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ORIGINAL ARTICLE

Are we helping or harming our insulin-treated diabetic patients during ambulatory treatment?

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Abstract

Introduction. Correctness of insulin treatment depends on both the experience and skills of the doctor and knowledge and behaviour of the patient.

Objective. Evaluation the adequacy of insulin doses administered to diabetes patients in ambulatory conditions.

Material and methods. The treatment of 59 patients hospitalized in the Diabetology Ward was evaluated at admission, discharge and 3 months after hospitalization.

Results. The mean daily doses of insulin significantly differed at times of evaluation and were: 53.90, 39.31 and 43.34 units, respectively ($p \approx 0.000001$). A significant reduction of body weight, 90.86 vs. 88.25 kg ($p \approx 0.000001$), was obtained only during hospitalization, and was maintained 3 months after discharge (87.86 kg). Significant differences were also noted in the body mass index (33.44 vs. 32.48 vs. 32.37 kg/m^2, $p \approx 0.000001$). The change in waist circumference was not statistically significant (107.87 vs. 104.89 cm; $p \approx 0.06$). A decrease in the number of hypoglycaemia episodes was observed, but were statistically insignificant (25 vs. 23; $p \approx 0.7$). Three months after hospitalization an insignificant decrease of HbA1c level was noted (8.41% vs. 8.03%; $p \approx 0.07$).

Conclusions. During treatment in the Diabetology Ward the procedure of choice was more frequently a reduction than an increase in insulin doses. This management led to the reduction of the patients' body weight, improvement of glycaemia, without any significant effect on the diabetes control determined by the HbA1c level.

Key words

diabetes mellitus, insulin therapy, body weight, glycated haemoglobin

INTRODUCTION

The discovery of insulin and method of its extraction by Frederick Banting and Charles Best in 1921, and the start of mass production of insulin a year later, was undoubtedly a turning point in the treatment of diabetes and one of the most important discoveries in medicine of the first half of the 20th century. The diagnosis of diabetes was no longer a death sentence. The life span of patients with diabetes considerably increased. Among the consequences of which was the necessity to struggle with the consequences of chronic complications associated with diabetes mellitus – micro- and macroangiopathies. To improve insulin treatment, new methods of insulin delivery (jet injectors and pumps) and new types of insulin were developed. However, despite many years of experience and excellent equipment mistakes in insulin treatment cannot be avoided.

Insulin therapy is the only method of type 1 diabetes treatment. It becomes indispensable when in type 2 diabetes a deficit of insulin secretion by the pancreatic beta cells joins with insulin resistance, and in special situations such a pregnancy, surgery, myocardial infarction (in some cases temporarily) soon after diabetes diagnosis [1, 2]. Publication of the results of the DCCT study [3], and subsequent UKPDS [4] and Kumamoto Study [5] resulted in intensive insulin treatment becoming recognized as a mandatory method, both for specialists and family doctors, and a significant reduction of chronic complications found in those studies gave them the sense that they possessed magic wand.

The results of the ACCORD [6] and VADT [7] studies, which suggested that there may possibly exist groups of patients who do not benefit from the intensification of treatment, were not received enthusiastically. A controversial report by Hemkens was widely criticized – especially due to the methodology of research, whereas the reports by other groups, which did not confirm the reports concerning glargine, did not refer to the section of the study pertaining to an increased cancer risk according to insulin doses [8]. 'Yellow lights' has been downplayed by many practitioners.

The aim of the study was evaluation of the doses, number of injections, and the adequacy of insulin doses administered in ambulatory conditions in patients admitted to the Diabetology Ward due to hyperglycaemia. Of special interest were the effect of the dose dependent effect of insulin (metabolic control of diabetes, changes in patients' body weight, number of hypoglycaemic episodes), and the influence of insulin dose change on diabetes control 3 months after discharge from hospital.

MATERIAL AND METHODS

The prospective study covered patients who received treatment in the Diabetology Ward during the period from 1 June 2010 – 31 December 2010. The inclusion criteria were

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age 18–80, and diabetes treated with insulin for at least one year, while the exclusion criteria were as follows:
– treatment with any oral medications, apart from metformin, during the period of the study and 3 months before the study;
– pregnancy;
– infectious disease;
– cancerous disease;
– heart failure > NYHA Class II;
– thyroid function disorders.

At admission, discharge and 3 months after hospitalization, anthropometric parameters were evaluated (body weight, height, waist circumference, body mass index – BMI), as well as glycated haemoglobin (HbA1c) level, number and size of doses, and types of insulin, presence of hyper- and hypoglycaemia registered in the patient's diabetes self-control diary.

