Integration of glucose and lipid metabolism: In silico models of adipose tissue and blood

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Introduction

Currently 311 million worldwide suffer from devastating complications of Type 2 Diabetes Mellitus (T2DM) [1], which is characterised by high blood glucose level accompanied by defective pancreatic insulin secretion and peripheral insulin resistance. Plasma free fatty acids (FFA) level fluctuates to maintain normal blood glucose level. Adipose tissues undergo lipogenesis and lipolysis to regulate plasma FFA level, such that a low plasma FFA level increases glucose uptake in skeletal muscle cells, and inhibits hepatic glucose production. Being a multi-factorial and polygenic disease, there is no direct distinctive cause that initiates the onset of T2DM. Yet, a common condition found among type 2 diabetics is elevated plasma FFA level [2]. Expansion in fat mass among obese individuals has been shown to result in elevated plasma FFA levels, and indeed, 80% of type 2 diabetics are obese [3]. Obesity, however, cannot explain the link between elevated plasma FFA levels among the 'lean' type 2 diabetics. Moreover, less than 10% of the obese population have T2DM [4], and in fact the metabolically healthy but obese individuals (MHO) exhibit normal blood glucose and plasma FFA level [5]. The differential mechanisms of lipid metabolisms among the obese diabetics, lean diabetics and MHOs remain unknown; especially as reliable *in vivo* data across adipose tissues are difficult to obtain both from laboratory and clinical settings. This research aimed to study, *in silico*, how alterations along the lipid metabolic pathways in adipose tissue regulate flux of FFA into blood, as well as their corresponding effects on blood glucose levels.

Methods and Materials

Design: A 2-compartment mathematical model between blood and adipose tissue was constructed. The sequence of interactive steps was modulated by M, the dietary glucose intake, simulated in the form of 3 consecutive oral glucose doses over a 12-hour period. 4 major metabolic pathways involved were: i) plasma insulin (I) upregulates glucose uptake from blood (Gb) to adipose tissues (GG), while I suppresses Gb and Gb promotes the rise of I; ii) lipogenesis, the synthesis of triglycerides (TG) from GG and from fatty acids (FA) in adipose tissues; iii) lipolysis, the breakdown of TG to FA in adipose tissue, with (I)-stimulated pathways inhibiting lipolysis; iv) FA enter blood and become free fatty acids (FFA) by simple diffusion, as shown in Figure 1. Ordinary differential equations (ODEs) were formulated to describe the change in concentration of substrates across the 12-hour period, as shown in Table 1. Parameters a, b1, b2, c and p, correspond to specific reaction rate constants for each corresponding metabolic reaction; while parameters k, q, r, x and y, represent sensitivity levels of specific reactants to each corresponding stimulus, as depicted in Figure 1 and Table 1. Simulations of ODEs were run in XPPAUT.

Assumptions: As this was only an adipose tissue-blood model, the effects of liver, skeletal muscles and pancreas on glucose homeostasis were not directly modelled. Thus Gb was reliant on M and I only, physical activity and active consumption of glucose elsewhere was assumed to be negligible. Also the regulatory role of FFA on Gb was omitted where FFA promotes hepatic gluconeogenesis and reduces glucose uptake in skeletal muscles. As no fasting condition was simulated, the effect of glucagon was also excluded in this study.

Model validation: Parameters were manually tuned and estimated by comparing against the published behaviour of the time-course variation of Gb, I and FFA in blood as shown in healthy individuals under conditions that, after an overnight fast, 3 high-sucrose diets were given to them every 4 hours, over a total time period of 12 hours [6]. Initial concentrations of Gb, I, FFA, GG, TG and FA, i.e. their concentration at t=0, after an overnight fast and before taking meals, were adopted from [6], [7], [8], and [9]. Figure 2 shows the simulations and clinical data of Gb, I, FFA and TG. The simulations fit qualitatively to the trend as shown in clinical blood test data from [6].

