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Study the Effect of Drug "Statin" On Hepatic Lipid Metabolism Using System Biology Approach

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Abstract

In developing countries, the cardiovascular diseases (CVD) are the major cause for death. Statin is the preferred medication for the treatment of cardiovascular diseases. The main objective of our research is to simulate the hepatic lipid metabolism (existing model) with drug of specific concentration and identify the effect on other metabolic molecules of the model and identify that how drug molecule associated with diseases like atherosclerosis and dyslipidemia in hepatic lipid metabolism. In our research, we are using mathematical modeling and computer simulation to study the effect of the drug "Statin" on lipid metabolism. Our research is very useful to investigate that how drug affects or reduce the LDL level.

1. Introduction

Metabolism is the total of all reactions occurring in the human body. The purpose of metabolism is to provide energy for the synthesis of proteins, nucleic acids, lipids and functioning of the body of the organisms. Metabolism is a highly interactive process in which many components convert to other new components or molecules according to the body requirement, for example- during a fast, our body need more energy for functioning of body and that energy comes from stored energy molecules - glycogen. This glycogen stores in the liver, adipose and muscles tissues and on hydrolysis or degradation releases energy. Cells are more complicated; they are capable of doing metabolic reactions and obtaining energy at the right time. It is important for the body to regulate the metabolic pathway because if any metabolic pathway of our body synthesizes a molecule more than or less than the requirement,

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it leads to metabolic diseases. In the human body, the reactions that occurs are known as the metabolic reactions and these metabolic reactions occurred in a specific way (or in series) are known as the metabolic pathway **(Lehninger, Nelson, and Cox 2013a)**. The metabolic pathway is of various types like some are straight or linear, branched, and circular. For example, glycolysis is a linear pathway process and citric acid cycle, or TCA cycle is a circular pathway. The molecules or components involved in metabolic reactions are known as the metabolite. Metabolic reactions that take place in the body are catalyzed by enzymes (protein molecule act as a catalyst). Metabolism is of two types: anabolism and catabolism. We shall briefly discuss them.

Anabolism involves the formation of molecules like amino acids, lipids, proteins, polysaccharides etc. The reactions involved in anabolism are called anabolic reactions. These anabolic reactions require the energy in the form of ATP, NADPH and NADH **(Pang et al. 2016)**. Therefore, anabolism is also known as the synthesis phase of metabolism. Anabolic reactions synthesize molecules to store the energy in a suitable form, so that when the body needs energy then that stored molecules break into release energy. For example, when pyruvate forms glucose, this is known as the gluconeogenesis, and when glucose form glycogen, this is known as glycogenesis.

Catabolism involves the breakdown of the molecules into smaller molecules and releases the energy in the form of ATP. Therefore, catabolism is also known as the degradative phase of metabolism and the reactions involved in the catabolism is known as the catabolic reactions. Like we discussed in anabolism about gluconeogenesis and glycogenesis, if we reverse these two processes then that shows catabolism. For example, In a liver, glycogen breakdown takes place to release glucose-6-phosphates, This is known as glycogenolysis and when glucose-6-phosphate breaks to form pyruvate, this is known as the glycolysis **(Lehninger, Nelson, and Cox 2013b)**.

There are various types of metabolism in the body like metabolism of proteins, amino acids, lipid etc. Each of these metabolisms have different metabolic pathways but they are interconnected with another metabolic pathways somewhere. The disease associated with metabolism is known as the metabolic syndrome or disease. In our research we are studying the effect of drug molecules on the hepatic lipid metabolism.

1.1 Lipid metabolism

Lipid metabolism describes lipid processes like lipid formation, lipid degradation, and storage. Lipids are the molecules that are involved in the storage of energy in the form of fatty molecules. There are various examples of the lipids: cholesterol, triacylglycerides (TAG), phospholipids, waxes, and vitamins. There are also various forms of lipids like storage lipids and structural lipids. Storage lipids are those lipid molecules that store energy such as fat and

