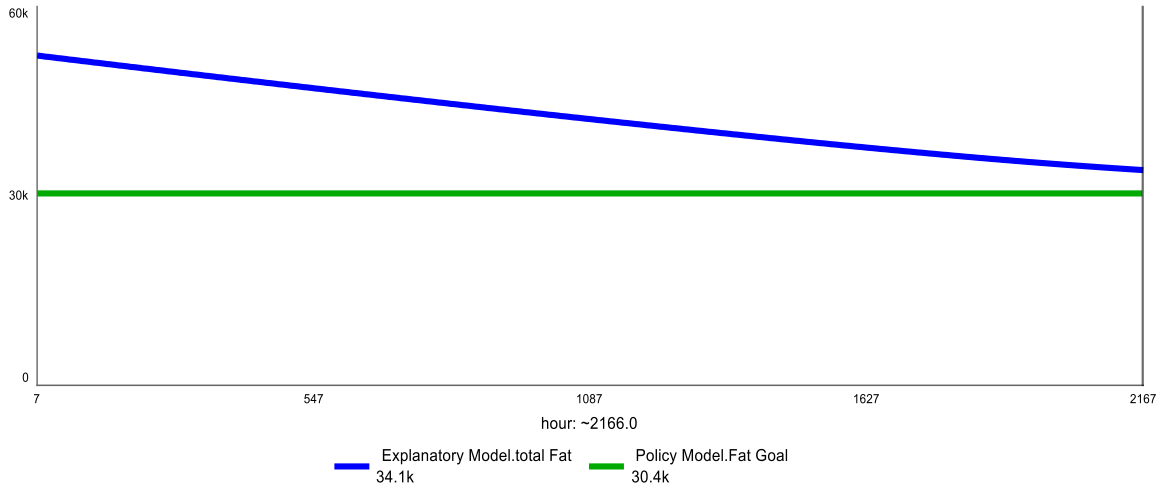

Figure 6-16. Simulated results of total fat and fat goal of the body during the treatment period.

Decreasing of the gap between fat oxidation rate and daily fat intake rate enforces total fat to decrease decreasingly at the end, decreasing of total fat influences BMI to decrease by following the shape of total weight since total fat, total body weight and BMI are directly related.

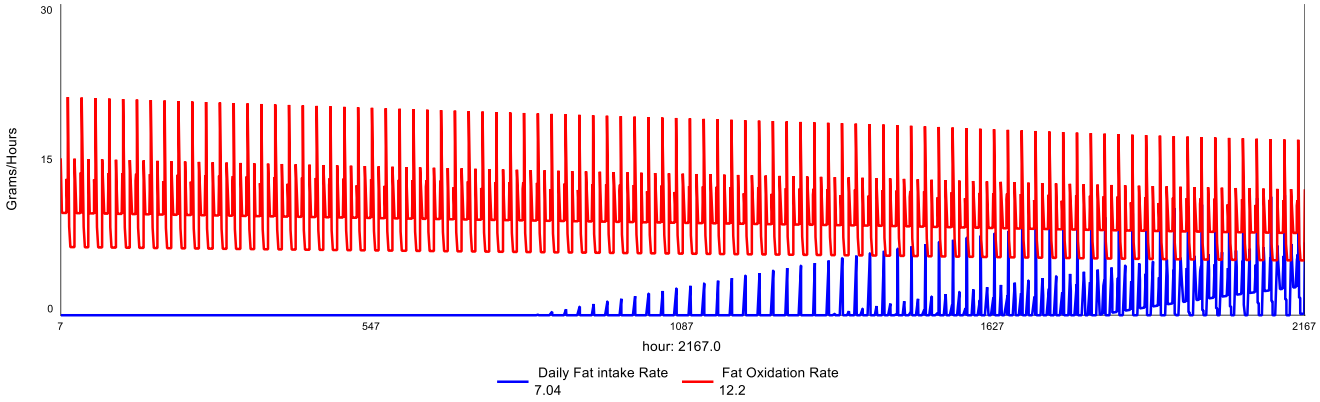

Figure 6-17. Simulated result for total oxidized fat and total daily fat intake.

Therefore, during the treatment phase (3 months stay) body weight/BMI/fat mass of the body decreases due to fat oxidation dominance through the balancing loop of B12 over daily fat intake through the balancing loop of B18 (see Figure 6-3).

The gradual reduction of body weight (see table 6-4) or body fat reduces the daily energy expenditure since energy expenditure directly proportional to body weight, this implies that the amount of glucose used by the cell decreases relative the amount of glucose used by the cell at the initial body weight of 103 kg.

Table 6-4. Weight change percentage of simulated and calculated result.

3 months treatment change								
Fat Weight			BMI			Body Weight		
Initial (Gram)	At the end of Treatment (Gram)	Change (%)	Initial (Kg/m)	At the end of Treatment (Kg/m2)	Change (%)	Initial (Kg)	At the end of Treatment (Kg)	Change (%)
52200	34100	83.02752	34	26.7	81.11111	103	84.8	66.64225

Based on the simulated result in figure 6-7, blood glucose concentration decreases and reaches 7.65 mmol/l at the last day of treatment, that means there is an improvement of morning blood glucose level from 14.9 mmol/l to 7.65 mmol/l , this indicates that there is an additional physiological improvement in the body that drains glucose as a source of energy from the blood vessel because the policy proposes daily carbohydrate intake is equal to glucose used by the body.

Intra-abdominal fat (IAF) reduction due to decreasing of total body weight influences muscle and adipose tissues glucose utilization through the reinforcing loops of R3 and R5, this glucose utilization multiplying effect in this treatment period shows an improvement from 0.42 to 0.72 for adipose tissue and from 0.47 to 0.74 for muscle tissues.

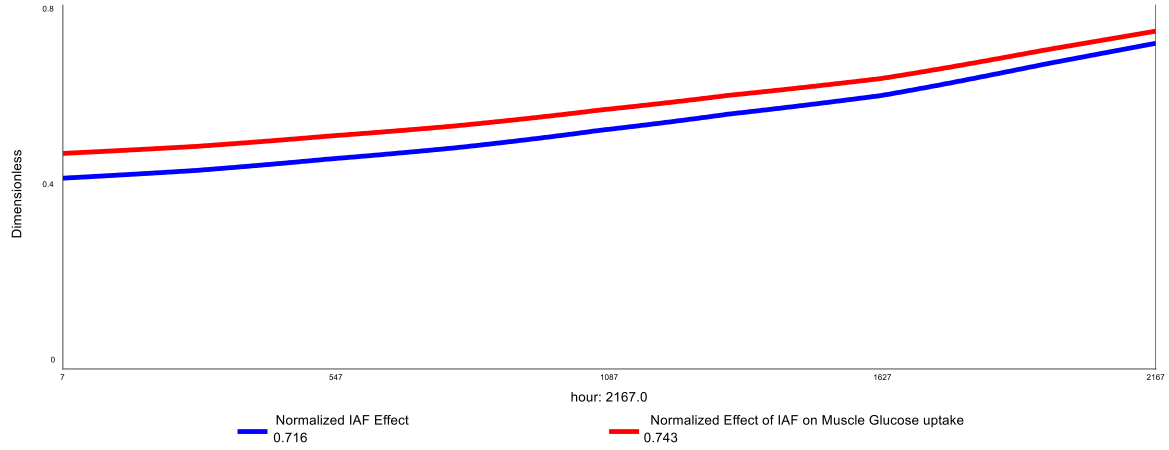

Figure 6-18. Simulated result of fat multiplying effect on muscle and adipose tissue glucose utilization.

So, the effect of body weight reduction on muscle and adipose tissue glucose utilization through the reinforcing loop of R3 and R5 together with a daily policy-based carbohydrate intake dominates over the rest of the physiological loops to have a morning blood glucose concentration improvement from 14.9 mmol/l to 7.65 mmol/l.

6.3.2. Testing blood glucose concentration Phase.

The participants involved in this procedure did a 3-hour blood glucose concentration test after the treatment phase by taking a 75-gram glucose, this procedure helps to see how the progress after treatment goes because there is visible change of body weight and blood glucose concentration registered at the last day of the treatment phase.

By using the procedure applied on the participants let us set the changed variables according to the simulated result and see how the simulated result behaves relative to the participants real blood glucose concentration level.

Model Setting.

Table 6-5. Model setting for testing blood glucose concentration after treatment.

Variable	Description
Start time	The model starts to simulate at 7 Since the first sample took at 7 A.M from those volunteers after the treatment phase.
Stop time	the model ends at 10 since the last sample took from the reference was at 10 A.M.
Initial Blood glucose in gram	Initial blood glucose in gram =6.95 (blood glucose in gram=6.95 g =blood glucose concentration =7.65mmol/l) Blood glucose concentration in the model will initialize automatically 7.65 mmol/l when initializing blood glucose in gram =6.95 gram since morning blood glucose concentration at the last day(t=2167) of the treatment is 7.65 mmol/l.
Food intake for Blood glucose concentration test	75 grams (has taken from the reference)
Average Body weight	84.8 kg (taken from the last day of the treatment phase, at t =2167)

Average height	1.74 m
Physical Activity level	Physical activity level is set at the basal level since no need of physical activity during the admission.
Time units	Hour
Sim duration	1.5 minutes
Integration Method	Euler
Delta time	0.1
software	Stella architecture 2.1 version software
Energy expenditure	Energy Expenditure during the test: energy expenditure is set (PAL=1.4) by considering the volunteers are admitted just to take the samples.

6.3.3. Test phase blood glucose concentration behavior result analysis.

Based on a 3-hour testing duration, the simulated result of blood glucose concentration level responds to 75 grams of glucose shown in figure 6-19 has three phases. Blood glucose concentration decreasing linearly, then increases for one hour and finally decreases for 2 hours, similarly the reference mode increases then decreases in the same direction of simulated result with different slope and different amplitude but at the beginning both goes in opposite direction.

Even if both the simulated result and the reference mode go in the same direction for 96% of the time horizon, additional methods should apply to see how the model is accurate to reproduce the reference mode, the accuracy of the model can be evaluated by using behavior reproduction test through the calculation formulated based on simulated and reference mode levels.

Figure 6-19. Simulated and data taken from the participants as a reference result of blood glucose concentration.

Behavior reproduction test in table 6-6 shows that the mean absolute percentage error deviates from the normal because the simulated and the real data taken from the participants has difference.

Table 6-6. Behavior reproduction test table for blood glucose concentration after treatment.

Behavior reproduction test after treatment					
Time	Reference Mode	Simulated Data	Mean absolute Error (MAE)	Mean absolute percent error (MAPE) %	Root Mean square error (RMSE)
7	7.26	7.65	6.618	65.4998	7.601606
7.5	8.8	18.9			
8	11	21.8			
9	11.6	18			
10	10	15.4			

6.3.3.1 Analysis of Testing blood glucose concentration.

Result of testing the blood glucose concentration for 3 hours shown in figure 6-19 indicates that model-based simulation decreases linearly for 6 minutes (3% of the time horizon) because glucose oxidation rate for 6 minutes is greater than glucose supplied to the blood vessel due to the delay during glucose ingestion and reaches its maximum value after 48 minutes since glucose utilization in different tissues and organs are less than glucose ingestion rate.

By following increasing decreasingly for 48 minutes, Blood glucose concentration stays at equilibrium at the peak value for 6 minutes because glucose utilized by the cell is equal to glucose supplied to blood vessel.

Following to the equilibrium at the peak value, blood glucose concentration decreases for 2 hours due to high amount of glucose used by the cell relative to glucose intake.

6.4. Summary of weight maintenance treatment effect on the vital tissues of insulin resistance.

Table 6-7. Summary of policy-based treatment improvement table for insulin resistance.

Summary of data before and After Insulin resistance Treatment.				
	Before treatment			
	Real Data from participants	Simulated Result	Difference	Remark
Morning Blood Glucose(mmol/l)	14.9	14.9	0	Models' initial morning blood glucose concentration from real data.
Weight(kg)	103	103	0	Models initial weight from real data.
BMI (kg/m2)	34	34	0	Models initial BMI from by calculating real data of weight and height.
Body fat multiplying effect on Adipose tissue glucose utilization	-	0.42	-	Has no given data from participants, only from the model based on the given body weight
Body fat multiplying effect on Muscle tissue	-	0.47	-	Has no given data from participants, only from the model based on the

glucose utilization.				given body weight.
	After treatment			
	Real Data from participants	Simulated Result	Difference	
Morning Blood Glucose(mmol/l).	7.26	7.65	0.39	There is a little difference between real data and the simulated result.
Weight(kg).	86.1	84.8	1.3	There is 1.3 kg difference between the simulated and the real data.
BMI (kg/m2).	28.7	26.7	2	BMI from the simulated result of body weight will be 28 kg/m2.
Body fat multiplying effect on Adipose tissue glucose utilization.	-	0.72	-	There is an improvement relative to the initial value.
Body fat multiplying effect on Muscle tissue glucose utilization.	-	0.74	-	There is an improvement relative to the initial value.

6.5. Policy evaluation and policy implementation.

Policy analysis on the previous part provides insight to see the advantage and disadvantage of each policy during implementation, advantage and disadvantage of the policy depends on the local variable included in this model (CICC) to reach the right goal of curing from Insulin resistance.

Implications in Policy A.

The daily intake of carbohydrate is more than enough when CICC is 1 because it is calculated based on daily maximum glucose oxidation by the organs in the body but when CICC decreases until 0.93, the carbohydrate as daily intake become optimized because as far as human body is under complex system, glucose utilization needs hormones that facilitate the process even if enough glucose is supplied. This implies if there is no enough amount of hormones in the process of oxidation, 7 % of the glucose considered as excess, this daily 7% excess glucose in life long converted to fat and the body fall again on the disease related to excess fat rather than being a solution for insulin resistance.

The advantage of Policy A is no doubt to face a problem related to shortage of blood glucose(hypoglycaemia) because at CICC=1 blood glucose concentration become in the intended range.

Implications in policy B.

The net daily flow between total glucose intake and total glucose oxidation become approaches to zero because the daily carbohydrate intake is calculated based on daily glucose oxidation, but if there is shortage of blood glucose, body can get enough glucose by converting fat to glucose through the process of gluconeogenesis.

