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Physical exercise impact on the risk of hypoglycemia in insulin-dependent patients

Impactul exerciţiului fizic asupra riscului de producere a hipoglicemiei în cazul pacienţilor insulino-dependenţi

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Abstract

Background. Studies of recent decades in the field of diabetology reveal the importance of physical exercise in achieving an adequate metabolic control of insulin-dependent patients. An effective therapeutic approach involves ongoing and personalized assessment of patients, related to the intensity and duration of physical exercise, as well as an appropriate adjustment of insulin dosage and diet, pre- and post-exercise, in order to lower the frequency and severity of hypoglycemic episodes.

Aims. Studying the glycemic response to exercise of 14-15 year old diabetic patients, as well as optimizing long term metabolic control, by a six month longitudinal experiment.

Methods. Clustered sampling brought about two investigated groups: the experimental group (A-12 subjects), to which a program of 45 minute moderate intensity exercise was applied, 4 sessions per week, with the duration of 6 months, and the control group (B-12 subjects), in which physical activity was limited to ADL (Activities of Daily Living). Glycemic control was accomplished by the initial and final evaluation of glycosylated hemoglobin (HbA1c) values. The frequency of hypoglycemic episodes was reported monthly by the questionnaire method. Inferential statistics results were assigned using the GraphPad InStat 3 statistical software.

Results. The mean HbA1c values were significantly different between the two groups, being decreased in the experimental group compared to the control group, in the final evaluation. Also, the frequency of reported hypoglycemic episodes decreased from 58% in the first month of the experiment to 17% at its end.

Conclusions. Moderate intensity exercise, systematically applied, induces significant decreases in blood glucose levels. Consequently, adjustments related to insulin requirements and carbohydrate intake significantly reduce the frequency of hypoglycemic episodes, ensuring the long-term adequacy of metabolic control of diabetes.

Key words: metabolic control, hypoglycemia, glycosylated hemoglobin, physical exercise

Rezumat

Premize. Studiile efectuate în ultimele decenii în domeniul diabetologiei relevă importanţa exerciţiului fizic în obţinerea unui control metabolic adecvat în cazul pacienţilor insulino-dependenţi. O abordare terapeutică eficientă presupune evaluarea permanentă şi individualizată a pacienţilor, privind intensitatea şi durata efortului fizic efectuat, precum şi ajustarea corespunzătoare a dozelor de insulină şi a dietei pre- şi postefort, în vederea reducerii frecvenţei şi intensităţii episoadelor hipoglicemice.

Obiective. Realizarea unui experiment de tip longitudinal cu o durată de şase luni, cu scopul studierii răspunsului glicemic imediat la efort în cazul unor pacienţi diabetici cu vârsta de 14-15 ani, precum şi optimizarea controlului metabolic pe termen lung al acestora.

Metode. Prin eşantionare dirijată au fost investigate două grupuri: grupul experimental (A-12 subiecţi), asupra căruia a fost aplicat un program de exerciţii fizice de intensitate moderată, cu durată de 45 minute, 4 şedinţe săptămânal timp de 6 luni şi grupul martor (B-12 subiecţi), la care activitatea fizică s-a rezumat la ADL (Activities of Daily Living). Monitorizarea glicemică s-a realizat prin evaluarea iniţială şi finală a valorilor hemoglobinei glicozilate (HbA1c). Frecvenţa episoadelor hipoglicemice a fost raportată lunar, prin metoda chestionarului. Rezultatele statisticii inferenţiale au fost obţinute utilizând softul statistic GraphPad InStat 3.

Rezultate. Media valorilor HbA1c diferă semnificativ, fiind diminuată la grupul experimental faţă de grupul martor, în etapa evaluării finale. De asemenea, frecvenţa episoadelor hipoglicemice raportate a scăzut de la 58% în prima lună a experimentului la 17%, la finalul acestuia.

Concluzii. Exerciţiul fizic de intensitate moderată, aplicat sistematic, induce scăderi semnificative ale nivelului glicemiei. Ajustările concomitente şi corelate ale necesarului de insulină şi carbohidraţi reduc semnificativ frecvenţa episoadelor hipoglicemice, asigurând pe termen lung un control metabolic adecvat al diabetului zaharat.

