International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 2, 2017

Original Article

THE EFFECTS OF PHYSICAL EXERCISE ON THE INSULIN-DEPENDENT DIABETES MELLITUS SUBJECTS USING THE MODIFIED MINIMAL MODEL

AGUS KARTONO[a,b], FEBRI DWI IRAWATI[a], ARDIAN ARIF SETIAWAN[a], HERIYANTO SYAFUTRA[a], TONY SUMARYADA[a,b]

[a]Computational Biophysics and Molecular Modelling Research Group (CBMoRG), Department of Physics, Faculty of Mathematical and Natural Sciences, Bogor Agricultural University (IPB), Jalan Meranti, Building Wing S, 2nd Floor, Kampus IPB Dramaga, Bogor 16680, Indonesia, [b]Tropical Biopharmaca Research Center, Bogor Agricultural University (IPB), Jalan Taman Kencana No. 3, Bogor 16128, Indonesia
Email: akartono70@gmail.com

Received: 11 Oct 2016 Revised and Accepted: 21 Dec 2016

ABSTRACT

Objective: In this paper, the modified minimal model (MM) with a mathematical function for describing the insulin infusion rates was used to study of the effects of physical exercise on the dynamics of glucose and insulin on the insulin dependent diabetes mellitus (IDDM), including type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) subjects.

Methods: In an intravenous glucose tolerance test (IVGTT) procedure, a dose of glucose was administered intravenously to overnight-fasted subjects, 20 min after the glucose bolus, insulin was injected over 1-2 min either into the portal vein or into the femoral vein, and subsequently the glucose and insulin concentrations in plasma were frequently sampled (usually 30 times) over a period of 180 min. The dynamic glucose and insulin responses to glucose and insulin injection were analysed using the modified MM without and with physical exercise from IVGTT data.

Results: Our simulation results shown physical exercise improved blood glucose control and enhanced insulin sensitivity (S_I) index in subjects with T1DM and T2DM. However, the T1DM and T2DM subjects need to be aware of the basic strategies to prevent hypoglycemia and maintain reasonable glucose control. It should be noted that the putative improvement in exercise-induced peripheral S_I index in subjects with T1DM and T2DM was not always coincidental with the improvement of the insulin dosage.

Conclusion: The feature increased physical exercise, along with knowledge about how to modify daily insulin dosage to prevent hypoglycemia, improved blood glucose control and enhanced S_I index.

Keywords: Insulin-dependent diabetes mellitus, Modified minimal model, Glucose plasma, Insulin plasma, Insulin sensitivity

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i2.15621

INTRODUCTION

The increasing prevalence of T2DM in patients over the past few decades in developed countries, population-based efforts to reduce the cardiovascular complications of T2DM are as critical as the measures to prevent the problem. A number of important clinical management issues are needed for the active patients with T1DM and T2DM to ensure proper health and prevention of long-term complications of the disease. Some evidence suggests that optimal metabolic control maximises physical performance in patients with diabetes, although more studies are needed to confirm this suggestion. With the increasing prevalence of T1DM and T2DM patients, the importance of physical exercise to help prevent T1DM and T2DM in patients is of more recent consideration [1, 2].

It has recently been suggested that most patients with T1DM and T2DM attain at least 30 min of exercise daily, and individuals in certain age groups, even exceed the levels of sporting activity of their non-diabetic counterparts, possibly due to intensive health education and diabetic intervention. A high level of sports participation is surprising as exercise is the leading cause of hypoglycemia, which is the patients' primary concern with exercise. Indeed, the influence of chronic exercise on improving blood glucose control in T1DM and T2DM patients is equivocal; some studies show an improvement in blood glucose control, but others show no effect. It is likely that excess caloric intake to prevent or treat hypoglycemia may counter the beneficial effects of exercise on glycemic control in some subjects because standardised carbohydrate and insulin modifications for active patients are not readily available. Nonetheless, the goal of physical exercise should be to increase S_I index of the patients with T1DM and T2DM, regardless of any putative benefits to blood glucose management [1, 2].

Through such research, specific prescriptions of physical exercise can be made to optimise health. Additional benefits specific to diabetes include improved S_I index, a diminished glycemic response to a meal, and a reduction in daily insulin needs [1, 3, 4].

Our results show, as has been widely reported that during physical exercise there is an improvement in glucose tolerance. This improvement is a consequence of a substantial increase in S_I index (300-700%) since the plasma glucose level of the hormone was lower during exercise [3, 4].

The importance of insulin for glucose uptake during physical exercise has been reported in many studies. Although it seems that the presence of insulin is not necessary for glucose uptake to increase during exercise, the hormone would exert a synergistic effect rather than just an additive one; it increases 300%.

The results suggest that S_I index after exercise returns to baseline in a time-dependent way. It is important to emphasise that the S_I index also includes the effect of insulin suppresses hepatic glucose output. However, in the case of physical exercise, the increment of S_I index must be mainly due to an increment in peripheral glucose uptake rather than to a suppression of hepatic glucose output, since exercise increases hepatic glucose output [3, 5].

The parameters for the effects of exercise on glucose-insulin dynamics were proposed by Derouich and Boutayeb in 2002 [6]. The parameters related to physical exercise are defined as follows: the effect of the physical exercise of accelerating the utilization of glucose by muscular and the liver, the effect of the physical exercise in increasing the muscles and liver sensibility to the action of the insulin, and the effect of the physical exercise in increasing the utilization of the insulin [6].

Our aim here was to introduce a new model which simulates the effects of physical exercise on the dynamics of glucose and insulin. The model allows us to point out the different behaviours corresponding to normal glucose tolerance (NGT), T1DM and T2DM patients. In this paper, the model proposes two new parameters: the effect of the physical exercise in increasing the disappearance of glucose and the effect of the physical exercise in increasing the secretion of insulin from the pancreas.

