Chapter 3

The Effects of Energy Intake, Insulin Therapy and Physical Activity on Glucose Homeostasis in Children and Adolescents with Type 1 Diabetes Mellitus

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1. Introduction

Insulin therapy, dietary management, and physical activity constitute an essential element in prevention and treatment for children and adolescents with type 1 diabetes mellitus (T1DM). Regular physical activity positively affects metabolic and cardiovascular functions, and its benefits include enhanced insulin sensitivity, decreased fat mass, improved lipid profile and cardiovascular fitness [1-5]. All of these metabolic changes prevent the development of metabolic syndrome, decrease the risk of type 2 diabetes mellitus (T2DM), and are beneficial for patients with type 1 diabetes mellitus (T1DM) [6-12].

The classification of the American Diabetes Association defines four major forms of diabetes mellitus [13]. The major groups are: type 1 and type 2, gestational diabetes and diabetes due to other known causes. Type 1 diabetes mellitus is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency [14-15]. Type 1 diabetes is also subdivided according to whether cell destruction is caused by the immune or other processes, and be classified as type1A or type 1B diabetes mellitus [13-14]. Type 1 diabetes, formerly known as juvenile-onset diabetes, accounts for 10-15 percent of all cases of diabetes mellitus. Approximately one-half of individuals develop the disease within the first two decades of life, making T1DM one of the most common chronic diseases of childhood. The reports of World Health Organization on the incidence of T1DM showed the greatest increase in the incidence rate among young children aged 4 to 9 years. Such high increase of incidence rate of type 1 diabetes mellitus suggests an epidemic tendency in many countries [17-18]. The

fact that the incidence of type 1 diabetes mellitus is the highest among young population has increased the interest in the role of physical activity in the treatment of the disease [7, 16].

Insulin is a hormone produced by the pancreatic β cells. It is not only central to regulating carbohydrate, protein and fat metabolism, but also acts as a critical T1DM autoantigen. Autoimmune distraction of pancreatic β cells leads to insulin deficiency and consequent metabolic decomposition of glucose homeostasis [19-22].

Multidisciplinary research on the pathogenesis of T1DM indicates an involvement of genes predisposing to autoimmune damage to the pancreatic β cells [23-24]. It has been suggested that type 1 diabetes is a complex polygenic disease. The main susceptibility genes code for polymorphic HLA molecules and, in particular, alleles of class II MHC genes [15, 25]. Risk of T1DM progression is conferred by specific HLA DR/DQ alleles (e.g., DRB1*03-DQB1*0201 [DR3] or DRB1*04-DQB1*0302 [DR4]. The HLA alleles such as DQB1*0602 are associated with dominant protection against the disease [26]. Polymorphism of a variable nucleotide tandem repeat of the proinsulin gene and a single amino acid change of a gene termed PTPN22, a tyrosine phosphatase that influences T cell receptor signaling, are associated with increased risk for diabetes [15]. In physiological conditions there is balance between pathogenic T cells that mediate disease and regulatory cells that control autoimmunity. However, in T1DM, the balance between pathogenic and regulatory T cells is altered [27]. Thus, the ability to identify individuals at high risk for type 1 diabetes using genetic and/or autoantibody markers has been a main goal of the diabetes research and T1DM prediction strategies [20, 28].

Early diagnosis has expanded the chance for pharmacological treatments for diabetic children and adolescents. Autoimmune destruction of insulin-producing pancreatic β cells requires constant administration of various insulin preparations designed to meet basal and meal-dependent insulin requirements. In recent years, several new insulin analogs have been developed including short-acting insulin analogs with different pharmacokinetic properties [29-30]; the preparations have been recommended for tight control of blood glucose concentrations and significantly reduction of diabetic complications [31].

There is compelling evidence indicating that individuals who have been using intensive insulin therapy should participate in regular physical activity [1, 7, 32]. Findings from most experimental and questionnaire studies in youth suggest a positive relationship between physical activity and health benefits [33-35]. Regular physical activity in people with diabetes increases the capacity to maintain appropriate plasma glucose levels and enhances the patient's metabolic capacity during and after exercise [36-37]. However, in children and adolescents with type 1 diabetes, it may also be responsible for the occurrence of some adverse reactions such as hypoglycemia, hyperglycemia, ketosis and diabetes-related complications. These effects of exercise on glycemic control depend on several factors, such as starting levels of glycaemia, type, intensity of exercise, and the use of exogenous insulin and insulin secretagogues [38].

Contraction of skeletal muscle increases glucose metabolism through an insulin-independent pathway. In this mechanism, glucose delivery is facilitated by an increase in blood flow to the working muscle groups. Regular aerobic exercise increases the synthesis of glucose transporter

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(ie. GLUT 4) and enzymes to exercising muscles [39]. At rest, muscles mainly draw their energy from fats; hormonal control is a result of balance between insulin and glucagon secretion.

The metabolic adaptation during exercise is sequentially characteristic for each different phase of requirement of the exercising muscle. The first mechanism available for muscle contraction is to access energy from adenosine triphosphate (ATP) breakdown. Then, the high-energy phosphate from creatine phosphate (CP) is used to resynthesize ATP from adenosine diphosphate (ADP). The limited supplies of CP in the muscle require increased energy production from the non-oxidative (anaerobic) glycolytic pathway [40]. The fuel for this pathway is glucose from the blood or glucose stored in the muscle in the form of glycogen. The end product of glycolysis is pyruvic acid, which may be further processed to produce energy in the oxidative pathway or can be removed to form lactic acid or alanine. In muscle cell mitochondria, the oxidative pathway can use fats or lipids as a fuel. Both glucose, through the formation of pyruvic acid, and lipids are oxidized in the tricarboxylic acid (TCA) cycle (Krebs cycle) [41]. It is well documented that the ATP resynthesis depends on glucose transport into the cell [42-43]. One of the beneficial effects of exercise on glucose homeostasis in people with diabetes is a marked stimulation of blood glucose utilization via the insulin independent mechanism. Increased synthesis of GLUT-4 through insulin-independent pathway in the muscles results in the enhancement of the glycolytic and oxidative energy produced during exercise and post-exercise glycogen stores [44]. Increased glucose uptake is usually observed after a single bout of exercise even when insulin level decreases [45-46].