Cuvinte cheie: control metabolic, hipoglicemie, hemoglobina glicozilată, efort fizic.

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Introduction

Insulin-dependent diabetes (T1D) is a chronic disease with onset in childhood or early adulthood, developing inflammatory destructive lesions of pancreatic beta cells, related to a decrease or loss of insulin secretion (Dumitrescu & Perciun, 2000). This condition requires compulsory insulin administration and essential lifestyle changes (continuous glycemic monitoring, proper diet, physical exercise) in order to meet an optimal metabolic control and maintain the quality of life.

The most relevant parameter for an accurate glycemic control is the concentration of glycosylated hemoglobin (HbA1c), which reflects the average blood glucose levels within the last 2-3 months, therefore, HbA1c is used for long-term glycemic control (Vereşiu et al., 2004; Ragnar & John, 2010). The correlation between HbA1c values and average daily blood glucose is shown in Table I. We note here that an adequate metabolic control requires HbA1c values below 7%, the range of reference values for healthy individuals being between 4-6%.

Table I
Correlation between HbA1c values and average daily blood glucose in T1D patients.

HbA1c values (%)	Average blood glucose (mg/dl)
7	150
8	180
9	210
10	245
11	280
12	310

(Vereşiu et al., 2004)

The immediate effects of achieving this therapeutic goal (HbA1c below 7%) inevitably involve the appearance of the most common side effect of insulin therapy, as well as the most feared complication of type 1 diabetes in children and young people - hypoglycemia.

Hypoglycemia involves the lowering of blood glucose levels below 55 mg/dl (Vereşiu et al., 2004), with a usual remission of its signs or symptoms by glucose administration.

In insulin-treated diabetes, hypoglycemia occurs due to the following conditions (De Vries et al., 2004):

- insulin excess
- inadequate carbohydrate ingestion
- late degradation of insulin in the body
- deficiency of counter-regulatory hormone response
- failure to recognize hypoglycemia symptoms.

Severe hypoglycemia requires assistance for correction, causes stress and anxiety (De Vries et al., 2004), significantly influencing glycemic self-monitoring, as well as patient adherence to insulin treatment (Brands et al., 2005). Conclusions of specialized studies in the field of insulin therapy show that severe and prolonged hypoglycemia could lead to irreversible damage of the nervous system (Wiltshire et al., 2006; Matyka et al., 1999).

Physical exercise is introduced as a therapeutic method in a TD1 patient educational program. Practicing regular exercise in a well balanced metabolic condition increases endogenous or exogenous insulin sensitivity, improves glucose tolerance and therefore leads to a decrease in blood glucose levels, as a short-term response, as well as in HbA1c values, as long-term control (Dumitrescu & Perciun, 2000). Despite these beneficial effects, increasing the risk of severe hypoglycemic episodes as a result of improper exercise induces panic in TD1patients and their families and may ultimately lead to the rejection of all forms of physical activity (McMahon et al., 2007; Kaufman et al, 2002). As such, the attention of specialists in the field of diabetology is now largely focused on identifying the most effective therapeutic modalities to reduce this major risk.

According to the *American Diabetes Association*, educational programs of children and young people diagnosed with type 1 diabetes, with a proper glycemic balance, should include at least 60 minutes of daily moderate aerobic exercise (Herbst et al., 2007).

Applying an exercise program to patients with type 1 diabetes must take into account that their insulinemia derived by exogenous administration has a different response to exercise compared with non-diabetic individuals (Guelfi et al., 2005). Inadequate insulin administration causes an imbalance of insulin metabolism, either by the liver production of glucose or through its peripheral use. The excess of exogenous insulin administration in an inflexible manner will lead to hypoglycemia by faulty glucose release from glycogen stores, as well as by excessive peripheral glucose expenditure (Vereşiu et al., 2004).

Conclusions of an impressive number of specialized studies in the field show that it is virtually impossible to determine a proper pattern, due to the insulin therapy features and the individual metabolic response to the *insulin-diet exercise* algorithm (Bota & Teodorescu, 2007).