Therefore, the advantage of policy B is that there is no problem related to excess glucose induced diseases in addition to considering body fat as a source of glucose in the daily plan, using body fat as glucose contributes body fat reduction. So, in Policy B weight reduction is practiced by using fat as a source of energy through fat oxidation and fat as a source of glucose through gluconeogenesis for the sack of blood glucose homeostasis. However, the disadvantage of Policy B needs curiosity of each minute activity, that means blood glucose and organs are more sensitive if daily plan does not follow the policy critically. In case there is any delay of daily activity, blood glucose totally falls in critical conditions of hypoglycaemia, this condition further worsen the physiology of the organ because Policy B proposes fat conversion to glucose is included in normal basis in addition to daily intake of carbohydrate.

Policy making by considering the basic policy implementation obstacles is better to get rid of the problem easily, implementing the designed policy has a lot of obstacles to make it practical on the ground. Generally, there may be other policy implications that are important to take into account but that are out of the scope of this thesis, such as: people living in different situations (country, culture, etc.), people prone to other health related issues, awareness on the health issues, financial status, diet habits, and limitations to access physical activity facilities.

- Other health related issues: To implement the policy being free from other health problems would have better effect on weight reduction period since the policy plan needs enough rest with long time energy demanding activity.
- Awareness: Being aware on the complication of insulin resistance and the solution on hand is a key point to generate daily motivation to be committed, early aware on the problem would be an efficient approach to prevent insulin resistance.
- Financial status: Shortage of finance on every body's daily life leads to be away from the line recommended policy for the treatment of insulin resistance since working environment and load of work varies from place to place.
- Diet habits: Daily diet mostly based on our finance and interest on the type of food, experiencing new policy diet in a short period of time is difficult since the content, test and the amount of the food indicates the interest of the user.
- Accessibility of physical activity infrastructure: Policy based physical activity needs to carefully take into account of the exact duration and monitoring activity level and consider aspects such as affordability and accessibility to physical activity infrastructure.

Chapter 7 . Conclusion

7.1. Conclusion.

Human anatomy and physiology are one of the complex and interesting nature in the world, the level of physiological complexity of different organs in the body makes difficult to get the real cause of the problem but instead the problem develops other problem on the other organs as a complication since human body is an integrated system of organs, insulin resistance is a problem in blood glucose homeostasis process. The presented model base studying of blood glucose homeostasis by using a system dynamic approach found as relevant and effective way to investigate the underline cause of the problem and to find a feasible solution, model building represents each organ function on the role of blood glucose homeostasis and its related problems.

Based on the structure and the generated dynamic behavior of model-based anatomy and physiology of adult blood glucose homeostasis, the author addresses and concludes related to the thesis objectives as follows.

1.To explore the main underlying dynamic interactions among variables (hormone, cell, organ, and nutrients) and feedback processes involved during blood glucose homeostasis.

The fundamental hormones in the blood glucose homeostasis are Insulin and Glucagon, both produced in the organ Pancreas. Excess of glucose stored as glycogen in the liver and muscle tissues by the help of insulin as a stimulator but during hypoglycemia hormone glucagon activates the process of converting carbohydrate and non-carbohydrate nutrients found in the body to glucose, body fat and protein found in the body are non-carbohydrate sources whereas stored glycogen in liver as a carbohydrate source.

Conversion of excess glucose to fat also occur when muscle storage of glycogen is full, and parallelly kidney removes excess blood glucose from the body during filtration.

Dynamic interaction of organs, hormones in the body explained in the hypothesis part of the thesis in detail.

2.To analyze dynamic effect of body hormones especially insulin on glucose metabolic process since less quantity (unproportionable) production of insulin in the body is an indication to the disease Diabetics mellitus.

In reference to the simulated results of insulin production on glucose utilization at 5.2, glucose utilization on insulin dependent tissues varies according to the amount of insulin in the body especially muscle and adipose tissues.

When insulin production decreases by half, adipose tissue gets 28.8 % and muscle tissue 20.3% of the energy required to keep its normal daily activity, and the rest of muscle and adipose tissues cell functionality face a problem. Glucose oxidation on adipose and muscle tissue become worse when the production of insulin decreases, and glucose in the blood as a primary complication stay high and develops further secondary complications on cardiovascular, kidney and eye in the long run, such reduction of insulin production could be an example of specifically Diabetes Mellitus II.

Insulin production 0 % means pancreas do not produce insulin at all, and this could be an example for Diabetes Mellitus type I. In this case Adipose tissue and muscle tissues do not burn glucose to get enough energy to carry out its normal daily activity otherwise the body needs external insulin administration; proper external administration of insulin prevents further complications on the body.

3. To study the dynamic implication of insulin resistance development in the body and to investigate potential management mechanisms to address insulin resistance.

As we see from the beginning of identifying the problem as Insulin resistance to the final designed and tested policy using the model, morning blood glucose approaches the normal level due to coupled policies applied on weight reduction treatment phase since human blood glucose homeostasis is concerned.

Those coupled policies are planned daily activity and daily activity based daily food intake, daily food intake takes the highest influential nutrients for the cause of weight gain into consideration, fat and carbohydrate are the main nutrients included in the model.

Based on the final simulation result, fat intake begins from zero at the first date and then increases gradually because excess fat in the body can be used as a source of energy during fat oxidation and sometimes this fat also uses as glucose through the process of gluconeogenesis since blood glucose homeostasis trying to keep the blood glucose level in the normal range by using different physiological processes in the body during falling phase of blood glucose concentration.

Interestingly at the policy, the relation between weight and the daily carbohydrate intake through daily energy expenditure decreases the amount of carbohydrate daily intake during weight reduction period, this relation during policy making prevents blood vessels from overloaded by excess glucose.

However, fat and carbohydrates are the vital and the dominant source of energy in the body, protein can be taken daily together with simulated fat and carbohydrate because protein do not have that much effect to aggravate the problem happened on Insulin resistance.

During the treatment phase of weight reduction, decreasing weight of fat in the body decreases the effect of excess fat on muscle and adipose tissue glucose utilization. Significant change on those insulin sensitive tissues recorded during simulation, those weight reduction base changes on utilization of glucose is improving the relation between the hormone insulin and the production of glucose transporters (GLUT 4) through insulin receptor.

A healthy relationship between hormone insulin and production of glucose transporters (GLUT 4) improves utilization of glucose on muscle and adipose cells, and decreases morning blood glucose concentration level, this implies that insulin resistance becomes less, and insulin gets better feedback by producing glucose transporter (GLUT 4).

Therefore, it can be observed that the policy tested in this thesis addresses the problem of insulin resistance and gives a better glucose utilization on insulin sensitive tissues by increasing sensitivity of cells to insulin and gives intended morning blood glucose concentration through all the processes included in blood glucose homeostasis since human blood glucose homeostasis is one of the complex systems that exist in nature.

7.2. Limitations and Further work.

On the presented study there are limitations that can be taken into consideration on future work Since during reviewing research, study limitations were confronted usually, limitations found in this study and recommendations to modify this thesis on the future work listed as follows.

- The level of aggregation in this study is high. The developed model uses fat in general, but it needs to differentiate fat into fatty acids and glycerol's, free fatty acids are a source of energy controlled by hormone glucagon. The availability of glycerol is again controlled by the hormone glucagon and used as a source of glucose during gluconeogenesis.
- Boundary extension on future work would be to include other hormones as an endogenous and exogenous, endogenous hormone are incretins and somatostatin whereas exogenous hormones are Adrenalin, Epinephrine, cortisol, and growth hormone.
- Gender and age are not included in this model but including gender and age on the future work advances the efficiency of the model to generate the adequate results for specific age and specific gender.
- To construct a robust model based on scientific evidence requires more time, blood glucose homeostasis-related topics are broad and needs sufficient time to develop and analyse the expected result. Therefore, more time and data are needed to add more detailed structure and test other possible scenarios and policies.
- Future work could be done on testing a new policy. Due to the availability of free fatty acid in the body, flexible energy source shift from fatty acids to glucose and from glucose to free fatty acid happens. This would require a new policy that takes availability of free fatty acid into consideration to burn more fat from the body.

Despite the limitations mentioned above, the model developed in this study helps to understand and identify influential factors and feedback processes involved in blood glucose homeostasis mechanisms and related problems such as insulin resistance, so that interventions can be identified and assessed to reduce and prevent diseases resulting from insulin resistance. The presentation of the model behaviour in a scenario and policy space, provides support to employ system dynamics as a powerful tool to examine complex problems in physiological systems.

Reference.

Abdel-Hamid, T. K. (2003). Exercise and diet in obesity treatment: an integrative system dynamics perspective.

Adeva-Andany, M. M., Funcasta-Calderón, R., Fernández-Fernández, C., Castro-Quintela, E., & Carneiro-Freire, N. (2019). Metabolic effects of glucagon in humans. Journal of clinical & translational endocrinology, 15, 45-53.

Adeva-Andany, M. M., González-Lucán, M., Donapetry-García, C., Fernández-Fernández, C., & Ameneiros-Rodríguez, E. (2016). Glycogen metabolism in humans. BBA clinical, 5, 85-100.

Ahmad, R., Khan, M., Mishra, P., Jahan, N., Ahsan, M. A., Ahmad, I., . . . Furukawa, H. (2021). Engineered hierarchical CuO nanoleaves based electrochemical nonenzymatic biosensor for glucose detection. Journal of the Electrochemical Society, 168(1), 017501.

Ashish, A., Shah, A., & Pandey, S. (2020). Interaction between oxidative stress and diabetes: a mini-review. J Diabetes Metab Disord Control., 7, 58-61.

Association, A. D. (2014). Diagnosis and classification of diabetes mellitus. Diabetes care, 37(Supplement 1), S81-S90.

Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726.

Barlas, Y. (1994). Model validation in system dynamics. Paper presented at the Proceedings of the 1994 international system dynamics conference.

Blanco, G., & Blanco, A. (2017). Medical biochemistry: Academic Press.

Burton, D. A., Stokes, K., & Hall, G. M. (2004). Physiological effects of exercise. Continuing Education in Anaesthesia Critical Care & Pain, 4(6), 185-188.

Castillo-Armengol, J., Fajas, L., & Lopez-Mejia, I. C. (2019). Inter-organ communication: a gatekeeper for metabolic health. EMBO reports, 20(9), e47903.

Chadt, A., & Al-Hasani, H. (2020). Glucose transporters in adipose tissue, liver, and skeletal muscle in metabolic health and disease. Pflügers Archiv-European Journal of Physiology, 1-26.

Chait, A., & den Hartigh, L. J. (2020). Adipose tissue distribution, inflammation and its metabolic consequences, including diabetes and cardiovascular disease. Frontiers in cardiovascular medicine, 7.

Chase, J. G., Benyo, B., & Desaive, T. (2019). Glycemic control in the intensive care unit: A control systems perspective. Annual Reviews in Control, 48, 359-368. doi:10.1016/j.arcontrol.2019.03.007

Coad, J., Pedley, K., & Dunstall, M. (2019). Anatomy and physiology for midwives e-book: Elsevier Health Sciences.

Cobelli, C., & Carson, E. (2019). Introduction to modeling in physiology and medicine: Academic Press.

Cohen, B. J., & Hull, K. L. (2020). Memmler's the human body in health and disease: Jones & Bartlett Learning.

Cole, J. B., & Florez, J. C. (2020). Genetics of diabetes mellitus and diabetes complications. Nature Reviews Nephrology, 16(7), 377-390.

Cole, L. A., & Kramer, P. R. (2015). Human physiology, biochemistry and basic medicine: Academic Press.

Czech, M. P. (2020). Mechanisms of insulin resistance related to white, beige, and brown adipocytes. Molecular metabolism, 34, 27-42.

Dashty, M. (2013). A quick look at biochemistry: carbohydrate metabolism. Clinical biochemistry, 46(15), 1339-1352.

Dave, H. D., Shook, M., & Varacallo, M. (2020). Anatomy, skeletal muscle. StatPearls [Internet].

Donath, M. Y., & Shoelson, S. E. (2011). Type 2 diabetes as an inflammatory disease. Nature reviews immunology, 11(2), 98-107.

Dong, R., Ma, P. X., & Guo, B. (2020). Conductive biomaterials for muscle tissue engineering. Biomaterials, 229, 119584.

Eckel, J. (2018). The Cellular Secretome and Organ Crosstalk: Academic Press.

El-Sayed, A. M., & Galea, S. (2017). Systems science and population health: Oxford University Press.

Ferrannini, E., Sironi, A. M., Iozzo, P., & Gastaldelli, A. (2008). Intra-abdominal adiposity, abdominal obesity, and cardiometabolic risk. European heart journal supplements, 10(suppl_B), B4-B10.

Fialkowski Revilla, M. K., Titchenall, A., Calabrese, A., Gibby, C., & Meinke, W. (2018). Human Nutrition.

