Assessment of Exercise Capacity in Children with Type 1 Diabetes in the Cooper Running Test

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Key words
type 1 diabetes, children, Cooper test, physical capacity, percentile charts

accepted 13.11.2018

Bibliography
DOI https://doi.org/10.1055/a-0805-1326
Published online: 17.12.2018
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0172-4622

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Introduction
Physical activity is crucial for the healthy development of a child. There is strong evidence that in children moderate and vigorous activity is associated with improvement of cardiometabolic risk factors regardless of their sedentary time [9].

Exercise seems to be even more important for children with type 1 diabetes mellitus (T1DM) in whom it improves glycemic control [25], body mass index (BMI) and reduces other cardiometabolic risk factors [25].

However, children with T1DM face unique, disease-related barriers when engaging in physical activity. Intensive training can cause both hypoglycemia and hyperglycemia, which makes blood glucose management much more difficult [28]. Moreover, the patients or their parents may be afraid of exercise-induced hypogly-
cemia [30] and such fear is often aggravated by insufficient knowledge about diabetes among school staff [11]. Finally, competitive athletes with T1DM must prove they have a good understanding and control of their disease before receiving clearance from sports medicine specialists [7]. All of these may discourage young people with T1DM from exercise and affect their fitness level.

As a result, insufficient physical activity of children with T1DM can be one of the reasons for the increased prevalence of overweight and obesity [19], which in a vicious circle, may further discourage them from practicing sports.

To date, a limited number of studies analyzed physical capabilities of children with T1DM [16, 20, 22, 23, 29, 32, 33]. Most of them were performed in laboratory settings which do not reflect real-life school or sport club conditions where school children and students are commonly tested. Thus, fitness of children with T1DM should be also evaluated in everyday conditions and compared to the population of healthy sex- and age-matched peers.

Aim

The aim of the study was to evaluate physical fitness of children with T1DM in the Cooper 12-min run test and to assess the test’s safety concerning diabetes-related acute complications in real-life conditions.

Materials and Methods

The study was conducted during an annual summer camp for children with T1DM who came from 12 pediatric diabetes centers in Poland. All the children received functional insulin therapy: continuous subcutaneous insulin infusion (CSII) or multiple daily injections (MDI).

The study was carried out in accordance with the Declaration of Helsinki and the journal’s principles [12]. The protocol was approved by the Ethics Committee of the Medical University of Lodz (NO RNN/195/17/KE). All children aged 10 years or older (N = 87) were offered participation in the study, with researchers as medical professionals dealing directly with parents and children without an intermediary gatekeeper. Informed written consent was obtained from the parents of all the children who agreed to participate and from the participating teenagers aged 16–18 years; informed assent was given by the participating children under the age of 16.

Medical history was obtained and physical examination was performed by pediatricians. Body height and weight were measured to calculate body mass index (BMI) using the same procedure as in the study by Kulaga et al. [18]. Body composition was estimated by bioimpedance analysis (BC-601, TANITA Health Equipment H.K. Ltd. Kowloon, Hong Kong). Capillary blood samples were collected for HbA1c assessment (D-10 Hemoglobin A1c Program [Bio-Rad Laboratories, Hercules, CA, BioRad, Marnes-la-Coquette, France]).

The participants performed the Cooper 12-min run test which involves continuous running (or, when needed, walking) for 12 min without any rest and subsequent measurement of the covered distance. The test was carried out at the local athletic stadium on a 400-meter running track in 3 consecutive sessions on 2 days, with 10–15 children per session. Each participant completed the Cooper run test once, however, all children were already familiar with the test as they had completed it at their schools. All the children were informed about the purpose and design of the test and encouraged to perform to the best of their abilities. The test was performed 2–2.5 h after breakfast. Before the run, children managed their glycemia under supervision of the medical staff [26]; in all the participants blood glucose (BG) was measured using the same brand of BG meters (Contour Plus One, Ascensia Diabetes Care US, Parsippany, USA). If BG was below 7.2 mmol/L, the child received oral dextrose and started a run. In case of BG < 3.9 mmol/L oral dextrose was provided and, if glucose levels had recovered to > 4.7 mmol/L and hypoglycemia symptoms subsided, the child participated in the next scheduled run session. In case of hyperglycemia defined as capillary BG > 13.9 mmol/L, beta-hydroxybutyrate (BOHB) was measured in the capillary blood (OptiumXido, Abbot Alameda, California, USA). If BOHB concentration exceeded 0.5 mmol/L, the child’s run was postponed until the next scheduled session provided that BG and BOHB concentration were normalized.