Muscle cells differ in their contractile and metabolic properties [47]. Their different recruitment depends on the exercise intensity and duration [48]. All the aforementioned processes allow describing the fuel mobilization and muscle metabolism at three levels of exercise intensity ie: low-, moderate-, and high-intensity exercise. During low-intensity exercise, energy for muscle contraction is supplied predominantly by oxidation of carbohydrates and free fatty acids (FFAs) mobilized from the adipose tissue and supplied by intramuscular triglycerides (TGs). The predominance of oxidative metabolism during low-intensity exercise is a consequence of selective recruitment of oxidative muscle fibers (type I). At moderate-intensity exercise, performed in the range of 50% to 75% of VO_{2max}, approximately half of the expended energy is derived from intramuscular lipids whereas the rest is derived from carbohydrates. Muscle glycogen and blood glucose contribute to carbohydrate utilization in 80 and 20%, respectively. Adipose tissue FFAs provide a bit more than half of the lipid fuel, and the rest is supplied by intramuscular TGs [49]. This pattern of fuel use is a consequence of the metabolic characteristics of the type IIa muscle fiber recruited during moderate-intensity exercise [50].

At high-intensity exercise (above 80% of VO_{2max}), about three quarters of total energy cost of exercise is supplied by glucose mainly derived from muscle glycogenolysis [36, 51]. FFA secretion is blocked by the vasoconstrictive action of catecholamine and increased concentration of lactic acid. High concentrations of lactate indirectly facilitate carbohydrate metabolism [52]. High concentrations of glycolytic enzymes activate ATP hydrolysis and anaerobic glycolysis [53]; type IIb glycolytic muscle fibers are preferentially recruited during high-intensity exercise [54-55].

It has been well documented that participation in low and moderate-intensity exercise by individuals with T1DM results in decreased blood glucose concentrations [6, 56-57]. In patients with diabetes, the effect of low-to-moderate intensity exercise varies according to the starting levels of glycaemia. In T1DM patients with pretraining hyperglycemia and ketosis resulting from insulin underdosing, a session of moderate-intensity exercise may increase hyperglycemia [36, 58]. In contrast, when patients with type 1 diabetes are treated with insulin and display mild to moderate hyperglycemia, exercise can lower plasma glucose concentrations thus preventing an episode of hypoglycemia [59-60].

The currently available data suggest that patients with T1DM are less likely to develop hypoglycemia during high-intensity exercise than when they engage in low-intensity exercise [57, 61]. There is evidence that high-intensity exercise added to low-or moderate-intensity exercise may maintain blood glucose levels within the normal physiological range and thus minimize the risk of hypoglycemia [62-63]. Guelfi et al. 2005 first demonstrated beneficial effects of the above mentioned exercise combinations on blood glucose levels. The effect is partly due to the fact that intermittent high-intensity exercise (defined as exercise involving repeated bouts of short duration), intense activity and alternating intervals of low-to moderate-intensity exercise are typical of many field sports and spontaneous physical activity in children and adolescents [36, 64-65].

The knowledge of the interactions between specific insulin preparations and various forms of exercise is essential to optimizing glycaemic control with minimizing the potential for derangements in glucose homeostasis [66]. The challenge in diabetic patients is to maintain glucose control during physical activity of varying intensity and to effectively decrease hyperglycemia as a result of lower catecholamine levels [67-68].

One of the most important therapeutic recommendations in type 1 diabetes is to lower the percentage of serum glycated hemoglobin, a long-term indicator of glycaemic status [69-70]. Glycated hemoglobin A_1c (HbA_1c) indicates the percentage of total hemoglobin that is bound by glucose and is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. International Expert Committee has recently recommended that HbA_1c might be a better means of diagnosing diabetes than measuring fasting and/or post-challenge glucose, and established HbA1c ≥ 6.5% as the cut point for diagnosing the disease [69-73].

Type 1 diabetes is among the most common chronic conditions in childhood, occurring with increasing frequency, particularly in children aged five years or less [74]. Considering its complexity as well as invasive and continuous treatment, the disease can have a significant effect on children, parents and other family members by affecting many aspects of their lives. One of the beneficial effects of exercise on glucose homeostasis in people with diabetes is a marked stimulation of blood glucose utilization via the insulin independent mechanism. However, the effect of exercise on glycemic control in diabetes depends on several factors including exercise intensity, starting levels of glycaemia and use of exogenous insulin [75-77]. Therefore, the aim of the study was to investigate the effect of physical activity on glycaemic control in children and adolescents suffering from type 1 diabetes mellitus. Another study objective was to evaluate changes in glucose concentrations, glyceaemia, and glycated hemoglobin level in diabetic patients in response to regular exercise during diabetes camps.

