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Metabolic control level and glucose variability in adolescents with type 1 diabetes during low and high-intensity exercise

M. SKALSKA[1], A. MYŚLIWIEC[2], A. MICHALAK[3], J. CHRZANOWSKI[4], A. LEJK[1], J. JASTRZĘBSKA[1], Ł. RADZIMIŃSKI[2], G.F. LOPEZ-SANCHEZ[5], K. MYŚLIWIEC[1], Z. JASTRZĘBSKI[2], K. WEISS[6], B. KNECHTLE[6,7]

[1]Department of Pediatrics, Diabetology and Endocrinology, Gdansk Medical University, Gdansk, Poland
[2]Department of Physiology, Gdansk University of Physical Education and Sport, Gdansk, Poland
[3]Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Medical University of Lodz, Lodz, Poland
[4]Department of Biostatistics and Translational Medicine, Medical University of Lodz, Lodz, Poland
[5]Division of Preventive Medicine and Public Health, Department of Public Health Sciences, School of Medicine, University of Murcia, Murcia, Spain
[6]Institute of Primary Care, University Hospital Zurich, Zurich, Switzerland
[7]Medbase St. Gallen Am Vadianplatz, St. Gallen, Switzerland

Abstract. – OBJECTIVE: **The main purpose of this study was to characterize the determinants of metabolic changes in young type 1 diabetes (T1DM) and to determine glycemic variability during low and high-intensity exercise.**

PATIENTS AND METHODS: **20 young male T1DM patients were divided into two subgroups characterized by levels of glycated hemoglobin (HbA1c): HbA1c<7.3% (better HbA1c subgroup, n=10) and with levels HbA1c>7.3% (worse HbA1c subgroup, n=10). All participants performed a maximal oxygen uptake test and two efforts of various intensities (45 minutes of aerobic exercise and 30 minutes of mixed aerobic-anaerobic intensity exercise). Continuous glucose monitors (CGM) were used to control the glucose concentration.**

RESULTS: **Changes in biomarkers describing the metabolic response were similar in both groups. A comparison of applied efforts exhibited that maximal capacity effort resulted in the highest values of blood glucose (BG) at the end (150.9-160.6 mg/dl) and 1 hour after the exercise (140.2-161.3 mg/dl). BG concentration before, during, 1 hour, and 24 hours after each exercise was insignificantly higher in the worse Hb1Ac group.**

CONCLUSIONS: **HbA1c levels are insufficient to confirm whether the applied effort is performed in acceptable glycemic values. The CGM monitors allow for precise control of BG variations and accurate planning of physical activity by adjusting the insulin and carbohydrate consumption dose.**

Key Words:
Type 1 diabetes, Blood glucose, HbA1c, Exercise intensity.

Abbreviations
ALT – alanine aminotransferase; AT – anaerobic threshold; BG – blood glucose; CGM – continuous glucose monitoring; HbA1c – glycated hemoglobin; HPLC – high-performance liquid chromatography; ISPAD – international Society for Pediatric and Adolescent Diabetes; T1DM – type 1 diabetes; TCH – total cholesterol; TGL – triglycerides; TSH – thyrotropic hormone; VO_{2max} – maximal oxygen uptake.

Introduction

Type 1 diabetes (T1DM) is considered one of the most common autoimmune diseases in children and adolescents[1,2]. The latest analysis demonstrated that 18% (1.5 million) of people with type 1 diabetes are under the age of 20[3]. Within the next 20 years, the number of cases will increase to 13.5-17.4 million (60-107% more than in 2021)[3]. Type 1 diabetes results in acute complications such as hypoglycemia and ketoacidosis and chronic damage of kidneys, eyes, nervous system, and cardiovascular system[4]. The main therapeutic goal is to minimize its side

Corresponding Author: Beat Knechtle, MD; e-mail: beat.knechtle@hispeed.ch

effects and to ensure a similar quality of life to healthy adolescents[5,6].

The physical activity of children and adolescents with T1DM is lower compared to the healthy population[7]. Based on current research, diabetologists often recommend their patients' physical activity or even sports practice[8,9]. During the physical effort, the glycemia changes can be very dynamic for people with T1DM. Monitoring the carbohydrate metabolism during and after exercise of different intensities is crucial for optimizing insulin doses and for adequate therapeutic decisions to metabolic changes[10]. The effect of regular physical activity on the metabolic compensation in diabetes has been previously described in literature[8,9]. It has been demonstrated[11] that physical effort positively affects the lipid profile, endothelial function, and insulin sensitivity in adults. Nevertheless, only a limited number of papers[12-14] have explored this topic in children and adolescents.