MATERIALS AND METHODS

Materials

In an IVGTT procedure, the patients were asked to fast for 12 h before being tested. At 9.00 am, a cannula was placed in the cephalic vein at the level of the cubital fossa for taking the blood samples, while glucose was injected into the contralateral cephalic vein. Glucose (0.5 g/kg body weight, 30% solution) was slowly injected over three minutes. Insulin (0.02 U/kg body weight) was injected intravenously over 19 min. Two blood samples were drawn before the glucose bolus and also at one, three, four, eight, 10, 15, 19, 20, 22, 30, 41, 70, 90 and 180 min after glucose injection. All of these samples were necessary for the MM calculations [3, 7, 8]. The MM has been used widely in physiological research on the metabolism of glucose, and also employed in clinical and epidemiological studies to estimate S_I and glucose effectiveness (S_G) index.

In this paper, experimental data on NGT subject published in reference [9]. The first column is the time in a minute to sample the blood with a two-minute shift. The second and third columns are the data for subject 6. The fourth and fifth columns are the data for the subject 7. The sixth and seventh columns are the data for subject 8 [9].

Table 1: Experimental data published in reference [9]

Time	Subject 6		Subject 7		Subject 8	
min	*G* (mg/dl)	*I* (µU/ml)	*G* (mg/dl)	*I* (µU/ml)	*G* (mg/dl)	*I* (µU/ml)
0	225.4717	41.3208 41.0378	299.3711	179.4549	226.4151	103.140
2	214.1509	30.5660	259.9581	103.9832	228.9308	91.570
4	203.7736	28.6793 23.4906	253.2495	99.7904	203.7736	75.970
6	200.0000	31.7925 27.8302	244.0252	93.9203 104.8218	201.2579	77.230
8	195.2830	23.8680 25.0000	225.5765	77.1488	196.2264	64.650
10	192.4528	23.3962 20.3774	223.8994	88.8889	183.6478	66.920
13	174.5283	15.3774 16.9811	203.7736	95.5975	173.5849	51.320
18	158.4906	11.5094 11.1321	188.6792	79.6646	148.4277	50.820
23	150.0000	5.3774	170.2306	97.2746	123.2704	44.030
28	131.1321	4.6226	150.9434	86.3732 108.1761	115.7233	32.700
33	118.8679	5.8491	134.1719	44.4444	100.6289	28.680
38	115.0943	6.4151	119.9161	24.3187	95.5975	22.640
48	106.6038	5.5660	101.4675	33.5430	85.5346	16.600
58	93.3962		89.7275	29.3501	75.4717	14.840
78	82.0755		85.5346	37.7358	72.9560	11.820
98	77.3585		85.5346	31.0273	77.9874	6.790
118	83.0189		88.0503	33.5430	80.5031	4.280
138	83.0189		87.2117	46.9602	77.9874	6.040
158	82.0755		86.3732		80.5031	5.790
178	85.8491		87.2117			

Methods

The modified minimal model without exercise from IVGTT

A mathematical function representing the insulin infusion process being introduced into the MM. The proposed modified MM of insulin kinetics is as follows [4]:

$$\frac{dI(t)}{dt} = \gamma(G(t) - G_b)t - k(I(t) - I_b) + U(t), \text{ if } G(t) > G_b,\ I(t_0) = I_0, \quad \ldots\ldots\ldots\ldots (1)$$

$$\frac{dI(t)}{dt} = -k(I(t) - I_b) + U(t), \text{ if } G(t) < G_b,\ I(t_0) = I_0, \quad \ldots\ldots\ldots\ldots (2)$$

Where k [min^{-1}] is the insulin clearance fraction, G_b [mg/dl] is the basal glucose level, γ [min^{-1}] is a measure of the secondary pancreatic response to glucose, $U(t) = \frac{u(t)}{V}$ [µU/ml], $u(t)$ [µU/kg body weight] stands for the exogenous insulin infusion rate and V [ml/kg] for the distribution volume.

In the IVGTT study, a dose of glucose was administered intravenously over a 60 second period to overnight-fasted subjects, 20 min after the glucose bolus, insulin was injected over 1-2 min either into the portal vein or into the femoral vein, and subsequently the glucose and insulin concentrations in plasma were frequently sampled (usually 30 times) over a period of 180 min. The intravenous glucose dose immediately elevates the glucose concentration in the plasma forcing the pancreas ß-cells to secrete insulin. The insulin in the plasma is hereby increased, and the glucose uptake in muscles, liver and tissue is raised by the remote insulin in action. This lowers the glucose concentration in plasma, implying the ß-cells to secrete less insulin, from which a feedback effect arises. The integrated glucose-insulin system can be described by the following non-linearly coupled system of differential equations. The dynamic insulin and glucose responses to glucose injection were analysed as previously described to yield the individual parameters of the MM. The MM was described by the following differential equations [4, 7]:

$$\frac{dG(t)}{dt} = p_1(G_b - G(t)) - X(t)G(t),\ G(t_0) = G_0, \quad \ldots\ldots\ldots\ldots (3)$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3(I(t) - I_b),\ X(t_0) = 0, \quad \ldots\ldots\ldots\ldots (4)$$

In the modified MM, parameters p_1, p_2, and p_3 were estimated by weighted nonlinear least-squares from glucose and insulin data collected during an IVGTT experiments. As was usual, measurements from the first 10 min after glucose were ignored in model identification. The S_I index was calculated as:

$$S_I = \frac{p_3}{p_2} \quad \ldots\ldots\ldots\ldots (5)$$

Parameter $p_1 = S_G$ was glucose effectiveness: a measure of the fractional ability of glucose to lower its own concentration in plasma independent of increased insulin [4].

