THE AUTOMATIC REGULATION OF THE BASAL DOSE ON THE INSULIN PUMP FOR THE TREATMENT OF PATIENTS THAT HAVE DIABETES TYPE 1

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Abstract

Diabetes mellitus type 1 is a chronic metabolic disorder, and its main characteristic is Hyperglycemia. It usually occurs in the early years because of the absolute or relative absence of the active insulin that is caused by the autoimmune disease of the β cells of the pancreas. Despite the numerous researches and efforts of the scientists, the therapy for Diabetes type 1 is based on the substitution of insulin. Even though the principles of the therapy have not changed so much, still some important changes have occurred in the production and usage of insulin. Lately, the insulin pumps are more frequent in the therapy for Diabetes type 1. The functioning of the pump is based on the continuing delivery of insulin in a small dose ("the basal dose"), that keeps the level of glycemia in the blood constant. The increase of glycemia during the meal is reduced with the additional dose of insulin ("the bolus dose"). The use of the insulin pumps and the continuing glucose sensors has provided an easier and more efficient monitoring of the diabetes, a better metabolic control and a better life quality for the patient and his/her family.

This work presents the way of automatic regulation of the basal dose of insulin through the synthesis of the functions of the insulin pump and the continuing glucose sensor. The aim is to give a contribution to the development of the controlling algorithm on the insulin pump for the automatic regulation of the glucose concentration in the blood. This could be a step further which is closer to the delivery of the dose of insulin that is really needed for the basic needs of the organism, and a significant contribution is given to the development of the artificial pancreas.

KEY WORDS: Diabetes mellitus type 1, glucose in the blood, insulin pump, basal dose, automatic regulation

Introduction

Diabetes Mellitus type 1 is a chronic metabolism disorder, and its main characteristic is Hyperglycemia. About 10% of all patients who have diabetes have the diabetes type 1. It usually occurs in the early years (< 35 years.) because of the absolute or relative absence of the active insulin that is caused by the autoimmune decadence of the β cells of the pancreas. The contemporary explanation for the occurrence of Diabetes type 1 takes into account the latest discoveries about the disturbed immunoregulation, about the breakdown of the β-cells in the pancreas, the inheritance predisposition and the influence of the environment. Prior to the occurrence of Diabetes type 1, there is a long and hidden process of self-destruction of the β- cells, the so called pre-diabetes. The symptoms of the disease occur after the destruction of 70-90% of the β-cells (1,2,3). The type 1 diabetes is characteristic as in early disease the symptoms that occur are very dramatic and they develop fast. Some of the symptoms are: frequency of urination, enhanced thirst, enhanced appetite, sudden weight loss, weakness etc. The diagnosis is established relatively easily and it is based on the clinical features and the laboratory tests: the blood sugar higher than 11mmol/l in a random blood sample, glucose on an empty stomack > 7 mmol/l along with the symptoms of the diabetes, often with ketonuria, and commonly with ketoacidose. The aim of the therapy for type 1 is to achieve normal concentrations of glucose in the blood, that is on an empty stomach from 3,5 to 6,1 mmol/l, and to 7,5 mmol/l in the period about 1,5-2 hours after the meal. The therapy is based on educating the patient, proper nutrition, physical activity, self-control of the glucose in the blood and the substitution with insulin (1,2). From the time the insulin was discovered (Banting and Best year 1922) until present time, the princips of the therapy for diabetes type 1, despite the numerous researches and efforts of the scientists have not changed so much, yet some significant changes have occurred in the production and usage of insulin. The insulins of animal origin have been substitued with human insulins that are a product of the Recombinant DNA technology. Syringes and needles were replaced by "pens" as well as the insulin pumps which are also used today. The therapy that includes the insulin pump represents a significant and qualitative step forward in the delivery of insulin and the regulation of Diabetes. The first prototype of the insulin pump was made in the year 1963. What prevented their wider usage were the size and ungainliness, as well as the battery duration of only 24 hours. As the interest for a continuing subcutaneous therapy became more frequent, a new generation of technologically improved and dimension adapted insulin pumps occurred during the 1990s (4).