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oil molecules, cholesterol. Lipids store large amounts of energy in the form of fatty molecules. Lipids also provide insulation to mammals which live in water to protect them from freezing, they form a fatty - thick layer called blubber which helps to warm them. Lipids form steroid hormones which are very helpful in cell-to-cell communication and regulate the growth and development of metabolism. On the other hand, the structural lipids provide strength, integrity, and mechanical support to the cell membrane. One specialized property of structural lipids is that they are amphipathic that means their one side is hydrophilic (ability to mix with water or water loving) and other side is hydrophobic (away from water). Lipid are synthesized in different forms via different metabolic pathway like synthesis of cholesterol (or mevalonate pathway), synthesis of phospholipids. In liver, cholesterol biosynthesis pathway, glycolysis pathway, fatty acid synthesis pathway is interlinked and responsible for the synthesis of the lipoprotein particle in which lipid molecules combine with protein for the transportation. Fig. 1-1, show that composition of these lipoproteins, HDL contain more protein than cholesterol and it is very helpful to carry LDL return to the liver. LDL contains more cholesteryl ester which is involved in the formation of the plaque in the blood vessel so we can say that LDL is more harmful lipoprotein. When a dietary chylomicrom digests in small intestine, they enter in blood vessel where lipoprotein lipase hydrolyzes them and release free fatty acid and chylomicron remnant these remnants enter the liver and use for another metabolic reactions. The VLDL molecules release from liver and enter in blood vessels, where lipoprotein lipase releases free fatty acid by hydrolyzing them and remaining VLDL remnant goes into liver and some of VLDL convert to IDL which further form LDL. This LDL goes into extrahepatic tissues (Fig. 1-2) and deposits there. High amount of LDL leads to atherosclerosis diseases. There are various types of lipoprotein particles present in our body. The description of these lipoprotein are as follows:

- Chylomicron,
- Very Low-Density Lipoproteins (VLDL),
- Low Density Lipoprotein (LDL),
- Intermediate Density Lipoprotein (IDL),
- High Density Lipoprotein (HDL).

Chylomicron

Chylomicrons are rich in lipid content (triacylglycerides) but less in protein and contain apoB-48, apoC-II and apoC. They are synthesis in small intestines and move through lymphatic system to enter the blood. In the blood chylomicron is hydrolyzed by lipoprotein lipase (LPL) to release free fatty acid and chylomicron remnant. These remnants are taken up by the liver.

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Very Low-Density Lipoprotein (VLDL)

Very Low-Density Lipoproteins (VLDL) are formed by the conversion of fatty acid into triacylglycerides with apolipoproteins in the liver. These VLDL composed of apoC-I, apoC-II, apoC-III, apoB-100, cholesterol, cholesteryl esters and triacylglycerides. When VLDL moves to blood their hydrolysis takes place by LPL by apoC-II leads to release of free fatty acid and VLDL remnants.

Intermediate Density Lipoprotein (IDL)

Intermediate density lipoproteins (IDL) are the VLDL remnants. When the triacylglycerol level reduces in VLDL molecules by the action of lipoprotein lipase (LPL), this leads to the formation of the intermediate density lipoprotein.

Low Density Lipoprotein (LDL)

Low density lipoproteins (LDL) have more cholesteryl esters (CE), major apolipoprotein (apoB-100) and a larger amount of cholesterol. LDL carries fats and cholesterol to other body tissues, but if it is present in very high amount in the blood, they deposited to form plaque which is called atherosclerosis. LDL is also known as bad cholesterol.

High Density Lipoprotein (HDL)

High density lipoproteins (HDL) are the lipoprotein particles that contain more protein content as compared to other lipoprotein particles. It formed and secreted by liver and small intestine. Apolipoprotein like apoA-I, apoC-I, apoC-II presents in HDL. It is also known as good cholesterol because whenever LDL level increases and deposits in the blood artery, this leads to diseases like atherosclerosis, dyslipidemia, stroke, angina, and other heart related diseases. HDL functions to remove these depositions of extra lipid (or LDL) and protect the body from harmful diseases. HDL is also known as good cholesterol.

1.2 Diseases associated with lipid metabolism

Dyslipidemia

Dyslipidemia is metabolic syndrome in which overproduction of lipoprotein takes place. Lipid amount reaches high in the blood also leads to dyslipidemia. Different types of dyslipidemia also categorized:

- In the first one of dyslipidemia, the LDL level reaches a high.
- In the second one of dyslipidemia, the HDL level reaches low.
- In the third one of dyslipidemia, the Triglyceride (TAG) level reaches a high.

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Atherosclerosis

Atherosclerosis is the plaque or deposition of LDL in blood artery, due to this artery lumen space is decreased this leads to the decrease in blood flow (fig.1-3) Atherosclerosis is appear in age of 35 years old in men. Food with high amount of fats and cholesterol is the main reason for atherosclerosis. The treatment involves surgical methods and medications. In surgical methods involves angioplasty (surgery which used to increase the space of the artery or veins to treat atherosclerosis) and other method involve the use of medication like statin, fibrates, niacin are the drugs used to treat atherosclerosis. In our research, we are using statin drug to treat atherosclerosis **(Brown 2002)**.