Foster, R. O., Tan, M. B., Guyton, J. R., & Soeldner, J. S. (1973). A Systems Dynamics Model of Glucose Homeostasis. IFAC Proceedings Volumes, 6(4), 475-483.
Freckmann, G., Hagenlocher, S., Baumstark, A., Jendrike, N., Gillen, R. C., Rössner, K., & Haug, C. (2007). Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. Journal of diabetes science and technology, 1(5), 695-703.
Fujikawa, T. (2021). Central regulation of glucose metabolism in an insulin-dependent and-independent manner. Journal of Neuroendocrinology, e12941.
Galsgaard, K. D., Pedersen, J., Knop, F. K., Holst, J. J., & Wewer Albrechtsen, N. J. (2019). Glucagon receptor signaling and lipid metabolism. Frontiers in physiology, 10, 413.
Ghadimi, M., Foroughi, F., Hashemipour, S., Rashidi Nooshabadi, M., Ahmadi, M. H., Ahadi Nezhad, B., & Khadem Haghighian, H. (2021). Randomized double-blind clinical trial examining the Ellagic acid effects on glycemic status, insulin resistance, antioxidant, and inflammatory factors in patients with type 2 diabetes. Phytotherapy Research, 35(2), 1023-1032.
Glovaci, D., Fan, W., & Wong, N. D. (2019). Epidemiology of diabetes mellitus and cardiovascular disease. Current cardiology reports, 21(4), 1-8.
Goodman, B. E. (2010). Insights into digestion and absorption of major nutrients in humans. Advances in physiology education, 34(2), 44-53.
Gowd, V., Jia, Z., & Chen, W. (2017). Anthocyanins as promising molecules and dietary bioactive components against diabetes–A review of recent advances. Trends in Food Science & Technology, 68, 1-13.
Gunton, J., & Girgis, C. M. (2012). Pancreatic beta-cell failure in the pathogenesis of type 2 diabetes. In: Sydney University Press.
Hall, J. E., & Hall, M. E. (2020). Guyton and Hall textbook of medical physiology e-Book: Elsevier Health Sciences.
Hamosh, M. (2020). Lingual and gastric lipases: their role in fat digestion: CRC press.
Hasan, N. M., Johnson, K. F., Yin, J., Baetz, N. W., Fayad, L., Sherman, V., . . . Zachos, N. C. (2021). Intestinal stem cell-derived enteroids from morbidly obese patients preserve obesity-related phenotypes: Elevated glucose absorption and gluconeogenesis. Molecular metabolism, 44, 101129.
Hatting, M., Tavares, C. D., Sharabi, K., Rines, A. K., & Puigserver, P. (2018). Insulin regulation of gluconeogenesis. Annals of the New York Academy of Sciences, 1411(1), 21.
Hayashi, Y. (2020). Glucagon regulates lipolysis and fatty acid oxidation through inositol triphosphate receptor 1 in the liver. Journal of Diabetes Investigation.
Heinonen, I., Kalliokoski, K. K., Hannukainen, J. C., Duncker, D. J., Nuutila, P., & Knuuti, J. (2014). Organ-specific physiological responses to acute physical exercise and long-term training in humans. Physiology.
Henry, R., Wallace, P., & Olefsky, J. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998.
Hinsberger, A., & Sandhu, B. (2004). Digestion and absorption. Current Paediatrics, 14(7), 605-611.
Hoeg-Jensen, T. (2021). Glucose-sensitive insulin. Molecular metabolism, 46, 101107.
Holloszy, J. O., Kohrt, W. M., & Hansen, P. A. (1998). The regulation of carbohydrate and fat metabolism during and after exercise. Front Biosci, 3, D1011-D1027.
Houghton, D., Wilcox, M. D., Brownlee, I. A., Chater, P. I., Seal, C. J., & Pearson, J. P. (2019). Acceptability of alginate enriched bread and its effect on fat digestion in humans. Food hydrocolloids, 93, 395-401.
Inghels, D. (2020). Causal Loop Diagrams. In Introduction to Modeling Sustainable Development in Business Processes (pp. 149-153): Springer.
Jensen, J., Rustad, P. I., Kolnes, A. J., & Lai, Y.-C. (2011). The role of skeletal muscle glycogen breakdown for regulation of insulin sensitivity by exercise. Frontiers in physiology, 2, 112.
Jeukendrup, A. (2003). Modulation of carbohydrate and fat utilization by diet, exercise and environment. Biochemical Society Transactions, 31(6), 1270-1273.
Joint, F. (2004). Human energy requirements. Report of a Joint FAO/WHO/UNU Expert Consultation, Rome, 17-24 October 2001.
Joyce, P., Meola, T. R., Schultz, H. B., & Prestidge, C. A. (2020). Biomaterials that regulate fat digestion for the treatment of obesity. Trends in Food Science & Technology.
Kahn, B. B. (1998). Type 2 diabetes: when insulin secretion fails to compensate for insulin resistance. Cell, 92(5), 593-596.

Kim, J. H., Ko, H. Y., Wang, H. J., Lee, H., Yun, M., & Kang, E. S. (2020). Effect of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on gluconeogenesis in proximal renal tubules. Diabetes, Obesity and Metabolism, 22(3), 373-382.
Kliemann, N., Murphy, N., Viallon, V., Freisling, H., Tsilidis, K. K., Rinaldi, S., . . . Boeing, H. (2020). Predicted basal metabolic rate and cancer risk in the European Prospective Investigation into Cancer and Nutrition. International journal of cancer, 147(3), 648-661.
Koepsell, H. (2020). Glucose transporters in brain in health and disease. Pflügers Archiv-European Journal of Physiology, 1-45.
Kroemer, G., López-Otín, C., Madeo, F., & de Cabo, R. (2018). Carbotoxicity—noxious effects of carbohydrates. Cell, 175(3), 605-614.
Kumari, A. (2017). Sweet Biochemistry: Remembering Structures, Cycles, and Pathways by Mnemonics: Academic Press.
Lakhtakia, R. (2013). The history of diabetes mellitus. Sultan Qaboos University Medical Journal, 13(3), 368.
Laughlin, S. B. (2001). Energy as a constraint on the coding and processing of sensory information. Current opinion in neurobiology, 11(4), 475-480.
Leto, D., & Saltiel, A. R. (2012). Regulation of glucose transport by insulin: traffic control of GLUT4. Nature reviews Molecular cell biology, 13(6), 383-396.
Lim, J., Park, H. S., Kim, J., Jang, Y. J., Kim, J.-H., Lee, Y., & Heo, Y. (2020). Depot-specific UCP1 expression in human white adipose tissue and its association with obesity-related markers. International Journal of Obesity, 44(3), 697-706.
Lin, G., Palopoli, M., & Dadwal, V. (2020). From Causal Loop Diagrams to System Dynamics Models in a Data-Rich Ecosystem. In Leveraging Data Science for Global Health (pp. 77-98): Springer, Cham.
Longo, M., Zatterale, F., Naderi, J., Parrillo, L., Formisano, P., Raciti, G. A., . . . Miele, C. (2019). Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. International Journal of Molecular Sciences, 20(9), 2358.
Lunn, J., & Buttriss, J. (2007). Carbohydrates and dietary fibre. Nutrition Bulletin, 32(1), 21-64.
Manuel-y-Keenoy, B., & Perez-Gallardo, L. (2012). Metabolic impact of the amount and type of dietary carbohydrates on the risk of obesity and diabetes. The Open Nutrition Journal, 6(1).
Martinez, K. E., Tucker, L. A., Bailey, B. W., & LeCheminant, J. D. (2017). Expanded normal weight obesity and insulin resistance in US adults of the National Health and Nutrition Examination Survey. Journal of diabetes research, 2017.
McIntyre, H. D., Catalano, P., Zhang, C., Desoye, G., Mathiesen, E. R., & Damm, P. (2019). Gestational diabetes mellitus. Nature reviews Disease primers, 5(1), 1-19.
Melkonian, E. A., Asuka, E., & Schury, M. P. (2020). Physiology, Gluconeogenesis. StatPearls [Internet].
Migliozzi, J. G. (2016). The muscular system. Fundamentals of Anatomy and Physiology: For Nursing and Healthcare Students.
Miyoshi, T., Hiratsuka, K., Saiz, E. G., & Morizane, R. (2020). Kidney organoids in translational medicine: disease modeling and regenerative medicine. Developmental Dynamics, 249(1), 34-45.
Mohammadi, A., Tavakolan, M., & Khosravi, Y. (2018). Developing safety archetypes of construction industry at project level using system dynamics. Journal of safety research, 67, 17-26.
Muhamad, I. I., Hassan, N. D., Mamat, S. N., Nawi, N. M., Rashid, W. A., & Tan, N. A. (2017). Extraction technologies and solvents of phytocompounds from plant materials: physicochemical characterization and identification of ingredients and bioactive compounds from plant extract using various instrumentations. In Ingredients extraction by physicochemical methods in food (pp. 523-560): Elsevier.
Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259.
Nadeem, B., Bacha, R., & Gilani, S. A. (2018). Correlation of subcutaneous fat measured on ultrasound with Body Mass Index. Journal of medical ultrasound, 26(4), 205.
Navale, A. M., & Paranjape, A. N. (2016). Glucose transporters: physiological and pathological roles. Biophysical reviews, 8(1), 5-9.
Oguntibeju, O. O. (2019). Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. International journal of physiology, pathophysiology and pharmacology, 11(3), 45.

Ojha, A., Ojha, U., Mohammed, R., Chandrashekar, A., & Ojha, H. (2019). Current perspective on the role of insulin and glucagon in the pathogenesis and treatment of type 2 diabetes mellitus. Clinical pharmacology: advances and applications, 11, 57.
Pang, G., Xie, J., Chen, Q., & Hu, Z. (2014). Energy intake, metabolic homeostasis, and human health. Food Science and Human Wellness, 3(3-4), 89-103.
Paschou, S. A., Papadopoulou-Marketou, N., Chrousos, G. P., & Kanaka-Gantenbein, C. (2018). On type 1 diabetes mellitus pathogenesis. Endocrine connections, 7(1), R38-R46.
Pellerin, L., & Magistretti, P. J. (2003). How to balance the brain energy budget while spending glucose differently. The Journal of physiology, 546(Pt 2), 325.
Petersen, M. C., & Shulman, G. I. (2018). Mechanisms of insulin action and insulin resistance. Physiological reviews, 98(4), 2133-2223.
Pielmeier, U., Andreassen, S., Nielsen, B. S., Chase, J. G., & Haure, P. (2010). A simulation model of insulin saturation and glucose balance for glycemic control in ICU patients. Computer methods and programs in biomedicine, 97(3), 211-222.
Plows, J. F., Stanley, J. L., Baker, P. N., Reynolds, C. M., & Vickers, M. H. (2018). The pathophysiology of gestational diabetes mellitus. International Journal of Molecular Sciences, 19(11), 3342.
Poudel, R. R. (2013). Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. Indian journal of endocrinology and metabolism, 17(4), 588.
Pruyt, E., & Kwakkel, J. (2007). Combining system dynamics and ethics: Towards more science. Paper presented at the 25th international conference of the system dynamics society, July.
Rix, I., Nexøe-Larsen, C., Bergmann, N. C., Lund, A., & Knop, F. K. (2015). Glucagon physiology.
Saltelli, A. (2020). Ethics of quantification or quantification of ethics? Futures, 116, 102509.
Saltelli, A., Bammer, G., Bruno, I., Charters, E., Di Fiore, M., Didier, E., . . . Mayo, D. (2020). Five ways to ensure that models serve society: a manifesto. In: Nature Publishing Group.
Sanders, L. (2016). Carbohydrate: digestion, absorption and metabolism.
Schinner, S., Scherbaum, W., Bornstein, S., & Barthel, A. (2005). Molecular mechanisms of insulin resistance. Diabetic Medicine, 22(6), 674-682.
Sears, B., & Perry, M. (2015). The role of fatty acids in insulin resistance. Lipids in health and disease, 14(1), 1-9.
Senge, P. M., & Forrester, J. W. (1980). Tests for building confidence in system dynamics models. System dynamics, TIMS studies in management sciences, 14, 209-228.
Shah, A. M., & Wondisford, F. E. (2020). Tracking the carbons supplying gluconeogenesis. Journal of Biological Chemistry, 295(42), 14419-14429.
Shan, Z., Guo, Y., Hu, F. B., Liu, L., & Qi, Q. (2020). Association of low-carbohydrate and low-fat diets with mortality among US adults. JAMA internal medicine, 180(4), 513-523.
Shuster, A., Patlas, M., Pinthus, J., & Mourtzakis, M. (2012). The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. The British journal of radiology, 85(1009), 1-10.
Siva, N., Thavarajah, P., Kumar, S., & Thavarajah, D. (2019). Variability in prebiotic carbohydrates in different market classes of chickpea, common bean, and lentil collected from the American local market. Frontiers in nutrition, 6, 38.
Solomon, E. P. (2015). Introduction to human anatomy and physiology: Elsevier Health Sciences.
Sterman, J. D. (2000). Business dynamics. System Thinking and Modeling for a Complex World. Boston: McGraw-Hill.
Stick, R. V., & Williams, S. (2010). Carbohydrates: the essential molecules of life: Elsevier.
Su, X., & Peng, D. (2020). Adipokines as novel biomarkers of cardio-metabolic disorders. Clinica Chimica Acta.
Tandon, P., Wafer, R., & Minchin, J. E. (2018). Adipose morphology and metabolic disease. Journal of Experimental Biology, 221(Suppl_1), jeb164970.
Tang, A., Coster, A. C., Tonks, K. T., Heilbronn, L. K., Pocock, N., Purtell, L., . . . Xu, A. (2019). Longitudinal changes in insulin resistance in normal weight, overweight and obese individuals. Journal of clinical medicine, 8(5), 623.
Tappy, L. (2020). Metabolism of sugars: a window to the regulation of glucose and lipid homeostasis by splanchnic organs. Clinical Nutrition.

Tunduguru, R., & Thurmond, D. C. (2017). Promoting glucose transporter-4 vesicle trafficking along cytoskeletal tracks: PAK-Ing them out. Frontiers in endocrinology, 8, 329.
Vargas, E., Joy, N. V., & Sepulveda, M. A. C. (2020). Biochemistry, Insulin Metabolic Effects. StatPearls [Internet].
Wallace, W. A. (1994). Ethics in modeling.
Wallig, M. A., Bolon, B., Haschek, W. M., & Rousseaux, C. G. (2017). Fundamentals of toxicologic pathology: Academic Press.
Walther, B., Lett, A. M., Bordoni, A., Tomás-Cobos, L., Nieto, J. A., Dupont, D., . . . Re, R. (2019). GutSelf: Interindividual variability in the processing of dietary compounds by the human gastrointestinal tract. Molecular nutrition & food research, 63(21), 1900677.
Wellmanns, A., & Schmiemann, P. Feedback loop reasoning in physiological contexts. Journal of Biological Education. doi:10.1080/00219266.2020.1858929
Westerterp, K. R. (2013). Physical activity and physical activity induced energy expenditure in humans: measurement, determinants, and effects. Frontiers in physiology, 4, 90.
Wilcox, G. (2005). Insulin and insulin resistance. Clinical biochemist reviews, 26(2), 19.
Wingerd, B., & Taylor, P. B. (2020). The human body: Concepts of anatomy and physiology: Jones & Bartlett Publishers.
Wu, H., & Ballantyne, C. M. (2020). Metabolic inflammation and insulin resistance in obesity. Circulation Research, 126(11), 1549-1564.
Wu, H., Yang, S., Huang, Z., He, J., & Wang, X. (2018). Type 2 diabetes mellitus prediction model based on data mining. Informatics in Medicine Unlocked, 10, 100-107.
Yaribeygi, H., Farrokhi, F. R., Butler, A. E., & Sahebkar, A. (2019). Insulin resistance: Review of the underlying molecular mechanisms. Journal of cellular physiology, 234(6), 8152-8161.
Yetkin-Arik, B., Vogels, I. M., Nowak-Sliwinska, P., Weiss, A., Houtkooper, R. H., Van Noorden, C. J., . . . Schlingemann, R. O. (2019). The role of glycolysis and mitochondrial respiration in the formation and functioning of endothelial tip cells during angiogenesis. Scientific reports, 9(1), 1-14.
Zajac, J., Shrestha, A., Patel, P., & Poretsky, L. (2010). The main events in the history of diabetes mellitus. In Principles of diabetes mellitus (pp. 3-16): Springer.
Zárate, R., el Jaber-Vazdekis, N., Tejera, N., Pérez, J. A., & Rodríguez, C. (2017). Significance of long chain polyunsaturated fatty acids in human health. Clinical and translational medicine, 6(1), 1-19.
Zatterale, F., Longo, M., Naderi, J., Raciti, G. A., Desiderio, A., Miele, C., & Beguinot, F. (2020). Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. Frontiers in physiology, 10, 1607.
Zorena, K., Jachimowicz-Duda, O., Ślęzak, D., Robakowska, M., & Mrugacz, M. (2020). Adipokines and obesity. Potential link to metabolic disorders and chronic complications. International Journal of Molecular Sciences, 21(10), 3570.

