

The effect of physical exercise on the dynamics of glucose and insulin

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Abstract

Regular physical activity is indicated either to prevent and delay the onset of non-insulin-dependent diabetes or to assure a good control of diabetes by increasing insulin sensitivity and ameliorating the metabolism of glucose disappearance. Many studies and experiments have dealt with this subject.

In this paper, we introduce the effect of physical activity via parameters of a mathematical model which allows us to compare the behaviour of blood glucose in normal, non-insulin-dependent diabetes and insulin-dependent diabetes people, with and without physical effort. Extreme cases of physical activity leading to hypoglycaemia or aggravating hyperglycaemia are also underlined. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The regular physical activity has been recommended to diabetic patients for a long time.

In the general population, a reduction of the vascular morbidity is observed in patients having a raised cardiorespiratory fitness and/or a high level of physical activity. The protective cardiovascular effect is partly explained by the fact that regular physical activity improves anomalies of the multi-metabolic syndrome: increase of the insulin sensitivity, diminution in the fatty mass, improvement of the lipid profile, increase of the fibrinolyse, arterial pressure decrease and incidence reduction of the non-insulin-dependent diabetes (NIDD) (Lakka et al., 1994).

For a healthy man, the principal energy substrates are the muscular glycogen, the plasma glucose (which includes the glucose produced by the liver), the plasmatic free fatty acids and the intramuscular triglycerides. The reserves of carbohydrates of the organism approximate 1200–2400 kcal and are mainly localized in the muscle (79% of the total stocks), the liver (14%) in glycogen form and in blood (7%) in the form of glucose (Coyle, 1995; Romijn et al., 1993).

Carbohydrates reserves are therefore weak and their depletions are a limitation to the prolonged exercise.

Regular physical activity reduces the risks of NIDD onset (Wasserman et al., 1991; Sigal et al., 1996). This protective effect is correlated to the level of physical activity during the previous years since the childhood. It is more noticed in people at risk (overweight, high blood pressure, family inheritance). On the other hand, physical activity is often indicated in the treatment of NIDD besides diet and tablets. However, two remarks can be made. First, for several reasons (age, sedentary life, weight, blood pressure), patients are unable to keep with sustained regular physical activity. Second, as, in general, NIDD affects people after the age of 40, intensive effort can be dangerous especially for patients with retinopathy, neuropathy, high blood pressure or heart problems.

For insulin-dependent diabetes (IDD), the problem is different, since, in general, at diagnosis, patients are young and often prone to sport and physical activity. Moreover, one of the major goals of the treatment is to convince the (young) patient that he (she) can have a “normal” life provided he (she) can assure a good control of the blood glucose. So physical activity is well recommended but not without risk of hypo- and hyperglycaemia. One should stress that no common recipe is available but each patient may find that a combination of insulin doses, carbohydrates intake and

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the kind of physical activity will lead him to an ideal fitness and control of diabetes.

Moreover, it is now proved (D.C.C.T., 1995; U.K.P.D.S., 1998; Boutayeb and Kerfati, 1994) that long-term complications can be avoided or at least delayed by a good regular control of glycaemia. Complications include retinopathy, nephropathy and peripheral neuropathy. Diabetes is the commonest cause of blindness in people under the age of 65 in the UK and has been reported to account for 46% of lower-limb amputations carried by the NHS (Lehman and Deutsch, 1992). Similar situations are reported in Europe and United States by The American Diabetic Association, The Association Française de Diabète and the International Federation of Diabetes. Whereas, the disaster caused by diabetes complications is more exacerbated in developing countries, due to general lack of diabetes care and unaffordable cost of regular monitoring.

According to the authors of a recent paper (Bellazi et al., 2001), the regulation of blood glucose concentration is mainly achieved by acting on three control variables: insulin, meals and physical exercise. However, all the proposed control systems have focused on the definition of insulin therapy strategies; meals and physical exercise are usually considered as (known) disturbances.

In this paper, taking into account the cost of diabetes monitoring and treatment, especially in populations in need (Jonsson, 1998; Ziyat et al., 1997; Boutayeb and Derouich, 2002), we opt for the regulation by means of physical exercise. A simple mathematical model is used to illustrate the role of physical activity in improving insulin sensitivity and regulating blood glucose concentration. Simulation is carried out with different values of parameters and graphs allow us to compare the behaviour of blood glucose in normal, NIDD and IDD people, with and without physical effort. Extreme cases of physical activity leading to hypoglycaemia or aggravating hyperglycaemia are also indicated.