Resting heart rates (HR) were measured with a pulse oximeter (Beurer, Ulm, Germany). The run was preceded by a short warm-up. During the test, camp staff members were assigned to particular children to provide their continuous clinical supervision and to count their run rounds. Once the 12th min of the run passed, the individual distance of each participant was recorded with a 50 m accuracy.

The second HR measurement was performed within 2 min after the end of the run. BG was measured immediately after the test and 30 and 60 min later. In case of hyperglycemia (BG > 13.9 mmol/L) and BOHB concentration was measured in the capillary blood. During the follow-up, children were allowed to engage freely in non-strenuous physical activity. They were asked to refrain from any snacks other than carbohydrates for management of hypoglycemia during 30 min after the run. This protocol was supposed to imitate conditions during school sports activities.

Safety assessment of the Cooper run test was focused on potentially health-threatening diabetes-related events: severe hypoglycemia (event with severe cognitive impairment), clinically significant hypoglycemia (BG < 3 mmol/L), and significant hyperglycemia (BG ≥ 13.9 mmol/L [14]) with increased BOHB (BOHB concentration in capillary blood > 0.5 mmol/L). All adverse events were reported together with frequencies estimated for the whole group.

Statistical analysis

The children’s BMI, body fat percentage (BF %) and Cooper test results were transformed into z-scores and percentiles based on the percentile charts [8, 18, 21] appropriate for the studied population and measurement methods and are presented as mean ± standard deviation (SD) or median and interquartile range (25 %–75 %). Continuous variables were checked for normality with the Shapiro-Wilk’s test.

BMI, BF % and Cooper test were compared to 0 with Student’s t-test for a single sample to evaluate any potential differences from the reference population [18].

To determine which variables affect Cooper test result, multiple linear regression model was constructed. It was preceded by an univariate analysis including the following predictors: gender, age,
Results

Six adolescents refused to participate in the study and one consenting individual was excluded due to an injury acquired during the camp. All participants who started the run completed it (N = 80, 33 boys, 45%, mean age 13.6 ± 2.1 years, mean diabetes duration 6.4 ± 3.5 years). Majority of the participants (N = 73, 91.3%) were treated with CSII, 7 patients were on MDI. Mean HbA1c was 7.46 ± 0.9% (58 ± 7 mmol/mol) with median at 7.35% i.e., 57 mmol/mol (25–75%: 6.9–8% i.e., 52–64 mmol/mol). Neither age (p = 0.15) nor HbA1c (p = 0.41) differed significantly as compared to a reference population of Polish children with T1DM [15]. 2 children experienced hypoglycemia before the run and it was managed with oral dextroside. Median BG before the test was 8.1 mmol/L (25–75%: 6.4 to 10.4 mmol/L) and immediately after the test median BG was 8.0 mmol/L (25–75%: 6.0 to 10.4 mmol/L); the difference between both values was not significant (signed test p = 0.91). Throughout the 60 min of the follow-up, BG levels decreased as compared to the values before and immediately after the test (p = 0.004) with a nadir observed 30 min after the run (Fig. 1). No severe hypoglycemia or increased ketone bodies (BOHB) concentration in blood were observed. Clinically significant hypoglycemia (BG < 3 mmol/L) occurred in 3 (3.8%) children; other 11 participants (13.75%) reached the glucose alert value (BG between 3.0 and 3.9 mmol/L, Fig. 2). All episodes of hypoglycemia or glucose alert values were recorded 30 or 60 min after the test (Fig. 2); no symptomatic hypoglycemia occurred during the run.

The mean distance covered by the participants was 1914 ± 298 m, and the median value corresponded to the 45th percentile of the reference values for this population (25–75%: 25th – 63rd). The adolescents’ results of Cooper test were −0.12 ± 0.71 SD below those of the reference population but the difference was not significant (p = 0.12, Fig. 3a). The Cooper test z-scores did not differ between the participants who experienced BG < 3.9 mmol/L and those whose BG levels did not decrease below 3.9 mmol/L over 60 min after the test (−0.1 ± 0.70 vs. −0.27 ± 0.34, p = 0.44), or between boys and girls (−0.16 ± 0.67 vs. −0.09 ± 0.75, p = 0.68). The raw distance covered by adolescents (in meters) showed no correlation with age (r = 0.18, p = 0.12).

The mean BMI z-score of the participants was 0.48 ± 0.94 (the median corresponded to the 73rd percentile of values for the reference population, 25–75%: 44–88). The difference between the study group and the reference population was significantly higher than the expected value of 0 (p < 0.001, Fig. 3b). Similarly, BF % z-score was higher in the study group as compared to the reference population (mean z-score: 0.37 ± 0.85, p < 0.001 vs. 0 value; the median corresponded to the 68th percentile of the values for reference population, 25–75%: 46th – 81st, Fig. 3c).