1.3 Inhibitors

The chemical reactions that occur in our body are called biochemical reactions. These biochemical reaction groups into series form metabolic pathways. Each chemical reaction in metabolic pathway is catalyzed by the catalyst (enzymes). A compound forms a metabolic pathway in each step which further participates in the reaction and leads to the formation of product at the end of the metabolic pathways. Inhibitors are the molecules that affect the reactions by slowing or stopping them. Inhibitors of enzymes (or also known as the enzyme inhibitors) are the molecules that affect or decrease enzyme activity, when bound with them. When metabolic reactions or pathway synthesize more product than the requirement, then these enzyme inhibitors bind with enzymes and inhibit the reactions. Inhibitors are those that inhibit the reactions, so if any molecule that bind with enzymes and increases their activity, then they are not inhibitors instead they are enzyme activators, for example - fructose 2,6 - bisphosphate, it is activator of the enzyme phosphofructokinase 1, it activates this enzyme and increases glycolysis rate. There are three types of inhibition:

1. Competitive inhibition

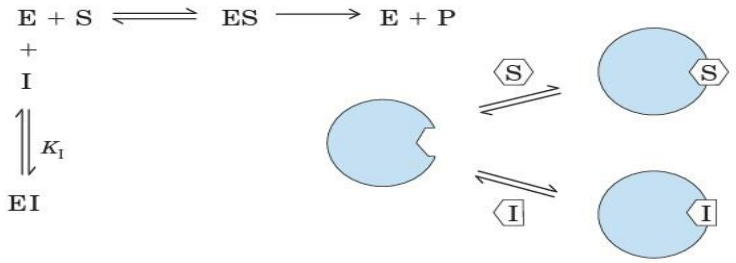

Figure 1-4: Competitive inhibition (adopted from leninger)

This type of inhibition shows the competition between the substrate and the inhibitor bound with enzymes. Fig 1-4 shows when inhibitor binds with enzyme, then it forms enzyme inhibitor (EI) complex.

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2. Uncompetitive inhibition

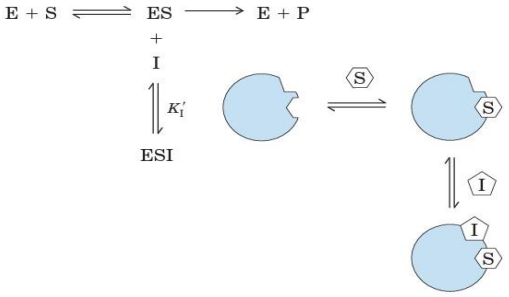

Figure 1-5: Uncompetitive inhibition (adopted from leninger)

This type of inhibition shows (fig 1-5), when enzyme bind with substrate to form the enzyme-substrate complex (ES), the inhibitor binds with these enzyme-substrate to form ESI complex.

3. Noncompetitive inhibition

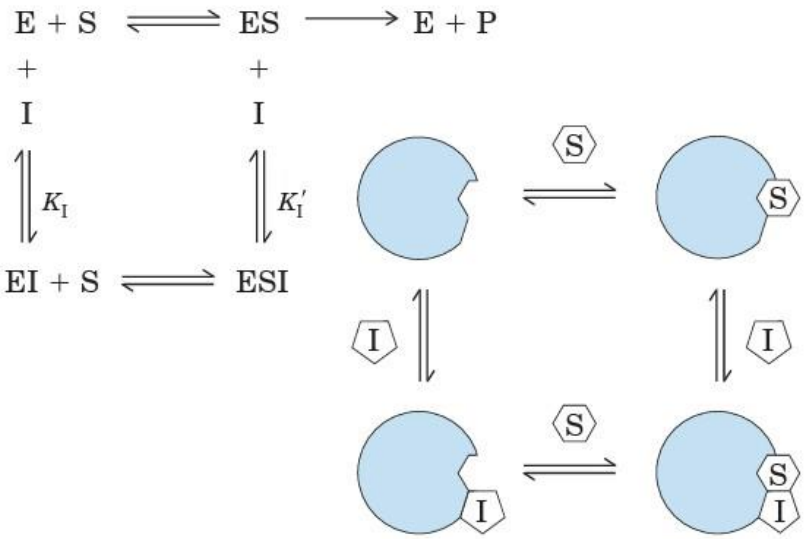

Figure 1-6: Noncompetitive inhibition (adopted from leninger)

In this type of inhibition, inhibitors have the ability to bind with enzyme substrate complex (ES) or enzyme only. Fig 1-6 show when inhibitor binds with enzyme it forms enzyme inhibitor (EI) complex and when inhibitor binds with ES, it forms enzyme substrate inhibitor (ESI) complex.