Appendix I. Table and figures.

Table 7-1. Glucose transporters and organs that glucose transporters responsible for.

Glucose transporters in the body				
Glucose Transporter Name	Diffusion Mechanism Class	Location in the body	Transportation for	Stimulated By
GLUT1	Class I	Pancreas Beta cells	Glucose	Non-Insulin
GLUT2	Class I	Pancreas, Liver and Kidney	Glucose	Non-Insulin
GLUT3	Class I	Mainly Brain	Glucose	Non-Insulin
GLUT4	Class I	Skeletal Muscle and Adipose Tissue	Glucose	Insulin
GLUT5	Class II	Small intestine, tests, and kidney	Fructose	Non-Insulin
GLUT6	Class III	Brain, Spleen cells and Peripheral leukocytes		Non-Insulin
GLUT7	Class II	Small intestine, Colon, Testis and Prostate	Glucose and Fructose	Non-Insulin
GLUT8	Class III	Testis and Brain	Glucose	Non-Insulin
GLUT9	Class II	Kidney, Liver and Placenta	Glucose	Non-Insulin
GLUT10	Class III	Skeletal Muscle, Lung Tissue, Heart, Brain, Placenta, Kidney, Liver and Pancreas	Glucose	Non-Insulin
GLUT11	Class II	Heart, skeletal muscle, Kidney, Placenta, Adipose tissue, Pancreas cell	Glucose and Fructose	Non-Insulin
GLUT12	Class III	Adipose, Small intestine, Skeletal muscle, and Placenta	Glucose	Translocation in skeletal muscle can be stimulated by Insulin
GLUT13	Class III	Brain, Adipose tissue, and Kidney cells	inositol-3-phosphate	H+ driven

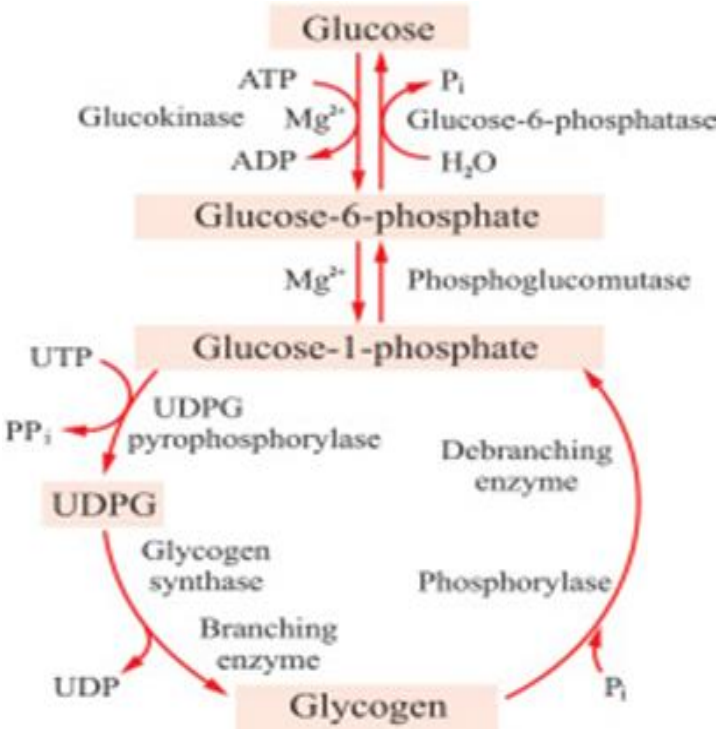

Figure 7-1. Formation of glycogen from glucose and glucose from glycogen, adapted from (Blanco & Blanco, 2017).

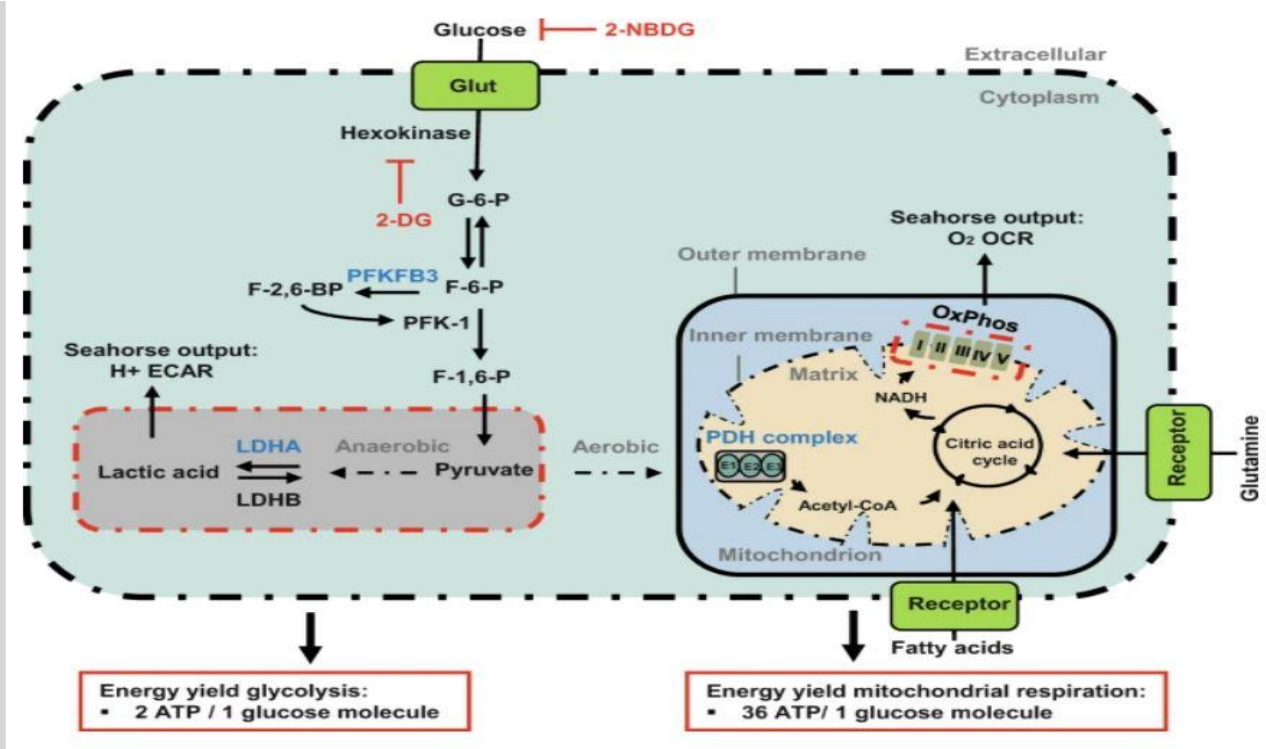

Figure 7-2. Diagram glucose as a source of energy through the process of glycolysis, adapted from (Yetkin-Arik et al., 2019)

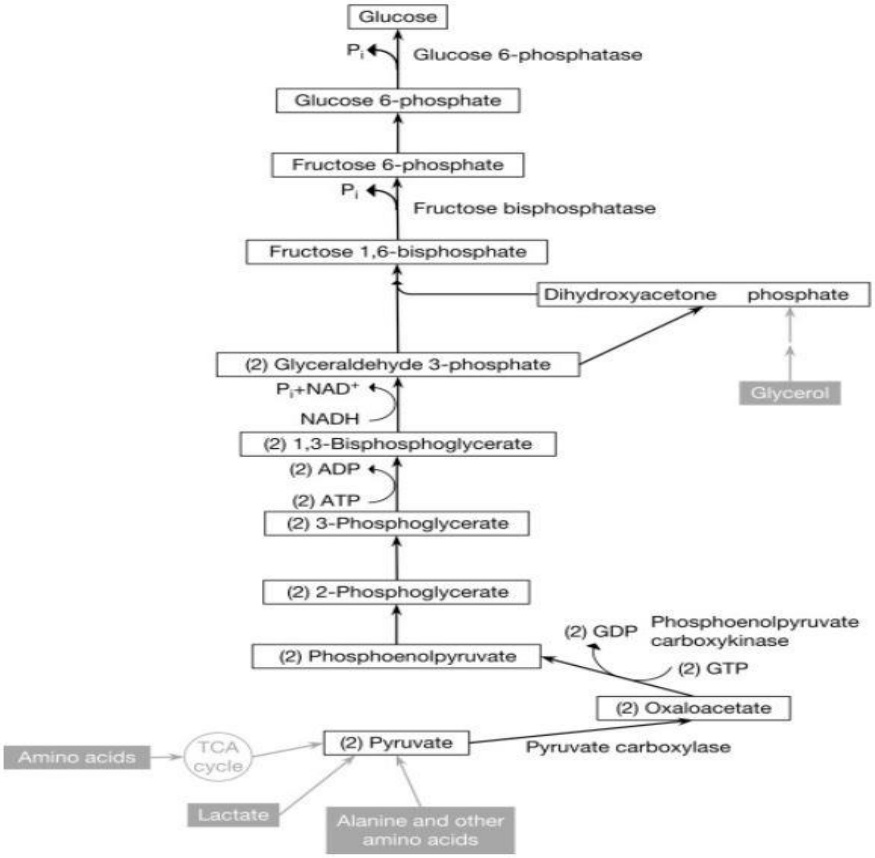

Figure 7-3. Diagram for non-carbohydrate substrates(glycerol as fat and amino acid as protein) in the process of gluconeogenesis adapted from (Sanders, 2016).

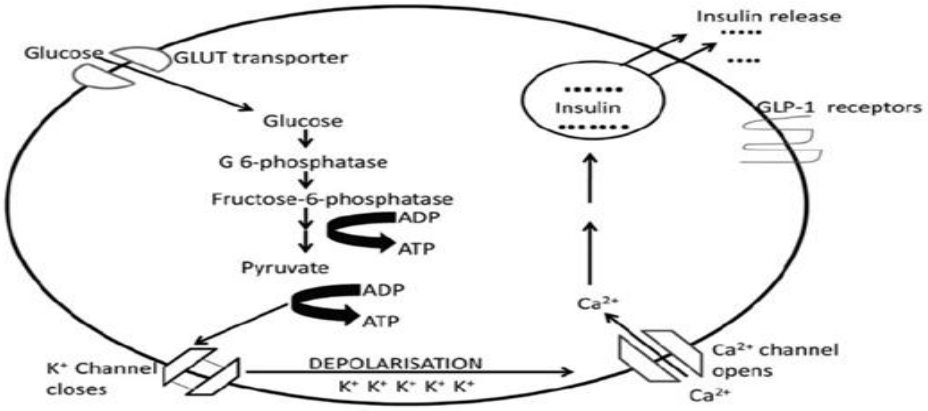

Figure 7-4. Process of insulin production in Pancreas adapted from (Gunton & Girgis, 2012).

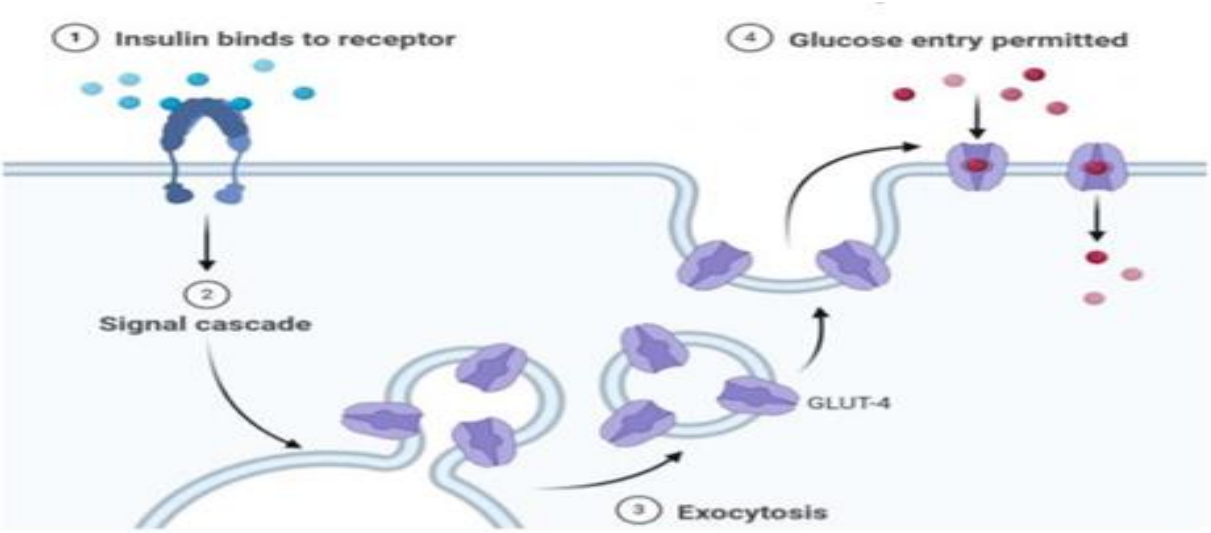

Figure 7-5. Insulin stimulated GLUT4 production adapted from (Ashish et al., 2020).