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2. Methods

2.1. Study participants

The study group comprised a total of 53 (27 girls and 26 boys) children and adolescents with type 1 diabetes mellitus (T1DM). Mean age was 11.8 ± 2.4 years (range 5 to 17 years); duration of diabetes was 2.8 ± 1.6 years (Table 1). All subjects lived and attended schools in Silesian Industrial Region in Poland and were recruited at the Diabetes Clinic of the Silesian Center for Child Health. They were treated with recombinant human insulin divided into daily doses, and performed self-monitoring of blood glucose on glycaemic control. The types of insulin used were: NovoRapid, Lantus, Humalog, Apidra. Only patients free of diabetic complications were enrolled. The other criteria for inclusion were no personal history of other cardiovascular or metabolic diseases, no simultaneous participation in another clinical trial, being free of any acute infections up to one week prior to the study, and HbA1c < 7.5%.

The medical history and information about diabetes etiology of the study participants were prepared by medical personnel. The adolescents and their parents were presented with a comprehensive description of the aim and methods of the study. Written consents were requested and obtained from all parents. The study protocol was approved by the Ethics Committee of the Academy of Physical Education in Katowice, Poland, and conformed to the standards set by the Declaration of Helsinki.

3. Measures

Height and body mass (mean ± SD) of the participants were measured according to standard procedures [78]. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. All subjects were characterized by normal-weight according to international BMI cutoff values and BMI centiles [79] (Table 1).

The first group were monitored during their school classes (GrS; n=25). We assessed glycemia, diet and physical activity during the school day and leisure time. The other group comprised participants of a rehabilitation programme at a summer camp for diabetic children, organized by the Polish Society for Children and Youth with Diabetes. (GrR; n=28).

Physical activity (PA) assessment was performed using accelerometers (accelerometer ActiGraph GT3X+, USA). The first PA indicator was the number of steps per day (steps/day) while the other indicator was daily energy expenditure of physical activity (kcal/kg/day). According to recommendations, the children wore a device placed firmly on an elastic belt on the right hip. During the seven-day monitoring period, the accelerometers were taken off only at bedtime and before potential contact with water [33, 80-81]. The criteria of the 2001–2002 President's Challenge Physical Activity and Fitness Awards Program were used to assess physical activity [82]. The authors recommended that the daily number of steps, hops or position changes should be about 13,000 in boys and 11,000 in girls at least 5 days a week for

a standard healthy base. Thus, the daily active energy expenditure should be at least 11 kcal/kg/day in boys and 9 kcal/kg/day in girls on most days within a week [83].

Considering the aim of the study, PA measurements were conducted in two groups:

- GrS (n=25)-children and adolescents who participated in their daily PA at school according to their educational program and own lifestyle
- GrR (n=28)-children and adolescents who participated in their daily PA during a rehabilitation summer camp.

The first group of subjects (GrS) were asked to wear an accelerometer for 7 consecutive days, starting on the day immediately after they had received monitors at school. The second group (GrR) was monitored during the second week of a summer camp for children and adolescents with diabetes.

4. Biochemical assessments

Blood samples were collected in the morning using venipuncture after overnight fast. To analyze the children and adolescents' glycemia, the measurements of glucose concentrations, and doses of insulin were repeated 6-8 times per day. The analyses of all individual daily insulin doses were compared to differences in glucose concentrations (Medtronic MiniMed Paradigm 715). Glycated hemoglobin (HbA1c) concentrations were checked (Ames DCA-2000™ Immunoassay Analyzer-normal range: 4.2-6.5%) before and at about two weeks after the end of the study.

For each subject the mean insulin dose and the average blood glucose concentrations were monitored in the morning, afternoon, and evening. Moreover, all incidents of hypo-and hyperglycemia were monitored and recorded and so was the time of their occurrence.

Food intake was recorded and compared to dietary recommendations for all study subjects [32, 84].

Variables	GrS (n=25)	GrR (n=28)
Age [yr]	11.5 (3.4)	12.2 (1.5)
Body height [m]	1.67 (0.1)	1.55 (0.1)
Body mass [kg]	56.0 (9.6)	45.0 (1.0)
BMI [kg/m^2]	19.8 (1.8)	18.9 (2.3)
BMI Centiles[centiles]	51.1 (22.1)	54.5 (23.2)
HgA1c [%]	7.16 (0.38)	7.02 (0.3)

Table 1. Anthropometric and physiologic features of the study population (mean, SD)

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5. Statistical analysis

All results are presented as means ± standard deviation. The data were analyzed by two-way ANOVA followed by the Student-Newman-Keuls test when appropriate. Significant differences in glucose concentrations and insulin doses and physical efficiency variables in relation to references ranges were determined using the Bonfferoni post-hock test. Pearson correlation coefficients were analyzed to determine the inter-variable relationships. All analyses were performed using the Statistica v. 9 statistical software package (StatSoft, Tulsa, OK, USA). Statistical significance was set at $p < 0.05$.

6. Results

We studied the effects of energy intake and physical activity on glycaemic control in children and adolescents suffering from diabetes type 1. The variables associated with glucose homeostasis (e.g. daily insulin doses, energy intake, and glycated hemoglobin (HbA1c) were compared during daily activities and in response to exercise/sports participation in a sample of children and adolescents with T1DM.

The assessment of nutritional status of all children and adolescents who participated in the study showed normal body mass and normal BMI percentile values (57.5 ± 20.5 and 52.7 ± 24.9, respectively). Before the study all children had similar levels of hemoglobin A_{1c} (HbA_{1c}). Anthropometric features of the two study groups (GrS vs. GrR) were similar for all subjects (Table 1.) Children from the GrS accumulated an average of 8904 ± 981 steps/day while the average activity-induced energy expenditure was 248 ± 40 kcal/day and the relative energy expenditure was 6.06 ± 0.86 kcal/kg/day. The mean number of steps per day during daily PA at school (GrS) was low compared to recommended values (Fig.1).