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There are various kinds of drugs available for the treatment of metabolic syndrome but in our research, we are going to study the effect of Statin on the hepatic lipid metabolism. Statin are the drug used for the decreases of the cholesterol level by inhibiting the HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, also abbreviated as HMGCR) enzyme in cholesterol biosynthesis pathway (or mevalonate pathway) and leads to the reduction in cardiovascular diseases (fig 1-7). Statin binds with HMG-CoA reductase in cholesterol pathway, due to which further reactions in this pathway stop and lead to the reduction in cholesterol level. Statin absorbs excess cholesterol from blood (fig 1-8). There are different types of statins available in the market: rosuvastatin, lovastatin, atorvastatin, simvastatin, Fluvastatin, pit-vastatin.

Statins are also known as HMG-CoA reductase inhibitors. This drug is prescribed by doctors to lowers cholesterol level. Rosuvastatin (fig 1-9) is a category of statin which is used in our research. There structure described below:

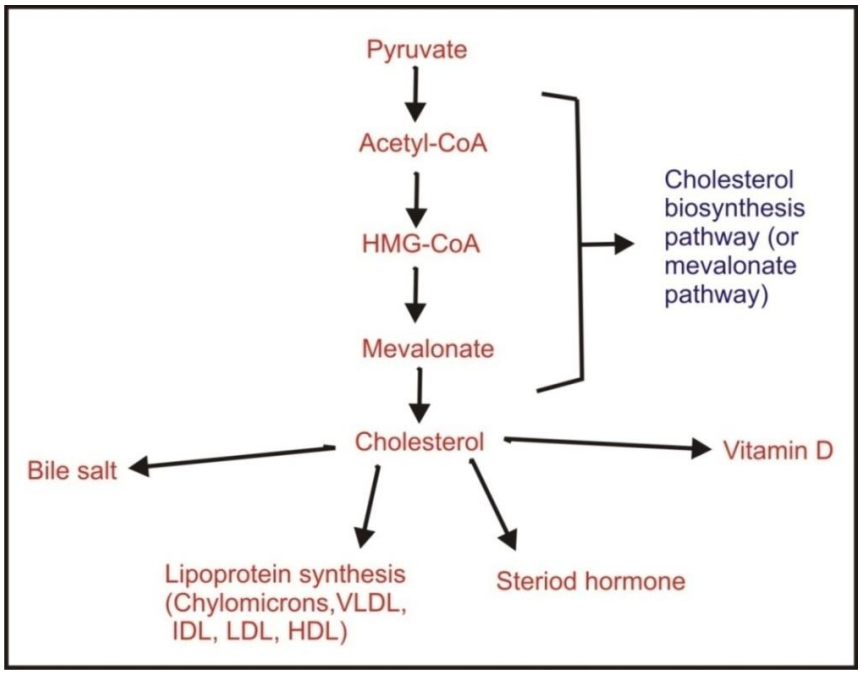

Figure 1-7: Mevalonate pathway

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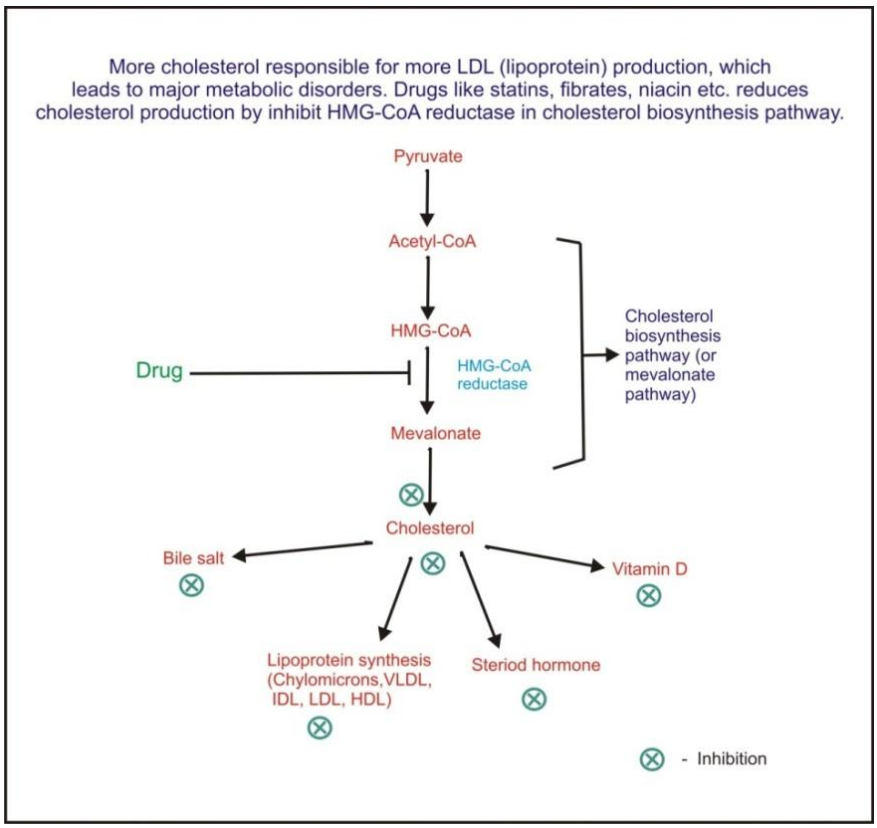

Figure 1-8: Showing drug effects on mevalonate pathway

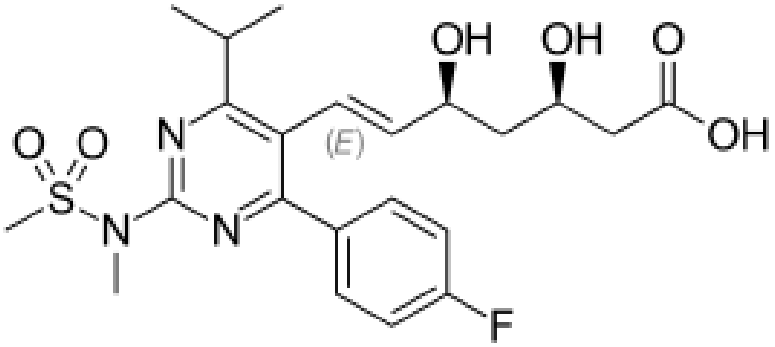

Fig 1-9: Rosuvastatin drug structure

1.4 Mathematical model

The real problem include the all information relevant to the system or the process like as how many genes interact with each other, how drug molecule affect the biological system etc. **(Ingalls 2013)**. Biological systems are more complex and complicated to understand. To understand biochemical pathways, diseases pathway, physiology of the organisms and other

