UNIVERSITÀ DEGLI STUDI DI MILANO

DOCTORAL PROGRAMME IN NUTRITIONAL SCIENCE

Physical Activity and Nutrient Intake in Youth with Type 1 Diabetes

Doctoral Dissertation of:
Elisa Giani

Tutor:
Prof. Gian Vincenzo Zuccotti

The Chair of the Doctoral Program:
Prof. Coordinator Luciano PINOTTI

2015-2018 – XXXI Cycle

Abstract

Objectives. Although physical activity (PA) is fundamental to T1D care, its impact on glycemia remain variable. This project was developped in three phases: i) We investigated the average and amount of PA in youth with T1D and we investigated possible associations with metabolic outcomes; ii) We examined associations between exercise energy expenditure (EE) and glycemia assessed by continous glucose monitoring (CGM) and between EE and dietary intakes in youth with T1D; iii) we tested the performance of the new isCGM system during high intensity interval PA, as a possible tool to and support exercise in youth with T1D.

Study A. Methods. Youth reported frequency, amount, and type of PA in a typical week; moderate and vigorous PA (4 and 8 METs, respectively) were combined. Youth were compared by frequency of PA (0-5 vs 6-7 days/week (d/wk)). Blood was assayed for glycemic control (A1c; 1,5-anhydroglucitol (1,5-AG)) and lipids. Body composition was assessed by DXA. **Results.** Youth (49% male) were 12.8±2.6 y/o, with T1D for 5.9±3.1 yrs, A1c 8.1±1.0%, 70% pump Rx, BG monitoring 5.7±2.4 X/d. Median PA was 9.5 hours/wk (range 0-42); 6% had PA 0 d/wk, 17% 1-3 d/wk, 29% 4-5 d/wk, 49% 6-7 d/wk. Youth with PA 6-7 d/wk were more likely to be male (62% vs 38%; p=.002), younger (12.3±2.5 vs 13.4±2.5 y/o; p=.01), with shorter T1D duration (4.8±2.6 vs 7.0±3.2 yrs; p< .0001) than youth with PA 0-5 d/wk. PA 6-7 d/wk associates with lower insulin resistance and glycemic excursions (1,5-AG), better body composition and lipid profile. No variables were significantly correlated with total hr/wk of PA when adjusting for d/wk of PA. **Conclusions**. These data in T1D youth suggest that PA frequency favorably impacts insulin resistance, body composition, lipids, and possibly glycemic excursions (1,5-AG). Further research is needed to determine a means to improve A1c with PA.

Study B. Methods. Youth (N=125, 49% male) with T1D wore masked CGM for 3 days; youth and/or parents documented youth physical activity (PA) by recording type, duration, and intensity of exercise. Using the Compendium of Energy Expenditure for youth (Ridley et al.), we assigned a MET value to each PA and calculated 24-hour adjusted EE (kcal/day). CGM data were categorized as % hypo (<70 mg/dL), % in range (70-180 mg/dL), and % hyperglycemia (>180 mg/dL). No differeneces were found in dietary intakes among the three EE groups. **Results.** Mean age was 12.9±2.6 years, T1D duration 5.9±3.2 years; 21% were overweight and 11% obese. Most (71%) were pump treated; youth received 0.9±0.3 U/kg/day and had a mean A1c of 8.1±1.0%. Median EE was 340 kcal/day (IQR 161-666), Youth were compared according to tertiles of EE. While tertiles did not differ by age, sex, or pump therapy, youth in the lowest tertile had the longest T1D duration and highest A1c. EE was significantly and inversely related to both % body fat by DXA and CGM% hyperglycemia and directly related to CGM % in range. **Conclusion:** PA can favorably impact glycemia assessed by CGM and body composition by DXA.

Study C. **Methods.** Seventeen youth (53% male), aged 13.7±3.8 years, with T1D for 5.4±3.8 years, HbA1c 7.4±1.0% (57±11 mmol/mol), were enrolled. Paired isCGM, plasma (PG) and capillary (CG) glucose values (total of 136) were collected during an interval exercise (45 min at 55% VO_{2max} load with 20 seconds sprints at 80% VO_{2max} every 10 minutes). Paired isCGM and CG (total of 832) were collected during free-living condition. **Results.** During exercise, isCGM absolute relative difference (ARDs) means/medians were 12.5/9.4% versus PG and 15.4/10.8% versus CG. During rest, ARDs means/medians were 16.6/12.0%. The Consensus Error Grid analysis showed 98.4% of readings during exercise and 97.24% during rest in zones A+B. Percentage of readings meeting the ISO criteria for CG levels <5.55 mmol/L was 62.5% during exercise, 53.4% during rest; for CG levels≥5.55 mmol/L was 64.0% during exercise, 60.4% during rest. **Conclusions.** isCGM demonstrated similar clinical safety and performance during exercise and in everyday life; further studies are needed to confirm its accuracy during exercise.

Riassunto

Introduzione. Benchè l'esercizio fisico (EF) sia fondamentale nel trattamento del diabete tipo 1 (DMT1), i suoi effetti sul controllo glicometabolico sono ancora discussi. Il seguente progetto è stato sviluppato in 3 fasi: i) valutazione della quantità e frequenza di EF in giovani con DMT1 e valutazione delle possibile associazioni tra EF e parametri metabolici; ii) valutazione delle associazioni tra spesa energetica da esercizio fisico (EE) e controllo glicemico valutato mediante sensore (CGM) e tra EE e assunzione di macronutrienti in giovani con DMT1; iii) valutazione della performance del sensore isCGM durante EF intenso, a intervallic e in condizioni di riposo.

Studio A. Metodi. I giovani hanno riportato quantità, frequenza e tipo di EF durante una settimana tipo; EF moderato e intenso sono stati combinati (4 e 8 METs, rispettivamente). Il campione è stato comparator in base alla frequenza di EF (0-5 vs 6-7 giorni/settimana (g/sett). Campioni ematici sono stati prelevati per A1c, 1,5-anhydroglucitol (1,5-AG)) e lipidi. La composizione corporea è stata determinata con DXA. **Risultati.** I giovani (49% maschi) avevano 12.8±2.6 anni, con DMT1 da 5.9±3.1 anni, A1c 8.1±1.0%, 70% era in terapia con pompa, la media di glicemie era di 5.7±2.4 prove/giorno. La quantità mediana di EF è risultata di 9.5 ore/sett. (range 0-42); 6% ha praticato EF 0 gg/sett, 17% 1-3 gg/sett, 29% 4-5 gg/sett, 49% 6-7 gg/sett. I giovani che hanno praticato EF 6-7 gg/sett erano maggiormente maschi (62% vs 38%; p=.002), di età inferiore (12.3±2.5 vs 13.4±2.5 y/o; p=.01), con durata di DMT1 minore (4.8±2.6 vs 7.0±3.2 anni; p< .0001) rispetto a chi praticava EF 0-5 gg/sett. EF 6-7 gg/sett si associava a minor insulin-resistenza e oscillazioni glicemiche (1,5-AG), miglior composizione corporea e profilo lipidico. Nessuna variabile correlava alla quantità di EF (ore/sett) quando aggiustata per frequenza di EF (gg/sett). **Conclusioni**. EF in giovani con DMT1 impatta positivamente su insulin-resistenza, composizione corporea, profilo lipidico, e oscillazioni glicemiche (1,5-AG).

Studio B. Metodi. I giovani (N=125, 49% maschi) con DMT1 hanno indossato CGM per 3 giorni e hanno riportato tipo, duarata e intensità di EF. Usando il Compendium of Energy Expenditure for youth (Ridley et al.), abbiamo assegnato un valore MET ad ogni EF e calcolato la EE aggiustata per 24 ore (kcal/day). I dati del CGM sono stati definiti come % ipoglicemia (<70 mg/dL), % in range (70-180 mg/dL), e % iperglicemia (>180 mg/dL). **Risultati.** I giovani avevano 12.9±2.6 anni, durata di DMT1 di 5.9±3.2 anni; 21% dei loro era sovrappeso e 11% obeso. Il 71% di loro era in pompa insulinica; il fabbisogno insulinico medio era 0.9±0.3 U/kg/giorno e la A1c media era 8.1±1.0%. La mediana di EE era 340 kcal/day (IQR 161-666). I giovani sono stati comparati in base a terzili di EE. Nessuna differenza per età, sesso, trattamento, è stata evidenziata tra i 3 gruppi di giovani. I giovani nel terzile minore di EE avevano durata maggiore di DMT1 e A1c maggiore. EE era significativamente e inversamente correlata alla % di massa grassa, valutata con DXA, e alla % di iperglicemie da CGM, e direttamente correlata alla % di glicemie in range da CGM. Nessuna differenza di intake nutrizionali è stata riscontrata tra i 3 gruppi di EE. **Conclusioni:** EF può avere effetti positivi sul controllo glicemico e sulla composizione corporea.

Study C. **Metodi.** Sono stati inclusi 17 giovani, (53% maschi), di età 13.7±3.8 anni, con DMT1 da 5.4±3.8 anni, A1c 7.4±1.0%. Sono state raccolte simultaneamente 136 glicemie da isCGM, plasma (PG) e capillare (CG) durante EF a intervalli (45 min al 55% VO_{2max} con 20 secondi di sprints all' 80% VO_{2max} ogni 10 minuti) e 832 glicemie da isCGM e CG a riposo. **Risultati.** Durante l'esercizio, la media/mediana di absolute relative difference (ARDs) di isCGM è stata di 12.5/9.4% rispetto al PG e 15.4/10.8% rispetto al CG. A riposo, la media/mediana ARDs è stata 16.6/12.0%. La Consensus Error Grid analysis ha mostrato in zona A+B il 98.4% delle letture durante esercizio e il 97.24% delle letture a riposo. La percentuale di valori compresi nei criteri ISO è stata del 62.5% per valori CG <5.55 mmol/L durante esercizio fisico, e del 53.4% a riposo; per valori CG ≥5.55 mmol/L del 64.0% durante esercizio, del 60.4% a riposo. **Conclusioni.** isCGM ha dimostrato simile accuratezza e sicurezza durante esercizio fisico e a riposo.

Contents

CHAPTER 1

General Introduction

The pivotal Diabetes Control and Complications Trial (DCCT) and Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrate that poor glycemic control is associated with an increased risk of developing complications in type 1 diabetes [1-2]. Various factors contribute to glycemic control [3]. Immutable parameters such as age, sex, diabetes duration, and socioeconomic status have a major effect on metabolic control [3–4]. Modifiable factors influencing metabolic control include diabetes-related knowledge, frequency of blood glucose monitoring, daily insulin dose [3-5].

In the 1950s, Joslin proposed physical activity as the third key component for the treatment of Type 1 Diabetes (T1D), complementary with insulin therapy and dietary management. Several benefits of physical activity have been demonstrated in children and adolescents with T1D, including improved body composition and weight, blood lipid profile, bone health, cardiovascular fitness, physiological wellness. However, the influence of exercise on improving blood glucose control in children and adolescents with T1DM is variable. Different study design, inadequate sample and the prevalence of cross-sectional data make difficult to achieve conclusive results [3-4].

Exercise recommendation from the International Society for Pediatric and Adolescent Diabetes (ISPAD) are the same as the general population. All children and adolescents between 6 and 18 years should exercise at least 60 minutes per day including moderate to vigorous aerobic activity, muscle and bone strengthening sessions. Higher intensity activity is recommended at least three times per week [6].