In this programming, glucose $G(t)$ and insulin $I(t)$ data were submitted to the modified MM program, which estimates the model

parameters from the real data. This program was based on the nonlinear least-squares estimation method. Insulin basal $I(t) = I_0$ was submitted to the modified MM program, which predicts a glucose time course, $G(t)$, which fits data $G(t)$ as closely as possible in the least-squares sense. In the course of the fitting, the model yields $X(t)$, an estimate of $X(t)$, as well as estimates of parameters p_1, p_2, p_3, k and γ. Parameters S_I (p_3/p_2) and S_G (p_1) index were calculated from parameter estimates. This latter parameter was represented as S_I and S_G index were equal to p_3/p_2 and p_1 as defined in equations (3) and (4), where the parameters were the prediction of the non-linear least-squares fit. In order to exemplify the computation of the proposed stability criteria, we considered sets of parameter values consistent with adaptation to data from actual IVGTT experiments. The glucose-insulin time course in IVGTT was a very complex process influenced by many factors. The modified minimal model could be used to simulate the plasma glucose and insulin profiles at a different subject, not only for NGT but also for T1DM and T2DM subjects. The coefficient of determination, R^2, was calculated from parameter estimates. The residuals between the best-fit curve and the data, $y_i - \hat{y}_i$, were used:

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y}_i)^2} \quad \text{..... (6)}$$

Where y was experimental data, $\hat{y}$ was the prediction of the non-linear least-squares fit and $\overline{y}$ was the averaged experimental data.

The modified minimal model with effect of physical exercise from IVGTT

In this model, the same assumptions of physical effort from Derouich and Boutayeb in 2002 [6] and two new parameters, as given below after the induction of physical exercise, we presented a new mathematical model of the glucose and insulin kinetics for the physical effort process. The model allowed us to point out the different behaviours corresponding to NGT, T1DM and T2DM patients.

We introduce a model which simulates the effect of physical exercise on the dynamics of glucose and insulin. The proposed modified MM of the glucose kinetics with exercise is as follows:

$$\frac{dG(t)}{dt} = (p_1 + q_1)(G_b - G(t)) - (1 + q_2)X(t)G(t), \quad G(t_0) = G_0 \quad \text{..... (7)}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + (p_3 + q_3)(I(t) - I_b), \quad X(t_0) = 0 \quad \text{..... (8)}$$

A new mathematical model representing the insulin infusion process in insulin therapy in T1DM and T2DM case with exercise was as follows:

$$\frac{dI(t)}{dt} = (\gamma + q_1 + q_4)(G(t) - G_b)t - (k + q_3 + q_5)(I(t) - I_b) + U(t), \quad \text{if } G(t) > G_b, \; I(t_0) = I_0 \quad \text{..... (9)}$$

$$\frac{dI(t)}{dt} = -(k + q_3 + q_5)(I(t) - I_b) + U(t), \text{ if } G(t) < G_b, \quad I(t_0) = I_0 \quad \text{..... (10)}$$

The detailed description all the exercise parameters were as follows:

q_1: the effect of the physical exercise of accelerating the utilisation of glucose by muscle and the liver;

q_2: the effect of the physical exercise in increasing the muscular and liver sensibility to the action of the insulin;

q_3: the effect of the physical exercise in increasing the utilisation of the insulin;

q_4: the effect of the physical exercise in increasing the disappearance of glucose;

q_5: the effect of the physical exercise in increasing the secretion of insulin from the pancreas.

RESULTS AND DISCUSSION

Normal glucose tolerant case without exercise

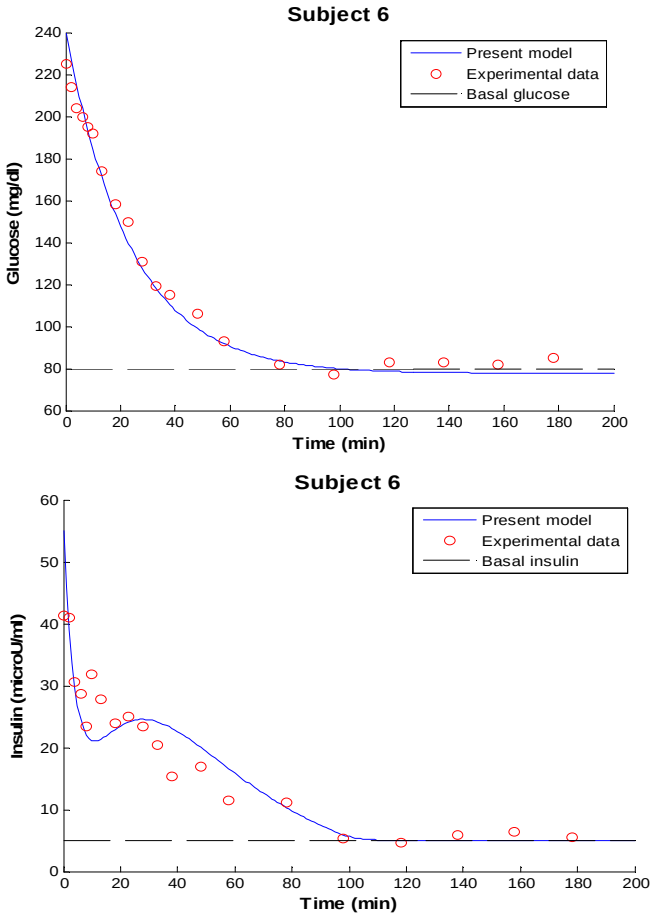

Fig. 1: Profiles of subject 6 in reference [9] were produced by modified MM without exercise, with parameters: k = 0.205 [min^{-1}], γ = 0.0030 [min^{-1}], G_b = 80 [mg/dl], I_b = 5 [µU/ml], p_2 = 0.00095 [min^{-1}], S_I = 11.60 × 10^{-4} [ml/kg/min. µU/ml], S_G = 0.0425 [min^{-1}], $U(t)$ = 0, and R^2 = 0.960

The optimised parameters obtained by fitting the modified MM to the experimental data of the three subjects were shown in fig. 1, fig. 2, and fig. 3. The values of R^2 between measured and calculated plasma concentrations were also shown in fig. 1, fig. 2, and fig. 3. The averaged R^2 value, including glucose and insulin concentrations, for these three subjects, were 0.960; this means that the modified MM was agreed. This could be explained by the increased flexibility of the modified MM, because of the assumption that the insulin decay rate was not always a first-order process. Another reason could be the introduction of the insulin kinetics function, which exactly reflects the actual IVGTT situations mathematically in the model. The observed and calculated blood glucose concentrations and the blood insulin profile were shown in fig. 1, fig. 2, and fig. 3. There were NGT subjects without additional insulin infusion. In the standard IVGTT, after an injection of glucose bolus, the blood glucose reaches a higher concentration and shows an apparent decay immediately to the basal line in 1 h. The corresponding insulin concentration stimulated by the injected glucose raises to form a peak, then an approximately exponential decay afterwards, and finally a secondary peak appears. It was not always the case that NGT subjects present a secondary insulin peak. The average value,

R^2, was 0.960 between experimental and calculated plasma glucose and the plasma insulin profiles.