2. A brief review of mathematical models for diabetes

2.1. The dynamics of insulin and glucose

In 1939, Himsworth and Ker (1939) introduced the first approach to measure the insulin sensitivity *in vivo*. Mathematical models have been used to estimate the glucose disappearance and insulin sensitivity. The pioneer in this field was Bolie (1961) who proposed in 1961 the simple model

$$\frac{dG}{dt} = -a_1G - a_2I + p, \quad \frac{dI}{dt} = -a_3G - a_4I,$$

where $G = G(t)$ represents the glucose concentration, $I = I(t)$ represents the insulin and p, a_1, a_2, a_3, a_4 are

the parameters. This model assumes that glucose disappearance is a linear function of both glucose and insulin. The insulin secretion is proportional to glucose and insulin disappears in proportion to the plasma insulin concentration. With minor modifications, this model was used by a variety of authors since it was proposed (Akerman et al., 1965; Della et al., 1970; Serge et al., 1973).

A huge number of publications dealt with insulin sensitivity. Bergman and Cobelli (1980) related that published models have usually been of one of two model classes: simple models and comprehensive models. The authors discussed and published a multitude of models on dynamics of glucose and insulin. Variant versions of the well-known minimal model were considered using optimal control (Ollerton, 1989; Fisher, 1991). A number of devices—microsystems and computer approaches—have been reported in the literature with open, closed and partially closed-loop algorithms (Chisolm et al., 1978; Selam and Charles, 1990; Lehman and Deutsch, 1995). Finally, two reviews on the intravenous route to blood glucose control and the subcutaneous route to insulin-dependent diabetes therapy were published recently (Bellazi et al., 2001; Parker et al., 2001). The authors focused on the current treatment methods for IDD. However, one should stress that the new control strategies take a long time before they become affordable on a large scale, especially in developing countries where the majority of diabetics are struggling just to get insulin doses and where the price of a blood strip exceeds the individual daily income.

2.2. Modelling the effect of physical exercise

Our aim here is to introduce a model which simulates the effect of physical activity on the dynamics of glucose and insulin. The model allows us to point out the different behaviours corresponding to normal, NIDD and IDD patients. The graphs give a simple and clear illustration of glucose and insulin dynamics in each case.

We start underlining that physical effort:

- lowers the glucose concentration during and after the exercise,
- increases the insulin use by cells.

Then, following Bergman et al. (1981), we consider the following model:

$$\begin{aligned} \frac{dG(t)}{dt} &= -(1 + q_2)X(t)G(t) + (p_1 + q_1)(G_b - G(t)), \\ \frac{dX(t)}{dt} &= (p_3 + q_3)(I(t) - I_b) - p_2X(t) \end{aligned}$$

with $G(0) = g_0$ and $X(0) = X_0$ and $I(0) = I_0$ where

- (i) $(I(t) - I_b(t))$ represents the difference between the plasma insulin concentration and the basal insulin,

- (ii) $X(t)$ is the interstitial insulin,
 - (iii) $(G_b - G(t))$ is the difference between the basal glucose concentration and the plasma glucose,
- p_1 , p_2 and p_3 are parameters defined by Bergman et al. (1981).

The parameters related to physical activity are defined as follows:

- q_1 : the effect of the physical exercise in accelerating the utilization of glucose by muscles 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 utilization of the insulin.

To determine the effect of exercise on the disappearance of glucose after injection of glucose, we consider the perturbed model

$$\frac{dG(t)}{dt} = -(1 + q_2)X(t)G(t) + (p_1 + q_1)(G_b - G(t)) + g_{inf}(t),$$

$$\frac{dX(t)}{dt} = (p_3 + q_3)(I(t) - I_b) - p_2X(t),$$

where g_{inf} is the infusion of glucose by a unit of volume (i.e. the glucose injected at time t).

Parameters q_1 , q_2 and q_3 increase with the increase of exercise intensity of the muscular exercise.

In the next sections, we discuss separately the normal, NIDD and IDD cases.