While more efforts have been dedicated to promote exercise among youth with T1D, regular physical activity still remain challenging for youth with diabetes and a greater proportion of kids with T1D remain inactive compared to their peers [6] The difficulties of managing glycemic excursions exercise-induced and the fear of hypoglycemia may constitute a barrier for youth and families to exercise.

Several trials have investigated the effects of different nutrient intakes before and after exercise in order to improve sport performance and glycemia. However, poor data exist on longitudinal nutritional patterns in youth physically active. Driven by the aim to prevent hypoglycemia, it is likely that excess caloric intake to prevent or treat hypoglycemia may counter the beneficial effects of exercise on glycemic control in some children, because standardized carbohydrate and insulin modifications for active children are difficult to achieve.

New technologies like continuous subcutaneous monitoring (CGM) systems can contribute in improving glycemic control and tailoring educational and therapeutic advices to manage physical activity [6-7].

In the current studies we first assessed amount and frequency of physical activity in youth with T1D and we investigated associations between exercise and metabolic outcomes. Secondly, we investigated the association between exercise energy expenditure and glycemic values assessed by 3-day masked continuous subcutaneous monitoring (CGM) system. Finally, we evaluated the dietary intakes in comparison with exercise energy expenditure.

In the last study, the performance of the Flash Glucose Monitoring system (isCGM) have been evaluated during a high intensity interval training session and in free-living conditions to assess accuracy of the system during exercise.

REFERENCES

1. Simmon JI et al. Differences in the Management of Type 1 Diabetes Among Adults Under Excellent Control Compared With Those Under Poor Control in the T1D Exchange Clinic Registry. Diabetes Care 34:2356–2359, 2011
2. Lehman R, Kaplan V, Bingisser R, Bloch KE, Spinas GA. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care 1997;20:1603–11.
3. Riddell MC, Iscoe KE. Physical activity, sport, and pediatric diabetes. Pediatric Diabetes 2006: 7: 60–70.
4. Robertson K, Adolfsson P, Riddell M, Scheiner G, Hanas R. Exercise in children and adolescents with diabetes. Pediatr Diabetes 2009;10(Suppl.12):154–68.
5. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017 May;5(5):377-390.
6. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, Scaramuzza AE, Hasnani D, Hofer SE. ISPAD Clinical Practice Consensus Guidelines 2018 Compendium Exercise in children and adolescents with diabetes. Pediatr Diabetes. 2018 Aug 22.
7. Moser O, Yardley JE, Bracken JM. Interstitial Glucose and Physical Exercise in Type 1 Diabetes: Integrative Physiology, Technology, and the Gap In-Between Nutrients. 2018 Jan; 10(1): 93.

CHAPTER 2

Clinical studies

2.1 Study A

Physical Activity in youth with Type 1 Diabetes: Variable Impact on Metabolic Outcomes

2.2 Study B

Exercise Energy Expenditure, Glycemic control and Nutrient Intake in Youth with type 1 Diabetes

2.3 Study C

Performance of the Flash Glucose Monitoring System during Exercise in Youth with Type 1 Diabetes

2.1 Study A

Physical Activity in youth with Type 1 Diabetes: Variable Impact on Metabolic Outcomes

ABSTRACT

Objectives. PA is often associated with favorable metabolic parameters due to enhanced insulin sensitivity and higher lean body mass. We studied associations of frequency and amount of PA with metabolic measures in 136 youth aged 8-17 y/o with T1D.

Methods. Youth reported frequency, amount, and type of PA in a typical week; moderate and vigorous PA (4 and 8 METs, respectively) were combined. Youth were compared by frequency of PA (0-5 vs 6-7 days/week (d/wk)). Blood was assayed for glycemic control (A1c; 1,5-anhydroglucitol (1,5-AG)) and lipids. Body composition was assessed by DXA. Clinical data (e.g., insulin dose, zBMI, BP) were obtained by chart review.

Results. Youth (49% male) were 12.8±2.6 y/o, with T1D for 5.9±3.1 yrs, A1c 8.1±1.0%, 70% pump Rx, BG monitoring 5.7±2.4 X/d. Median PA was 9.5 hours/wk (range 0-42); 6% had PA 0 d/wk, 17% 1-3 d/wk, 29% 4-5 d/wk, 49% 6-7 d/wk. Youth with PA 6-7 d/wk were more likely to be male (62% vs 38%; p=.002), younger (12.3±2.5 vs 13.4±2.5 y/o; p=.01), with shorter T1D duration (4.8±2.6 vs 7.0±3.2 yrs; p< .0001) than youth with PA 0-5 d/wk. PA 6-7 d/wk associates with lower insulin resistance and glycemic excursions (1,5-AG), better body composition and lipid profile. No variables were significantly correlated with total hr/wk of PA when adjusting for d/wk of PA.

Conclusions. These data in T1D youth suggest that PA frequency favorably impacts insulin resistance, body composition, lipids, and possibly glycemic excursions (1,5-AG). Further research is needed to determine a means to improve A1c with PA.

INTRODUCTION

Guidelines recommend for all children and adolescents aged 6 to 18 years at least 60 minutes of physical activity every day, including moderate to vigorous exercise and muscle and bone strengthening activities, while vigorous exercise should be performed at least 3 times per week [1-2].

Adherence to physical activity recommendation is particularly important for patients with diabetes, as regular exercise has been correlated with positive metabolic outcomes, and it is associated with a decrease in cardiovascular and all-cause mortality [3]. In particular, physical activity can help controlling weight and body composition, and it can improve insulin sensitivity, lipid profile and blood pressure [4]. The recent evidences that antecedents of cardiovascular risk begin early in type 1 diabetes (T1D), suggest the need for major efforts to get children and adolescents with T1D engaged in healthy lifestyle habits, including regular physical activity [5].

Indeed, a great proportion of pediatric patients with T1D are less fit compared to their non-diabetic peers, as management of physical activity in diabetes remains challenging for both youths and their families, requiring a tailored approach for both carbs intake and insulin adjustments before, during and after the workout session [6-7]. Moreover, hypoglycemic events potentially associated with prolonged exercise increase patients and families fear and contribute to adopt sedentary behaviors. Also, the need to avoid hypoglycemia may increase the intake of extra-snacks and carbs, vanishing the positive effects of exercise on both glycemic control and body composition [8-9].

The relationship between PA and glycemic control is complex and controversial. Some studies have shown no benefit of PA on A1c, others have shown that PA can reduce insulin requirements and improving glycemic control [10-26]. In the large study based on the Swedish registry including pediatric patients with T1D, individuals who increased their physical activity frequency over a 1-year period, showed an improvement in their A1c ($ß = 0.14$; $p = 0.002$) compared to patients with unchanged level of PA [27]. However, heterogeneity in study design, methods and reporting remains a barrier to fully understanding the influence of physical activity on glycemic control in youth with T1D.

Recently, huge efforts have been risen internationally to support physical activity programs for pediatric patients with diabetes and to train health care professionals in tailoring personalized treatment plans for diabetes management during sports [1]. The goal is to allow T1D youth to perform all types of exercise consistently avoiding glycemic excursion and hypoglycemic events possibly related with physical activity.

The objective of this cross-sectional study was to assess the frequency of pediatric patients with T1D meeting the international recommendation for moderate and vigorous daily physical activity and to examine the influence of exercise on metabolic outcomes and glycemic control.

RESEARCH DESIGN AND METHODS

Study population and design

For this cross-sectional study, medical records of youth with T1D attending an outpatient, free-standing, tertiary diabetes center in Boston, Massachusetts, were screened to identify eligible patients. Eligibility criteria included youth 8-17 years of age; type 1 diabetes duration of ≥1 year at enrollment; daily insulin dose of ≥0.5 units/kg; most recent A1c of 6.5 to 10%; at least 3 blood glucose checks per day; intensive insulin therapy; ability to communicate in English; willingness to participate in the study. Exclusion criteria included the presence of significant mental illness, or use of medications that interfere significantly with glucose metabolism. A final sample of 136 youth with T1D provided complete data for analysis.

The local Institutional Review Board (IRB) approved the study protocol, and all youth/parents provided written informed assent/consent before beginning any study procedures.

Data sources

Demographic and clinical data (including diabetes treatment, blood pressure) were collected by chart review and youth-parent interview. Youth height and weight were based on electronic medical record review, and body mass index percentiles and z-scores (z-BMI) were calculated using age- and sex-standardized norms from the Centers for Disease Control and Prevention (CDC).

Glycemic control was assessed by A1c, measured using an assay standardized to the Diabetes Control and Complications Trial (reference range, 4.0-6.0% {20-42mmol/mol}) (Roche Diagnostics, Indianapolis, IN). Total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and 1,5-anhydroglucitol were assayed from blood samples and measured using Ortho Vitros Chemical in the Joslin Diabetes Center laboratory in Boston, MA. Fasting was not required for lipids.

Body composition was analyzed by means of a DXA scan (Hologic Discovery).

Physical Activity assessment

Youth physical activity (PA) was measured using a Brief Standardized Interview adapted from the physical activity module of the BRFSS Questionnaire [28].

Youth were asked about the frequency and duration of moderate and vigorous PA lasting at least 10 minutes in a typical week. Moderate PA was referred as exercise causing a small increase in breathing or heart rate and vigorous PA was reported as exercise causing a large increase in breathing and heart rate. Intensity of moderate and vigorous PA was defined according to metabolic equivalents (METs) and some example were provided for each type of intensity (e.g. moderate intensity, 4 METs/hr, walking quickly, gym class, dance, baseball; vigorous intensity, 8 METs/hr, jogging or running, swimming laps, basketball).

The total amount of PA was defined as hours/week.

After checking for distribution of the self-reported frequency of PA, participants were stratified as follow: PA 0-5, youth exercising 0 to 5 days per week, PA 6-7, youth exercising 6 to 7 days per week.

Statistical analysis

Demographic, clinical and metabolic data are presented as means±SD or percentages. Statistical analyses included Chi-square and Wilcoxon rank sum to compare clinical and metabolic characteristics between the two different groups of PA frequency (0-5 days/week vs 6-7 days/week). Spearman' correlations were used to test the associations between outcomes and frequency/amount of PA.

An alpha level of ≤.05 was used to determine statistical significance.

All analyses were implemented using SAS software (version 9.4; SAS Institute, Inc., Cary, NC).

RESULTS

The 136 participants (49% female) had a mean age of 12.8 ± 2.6 years, diabetes duration of 5.9 ± 3.1 years, and HbA1c of 8.1 ± 1.0% (Table 1). The majority of participants were treated with an insulin pump (70%).