Analysis of variance revealed a significant effect of physical activity programme during diabetes camp on daily steps ($F=44.0$; $p<0.001$) and daily energy expenditure ($F=21.0$; $p<0.001$). The two-week adherence to a structured exercise programme increased children and adolescents physical activity. Diabetic children who participated in the camp (GrR) accumulated an average of 14378 ± 1699 steps/day, corresponding to 466 ± 48 kcal/day; the relative energy expenditure was 10.4 ± 0.85 kcal/kg/day. A comparison of the study subjects who took part in their daily PA at school according to their educational program (GrS) and participants of the camp for diabetics (GrR) revealed significant differences regarding steps per day ($p<0.001$) and daily energy expenditure ($p<0.01$) between these groups (Table 2).

T1DM children participated in the camp exhibited a higher tolerance of physical exercise on each day of the investigations (Fig. 1). The average daily dose of insulin (Ins/kg) was similar for all subjects, and no significant differences were observed in GrS compared to GrR. No differences were observed in mean daily serum glucose levels between GrS vs GrR groups ($p>0.05$) (Table 2). However, based on the measurements of blood glucose concentrations during the day, several incidents of hypo-and hyperglycemia were observed. Two-way ANOVA revealed a significant effect of physical activity levels on hyperglycemic but not hypoglycemic incidents (GrS vs GrR; $F=1014.7$ $p<0.001$). GrR exhibited a trend to higher

number of hypoglycemic events between 10.00 to 12.00 hours compared to GrS (Fig. 2).The number of hyperglycemic events differed depending on the day of the study (F=442.0, p<0.001). Higher risk of hyperglycemia was noted in children with T1DM who participated in the sports camp. A significant increase in hyperglycemic incidents was diagnosed between 12.00 to 20.00 hours (Fig.3). This trend coincided with the distribution of physical activities carried out during the camp. In the morning we used low-intensity exercise of longer duration while the intensity of afternoon exercises was higher. This might suggest that intense exercise increased the rate of hyperglycemic episodes. A large number of episodes of hyperglycemia directly related to the high intensity exercise may suggest higher glucose levels as a defense mechanism against hypoglycemia.

The analysis of variance indicated a significant effect of the week day on the insulin dose (F=2.2; p<0.05) with significantly higher doses on Sunday compared to Saturday (p<0.05). The average daily glucose concentrations were similar in both groups with a tendency to higher differences in insulin doses in GrR compared to GrS. Sunday results showed an individualized decrease of daily steps, significant increase of insulin doses, and a tendency to hyperglycemia in all investigated diabetics.

Analysis of variance revealed a significant effect of daily energy expenditure during school and rehabilitation programme activities on glycated hemoglobin (HbA1c) concentrations (F=5.3; p<0.05). A tendency to increased HbA1c levels was observed in GrS after the two weeks of study while GrR subjects had slightly lower levels after the summer camp (Fig. 4).

Participation in a particular study group had a significant effect on fat consumption (F=15.1; p<0.001) and protein content of the diet (F=6.9; p<0.01). Children with T1DM from GrR group showed higher fat intakes (p<0.05) and lower protein intakes compared to GrS group (p<0.05) (Table 3). Protein consumption was higher compared to standard dietary guidelines for children in both GrS and GrR groups (4.7 % vs 2.6% above, respectively). The average values of fat consumption exceeded standard recommendations for children being higher in GrR compared to GrS (9% vs 3.5% above). Carbohydrates consumption was lower than recommended in all investigated diabetics (12% for GrS and 15.3% for GrR below the normal ingestion). Significant correlation was observed between total energy intake and insulin dose (r=0.57; p<0.01). Lower physical activity was associated with an individualized increase of daily insulin doses in all investigated subjects.

Variables	GrS (n=25)	GrR (n=28)
Energy expenditure [kcal/kg/day]	6.06 (0.86)	10.4 (0.85)**
Average number of steps [steps/day]	8904 (981)	14378 (1699)***
Dose of insulin [u/kg/day]	0.39 (0.03)	0.41 (0.03)
Glucose concentration [mg/dl]	125.1 (8.6)	129.8 (4.5)

**p<0.01; ***p<0.001 significant differences between GrS and GrR.

Table 2. Mean energy expenditure, average number of steps, mean daily dose of insulin, and glucose concentrations on successive week days in the GrS and GrR.