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biological processes, system biology is used. The main objective of system biology is to predict behavior of the system with the help of technologies like bioinformatics, proteomics, genomics, computational and mathematical modeling and simulation **(Nandikolla and Shaik 2011)**. Mathematical modeling and simulation are the one of the most important approaches in system biology. The recent trend in system biology is from theoretical to prediction sciences, and this prediction ability is very useful to investigate the results of therapeutic ways. The importance of system biology is to discover the properties and description, which is possible by the technologies of system biology and modeling. Mathematical modeling is the study of processes by using formulas, math concepts, and ODE equations. The major role of mathematical modeling in system biology is to create framework for the generation of hypothesis and prediction based on the time course simulation. There are various softwares of system biology available like MATLAB, celldesigner, copasi, cytoscape, yEd etc. These softwares exchange files in SBML (System biology markup language). SBML are the medium for representation and exchange of biochemical network **(Hucka et al. 2003)** The modeling is also useful for the drug discovery and also helpful to analyze the site (or point) easily in disease pathway where drug binding takes place **(Prathipati and Mizuguchi 2016).**

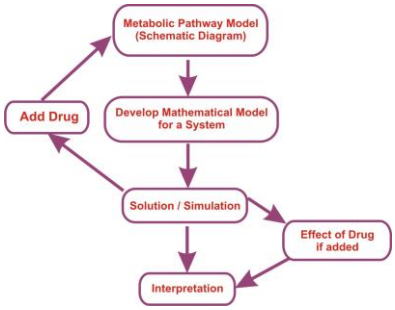

Figure 3-1: Flow chart summarization of methodology which we are adopting.