The insulin pump is an instrument size of a mobile phone. It consists of a storage that contains insulin and the infusion set through which the insulin is injected into the body. There is a plastic cannula 6-9 mm in size at the end of the set that is put under the skin through a thin needle which is taken out immediately after the cannula is in the skin. The places where the infusion set is put, are the same as where the subcutaneous usage of insulin. The place of usage, the infusion set and the storage should be changed every 3-4 days. The insulin pump is worn around the waist or attached to the clothes. A special remote that provides a remote control of the pump is available. In special cases (for example in contact sports or swimming) it is possible to separate the infusion set, where one part still remains in the body and is ready to be connected again later (3,4,5). The functioning of the pump is based on the continuing delivery of insulin in a small dose ("the basal dose"), that keeps the level of glycemia in the blood constant, and the increase of glycemia during the meal is reduced with the additional dose of insulin ("the bolus dose"). The delivery of the basal dose of the insulin in the insulin pump has been programmed in advance by the doctors, while the bolus dose needed for the meal is calculated by the patient or his parents based on the contents of carbohydrates in the meal and the concentration of the glucose in the blood (4,5,6). The indications that an insulin pump therapy is needed are: poorly regulated diabetes, increased values of the glycosed haemoglobin (HbA1c), unpredictable oscillations of glycemia, "brittle diabetes", the "dawn phenomenon", the recurrence of hypoglycemia, night hypoglycemia, the recurrence of the diabetic cetoacidose, early occurrence of complications, the school/ work in shifts, adolescents, pregnancies (6,7,8). For a successful therapy what is needed above all is a motivated and educated patient, one who has real expectations concerning the possibilities of the insulin pump.

There is a very small number of patients who are not recommended to use the insulin pump. Those patients are: those with a low level of education, mentally disordered persons, unmotivated patients, patients with an alergy on the infusion sets, children without parent control, a poor collaboration with the diabetic team (4,5). The advantages of the usage of the insulin pump are multiple: an easier and simpler control of the diabetes, the decrease of glycaemia, a better absorption of

the insulin (the variation of the absorptions on the pump is 3%, and on the pen till 52%), a lower daily dose of insulin, minimal subcutaneous depots of insulin, lower number of heavier hypoglycemia, lower number of ketoacidosis cases, better metabolic control (lower HbA1c), higher flexibility in planning the meals and activities, better life quality both of the patient and his family, a smaller number and later occurrence of complications, fewer number of stings in the subcutaneous tissue (with 1460 to 2190 – pen/syringe, on 125 to 140 stings per year - the pump) (8,9,10). Because of the absence of the insulin supplies in the subcutaneous tissue, the disadvantge of the use of the insulin pump is the possibility of developing ketoacidosis (4,11). This occurs because only insulins with quick effects are used in the insulin therapy (7,9). The pump, as a programmable equipment and the sensor of a continuing detection of the glucose, imposes the idea of making a system of automatic regulation of the concentration of glucose in the blood, which aim is basically to imitate the artificial pancreas. However, because of the imperfection of the pump, especially the sensor for the continuing measuring of glucose, this task is not easy to achieve. Today, the insulin pumps work on the so-called open knot (4,6), i.e. the delivery of insulin is carried out based on a model programmed in advance determined by the doctor, without the use of any feedback about the instantaneous value of glucose in the blood. Huge efforts are made today to close the open controlling structure along the variable, which represents the value of glucose in the blood. A closed regulatory knot formed in that way enables a synthesis of the controlling algorithm, with which a invariability of the regulatory structure on the external disruptions-disturbances can be achieved. The final aim is the installation of the sensor for a continuous measuring of the glucose in the blood into the insulin pump, with the integral controlling law that connects both those instruments into a functional unit. The first problem that occurs during the realization of this idea is the delivery of insulin, that should be basically continuous when using the insulin pump, and the value of the amplitude of the continual entrance height of insulin into the body should be changeable with the demanding dynamics. However in reality it is not like that as the pump delivers the insulin to the body by a discreet supply, where the minimal value of the discreet amplitude of insulin is limited, whereby the minimal supply of the insulin is bounded. Second problem in creating an artificial pancreas is the imperfection of the sensor for a continuous measuring of the glucose in the blood.

Hardware structure and the methods of driving algorithm synthesis - the description of the conditions for analysis

For the purpose of examining as detailed as possible the regulatory effects of the delivering system of the basal dose of insulin into the patient's body, it is necessary to identify the mathematical correlations of some variables, i.e. to define the mathematical model of components that comprise a control cycle (circle).