Appendix II. Model documentation.

		Equation	Properties	Units	Documentation
	Top-Level Model:				
	Explanatory_Model:				
	Blood_glucose_in_gram(t)	Blood_glucose_in_gram(t - dt) + (Liver_Glycogenolysis_Rate + Glomerular_Glucose_Reabsorption_Rate + Glucose_Assimilation_Rate_from_GIT + Gluconeogenesis_Rate - Liver_Glycogenesis_Rate - Muscle_Glycogenesis_Rate - Glomerular_Glucose_filtration_Rate - Brain_Glucose_Oxidation_Rate - Glucose_to_fat_Convertion_rate - Splanchnic_Organs_Glucose_Oxidation_Rate - Adipose_Tissue_glucose_utilization_Rate) * dt	INIT Blood_glucose_in_gram = 13.5	Gram	1. Henry, R. R., Wallace, P., & Olefsky, J. M. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. Reference mode before treatment Initial blood glucose =13.5 gram 2-Freckmann, G., Hagenlocher, S., Baumstark, A., Jendrike, N., Gillen, R. C., Rössner, K., & Haug, C. (2007). Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. Journal of diabetes science and technology, 1(5), 695-703. Reference mode for normal participants initial blood glucose = 3.9 gram

	BMI(t)	BMI(t - dt) + (Change_in_BMI) * dt	INIT BMI = INIT(Body_Weight/(Height^2))	kg/Meters^2	Body Mass Index initialize with the initial body weight and takes in to account any body weight change every hour through Change in BMI.
	Body_Fat(t)	Body_Fat(t - dt) + (- Fat_Oxidation_Rate - Fat_share_on_Gluconeogenesis) * dt	INIT Body_Fat = INIT(Initial_fat)	Grams	Initialize with the total fat of the body (Fat weight in the body)
	Body_Weight(t)	Body_Weight(t - dt) + (Change_in_Weight) * dt	INIT Body_Weight = Body_Weight_in_Kg	Kg	Initialize with initial body weight.
	Commulative_excreted_Glucose_with_urin(t)	Commulative_excreted_Glucose_with_urin(t - dt) + (Glucose_Removal_rate_with_urine) * dt	INIT Commulative_excreted_Glucose_with_urin = 0	Gram	Total glucose excreted out of the body due to kidney re-absorption capacity limitation relative to kidney filtration.
	Fat_stored_from_Glucose(t)	Fat_stored_from_Glucose(t - dt) + (Fat_production_from_Glucose) * dt	INIT Fat_stored_from_Glucose = 0	Grams	Fat from excess glucose.
	Gastrointestinal_Tract(t)	Gastrointestinal_Tract(t - dt) + (Ingestion_Rate - Glucose_Assimilation_Rate_from_GIT) * dt	INIT Gastrointestinal_Tract = 0	Gram	Total accumulated amount of carbohydrate accumulated in the gastrointestinal tract before assimilation.
	Glucagon_in_the_blood(t)	Glucagon_in_the_blood(t - dt) + (Glucagon_Changing_rate) * dt	INIT Glucagon_in_the_blood = INIT(Initial_Glucagon_in_the_blood)	Dimensionless	Total glucagon in the blood vessel is the net glucagon concentration in the blood vessel.
	Glucose_stored_as_Fat(t)	Glucose_stored_as_Fat(t - dt) + (Glucose_to_fat_Convertion_rate) * dt	INIT Glucose_stored	gram	Total glucose converted to fat.

			_as_Fat = 0		
	Insulin_in_the_blood(t)	Insulin_in_the_blood(t - dt) + (insulin_Changing_rate) * dt	INIT Insulin_in_the_blood = INIT(Initial_insulin_in_the_blood)	Dimensionless	Total amount of Insulin in the blood vessel, initial value of insulin varies according to the initial glucose level in the blood.
	Kidney_Glucose_Filtiration(t)	Kidney_Glucose_Filtiration(t - dt) + (Glomerular_Glucose_filtration_Rate - Glomerular_Glucose_Reabsorption_Rate - Glucose_Removal_rate_with_urine) * dt	INIT Kidney_Glucose_Filtiration = 0	Gram	calculated from net flow between total glucose into the kidney and the rest (glucose back to the blood vessel and out from the body) Net accumulated glucose in the kidney
	Liver_Glycogen(t)	Liver_Glycogen(t - dt) + (Liver_Glycogenesis_Rate - Liver_Glycogenolysis_Rate) * dt	INIT Liver_Glycogen = INIT(Initial_Liver_Glycogen)	Gram	Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259 The glycogen content of liver Liver Normal range (g) 0–160 Average (g)80
	Muscle_Glycogen(t)	Muscle_Glycogen(t - dt) + (Muscle_Glycogenesis_Rate - Muscle_glycogen_burning_rate) * dt	INIT Muscle_Glycogen = 200	Gram	1. Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259. Total muscle glycogen storage Muscle tissue glycogen normal range is 300–700 gram
	Total_daily_fat_intake(t)	Total_daily_fat_intake(t - dt) + (Daily_Fat_intake_Rate) * dt	INIT Total_daily_fat_intake = 0	Grams	Total daily fat intake is the total amount of fat intake through daily ingested fat.
	Adipose_Tissue_glucose_utilization_Rate	Glucose_required_by_Adipose_tissue*Both_insulin_and_fat_effect_on_adipose_tissue_glucose_Utilization	OUTFLOW PRIORITY: 7	gram/hour	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. total required glucose, effect of fat on the productiion of Glucose transporters

					during insulin action is under consideration. =>Glucose_required_by_Adipose_tissue*Both_insulin_and_fat_effect_on_adipose_tissue_glucose_Utilization
	Brain_Glucose_Oxidation_Rate	Glucose_required_by_Brain	OUTFLOW PRIORITY: 4	gram/hour	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Glucose utilization grouped in to 6 tissues in the body. These include the brain 45-60 % (55% taken from the rest of the tissues) of the total but now the remaining glucose is calculated from the remaining value of glucose used by the muscle. this implies 55/ (100-17.5) = 0.666 = 66.67 %
	Change_in_BMI	(Indicated_BMI-BMI)/Time_needed_to_change_BMI		kg/Meters^2/hour	Change of BMI considers any BMI change every 1 hour.
	Change_in_Weight	((((Total_Fat)/kg_to_gram)+(Fat_free_mass-Body_Weight))/Time_needed_to_change_Weight)-(Non_fat_weight_reduction_rate_due_to_gluconeogenesis/kg_to_gram)		kg/hour	Change of weight at every time on fat mass and fat free mass.
	Daily_Fat_intake_Rate	Daily_fat_intake+Policy_base_Fat_daily_intake		Grams/Hours	
	Fat_Oxidation_Rate	Required_Fat_in_gram		gram/hour	Unit is changed from Kcal/hour to gram/hour.
	Fat_production_from_Glucose	Glucose_to_fat_Convertion_rate*Unit_Fat_per_Unit_Glucose		Grams/Hours	Jensen, J., Rustad, P. I., Kolnes, A. J., & Lai, Y. C. (2011). The role of skeletal muscle glycogen breakdown for regulation of insulin sensitivity by exercise. Frontiers in physiology, 2, 112 healthy humans were able to convert 475 g carbohydrate to 150 g lipid per day Calculation conversion rate =475/(24) =19.79 gram per hour =0.3665 mmol/l/minute and 3.17g glucose is converted to 1 gram fat 1 gram glucose =0.316 gram fat
	Fat_share_on_Gluconeogenes	GRAPH(Gluconeogenesis_Rate) Points: (0.000, 0.0000), (1.700,		gram/hour	Brosnan, J. T. (1999). Comments on metabolic needs for glucose and the role

	is	0.4567), (3.400, 0.7124), (5.100, 0.8330)			of gluconeogenesis. European journal of clinical nutrition, 53(1), s107-s111. *Gluconeogenesis total =124 per day=5.1 gram/hour *Fat share for gluconeogenesis =20 gram per day=0.833 gram/hour glycerol is a fat which can convert to glucose during gluconeogenesis *fat share in percentage for gluconeogenesis =20/120 =16 %
	Glomerular_Glucose_filtration_Rate	GRAPH("\"Blood_Glucose_Concentration\"") Points: (0.0, 0.0), (100.0, 187.5)		gram/hour	Poudel, R. R. (2013). Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. Indian journal of endocrinology and metabolism, 17(4), 588. Glomerular Glucose filtration Rate has taken from the graph, figure 1
	Glomerular_Glucose_Reabsorption_Rate	GRAPH("\"Blood_Glucose_Concentration\"") Points: (0.0, 0.00), (10.0, 18.75), (10.5, 19.56), (11.0, 20.40), (11.5, 21.00), (12.0, 21.42), (12.5, 21.72), (13.0, 22.14), (13.5, 22.32), (14.0, 22.50), (100.0, 22.50)		gram/hour	Poudel, R. R. (2013). Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. Indian journal of endocrinology and metabolism, 17(4), 588. Glomerular Glucose re-absorption Rate has taken from the graph, figure 1.
	Glucagon_Changing_rate	((Glucagon_Production)-Glucagon_in_the_blood)/Time_needed_for_Glucagon_to_reach_the_cells		Per Hour	Glucagon change rate is net amount of glucagon in the blood vessel, change rate is calculated by taking produced glucagon from alpha cell of pancreas and glucagon usage rate into consideration.
	Gluconeogenesis_Rate	Share_of_Gluconeogenesis_from_the_total_Production		gram/hour	Main Gluconeogenesis sources are fats and proteins here is the total amount of glucose converted from non-carbohydrate sources (Fats and proteins) Proteins are in this model considered as exogenious since it is involved only on Gluconeogenesis
	Glucose_Assimilation_Rate_from_GIT	Gastrointestinal_Tract/Time_needed_to_GIT_to_release_all_type_of_carbohydrate_to_be_assimilated		gram/hour	Choy, S., Hénin, E., van der Walt, J. S., Kjellsson, M. C., & Karlsson, M. O. (2013). Identification of the primary mechanism of action of an insulin secretagogue from meal test data in healthy volunteers based on an integrated glucose-insulin model. Journal of pharmacokinetics and pharmacodynamics, 40(1), 110 From the graph average time needed for glucose absorption =2.15 hours therefore, Assimilation rate of

					carbohydrate from the wall intestine is equal to total amount of carbohydrate/ 2.15 hour.
	Glucose_Removal_rate_with_urine	Glomerular_Glucose_filtration_Rate-Glomerular_Glucose_Reabsorption_Rate	OUTFLOW PRIORITY: 2	gram/hour	Poudel, R. R. (2013). Renal glucose handling in diabetes and sodium glucose cotransporter 2 inhibition. Indian journal of endocrinology and metabolism, 17(4), 588. Glucose removal rate with urine has taken from figure 1
	Glucose_to_fat_Convertion_rate	IF Muscle_Glycogen>(Maximum_Muscle_glycogen_Capacity-1) THEN 19.79 ELSE 0	OUTFLOW PRIORITY: 5	gram/hour	6- Fialkowski Revilla, M. K., Titchenall, A., Calabrese, A., Gibby, C., & Meinke, W. (2018). Human Nutrition. the flow begins when the glycogen in the muscle is reaching max. page.232 and 297 Jensen, J., Rustad, P. I., Kolnes, A. J., & Lai, Y. C. (2011). The role of skeletal muscle glycogen breakdown for regulation of insulin sensitivity by exercise. Frontiers in physiology, 2, 112 *475-gram carbohydrate become 150 g lipid/ day. Calculation conversion rate =475/ (24) =19.79 gram per hour =0.3665 mmol/l/minute and 3.17g glucose is converted to 1 gram fat 1gram glucose =0.316 gram fat
	Ingestion_Rate	Total_Carbohydrate_intake		gram/hour	Sum of the carbohydrate taking rate as a diet.
	insulin_Changing_rate	((("Insulin_production."*Insulin_production_test)-Insulin_in_the_blood)/Time_needed_for_insulin_to_reach_the_cells)		Per Hour	Insulin change rate indicates net insulin in the blood vessel, includes production of Insulin from beta cell of pancreas entering to the blood vessel and used insulin.
	Liver_Glycogenesis_Rate	IF Liver_Glycogen < 79 THEN LG_Rate ELSE 0	OUTFLOW PRIORITY: 1	gram/hour	Roden, M., Perseghin, G., Petersen, K. F., Hwang, J. H., Cline, G. W., Gerow, K., ... & Shulman, G. I. (1996). The roles of insulin and glucagon in the regulation of hepatic glycogen synthesis and turnover in humans. The Journal of clinical investigation, 97(3), 642-648. Glycogen synthesis in the liver taken from from figure 3 the unit is gm/hr, when glycogen in the liver is full, no more glycogenesis. Hers, H. G. (1990). Mechanisms of blood glucose homeostasis. Journal of inherited metabolic disease, 13(4), 395-410

					the rate is changed from micro mol to milli mol and the equilibrium point is at the blood glucose is at 5.7 mmol /l this implies that glucagon=195 and insulin =12.66
	Liver_Glycogenolysis_Rate	Effect_of_Glucagon_on_Liver_glycogenolysis*Body_Weight		gram/hour	Ramnanan, C. J., Edgerton, D. S., Kraft, G., & Cherrington, A. D. (2011). Physiologic action of glucagon on liver glucose metabolism. Diabetes, Obesity and Metabolism, 13, 118-125. Has taken from figure 3.
	Muscle_glycogen_burning_rate	(Glycogen_Required_by_Muscle*Normalized_Effect_of_IAF_on_Muscle_Glucose_uptake)		gram/hour	Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259. total glucose utilization = the effect of fat on utilization*the amount of glucose needed from the muscle during physical movement since ectopic fat in the muscle hinders glucose utilization.
	Muscle_Glycogenesis_Rate	Glycogen_Gap*Effect_of_Insulin_on_Glucose_Utilization/Time_needed_for_glycogen_synthesis	OUTFLOW PRIORITY: 2	gram/hour	Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259. Glycogen synthesis is mediated by the hormone insulin and the amount of of glycogen synthesis is depends on the vacant space of muscle glycogen.
	Splanchnic_Organs_Glucose_Oxidation_Rate	(Glucose_required_by_Splanchnic_Organs)	OUTFLOW PRIORITY: 6	gram/hour	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Glucose utilization grouped in to 6 tissues in the body. this varible inclues kidney, blood cell and Splanchnic organs kidney is between 10-15% (Avg. 12.5%) blood cells is between 5-10% Avg.7.5%), Splanchnic organ is between 3-6% Avg.4.5%) 24.5/82.5=0.2969=> 29.69 % of glucose is for Splanchnic Organs.
	"\"Blood_Glucose_Concentrat	Blood_glucose_in_gram*glucose_gram_to_mmol/Total_blood_vol		mmol/l	Concentration of glucose in the blood Calculated from total glucose in gram