The flow chart in fig 3.1 represents the general overview of methodology which we are using in the dissertation. The work is divided in the two parts. The first one is to develop mathematical model of chosen system, here we have chosen hepatic lipid metabolism. Fig 3.2 represents the schematic diagram of hepatic lipid metabolism.

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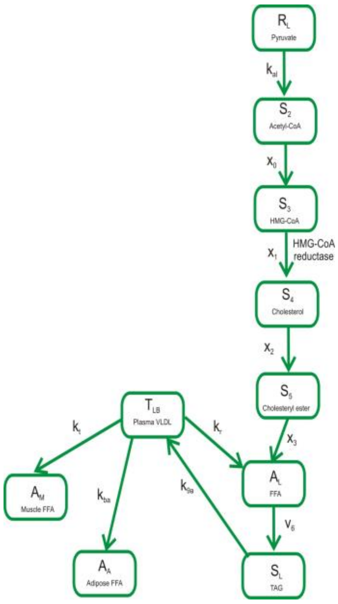

Figure 1-1: Schematic diagram showing model of lipid metabolism.

$$\frac{dR_L}{dt} = \frac{1}{\propto_L}(-\,k_{al}R_L I) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

$$\frac{dS_2}{dt} = \frac{1}{\propto_L}(k_{al}IS_2 - x_0S_2) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

$$\frac{dS_3}{dt} = \frac{1}{\propto_L}(x_0S_3 - x_1S_3) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

$$\frac{dS_4}{dt} = \frac{1}{\propto_L}(x_1S_4 - x_2S_4) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

$$\frac{dS_5}{dt} = \frac{1}{\propto_L}(x_2S_5 - x_3S_5) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

$$\frac{dA_L}{dt} = \frac{1}{\propto_L}\left(k_rT_{LB} + x_3S_5 - \frac{v_6A_L}{k_6 + A_L}\right) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (6)$$

$$\frac{dS_L}{dt} = \frac{1}{\propto_L}\left(\frac{v_6A_L}{k_6+A_L} - k_{9a}S_L\right) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (7)$$

$$\frac{dT_{LB}}{dt} = k_{9a}S_L - k_rT_{LB} - k_tT_{LB} - k_{ba}T_{LB} \ldots\ldots\ldots\ldots\ldots\ldots\ldots (8)$$

Equations (1-8) represent the mathematical model which is corresponding to the schematic diagram as drawn in fig 3.2. These derivations of ODE introduce variables corresponding to the evolution of various species over time. We use R_L to represent liver pyruvate, S_2 for acetyl CoA, S_3 for HMG-CoA, S_4 for cholesterol, S_5 for cholesteryl ester, A_L for FFA, S_L for TAG, T_{LB} for plasma VLDL, A_A for adipose FFA and A_M for muscle FFA. The rate constant k_{al} used for conversion of R_L to S_2, x_0 used for conversion of S_2 to S_3, x_1 used for conversion for S_3 to

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S_4, x_2 used for conversion of S_4 to S_5, x_3 used for conversion of S_5 to A_L, V_6 used for conversion of A_L to S_L, S_L used for conversion of S_L to T_{LB}, k_t used for conversion of T_{LB} to A_M, k_{ba} used for conversion of T_{LB} to A_A, k_r used for conversion of T_{LB} to A_L and K_i used inhibitor (drug) rate constant.

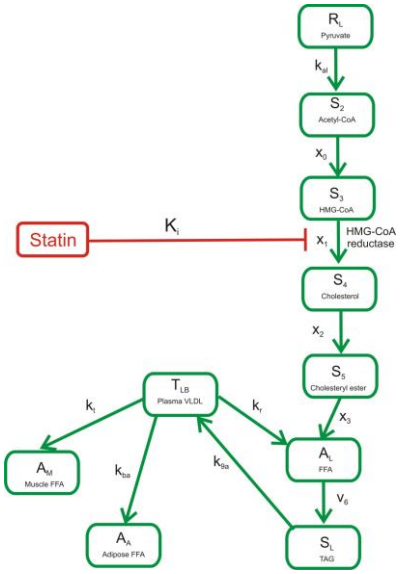

Figure 1-2: Schematic diagram showing drug effect on model of lipid metabolism.