Measurements of the percentage of HbA1c in capillary blood samples collected by finger stick were performed using immunological tests and a chemical technique with the use of Bayer A1cNow+ analyzer.

Statistical analysis was conducted by means of Statistica 8.1 PL package. In order to compare co-variance of the dynamics of the selected quantitative characteristics (body weight, HbA1c level, insulin doses), apart from comparing changes in absolute value, these characteristics were standardized by recalculation to the fraction of the initial value. In 3-month observation the decreases in parameters were noted negatively, while increases – positively. Due to the deviations from normal distribution, the significance of the relationships were investigated by means of Spearman rank correlation test. In the case of ordinal scale, Kruskal-Wallis ANOVA test by ranks was applied. In order to compare the changes of distribution in 3 paired variables, Q Cochran test for dychotomic variables and ANOVA Friedman test were used for the remainder.

RESULTS

The study covered 59 patients: 12 (20.3%) with type 1 diabetes, 45 (76.3%) with type 2 diabetes and 2 (3.4%) with secondary diabetes – 27 females (46%) and 32 males (54%). The mean age of the respondents was 59.4 years (20–79). The mean duration of diabetes was 14.8±7.87 years (1–40), and duration of treatment with insulin – 8.4±5.8 years (1–24). In 32 respondents (54%) macrovascular complications were diagnosed, whereas in 49 (83%) – microvascular complications.

The mean daily insulin dose at admission was 53.9±23.71 IU, at discharge – 39.31±15.59 IU, while 3 months after hospitalization (follow-up) – 43.34±17.01 IU. The differences were statistically significant ($p<0.00001$). During the study, there were no significant differences in the number of insulin injections per day: 3.86±1.11, 3.9±1.11 and 4.07±1.06; $p \approx 0.1$, respectively (Tables 1 and 2).

Among patients with type 2 diabetes, 25 (56%) were administered metformin at admission, 28 (62%) at discharge, and 30 (67%) 3 months after discharge ($p \approx 0.4$). The mean daily dose of metformin in mg (calculated as 0, when a patient with type 2 diabetes did not take it) was: 1,128.26±1,156.65, 1,370.21±1,207.34 and 1,426.60±1,198.32, respectively. The differences were statistically significant ($p \approx 0.04$).

Table 1. Dynamics of changes in insulin doses during the study.

Daily insulin dose	admission/ discharge		discharge/ follow up		admission/ follow up	
	N	%	n	%	n	%
Increase	9	15	34	58	14	24
Without change	4	7	16	27	5	8
Reduction	46	78	9	15	40	68

Table 2. Changes of daily insulin doses per kilogram of body weight in different types of diabetes.

Type of diabetes	n	admission		discharge		follow up		p
		Mean	SD	Mean	SD	Mean	SD	
type 1	12	0.63	0.28	0.57	0.18	0.58	0.20	0.98
type 2	45	0.60	0.22	0.43	0.19	0.49	021	**0.00000**
secondary	2	0.46	0.01	0.35	0.08	0.45	0.01	0.14
all	59	0.60	0.22	0.45	0.19	0.51	0.21	**0.00000**

Due to changes introduced in the management of diabetes, an improved glycaemic control was obtained, understood as the HbA1c level, and also a decrease in glycaemic variability. The mean HbA1c level at admission was determined to be 8.41±1.68%, and during follow-up examinations – 8.03±1.57%; $p \approx 0.07$. Hyperglycaemia of over 200 mg% at admission was found in 52 (88%) respondents, while 3 months after hospitalization – in 36 (61%); $p \approx 0.008$, whereas hypoglycaemia defined as the level of glycaemia below 60 mg% was diagnosed in 25 (42%) and 23 (39%) respondents, respectively; $p \approx 0.8$.

Table 3 presents changes of anthropometric parameters during the study. Waist and hips circumferences were not measured at discharge from hospital.

Table 3. Changes in anthropometric parameters during observations.

	admission		discharge		follow up		p
	Mean	SD	Mean	SD	Mean	SD	
body weight (kg)	90.86	20.53	88.25	18.75	87.86	18.77	**0.00000**
body mass index (kg/m^2)	33.44	7.38	32.48	6.74	32.37	6.90	**0.00000**
waist circumference (cm)	107.87	14.63	---	---	104.89	14.97	0.07
hips circumference (cm)	110.63	13.64	---	---	108.39	12.98	**0.04**
waist/hips ratio	0.98	0.07	---	---	0.97	0.08	0.80

Table 4 presents the relationship between the dynamics of selected parameters during 3-months observation, according to the evaluation by Spearman rank correlation test (correlation coefficient, *$p < 0.05$).