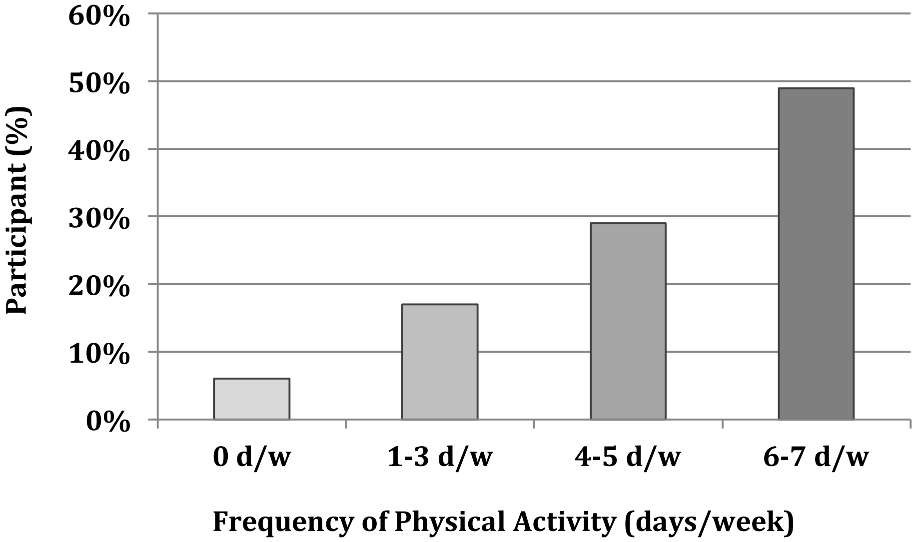
Table 1. *Participant Characteristics.*

Youth	**Mean± SD or %**
Sex (% male)	49
Age (years)	12.8±2.6
Race/ethnicity (% white)	90
z-BMI (SDS)	0.7±0.8
T1D duration (years)	5.9±.3.1
BG monitoring (times/day)	5.7±2.4
Insulin dose (U/kg/day)	0.9±0.3
Insulin regimen (% pump)	70
A1c (%)	8.1±1.0

Data are mean ± SD or %.
z-BMI, body mass index z-score; SDS, SD score; BG, blood glucose monitoring, A1c, hemoglobin A1c.

The median amount of physical activity was 9.5 hours/week, with a range of 0 to 42 hours/week. The median frequency of PA was 5 days/week. In particular, 6% percent of participants reported no PA; 17% reported PA 1-3 days/week; 29% reported PA 4-5 days/week and 49% reported PA 6-7 days/week (Figure 1).

Figure 1. *Frequency of Physical Activity.*



About half of youth had physical activity 6-*7 days/week (49%), and about one third (29%) of reported physical activity 4-5 days/week.*

Females reported less frequent PA compared to males, with just 38% of females active 6 to 7 days/week compared to 62% of males (p=.002).

Youth who reported more frequent PA (6-7 days/week) were younger (12.3 ± 2.5 vs 13.4 ± 2.5 years, p=.01), and had a shorter diabetes duration (4.8 ± 2.6 vs 7.0 ± 3.2 years, p<.0001), compared to youth who reported PA 0 to 5 days/week (Table 2).

Insulin regimen and number of blood glucose checks/day did not differ significantly by frequency of PA (0-5 or 6-7 days/week).

Table 2. *Participant Characteristics according to Frequency of Physical Activity.*

	PA 0-5 days/week (n=70, 51%)	**PA 6-7 days/week (n=66, 49%)**	**P**
Sex (% male)	36	62	.002
Age (years)	13.4±2.5	12.3±2.5	.01
Race/ethnicity (% white)	90	91	.9
T1D duration (years)	7.0±3.2	4.8±2.6	<.001
BG monitoring (times/day)	5.4±2.6	5.9±2.2	.13
Regimen (% pump)	69	71	.7

Data are mean±SD or %. BG, blood glucose monitoring.

Metabolic Outcomes

Metabolic parameters stratified by frequency of PA group are shown in Table 3.

Body composition was significantly better in youth reporting exercise 6-7 days/week: the z-BMI (SDS) was lower in youth exercising more consistently (0.5 ± 0.9 in youth exercising 6-7 d/w vs 0.8 ± 0.7 in youth 0-5 d/w) and approached significance (p=0.05). This association was also present when DXA data were considered, as the percentage of fat mass was significantly lower in youth exercising 6-7 days/week (25 vs 30%, p<.0001).

Glycemic control expressed as HbA1c, was not significantly different between the two groups (8.1 ± 0.9 vs 8.1 ± 1.2%, p=.7). However, youth exercising 6-7 days/week had a higher mean of 1,5-anhydroglucitol (3.7 ± 2.1 vs 2.9 ± 1.8 mcg/mL, p=.02), suggesting less hyperglycemia above 180 mg/dL in the previous weeks. Interesting, insulin requirement was also lower in youth exercising more.

Youth exercising 6-7 days/week had better lipid profile than youth exercising 0-5 days/week, as more active youth had higher levels of HDL (59 ± 14 vs 54 ± 13 mg/dL, p=.04) and lower levels of LDL (81 ± 21 vs 91 ± 26 mg/dL, p=.04) than less active youth. There were no differences in blood pressure parameters among the two groups. None of the metabolic outcomes were significantly associated with total amount of PA when controlling for frequency (days/week) of PA.

Table 3. *Metabolic Characteristics According to Frequency of Physical Activity.*

	PA 0-5 days/week (n=70, 51%)	**PA 6-7 days/week (n=66, 49%)**	**P**
z-BMI (SDS)	0.8±0.7	0.5±0.9	.05
Fat mass (%)	30	25	<.0001
Insulin dose (U/kg/day)	1.0±0.3	0.9±0.2	.03
A1c (%)	8.1±0.9	8.1±1.2	.7
1,5-anhydroglucitol (µg/dL)	2.9±1.8	3.7±2.1	.02
Total cholesterol (mg/dL)	169±31	162±24	.19
HDL (mg/dL)	54±13	59±14	.04
LDL (mg/dL)	91±26	81±21	.04
Triglycerides (mg/dL)	118±61	103±50	.09
Systolic BP (mmHg)	110±7	108±7	.07
Diastolic BP (mmHg)	67±5	66±6	.3

Data are mean ± SD or %. z-BMI, body mass index z-score; SDS, SD score; A1c, hemoglobin A1c; BP, blood pressure.

DISCUSSION AND CONCLUSIONS

In this cross-sectional study we investigated the frequency and amount of self-reported PA in youth with T1D and the potential associations with metabolic measures. Overall, results from this study showed a positive impact of daily- frequency PA on several metabolic outcomes compared to a less consistent practice. Moreover, the total amount of hours per week spent physically active resulted not significantly associated with better metabolic values when the frequency of PA was considered.

In this study, about half of youth reported moderate to vigorous PA 6-7 days per week, while another third reported exercise 4-5 days/week. Only 6% of youth included were not physically active. This proportion of active patients is higher compared with data from the 2016 Centers for Disease Control and Prevention Youth Risk Behavior Surveillance System, which indicate that only 21.6% of 6 to 19-year-old children and adolescents in the United States attained 60 or more minutes of moderate-to-vigorous physical activity on at least 5 days per week [29]. Particularly, adolescents with T1D have been previously demonstrated to spend 17 fewer minutes practicing PA and to have lower levels of fitness, compared to their peers without diabetes [7;30]. A possible explanation for the higher percentage of youth reporting to exercise consistently in our sample might be a higher adherence to diabetes treatment recommendation of the patients, as well as greater opportunity for educational and behavioral supports in the local area compared to other regions.

For children and youth with T1D in the age 6-18 years, at least 60 min or more of physical activity are recommended each day, including moderate to vigorous aerobic activity, muscle strengthening and bone strengthening activities [1;31]. Although in this study the median amount of PA was 9.5 hours/week, only half of participants exercised every day, fully meeting the guidelines recommendations for this age group. Among study participants, males reported to exercise more frequently compared to females, confirming that sedentary habits are more common in women than in men with T1D, as previously described [27;32]. Moreover, in this study, younger children with a shorter duration of diabetes were more likely to exercise 6-7 days/week. This may be explained with the fact that physical inactivity and sedentary habits increase gradually with age in youth with T1D, and are related to a worst glycemic control [33]. However, a younger age and a shorter diabetes duration are often associated with a greater fear of hypoglycemic episodes as well as the difficulty in managing glycemic control during and after exercise for families [8;34]. The effect of physical activity on the occurrence of hypoglycemia is still controversial, as some studies have shown an increased risk of hypoglycemic events in physically active subjects, while some others did not confirm the correlation [11;35-36]. For sure, the complexity of the physiological mechanism and insulin treatment approaches related to different types of exercise, and the young age, make the need for education and individualized feedback an essential tool to overcome possible barriers to a regular physical activity in youth with T1D [37].

The importance of physically active habits on metabolic outcomes have been greatly demonstrated, but the impact of exercise on glycemic control remains controversial [10-26]. In the current study A1c level was not significantly different in youth exercising 6-7 days/week compared to youth exercising 0-5 days/week. This may due to the elevated percentage of youth physically active in the overall study sample. Similarly, data from a meta-analysis of twelve studies in both adults and youth with T1D, reported A1c was not significantly affected by exercise [38]. On the contrary, the DPV studies on pediatric patients with T1D showed higher A1c levels in youth less frequently active and a meta-analysis including 10 intervention studies demonstrated physical activity inducing a significant beneficial reduction of A1c [4;11]. Also, in the large cross-sectional study based on the Swedish pediatric diabetes registry, the group of patients exercising less during week reported the highest A1c level [27].

It is commonly discussed among caregivers that positive effects of exercise on glycemic control may be mitigated by the challenges in managing insulin doses leading to both hypo- or hyperglycemia and a great glycemic fluctuation. In the current study, even if A1c level was not significantly different in the group of patients exercising more frequently, the level of 1,5-anhydroglucitol was higher in youth reporting physical activity 6-7 days/week, compared to the others. This data may suggest that, against all odds, patients exercising consistently had a lower glycemic variability and a more stable glycemic profile compared to their less active peers. In a previous study evaluating the association of fitness with glycemic variability in adolescents with T1D, it was found an inverse association between glycemic variability with fitness and MET load, resulting in fewer extremes in hypo- and hyperglycemia [39]. This emphasizes the need for extra efforts in increasing knowledge and education of patients and families on diabetes management during sports. Patient-tailored recommendations for glycemic control according to the age, the type of physical activity, the duration, the time of the day for exercising, the dietary intake and the insulin regimen should be considered by the health care teams for implementing the safety and the effectiveness of the training. Indeed, it has been noted that given consistent timing of exercise, insulin and carbs intake can make the response to 60 minutes of exercise reproducible and safe in youth with T1D [12].

Beyond A1c level, the beneficial effects of physical activity include weight control and associated insulin resistance. Regular physical activity has been demonstrated effective in improving body weight and body composition in children and adolescents with diabetes. In the current study, youth who reported exercise 6-7 days/week had a lower zBMI (which approached the statistical significance, $p=0.05$) and a significantly lower percentage of fat mass compared to their less active peers. Similarly, in previous study, a decrease in the fat-mass was observed after exercise intervention, even if different methods to evaluate body composition make the comparison among studies hard [40].

As overweight associates with insulin resistance, higher insulin requirements are expected in youth less active. In this study, patients who reported physical activity 6-7 days/week had a lower insulin requirement compared to youth exercising less frequently. However, this could also be related to the younger age of this group of patients. Investigations in adults have described improved insulin sensitivity in pre-diabetic adults and obese men with metabolic syndrome following a single bout of moderate or high intensity aerobic exercise [41-42]. Also in youth with T1D, physical activity activity is known to improve glucose uptake in skeletal muscle and enhance insulin sensitivity [27].

Recent data, indicate that one third of youth with type 1 diabetes are overweight and obese, yielding rates similar to those found in the general pediatric population [43-45]. The combination of increasing weight in youth with T1D and cardio-metabolic risks early associated with diabetes, made efforts to reduce sedentary behaviors among youth urgently needed. A recent meta-analyses identified significant effects of physical activity on reductions in HbA1c, BMI, triglycerides and total cholesterol, which reinforce the importance of a physical activity in the clinical management of diabetes to delay or reduce the risk of microvascular complications and cardiovascular disease [40]. In the current study, compared to youth who reported exercise 0-5 days/week, patients who reported physical activity 6-7 days/week had a significantly better lipid profile (higher HDL and lower LDL).