$$\frac{dR_L}{dt} = \frac{1}{\propto_L}(-k_{al} I R_L) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (9)$$

$$\frac{dS_2}{dt} = \frac{1}{\propto_L}(k_{al} I S_2 - x_0 S_2) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (10)$$

$$\frac{dS_3}{dt} = \frac{1}{\propto_L}(x_0 S_3 - x_1 S_3) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (11)$$

$$v = \frac{V_{max}[S_3]}{[S_3]+K_m(1+K_i[Statin])} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (12)$$

$$V_{max} = K_m[E] \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (13)$$

$$\frac{dA_L}{dt} = \frac{1}{\propto_L}\left(k_r T_{LB} + x_3 S_5 - \frac{v_6 A_L}{k_6 + A_L}\right) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (14)$$

$$\frac{dS_L}{dt} = \frac{1}{\propto_L}\left(\frac{v_6 A_L}{k_6+A_L} - k_{9a} S_L\right) \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (15)$$

$$\frac{dT_{LB}}{dt} = k_{9a} S_L - k_r T_{LB} - k_t T_{LB} - k_{ba} T_{LB} \dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots\dots (16)$$

As we have discussed earlier in the objective section of the introduction, we would like to see the effect of drug "Statin" on the lipid metabolism (fig 3-3). Thus, we have added drug as shown in schematic diagram according to previous model **(Pratt, Wattis, and Salter 2015b)**.

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Therefore, we can develop mathematical model equations (9-16) with the incorporation of drug using law of mass action & kinetics mass balance.

1.2 List of parameters

Table 3.1 summarizes the initial value of the variable during simulation. The value used for the parameter and, source further value are quoted in Table 3-2 **(Pratt, Wattis, and Salter 2015b).**

Table 3.1: Represent the initial values.

Description	Notation of Variables	Initial values
Liver pyruvate	R_L	0.37 mmol/l
Acetyl CoA	S_2	870 µM
HMG-CoA	S_3	0.1 µM
Cholesterol	S_4	0.4 µM
Cholesteryl ester	S_5	0.4 µM
Liver FFA	A_L	0.57 mmol/l
Liver TAG secretory pool	S_L	0.0149 mmol/l
Muscle FFA	A_M	0.53 mmol/l
Plasma endogenous LP TAG	T_{LB}	1 mmol/l
Adipose FFA	A_A	0.57 mmol/l

Table 3.2: Rate constant values used in simulation.

Rate constant	Values
k_{al}	0.00002 $l^2 mmol^{-1} min^{-1}$
x_0	0.00169 l/min
x_1	45 mmol/l
x_2	5l/min
K_i	5l/min
K_m	45µM
x_3	4l/min
[E]	5.5×10^{-3} mmol/l

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2. Result and discussions

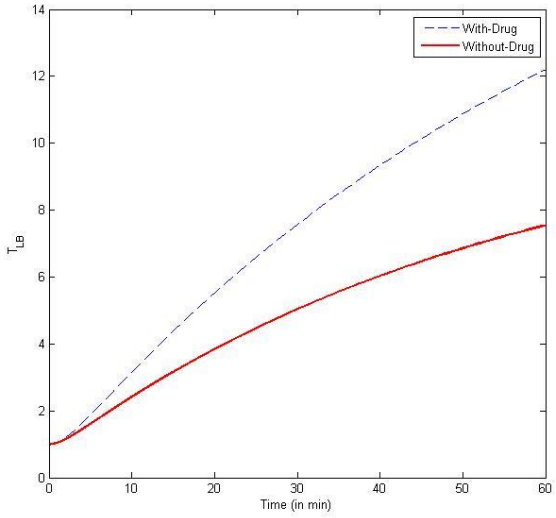

Figure 4-1: Simulation of T_{LB} with time

The T_{LB} (Plasma VLDL) molecule which is represented by dotted line in the simulation show that VLDL amount increases with time from 1 mmol/l to above 12 mmol/l. The red line represents that when we add drug, they reduced the T_{LB} concentration from above 12 mmol/l to below 8 mmol/l in fig 4-1. This proved that the drug "Statin" responsible for the reduction of T_{LB}.