Due to its complexity, carbohydrate metabolism during exercise requires individual analysis of the type and intensity of the effort, applied insulin dose, the occurrence of night hypoglycemia, and hormonal changes during adolescence[12,15]. Previous studies[16-19] have reported that the type of exercise determines the glycemic response. For example, a 30-minute-long aerobic activity below the anaerobic threshold could immediately lead to several hours of lasting hypoglycemia. This is probably the result of a lack of endogenous insulin production in type 1 diabetes patients, leading to the deregulation of constant glycemia levels. During exercise, stored glycogen levels are reduced, and myocytes start to use the blood glucose for further energy production. Different reactions are observed in diabetics exposed to high-intensity (mixed aerobic-anaerobic) activities. Such activities could lead to hyperglycemia immediately after the exercise. This is probably the effect of increased secretion of hormones such as adrenaline, cortisol, glucagon, and human growth hormone[20-22].

The glycated hemoglobin (HbA1c) is considered the "golden standard" parameter used in diabetes treatment evaluation[23]. It is defined[24] as a percentage of circulating hemoglobin that has undergone glycation (non-enzymatic reaction of attaching a glucose molecule to the amino group of the β-globin chain). This biomarker reflects the average glucose concentration in the blood plasma in the last 2-3 months. HbA1c does not provide direct information about glycemic variability and hypoglycemia incidence but correlates with the risk of long-term microvascular diabetes complications[25]. It was previously observed[26] that patients with similar HbA1c levels and average daily glucose concentration could have different glycemic variability. According to Monnier et al[27], patients with higher glycemic variability are at higher risk of hypoglycemia. The literature lacks information about potential relations between glycated hemoglobin and glycemic variability involving the risk of hypoglycemia during physical exercise of various intensities.

The current experiment aimed to introduce the differences in determinants of metabolic changes in young T1DM patients characterized by low and high blood serum glycated hemoglobin concentration at rest. Secondly, it was aimed to determine glycemic variability during low and high-intensity exercise. It was hypothesized that a similar level of metabolic changes independent of the HbA1c levels would characterize all patients. Moreover, it was assumed that lower glucose variation would be reported in patients with better levels of HbA1c concentration at rest and during low and high-intensity activities.

Patients and Methods

Participants

20 young male T1DM patients took part in the study (age: 14.4±1.6 years, disease duration: 6.7±4.1 years, weight: 59.5±12.8 kg, BMI: 20.2±2.6 kg/m^2). T1DM was diagnosed following the International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines[28]. All the participants were patients of the same pediatric clinic and did not practice high-performance sports. The participants were assigned to one of the two groups according to the level of HbA1c: HbA1c<7.3% (better HbA1c subgroup, n=10) and HbA1c>7.3% (worse HbA1c subgroup, n=10).

The Bioethical Committee at the Medical University of Gdansk, Poland, analyzed the study design and provided an appropriate agreement (approval number: NKBBN/397/2018). A detailed description of the research was introduced to the patients and their parents, who signed the written informed consent form.

Study Design

All participants performed the exercises in three different stages. During the project's first stage, patients completed a progressive test on the cyclo-

ergometer (Eos Sprint, Jeager, Hoechberg, Germany) to determine the level of maximal oxygen uptake (VO_2max) and anaerobic threshold (AT) values. The second stage of the experiment occurred after two weeks, during which participants performed a 45-minute continuous exercise with a 40% lower load than AT (expressed in Watts). The third stage of the study consisted of 30 minutes of activity with mixed (aerobic and anaerobic) intensity, involving 6 bouts of cycling without recovery. Each bout contained 2 minutes of aerobic cycling (AT –40% in Watts) and 4 minutes of anaerobic cycling (AT +10% in Watts). All the efforts were monitored in real time with the use of a gas analyzer (Oxycon Pro, Erich Jaeger GmbH, Hoechberg, Germany).

All participants received the same meal two hours before each exercise, according to the previously described composition and proportions[29]. Moreover, a bolus of rapid-acting analog insulin was applied before the meal. Continuous glucose monitors (CGM) were used to control the glucose concentration during each exercise. The data from pre-exercise measurement, 5 minutes after the exercise (after), and 30 minutes after the exercise (rest) were taken into consideration.