2.3. Normal case

In non-diabetic people, the beta-cells, responsible for the production of insulin, are not affected. On the one hand, Insulin may be produced in sufficient quantity in reply to the amount of carbohydrate intake or to other needs. On the other hand, there is an automatic shut off that avoids excess of insulin when the reserves of glucose are exhausted. Hence, the blood sugar concentration may slightly increase or decrease but it does not cross the thresholds leading to severe hypo- or hyperglycaemia. Consequently, we can study the effect of physical exercise and compare it to situations of rest or minimum effort.

From the previous equations, we can see that the stationary state of the model is given by

$$X^* = \frac{p_3 + q_3}{p_2}(I_e - I_b),$$

$$g_{inf}^* + (p_1 + q_1)(G_b - G^*) - (1 + q_2)X^*G^* = 0,$$

where g_{inf}^* represents the amount of glucose (independent of time) injected at equilibrium:

$$g_{inf}^* = (1 + q_2)X^*G^* - (p_1 + q_1)(G_b - G^*),$$

$$g_{inf}^* = \frac{(p_3 + q_3)(1 + q_2)}{p_2}(I_e - I_b)G^* - (p_1 + q_1)(G_b - G^*).$$

Then the dependence of the glucose infusion rate on glucose is given by

$$\frac{\partial g_{inf}^*}{\partial G^*} = \frac{(p_3 + q_3)(1 + q_2)}{p_2}(I_e - I_b) + (p_1 + q_1)$$

and the insulin sensitivity is given by

$$\frac{\partial^2 g_{inf}^*}{\partial I_e \partial G^*} = \frac{(p_3 + q_3)(1 + q_2)}{p_2}.$$

Then we can notice that the disappearance of glucose depends on

- the effect of the exercise to accelerate the disappearance of glucose via a factor $(p_1 + q_1)$ that is independent of the increase of insulin, and
- a second factor (insulin sensitivity) which is a function of the increase of insulin $(I_e - I_b)$.

The insulin sensitivity is given by

$$S_{I_I} = \frac{\partial^2 g_{inf}^*}{\partial I_e \partial G^*} = \frac{(p_3 + q_3)(1 + q_2)}{p_2}$$

which becomes in the absence of physical effort

$$S_{0I} = p_3/p_2.$$

S_{0I} is smaller than S_{I_I} , hence physical exercise improves insulin sensitivity.

The effect of physical exercise on the dynamics of glucose and insulin is illustrated in Fig. 1.

2.4. Limit cases

At equilibrium we have

$$G^* = \frac{(p_1 + q_1)G_b + g_{inf}^*}{\frac{(1 + q_2)(p_3 + q_3)(I_e - I_b)}{p_2} + (p_1 + q_1)}.$$

If we put $I = I_e - I_b$ then the function $G^*(I)$ is given by

$$G^*(I) = \frac{(p_1 + q_1)G_b + g_{inf}^*}{\frac{(1 + q_2)(p_3 + q_3)I}{p_2} + (p_1 + q_1)}.$$

So G^* is a decreasing function of I and

$$\lim_{I \rightarrow 0} G^*(I) = G_b + \frac{g_{inf}^*}{p_1 + q_1} \tag{1}$$

and

$$\lim_{I \rightarrow \infty} G^*(I) = 0. \tag{2}$$

The first limit indicates that in the absence of insulin, glucose will not disappear even with physical effort, and a risk of hyperglycaemia or even ketoacidosis may occur as in the case of IDD or NIDD in need of insulin. Whereas, the second limit shows the opposite case when excess of insulin can lead to hypoglycaemia as in the case of IDD with overdose of insulin.