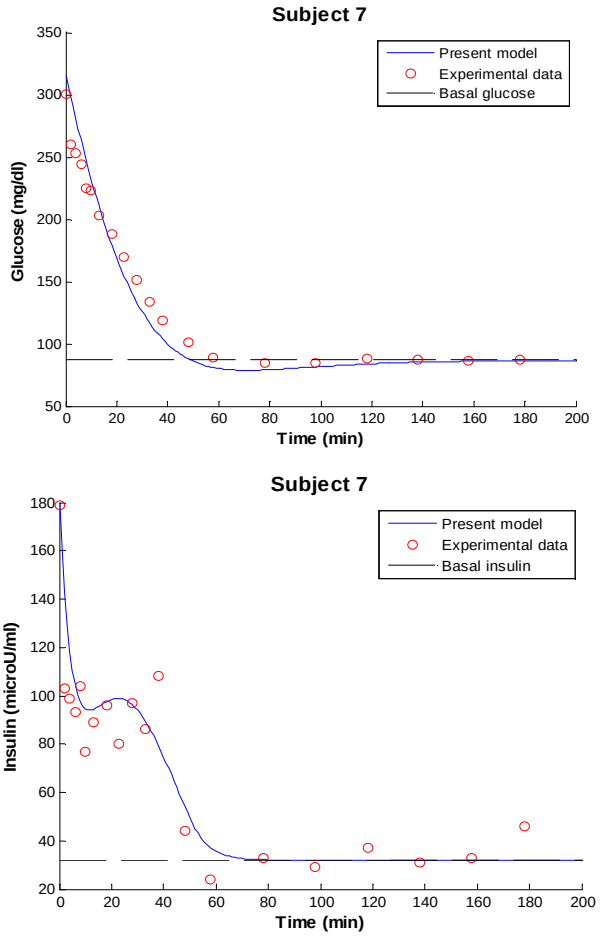

Fig. 2: Profiles of subject 7 in reference [9] were produced by modified MM without exercise, with parameters: k = 0.16 [min^{-1}], γ = 0.0125 [min^{-1}], G_b = 87 [mg/dl], I_b = 32 [µU/ml], p_2 = 0.06 [min^{-1}], S_I = 11.5 × 10^{-4} [ml/kg/min. µU/ml], S_G = 0.035 [min^{-1}], $U(t)$ = 0, and R^2 = 0.960

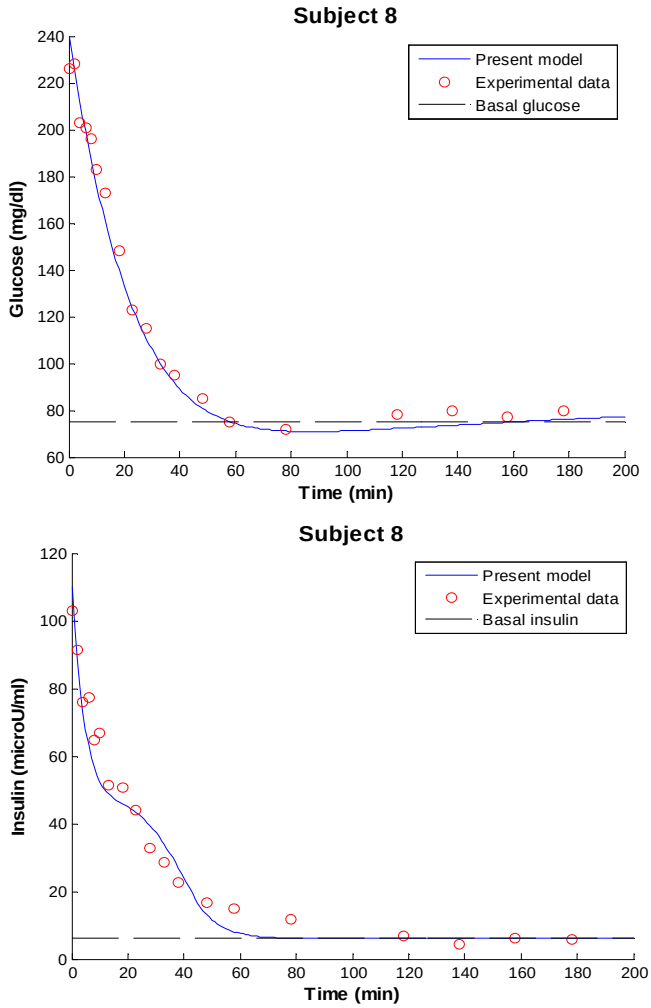

Fig. 3: Profiles of subject 8 in reference [9] were produced by modified MM without exercise, with parameters: k = 0.105 [min^{-1}], γ = 0.00455 [min^{-1}], G_b = 85 [mg/dl], I_b = 6 [µU/ml], p_2 = 0.0075 [min^{-1}], S_I = 11.45 × 10^{-4} [ml/kg/min. µU/ml], S_G = 0.0445 [min^{-1}], $U(t)$ = 0, and R^2 = 0.960

Table 2: Comparison of parameters between MM millennium was published in reference [8] and present model

Clinical index	**Typical normal**			
***Name* (*unit*)**	***Range***	***Subject 6***	***Subject 7***	***Subject 8***
Insulin sensitivity (ml/kg/min. µU/ml)	5.0 × 10^{-5}-2.2 × 10^{-3}	11.60 × 10^{-4}	11.5 × 10^{-4}	11.45 × 10^{-4}
Glucose effectiveness (min^{-1})	0.0012-0.045	0.0425	0.035	0.0445
Basal glucose (mg/dl)	70-103	80	87	85
Basal insulin (µU/ml)	1-32	5	32	6

Type 1 diabetes mellitus case without exercise

The T1DM was a form of diabetes that results from autoimmune destruction of insulin-producing *ß*-cells of the pancreas. This insulin deficiency once quickly caused death in patients, but technological advances in insulin therapy and diabetes management tools now allow for a near full life expectancy with dramatically improved patient quality of life. Nonetheless, poor diabetes management could lead to diabetes-related complications and patients should be a time in which good diabetes control habits should be developed. Since the diagnosis of T1DM often occurs in a patient, age and maturation of that patient bring an elevated risk of developing microvascular (diabetic retinopathy, nephropathy, and neuropathy) and macrovascular complications. Therefore, patient represents a very good time frame to focus on the prevention of micro and macrovascular disease through good diabetes management.