The univariate analysis demonstrated that age (r = −0.27, p = 0.020), T1DM duration (r = −0.21, p = 0.079), BMI z-score (r = −0.33, p = 0.004), BF % z-score (r = −0.35, p = 0.002), HR (r = 0.23, p = 0.048) and BG (r = −0.29, p = 0.014) after the test correlated with the Cooper test.
Due to a strong correlation between BMI and BF % z-scores (r = 0.73, p < 0.001), we decided to keep BF % z-score in the model as a better clinical measure of adiposity. After the forward-stepwise regression 4 independent predictors of Cooper test results entered the multiple linear regression model: age, BF %, HR after the test and BG immediately after the test (▶ Table 1). Older age and higher adiposity (BF %) predicted a worse outcome while higher HR and higher BG glycemia were associated with better performance. The whole model was proved to be significant (F statistics p < 0.001), accounted for 30% of the overall variation in Cooper test results (adjusted $R^2 = 0.3$) and had normally-distributed residuals ($p = 0.69$).

#### Table 1

<table>
<thead>
<tr>
<th>Parameter (SE) [95%CI]</th>
<th>Beta (SE) [95%CI]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>$-0.95$ (0.7)</td>
<td>[−2.36 to 0.46]</td>
</tr>
<tr>
<td>Age</td>
<td>$-0.1$ (0.03)</td>
<td>[−0.17 to −0.03]</td>
</tr>
<tr>
<td>Body fat % z-score</td>
<td>$-0.26$ (0.08)</td>
<td>[−0.41 to −0.09]</td>
</tr>
<tr>
<td>HR after the test</td>
<td>$0.01$ (0.003)</td>
<td>[0.002 to 0.016]</td>
</tr>
<tr>
<td>BG after the test</td>
<td>$0.004$ (0.0001)</td>
<td>[0.001 to 0.006]</td>
</tr>
</tbody>
</table>

**Whole model:** $R^2 = 0.33$. adjusted $R^2 = 0.3$. p < 0.001

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**Discussion**

**Safety of the Cooper test in children with T1DM**

The Cooper 12-min run is a simple test designed to assess physical capacity. The test requires very simple equipment: a watch and a measuring tape, which makes it perfect for in-the-field research. Moreover, due to its simplicity, it is widely used in schools during physical education lessons, and population-scale reference values for interpreting its results are available. However, many physical education teachers have rudimentary knowledge about T1DM [11] and may be concerned about a young patient with T1DM participating in Cooper test. Our study demonstrated that a short-term, excessive effort during the Cooper test did not cause an immediate fall in BG concentration. This is in line with current knowledge, because the Cooper test is designed to provoke extreme, submaximal effort which is anaerobic in nature and rarely decreases glycemia [26]. The 1-h follow-up after the test was designed to reproduce school-day conditions as in real-life, after finishing the Cooper test, children may participate in some light physical activity throughout the following lessons. A gradual decrease in BG levels was observed over the first 30 min following the run. No severe hypoglycemia with cognitive impairment was recorded. The episodes of BG < 3.9 mmol/l, which occurred in 17.5% of the participants, were probably related to the study protocol regulation preventing the participants from taking carbohydrates over the first 30 min following the run unless hypoglycemia was detected; all these episodes were perfectly self-managed by the children. Therefore, patients should be educated to compensate physical activity with adequate carbohydrate consumption and/or insulin dose adaptation before and/or after such activities, according to self BG monitoring results. Although in few patients BG levels increased notably, in none of them increased BOHB concentration indicative of risk for ketoacidosis was recorded. Overall, we assume that performing the Cooper 12-min running test is safe for children and adolescents with T1DM who are well-educated, prepared for the exercise and...
know how to follow glucose levels and how to respond to them before and after exercise.

**Physical fitness of children with T1DM**

To date, several studies compared the fitness of children with T1DM and their healthy peers. Some of them revealed worse exercise capacity in children with T1DM [16, 32], others failed to find any disparities [1, 13, 20, 22, 29]. In most of these studies children’s oxygen uptake during incremental progressive cycling test was assessed, either by direct measurement of peak oxygen uptake (VO2peak) with breath-by-breath gas exchange [1, 16, 20, 23, 29] monitoring or by estimation of maximal oxygen uptake (VO2max) based on maximal workload [22]. While this method is perceived a golden standard, it imposes certain limitations that may affect measurements. Its most important limitations are difficulties in cooperation with children and age-related variability in cardiometabolic parameters [27]. Moreover, performing exercise tests with increasing workload and gas exchange monitoring is a costly and time-consuming procedure that must be carried out in a highly controlled lab environment, thus small numbers of participants are usually recruited to such studies. Our study adds to the current knowledge by providing insight gathered from a large number of T1DM children assessed in real-life conditions with a simple yet reliable Cooper 12-min run test.