An effective therapeutic approach involves an ongoing and individualized assessment of the intensity and duration of exercise performed, as well as an appropriate adjustment of diet and insulin dosage before and after exercise, in order to reduce the frequency and severity of hypoglycemic episodes (Chase et al., 2001). Thus, our research frames a complex therapeutic algorithm, developed within a team (diabetologist, nutritionist, coach) with permanent interaction, according to the fundamental principles of T1D therapy (Herbst et al., 2007), such as:

- performing physical exercise given that glucose does not exceed 250 mg/dl, without signs of ketosis;
- a blood glucose value below 100 mg/dl pre-exercise requires the intake of adequate amounts of both fast and slow absorbable carbohydrates;
- exercise is permitted under the knowledge of its type, intensity and duration;
- performing scheduled exercise that allows the adjustment of insulin doses and carbohydrate intake;
- avoidance of insulin administration in a region where the muscle mass is to be exercise trained;
- blood glucose monitoring before, during and after exercise;
- exercise to be delayed to the moment of insulin administration.

Hypothesis

Performing systematic and controlled moderate-intensity exercise reduces the frequency and severity of

hypoglycemic episodes under a flexible scheme of insulin treatment and permanent adjustment of carbohydrate intake, leading to a long-term metabolic control in patients with type 1 diabetes.

Material and methods

Research protocol

We mention that according to the Helsinki Declaration, Amsterdam Protocol and Directive 86/609/EEC, we obtained the subjects' informed consent for their personal participation in the research.

a) *Period and place of the research*

Our research was conducted as a longitudinal experiment type, with a duration of 6 months (November 2012-April 2013), aiming to study the immediate glycemic response to exercise, to assess and reduce the risk of post-exercise hypoglycemia, as well as to improve long-term metabolic control in patients diagnosed with type 1 diabetes from the *Association of Children and Youth with Diabetes* (ASCOTID Mures).

The research protocol used the following methods:

- the observation method (for a relevant case history research);
- the questionnaire method (to determine the inclusion and exclusion criteria, as well as for the periodic report of hypoglycemic episodes);
- testing of glycemic parameters (pre- and post-exercise blood glucose levels, HbA1c values);
- statistical and mathematical methods („t" Student test – for assignment and interpretation of statistical significance).

b) *Subjects and groups*

Two groups were investigated by conducted sampling: the experimental group (A-12: 5 girls, 7 boys, normal weight, with a length of 2-3 years of T1D), to which a 45 minute program of moderate intensity aerobic exercise was applied, 4 sessions per week, with a duration of 6 months, and the control group (B-12: 6 girls, 6 boys, normal weight, with a length of 1-3 years of T1D), in which physical activity was limited to ADL (activities of Daily Living), as well as unscheduled exercise, thus undirected, with various degrees of intensity.

The experiment inclusion criteria were as follows:

- patients diagnosed with type 1 diabetes within the 14-15 year age group;
- patients diagnosed for at least one year, with a good metabolic balance and without major side effects;
- patients with good adherence to multiple insulin administration (2 doses daily in the control group/4-5 doses daily in the experimental group);
- patients with good response to our experimental program.

c) *Tests applied*

Short-term glycemic monitoring was performed by testing pre- and post-exercise blood glucose levels, while long-term monitoring included the initial (November 2012) and final (April 2013) assessment of glycosylated hemoglobin (HbA1c) values. The frequency of hypoglycemic episodes was reported monthly by the questionnaire method.

d) *Statistical processing*

Inferential statistics results were assigned using the statistical software GraphPad InStat 3.

The interpretation of results, by comparing the "p" value significance and the periodic analysis of the subjects' reports covered two key areas:

- statistical significance of the frequency and intensity of hypoglycemic episodes between the experimental group (A) and the control group (B), and the progress of the experimental group throughout the investigation, based on the response to the conducted exercise program;
- statistical significance of HbA1c values in both groups between the initial and final testing.