Basic Physical Examination Performed

All children underwent physical examination, and height and weight were taken in a standard way using a Harpenden stadiometer and a digital scale (Seca, Hamburg, Germany). The BMI-z score (body mass index) and SDS (standard deviation score) of BMI were calculated with standard formulas using the results of the OLAF study of Polish children[30].

VO_2max Measurement

The VO_2max was measured during a progressive test performed on the cycloergometer (Eos Sprint, Jeager, Hoechberg, Germany) with the use of an expiratory gas analyzer Oxycon Pro (Erich Jaeger GmbH, Hoechberg, Germany) in the laboratory under standard conditions (temperature: 21°C; atmospheric pressure: 1,010 hPa; air humidity: 55%). The test contained a 5-minute warm-up with a load of 1 W/kg and a pedaling frequency of 60 repetitions per minute. After the warm-up, the load continuously increased every minute by 0.25 W/kg until exhaustion. The anaerobic threshold (AT) was calculated using the ratio between exhaled carbon dioxide and oxygen consumption (respiratory exchange ratio – RER). AT was reached when RER exceeded 1.

The Control of Blood Glucose Concentrations

The level of blood glucose concentrations on the exercise days was registered using the CGM. Glycemic control parameters were calculated with Glyculator 2.0 (available at: https://apps.konsta.com.pl/modules/glyculator/)[31]. The insulin dose was individualized according to the participant's weight (DDI IU/kg).

Biochemical Analyses

All the blood samples were collected from fasting patients before the tests. HbA1c was determined using the Bio-Rad VARIANT™ HbA1c Program (Bio-Rad Laboratories, Inc., Hercules, CA, USA). Other biochemical analysis procedures were performed according to the previously described methodology[29].

Statistical Analysis

All the data were presented as means ± standard deviations. After verification of the data distribution, the *t*-test for independent variables or Mann-Whitney U test was performed to compare the results between the groups. Moreover, the ANOVA for repeated measures was used to calculate potential significant differences between the physical efforts. In case of reaching the significance level, the Bonferroni post-hoc test was applied to identify where exactly these differences occurred. The significance level was set at $p \leq 0.05$. All the calculations were carried out using Statistica 13.0 software (Tulsa, OK, USA).

Results

The basic characteristics of the patients are presented in Table I. Significant differences between the groups were noted in the average thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT) and triglyceride (TGL) values. Moreover, patients from the worse HbA1c group used the insulin pumps for 2.4 years longer (33%, insignificant). Higher values of 25OHD concentration (6.5 ng/dL, 26.9%, insignificant) were reported in the better HbA1c group.

Blood glucose concentration before the exercise, 1 hour, and 24 hours after the exercise was higher in the worse Hb1Ac group. Moreover, the significance (p=0.0061) between the group effect and insignificance (p=0.2641) between the effect of the effort was reported. Before each exercise, patients with worse Hb1Ac consumed fewer

carbohydrates, while 1 hour after the effort, the consumption in this group was higher (significant between-group effect, p=0.020). In the final stage of the exercise and after 30 minutes of rest, BG was higher in >7.3% of the HbA1c group. Furthermore, the significance of interaction between groups and between exercises was calculated as well. Higher differences were found after 30 minutes of recovery and then in the final stage of the exercise (Table II, Figure 1).

Taking into account the correlations between the blood glucose concentrations of patients of both groups before and after performing work of various intensities, it was calculated that those related to the type of physical effort (p=0.0009) and not the type of the study group (p=0.2555) could be considered statistically significant. Despite the lack of significant correlations between both groups, data presented in Figure 2 demonstrate that more dynamic changes in BG were recorded in the group with a worse level of HbA1c (>7.3%, chequered black line).

The high-resolution CGM data are presented in Figure 3. Due to technical problems (e.g., sensor disconnection during the exercise), only 16-17 patients were completely monitored. Solid, bold lines demonstrate the average BG concentration in groups with better and worse levels of HbA1c. During each exercise, lower values of BG were reported in the better HbA1c group. However, no significant differences were found between before exercise and during exercise. Moreover, average BG concentration levels in analyzed patients did not differ significantly (p=0.2713) during consecutive types of physical exercise. However, in relation to the type of the study group, the significance of the results was confirmed for p=0.0377. In addition, the interaction of results by type of exercise and group was also calculated as statistically significant (p=0.0479).