In adults, the distance covered by a participant during Cooper run can be used to estimate VO2max [3, 6], however, in children the relationship is not that straightforward [31]. Therefore, the results must be interpreted by comparing a child’s distance with a reference population percentile charts. Such charts, created for the Polish pediatric population [8], allowed us to quantify the children’s performance according to their sex and age.

We demonstrated that children with T1DM who participated in the present study, all with good or suboptimal glycemic control, displayed fitness level similar to that of the general population of their peers. Our observation is in line with the aforementioned studies [22, 23]. In our study group we did not find any relationship between HbA1c concentration and Cooper test results, which is consistent with the findings of Nascimiento et al. [22]. On the other hand, Nguyen et al. demonstrated that children with poor glycemic control (HbA1c > 7.4 mmol/mol for > 9 months) displayed lower maximum VO2 peak than healthy controls [23], while those with HbA1c < 5.8 mmol/mol were not different from healthy peers. Similarly, Williams et al. found a negative association of cardiorespiratory fitness expressed as recovery heart rate with HbA1c [32], whereas Komatsu demonstrated lower aerobic capacity in adolescents with T1DM and rather suboptimal diabetes control (HbA1c 6.7 ± 12.3 mmol/mol) compared to the reference group. This proves that adequately treated T1DM does not affect children’s physical capabilities, while poor glycemic control may negatively affect their performance.

Both higher immediate post-test BG and HR values predicted better Cooper test results. This may be explained by exercise-associated adrenergic response [2]. These parameters could be indirectly affected by children’s emotions and motivation involved in the competition. We found that also diabetes-unrelated factors affect youth’s performance, as older age and increased adiposity proved to be independent predictors of worse physical capacity (expressed in z-scores). The relation between adiposity and running performance comes as no surprise, as it was demonstrated that increased body fat % or BMI impair cardiorespiratory performance, in both adults [24] and children [4, 5].

The impact of age, however, deserves deeper insight. Most of the populational studies agree that in healthy children physical capacity (expressed in absolute values) improves with age and older children generally run faster and longer distances, jump higher etc. compared to younger children. However, in the studied group that effect was smaller than expected. The negative correlation between age and performance (expressed in z-scores of distance covered in Cooper run test) revealed that older individuals fared worse than expected for their sex and age. This may be due to inadequate motivation of adolescents to compete during the test. However, no tool was applied to quantify the participants’ motivation, which creates a possible confounder that could be age-dependent. Nonetheless, the results are unnerving and suggest that the current generation of teenagers with T1DM is less fit than expected, which warrants further studies and possibly interventions.

In this light elevated BMI and body fat percentage observed in children with T1DM are alarming. It reflects the population-scale increase in pediatric overweight and obesity prevalence in Poland [10, 17]. Overweight and obesity remain the most prevalent and impactful cardiovascular risk factors worldwide and should be counteracted especially in at-risk groups such as patients with T1DM.

There are some weaknesses of the study that should be pointed. Carrying out the Cooper 12-min run test provides only a one-dimensional assessment of physical capacity which can be considered a limitation. When preparing future studies it would be beneficial to include more than one type of a test to evaluate children’s fitness more comprehensively. Another possible disadvantage was carrying out the test only once, which does not allow us to rule out the effect of random factors (e.g., weather conditions, current participant disposition) on test results. Moreover, measurement of VO2max might better reflect the cardiorespiratory capacity but would be unfeasible during a summer camp conditions in such a large number of patients.

**Conclusions**

Physical capacity of children with T1DM is similar to that of general population. Young T1DM patients’ physical performance is affected by age and body fat percentage. Performing the Cooper 12-min run test in children with T1DM is safe and can be used to assess their physical fitness provided that patients are well-educated in their glucose levels management. Cooper test results are related to BG concentration and HR after the test. As T1DM children exhibit increased BMI and adiposity compared to general population, it calls for multi-dimensional, structured interventions aimed at promoting healthy dietary habits and physical activity in this population.

**Acknowledgements**

The authors would like to thank the “Diabeciaki” Foundation for enabling research during a summer camp for T1DM children, and the camp staff for their help in conducting the research. The authors especially thank Iwona Dachowska MD PhD and Małgorzata Szymańska MD for their supervision of the study participants.
Conflict of Interest

None of the authors have a real or potential conflict of interest related to this study or manuscript.

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