It was observed that the reduction in insulin dose per day was accompanied by a significant reduction in body weight (Fig. 1). No significant relationships were observed between changes of daily insulin dose and HbA1c level.

Changes in daily insulin doses, HbA1c level and body weight were also analyzed relative to each other in the groups. For statistical analysis, changes of ≥10% in daily insulin dose and ≥5% in body weight were considered significant. (Fig. 2–4).

Table 4. Relationship between dynamics of selected parameters in 3-months observation.

Changes in parameters in fraction of initial value			
	change of body weight	**change of daily insulin dose**	**change of HbA1c level**
change of body weight	----	*0.48	0.09
change of daily insulin dose	*0.48	----	-0.04
change of HbA1C level	0.09	-0.04	----
Changes of parameters in absolute units			
	Change in body weight	Changes in insulin doses per day	Change in HbA1C level
change of body weight	----	*0.55	0.07
change of daily insulin dose	*0.55	----	-0.07
change of HbA1C level	0.07	-0.07	----

* statistically significant correlation coefficient.

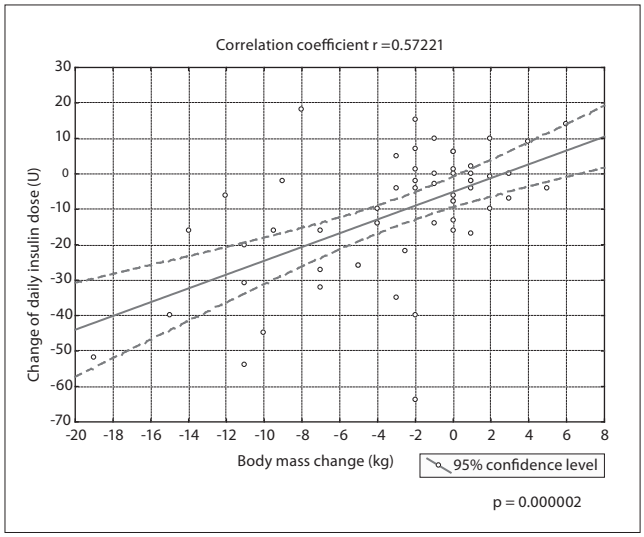

Figure 1. Scatter of changes in insulin doses by changes in body weight during the study (admission vs. follow-up).

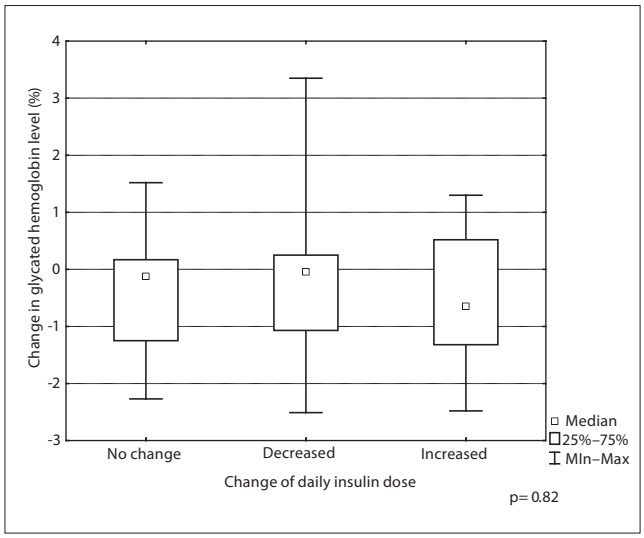

Figure 2. Change in glycated haemoglobin level (%) vs. change in insulin dose per day in 3-months observation (lack of change – up to 10% of dose change).