Qualitative parameter sensitivity analysis: Each parameter (i.e. a, b1, b2, c, x, y, p, q, r and k) was varied in degrees of 10 times and 0.1 time of its original estimated value from the model validation. The maximum TG range obtained from 10 times and 0.1 time of a particular parameter was compared to the maximum TG range with the original set of estimated parameters. The number of folds of changes in TG range for each corresponding parameters were compared, hence to identify the top 3 parameters that TG was most sensitive to. The same procedures were performed to FFA. Also, the initial TG concentration was doubled and simulated to compare against healthy TG concentration in healthy individuals, thus to investigate the correlation of fat mass and FFA release.

Results and Discussion

Simulations of adipose tissue metabolism: The aim of this model was to study lipid metabolisms in adipose tissue, hence GG to TG was the only glucose utilization step modelled. Other routes that would otherwise be actively taking place, including oxidation of glucose for energy release and conversion of glucose to lactate, were not included. Simulation of abnormally elevated levels of GG agreed with [10] and confirmed the importance of these glycolytic pathways in maintaining normal glucose utilization in adipose tissues. Despite the abnormal simulated GG trend, simulated dynamics of TG and FA corresponded to inhibition of lipolysis imposed by I: as TG increases, FA decreases; TG peaks at the spot when FA dips, suggesting that lipogenesis and lipolysis are constantly taking place in the adipose tissue in a regulated state upon meal intake.

Disease hypotheses: Since the total body fat percentage among obese subjects is at least double that of healthy subjects, the initial TG concentration was varied to twice the healthy TG concentration. The resultant simulated FFA output range, as shown in Figure 3, was twice the healthy FFA range, and it fell into the elevated FFA range found in type 2 diabetic patients collected in [11], suggesting TG concentration in adipose tissues could be a risk factor for T2DM.

MHO: ‘x’, ‘k’ and ‘p’ are the top 3 parameters that TG was most sensitive to. Large values of ‘x’ represent a metabolic system that is highly sensitive to blood glucose concentration, resulting in an increased pancreatic insulin secretion; while a small ‘p’ and a large ‘k’ reciprocate high insulin sensitivity of the adipose tissue, thus lowering blood glucose level, increasing glucose uptake into adipose tissues for TG synthesis, and facilitating lipolysis. These findings are consistent with clinical blood tests from MHO [5], as they usually have a high TG storage in adipose tissues but normal blood glucose level and insulin concentration, yet an average or lower than average plasma FFA level, suggesting discrepancies in pancreatic insulin secretion, blood flow and insulin sensitivity of lipases could play the roles in the development of the MHOs. Our proposed mechanism is also consistent with the findings in [11], where MHO women are presented with high insulin sensitivity.

Lean T2DM: FFA was most sensitive to parameters ‘a’, ‘b1’ and ‘b2’. ‘b1’ determines the reaction rates of lipolysis, while ‘a’ and ‘b2’determine rate of TG synthesis. Since TG can only be made from glucose and pyruvate in the adipose tissues, ‘a’ refers to the process of TG synthesis from glucose and ‘b2’ refers to glyceroneogenesis, the process of synthesising TG from pyruvate. Figure 4 shows, at a reduced rate of glyceroneogenesis (0.1 times b2), plasma FFA level was raised and doubled to diabetic FFA level [12] and TG storage was lowered when compared to original sets of data. Assuming there is no ectopic fat deposition and their total fat content is of average as the healthy individuals, this simulation could be extended to a hypothesis of dysregulation of glyceroneogenesis to have a major impact on the development of T2DM among lean individuals; where studies from [13] have also suggested dysregulation of glyceroneogenesis and its key enzyme PEPCK-C to be involved in the development of T2DM.