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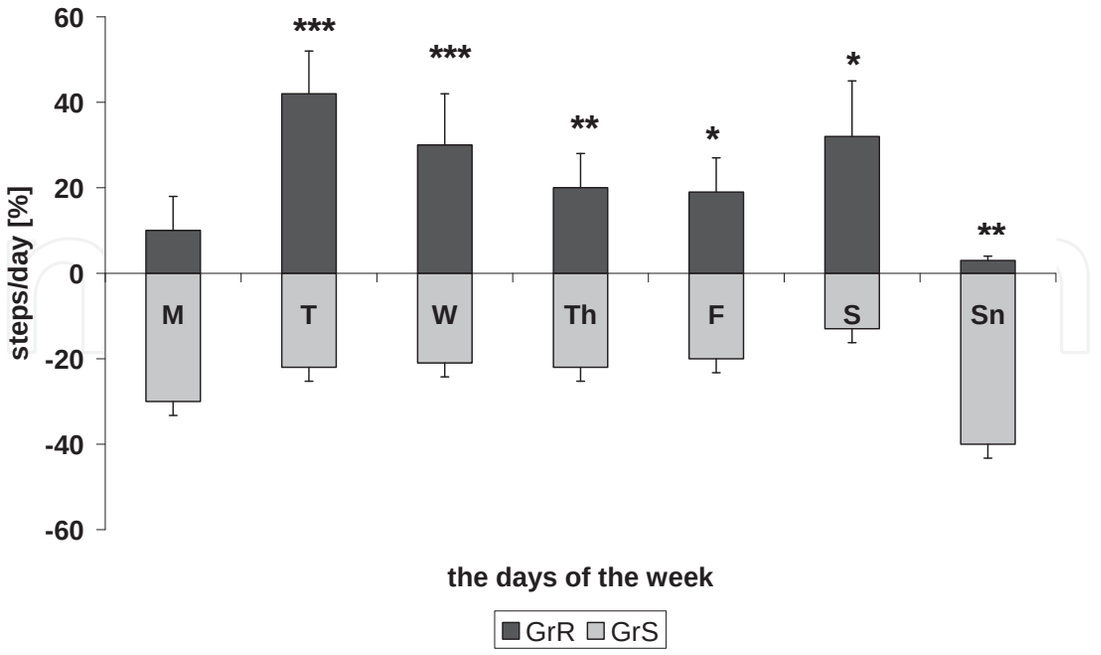
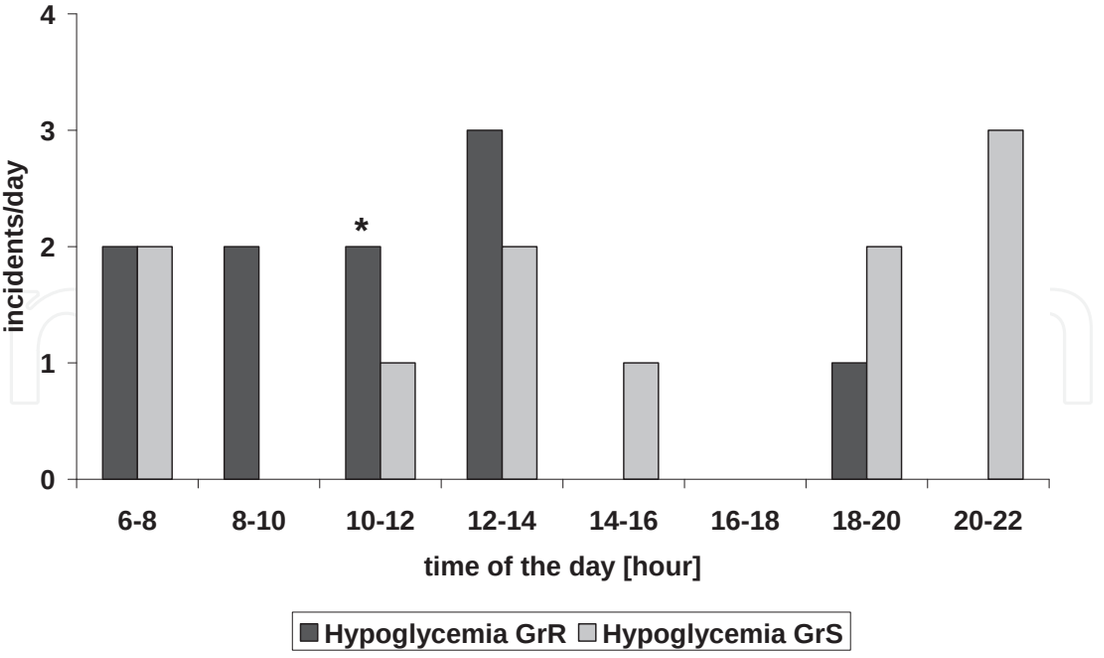


*p<0.05; **p<0.01; ***p<0.001 significant differences between GrS and GrR.

Figure 1. The number of steps compared to the standards in GrS and GrR. (values presented as percentages differences)



*p<0.05 significant differences between GrS and GrR.

Figure 2. The number of hypoglycemic events at particular time of the day.