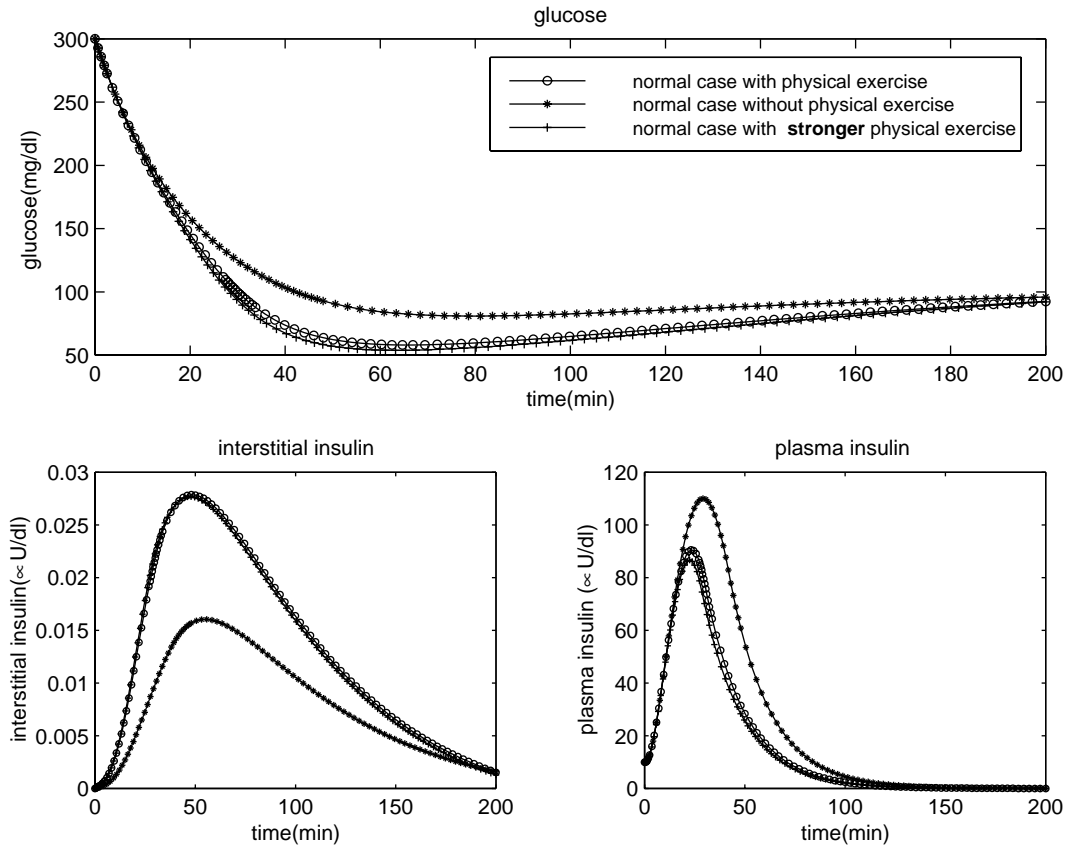


Fig. 1. Normal case: normal case with exercise, i.e. $q_1 = 0.00001$, $q_2 = 0.65$ and $q_3 = 0.000009$; normal case with stronger exercise, i.e. $q_1 = 0.00003$, $q_2 = 0.95$ and $q_3 = 0.00001$.

2.4.1. Non-insulin-dependent diabetes

Consider the expression of G at equilibrium:

$$G^* = \frac{(p_1 + q_1)G_b + g_{inf}^*}{\frac{(1 + q_2)(p_3 + q_3)(I_e - I_b)}{p_2} + (p_1 + q_1)}$$

Assuming that for NIDD, $I_e \approx 0$ we get

$$G^* \approx \frac{(p_1 + q_1)G_b + g_{inf}^*}{p_1 + q_1 - \frac{(1 + q_2)(p_3 + q_3)I_b}{p_2}}$$

and in the absence of physical effort the expression becomes $G^* \approx [p_1 G_b + g_{inf}^*] / [p_1 - (p_3/p_2)I_b]$.

Fig. 2 shows the behaviour of glucose as a function of time.

2.4.2. Insulin-dependent diabetes

People with IDD have no endogenous insulin production, so insulin level in their plasma depends totally on insulin injection. Therefore, before the injection of insulin, we can assume that $I_e \approx 0$ and

$I_b \approx 0$ so that

$$G^* \approx \frac{(p_1 + q_1)G_b + g_{inf}^*}{p_1 + q_1} \approx G_b + \frac{g_{inf}^*}{p_1 + q_1}$$

This expression illustrates clearly what happens, for example, at the beginning of IDD onset and before insulin treatment when a hyperglycaemia is not reduced by physical effort, moreover, which often evolves to the ketoacidosis.

On the other hand, if a patient with IDD combines physical effort with large doses of insulin and without too much of carbohydrate intake, he will risk a severe hypoglycaemia.

However, between these two extreme cases, IDD people may practice physically without problem provided they adjust the insulin dose and the carbohydrate intake to the level of physical effort they intend to accomplish.