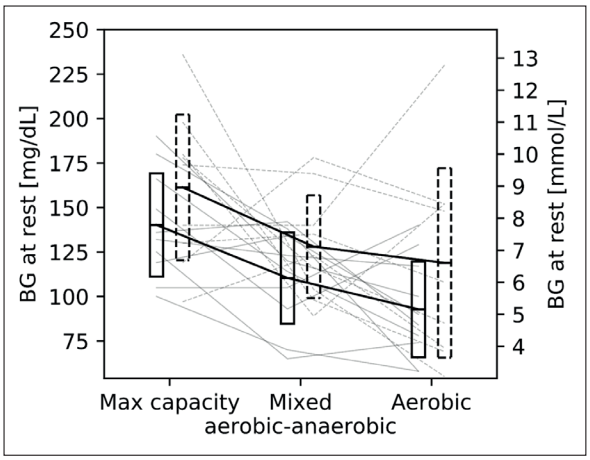

Figure 1. Blood glucose concentration in patients with better (solid line) and worse (dotted line) level of Hb1Ac reported 30 minutes after exercise.

Discussion

In the current research project, 20 young boys with type 1 diabetes were divided into two subgroups according to their HbA1c glycated hemoglobin index levels based on ISPAD recommendations, which define an HbA1c value of 7% as a target for young diabetics[32]. Therefore, patients with HbA1c <7.3% were allocated to the better HbA1c group (n=10), while those with HbA1c >7.3% were assigned to the worse HbA1c group (n=10). No significant differences in biological maturation, biometric characteristics, and physical capacity were reported (Table I).

The main purpose of this experiment was to introduce the percentage values of HbA1c as a significant biomarker in metabolism regulation and glycemia variability in analyzed patients during exercises performed at low and high intensity. To the best of our knowledge, there is a lack of research in the available literature describing the relations between HbA1c and the glycemia response in young T1DM patients during and after physical activity. The obtained results demonstrated that the changes in biomarkers describing the metabolic response were similar in both groups. However, a higher blood glucose concentration after the three applied efforts was reported in the worse HbA1c group. The significant interaction was calculated before exercise for group type (p=0.0061) and at the end of the test and after the recovery phase, respectively: p=0.0426 and p=0.0347 and exercise (p=0.0009 and p=0.0029). Before and after each exercise, patients from worse HbA1c groups consumed fewer carbohydrates than patients from the better HbA1c group (p=0.0020). The inverse relation was observed after the 30-minute recovery period when boys from the worse HbA1c group consumed more carbohydrates and the interaction of the results concerned only the type of exercise performed (p=0.0002). Thanks to the application of modern CGM devices, the average BG values before, during, and after the exercise were calculated and presented (Figure 3). Significantly lower BG values (p=0.0377) were found in the better HbA1c group after the 30-minute recovery

Table I. Characteristics of the participants.

	Better HbA1c (N=10)	Worse HbA1c (N=10)	*p*-value
HbA1c (%)	7.09±0.82	7.55±0.84	
Diabetes duration [years]	5.6±3.8	7.7±4.3	0.2670
CSII duration (years)	4.8±3.1	7.2±4.3	0.1712
Age at exmination [years]	14.7±1.7	14.0±1.5	0.3505
BMI z-score	0.0±0.6	0.3±0.8	0.4116
Body fat [%]	14.3±5.0	15.2±7.8	0.7604
WHR [Inches]	0.8±0.0	0.8±0.0	0.8061
TSH [uU/mL]	1.3±0.6	1.5±0.9	0.4053[#]
fT4 [pmol/L]	11.9±1.1	11.9±1.2	0.9190
ALT [U/L]	19.6±9.9	18.9±4.7	0.6217[#]
AST [U/L)	14.5±4.1	15.4±4.4	0.6434
TCH [mg/dL]	162.6±20.2	157.4±30.8	0.6606
HDL chlesterol [mg/dL]	59.9±13.1	60.9±19.8	0.8955
LDL cholesterol [mg/dL]	93.6±12.3	80.1±26.0	0.1547
TGL [mg/dL]	52.2±16.2	80.8±44.5	0.0693[#]
$25(OH)D_3$ [ng/dL]	24.2±11.5	17.7±6.8	0.1428
mean DDI [UI/kg]	0.8±0.2	0.9±0.4	0.4150
VO_2max [ml/kg/min]	41.2±4.1	39.2±7.2	0.4543

[#]significant differences in post-hoc tests (Bonferroni); CSII - continuous subcutaneous insulin infusion; BMI - body mass index; WHR - waist-hip ratio; TSH - thyrotropic hormone; fT4 - free thyroxine hormone; ALT - alanine aminotransferase; AST - aspartate aminotransferase; TCH - total cholesterol: HDL - high-density lipoprotein; LDL - low-density lipoprotein; TGL - triglycerides; DDI - daily insulin dose; VO_2max - maximal oxygen uptake.