The response of the glucose concentration in the blood S_s is a result of the delivery of insulin into the patient's body u_i, and this dependence can be presented through a simple model as given on the Figure 1.

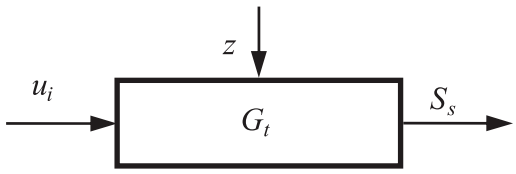

FIGURE 1. Modul dependance of the glucose value from the basal delivery

What is certain is that the dependence $S_s = f(u_i)$ is very complex, and the obstacle (interference) z does not have a deterministic mark, the change is unpredictable and its study is based on the calculus of possibility. The delivered insulin u_i represents the basal dose that has been determined by the number of units of insulin per hour. Despite the existence of quite improved methods of setting up the dose, it is very hard to determine the optimal value of the variable. The variation of the true value of glucose S_s from the given variable u_i, represents the error of regulation $x=S_z-S_s$. The obstacle z can appear because of various reasons depending on how much the antagonist of the insulin affects the concentration of glucose in the blood (glucagon, adrenalin, cortisol and the growth hormone) in different situations: psychological or traumatic stress, infections, "brittle diabetes", "the morn (dawn) phenomenon" etc. (1).

Hence, we are free to say that in this case, it is difficult to presuppose the form and the parameters of the model of transmitted function G_t that connects the response of the true value of the glucose in the blood S_s, i.e. the output system and the delivered insulin that is the entrance u_i The identification of G_t requires experimental measurements of the entrance and output, through the us-

age of methods that enable the usage of sensors of size S_s that are available today. One of the most important facts that has to be taken into consideration during the experimental analysis is that if the S_s reaches the level over the maximal allowed value it can be very dangerous for the patient, which is why it has to be avoided (the advisable concentrations of the glucose in the blood is from 4 to 11 mmmol/l). That lowers the comfort in the pursuit and adjustment of the theoretical and experimental analysis. According to the view of Pharmacokinetics and Pharmacodynamics of the used insulin, it is important to know the developmental process of the activity of the used insulin in time, which directly affects the dynamics of the response change S_s. Namely, the used dose of insulin u_i is organized along the time boundary, including transportation delay, time of response and duration of action according to dynamics, which is above all, specific to the type of insulin. This plan of the applied insulin is determined by the producer of insulin, and in the later text it will be mentioned under the term active insulin and marked with u_{akt}. The Figure 2. shows the time dependence of the active insulin, for the insulin type lispro (9,12) and the regular human insulin. What can be shown with the experimental testing is the approximate dependency of the variables uakt and S_s, which leads to the research of the transfer function G_t. Figure 3. shows the general functional frame scheme of the controlling system. In Figure 3. we can see S_z, S_s - which is the given and true value of the glucose in the blood system, the x is the error of regulation, *Gr, Gi, Gsmt i Gpr* are the transmitting functions of the regulator, the controlled system, compensator for the late response of glucose on insulin, and the estimator of the glucose value, respecitively.

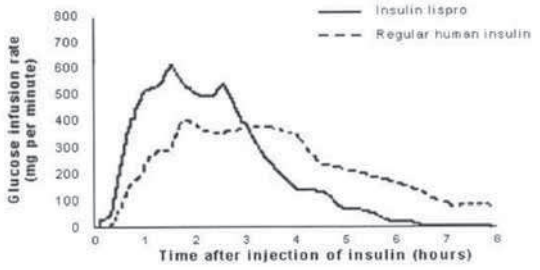

FIGURE 2. The time response of the active insulin

The experimental analysis of the functioning of the projected controlling system has been performed on a true subject, an 18 years old female patient who has had the diabetes mellitus type 1 from September 2002. She has been on the insulin pump therapy from June 2005. The glucose was very well regulated and the patient was quite disciplined. During the performing of the experiment it was important to pay attention to that the possible high or low values of glucose couldn't be tolerated for a longer period. The experiments were performed at night, in the morning and during the day, without any use of glucose at least five hours before the experiment. During the night experiments, the patient was not woken up, so there was no sleep disturbance or any other kinds of disturbances concerning the psychological system in that period (secreting of the growth hormon, cortisol and other). The daily experiment was performed while the patient was relatively calm, without any meal or any hard physical activities performed before that. What needs to be mentioned is the absence of all conditions needed to perform a high-quality experiment. During the experiment a minimal hardware structure was used and it included: an insulin pump "Paradigm 722", a Mini link transmitter, a sensor for the continuing measuring of glucose in the blood system (5), as well as the PC computer with a specially prepared controlling algorithm installed. The communications between the pump and the computer were done by hand, through the transmission of the information on the pump-computer relation, which included the transmission in both directions.