Fig. 3 gives a comparison of glucose curves for different values of initial insulin.

Fig. 4 illustrates the effect of physical exercise with large amount of insulin injected. Hypoglycaemia may occur at any time if sufficient carbohydrates are not supplemented.

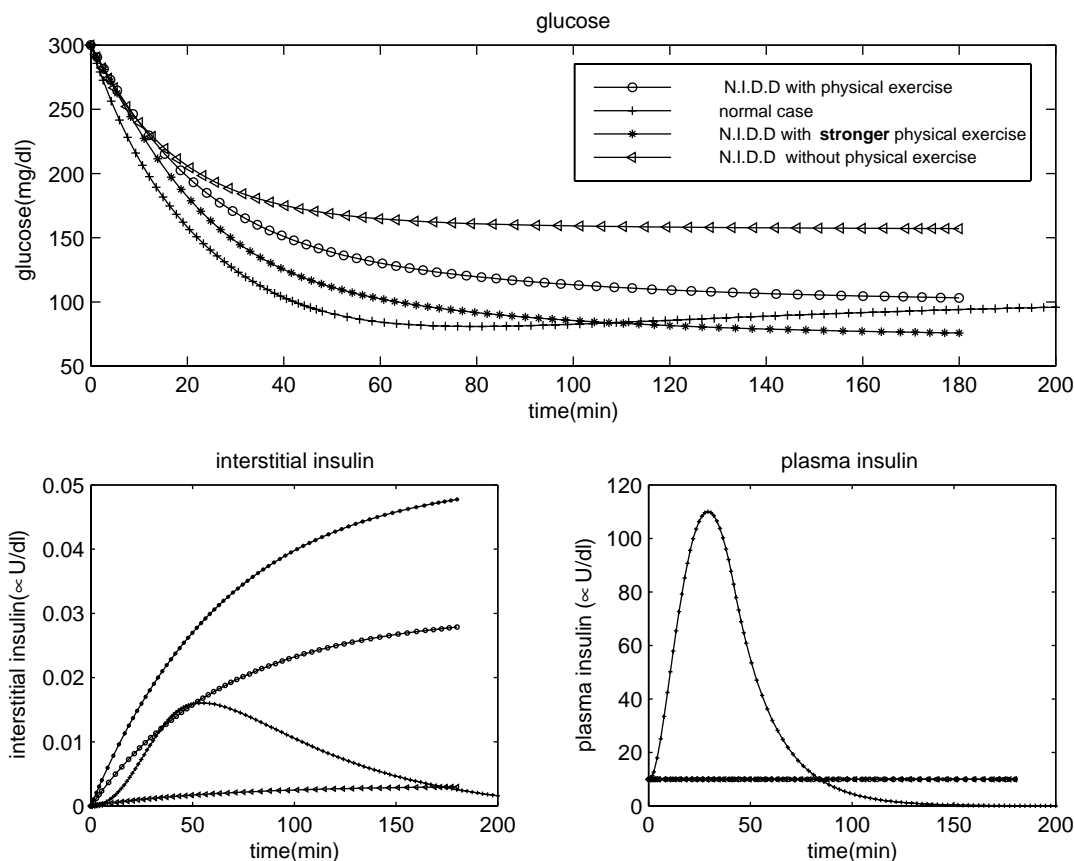


Fig. 2. NIDD case: NIDD case with exercise, i.e. $q_1 = 0.0028$, $q_2 = 0.75$ and $q_3 = 0.00005$; NIDD case with stronger exercise, i.e. $q_1 = 0.0028$, $q_2 = 0.85$ and $q_3 = 0.00009$.

3. Discussion

It was noted in the introduction that diabetes control is mainly achieved by acting on insulin, meals and physical activity but all the proposed control systems have focused on insulin therapy. We also stressed that the new control strategies take a long time before they become affordable on a large scale. Moreover, with low income and poor health (service care), a large number of diabetics over the world are struggling to get just the necessary insulin dose. These remarks lead us to focus on physical activity as a natural and inexpensive parameter in the control of diabetes and its complications. Our model confirms the well-known doctor advices on the practice of physical activity and gives a clear illustration of the glucose and insulin dynamics. In normal people, physical exercise improves insulin sensibility and lowers glucose concentration (Fig. 1). This illustration confirms once more that everybody should incorporate some physical activity in daily life. This recommendation is more indicated to people at risk (overweight, stress, family inheritance). Our model gives a general pattern, it is not possible to give a recipe quantified and useful. Each individual should find the

intensity and kind of physical activity suitable for his (her) situation.