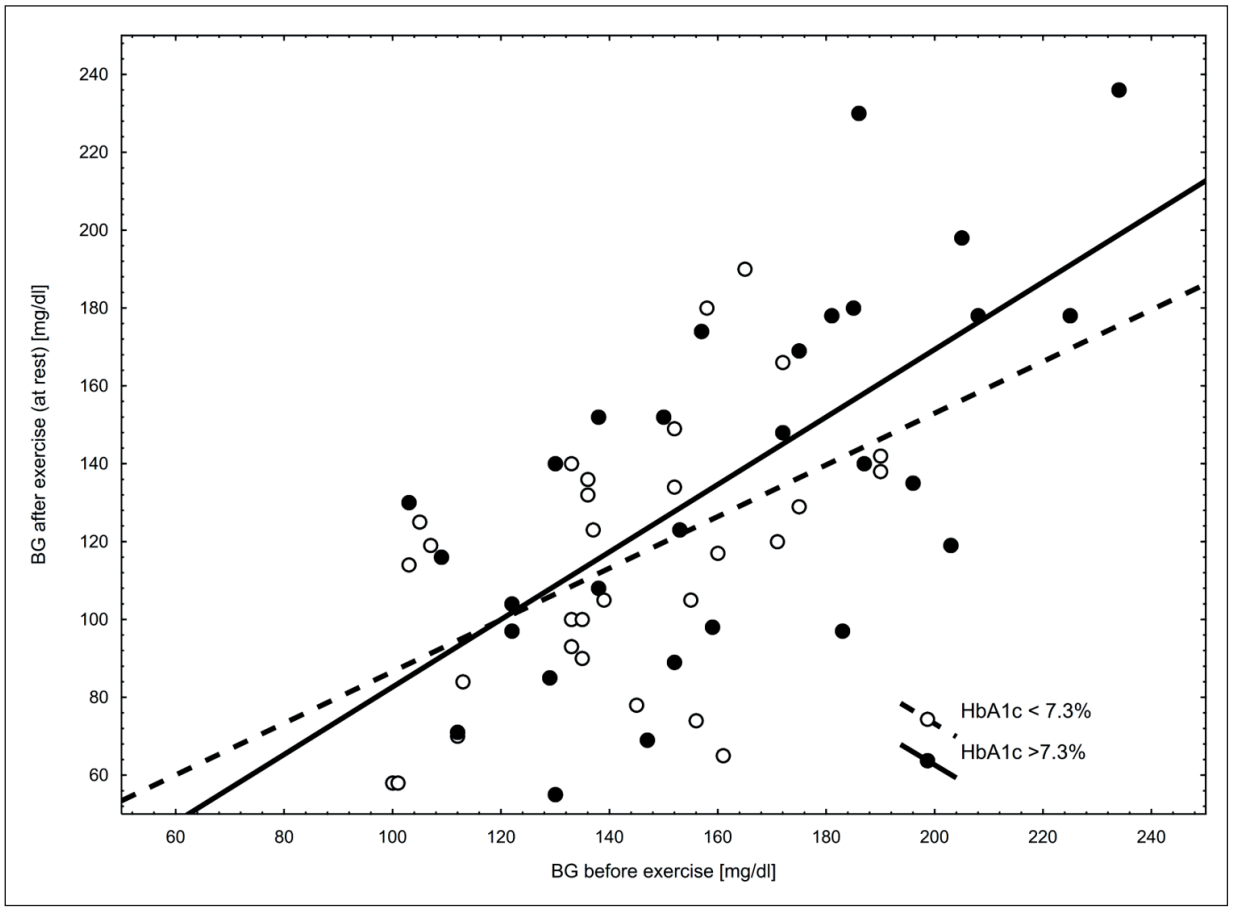

Figure 2. Correlations between blood glucose levels in patients with better (white symbols) and worse (black symbols) levels of HbA1c at the beginning and 30 minutes after the exercise.