	ion\""	ume			divided by the total amount of blood in the body. (Blood_glucose_in gram*glucose_gram_to_mmol)/Total_blood_volume
○	"Food_intake_for_24_hours_Blood_glucose_Con._test"	0		Gram	Freckmann, G., Hagenlocher, S., Baumstark, A., Jendrike, N., Gillen, R. C., Rössner, K., & Haug, C. (2007). Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. Journal of diabetes science and technology, 1(5), 695-703. 50 gram is administered orally 3 times daily during testing blood glucose concentration for normal volunteries.
○	"Food_intake_for_Blood_glucose_Con._test"	0		Grams	Henry, R. R., Wallace, P., & Olefsky, J. M. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes melli-tus. Diabetes, 35(9), 990-998. 75 gram of glucose is administered orally to measure blood glucose concentration in the morning both before and after weight reduction.
○	"Insulin_production."	GRAPH("\"Blood_Glucose_Concentration\"") Points: (0.00, 1.5), (3.30, 1.5), (6.60, 3.0), (9.90, 5.0), (13.20, 7.5), (16.50, 10.5), (19.80, 50.0), (23.10, 80.0), (26.40, 95.0), (29.70, 100.0), (33.00, 100.0)		Dimensionless	Hall, J. E., & Hall, M. E. (2020). Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences. taken from insulin production graph, figure 79-9.
○	"24_hours_blood_glucose_sample_as_a_reference"	GRAPH(TIME) Points: (7.00, 4.290429043), (7.50, 4.400440044), (8.50, 5.830583058), (9.50, 4.95049505), (10.50, 4.675467547), (12.50, 4.510451045), (13.50, 5.665566557), (14.50, 5.390539054), (15.50, 4.895489549), (17.00, 4.675467547), (18.00, 4.675467547), (19.00, 6.160616062), (20.00, 5.500550055), (21.00, 5.115511551), (22.00, 4.730473047), (27.00, 4.290429043)		mmol/l	Freckmann, G., Hagenlocher, S., Baumstark, A., Jendrike, N., Gillen, R. C., Rössner, K., & Haug, C. (2007). Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. Journal of diabetes science and technology, 1(5), 695-703. (BMI) 22.6 ± 1.7 kg/m2] ~ 23 kg/m2 Assume height = 1.74 because height is not given, took from the previous reference mode. => weight = 1.74*1.74 *23 = 69.63 ~ 70 kg remember initializing blood glucose in gram = 3.9 gram (has taken from the

					reference above) since 3.9 gram = 4.3 mmol/l
○	Average_BMR_per_Day	("Average_BMR/Kg")*(Body_Weight)		kcal/day	United Nations University, & World Health Organization. (2004). Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17-24 October 2001 (Vol. 1). Food & Agriculture Org. Total BMR by taking whole body weight under consideration => Average BMR per day =("Average_BMR/Kg") * (Body_Waight) BMR= Basal Metabolic rate.
○	"Average_BMR/Kg"	GRAPH(Body_Weight) Points: (45.00, 25.50), (50.00, 24.75), (55.00, 23.50), (60.00, 22.50), (65.00, 21.50), (70.00, 20.50), (75.00, 20.00), (80.00, 19.25), (85.00, 19.00), (90.00, 19.50)		kcal/kg/day	United Nations University, & World Health Organization. (2004). Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17-24 October 2001 (Vol. 1). Food & Agriculture Org. Basal metabolism rate (BMR) is the minimum energy required by our body per kg of body weight the graph here is the average for men,women in two different age groups (30-59.9 and greater than 60 years both women and men)
○	Body_Weight_in_Kg	103		Kg	1.for Insulin resistance participants Weight =103 kg 2.Freckmann, G., Hagenlocher, S., Baumstark, A., Jendrike, N., Gillen, R. C., Rössner, K., & Haug, C. (2007). Continuous glucose profiles in healthy subjects under everyday life conditions and after different meals. Journal of diabetes science and technology, 1(5), 695-703. (BMI) 22.6 ± 1.7 kg/m2] ~ 23 kg/m2 Assume height = 1.74 because height is not given, took from the previous reference mode. => weight = 1.74*1.74 *23 = 69.63 ~ 70 kg remember initializing blood glucose in gram = 3.9 gram (has taken from the reference above) since 3.9 gram = 4.3 mmol/l
○	Both_insulin_and_fat_effect_on_adipose_tissue_glucose_Utilization	GRAPH(Effect_of_Insulin_on_Glucose_Utilization*Normalized_IAF_Effect) Points: (0.000, 0.000), (0.100, 0.33583091167), (0.200, 0.560945103841), (0.300,		unitless	The effect of insulin to produce glucose transporter increases during reduction of fat, therefore =Effect_of_Insulin_on_Glucose_Utiliza

		0.7118436595), (0.400, 0.812993986277), (0.500, 0.880797077978), (0.600, 0.926246849528), (0.700, 0.956712742486), (0.800, 0.977134641257), (0.900, 0.99082384938), (1.000, 1.000)			tion*Normalized_IAF_Effect
○	Cyclic_time_Generator	24*INT(TIME/24)		Hr	To generate a cyclic time every 24 hours.
○	"Cyclic_time_Generator_for_multiples_of_24-31"	IF TIME < 31THEN 0 ELSE 24*(1+INT ((TIME-31)/24))		Hr	To generate a cyclic clock for time between 24-31 because simulation starts at 7 oclock and one day ends at 31.
○	Daily_fat_intake	0		gram/hour	Daily fat intake is total amount of fat taken per hour.
○	Day_to_hour_converter	1		Days/hour	one day is 24 hours, in this variable one day is distributed to 24 hours.
○	Effect_of_BMI_on_%_Fat_in_the_body	GRAPH(BMI) Points: (15.00, 17.00), (20.00, 27.50), (25.00, 37.50), (30.00, 45.50), (35.00, 52.00), (40.00, 57.50), (45.00, 61.00)		Dimensionless	Meeuwsen, S., Horgan, G. W., & Elia, M. (2010). The relationship between BMI and percent body fat, measured by bioelectrical impedance, in a large adult sample is curvilinear and influenced by age and sex. Clinical nutrition, 29(5), 560-566. From the graph, as BMI increases body fat also increases
○	"Effect_of_BMI_on_VAT(IAF)"	GRAPH(BMI) Points: (24.30, 0.630), (25.2727272727, 0.7245), (26.2454545455, 0.8845), (27.2181818182, 1.0365), (28.1909090909, 1.200), (29.1636363636, 1.323), (30.1363636364, 1.4765), (31.1090909091, 1.625), (32.0818181818, 1.760), (33.0545454545, 1.918), (34.0272727273, 2.045), (35.00, 2.155)		unitless	Ferrannini, E., Sironi, A. M., Iozzo, P., & Gastaldelli, A. (2008). Intra-abdominal adiposity, abdominal obesity, and cardiometabolic risk. European heart journal supplements, 10(suppl_B), B4-B10.:- there is a difference between man and women intra abodminal fat/Visceral Adipose Tissue (IAF or VAT) based on BMI but now average is taken from the graph on the reference
○	Effect_of_Glucagon_on_Liver_glycogenolysis	GRAPH(Normalized_Glucagon) Points: (0.2000, 0.000), (0.4500, 0.600), (0.7500, 1.300), (1.0000, 1.483)		gram/kg/hr	Ramnanan, C. J., Edgerton, D. S., Kraft, G., & Cherrington, A. D. (2011). Physiologic action of glucagon on liver glucose metabolism. Diabetes, Obesity and Metabolism, 13, 118-125. Has taken from figure 3.
○	Effect_of_IAF_on_IAF_Glucose_uptake	(7+(23/"Effect_of_BMI_on_VAT (IAF)"))		unitless	Virtanen, K. A., Iozzo, P., Hällsten, K., Huupponen, R., Parkkola, R., Janatuinen, T., ... & Knuuti, J. (2005). Increased fat mass compensates for insulin resistance in abdominal obesity and type 2 diabetes: a positron-emitting

					tomography study. Diabetes, 54(9), 2720-2726 the graph or the formula found on the above reference shows that as the intra-abdominal fat (IAF) increases the glucose uptake on the fat decrease.
○	Effect_of_IAF_on_Muscle_Glucose_Uptake	(15+(30/"Effect_of_BMI_on_VAT(IAF)"))		unitless	Ferrannini, E., Sironi, A. M., Iozzo, P., & Gastaldelli, A. (2008). Intra-abdominal adiposity, abdominal obesity, and cardiometabolic risk. European heart journal supplements, 10(suppl_B), B4-B10 Muscle Glucose uptake decreases as Intra-abdominal fat (IAF) increases (Has inverse relation)
○	Effect_of_Insulin_on_Glucose_Utilization	GRAPH(Insulin_in_the_blood/100) Points: (0.000, 0.00669285092428), (0.100, 0.0179862099621), (0.200, 0.0474258731776), (0.300, 0.119202922022), (0.400, 0.26894142137), (0.500, 0.500), (0.600, 0.73105857863), (0.700, 0.880797077978), (0.800, 0.952574126822), (0.900, 0.982013790038), (1.000, 0.993307149076)		Dimensionless	Rizza, R. A., Mandarino, L. J., & Gerich, J. E. (1981). Dose-response characteristics for effects of insulin on production and utilization of glucose in man. American Journal of Physiology-Endocrinology And Metabolism, 240(6), E630-E639. on Fig 3 as Insulin concentration increases Glucose utilization follows an S shape, here the effect is running between 0 and 1 since glucose utilization rate varies in different tissues.
○	Effect_of_PAL_on_%_of_%VO2_Max	GRAPH(PAL) Points: (1.4000, 25.00), (1.4590, 31.50), (1.5180, 38.00), (1.5770, 44.50), (1.6360, 51.00), (1.6950, 57.50), (1.7540, 64.00), (1.8130, 70.50), (1.8720, 77.00), (1.9310, 83.50), (1.9900, 90.00)		Dimensionless	Burton, D. A., Stokes, K., & Hall, G. M. (2004). Physiological effects of exercise. Continuing Education in Anaesthesia Critical Care & Pain, 4(6), 185-188. Vo2 % increases as working rate increases=> %Vo2 proportion to Physical activity level
○	"Effect_of_VO2_on_Carbohydrate_and_fat_share_(Untraind)"	((Effect_of_PAL_on_%_of_%VO2_Max*1.16)-6)/100	INIT "Effect_of_VO2_on_Carbohydrate_and_fat_share_(Untraind)" = IF PAL >= 1.4 AND PAL <= 1.69	Dimensionless	Holloszy, J. O., Kohrt, W. M., & Hansen, P. A. (1998). The regula-tion of carbohydrate and fat metabolism during and after exer-cise. Front Biosci, 3, D1011-D1027 Calculate the Carbohydrate share as a function of % Vo2 40-100% Vo2 max and %Vo2 max less than 40 % is described on the paragraph next to figure 1. additional reference which shows the

			THEN (172.4* PAL-201.36) ELSE IF PAL > 1.69 AND PAL <=1.99 THEN (172.4* PAL-253.1) ELSE IF PAL > 1.99 AND PAL <= 2.4 THEN (125*P AL-210) ELSE 0		share of fat demand increases as % Vo2 max decreases 2. (Wolfe, R. R. (1998). Metabolic interactions between glucose and fatty acids in humans. The American journal of clinical nutrition, 67(3), 519S-526S. Calculate the carbohydrate and fat share at 25% Vo2 Max).
○	Fat_effect_on_BMI	GRAPH(New_fat_percentage) Points: (17.00, 15.00), (27.50, 20.00), (37.50, 25.00), (45.50, 30.00), (52.00, 35.00), (57.50, 40.00), (61.00, 45.00)		Kilograms/Meters^2	Ferrannini, E., Sironi, A. M., Iozzo, P., & Gastaldelli, A. (2008). Intra-abdominal adiposity, abdominal obesity, and cardiometabolic risk. European heart journal supplements, 10(suppl_B), B4-B10.:- data has taken from the effect of BMI on Fat.
○	Fat_free_mass	Body_Weight_in_Kg-(HISTORY(Fat_weight_in_the_body,0))		Kg	Fat free mass = Total mass (Total body weight) - Fat mass.
○	Fat_Share_as_Energy	(1-"Effect_of_VO2_on_Carbohydrate_and_fat_share_(Untraind)")*(Time_based_Energy_Expenditure_Sedentary_or_light_activity_life_style)		Kcal/Hours	Calculation of fat share from total energy expenditure for sedentary life.
○	Fat_weight_in_the_body	(Body_Weight*Effect_of_BMI_on_%_Fat_in_the_body)/100		Kg	Body fat calculation based on the total body weight (Body_Weight*Effect_of_BMI_on_%_Fat_in_the_body)/100
○	Full_day_Scheduled_glucose_intake_for_measuring_Blood_glucose	STEP("Food_intake_for_24_hours_Blood_glucose_Con._test", 7.5)-STEP("Food_intake_for_24_hours_Blood_glucose_Con._test",7.6)		gram	Freckmann, G., Hagenlocher, S., Baumstark, A., Jendrike, N., Gillen, R. C., Rössner, K., & Haug, C. (2007). Continuous glucose profiles in healthy subjects under everyday life conditions