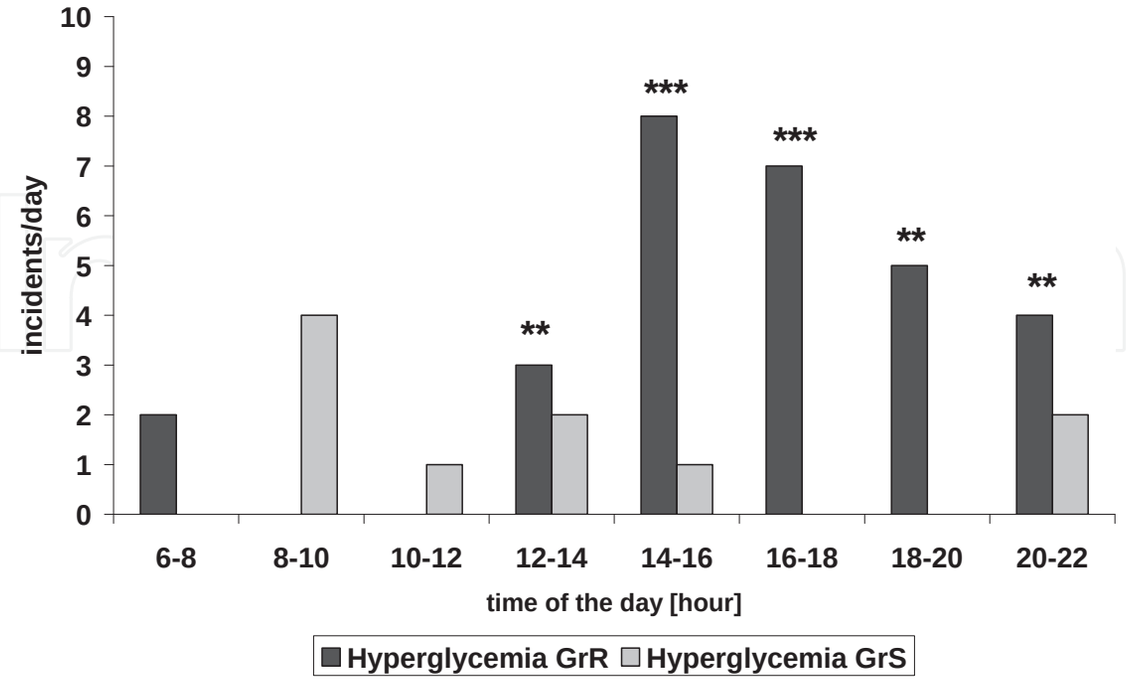


Figure 3. The number of hyperglycemic events at particular time of the day. **p<0.01; ***p<0.001 significant differences between GrS and GrR.

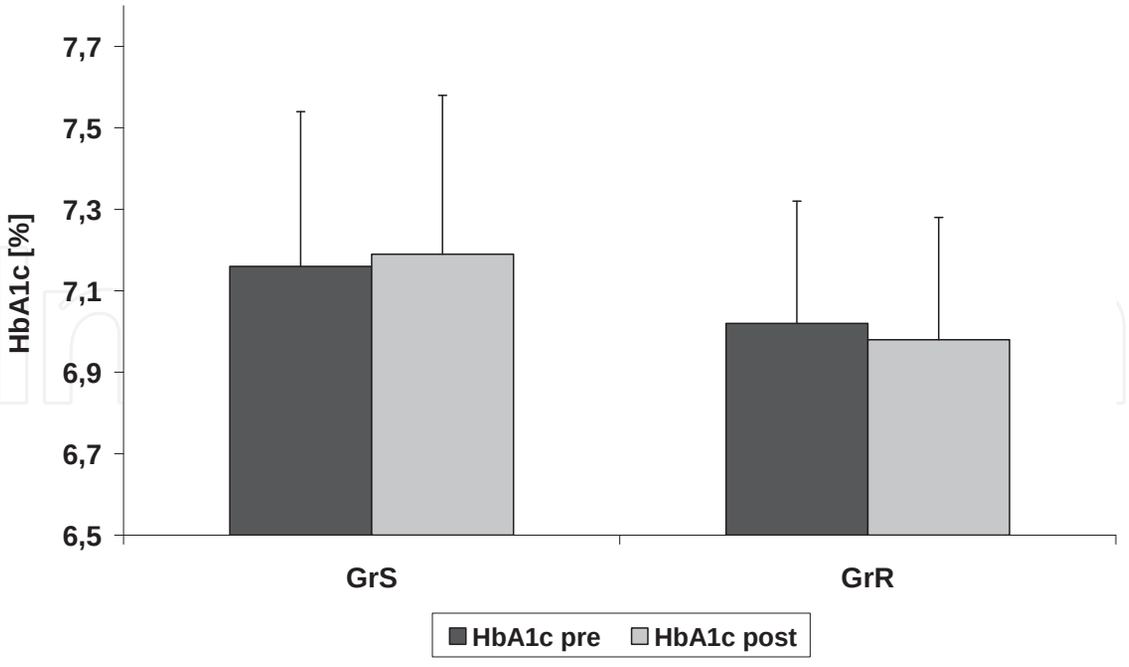


Figure 4. Glycated hemoglobin concentrations (HbA1c%) in GrS and GrR before and after two weeks of study.

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Variables	GrS (n=25)	GrR (n=28)
Energy supply with diet [kcal/kg/day]	38.8 (15.6)	35.6 (10.8)
Fat intake [g/kg/day]	1.4 (0.8)	1.7 (0.7)*
Carbohydrate intake [g/kg/day]	3.5 (1.8)	3.2 (1.2)
Protein intake [g/kg/day]	2.1 (1.5)	1.9 (0.8)*

*p<0.05 significant differences between GrS and GrR.

Table 3. Mean energy supply with diet, mean daily fat, carbohydrate, and protein intake on successive days of the week in the GrS and GrR.

7. Discussion

Children and adolescents engage in different types of exercise, most frequently in unplanned and spontaneous physical activities, which can, of course, be associated with immediate and long-term health benefits [36, 62, 85-86]. Children with T1DM gain similar health benefits from physical exercise as their healthy peers; however, due to several consequences of the disease, some specific characteristics of their adaptation to exercise should be considered. Diabetic children and adolescents differ from the healthy pediatric population in their physiological responses to exercise. They are characterized by impaired utilization of exogenous glucose as an energy source during exercise despite hyperinsulinemia and higher rates of perceived exertion, which persist after glucose ingestion [60, 87]. In patients with diabetes, exercise may increases insulin sensitivity and insulin absorption from the site of administration. Plasma glucose levels decrease during and after low-and moderate intensity exercise in response to enhanced glucose utilization in skeletal muscle [88]. In contrast, high-intensity exercise protocols may increase the risk of hyperglycemic episodes [51, 57, 62, 89].

In the present study we analyzed the level of physical activity of children and adolescents with type 1 diabetes and the effect of exercise intensity to compensate blood glucose level depending on the insulin treatment and the diet. Furthermore the aim of the study was to determine the energy expenditure associated with the programmed physical activity which is effective for maintaining normoglycemia in children with type 1 diabetes.