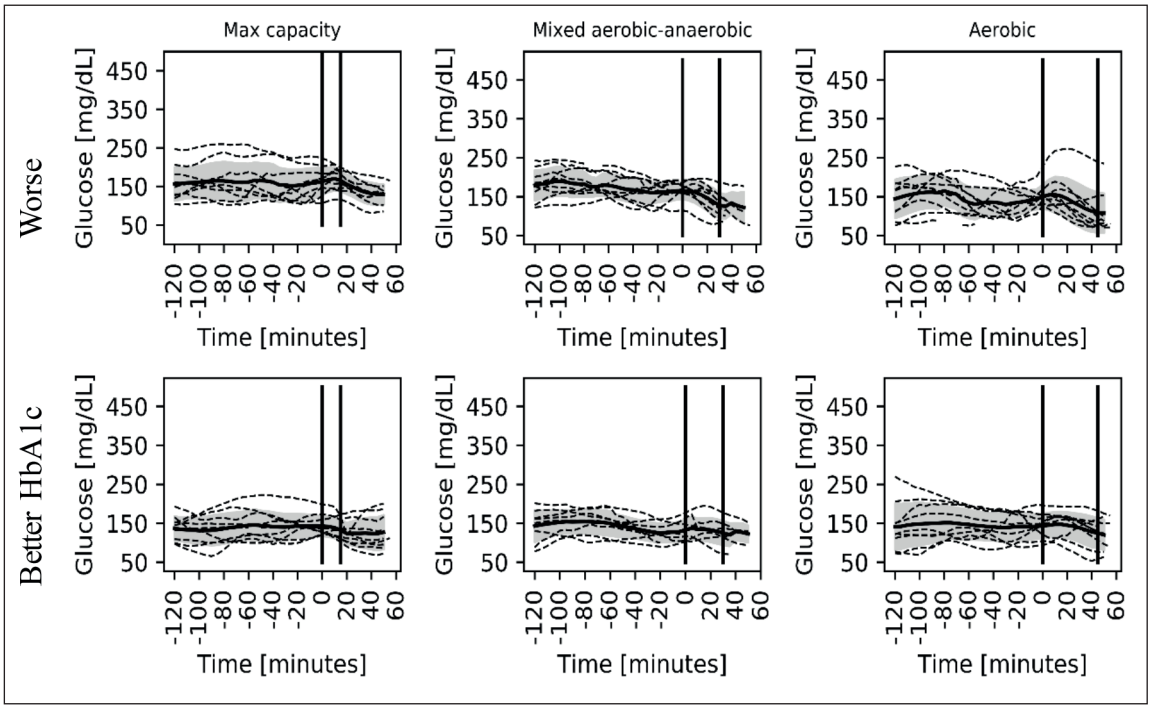

Figure 3. The record of CGM in tested adolescents during three types of exercise.

period. At this phase, significant interaction in reference to the group and type of the exercise was noted (p=0.0479).

This is the first study where modern CGM devices were used in young T1DM patients during various intensities and durations of physical exercise. Biagi et al[33] and Moser et al[15] presented such data for adult patients. CGM systems make up to 288 BG concentration measurements per day and allow for optimal glycemia self-control, indicating numeric BG values and so-called trend arrows showing the direction and rate of glycemia changes in real time[34]. Based on the provided information, the patient or his/her guardian can immediately react to life-threatening situations such as hypoglycemia or hyperglycemia. This method allows the registration of unaware hypoglycemia (<70 mg/dl) and glycemic fluctuations during physical activity of various intensities and duration[35-37]. Moreover, all the patients participating in the research were treated with individual insulin pumps. Hyperglycemia occurrence and the fear of hypoglycemia are still the most important limitations in performing physical activity for people with T1DM. The largest problems in maintaining normal glycemia are observed during the submaximal and maximal intensity exercise. After such activities, late- or even-night hypoglycemia could occur. Recent research[38] suggests that poor glycemic control may result in low sleep quality in T1DM children and adolescents. Therefore, continuous blood glucose monitoring integrated with an automatic insulin pump enables automatic insulin delivery suspension and prevents hypoglycemia[39].