The positive effect of physical activity on cholesterol level have been deeply described in previous studies both in adults and in pediatrics. In a large cross-sectional multicenter study, physical activity was inversely associated with total cholesterol, LDL cholesterol and triglycerides [32]. This beneficial effect on lipid profile is of particular clinical relevance, as young people with diabetes are known to have abnormal lipid levels compared with those without diabetes and this is strictly correlated with the increased risk for cardiovascular mortality in diabetes patients [46].

In summary, in this study, daily-regular physical activity resulted favorably associated with several metabolic outcomes, while the amount of physical activity, defined as hours/week, did not seem to have any impact when adjusting for frequency of exercise. Therefore, regular physical activity should be supported starting from childhood, in order to prevent early cardiovascular complications. The strength of this study is the unique characteristic of this intensive-treated young patients, which demonstrated that tailored treatment approaches allow the youngest to exercise safely with no occurrence of major severe events either higher glycemic excursion compared to youth less active. However, this study has some limitations. First, the cross-sectional design only allows to speculate associations among factors and cannot prove casual effects. Moreover, the use of self-reported information on physical activity may limit the reliability of these data. Additionally, there were no dietary measures available to better define the impact of multiple factors on metabolic profile. Further studies are needed to determine safely means to improve A1c with physical activity and get children and adolescents engaged with regular exercise.

REFERENCES

1. Adolfsson P, Riddell MC, Taplin CE, et al. ISPAD Clinical Practice Consensus Guidelines 2018 Compendium Exercise in children and adolescents with diabetes.
2. US Department of Health and Human Services 2008 Physical activity guidelines for americans. Whashington, DC Govt Printing Office, 2008
3. Nocon M, Hiemann T, Muller-Riemenschneider F, et al. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil 2008; 15: 239-246.
4. Herbst A, Kordonouri O, Schwab KO et al.: DPV initiative of the German Working Group for Pediatric Diabetology Germany. Diabetes Care 2007: 30; 2098-2100.
5. Margeirsdottir HD, Larsen JR, Brunborg C, et al; Norwegian Study Group for Childhood Diabetes. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia. 2008 Apr;51(4):554-61.
6. Maggio ABR, Hofer MF, Martin XE, et al. Reduced physical activity level and cardiorespiratory fitness in children with chronic diseases. 2010;169:1187-93.
7. Lukacs A, Mayer K, Juasz E, et al. Reduced physical fitness in children and adolescents with type 1 diabetes. Pediatr Diabetes 2012;13:432-37.
8. Brazeau AS, Rabasa-Lhoret R, Strychar I, at al. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008;31:2108-09.

9. Bernardini AL, Vanelli M, Chiari G. Adherence to physical activity in young people with type 1 diabetes. Acta Biomed 2004;75:153-157.
10. Miculis CP, Mascarenhas LP, Boguszewski MCS, et al. Physical activity in children with type 1 diabetes. J Pediatr (Rio J) 2010;86:271–8.
11. Herbst A, Bachran R, Kapellen T, et al. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Arch Pediatr Adolesc Med 2006;160:573–7.
12. Robertson K, Adolfsson P, Riddell M, et al. Exercise in children and adolescents with diabetes. Pediatr Diabetes 2009;10(Suppl.12):154–68.
13. Williams BK, Guelfi KJ, Jones TW, et al. Lower cardiorespiratory fitness in children with Type 1 diabetes. Diabet Med 2011;28:1005–7.
14. Schweiger B, Klingensmith G, Snell-Bergeon JK. Physical activity in adolescent females with type 1 diabetes. Int J Pediatr 2010;2010:328318.
15. Salvatoni A, Cardani R, Biasoli R, et al. Physical activity and diabetes. Acta Biomed 2005;76:85–8.
16. Michaliszyn SF, Faulkner MS. Physical activity and sedentary behaviour in adolescents with type 1 diabetes. Res Nurs Health 2010;33:441–9.
17. Valerio G, Spagnuolo MI, Lombardi F, et al. Physical activity and sports participation in children and adolescents with type 1 diabetes mellitus. Nutr Metab Cardiovasc Dis 2005;17:376–82.
18. Zoppini G, Carlini M, Muggeo M. Self-reported exercise and quality of life in young type 1 diabetic subjects. Diabetes Nutr Metab 2003;16:77–80.
19. Sideraviciute S, Gailiuniene A, Visagurskiene K, et al. The effect of long-term swimming program on glycemia control in 14–19-year aged healthy girls and girls with type 1 diabetes mellitus. Medicina (Kaunas) 2006;42:513–8.

20. Roberts L, Jones TW, Fournier PA. Exercise training and glycemic control in adolescents with poorly controlled type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2002; 15:621–7.
21. Sarnblad S, Ekelund U, Aman J. Physical activity and energy intake in adolescent girls with Type 1 diabetes. Diabet Med 2005;22:893–9.
22. A man J, Skinner TC, De Beaufort CE, et al. Associations between physical activity, sedentary behaviour, and glycemic control in a large cohort of adolescents with type 1 diabetes: the Hvidoere Study Group on Childhood Diabetes. Pediatr Diabetes 2009;10:234–9.
23. Edmunds S, Roche D, Stratton G. Levels and patterns of physical activity in children and adolescents with type 1 diabetes and associated metabolic and physiologic health outcomes. J Phys Act Health 2010;7:68–77.
24. Wallberg-Henriksson H, Gunnarsson R, Henriksson J, et al. Increased peripheral insulin sensitivity and muscle mitochondrial enzymes but unchanged blood glucose control in type 1 diabetics after physical training. Diabetes 1982;31:1044–50.
25. Raile K, Kapellen T, Schweiger A, et al. Physical activity and competitive sports in children and adolescents with type 1 diabetes. Diabetes Care 1999;22:1904–5.
26. Lehman R, Kaplan V, Bingisser R, et al. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care 1997;20:1603–11.
27. Beraki A, Magnuson A, Sarnblad S, et al. Increase in physical activity is associated with lower HbA1c levels in children and adolescents with type 1 diabetes: Results from a cross-sectional study based on the Swedish pediatric diabetes quality registry (SWEDIABKIDS). Diabetes Res Clin Pract 2014;105:119-25.

28. https://www.cdc.gov/brfss/questionnaires/index.htm
29. National Physical Activity Plan Alliance. 2016 US report card on physical activity for children and youth. Columbia, SC; 2016.
30. Komatsu WR, Gabbay MA, Castro ML, et al. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. Pediatr Diabetes 2005;6;145-149.
31. Robertson K, Riddell MC, Guinhouya BC, et al. Exercise in children and adolescents with diabetes. Pediatr Diabetes 2014; 15 (suppl 20): 203–23.
32. Bohn B, Herbst A, Pfeifer M, et al. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. Diabetes Care 2015;38:1536-43.
33. Galler A, Lindau M, Ernert A, et al. Associations between media consumption habits, physical activity, socioeconomic status, and glycemic control in children, adolescents, and young adults with type 1 diabetes. Diabetes Care 2011; 34: 2356–59.
34. Jabbour G, Henderson M, Mathieu ME. Barriers to active lifestyles in children with type 1 diabetes. Can J Diabetes 2016; 40: 170–72.
35. Davey RJ, Howe W, Paramalingam N, et al. The effect of midday moderate-intensity exercise on postexercise hypoglycemia risk in individuals with type 1 diabetes. J Clin Endocrinol Metab 2013;98:2908–2914.
36. Brazeau AS, Leroux C, Mircescu H, et al. Physical activity level and body composition among adults with type 1 diabetes. Diabet Med 2012;29:e402–e408.

37. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017 May;5(5):377-390.

38. Kennedy A, Nirantharakumar K, Chimen M, et al. Does exercise improve glycaemic control in type 1 diabetes? A systematic review and meta-analysis. PLoS ONE 2013;8:e58861.

39. Singhvi A, Tansey MJ, Janz K, et al. Aerobic fitness and glycemic variability in adolescents with type 1 diabetes. Endocr Pract. 2014 Jun;20(6):566-70.

40. Quirk H, Blake H, Tennyson R, et al. Physical activity interventions in children and young people with type 1 diabetes mellitus: a systematic review with meta-analysis. Diabet Med J Br Diabet Assoc 2014; 31: 1163–73.

41. Rynders CA, Weltman JY, Jiang B, et al. Effects of Exercise Intensity on Postprandial Improvement in Glucose Disposal and Insulin Sensitivity in Prediabetic Adults. J Clin Endocrinol Metab, January 2014, 99(1):220–228.

42. Whyte LJ, Ferguson C, Wilson J, et al. Effects of single bout of very high intensity exercise on metabolic health biomarkers in overweight/obese sedentary men. Metabolism, 2013 Feb; 62 (2):212-9.

43. Liu LL, Lawrence JM, Davis C, et al.; SEARCH for Diabetes in Youth Study Group. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. Pediatr Diabetes. 2010 Feb;11(1):4-11.

44. Sands AL, Higgins LA, Mehta SN, et al. Associations of youth and parent weight status with reported versus predicted daily energy intake and hemoglobin A1c in youth with type 1 diabetes mellitus. Diabetes Sci Technol. 2013 Jan 1;7(1):263-70.
45. Baskaran C, Volkening LK, Diaz M, et al. A decade of temporal trends in overweight/obesity in youth with type 1 diabetes after the Diabetes Control and Complications Trial. Pediatr Diabetes. 2014 Jul 12).
46. Guy J, Ogden L, Wadwa RP, et al. Lipid and Lipoprotein Profiles in Youth With and Without Type 1 Diabetes The SEARCH for Diabetes in Youth Case-Control Study. Diabetes Care 2009; 32: 416–420.

2.2 Study B

Exercise Energy Expenditure, Glycemic control and Nutrient Intake in Youth with type 1 Diabetes

ABSTRACT

Objectives. Although exercise is fundamental to T1D care, challenges with insulin therapy often lead to unpredictable bouts of exercise-induced hypo-and hyperglycemia. We examined associations between exercise energy expenditure (EE) and glycemia assessed by continous glucose monitoring (CGM) and between EE and dietary intakes in youth with T1D.

Methods. Youth (N=125, 49% male) with T1D wore masked CGM for 3 days; youth and/or parents documented youth physical activity (PA) by recording type, duration, and intensity of exercise. Using the Compendium of Energy Expenditure for youth (Ridley et al.), we assigned a MET value to each PA and calculated 24-hour adjusted EE (kcal/day). CGM data were categorized as % hypo (<70 mg/dL), % in range (70-180 mg/dL), and % hyperglycemia (>180 mg/dL).

Results. Mean age was 12.9±2.6 years, T1D duration 5.9±3.2 years; 21% were overweight and 11% obese. Most (71%) were pump treated; youth received 0.9±0.3 U/kg/day and had a mean A1c of 8.1±1.0%. Median EE was 340 kcal/day (IQR 161-666), Youth were compared according to tertiles of EE. While tertiles did not differ by age, sex, or pump therapy, youth in the lowest tertile had the longest T1D duration and highest A1c. EE was significantly and

inversely related to both % body fat by DXA and CGM% hyperglycemia and directly related to CGM % in range.