The major findings of our study are that: 1) physical activity in children with type 1 diabetes was lower than the standards for the population of healthy children and recommendations for health training, 2) programmed physical activity significantly increased daily energy expenditure; however, may also increase the risk of hyperglycemia, 3) greater physical activity

seemed to provide more effective control of glucose homeostasis as demonstrated by reductions in HbA_{1c}. Our results also show that children with T1DM do not meet the standards of consumption of basic nutrients; higher fat and protein intake with lower carbohydrate values might induce glucose imbalance.

The American Diabetes Association recommends that young patients with diabetes should be given the opportunity to benefit from participating in every type of physical activity, including both recreational and competitive exercises. The understanding of the mechanism of glycemic changes in exercising muscles, modulation of both insulin dose and injection site and appropriate dietary supplementation in T1DM patients prevent the occurrence of adverse events during physical activity [90]. Thus, a thorough understanding of the interactions between exogenous insulin and insulin secretagogues, diet and various forms and intensities of exercise seems to be of great importance to achieve tight metabolic control in diabetic patients. The dose and type of insulin administration (multiple injections/continuous subcutaneous insulin infusion), the site of injection and the timing of insulin dose and food intake before exercise may influence the metabolic and hormonal responses to physical activity among T1DM patients [32, 60, 91].

Plasma glucose concentration is a function of glucose supply, transport rate in the circulation, and metabolism [92-93]. The glucoregulatory hormones, of which insulin is the most important, are designed to maintain circulating glucose concentrations in the physiological range. Initially, insulin stimulates the cells of insulin-sensitive tissues, primarily skeletal muscle, to increase their glucose uptake [6, 43]. Secondly, insulin acts on the liver to inhibit glucose production [42]. The insulin dependent mechanism of glucose transport may be exacerbated by the skeletal muscle contractions. Insulin enhances translocation of specific transporter proteins (GLUT-4) which carry glucose into muscle and adipose cells. In patients with type 1 diabetes mellitus, the insulin-independent mechanism is the most important. Translocation of glucose transporter proteins to cell membrane is initiated by muscle contractions when calcium is released. Recent investigations also indicate that autocrine/paracrine mechanisms observed during exercise (e.g., nitric oxide, adenosine, bradykinin, insulin-like growth hormone-1 may exert alternative or parallel actions [2, 94-96].

It is well established that hypoglycemia is the most common response to exercise; however, in a diabetic patient blood glucose concentrations may also increase or remain unchanged. It is also possible that, even in well-controlled patients, exercise-induced increases in glucose utilization may lead to hypoglycemia [88] both during exercise and up to 31 hours of recovery [90, 97]. Conversely, excessive snacking before exercise, exercise protocols characterized by high intensity and sympathetic nervous systems activation may influence the metabolic response to exercise and increase the risk for hyperglycemia [36, 98]. Several factors may contribute to these adverse reactions during and after exercise [42]. In patients requiring exogenous insulin therapy, insulin levels are predominantly associated with medication; consequently, these levels do not decrease in response to exercise. At the normal exercise-induced decrease in the portal insulin level, hepatic glucose production remains suppressed and cannot increase proportionally to the muscle glucose utilization. As a result, blood glucose declines to hypoglycemic levels [36]. As mentioned above, plasma insulin concentration does

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not decrease during exercise in T1DM compared to healthy subjects. Quite the opposite-it may even rise, first due to the higher absorption, secondly due to the increased insulin sensitivity, and, finally, in the case when insulin injection is given shortly before exercise. Consequently, the ability to mobilize fat and carbohydrate fuels for exercise may be compromised [3] which facilitates the onset of hypoglycaemia during moderate-intensity exercise [92, 97]. As it was suggested, low-to-moderate intensity exercise was generally recommended for patients with type 1 diabetes since numerous benefits on glucose homeostasis had been observed [91, 95, 99]. However, hypoglycemia can be minimized by appropriately reducing insulin dosage or ingesting additional carbohydrates [60, 90].

Processes regulated by insulin-independent mechanisms are generally preserved when people with diabetes engage in high-intensity exercise. These processes include normal increases in glucose production and disposal during and immediately after the exercise [63, 100-101]. After high-intensity exercise appropriate control of glycaemia is more challenging than in low-intensity exercise due to the role of insulin in modulating the postexercise decline in glucose disposal. Low circulating levels of insulin can prolong hyperglycemia during the recovery after high-intensity exercise, partially counteracting the beneficial effects of exercise on glucose control. If a patient recognizes that a given exercise leads to postexercise hyperglycemia, insulin should be administered shortly after the completion of high-intensity exercise. However, there is evidence that high-intensity exercise, used in combination with low-or moderate-intensity exercise, may maintain blood glucose levels within the normal physiological range and thus minimize the risk of hypoglycemia [62-63].

In the present study, we investigated weekly engagement of children and adolescents with type 1 diabetes in physical activity using an accelerometer. Data regarding their physical activity were obtained through the calculation of mean energy expenditure and compared to reference ranges for children and adolescents. The participants were asked to monitor their physical activity for 7 days during school classes (5 days) and weekend days (2 days). We observed that children and adolescents with T1DM did not adhere to recommended levels of physical activity. Sedentary time was higher on Sunday in all participants and higher in the older group. The proportion of diabetics who did not meet the physical activity recommendations in the present study is consistent with the results of previous studies. Sporting habits in children and adolescents with diabetes were analyzed by Vanelli et al. [102] and Admon et al. [91]. Weekly levels of moderate/vigorous physical activity and sports participation were investigated using a questionnaire. The results showed that children with T1DM appeared to spend less time engaged in physical activity than their non-diabetic peers. Regular physical activity was associated with better metabolic control and lipid profile [103-105]. The association between physical activities, sedentary behavior, and metabolic control in adolescents with T1DM was also observed by Åman et al. [11], who reported that PA was associated with positive health perception but not with glycaemic control, frequency of hypoglycemia or other beneficial effects. In youth with T1DM, prolonged moderate aerobic exercise results in a consistent reduction in plasma glucose and frequent occurrence of hypoglycemia when pre-exercise

glucose concentrations are < 120 mg/dl. It also seems that treatment with 15 g of oral glucose is insufficient to reliably treat hypoglycemia during exercise in children and adolescents [88].