		+ STEP("Food_intake_for_24_hours_Blood_glucose_Con._test", 12.5)- STEP("Food_intake_for_24_hours_Blood_glucose_Con._test",12.6)+STEP("Food_intake_for_24_hours_Blood_glucose_Con._test", 18)- STEP("Food_intake_for_24_hours_Blood_glucose_Con._test",18.1)			and after different meals. Journal of diabetes science and technology, 1(5), 695-703. 50 gram is administered orally 3 times daily during testing blood glucose concentration for normal volunteries.
○	Glucagon_Production	GRAPH("\"Blood_Glucose_Concentration\"") Points: (0.00, 100.0), (3.30, 83.33333333), (6.60, 23.33333333), (9.90, 17.14285714), (13.20, 11.9047619), (16.50, 9.523809524), (19.80, 8.80952381), (23.10, 8.80952381), (26.40, 8.80952381), (29.70, 8.80952381), (33.00, 8.80952381)		Dimensionless	Hall, J. E., & Hall, M. E. (2020). Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences. Took from FIGURE 79-10, glucagon level as a function of blood glucose concentration.
○	Glucose_energy_Required	"Effect_of_VO2_on_Carbohydrate_and_fat_share_(Untraind)"*0.825*(Time_based_Energy_Expenditure_Sedentary_or_light_activity_life_style)		Kilocalories/Hours	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Glucose utilization grouped in to 6 tissues in the body. Brain between 45-60 %(Avg.52.5%), skeletal muscle between 15-20% Avg.17.5%), kidney between 10-15% (Avg. 12.5%) blood cells between 5-10% Avg.7.5%), Splanchnic organ between 3-6% Avg.4.5%), and Adipose tissue 2-4% Avg.3%), Muscle share is 17.5 and then the rest 100-17.5 = 82.5 considered as Glucose energy Required
○	glucose_gram_to_mmol	5.5		mmol/grams	Riemsma, R., Ramos, I. C., Birnie, R., Büyükkaramikli, N., Armstrong, N., Ryder, S., ... & Kleijnen, J. (2016). Integrated sensor-augmented pump therapy systems [the MiniMed® Paradigm™ Veo system and the Vibe™ and G4® PLATINUM CGM (continuous glucose monitoring) system] for managing blood glucose levels in type 1 diabetes: a systematic

					review and economic evaluation. Health technology assessment (Winchester, England), 20(17), 1. Appendix 5 table 86 1 mg/dl =18.18*mmol/l mmol/l = 0.055 mg/dl =>mmol/mg=5.5
○	Glucose_required_as_Energy	(Glucose_energy_Required/Kcal_to_glucose_gram)		Grams/ Hours	Unit is changed from Kcal/hour to gram/hour.
○	Glucose_required_by_Adipose_tissue	0.036*Glucose_required_as_Energy		Grams/ Hours	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Glucose utilization grouped in to 6 tissues in the body., one of the tissues is adipose tissues Average from the total glucose utilization is 3% but now glucose is deducted to skeletal muscles then Adipose tissue share is 3/(82.5)=0.036 = 3.6 %
○	Glucose_required_by_Brain	0.6666*Glucose_required_as_Energy		Grams/ Hours	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Glucose utilization grouped in to 6 tissues in the body. These include the brain 45-60 % (55% taken from the rest of the tissues) of the total but now the remaining glucose is calculated from the remaining value of glucose used by the muscle this implies 55/ (100-17.5) = 0.666 = 66.67 %
○	Glucose_required_by_Splanchnic_Organs	0.2969*Glucose_required_as_Energy		Grams/ Hours	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Glucose utilization grouped in to 6 tissues in the body. this varible inclues kidney, blood cell and Splanchnic organs kidney is between 10-15% (Avg. 12.5%) blood cells is between 5-10% Avg.7.5%), Splanchnic organ is between 3-6% Avg.4.5%) 24.5/82.5=0.2969=> 29.69 % of glucose is for Splanchnic Organs.
○	Glycogen_Ener	"Effect_of_VO2_on_Carbohydrat		Kilocal	Bano, G. (2013). Glucose homeostasis,

	gy_Required	e_and_fat_share_(Untraind)"*0.175*(Time_based_Energy_Expenditure_Sedentary_or_light_activity_life_style)		ories/Hours	obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Muscle is using Glycogen as a glucose, glucose utilized by the muscle is 15-20% of the total glucose average =17.5%
○	Glycogen_Gap	(Maximum_Muscle_glycogen_Capacity-Muscle_Glycogen)		Gram	Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259. during usage of glucose by muscle, the glycogen level will decrease in the Muscle storage => Glycogen Gap = (Maximum_Muscle_glycogen_Capacity-Muscle_Glycogen)
○	Glycogen_Required_by_Muscle	(Glycogen_Energy_Required/Kcal_to_glucose_gram)		Grams/Hours	Bano, G. (2013). Glucose homeostasis, obesity and diabetes. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(5), 715-726. Muscle is using Glycogen as a glucose, glucose utilized by the muscle is 15-20% of the total glucose average =17.5% and the unit is changed to gram /hour.
○	gm_to_mg	1000		mg/grams	
○	gm_to_mmol	5.5		mmol/gm	
○	Height	1.74		meter	
○	Indicated_BMI	Fat_effect_on_BMI		Kilograms/Meters^2	Delay is 1 hour since our daily activity and our diet is set up in this model in hourly base.
○	Initial_fat	Fat_weight_in_the_body*kg_to_gram		Grams	Initial Body fat is from the initial body weight.
○	Initial_Glucagon_in_the_blood	GRAPH("\"Blood_Glucose_Concentration\"") Points: (0.00, 100.0), (3.30, 83.33333333), (6.60, 23.33333333), (9.90, 17.14285714), (13.20, 11.9047619), (16.50, 9.523809524), (19.80, 8.80952381), (23.10, 8.80952381), (26.40, 8.80952381), (29.70, 8.80952381), (33.00, 8.80952381)		Dimensionless	This variable is only to initialize the Glucagon stock in the body since we have initial value of blood glucose. Hall, J. E., & Hall, M. E. (2020). Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences. taken from Glucagon production graph.

○	Initial_insulin_in_the_blood	GRAPH("\"Blood_Glucose_Concentration\"") Points: (0.00, 1.5), (3.30, 1.5), (6.60, 3.0), (9.90, 5.0), (13.20, 7.5), (16.50, 10.5), (19.80, 50.0), (23.10, 80.0), (26.40, 95.0), (29.70, 100.0), (33.00, 100.0)		Dimensionless	This variable is only to initialize the insulin stock in the body since we have initial value of blood glucose. Hall, J. E., & Hall, M. E. (2020). Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences. taken from insulin production graph.
○	Initial_Liver_Glycogen	GRAPH("\"Blood_Glucose_Concentration\"") Points: (5.000, 0.00), (5.500, 40.00), (6.000, 80.00)		Gram	liver glycogen begins to decrease when there is low amount of glucose in the blood vessel, and when blood glucose is above the normal range, liver glycogen become full
○	Insulin_production_test	1		Dimensionless	Insulin production test is normally 1 but we can vary to see different senario by varying from 0 to 1, * 1 means pancreas produces 100% ...normal person. * 0.5 means pancreas produces 50%....has problem on pancreas productivity example diabetic type 2. * 0 means pancreas do not work example on diabetic type I.
○	Kcal_to_fat_gram	9		kcal/gram	Tirone, T. A., & Brunicardi, F. C. (2001). Overview of glucose regulation. World journal of surgery, 25(4), 461. one gram fat gives 9 kcal energy
○	Kcal_to_glucose_gram	4		kcal/gram	Tirone, T. A., & Brunicardi, F. C. (2001). Overview of glucose regulation. World journal of surgery, 25(4), 461. one gram Carbohydrate gives 4 Kcal energy.
○	kg_to_gram	1000		grams/kg	1 kg = 1000 gram
○	LG_Rate	(Liver_Glycogen_synthesis_Rate *Total_blood_volume)/glucose_gram_to_mmol		Grams/Hours	Roden, M., Perseghin, G., Petersen, K. F., Hwang, J. H., Cline, G. W., Gerow, K., ... & Shulman, G. I. (1996). The roles of insulin and glucagon in the regulation of hepatic glycogen synthesis and turnover in humans. The Journal of clinical investigation, 97(3), 642-648. Glycogen synthesis in the liver taken from from figure 3 the unit is changed from mmol/l/hr to gm/hr. LG =Liver glycogen synthesis rate.
○	Liver_Glycogen_synthesis_Rate	GRAPH(Insulin_in_the_blood) Points: (4.00, 0.00), (4.10, 4.30), (5.60, 4.50), (7.20, 5.40), (8.40, 9.60), (10.60, 24.00), (11.20, 25.80), (14.00, 27.00)		mmol/l/hr	1.Roden, M., Perseghin, G., Petersen, K. F., Hwang, J. H., Cline, G. W., Gerow, K., ... & Shulman, G. I. (1996). The roles of insulin and glucagon in the regulation of hepatic glycogen synthesis

					and turnover in humans. The Journal of clinical investigation, 97(3), 642-648. Glycogen synthesis in the liver have taken from from figure 3.
○	Maximum_Muscle_glycogen_Capacity	300		Gram	1. Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259. the normal muscle glycogen storage is 300-700 gram now in this model we are considering people who is in sedentary lifestyle, 300 g
○	New_fat_percentage	(Total_Fat/(Body_Weight*kg_to_gram))*100		grams/kg	Calculation of fat from the whole-body fat.
○	Non_fat_weight_reduction_rate_due_to_gluconeogenesis	Gluconeogenesis_Rate-Fat_share_on_Gluconeogenesis		gram/hour	Difference between total Gluconeogenesis rate- Fat share on Gluconeogenesis, Non-fat means from protein and others converted to glucose when less blood glucose in the blood vessel, the process is gluconeogenesis.
○	Normalized_Effect_of_IAF_on_Muscle_Glucose_uptake	Effect_of_IAF_on_Muscle_Glucose_Uptake/62.6		unitless	The value varies from 0 to 1 to simplify the mathematical relation.
○	Normalized_Glucagon	Glucagon_in_the_blood/100		Dimensionless	
○	Normalized_IAF_Effect	Effect_of_IAF_on_IAF_Glucose_uptake/43.5		unitless	Making simplified for calculation purpose, the variable run between 0 and 1.
○	PAL	1.4		Dimensionless	United Nations University, & World Health Organization. (2004). Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17-24 October 2001 (Vol. 1). Food & Agriculture Org. " PAL = Physical activity level 1.Sedentary or light activity lifestyle (1.40-1.69=PAL value). 2. Active or moderately active lifestyle (1.70-1.99=PAL value). 3. Vigorous or vigorously active lifestyle (2.00-2.40=PAL value)."
○	Policy_base_carbohydrate_inta	DELAY(Policy_Model.Desired_hourly_corbohydrate_intake,1.5,		gram/hour	1.Choy, S., Hénin, E., van der Walt, J. S., Kjellsson, M. C., & Karlsson, M. O.

	ke	0)			(2013). Identification of the primary mechanism of action of an insulin secretagogue from meal test data in healthy volunteers based on an integrated glucose-insulin model. Journal of pharmacokinetics and pharmacodynamics, 40(1), 1-10. Carbohydrate delay in the gastrointestinal tract varies from 45-90 minutes due to digestion due to digestion of complex carbohydrates. 90 minute has taken as a delay in the Gastrointestinal tract.
○	Policy_base_Fat_daily_intake	Policy_Model.Fat_daily_intake_adjustment_Rate*Policy_Model.policy_switch		Grams/ Hours	
○	Reference_mode_after_weight_Reduction	GRAPH(TIME) Points: (7.000, 7.260726073), (7.500, 8.800880088), (8.000, 11.00110011), (9.000, 11.60616062), (10.000, 10.0110011)		mmol/liter	Henry, R. R., Wallace, P., & Olefsky, J. M. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. Blood glucose concentration is changed from mg/dl to mmol/l
○	Reference_Mode_Before_treatment	GRAPH(TIME) Points: (7.000, 14.85148515), (7.500, 18.15181518), (8.000, 20.62706271), (9.000, 20.0770077), (10.000, 17.32673267)		mmol/l	Henry, R. R., Wallace, P., & Olefsky, J. M. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. Blood glucose concentration is changed from mg/dl to mmol/l
○	Required_Fat_in_gram	Fat_Share_as_Energy/Kcal_to_fat_gram		Grams/ Hours	Unit is changed from Kcal/hour to gram/hour.
○	Scheduled_glucose_intake_for_measuring_Blood_glucose	STEP("Food_intake_for_Blood_glucose_Con._test", 7)-STEP("Food_intake_for_Blood_glucose_Con._test",7.1)		Gram	Henry, R. R., Wallace, P., & Olefsky, J. M. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. 75 gram of glucose is administered orally to measure blood glucose concentration in the morning both before and after weight reduction.
○	Share_of_Gluconeogenesis	GRAPH(Total_new_Glucose_production_per_kg) Points: (0.0000, 0.000), (0.0900, 0.000), (0.1000, 0.640), (0.1300, 0.820), (0.1500, 0.960)		Dimensionless	1.Rothman, D. L., Magnusson, I., Katz, L. D., Shulman, R. G., & Shulman, G. I. (1991). Quantitation of hepatic glycogenolysis and gluconeogenesis in fasting humans with 13C NMR. Science, 254(5031), 573-576. share of Gluconeogenesis on total glucose production According to the journal gluconeogenesis at 22 hours fasting is