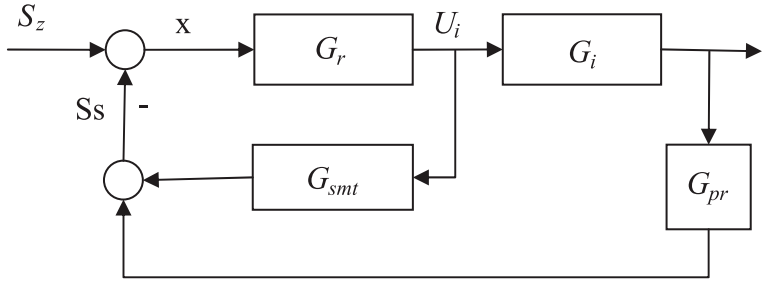

FIGURE 3. Functional frame scheme of the controlling system

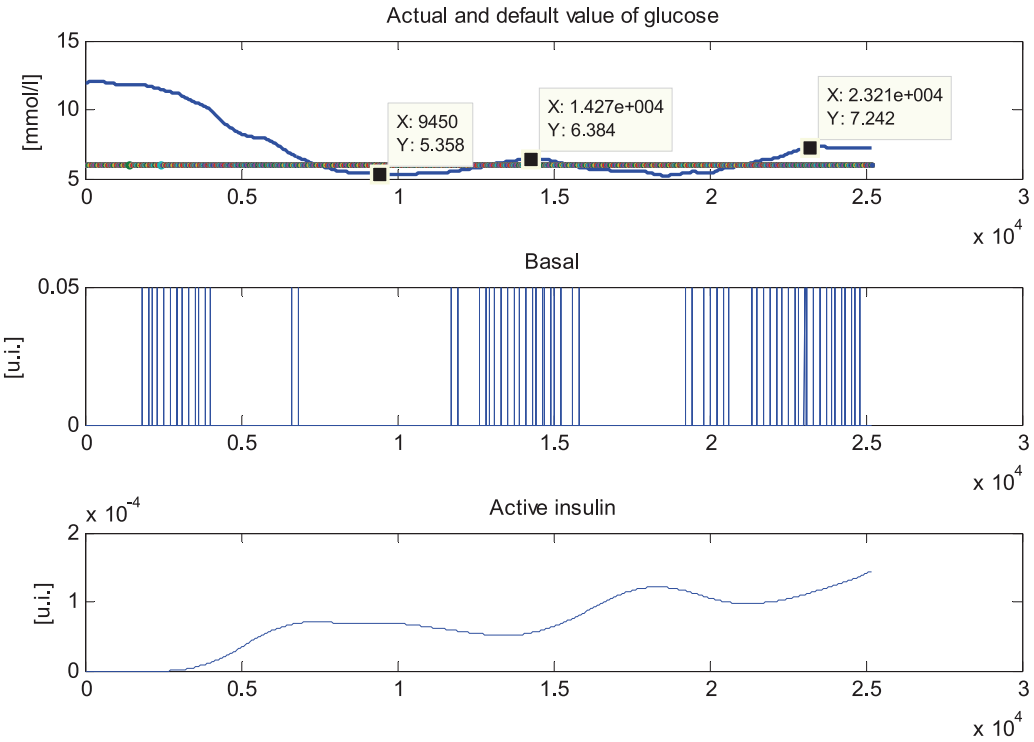

FIGURE 4. The results of the first glucose regulation during night hours

An overview of the experimental testing results

The results of the experimental testing are given on the charts that follow. The value of glucose in all measurements was 6 mmol/l. The information from the testing is saved on the PC in the Matlab/Simulink encirclement where an M_File was formed and in which the algorithm for the regulation of glucose was performed. The horizontal axis on the chart contains the measure of time in seconds, so that the range from 0 to 104 seconds matches the time period of about 2,77 hours. The charts show three variables that are separated from others, even though other variables that were calculated during the regulation were monitored as well. Those three variables are:

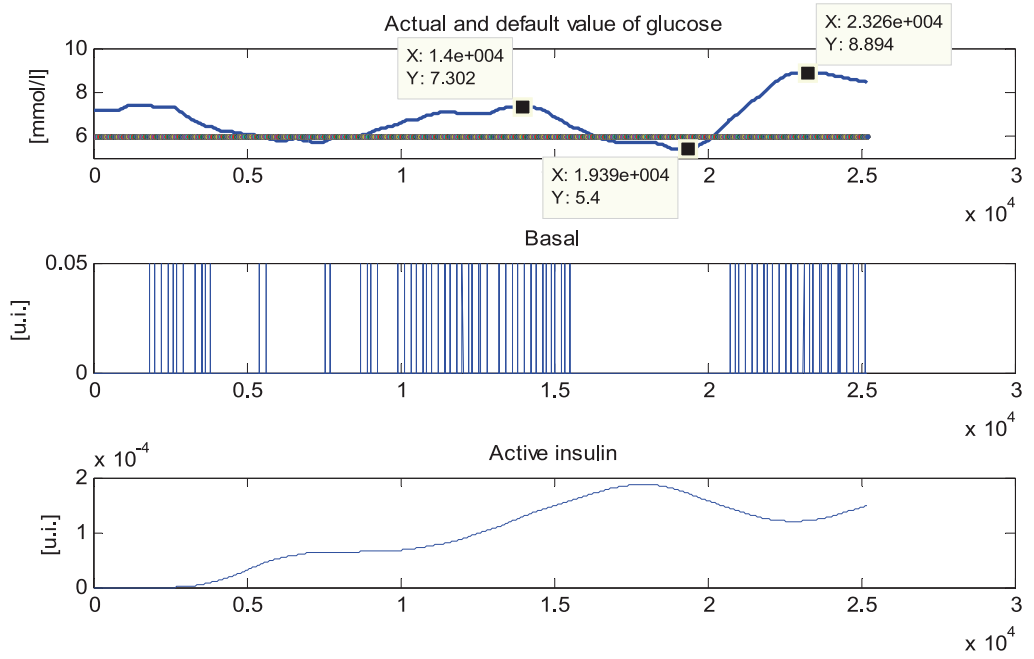

FIGURE 5. The results of the second regulation of glucose in the night and morning hours