Conclusion

A simple mathematical model has been generated to link blood glucose level to lipid metabolism in the adipose tissue, under the regulation of plasma insulin level. It successfully predicted in vivo lipid metabolism based on available blood metabolite data; postulated that with an expansion of fat mass, plasma FFA levels would be elevated; and provided insights into the possible underlying mechanisms to normal blood glucose and plasma FFA level among the MHO; as well as proposed a hypothesis in which a dysregulation of glyceroneogenesis might be the one of the underlying mechanisms to the progression of T2DM among lean individuals.

Table 1 shows ODEs describing the change in concentration of substrates with time.

Blood compartment	Adipose tissue compartment
ODE 1. The change of (Gb) over time: $\frac{dGb}{dt} = q*(M) - p*(Gb) - v*y*(I) - v*r*(I)$	ODE 4. The change of GG over time: $\frac{dGG}{dt} = p*(Gb) - a*(GG) + v*r*(I)$
ODE 2. The change of (I) over time: $\frac{dI}{dt} = z*x*(Gb)$	ODE 5. The change of TG over time: $\frac{dTG}{dt} = a*(GG) - b1*(TG) + v*k*(I) + b2*(FA)$
ODE 3. The change of FFA over time: $\frac{dFFA}{dt} = c*(FA - FFA)$	ODE 6. The change of FA over time: $\frac{dFA}{dt} = -c*(FA - FFA) - v*k*(FA - FFA) + b1*(TG) - b2*(FA)$

Figure 1

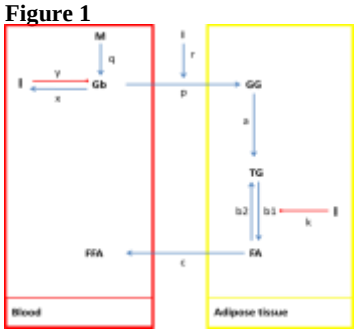

Figure 2

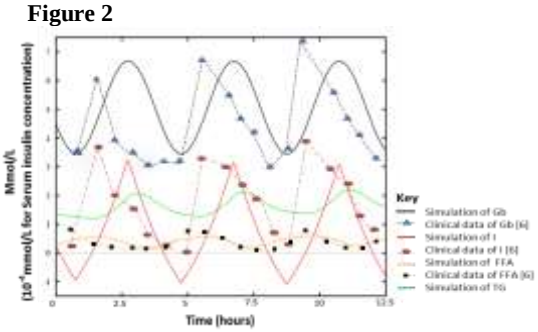

Figure 3

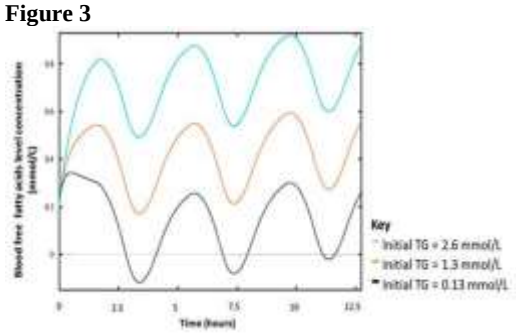

Figure 4

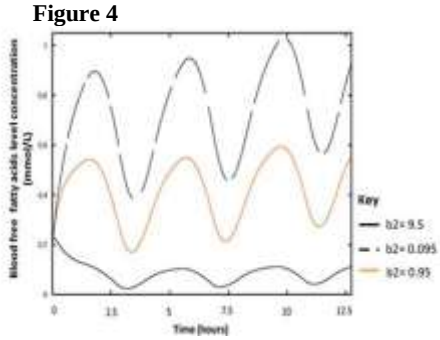

Figure 1.The framework of the metabolic pathway model; Figure 2. Simulated and Clinical trends of Gb, I, TG and FFA;
Figure 3. Simulated trends of TG at initial TG concentrations of 0.13mmol/L, 1.3mmol/L and 2.6mmol/L;
Figure 4. Simulated trends of FFA with parameter b2 in value of 0.095, 0.95, 9.5.

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