Fig. 2 shows that while a person with NIDD may adapt to a blood sugar concentration over 200 mg/dl at rest, he (she) can achieve approximately a normal glycaemia around 100 mg/dl with physical activity. Again, a case-by-case practice is necessary and individual data determine the efficient way of including the physical activity as a part of the treatment.

For IDD people who may think that insulin is not needed when physical activity is practised, our model shows that insulin is necessary (Fig. 3). Obviously, a dose-effort adaptation is needed. Precisely, it is shown in Fig. 4 that physical activity can help IDD people to achieve a good control of blood sugar but a warning is given in case of too much insulin which can lead to hypoglycaemia.

4. Conclusion

The practice of a regular physical activity is recommended to diabetic and non-diabetic people. It is specially indicated to people at risk of diabetes and to

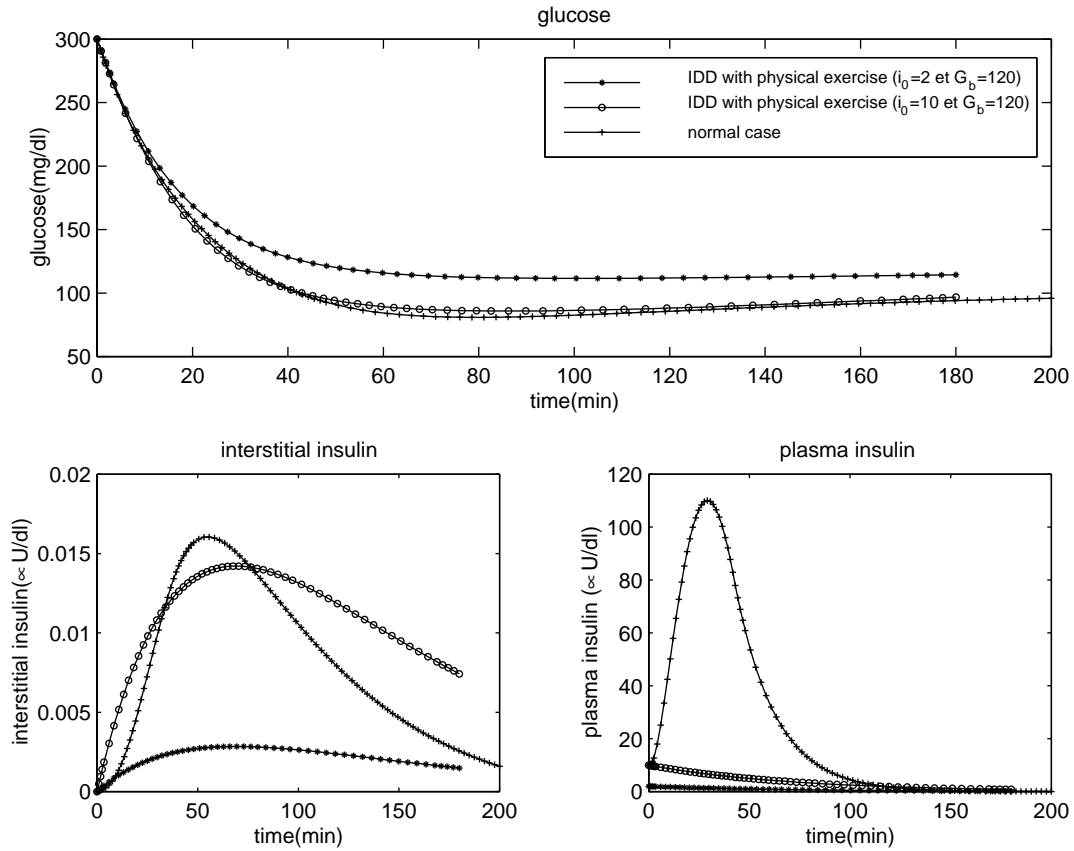


Fig. 3. IDD case: IDD case with exercise, i.e. $q_1 = 0.0028$, $q_2 = 0.75$ and $q_3 = 0.00005$.