Treatment of T1DM was based on exogenous insulin injection, diet control and physical exercise. A basal insulin concentration was needed throughout the day, but insulin boluses were also required at mealtimes and for corrections for hyperglycaemia.

However, other parameters, such as physical exercise, illness and stress levels had to be constantly monitored to determine the appropriate insulin dosage. It is generally well accepted that physical exercise along with a good diet was helpful in maintaining glycemic control since very sedentary behaviour was associated with poor control [10].

In T1DM case, the pancreas undergoes an autoimmune attack by the body itself and was rendered incapable of making insulin. It was an autoimmune disorder in which body's own immune system attacks *ß*-cells of the pancreas, destroying them or damaging them

sufficiently to reduce insulin production. The pancreas then produces little or no insulin. The TIDM patients were treated by giving insulin injection or an insulin pump to deliver insulin in the body.

We had carried out a simple simulation experiment of modified MM applied to the identified T1DM experimental data. The simulation conditions at present during IVGTT have been replicated-identified model received the equal amount of glucose (see fig. 4). The situation of T1DM was shown in fig. 4. In the modified minimal model, the blood glucose concentration of the T1DM subject returned to the basal lines more than 1 h regardless of the insulin injection. In T1DM case, both the experimental and calculated glucose concentrations showed a small response to the insulin infusion. For the blood insulin, besides the peak caused by stimulation by a glucose injection, there was a large peak after 5 min because of the insulin injection. The values of R^2 = 0.970 for glucose between experimental and calculated plasma concentrations indicate that the simulation using the proposed model was agreed.

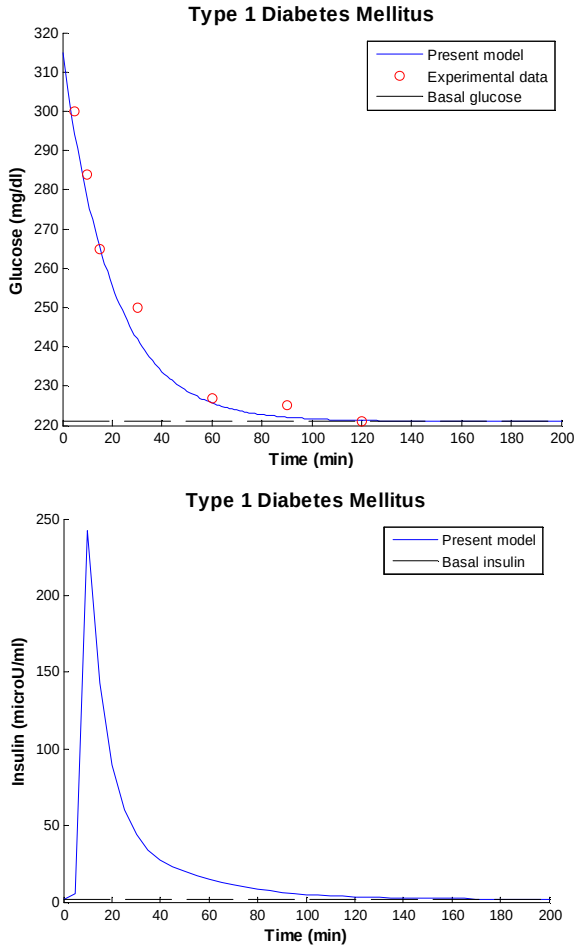

Fig. 4: Profiles of T1DM (IDDM) subject in reference [11] were produced by modified MM without exercise, with parameters: k = 0.12, γ = 0.004, G_b = 221 [mg/dl], I_b = 2 [µU/ml], p_2 = 0.01 [min^{-1}], S_I = 5.3 × 10^{-9} [ml/kg/min. µU/ml], S_G = 0.05 [min^{-1}], U = 240 [µU/ml], and R^2 = 0.970

Type 2 diabetes mellitus case without exercise

The pancreas plays a vital role in regulating blood glucose concentration in the body. Glucose-regulatory hormones, such as insulin, secreted by the pancreas *ß*-cells facilitate transport of glucose from the circulatory system into the tissues. Absolute or partial deficiency in insulin secretion by the pancreas, lack of glucose-regulatory action of insulin, or both, leads to a metabolic disease known as diabetes mellitus (DM). The much more prevalent form was termed IDDM, commonly known as T2DM. The cause of T2DM was a combination of resistance to insulin action and an inadequate compensatory insulin secretion response. Most patients with this form of diabetes were obese, and obesity may itself cause some degree of insulin resistance. Non-obese T2DM individuals often reflect elevated circulating levels of free fatty acids (FFA) and triglycerides (TG). In T2DM case, initially and often throughout the lifetime, the patients do not require insulin replacement treatment to survive.

The T2DM was diagnosed with insulin resistance in which the pancreas is producing enough insulin, but for unknown reasons, the body could not use the insulin effectively. So, the onset of T2DM could be delayed with physical exercise, diet and lifestyle modifications. Changes in glucose and insulin without physical exercise had been simulated and represented in this paper.

In T2DM cases without exercise, the IVGTT experimental and calculated plasma glucose and the plasma insulin profiles were shown in fig. 5, the blood glucose takes more than 2 h to return to the basal line in spite of an insulin infusion for 5 min starting at 20 min. In fig. 5, there was a great insulin peak from 20 to 30 min, because an insulin amount was injected. The proposed model described well the actual IVGTT operation and reached the R^2 values of 0.930 for plasma glucose and 0.930 for insulin.