Because glycated hemoglobin assesses the long-term glycemic balance, it is not an optimal biomarker. However, the conjunction of a properly conducted interview and BG measurements gives a reliable evaluation of the treatment and is still widely used by clinicians. The problem of evaluation of metabolic control in diabetes is more complex during physical activity. The values within the reference range (<7%) may result from adequate exercise planning and maintaining the normoglycemia or large BG fluctuations during and after the exercise. HbA1c does not confirm whether the applied effort is performed in acceptable glycemic values. Undoubtedly, the measurements of BG received from the correctly installed and calibrated CGM sensor are more accurate biomarkers. Determining glycemia during the exercise, post-exercise, and the night is very important in active patients with T1DM. The CGM monitors allow for precise control of BG variations and accurate physical activity plan-

Table II. Blood glucose concentration and amount of consumed carbohydrates in patients with better and worse Hb1Ac levels during three different types of exercise.

	Maximum capacity exercise			Mixed aerobic-anaerobic exercise			Aerobic exercise			*p*-value*	
	Better HbA1c (N=10)	Worse HbA1c (N=10)	All (N=20)	Better HbA1c (N=10)	Worse HbA1c (N=10)	All (N=20)	Better HbA1c (N=10)	Worse HbA1c (N=10)	All (N=20)	Type of exercise	HbA1c division
BG at the start of exercise [mg/dl]	140.3±22.4	173.0±44.9	156.7±38.4	150.4±29.6	164.2±31.6	157.3±30.6	135.3±25.0	148.5±24.6	141.9±25.1	0.2641	0.0061
Carbohydrates consumed before exercise [g/kg]	0.4±0.3	0.1±0.1	0.3±0.3	0.3±0.2	0.2±0.2	0.2±0.2	0.4±0.3	0.3±0.2	0.3±0.3	0.3674	0.0020
Carbohydrates consumed during or immediately after exercise [g/kg]	0.0±0.1	0.2±0.3	0.1±0.3$	0.1±0.2	0.2±0.3	0.2±0.2#	0.4±0.3	0.4±0.3	0.4±0.3$,#	0.0002	0.4464
BG at the end of exercise [mg/dl]	150.9±27.0	160.6±36.7	155.8±31.8$	117.1±32.6	149.1±34.1	133.1±36.4	99.7±24.6	129.7±51.4	114.7±42.2$	0.0009	0.0426
BG after rest [mg/dl]	140.2±30.6	161.3±43.4	150.2±37.7$,#	110.4±27.1	133.0±33.0	121.7±31.6$	92.8±28.4	116.7±53.7	104.8±43.6#	0.0029	0.0347

BG – blood glucose, $,#significant differences in post-hoc tests (Bonferroni) between types of exercise, *interactions tested, not significant.

ning by adjusting the insulin and carbohydrate consumption dose. However, the scientific topic undertaken in the current research is justified since patients still rarely use insulin pumps. The high costs of such solutions cause the evaluation of HbA1c in physically active patients to still be useful.

The metabolic function biomarkers in the reference level did not differ between the groups except the TSH, Alt, and TG. However, further analysis of the data suggests that values of BMI, body fat, VO_2max, 25(OH)D and TG were more beneficial from a metabolic point of view in the better Hb1Ac group. Moreover, in the worse HbA1c group, the disease duration was longer than 2.1 years, and the duration using the CSII was 2.4 years. These significant differences in TSH, ALT, and TG observed between the groups did not result in further diagnostics modification. However, this could indicate the unfavorable trend typical for patients with poorer metabolic control (worse HbA1c values). In their research, Ladeia et al[40] presented that lipid profile disturbances, including increased TG level, are related to the worse glycemic control of young T1DM patients. Furthermore, the significantly increased level of ALT indicated liver damage, potentially caused by chronically ill-treated diabetes.

The relationship between thyroid dysfunctions and diabetes is widely known. Changes in the thyroid hormone concentration may negatively affect glucose metabolism. On the other hand, Bellastella et al[41] claimed that glycemic variability affects the TSH level in patients with T1DM regardless of changes in thyroid hormones. Therefore, to diagnose hypo- or hyperthyroidism, more detailed tests for patients with large glycemic variability are necessary. The CGM measurements are very useful in such a situation despite the Hb1Ac values.

Scott et al[18] stated that long-term aerobic exercise could lead to hypoglycemia not only during the activity but also immediately after the effort and several hours later. Such disruptions in constant glycemia are possibly caused by impaired insulin secretion and lack of endogenous regulation in T1DM patients[42]. Different reactions are observed as a result of physical exercise reaching the intensity corresponding to VO_2max or at the intensity exceeding the anaerobic threshold level. Short efforts often lead to short-term glycemia immediately after the exercise. This reaction is probably caused by the increased secretion of hormones such as adrenaline, cortisol, glucagon, and human growth hormone[21].