Results

a) *Frequency and intensity of hypoglycemia*

The results of the experiment showed a significant difference in the frequency of hypoglycemia between groups A and B, as well as within group A, throughout the duration of the exercise program. In group B, the average frequency of hypoglycemic episodes ranged between 38-45% throughout the experiment, with significant daily fluctuations. Group A showed a significant decrease in frequency from 58% in the first month of the experiment to 17% at its end. Regarding the intensity of hypoglycemia, group B reported a number of 7 severe episodes, while group A only recorded 3 such cases.

b) *Blood glucose monitoring*

In group B, the average of daily blood glucose levels showed major fluctuations, between 68-285 mg/dl, throughout the course of the experiment. Group A had an average of 176 mg/dl during the first month of the experiment, which lowered to 142 mg/dl at its end. Also, in group A, significant fluctuations could be seen in the first month of the experiment (80-206 mg/dl), then daily blood glucose levels stabilized during the program implementation (88-152 mg/dl).

c) *Long term blood glucose control by HbA1c values*

The initial and final HbA1c values of the control and experimental groups are shown in Tables II and III. In group B there were no statistically significant differences ($t = 0.72$; $p > 0.05$) in the mean HbA1c values between the initial (8.35%) and final (8.34%) testing. Group A showed a significant decrease ($t = 3.74$; $p < 0.05$) in these values between the two tests, namely from 8.08% to 6.83% from the initial to the final testing. Also, the final HbA1c values of group A showed a significant decrease compared to group B subjects (Fig. 1).

Table II

HbA1c values of the experimental group (A).

n	Subjects	Initial test HbA1c values (%)	Final test HbA1c values (%)
1	B.A.	7.9	6.5
2	B.C.	8.2	7.2
3	B.M.	8.4	7.5
4	B.R.	7.8	6.9
5	D.F.	8.7	7.6
6	F.S.	8.1	6.8
7	H.K.	7.5	6.2
8	J.T.	7.6	6.1
9	N.N.	7.9	6.4
10	N.S.	7.8	7.1
11	P.I.	8.8	7.5
12	V.O.	8.2	6.1
	Mean	8.08	6.83

Table III
HbA1c values of the control group (B).

n	Subjects	Initial test HbA1c values (%)	Final test HbA1c values (%)
1	A.F.	8.1	7.9
2	B.L.	7.4	7.6
3	C.S.	8.7	8.7
4	C.R..	9.3	9.1
5	D.M.	7.9	7.6
6	E.P.	7.8	8.00
7	K.B.	8.9	8.5
8	M.S.	6.9	7.1
9	M.R.	10.2	10.1
10	O.J.	7.7	8.0
11	R.D.	9.1	8.6
12	Z.A.	8.2	8.9
	Mean	8.35	8.34

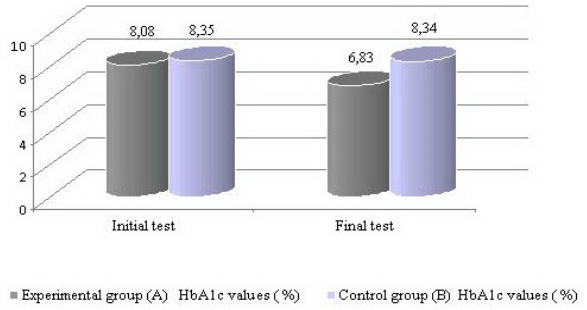

Fig. 1 – Chart of the progress of the mean HbA1c values.

Discussion

The analysis and interpretation of the experimental results revealed significant differences between the two groups of subjects in terms of metabolic response to predicted (group A) and unpredicted (group B) exercise, so (Tables II and III):

- The risk of hypoglycemic episodes decreased significantly with the conducted physical exercise program of known duration and intensity, evidencing the possibility of an adequate intervention on insulin dosage and carbohydrate intake. The episodic presence of severe hypoglycemia, as well as the persistence of moderate or mild hypoglycemia, even in a low percentage, acknowledges the results of specialized studies conducted in recent decades, according to which hypoglycemia is the limiting factor when performing exercise sessions in insulin-treated diabetic patients (Wentholt et al., 2007).