The fitting process combined with the modified MM took the glucose-insulin system as a dynamic integrated system and generates a set of real optimised model parameters of the experimental data.

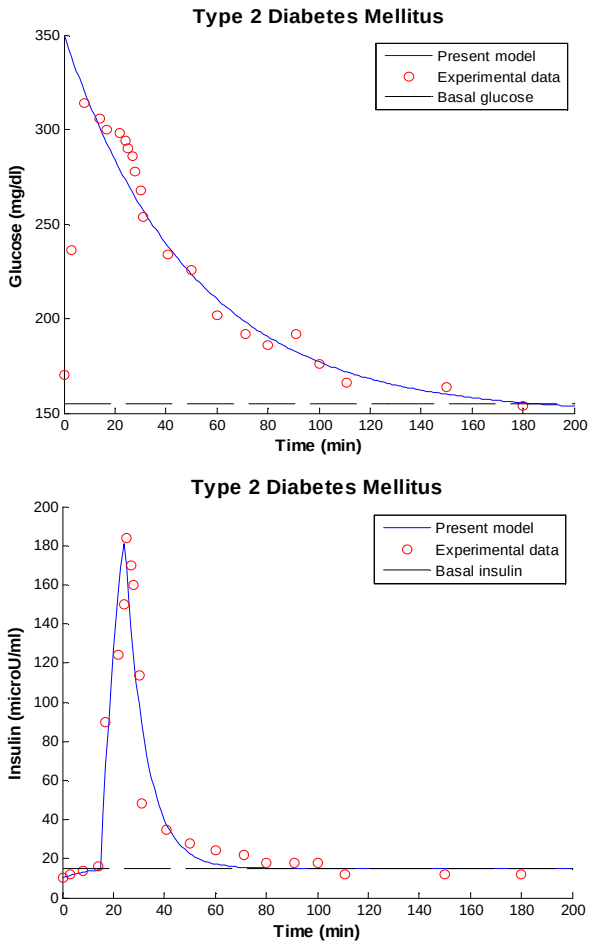

Fig. 5: Profiles of T2DM (IDDM) subject in reference [12] were produced by modified MM without exercise, with parameters: k = 0.121, γ = 0.00043, G_b = 150 [mg/dl], I_b = 15 [µU/ml], p_2 = 0.0001 [min^{-1}], S_I = 12.0 × 10^{-7} [ml/kg/min. µU/ml], S_G = 0.02 [min^{-1}], U = 30 [µU/ml], and R^2 = 0.930

Normal glucose tolerant case with exercise

A person has hyperglycemia, when the blood glucose level was above 150 mg/dl. This could arise e. g. when a diabetic ate a large meal or had a low level of insulin in the blood. Hyperglycemia was extremely dangerous if not treated.

A person had hypoglycemia when the blood glucose level was below 60 mg/dl. This could happen, after too much exercise, a too large insulin dosage, a small amount of carbohydrates in the food or if the diabetic skipped meals. Hypoglycemia could result in loosing of the conscience. Avoiding hypoglycemia was an important issue when subjects were using insulin as treatment.

In this case, a modified MM with exercise was developed to capture the effects of exercise on glucose and insulin dynamics. The model successfully captured insulin-glucose concentrations during and immediately after physical exercise. The model was also capable of predicting the plasma glucose excursion towards hypoglycemia during prolonged exercise periods.

In healthy subjects, precise autonomic and endocrine regulation allowed blood glucose levels to remain relatively stable, except for a transient decreased in blood glucose at the start of exercise. Hypo- and hyperglycemia was rare in healthy subjects who did not have diabetes because insulin secretion was lowered and counter-regulatory hormones were elevated, thereby causing glucose production by the liver to match utilisation by the working muscles. This study acknowledged the fact that blood glucose levels decreased during physical exercise. Thus, the fear of hypoglycemia could become a major barrier to physical exercise participation in this NGT subject.

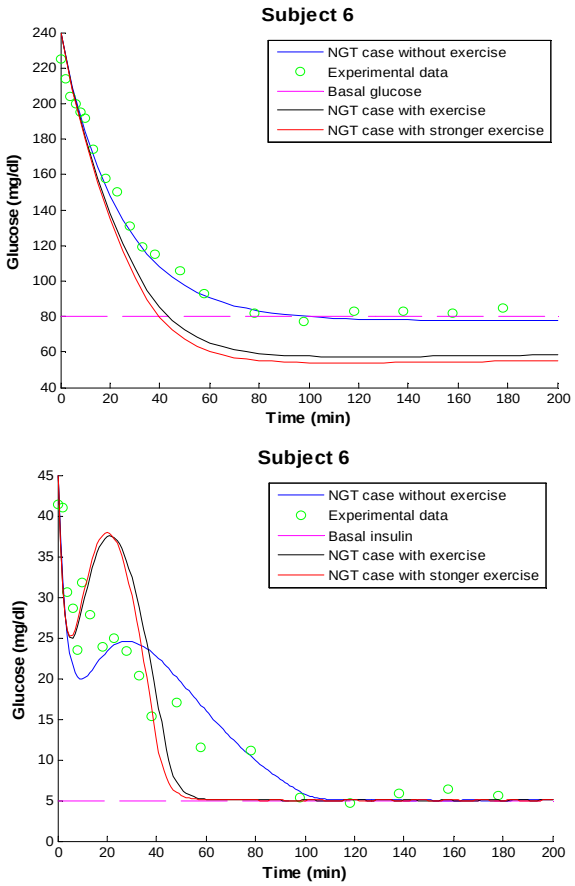

Fig. 6: Profiles simulations of NGT case with exercise, subject 6 in reference [11] were produced by modified MM with exercise. Parameters of NGT cases with normal exercise were q_1 = 0.00001, q_2 = 0.65, q_3 = 0.000009, q_4 = 0.004 and q_5 = 0.04; with stronger exercise were q_1 = 0.00003, q_2 = 0.95, q_3 = 0.00001, q_4 =0. 0045 and q_5 = 0.045 (q_1, q_2, and q_3 data from Derouich and Boutayeb in 2002 [6])