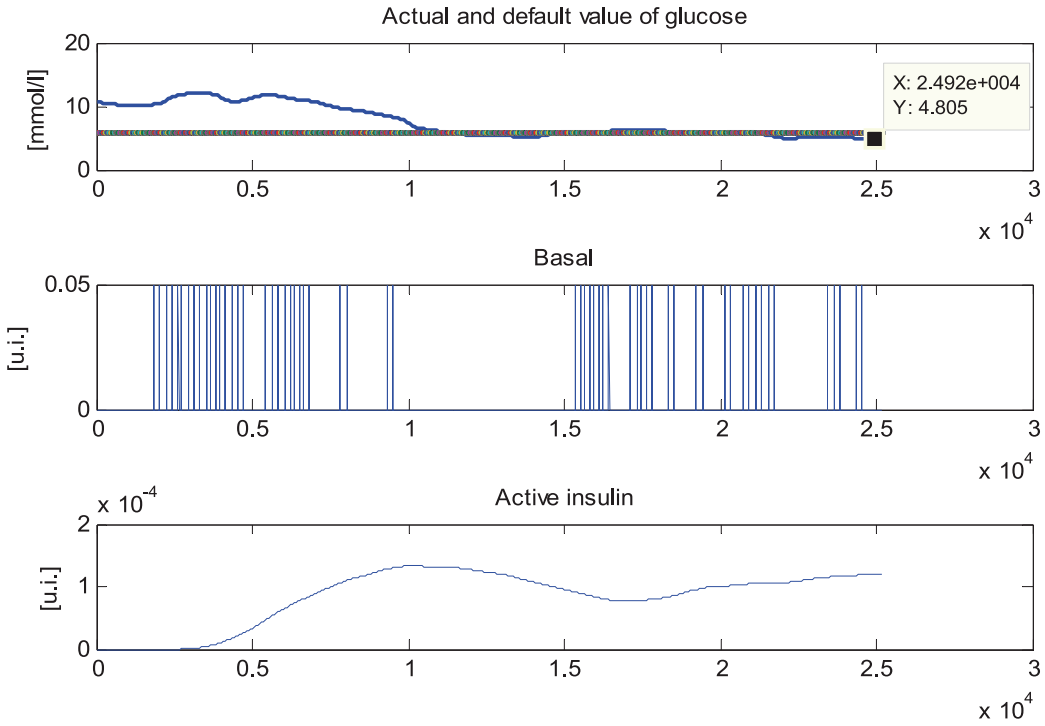

FIGURE 6. The results of the regulation of glucose during the day

- the actual value of glucose, where its default value of 6 mmol/l is presented on the same chart
- the delivered basal dose of insulin, where the activity of the pump can be monitored during the regulation
- the active insulin calculated on the basis of the delivered basal.

Figure 4. shows the results of the testing during the night, with the start at 11.00 p.m. and ending at 06.00 a.m. The patient slept the whole time. After the start of the regulation, the glucose in the blood was 13 mmol/l). Immediately after having been regulated with a supplied basal dose of insulin, the value of glucose dropped to the default value 6 mmol/l through the adjusted dynamics. The value of glucose changed further in the boundaries from 5,38 mmol/l to 7,24 mmol/l when the "dawn syndrome" (growth hormone, cortisol) effect occurred. However, after having reached these values, glucose started falling to the aimed value of 6 mmol/l. So, the effect of its constant stabilization around its default value is noticeable. The results of the second testing of the regulated glucose during the night and morning hours are shown in Figure 5. The measurement was taken in the period between 02:15 a.m. to 09:30 a.m. The radix of the glucose was about 7 mmol/l, and then under the action of the regulated supply of the basal it dropped toward the default value 6 mmol/l. The chart clearly displays the effects of the growth hormone and the cortisol, on the concentration of glucose during the morning hours. Beside the insulin antagonist, the increased need for insulin in the early morning hours has an effect on the boost of glucose and the increased delivery of the basal dose. Even though these reasons caused the increase of glucose to the value of 8,89 mmol/l, yet the reaction of the controlling algorithm responded with a higher frequency of supply of the projected basal, which again led to the dropping of glucose toward the default value 6 mmol/l. The effect of the stabilization of the default value is emphasised in this case as well.

Figure 6. displays the results of the regulation of glucose during the day. The measuring took place from 11.00 a.m. till 6.00 p.m. The patient did not consume any food and was in the state of relative rest. The radix of glucose was around 11 mmol/l, but with the controlling logic it was reduced to around the default value of 6 mmol/l. Again, the regulated supply of the basal keeps the value of glucose around the default value.

Discussion

The results of the experimental research show the justification for the introduction of the planned controlling algorithm. It is obvious that what we achieve with the automatic regulation of the basal dose on the insulin pump is the stabilization of the glucose in the blood when in

state of rest, but also in situations that we can not predict with certainty because of the effects of the insulin antagonist. Namely, because of the periodical and pulsating secretion of the growth hormone, the basal dose can't be determined in advance, nor we can predict the stress (enhanced secretion of the adrenaline), infections and similar situations that lead to the enhanced secretion of the insulin antagonist and the increase of the concentration of glucose in the blood. A better compensation for the increased value of glucose in the blood can be achieved by selecting a larger dose of basal. However, in that case, there is a higher possibility for the occurrence of hypoglycaemia, which would certainly disappear with the passage of time because of the controlling effect of the system. For the purpose of getting the value of glucose that would represent the compromise between the avoidance of hypoglycemia and the achievement of the minimal regulation error, an idea about the optimization of the basal value is imposed. During the measurement, apart from the value of glucose, a lower usage of insulin during the use of this controlling algorithm was noticed than in the situation when the basal was given manually. That use of insulin was even to 1/3 in favour of the controlling algorithm.

Conclusion

Based on the given research results it can be said that the main gains of introduction of the regulated system of the insulin delivery are:

- A considerable improvement of the regulation of glucose concerning the given value, regardless of the effects of the mentioned psychological disturbances.
- The delivery of the optimal dose of insulin needed for the maintenance of the normoglycaemia and the basal needs of the organism.
- Less hypo – hyperglycemia.
- In case that the regulating system gets out of function, the patient can easier feel the problem of hyperglycemia and react on time.
- Economic justification because of a lower use of insulin. The true value of the insulin savings can be examined through further studies.

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