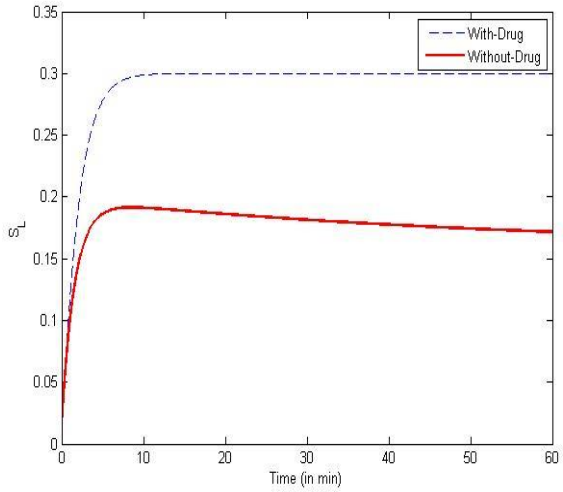

Figure 4-2: Simulation of S_L with time

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The dotted line represents the concentration of SL increases from 0.0149 mmol/l to 0.3 mmol/l and then remains constant over time. The red line represents the concentration of S_L which is decreases from 0.3 mmol/l to below 0.2 mmol/l in time (in min.) from 0 to 60 and further after adding drug with the model, this proved that drug responsible for the reduction of S_L (liver TAG) in fig 4-2. Therefore, we can say that SL concentration was also reduced due to the inhibition of the enzyme HMG-CoA reductase in cholesterol biosynthesis pathway (or mevalonate pathway).

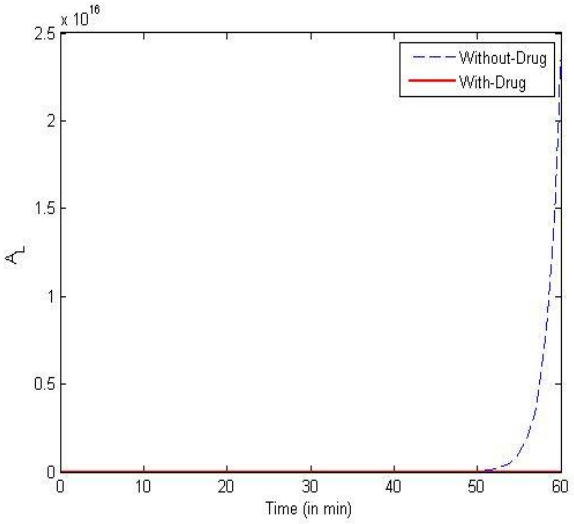

Figure 2-3: Simulation of A_L with time.

The dotted line in the simulation shows the concentration of A_L which remains constant for 50 minutes and then suddenly starts increasing with time up to 2 mmol/l. The red line shows the concentration of A_L with time which remains constant over time after adding drug with the model in fig 4-3. This proves that drug stops the A_L production.

3. Conclusions

Acetyl CoA is a very important molecule of our metabolism. It is produced by pyruvate, when pyruvate dehydrogenase complex catalyzes the conversion of pyruvate to acetyl coal molecule. This acetyl CoA further participates in other metabolic pathways like citric acid cycle or tricarboxylic cycle, cholesterol biosynthesis pathway or mevalonate pathway. In our experiment depend on lipid metabolism which is related to cholesterol synthesis pathway. When acetyl CoA enters the cholesterol synthesis pathway, they form HMG-CoA molecule which further convert into mevalonate by the action of enzyme HMG-CoA reductase (this is rate limiting step in the cholesterol synthesis pathway), mevalonate further convert squalene then to cholesterol. Then this cholesterol further participates in lipoprotein synthesis like Chylomicrons, VLDL, LDL, IDL, HDL. Some lipoprotein like VLDL, LDL are known as bad

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cholesterol because they deposit in blood artery and cause cardiovascular diseases like dyslipidemia, atherosclerosis. Medication include drug therapy like Statin, fibrates, niacin etc. In our experiment we analyze the effect of drug on this pathway. We take a drug of 0.050 mmol/l of amount and bind this to HMG-CoA reductase, then simulate the equations , then we find that in presence of this drug the production of cholesterol reduced which leads to reduction in T_{LB} (Plasma VLDL, which is responsible for the production of LDL), A_L (FFA) and S_L (TAG) and simulation which we obtained are predict the behavior of the molecule. So, we can say that reduction in cholesterol leads to reduction in fat molecules (which in excess concentration responsible for major metabolic diseases) are further responsible for reduction in diseases. These simulations also explain that at 0.050 mmol/l amount of drug "Statin" responsible for the reduction of lipoproteins molecules, through which we can further predict that what concentration of Statin is optimum for reduction of the cholesterol. If VLDL further forms free fatty acid in the muscle and adipose tissue. So, if VLDL concentration decreases after drug effect, then FFA concentration of muscle and adipose tissue also reduced. The stoichiometry matrix analysis shows the number of reactants and products which participate in the model.

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