The levels of BG reported in our research after each type of exercise were higher in the worse Hb1Ac group. Furthermore, statistically significant interactions were reported according to the type of exercise and the subgroup. Thus, the question of whether such responses are caused by unstable glycemia in worse HbA1c patients or by carbohydrate consumption after the exercise seemed justified. In our opinion, the increased amount of consumed carbohydrates after the exercise could be the result of larger glycemia variations caused by increased activity and a less effective regulation process (Table II). According to Riddel et al[43], the carbohydrate supply should depend on actual glycemic values and the trends observed in real-time CGM. These authors claim that the applied algorithm prevents hypoglycemia and maintains glycemic control during long-term exercise in active adolescents with T1DM. However, in our opinion, lower pre-exercise carbohydrate consumption (as a result of higher acute glycemia and stable trend) could lead to rapid BG reduction after exercise in patients with large glycemic variability. Therefore, an additional amount of carbohydrates could be applied to protect patients against hypoglycemia.

Lower glycemic variations during and after the exercise and lower additional carbohydrate consumption in the better HbA1c group could suggest that better glycemic control enables maintaining normoglycemia during exercise of various intensities. The continuous analysis of BG during three different physical exercises seems to be the most recommended method for efficiently preventing eventual hypo and hyperglycemia. It is also very useful for acute glucose concentration control during daily activities and sleep. Similar conclusions were demonstrated by Biagi et al[33], who investigated glycemic variability in T1DM patients during aerobic and anaerobic exercise using CGM. Thus, continuous monitoring of glycemia may be considered as an alternative for glycated hemoglobin in controlling BG changes. The metanalysis by Kennedy et al[44] did not confirm the positive influence of physical exercise on the glycemic variability expressed as HbA1c. The authors suggest that the low efficiency of this biomarker could be affected by increased calory consumption or lower insulin supply during exercise. Despite such observations, other benefits of physical activity in T1DM patients are highlighted in this study as well.

The current study suggests that each T1DM patient can practice sports under medical super-

vision and using a CGM system, which can be highly useful in glycemia control during physical exercise with various intensities.

Limitations

Scientific experiments concerning the variability of glycemia in T1DM patients during exercise are not without limitations. Limitations such as insufficient sample size or fulfilling the inclusion criteria are common in research in this scientific area. Moreover, it is difficult to complete a homogenous group using the same devices for measuring the BG concentration with a similar level of physical fitness. Furthermore, ensuring that there are no significant differences in the biological age of young participants is another challenge.

Conclusions

The authors would like to clearly underline the need for further development of this topic in future research. Training interventions lasting 8-12 weeks carried out on numerous patients from different age categories seem necessary to explore the reaction of T1DM patients to physical exercise. From the logistical point of view, in this case, the largest challenge is to perform the training interventions under the supervision of the medical doctors and trainers responsible for adequate training load programming.

Conflict of Interest

The authors declare that they have no potential conflict of interest.

Authors' Contributions

Maria Skalska – conceptualization, methodology, writing original draft, data collection, project administration, data curation; Artur Myśliwiec – methodology, investigation, data collection; Arkadiusz Michalak – validation, visualization, formal analysis, data analysis; Jędrzej Chrzanowski – editing, visualization, formal analysis, software, data analysis; Agnieszka Lejk – investigation, methodology, data curation; Joanna Jastrzębska – investigation, methodology, writing original draft, data curation; Łukasz Radzimiński – investigation, writing original draft, editing, supervision; Guillermo F. Lopez-Sanchez – validation, editing, methodology; Karolina Myśliwiec – methodology, investigation, data collection; Zbigniew Jastrzębski – conceptualization, project administration, resources, writing original draft, supervision; Katja Weiss – supervision, editing, validation, writing-review; Beat Knechtle – conceptualization, writing-review, resources, methodology, project administration.

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Availability of Data and Materials

The data presented in this research are available upon reasonable request from the corresponding author.

Ethics Approval

The research was approved by the Bioethical Committee at the Medical University of Gdansk, Poland (approval number: NKBBN/397/2018).

Informed Consent

A detailed description of the research design was introduced to the parents or legal guardians of the patients. Moreover, they signed the written informed consent form that included information about the publication of the results.

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