Our results showed significantly higher frequency of hyperglycemic events in GrR compared to GrS, with similar amount of hypoglycemic events. It is worth pointing out that GrR exhibited lower glucose levels in the morning whereas hyperglycemia usually appeared in the afternoons and evenings. This coincided with the distribution of physical activities during the camp. In the morning children performed low-intensity exercise of longer duration while the intensity of afternoon exercise was higher.

Our investigations revealed that, compared to dietary standards for children, our study participants showed an excessive intake of proteins and fats and very low carbohydrate intake. Children with T1DM do not meet the standards of basic nutrients consumption [106]. The energy intake from proteins, fat and of carbohydrates compared to dietary standards for children showed an excessive intake of proteins and fats and very low carbohydrate intake. The analysis of variance showed a significant effect of age on the level of fat consumption and positive correlation between the value of energy intake and insulin dose.

Increased intake of fat and protein and lower carbohydrate values can cause problems with insulin administration in response to diet and/or physical activity.

It should be mentioned, that proper nutrition is important in the prevention and treatment of chronic complications of diabetes [107-110]. According to clinical guidelines [71] 40-50% of energy should provide carbohydrate diet, especially a low glycemic index (<50 IG), the fats should provide 30-35% of the energy value of the diet; and protein should be 15-20 %. The ratio of animal protein to vegetable protein should be at least 50/50%. For important recommendations should supplement meals with fluids, vitamins, minerals and fiber [32]. Despite the important role of a balanced diet in the treatment of T1DM, standard recommendations that could help clinicians manage glycemia during exercise are still lacking [111]. The type, duration, and timing of exercise as well as its temporal relation to meals and premeal insulin doses may affect glucose homeostasis during and after exercise. Moreover, regulation of blood glucose associated with physical exercise and anabolic hormonal secretion could be important for long-term glycemic control [112-113]. In the above mentioned studies glycated hemoglobin (HbA1c) could be a better index of long-term glucose homeostasis than measuring fasting and/or post-challenge glucose [69-70, 73].

The results of the previous study suggested improvement in long-term glycemic control in T1DM youth after a programme of physical activity [10, 105] associated with an increase in aerobic capacity or fitness. Austin et al. [103] also observed a negative correlation between aerobic physical effort and HgA1c levels and daily insulin doses in diabetic patients.

Consistent with these findings, our data also indicated a tendency to HbA1c levels increase in children with lower physical activity (GrS) compared to summer camp participants (GrR).

Our results also demonstrate that participation in an organized rehabilitation programme increased the daily energy expenditure and was associated with tendency to lowering indices

of long term glycaemic control (HbA1c%) compared to pretraining levels. This study has limitations that need to be considered before interpreting the findings. The rehabilitation programme might have been too short to significantly improve glycemic control which could be documented by decrease HbA1c level. Also, since the baseline HbA1C levels were slightly over the reference range, ie., below 7.2%, the effects of physical activity in GrR were not so spectacular.

There is evidence that high-intensity exercise along with low-or moderate-intensity exercise might be recommended to diabetic patients. The most important exercise-related benefits in patients with T1DM include reduced serum glucose levels, improved insulin sensitivity and lipid profile, reduced daily dosage of insulin, improved cardiovascular function, reduced body weight and fat accumulation, increase in physical efficiency, and quality of life improvement. Thus, parents, physical education teachers and physical therapists should motivate type 1 diabetic children to engage in physical activity, and supervise them during exercise in order to create a proper approach to physical exercise and reduce the risk for exercise-related complications [110-114].

It should be emphasized that, general exercise recommendations for children and adolescents with T1DM are that they should exercise systematically, for about 30 to 60 minutes, four to five times a week at a low to moderate intensity [115]. In this way they utilize glucose slowly and the effects of preferential fat oxidation improve. Apart from aerobic exercises, diabetics should perform intermittent high-intensity exercise to minimize the occurrence of hypoglycemic events. High-intensity physical exercise causes severe lactic acidosis and increases adrenergic system activation as compared to low-intensity exercise. Consequently, endurance sports activities performed under aerobic threshold are recommended for T1DM patients [98]. On the other hand, a combination of moderate-and high-intensity exercise, a pattern of physical activity referred to as intermittent high-intensity exercise, may also be recommended for youth with T1DM [61, 63, 116]. It is worth to point out that, individual insulin administration scheme (insulin injections and pump) and blood glucose monitoring are of great importance [91]. The authors mentioned that the pump should be removed or turned off during unplanned prolonged exercise to reduce the risk of hypoglycemia.

8. Conclusions

Regular physical activity is an essential element in blood glucose regulation for children and adolescents with type 1 diabetes mellitus. The obtained results indicate that children with type 1 diabetes are not meeting recommended physical activity and dietary guidelines, and especially regarding fat intake. Regular physical activity with high energy expenditure may effectively control glucose homeostasis as documented by HbA_{1c} reduction. However, incorrect dietary behaviors and/or exercise load in T1DM patients may increase the risk of hypo-or hyperglycemia and long-term metabolic complications.

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