- The high glycemic fluctuations and the persistence of hypoglycemia recorded in a high percentage in the control group (B) confirm the theories according to which unplanned exercise averts from appropriate corrective interventions, metabolic response being unpredictable in this case. In these situations, practicing physical exercise outside advice and medical supervision could lead to an altered metabolic balance and to a higher risk of diabetes side effects (severe hypoglycemia, hyperglycemia, ketosis) (Chase et al., 2001).

- The significant difference between the mean HbA1c values of the two groups, as well as within the experimental group between the initial and final testing, reveals the beneficial effect of exercise on a long-term glucose balance in T1D patients. In group A, 58% of the subjects managed through the conducted program to achieve an optimal therapeutic target, i.e. lowering HbA1c values below 7%. The remaining 42% of the subjects in the same group reached by controlled exercise mean HbA1c values slightly above the optimal average of 7%, which is explained by their higher initial values at the beginning of the experiment. The results of inferential statistics for this group, by assessing „t" Student test, indicates a statistically significant difference ($t=3.74$, $p<0.05$) between the initial and final HbA1c values for groups with n=12. As for the control group (B), assessing „t" Student test indicates a statistically insignificant difference ($t=0.72$, $p>0.05$) between the initial and final HbA1c values for groups with n=12.

- The correlation of the mean HbA1c values at the end of the exercise program with the progress of hypoglycemic episodes in the control group (B) is insignificant, unlike in the experimental group (A), where the essential correction criteria were applied, so the subsequent therapeutic objective pursued is coupled with a significant reduction of this side effect of type 1 diabetes.

- Regarding insulin dosage, regular reports analyzing the subjects of the two investigated groups show different approaches to its management strategy. Group A consists of subjects treated with multiple insulin administration (4-5 times daily). This scheme was shown to be highly effective for the duration of the exercise program, allowing appropriate insulin dose adjustments by 10-30% decreases during exercise practice. The correction at a narrower range of group B subjects (5-10%) confirms the results of previous studies, whereby twice-daily insulin dosing is a more rigid regimen, requiring a greater amount of time to achieve the therapeutic goals (Vereşiu et al., 2004; Nita & Hâncu, 2008).

- Achieving a good glycemic control in the subjects of the experimental group (A) was also due to their adequate diet adjustment. The slowly absorbed carbohydrate intake 2-3 hours prior to exercise significantly contributed to the restoration of glycogen stores and their slow depletion rate, which led to a significant decrease in post-exercise hypoglycemia. Most subjects in this group were able, during the course of the experiment, to develop their own algorithm based on individual glucose metabolic response.

Conclusions and proposals

1. The results of our experimental study confirms the research hypothesis, according to which the implementation of a systematic and conducted moderate-intensity exercise program reduces the frequency and severity of hypoglycemic episodes, under a flexible insulin treatment scheme and a permanent adjustment of carbohydrate intake, leading to a long-term metabolic balance in patients with type 1 diabetes.

2. The continuous evaluation of our experiment subjects meets previous findings in this field, according to which therapeutic T1D management team experience, as well as the patient are key elements in choosing the appropriate treatment scheme.

3. The progress of the subjects' metabolic response to our program leads to the proposed extension of systematic exercise programs for all age groups within ASCOTID

Mureş, where initial glycemic balance and the absence of major T1D complications allow their performance.

4. We propose a screening procedure within primary, secondary and high school institutions of Mureş county, based on the necessity of practicing exercise among children and young insulin-treated patients, as well as presenting the results of our program during ASCOTID events, in order to increase patient responsiveness to new insulin-treatment experimental therapeutic programs.

5. The consolidation of the therapeutic T1D management team of ASCOTID Mureş (patient, physician, diabetologist, nutritionist, coach, psychologist) is vital, in order to meet a complex and effective approach to T1D treatment.

6. Encouraging sport performance in highly metabolically balanced patients or restarting it in patients reluctant to „assume this risk" are benchmarks for providing good practice examples.

7. The development of training programs organized by ASCOTID Mureş with the target group of physical education teachers will have as a main purpose the adaptation of curricula and sports training to the category of practitioners, where exercise is a way of treatment and maintenance of the quality of life.

Conflicts of interests

There are no conflicts of interests.

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