Conclusion: PA can favorably impact glycemia assessed by CGM and body composition by DXA. Youth with T1D should receive exercise education and encouragement to participate in PA.

INTRODUCTION

Exercise is a fundamental component of type 1 diabetes (T1D) self-care, complementing dietary management and insulin therapy. Indeed, body composition, cardiorespiratory fitness, triglycerides and cholesterol blood levels have been demonstrated to improve with regular physical activity in youth with T1D [1].

However, the impact of physical activity on metabolic outcomes remains variable [2-4]. Previous studies on glycemic control related to physical activity have reported controversial results, as multiple factors may interfere with the glycemic status [2-7]. Different types and duration of physical activity may have a different impact on glycemic control. Also, extra snacks and higher carbs intake often consumed to prevent hypoglycemic events, may contribute to further deteriorate glucose control, and nullify beneficial effects of exercise on body composition and metabolic status [8-9].

Mainly driven to the fear of hypoglycemia, and the challenges in managing insulin therapy and dietary intakes in occasion of exercise, a great proportion of pediatric patients with T1D are less active compared to their peers without diabetes [10-11]. Indeed, the effects of exercise on glucose variability, and the lack of predictability of exercise-related hypoglycemic events still remain important issues for type 1 diabetes patients and medical staff in daily practice.

New technologies may offer a good possibility to better manage exercise [12]. Recently, continuous blood glucose monitoring (CGM) has made it possible to monitor in detail glucose fluctuations in daily life, including during physical activity [12]. Time spent in the glycemic target range is a simple and absolute assessment of glycemic control, reflecting both mean glucose level and glucose excursions. Thus, it can be a good indicator of the impact of exercise on glycemic excursion.

In this study we first evaluated exercise amount in a sample of children and adolescents with T1D and we investigated the associations between exercise energy expenditure (EE) and glycemic control, assessed by masked continuous glucose monitoring (CGM). Secondly, we investigated possible associations between EE and other metabolic parameters. Last, we analyzed dietary intakes with respect to EE and glycemic control.

METHODS

Eligibility Criteria and Assessment

The study was conducted at an outpatient, free-standing, multidisciplinary tertiary diabetes center in Boston, Massachusetts. Eligibility criteria for this study included willingness and ability to complete all study requirements, age between 8 and 17 years, diabetes duration ≥1 year, daily insulin requirement ≥0.5 units/kg, most recent hemoglobin A1c between 6.5 and 10% and intensive insulin therapy with at least ≥3 blood glucose checks per day. Chronic illness or medications that could interfere with glucose metabolism were exclusion criteria.

Data sources

Demographic and clinical data were collected by electronic medical records, chart review and parent-youth interview. Height and weight were measured using calibrated scales and stadiometers; age- and sex-adjusted body mass index z score (zBMI) was calculated using the Centers for Disease Control and

Prevention normative [13]. Blood pressure (BP) was measured in the sitting position, and percentiles for systolic and diastolic BP were based on CDC reference ranges [14]. Body composition was analyzed by means of a DXA scan (Hologic Discovery). Hemoglobin A1c (HbA1c) was measured using an assay standardized to the Diabetes Control and Complications Trial (reference range, 4.0-6.0% {20-42mmol/mol}) (Roche Diagnostics, Indianapolis, IN). Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were assayed from blood samples and measured using Ortho Vitros Chemical in the Joslin Diabetes Center laboratory in Boston, MA. Fasting was not required for lipids.

Physical activity Assessment

Youth with type 1 diabetes and/or their parents/guardians were instructed in recording detailed activity information for 3 days during a typical school week, including reports on type, duration, and intensity of youths' physical activity. Families were instructed to explicitly write "no activity" if the child did not perform any physical activity during the day.

Intensity of physical activity was defined according to metabolic equivalents (METs) based on activity type and intensity. A MET value was assigned to each activity reported by participants, using the Compendium of Energy Expenditures for Youth: e.g. playing catch, moderate effort, 2.6 METs; riding a bicycle, hard effort, 7.8 METs [15]. Energy expenditure (kcal) was then calculated considering the MET value, the duration of activity (minutes) and the resting metabolic rate per body weight (kg) according to the Schofield equation [16].

Based upon the 3-day data collection, we then calculated the exercise energy expenditure rate (EE) per 24-hour period (kcal/day). For the analyses of the outcomes, we grouped participants according to tertile of energy expenditure: 1) Low EE, 2) Middle EE and 3) High EE.

Glycemic Assessment

Youth received intermittent, masked continuous glucose monitoring (CGM) for three consecutive days, paired with completion of physical activity and diet records. After the 3-days study period, CGM data were downloaded and feedbacks on the personal glucose patterns were furnished by diabetes caregivers.

CGM glucose values were collected and grouped as: 1) hypoglycemia, for values below 70 mg/dL; 2) in-range, for values between 70 and 180 mg/dL, 3) hyperglycemia, for values above 180 mg/dL.

Nutrition Assessment

Participants' dietary intake was estimated using three-day food records. Patients and families were instructed on accurately reporting food and beverage intake for the three days CGM-wear study period. When at home, families were asked to carefully measuring foods and reporting portions, while, if away from home, to provide their best estimate of portion size. For each food item, participants and families were instructed to provide details, including names of brands or restaurants and specific item labeling (e.g., low fat, 1% milk), and to leave no blank fields on the form. All forms were reviewed and checked for missing information by research assistants. Diet records were then entered by two registered dietitians and verified for consistency and accuracy. Nutrition Data System for Research software (NDSR 2012; Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) was used to analyze the records and assess nutrient intake and food group servings.

Consent Procedures

The Institutional Review Board (IRB) approved the study protocol. A parent or guardian provided written consent and participants provided assent before beginning any study procedure.

Statistical Analyses

Descriptive analyses are presented as mean±SD values or percentage as appropriate. We divided 24-hour exercise energy expenditure into tertiles for analysis. Chi-square tests, unpaired t tests and ANOVA were performed for comparison of clinical and metabolic outcomes and dietary intakes among youths in different energy expenditure tertiles. Correlations between metabolic outcomes and dietary intakes were assessed with Spearman tests. A value of $P<0.05$ was considered significant. Statistical analyses were performed with SAS V.9.4 (SAS Institute, Cary, NC).

RESULTS

Participants characteristics

A total of 125 youth participated in the study, 49% were male and 90% white, with a mean age of 12.9±2.6 years and a mean diabetes duration of 5.9±3.2 years.

Twenty-one percent of participants were overweight and 11% were obese. The majority of youth were pump users (71%) with a mean frequency of blood glucose controls of 5.6±2.5 per day. Youth received a mean of 0.9±0.3 U/kg/day of insulin and the mean A1c level was 8.1±1.0% (Table 1).

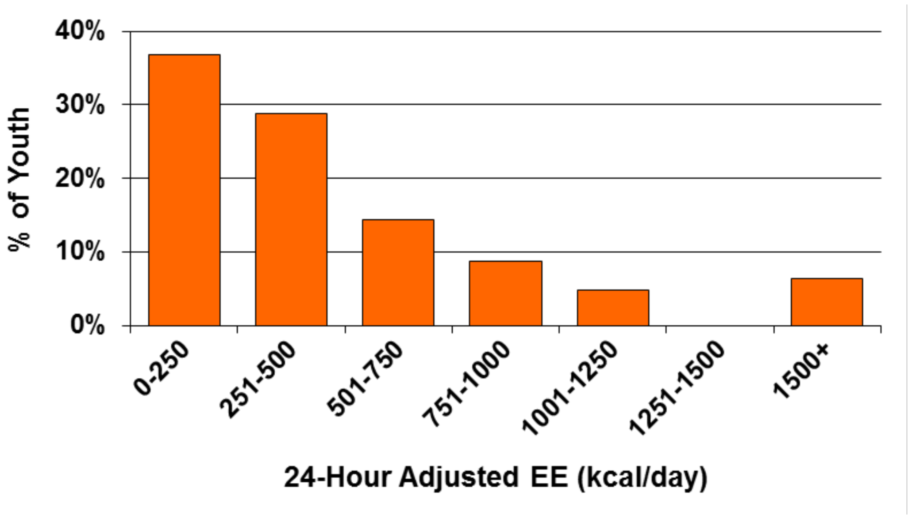
Table 1. Participant Characteristics.

Youth	**Mean± SD or %**
Sex (% male)	49
Age (years)	12.9±2.6
Race/ethnicity (% non-white)	10
z-BMI (SDS)	0.7±0.8
Body fat by DXA (%)	28±8
Overweight / Obese (%)	21 / 11
T1D duration (years)	5.9±.3.2
BG monitoring (times/day)	5.6±2.5
Insulin dose (U/kg/day)	0.9±0.3
Insulin regimen (% pump)	71
A1c (%)	8.1±1.0

Data are mean ± SD or %. z-BMI, body mass index z-score; SDS, SD score; BG, blood glucose monitoring, A1c, hemoglobin A1c.

The calculation of the 24-hour exercise energy expenditure resulted in a median of 340 kcal/day (IQR 161-666), with the highest percentage of youth falling in the range 0-250 kcal/day (Figure 1). When we grouped participants by exercise energy expenditure tertile, we had: the lowest tertile between 0 and 240 kcal/day of exercise energy expenditure, including, for example, a normal-weight 12-years old boy who reported a light walk for 30 min/day; the middle tertile between 241 and 510 kcal/day, including, for example, a 12-years old boy playing basket for 30 min/day; the highest tertile as energy expenditure >510 kcal/day, including a 12-years old boy playing basket with a moderate intensity for 60 min/day.

Figure 1. Distribution of 24-hour energy expenditure (EE



EE, energy expenditure tertiles.

Youth's characteristics were compared according to tertiles of exercise energy expenditure (Table 2). Youth in the low energy expenditure tertile had a significantly longer diabetes duration (7.3±3.3 years) than youth in the middle tertile (5.2±2.8 years) and high (5.3±3.1 years) tertile (p=0.002).

No differences among youths in different tertiles were found with regards to age, sex, insulin regimen, and insulin requirement or self-blood glucose monitoring (Table 2).

Table 2. Youth Characteristics according to Tertiles of Energy Expenditure.

	Low EE (n=41)	**Medium EE** (n=42)	**High EE** (n=42)	**p**
Sex (% male)	44	45	57	.41
Age (years)	13.4±2.3	12.7±2.6	12.8±2.7	.47
Body fat by DXA (%)	31±9	28±7	24±7	.002
T1D duration (years)	7.3±3.3	5.2±2.8	5.3±3.1	.002
Insulin dose (U/kg/day)	1.0±0.3	0.9±0.2	0.8±0.3	.07
Insulin regimen (% pump)	61	81	71	.13
BG monitoring frequency (times/day)	5.3±2.9	5.9±2.3	5.6±2.1	.6
A1c (%)	8.4±1.1	7.9±0.8	7.9±1.0	.04

Data are mean ± SD or %. BG, blood glucose; A1c, hemoglobin A1c.