					64 %,36 hours is 82% and 54 hours 96 % of glucose is from gluconeogenesis. there for the maximum share is 96 % at 0.15
○	Share_of_Gluconeogenesis_from_the_total_Production	Share_of_Gluconeogenesis*Total_new_Glucose_production_per_kg*Body_Weight		Grams/ Hours	Chourpiliadis, C., & Mohiuddin, S. S. (2020). Biochemistry, gluconeogenesis. StatPearls [Internet]. share of final gluconeogenesis
○	Share_of_Liver_Glycogenesis	(Total_new_Glucose_production_per_kg*Body_Weight)-Share_of_Gluconeogenesis_from_the_total_Production		Grams/ Hours	
○	Start_Time	7		Hour	
○	Stop_time	10		Hour	
○	Time_based_Energy_Expenditure_Sedentary_or_light_activity_life_style	IF(("Food_intake_for_Blood_glucose_Con._test">0)OR ("Food_intake_for_24_hours_Blood_glucose_Con._test">0)) THEN (STEP(32.7/8,7)-STEP(32.7/8,10000))* (Total_Energy_Expenditure*Day_to_hour_converter/100) ELSE ((STEP(6.3,7+Cyclic_time_Generator)- STEP(6.3, 7.5+Cyclic_time_Generator)+ STEP(4.11,7.5+Cyclic_time_Generator)- STEP(4.11, 7.8+Cyclic_time_Generator)+ STEP(5.48, 7.8+Cyclic_time_Generator)- STEP(5.48, 8.8+Cyclic_time_Generator)+ STEP(32.88/8, 8.8+Cyclic_time_Generator)- STEP(32.88/8, 14+Cyclic_time_Generator)+ STEP(4.11,14+Cyclic_time_Generator)- STEP(4.11, 14.3+Cyclic_time_Generator)+ STEP(32.88/8, 14.3+Cyclic_time_Generator)- STEP(32.88/8, 17+Cyclic_time_Generator)+ STEP(5.48, 17+Cyclic_time_Generator)- STEP(5.48, 18+Cyclic_time_Generator)+ STEP(5.75, 18+Cyclic_time_Generator)- STEP(5.75,		Kcal/Hours	United Nations University, & World Health Organization. (2004). Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17-24 October 2001 (Vol. 1). Food & Agriculture Org. Sedentary or light activity life style scheduled as follows 1.Sleeping..8 hour...21.92% 2.Personal care (dressing, showering)...1 hour...6.30% 3.Eating...1 hour...4.11% 4.Cooking....1 hour...5.75% 5.Sitting(Office work, selling, produce, tending shop)...8 hour...32.88% 6.General household work...1 hour...7.67% 7.Driving car to/from work...1 hour...5.48% 8.Walking at varying paces without a load...1 hour...8.77% 9.Light leisure activities (watching TV, chatting)...2 hour...7.12%

		19+Cyclic_time_Generator)+ STEP(4.11, 19+Cyclic_time_Generator)- STEP(4.11, 19.4+Cyclic_time_Generator)+ STEP(8.77, 19.4+Cyclic_time_Generator)- STEP(8.77, 20.4+Cyclic_time_Generator)+ STEP(6.3, 20.4+Cyclic_time_Generator)- STEP(6.3, 21+Cyclic_time_Generator)+ STEP(7.12/2, 21.+Cyclic_time_Generator)- STEP(7.12/2, 23+Cyclic_time_Generator)+ STEP(21.92/8,23+Cyclic_time_Generator)- STEP(21.92/8,24+Cyclic_time_Generator)+ STEP(21.92/8,24+"Cyclic_time_Generator_for_multiples_of_24-31")- STEP(21.92/8,31+"Cyclic_time_Generator_for_multiples_of_24-31"))* Total_Energy_Expenditure*Day_to_hour_converter)*1/100			
○	Time_needed_for_Glucagon_to_reach_the_cells	0.3		Hr	Hall, J. E., & Hall, M. E. (2020). Guyton and Hall textbook of medical physiology e-Book. Elsevier Health Sciences. Glucagon hormone make change on blood concentration level within 20 minutes.
○	Time_needed_for_glycogen_synthesis	24		Hr	Murray, B., & Rosenbloom, C. (2018). Fundamentals of glycogen metabolism for coaches and athletes. Nutrition reviews, 76(4), 243-259. time require for resynthesis of Glycogen is 24 hours.
○	Time_needed_for_insulin_to_reach_the_cells	0.5		Hr	1.Fu, Z., R Gilbert, E., & Liu, D. (2013). Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Current diabetes reviews, 9(1), 25-53. Insulin fully reaches to blood stream 30 minutes Basal insulin =20-30 pmol/l and delay 30 min 30 minute =0.5 hour.

○	Time_needed_to_change_BMI	1		Hour	Model run every 1 hour, therefore time =1 hour.
○	Time_needed_to_change_Weight	1		Hours	Model run every 1 hour, therefore time =1 hour
○	Time_needed_to_GIT_to_release_all_type_of_carbohydrate_to_be_assimilated	2.15		Hours	Choy, S., Hénin, E., van der Walt, J. S., Kjellsson, M. C., & Karlsson, M. O. (2013). Identification of the primary mechanism of action of an insulin secretagogue from meal test data in healthy volunteers based on an integrated glucose-insulin model. Journal of pharmacokinetics and pharmacodynamics, 40(1), 110 From the graph average time needed for glucose absorption =2.15 hours
○	Time_needed_to_ingest	0.1		Hour	
○	Total_blood_volume	5		Liters	Sani, M. H., & Khosroabadi, S. (2020). A novel design and analysis of high-sensitivity biosensor based on nano-cavity for detection of blood component, diabetes, cancer and glucose concentration. IEEE Sensors Journal, 20(13), 7161-7168. Average blood volume = 5 liter
○	Total_Carbohydrate_intake	Policy_base_carbohydrate_intake +((Full_day_Scheduled_glucose_intake_for_measuring_Blood_glucose+Scheduled_glucose_intake_for_measuring_Blood_glucose)/Time_needed_to_ingest)		gram/hour	Sum of the carbohydrate taking rate as a diet.
○	Total_Energy_Expenditure	PAL*Average_BMR_per_Day		kcal/day	United Nations University, & World Health Organization. (2004). Human Energy Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation: Rome, 17-24 October 2001 (Vol. 1). Food & Agriculture Org. Total Energy required per day:the daily required amount of energy depending on the type of physical activity PAL*Average_BMR_per_Day = total energy Expenditure where PAL = Physical Activity Level.
⊕	Total_Fat	Total_daily_fat_intake + Body_Fat + Fat_stored_from_Glucose		Grams	Total fat = fat in the body + daily fat intake + fat from glucose.
○	Total_Glucose_	Glycogen_Required_by_Muscle+		gram/h	Total glucose required by the body cell

	required	Glucose_required_by_Adipose_tissue+Glucose_required_by_Splanchnic_Organs+Glucose_required_by_Brain		our	in order to function well.
○	Total_new_Glucose_production_per_kg	GRAPH(Glucagon_in_the_blood) Points: (0.0, 0.0000), (70.0, 0.0000), (80.0, 0.0420), (95.0, 0.1500), (100.0, 0.1500)		grams/kg/hour	Rizza, R. A., Mandarino, L. J., & Gerich, J. E. (1981). Dose-response characteristics for effects of insulin on production and utilization of glucose in man. American Journal of Physiology-Endocrinology And Metabolism, 240(6), E630-E639. on Fig 3. it is as a function of insulin but changed to as a function of glucagon concentration since Insulin and Glucagon inversely proportional (calculated from insulin and glucagon production).
○	total_Oxidized_glucose	Muscle_Glycogenesis_Rate+Adipose_Tissue_glucose_utilization_Rate+Splanchnic_Organs_Glucose_Oxidation_Rate+Brain_Glucose_Oxidation_Rate		gram/hour	
○	Unit_Fat_per_Unit_Glucose	0.316		unitless	Jensen, J., Rustad, P. I., Kolnes, A. J., & Lai, Y. C. (2011). The role of skeletal muscle glycogen breakdown for regulation of insulin sensitivity by exercise. Frontiers in physiology, 2, 112 *475 gram converted to 150 g lipid/ day Calculation conversion rate =475/ (24) =19.79 gram per hour =0.3665 mmol/l/minute and 3.17g glucose is converted to 1 gram fat 1gram glucose =0.316-gram fat
	Policy_Model:				
	Desired_intake_Glucose(t)	Desired_intake_Glucose(t - dt) + (Glucose_required_Rate - Glucose_removal_rate) * dt	INIT Desired_intake_Glucose = 400	Gram	Desired intake glucose is the total glucose required by the cell, the initial value for the first day is given because glucose as energy requirement is every seconds demand since all the cells need enough glucose, on the other hand the policy is designed to have a diet three times a day(that means we cannot get instantaneously the amount of glucose that the body used) , there for in order to calculate the total energy, the first day is initialized by some amount of glucose but for the next day the model by itself calculates the amount of glucose from today.

	Glucose_removal_rate	Desired_intake_Glucose/One_day_duration		gram/hour	Glucose removal rate is taking out all amount of glucose requested by the cell (before 24 hours of the stock desired intake glucose) in order to calculate today glucose from yesterday.
	Glucose_required_Rate	Explanatory_Model.Total_Glucose_required*policy_switch		Grams/Hours	Policy based total required glucose rate by the body cell
	"Policy_Adj_._period"	1/(Policy_duration/(3))		Per Hour	the gap we want to adjust each hour ((1/3 due to the adt. rate) hourly gap adj fraction, each hour the gap closes the goal a minimum of 15%, when the fat oxidation is grater, the gap approaches the goal more than 15%.
	BMI_Goal	25		kg/m2	BMI Goal is 25 kg/m2 since 25 is the upper limit of healthy BMI (kg/m2) healthy BMI ≤ 25, overweight between 25 and 35. obese BMI ≥ 35. Hasan, N. M., Johnson, K. F., Yin, J., Baetz, N. W., Fayad, L., Sherman, V., . . . Zachos, N. C. (2021). Intestinal stem cell-derived enteroids from morbidly obese patients preserve obesity-related phenotypes: Elevated glucose absorption and gluconeogenesis. Molecular metabolism, 44, 101129.
	Breakfast	((STEP(1,7.5+Cyclic_time_Generator)-STEP(1,7.51+Cyclic_time_Generator))*Breakfast_1)*Desired_intake_Glucose		Gram	Breakfast is at 7.5 hour (7:30 A.M in the morning every day)
	Breakfast_1	1/5		unitless	Henry, R., Wallace, P., & Olefsky, J. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. Given (1/5=0.2) from the daily consumption of carbohydrate 1/5 is given at breakfast time.
	Carbohydrate_intake_calibration_coefficient	1		Dimensionless	Daily carbohydrate intake= (Carbohydrate intake calibration coefficient) * (Total daily energy expenditure) where, Carbohydrate intake calibration coefficient (CICC) shows how much (percentage or it can be between 0 and 1) is the daily carbohydrate intake relative to total daily energy

					expenditure. CICC = Total Energy Oxidized / Total Glucose Given.
○	Cyclic_time_Generator	24*INT(TIME/24)		Hour	To generate a cyclic time every 24 hours.
○	Desired_hourly_corbohydrate_intake	Desired_Meal_time_Carbohydrate_Intake*Carbohydrate_intake_calibration_coefficient/Required_Time		gram/hour	Desired hourly carbohydrate intake relies on the type of Policy following (Policy A or Policy B) by varying Carbohydrate intake calibration Coefficient (CICC).
○	Desired_Meal_time_Carbohydrate_Intake	(((Dinner+Lunch+Breakfast))*policy_switch)		Gram	Recommended glucose amount during the policy period.
○	Dinner	((STEP(1,19+Cyclic_time_Generator)-STEP(1,19.1+Cyclic_time_Generator))*Dinner_1)*Desired_intake_Glucose		Gram	Breakfast is at 19 hours (7:00 P.M in the evening every day).
○	Dinner_1	2/5		unitless	Henry, R., Wallace, P., & Olefsky, J. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. Given (2/5=0.4) from the daily consumption of carbohydrate 2/5 is given at Dinner time
○	Effect_of_BMI_goal_on_%_Fat_in_the_body	GRAPH(BMI_Goal) Points: (15.00, 17.00), (20.00, 22.21), (25.00, 29.54), (30.00, 37.84), (35.00, 45.75), (40.00, 52.51), (45.00, 58.49)		Dimensionless	Reference:Meeuwsen, S., Horgan, G. W., & Elia, M. (2010). The relationship between BMI and percent body fat, measured by bioelectrical impedance, in a large adult sample is curvilinear and influenced by age and sex. Clinical nutrition, 29(5), 560-566. From the graph, as BMI increases body fat also increases
○	Effective_Fat_Goal	Fat_Goal*policy_status		Gram	
○	Fat_daily_intake_adjustment_Rate	(Fat_Gap*"Policy_Adj_._period")+Explanatory_Model.Fat_Oxidation_Rate		gram/hour	Desired hourly fat intake to reach the goal.
○	Fat_Gap	Effective_Fat_Goal-Explanatory_Model.Total_Fat		Gram	The difference between the actual fat and the goal of fat.
○	Fat_Goal	((Explanatory_Model.Body_Weight_in_Kg*Effect_of_BMI_goal_on_%_Fat_in_the_body)/100)*Explanatory_Model.kg_to_gram		Gram	30.4 kg =30400 gram => healthy BMI maximum value is 25 kg/m2 =30.4 kg
○	Lunch	((STEP(1,14+Cyclic_time_Generator)-STEP(1,14.1+Cyclic_time_Gener		gram	Lunch is at 14 hours (2 P.M every day)

		ator))*Lunch_1)*Desired_intake_Glucose			
○	Lunch_1	2/5		unitless	Henry, R., Wallace, P., & Olefsky, J. (1986). Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes, 35(9), 990-998. Given (2/5=0.4) from the daily consumption of carbohydrate 2/5 is given at Lunch time
○	One_day_duration	24		Hour	One day duration is designed to take out the amount of glucose required by the body the day before yesterday, that means in desired intake glucose intake stock only holds one day glucose (24 hour)
○	Policy_duration	(Policy_end_Time-Policy_start_Time)		Hour	
○	Policy_end_Time	2167		Hour	
○	Policy_start_Time	7		Hour	
○	policy_status	IF policy_switch = 1 AND TIME > Policy_start_Time THEN 1 ELSE 0		Dimensionless	
○	policy_switch	0		Dimensionless	Policy switch become 1 when policy is on and 0 when policy is off.
○	Required_Time	0.1		Hour	

Run Specs	
Start Time	Explanatory Model.Start Time
Stop Time	Explanatory Model.Stop time
DT	1/10
Fractional DT	True
Save Interval	0.1
Sim Duration	1.5
Time Units	Hour
Pause Interval	0
Integration Method	Euler
Keep all variable results	True
Run By	Run

Calculate loop dominance information	True
Exhaustive Search Threshold	1000

Array Dimension	Indexed by	Elements
PAL_Exostive	Number	1
PAL_Moderate	Number	1
PAL_Sedentary	Number	1