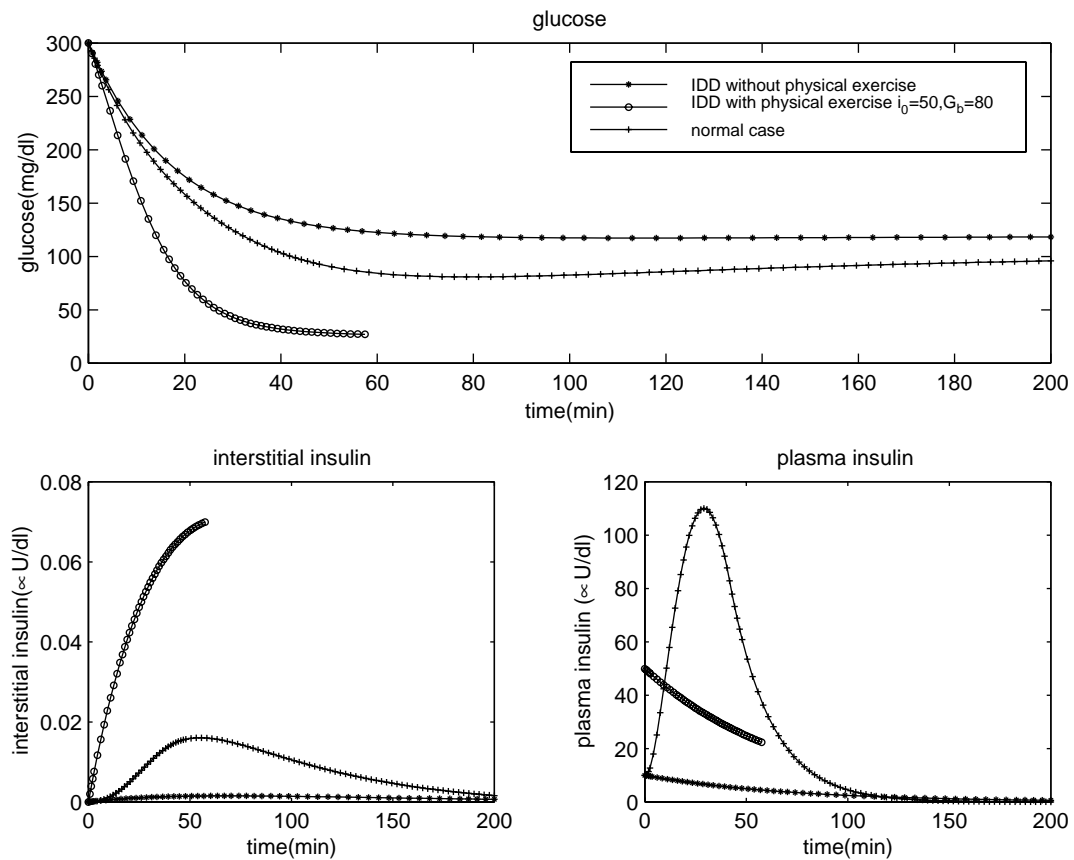


Fig. 4. IDD case: IDD case with exercise, i.e. $q_1 = 0.0028$, $q_2 = 0.75$ and $q_3 = 0.00005$.

NIDD for whom it should be a part of the treatment since it improves insulin sensitivity, lowers the average blood glucose concentration and may improve weight reduction. For IDD people, the emphasis must be on adjusting the therapeutic treatment (insulin and diet) to allow safe participation in all forms of physical activity according to the individual goal and his predisposition.

In the context of diabetes, the psychological side of physical exercise is indisputable. Moreover, it is becoming clear that diabetes is sweeping the globe as a silent epidemic encouraged by decreasing levels of activity and increasing prevalence of obesity.

In using mathematical modelling of physical activity in this paper, our first purpose was to illustrate clearly the effect of exercise on the dynamics of insulin and glucose in order to confirm the role of physical activity as a prevention for people at risk, to stress the benefit that can be gained by NIDD from improving insulin sensitivity and compensating its eventual partial lack, and finally, to reassure IDD people that no exclusion is made provided 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 hypoglycaemia or other problems, and the opposite situation of hyperglycaemia or ketoacidosis where exercise may have negative effect.

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