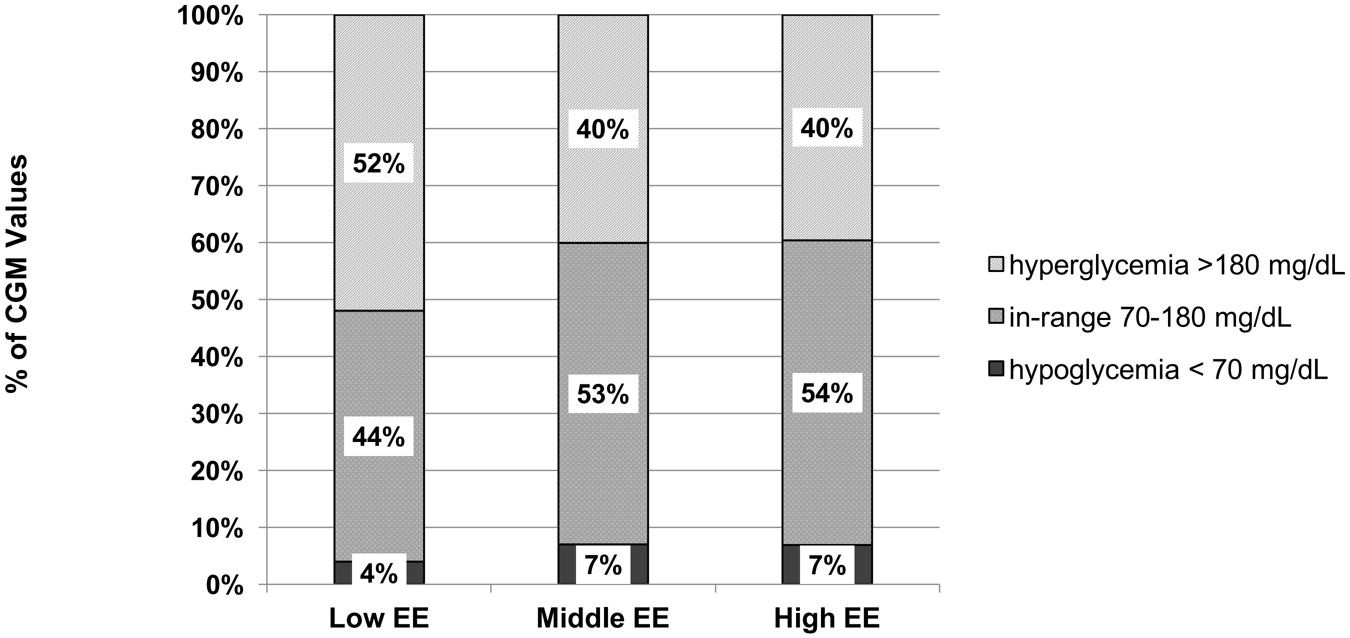
Glycemic control by exercise energy expenditure tertiles

Mean duration of masked CGM wear and physical activity records were 3.0±0.3 days, median 3.0 days. When CGM data were downloaded, youth in the low EE tertile reported a higher mean sensor glucose value of 195.4±39.6 mg/dL, compared to youth in the middle (171.0±32.7 mg/dL) and high (171.9±34.3 mg/dL) EE tertile.

Youth in the middle and high EE tertiles had significantly less CGM values >180 mg/dL (p=0.004) and more CGM values in range (p=0.01), compared to youth in the low EE tertile (Figure 2). Additionally, no significantly more CGM values below 70 mg/dL occurred in these youth with respect to the low EE tertile group (Figure 2).

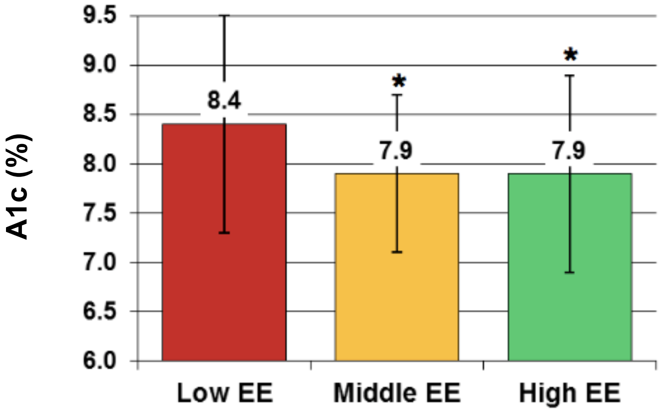
Accordingly, the A1c value of youth in the low EE tertile was significantly higher (8.4±1.1%) compared to youths in middle (7.9±0.8%) and high (7.9±1.0%) EE tertile (p=0.04), supporting the representativeness of this 3-days CGM data (Figure 3).

Figure 2. CGM data by energy expenditure tertile (EE).



CGM, continuous glucose monitoring; EE, energy expenditure tertiles.

Figure 3. A1c values by energy expenditure tertile (EE).



EE, energy expenditure tertiles; A1c, haemoglobin A1c. Values are expressed as mean±SD.

Dietary intake by exercise energy expenditure tertiles

Overall, participants consumed 1881.9±458.5 kcal/day, with no significant differences in calorie intake among the three EE groups (p=0.2). Compared to the ISPAD guidelines for dietary intake, 36% of youth met the recommendations for carbs, 42% of youth met the reccomedations for fat, and 63% met the reccomendations for protein. If we consider the rate of yout meeting all the ISPAD recommendations for macronutrient intakes, only 14% of yout met the all guidelines goals (Table 3).

Table 3. ISPAD 2018 nutritional reccomedations for macronutrients and percentage of youth meeting guidelines.

	Goals	**% meeting goals**
All macronutrients goals		14.4
Carbohydrate	45-50% TEI	36.0
Protein	15-20% TEI	63.2
Fat	30-35% TEI	42.4

ISPAD: International Society for Pediatric and Adolescent Diabetes; TEI, total energy expenditure.

In analysis by energy expenditure tertile, there was no significantly different intake of carbs, protein or fat among the three groups (Table 4). In particular, youth in the high EE tertile did not report a higher intake of carbs (48.9 vs 47.6%, p=0.5) compared to youth in the low EE tertile. Indeed, the percentage of carbohydrate intake was not correlated with the 24-hours energy expenditure (r=0.05; p=0.56). Similarly, there was no significant association between fat (r=-0.11; p=0.2) or protein (r=0.12; p=0.16) intake and 24-hours energy expenditure. When glycemic control was considered, the intake of carbs was not significantly correlated with A1c level (r=-0.06; p=0.49) or with sensor glucose coefficient of variation (r=0.06; p=0.54). There was no association between intake of fat (r=0.05; p=0.6) or intake of protein (r=0.07; p=0.44) with A1c levels.

Table 4. Nutrient intake in the study population and according to Tertiles of Energy Expenditure.

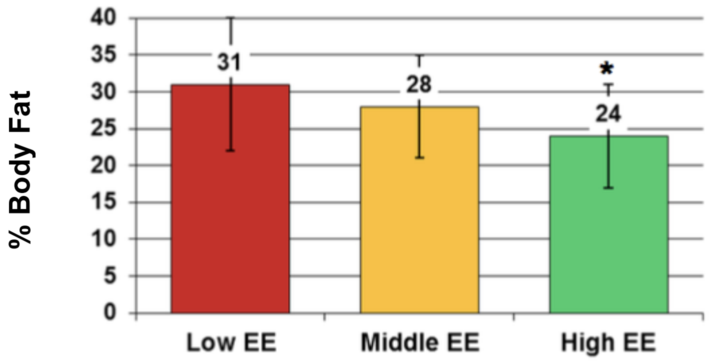
	Overall	**Low EE** (n=41)	**Medium EE** (n=42)	**High EE** (n=42)	**p**
Total calories - kcal	1881.9±458.5	1817.5±444.5	1832.72±442.04	1993.9±477.6	0.2
Carbohydrate					
g/1000 kcal	123.0±14.8	120.7±16.3	124.3±16.2	123.9±11.6	0.5
% kcal	48.5±5.7	47.6±6.3	48.9±6.1	48.9±	
Protein					
g/1000 kcal	40.0±6.7	38.9±7.9	40.5±6.3	40.7±5.9	0.4
% kcal	15.8±2.7	15.4±3.2	15.9±2.5	16.1±2.3	
Fat Total					
g/1000 kcal	40.3±5.8	41.8±6.3	39.6±5.7	39.4±5.0	0.1
% kcal	35.7±5.1	37.1±5.5	35.1±5.2	35.0±4.5	
Fat, monosaturated fat					0.6
g/1000 kcal	14.0±2.6	14.3±2.6	13.9±2.8	13.8±2.4	
Fat, polysaturated fat					0.8
g/100 kcal	8.7±2.4	8.9±2.6	8.5±2.3	8.6±2.2	
Fat Saturated					0.02
g/1000 kcal	14.2±2.7	15.12±2.8	13.8±2.8	13.6±2.3	
Fiber Total					0.5
g/1000 kcal	8.3±2.7	8.0±2.7	8.6±2.5	8.3±2.8	
Total Sugar					0.8
g/1000 kcal	49.8±13.8	49.8±16.0	48.7±14.4	50.9±10.9	

Body composition and other metabolic variables by exercise energy expenditure tertiles

Body composition was significantly different in the three groups of energy expenditure. Youth in the high EE tertile had significantly lower percentage of body fat (p=0.002) than youth in the low EE (Figure 4). The rate of obesity was also different among tertiles, with only 2% of youth obese in the high EE tertile compared to 17% of youth in the low EE tertile and 14% if youth in the middle EE tertile (p=0.07).

Among the three EE groups, there was no significant difference in respect to total cholesterol levels (p=0.8), cholesterol HDL (p=0.2), cholesterol LDL (p=0.8), and triglycerides (p=0.06). There were no significant differences in systolic (p=0.06) and diastolic (p=0.35) blood pressure among groups.

Figure 4. Body composition by energy expenditure tertile (EE).



EE, energy expenditure tertiles. Values are expressed as mean±SD.

DISCUSSION

In this study in youth with T1D, higher self-reported exercise energy expenditure was associated with a lower A1c, a lower percentage of hyperglycemic CGM values and a significantly higher percentage of in-range CGM values, without a significantly higher percentage of hypoglycemic CGM values. Previous studies have reported variable results on the impact of exercise on A1c and glycemic excursions assessed with CGM systems [1-3;17]. Different study design and the use of activity questionnaires may limit somewhat the reliability of results and make difficult comparison among studies [18]. However, data from large pediatric populations have confirmed the benefits of exercise on glycemic metabolism. In the study by Beraki A. et al on 4,655 children and adolescents with T1D, a significant negative association between amount of physical activity and A1c levels has been reported [19]. Data from the DPV registry showed higher A1c levels in youth less frequently active compared to youth reporting to exercise regularly (8.4% vs 8.1%; p<.001), without increased risk for severe hypoglycemia [20-21]. Ten intervention studies recently included in a meta-analysis demonstrated that physical activity induce a significant beneficial reduction of A1c [22].

The use of CGM can contribute in gleaning information about glycemic trends during physical activity, including frequency, severity and timing of possible hypoglycemia exercise-induced. It is well known that exercise evokes rapid changes in many physiological systems and demands constant adjustment to facilitate glucose provision to the exercising tissues in both healthy individuals and people with type 1 diabetes [23-24].