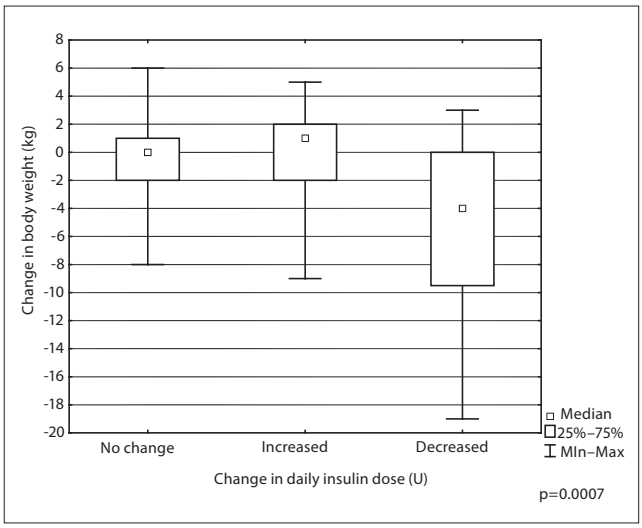

Figure 3. Change in body weight (kg) vs. change in daily insulin dose in 3-months observation.

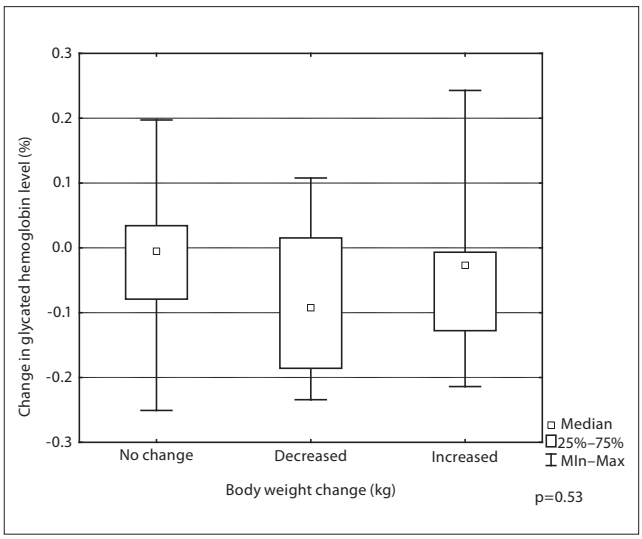

Figure 4. Change in glycated haemoglobin level (%) vs. change in body weight in 3-months observation.

DISCUSSION

The inspiration for the study was an observation made in our ward that patients hospitalized due to inadequate control of diabetes are often discharged with lower insulin doses than those taken prior to admission to hospital. It was hypothesised that that due to an easiness of administration of insulin by means of modern jet injectors, and safety profiles of new types of insulin (rapid-acting and long-acting, peakless analogues) reported in many studies, an illusion arose about the complete safety of their use in ambulatory treatment. Such a conviction, in combination with an incomplete education promoting, in a certain sense, intensive treatment also by means of high insulin doses without full knowledge of pathogenetics and pharmacodynamics, may cause – and according to our observations, does cause – a danger of administration of excessive doses. This not only fails to produce the anticipated therapeutic effects, but is associated with body weight gain, increased risk of hypoglycaemia, and may be related with an increased risk of selected cancerous diseases.

In the group of patients examined in the presented study, insulin doses per day were successfully reduced without deterioration in glycaemia, with even a contradictory tendency towards improvement, although the results were statistically insignificant.

The reduction of insulin doses in the majority of patients resulted in a lower instability of glycaemia control, an improvement of diabetes control (HbA1c) and reduction in body weight, provided that the patient complied with the recommendations of diet regime.

The administration of excessive doses of insulin makes a difference for the patients, and obviously exposes them to the risk of hypoglycaemia. In the DCCT study, severe hypoglycaemia was defined in such way that a patient requires assistance from others, and was noted in 26% of patients who received intensive therapy, with 1.9 episodes of severe glycaemia in a patient annually [9]. In the UKPDS study, such an event was reported by 1–2% of respondents, more if the patient was administered insulin, compared to other methods [4]. Hypoglycaemia during insulin therapy increases the risk of injuries (falls, road accidents) [10], while recurrent hypoglycaemia damages the central nervous system [11]. According to recent clinical studies, it also increases the risk of cardiovascular complications and associated with them mortality among patients with a many-year course of diabetes (ACCORD, VADT) [6, 7].

An additional effect of hypoglycaemia may be so-called rebound or contra-regulation, i.e. the production of hormones with the opposite effects of insulin (mainly epinephrine and glucagon, also corticosteroids) in response to the decrease in the level of glycaemia. This may cause a subsequent uncontrolled production of glucose in the liver, the breakdown of glycogen stored in the liver and muscles, and in consequence, hyperglycaemia. This introduces the organisms into the mechanism of a 'vicious circle', and in the case of being unaware of hyperglycaemia leads to wrong management by the patient and the physician in charge [12, 13]. This phenomenon has been known for many years but is frequently ignored. As early as 1938, a Hungarian professor of biochemistry, Michael Somogyi, while engaged in research at the University of Saint Louis, described that excessive insulin doses may cause glycaemia decreases of which patients are unaware, especially at night, which results in morning hyperglycaemia and instability of diabetes [14]. Although some later reports have somewhat discredited this theory [15, 16], nevertheless, it has been confirmed many times in our everyday practice.