Type 1 diabetes mellitus case with exercise

The T1DM treatment was based on exogenous insulin injection and physical exercise. A basal insulin concentration was needed throughout the day, but insulin boluses were also required at mealtimes and for corrections for hyperglycemia. However, other parameters, such as physical exercise, illness and stress levels had to be constantly monitored to determine the appropriate insulin dosage. It was generally well accepted that physical exercise along with a good diet was helpful in maintaining glycemic control since very sedentary behaviour was associated with poor control. Diet recommendations were relatively straightforward in patients with T1DM, and were similar to the general dietary guidelines for NGT. When respected, this helps to avoid unbalanced and irregular carbohydrate intake. The aim of physical exercise in patients with T1DM was to improve the quality of life and to enhance both short-term and long-term health. Due to the possibility of worsening metabolic control during exercise (resulting in either hypoglycemia or hyperglycemia), guidelines regarding metabolic control, blood glucose monitoring and food intake for physical exercise must be followed. Some review papers have focused on glycemic variations with physical exercise and on practical considerations for the clinical management of T1DM subjects. Other reviews previously presented physical exercise-induced benefits of glycemic control in T1DM subjects, but not on different other important health-related parameters [10].

The purpose of this paper was to focus on the effects of physical exercise model in patients with T1DM and to understand which mechanisms were involved. Physical exercise improved S_I index in subjects with T1DM. However, it should be noted that the putative improvement in exercise-induced peripheral S_I index in subjects with T1DM was not always coincidental with the improvement of the following parameters (usually linked to improved S_I index): daily insulin dose decrease and glycemic control improvement. Physical exercise was challenging for the subjects with T1DM. The T1DM subjects need to be aware of the basic strategies to prevent hypoglycemia and maintain reasonable glucose control (see fig. 7). Initial glycemia, time of the last rapid acting insulin injection, injection site, diet, time of the day, exercise type, etc.... were all factors to be considered in order to anticipate the hypoglycemic effect of physical exercise. Moreover, the individual response to exercise could be different for each patient and sometimes even within a patient, thus making general recommendations around exercise and blood glucose management strategies was difficult. Therefore, it would be interesting in future investigations to study different individualised responses to exercise, while taking into consideration the previously shown parameters that were established to influence glucose control. Thus, it could be possible to anticipate glycemic variations better during exercise and recovery. These tests could be taken into consideration in the patient's therapeutic approach.

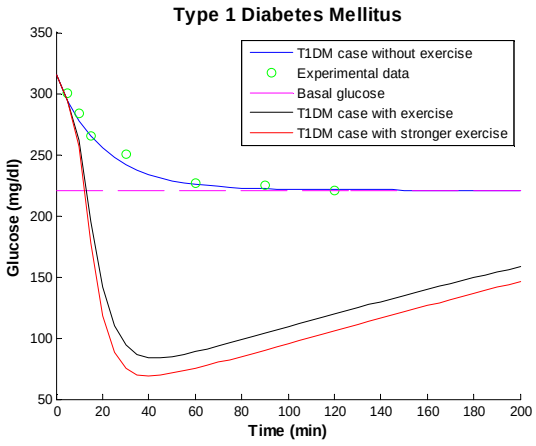

Fig. 7: Profiles simulations of T1DM case with exercise, subject in reference [11] were produced by modified MM with exercise. Parameters of T1DM cases with normal exercise were q_1 = 0.00001, q_2 = 0.65, q_3 = 0.000009, q_4 = 0.004 and q_5 = 0.04; with stronger exercise were q_1 = 0.00003, q_2 = 0.95, q_3 = 0.00001, q_4 =0. 0045 and q_5 = 0.045 (q_1, q_2, and q_3 data form Derouich and Boutayeb in 2002 [6])

Type 2 diabetes mellitus case with exercise

Physical exercise, which was often viewed in relation to glycemic control, has important effects on the development of cardiovascular complications in T2DM subjects. For the purpose of this statement, physical exercise was defined as planned and structured activity that was aimed at improving cardiovascular health and metabolic control. The goals of this scientific statement, were to document the mechanisms whereby physical exercise was important in T2DM management, analyze the existing evidence regarding exercise interventions, and provide practical guidelines about preparation for physical exercise training programs and safety issues, as well as specific exercise training guidelines that could be used to initiate an exercise program. In addition, previous research has reported improved insulin sensitivity/resistance and reductions in hyperglycemia-related medications as a result of physical exercise. These changes typically have been reported in obese subjects with T2DM, which suggests that there was a good relationship between loss of body fat and improved glycemic control. However, improvement in glycemic control might be independent of fat loss. Moreover, patients with greater metabolic disturbances have shown the greatest improvement in glycemic control. Other potential mechanisms for better glucose control include improvement in S_I index and effects on glucose transporters (e. g., GLUT4). The muscle contractions could elicit movement of glucose transporters (GLUT4) to the plasma membrane independently of insulin, and it was further speculated that muscle hypertrophy and blood flow were also contributing mechanisms.