Patterns of glycemic fluctuation during physical activity vary greatly in consider of the type of exercise, its duration and intensity, the insulin level in the circulation, the blood glucose concentration and the dietary intakes before the exercise [25]. In general, aerobic exercise tends to lower blood glucose, while anaerobic exercise is associated with increasing glucose values [1;25]. However, variable factors may induce different metabolic patterns. In case of intense aerobic exercise, for example, a stable elevated hyperglycemia can occur several hours after aerobic exercise. On the contrary, when physical activity is performed in the afternoon, declining glucose levels can occur hours after exercise, increasing the risk for nocturnal hypoglycemia [1;25]. This variability of factors influencing glucose values during and after exercise, may lead to a sub-optimal glycemic control in youth more physically active, due to the non-predictable glycemic fluctuations. Nevertheless, in the current study, youth with higher exercise energy expenditure showed more CGM values in-range, with less values above 180 mg/dL and below 70 mg/dL, compared to youth less active. Further, in the current study, youth with higher exercise energy expenditure did not reported higher dietary intake or higher percentage of carbohydrate intake.

A possible reason for these results may be that, compared to sporadic exercise session, regular physical activity may allow to better understand personal physiologic reactions to training programs, allowing to optimize tailored approaches for glycemic management. Indeed, it has been previously reported that in subjects stratified according to their level of participation, metabolic control is significantly better in those who exercise frequently, regardless of the type of activity [1;26].

Despite the positive associations between fitness level and glycemic control in cross-sectional studies, the influence of chronic exercise on improving blood glucose control in children and adolescents with T1DM is variable; some studies show an improvement in blood glucose control, but others show no effect [1;20]. It is likely that excess caloric intake to prevent or treat hypoglycemia may counter the beneficial effects of exercise on glycemic control in some children, because standardized carbohydrate and insulin modifications for active children are difficult to achieve.

Diabetes specific nutrition recommendations for youth with T1D during physical activity are limited, as most studies address hypoglycemia prevention rather than sports nutrition needs. However, advice on overall nutritional intake with a focus on carbohydrate, protein, fluid and micronutrient intake should be provided by diabetes team, as adequate nutrition intake are essential to optimize both glycemic control and exercise performance [18]. Recently, an international consensus statement on exercise management in type 1 diabetes provides guidance regarding nutritional requirements for exercise performance and hypoglycemia prevention [19]. The net exercise-induced glucose response in the circulation results from changes in carbohydrate ingestion, hepatic release and uptake, skeletal muscle and adipose tissue uptake (amongst other organs), or hepatic gluconeogenesis, and is dependent on the exercise characteristics: type, mode, intensity, and duration [24-25]. Age, sex and fitness level also play a role in defining nutritional needs. Youths who attend camps that promote increased regular physical activities, along with education about how to modify dietary intake or daily insulin dosage to prevent hypoglycemia, show improved metabolic control and fitness [27-28]. For this reason, individual plans for exercise management should be tailored for each patient, based on the youth's personal experiences.

The goal of regular exercise should be promoted regardless of any possible benefits to blood glucose management, as consistent physical activity is associated with increased insulin sensitivity and an overall better cardio- vascular and psychological profile in youth with T1D. Results from the current study showed a lower percentage of body fat and a lower triglycerides level in youth who reported higher exercise energy expenditure. These findings are in line with results of meta-analyses [29-30] and other cross-sectional studies [21-31]. In the DPV studies, data from on 19 143 patients showed that in female youth the body mass index z score decreased from 0.60 in the less active groups to 0.51 in group exercising regularly (p<.001) [2]. Moreover, the inverse association between physical activity and triglycerides and other lipid values has been demonstrated in previous studies in both adults and youths [29;32]. The positive impact of exercise on weight control and metabolic status results in reduced cardiovascular risk and improved microvascular function [28]. The study TRAILS showed that increased cardio-metabolic risk related to fat mass in youth with T1D can be modulated by regular fitness [33]. In the systematic review of Nocon et al. a positive association between physical activity and decrease in cardiovascular and all-cause mortality have been demonstrated in adults with T1D [34].

In this study, findings comparing dietary intake of youth with ISPAD (International Society for Pediatric and Adolescent Diabetes) 2018 nutritional recommendations, demonstrated that just a few percentage of youth met the goals. This was mostly related to an excess in fat intake, and it hs been previously well described [35]. However, there is a lack of studies on nutritional intakes for sports, as most evidences are limited and based on adult data and because most studies address hypoglycemia prevention rather than sports nutrition needs [28].

The major strength of the current study includes the use of 3-day CGM data, as previous studies have been focused on the use of rt-CGM information for managing exercise or on the impact of specific type of exercise protocols on glycemic control. Moreover, both exercise and dietary intake were investigated in regards to CGM values, allowing a more comprehensive understanding of metabolic and nutritional changes with regards to physical activity in youth with T1D. Nevertheless, the cross-sectional study design cannot prove causal effects of the observed associations. Moreover, reliability of the information on physical activity is limited, as it was based on self-reports. Further studies are needed to confirm these results in larger pediatric cohorts to support clinical recommendations and promote physical activity in youth with T1D.

In conclusion, regular exercise appears to offer benefits to youth with T1D. In the current study a positive association between exercise energy expenditure, glycemic control (A1c) and metabolic parameters has been demonstrated without increased risk of hypoglycemia and glycemic instability (CGM values).

REFERENCES

1. Riddell MC, Iscoe KE. Physical activity, sport, and pediatric diabetes. Pediatric Diabetes 2006:7:60–70.
2. Herbst A, Bachran R, Kapellen T, et al. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Arch Pediatr Adolesc Med 2006;160:573–7.
3. Robertson K, Adolfsson P, Riddell M, et al. Exercise in children and adolescents with diabetes. Pediatr Diabetes 2009;10(Suppl.12):154–68.
4. Lehman R, Kaplan V, Bingisser R, et al. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care 1997;20:1603–11.
5. Sarnblad S, Ekelund U, Aman J. Physical activity and energy intake in adolescent girls with Type 1 diabetes. Diabet Med 2005;22:893–9.
6. Aman J, Skinner TC, De Beaufort CE, et al. Associations between physical activity, sedentary behaviour, and glycemic control in a large cohort of adolescents with type 1 diabetes: the Hvidoere Study Group on Childhood Diabetes. Pediatr Diabetes 2009;10:234–9.
7. Edmunds S, Roche D, Stratton G. Levels and patterns of physical activity in children and adolescents with type 1 diabetes and associated metabolic and physiologic health outcomes. J Phys Act Health 2010;7:68–77.
8. Brazeau AS, Rabasa-Lhoret R, Strychar I, et al. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008;31:2108-09.
9. Bernardini AL, Vanelli M, Chiari G. Adherence to physical activity in young people with type 1 diabetes. Acta Biomed 2004;75:153-157.

10. Maggio ABR, Hofer MF, Martin XE, et al. Reduced physical activity level and cardiorespiratory fitness in children with chronic diseases. 2010;169:1187-93.
11. Lukacs A, Mayer K, Juhasz E, et al. Reduced physical fitness in children and adolescents with type 1 diabetes. Pediatr Diabetes 2012;13:432-37.
12. Houlder SK, Yardley JE. Continuous Glucose Monitoring and Exercise in Type 1 Diabetes: Past, Present and Future. Biosensors 2018;8(3):73-79.
13. National Institutes of Health: Clinical Guidelines on the identification, evaluation, and treatment of overweight and obesity in adults-the evidence report. Obes Res 1998;6(Suppl 2):51S-209S
14. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents.The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatr. 2004;114:555–576.
15. Ridley K, Ainsworth BE, Tim S Olds. Development of a Compendium of Energy Expenditures for Youth. Inter J of Behav Nutr and Phys Act. 2008;5:45.
16. Kaplan AS, Zemel BS, Neiswender KM, et al. Resting energy expenditure in clinical pediatrics: measured versus prediction equations. J Pediatr. 1995 Aug;127(2):200-5.

1. Kennedy A, Nirantharakumar K, Chimen M, et al. Does Exercise Improve Glycaemic Control in Type 1 Diabetes? A Systematic Review and Meta-Analysis. PLoS One. 2013;8(3):e58861.
2. Pasieka AM, Nikoletos N, Riddell MC. Advances in exercise, physical activity and diabetes mellitus. Diabetes Technol Ther. 2016;18(Suppl 1).

3. Beraki A, Magnuson A, Sarnblad S, et al. Increase in physical activity is associated with lower HbA1c levels in children and adolescents with type 1 diabetes: Results from a cross-sectional study based on the Swedish pediatric diabetes quality registry (SWEDIABKIDS). Diab Res Clin Pract 2014;105:119-25.
4. Herbst A, Bachran R, Kapellen T, et al. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Arch Pediatr Adolesc Med 2006;160:573–7.
5. Herbst A, Kordonouri O, Schwab KO et al. DPV initiative of the German Working Group for Pediatric Diabetology Germany. Diabetes Care 2007:30;2098-2100.
6. MacMillan F, Kirk A, Mutrie N, et al. A systematic review of physical activity and sedentary behavior intervention studies in youth with type 1 diabetes: study characteristics, intervention design, and efficacy. Pediatr Diabetes. 2014 May;15(3):175-89.
7. Galassetti P, Riddell MC. Exercise and type 1 diabetes (T1DM) Compr. Physiol. 2013;3:1309–1336
8. Richter EA, Derave W, Wojtaszewski JFP. Glucose, exercise and insulin: Emerging concepts. J. Physiol. 2001;535:313–322
9. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017;5(5):377-390.
10. Huttunen NP, Lankela SI, Knip M, et al. Effect of once-a-week training program on physical fitness and metabolic control in children with IDDM. Diabetes Care 1989;12:737–740.

11. Moser O, Yardley JE, Bracken JM. Interstitial Glucose and Physical Exercise in Type 1 Diabetes: Integrative Physiology, Technology, and the Gap In-Between Nutrients. 2018;10(1):93.
12. Adolfsson P, Riddell MC, Taplin CE, et al. ISPAD Clinical Practice Consensus Guidelines 2018 Compendium Exercise in children and adolescents with diabetes. Pediatr Diabetes, 2018.
13. Quirk H, Blake H, Tennyson R, et al. Physical activity interventions in children and young people with Type 1 diabetes mellitus: a systematic review with meta-analysis. Diabet Med 2014;31:1163–1173.
14. Qiu S, Cai X, Schumann U, et al. Impact of walking on glycemic control and other cardiovascular risk factors in type 2 diabetes: a meta-analysis. PLoS ONE 2014;9:e109767.
15. Brazeau AS, Leroux C, Mircescu H, et al. Physical activity level and body composition among adults with type 1 diabetes. Diabet Med2012;29:e402–e408.
16. Chimen M, Kennedy A, Nirantharakumar K, et al. What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. Diabetologia 2012;55:542–551.
17. Brouwer SI, Stolk RP, Liem ET, et al. The role of fitness in the association between fatness and cardiometabolic risk from childhood to adolescence. Pediatr Diabetes. 2013;14(1):57-65.
18. Nocon M, Hiemann T, Müller-Riemenschneider F, et al. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239-46.

19. Katz ML, Mehta SM, Nansel T, et al. Associations of nutrient intake with glycemic control in youth with type 1 diabetes: difefrenecs by insulin regimen. Diabetes Technol Ther. 2014;16(8):512-518.

Performance of the Flash Glucose Monitoring System during Exercise in Youth with Type 1 Diabetes

ABSTRACT

Objective. Metabolic changes during exercise may affect the accuracy of glucose sensors impacting on Type 1 diabetes (T1D) management. The present study aimed at assessing the performance of the Flash Glucose Monitoring system (isCGM) during exercise and in free-living condition in youth with T1D.