The subsequent unfavourable effect of the application of insulin is body weight gain. In type 1 diabetes, initially, it is not always an undesirable effect – it evidences the balancing of deficiencies developed during the period of metabolic decompensation. During the later period, an intensive insulin therapy favours a higher frequency of unaware and mild hypoglycaemias, resulting in the necessity to consume additional meals. A similar mechanism is responsible for increased appetite in patients with type 2 diabetes. Apart from that, it should be remembered that insulin is a anabolic hormone, which is conducive to the driving of carbohydrates, proteins and fats into the cells.

An increase in body weight is associated with increased insulin resistance, which in type 2 diabetes produces the effect opposite to the intended clinical effect. In the DCCT study, patients with type 1 diabetes intensively treated with insulin increased their body weight by 4.75 kg more than those who received a conventional treatment [17]. In the UKPDS study, insulin therapy was related to body weight gain by 1.4–2.3 kg [4]. An unfavourable effect of insulin on body weight in patients with type 2 diabetes may be minimized using so-called sensitizers, especially metformin. Due to its administration, the insulin doses applied may be lower, with the simultaneous improvement in glycaemia control [1].

In recent years, an increased risk of selected cancerous diseases while applying insulin has also been reported [8, 18, 19, 20]. Both endogenous and exogenous hyperinsulinemia in combination with insulin resistance promotes phosphorylation and activation of farnesyltransferase – an omnipresent enzyme responsible for the farnesylation of Ras proteins. An increased activity of farnesylated Ras on the surface of cellular membranes intensifies mitogenic response to the effect of various growth factors, which is related with the advancement of atherosclerosis and carcinogenesis. This effect is specific for insulin, irrespective of its type [21]. It is noteworthy that metformin, which was frequently omitted in our patients with type 2 diabetes, or applied in too small doses, has a confirmed anti-cancerous effect [20, 22, 23].

Many patients become in a way accustomed to higher levels of glycaemia, and do not feel well during its rapid decrease, and may suffer complaints on the part of nerves and muscles. A rapid intensification of insulin therapy in order to obtain normoglycaemia in patients with chronically uncontrolled diabetes complicated by retinopathy may lead to progress in ocular complications [24]. Hence, it is recommended not to reduce the HbA1c level by more than 2% annually in patients with long-lasting, inadequately controlled diabetes, with the diagnosis of retinopathy [1].

Despite the above-mentioned threats, one should not be afraid to apply insulin. It is certainly a life saving medication, irreplaceable in everyday diabetologic practice. We do not advocate against an intensive treatment of patients with diabetes, nor against its adequate control. On the contrary, considering the results of the studies EDIC [25], post-UKPDS [26] and the Kumamoto Study [5], we are its enthusiasts. Many studies indicate that a too delayed onset of insulin therapy may be unfavourable for the patient; 53% of patients with type 2 diabetes treated with sulphonylureas require the inclusion of insulin into the treatment after 6 years, while 80% after 9 years [1]. An early insulin therapy may prevent the complete loss of capability of β cells of the pancreas to secrete insulin [27, 28], and the development of its chronic complications [4]. Such a treatment also exerts a favourable effect on lipid metabolism [29] and decreases mortality after myocardial infarction [30]. In addition, an intensive insulin therapy in patients with type 2 diabetes, by decreasing the number of chronic complications, allows a considerable reduction in the costs of treatment of patients with diabetes, both those who had previously been treated with sulphonylureas, and those conventionally treated with insulins [5, 31].

Despite these premises, when seeing high levels of glycaemia in a patient's diary, before inclusion of insulin or increasing its dose, it should be considered whether they do not the result of causes other than insulin deficiency.

CONCLUSIONS

Patients with diabetes, especially type 2, are frequently treated with excessive doses of insulin, which is associated with body weight gain and a greater instability of glycaemia. These tendencies may be reversed by means of education and the reduction of insulin dose per day. Paying attention to an adequate life style, and a comprehensive analysis of the causes of hyperglycaemia, should prevail over a mechanical increase of insulin doses. In patients with type 2 diabetes the administration of high doses of metformin may also be important.

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