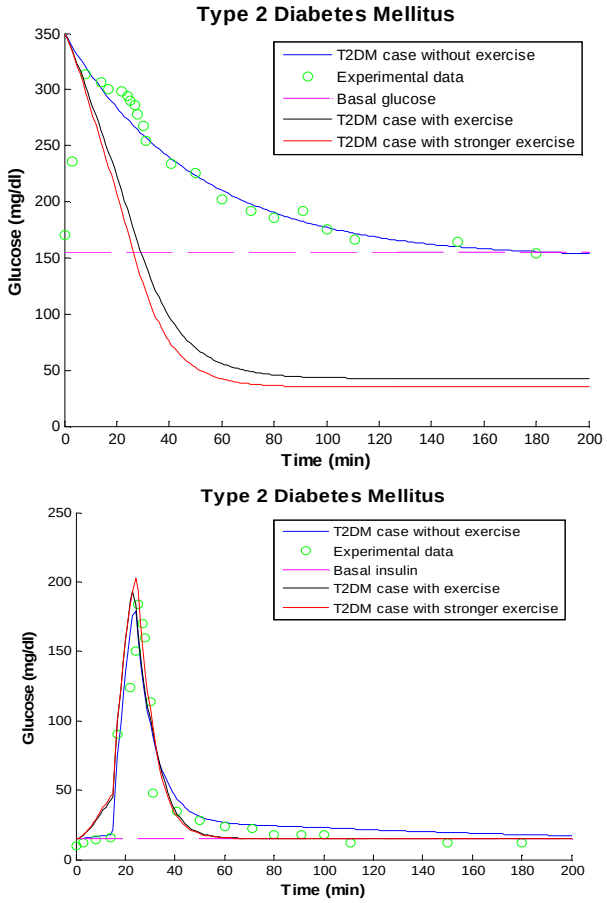

Fig. 8: Profiles simulations of T2DM case with exercise, subject in reference [12] were produced by modified MM with exercise. Parameters of T2DM cases with normal exercise were q_1 = 0.00001, q_2 = 0.65, q_3 = 0.000009, q_4 = 0.004 and q_5 = 0.04; with stronger exercise were q_1 = 0.00003, q_2 = 0.95, q_3 = 0.00001, q_4 =0. 0045 and q_5 = 0.045 (q_1, q_2, and q_3 data from Derouich and Boutayeb in 2002 [6])

In general, the new information provided by our study was that S_I index as measured by the modified MM was dramatically improved in T2DM patients and, in the short term of physical exercise, could even achieve the zone of control values at rest. This resulted in a marked, albeit incomplete, improvement in the disposition index. In contrast, the exercise-induced increase in S_G observed in control subjects using the same protocol was not seen in diabetics, suggesting little or no effect of short bouts of acute exercise on S_G in T2DM subjects. This finding was important for interpreting modified MM measures of S_I and S_G index in diabetics during exercise training protocols, as the acute effects of physical exercise were quantitatively important and need to be separated from chronic effects. Also, the magnitude of the short-term rise in S_I index suggested that repeated physical exercise might be, on its own, a powerful insulin-sensitizer independent of the additional and well-demonstrated long-term effects of regular exercise training.

CONCLUSION

In using a modified MM of physical exercise in this paper, our purpose was to illustrate clearly the effect of physical exercise on the dynamics of glucose and insulin in order to confirm the role of physical exercise as a prevention for subjects at risk, to stress the benefit that can be gained by T2DM from improving S_I index and compensating its eventual partial lack, and finally, to reassure T1DM subjects that no exclusion is made to provide a good combination is found to balance between insulin doses, carbohydrates and physical intensity. It is interesting to note the output of the model concerning extreme cases where exercise may be dangerous, leading to severe hypoglycemia or other problems where exercise may have a negative effect.

Research has provided some understanding of the physiological responses to exercise in the subjects with diabetes, and as a result, there are some general guidelines for the modification of insulin to limit excursions in blood glucose levels. The goal for all subjects with diabetes should be to learn their individual glycemic responses to exercise and to control glucose fluctuations by modifying insulin dosage diet appropriately.

ACKNOWLEDGMENT

This study was funded by the Direktorat Riset dan Pengabdian Masyarakat Direktorat Jenderal Penguatan Riset dan Pengembangan Kementerian Riset, Teknologi dan Pendidikan Tinggi, Indonesia sesuai dengan Surat Perjanjian Penugasan Pelaksanaan Program Penelitian Nomor: 079/SP2H/lT/DRPM/II/2016 tanggal 17 Februari 2016.

CONFLICT OF INTERESTS

The authors report no conflicts of interest

REFERENCES

1. Riddell MC, Iscoe KE. Physical activity, sport, and pediatric diabetes. Pediatric Diabetes 2006;7:60-70.
2. Marwick TH, Hordern MD, Miller T, Chyun DA, Bertoni AG, Blumenthal RS, *et al.* Exercise training for type 2 diabetes mellitus impact on cardiovascular risk. A scientific statement from the american heart association. Circulation 2009;119:3244-62.
3. Bordenave S, Brandou F, Manetta J, Fe´dou C, Mercier J, Brun JF. Effects of acute exercise on insulin sensitivity, glucose effectiveness and disposition index in type 2 diabetic patients. Diabetes Metabolism 2008;34:250–7.
4. Kartono A. Modified minimal model for the effect of physical exercise on insulin sensitivity and glucose effectiveness in type 2 diabetes and healthy human. Theory Biosci 2013;132:195-206.
5. Vilar DA, Osifo E, Kirk M, Estevez DAG, Cerrato JC, Hockaday TDR. Influence of moderate physical exercise on insulin-mediated and non-insulin-mediated glucose uptake in healthy subjects. Metabolism 1997;46:203-9.
6. Derouich M, Boutayeb A. The effect of physical exercise on the dynamics of glucose and insulin. J Biomechanical 2002; 35:911-7.

7. Pacini G, Bergman RN. MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Computer Methods Program Biomed 1986;23:113–22.
8. Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, Bergman RN. MINMOD millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. Diabetes Technol Ther 2003;5:1003-15.
9. Li J, Wang M, De Gaetano A, Palumbo P, Panunzi S. The range of time delay and the global stability of the equilibrium for an IVGTT model. Math Biosci 2012;235:128-37.
10. Leclair E, de Kerdanet M, Riddell M, Heyman E. Type 1 diabetes and physical activity in children and adolescents. J Diabetes Metab 2013;S10004:1-10.
11. Ludwig T, Ottinger I. Identification of T1DM minimal model using non-consistent data from IVGTT. J Electrical Systems Information Technol 2014;1:144-9.
12. Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, *et al.* Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinal Metab 2000;85:2402-10.

How to cite this article

13. Agus Kartono, Febri Dwi Irawati, Ardian Arif Setiawan, Heriyanto Syafutra, Tony Sumaryada. The effects of physical exercise on the insulin-dependent diabetes mellitus subjects using the modified minimal model. Int J Pharm Pharm Sci 2017;9(2):179-186.