Methods. Seventeen youth (53% male), aged 13.7±3.8 years, with T1D for 5.4±3.8 years, HbA1c 7.4±1.0% (57±11 mmol/mol), were enrolled. Paired isCGM, plasma (PG) and capillary (CG) glucose values (total of 136) were collected during an interval exercise (45 min at 55% VO_{2max} load with 20 seconds sprints at 80% VO_{2max} every 10 minutes). Paired isCGM and CG (total of 832) were collected during free-living condition.

Results. During exercise, isCGM absolute relative difference (ARDs) means/medians were 12.5/9.4% versus PG and 15.4/10.8% versus CG. During rest, ARDs means/medians were 16.6/12.0%. The Consensus Error Grid analysis showed 98.4% of readings during exercise and 97.24% during rest in zones A+B. Percentage of readings meeting the ISO criteria for CG levels <5.55 mmol/L was 62.5% during exercise, 53.4% during rest; for CG levels≥5.55 mmol/L was 64.0% during exercise, 60.4% during rest.

Conclusions. isCGM demonstrated similar clinical safety and performance during exercise and in everyday life; further studies are needed to confirm its accuracy during exercise.

INTRODUCTION

The Flash Glucose Monitoring System FreeStyle Libre Flash the intermittently scanned continuous glucose monitoring (isCGM, Abbot Diabetes Care, Alameda, California, USA) became recently available in the European marketplace for both adults and youth with diabetes. The system includes a patch sensor for interstitial glucose monitoring which is usually wore on the back side of the upper arm and of a reader to scan glucose results, trends, alerts and records for up to 8 hours.

The novelty of the system is that there is no need for calibration by the user during the 14 days-wear period as the sensor is factory-calibrated. This means that there is no need for fingerstick during the sensor-wear period, thus reducing burden potentially related to frequent blood glucose checks and may allowing a more frequent sensor use, especially in children and young people.

The FreeStyle Libre Flash (isCGM) was first introduced in Europe in 2014 and it has been approved for use in children aged > 4 years in January 2016. In 2017 a slightly different version has been introduced in US [1].

The system has been proved to be accurate and safe compared to laboratory methods or traditional blood glucose checks in adults with Type 1 diabetes (T1D) [2-5]. Few studies have been published on the accuracy, safety and acceptability of isCGM in children with T1D during routine condition, anticipating that the system could enhance diabetes management [5-8].

The unique features of the isCGM make the system suitable for being particularly useful in different conditions of everyday life, including exercise, especially in the pediatric age. Indeed, the rapid change of blood glucose levels during physical activity and the fear of hypoglycemic events remain an important barrier to consistent physical activity for youth with diabetes [9-10]. Also it can be very difficult for families to manage insulin therapy and carbs intake, due to variable impacts of different exercise on metabolic outcomes [11].

Real time information on glycemic trends can help to manage diabetes treatment during and after exercise and may reduce hypoglycemic events. On the other side metabolic changes and glycemic fluctuations occurring during exercise may affect the performance of sensor systems [12-13].

High intensity interval sprint exercise may be of particular benefit to optimize exercise-associated glycaemia in T1D as it increases oxidative capacity of skeletal muscle and attenuates the rates of glycogen breakdown [11;14]. However, interval exercise is also associated with changes in pH, microcirculation, and oxygen tension, which may potentially interfere with sensor accuracy [15].

In this study we evaluated isCGM performance in youth with T1D during everyday life, and scheduled moderate-intense physical activity over a two weeks of free-living condition in youth with T1D.

MATERIAL AND METHODS

Study Design and Participants

For this prospective, single arm study, youth with T1D were recruited from a pediatric diabetes clinic to assess accuracy and safety of isCGM system during a moderate-intense interval exercise and during 2-weeks of free-living conditions.

Eligibility criteria included youth 9-17 years of age, willingness to wear isCGM, type 1 diabetes duration of ≥1 year at enrollment, body mass index (BMI) of 5° to 95° centile for age and sex, daily insulin dose of ≥0.5 units/kg, blood glucose (BG) monitoring frequency of ≥2 times per day, and HbA1c of 6.5-9% (48-75 mmol/mol). Exclusion criteria included severe hypoglycemia episodes requiring third-part assistance in the previous 6 months, DKA episodes within the past 6 months, macro-and micro-vascular complications clinically significant within the past 6 months or other concomitant medical conditions compromising the participation in the study, history of skin reactions to adhesive patches, ongoing pregnancy, inability to comply with the study protocol, difficulty with venous access, and any other medical or cognitive disorder that could prevent the full participation in the required exercise sessions.

All enrolled participants received the FreeStyle Libre System® (Abbott Diabetes Care) and a BG meter (Contour Next One®, Bayer).

The study was performed according to Good Clinical Practice in accordance with the Helsinki declaration. The Ethics Committee of the hospital approved the protocol and all participants and parents/guardians provided signed assent (as appropriate for the youth’s age) and a written informed consent, respectively, prior to enrollment.

Procedures

Over the 2-weeks study period, participants attended 4 in-person visits and received 2 phone contacts by the study staff, checking for adverse events.

Visit 1 included screening for eligibility and enrollment procedures.

Visit 2 (day 0) included collection of contact information forms, general information as well as medical records. Both general physical examination and full neurological examination were performed. A resting electrocardiography (ECG) and the determination of the maximal oxygen consumption rate (VO2max) on a cycle ergometer (Ganshorn Power Cube LF8.5G, Schiller software) were performed. A venous blood sample was collected for blood glucose value, safety and lactate, right before and after the physical activity. After the cycle ergometer test, capillary BG was tested every 20 minutes. When a stable BG trend was assessed, a FreeStyle device training was started and the sensor was inserted on the back of the upper arm.

Participants were asked to wear the sensor for the 14-days study period and they were instructed to perform 4 capillary BG tests daily at least using the BG Contour One device (furnished by the research staff), each immediately followed by a isCGM measurement to allow comparison of results between sensor and BG. No changes in the pre-existing diabetes treatment plan were made or suggested by the research staff during the study period and participants were asked to maintain their pre-existing diabetes self-management plan during the 14-days study period. A study diary was provided to each participant to collect BG records and hypoglycemic episodes during the whole study period. Moreover, an adverse event report form was provided to participants to monitor any adverse event related to study procedures, device use and skin irritation, erythema, oedema, haematoma, soreness, pain or any other reaction.

At Visit 3 (day 1) as well as at visit 5 (day 8) study staff assessed by phone isCGM use and checked for any adverse event eventually occurred.

At visit 4 (day 5) the exercise intervention was performed.

After a clinical evaluation and venous catheterization, fasting plasma blood glucose, capillary BG test and isCGM measurements were performed.

After the collection of fasting samples, around 9.00 am, participants were instructed to administer an insulin dose, according to the personal ongoing therapeutic plan, and a standardized breakfast (37 g CHO for youth aged <15 years and 58 g CHO for youth ≥15 years) was offered about 15 miutes later.

At 10.30 capillary BG test was checked and were adopted procedures based on glucose level. Glucose target levels were set at 5.0 to 15.0 mmol/L [11].

For participants in CSII therapy and glycemic values between 5.0 and 6.9 mmol/L, 10 g of CHO and a 50% temporary basal, starting from 30 min before the exercise until the end of the workout, were indicated by the study protocol [11]. For glycemic values between 7.0 and 15.0 mmol/L, a 50% temporary basal starting from 30 min before the exercise until the end of the workout were indicated by the study protocol [11].

For participants in MDI and glycemic values between 5.0 and 6.9 mmol/L, 20 g of CHO before the exercise was indicated [11].In case of hypoglycemia below 5.0 mmol/L, the protocol indicated to administer 10 extra g of CHO in MDI participants and 20 g of CHO in CSII participants while suspending the pump until the end of the exercise [11].

For hyperglycemia (BG > 15.0 mmol/L) and MDI therapy, a corrective insulin dose according to the ongoing therapuetic plan was indicated; in case of CSII therapy, a corrective insulin dose and a 50% temporary basal to be set starting from 30 min before the exercise until the beginning of the lunch was indicated by the protocol [11].

Blood glucose values < 2,8 mmol/L or >16.6 mmol/L or the presence of blood ketones (≥0.6 mmol/L) were considered as contraindications to exercise [11].

At 11.00 participants were admitted at the facility of the Respiratory Department and the exercise session started. The standardized exercise protocol consisted of approximately 45 min moderate exercise periods at 55% VO_{2max} load (starting work rate set to 30 watts (W) with linear loading to reach 55% VO_{2max} on a 5-minutes exercise time) and alternating 4x20 seconds sprint reaching 80% VO_{2max} at minute 10 and every 10 minutes until the end of the bike session (Figure1). The exercise protocol was designed based on previous experiences of the authors testing closed loop systems during physical activity [16].

Speed and slope of the bike were individually tailored to achieve VO2 maximal rate goals, which were calculated in the visit number 2.

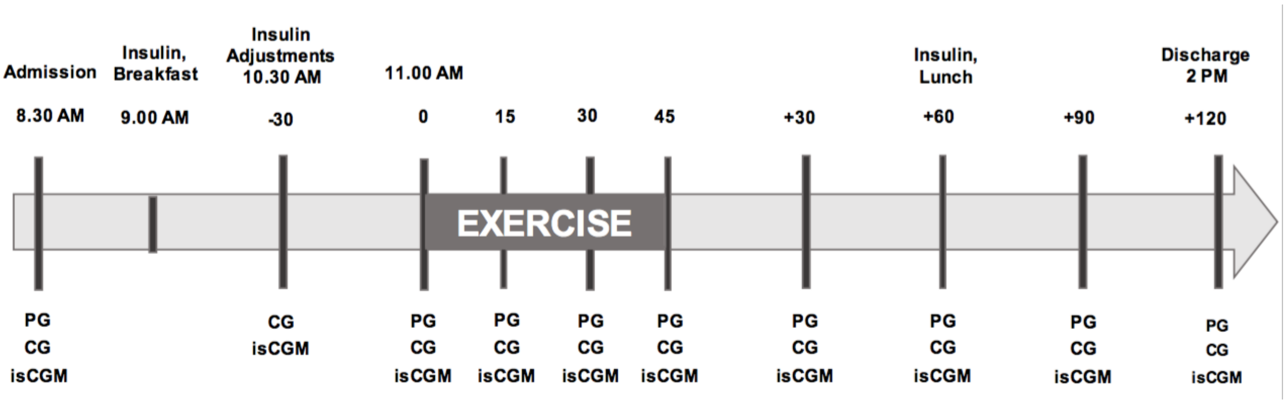
A basal ECG was performed before the exercise to rule out any concomitant contraindication to exercise and the overall exercise duration was conducted under continuous ECG, respiratory gas exchange monitoring, SpO2 and blood pressure measurements. The moderate-to-vigorous exercise was immediately preceded and followed by evaluation of plasma glucose and capillary BG and lactate levels. Plasma BG, capillary BG and isCGM were collected at the beginning of the exercise and every 15 min during the physical activity until the end of the exercise session (Figure 1).

Moreover, isCGM, plasma and capillary BG monitoring were performed every 30 minutes for the 2 hours after the exercise.

Before discharge, around 1.00 pm, an insulin dose was administered according to the ongoing therapeutic plan, and a standardized lunch (80 g CHO for youth aged <15 years or 110 for youth aged ≥15 years) was offered.

During the final clinic visit (visit 6, day 14), isCGM was removed and the insertion site inspected for any adverse reaction. isCGM and BG meter data were downloaded. Adverse events home-diary was also collected and reviewed by trained research staff.

Figure 1. *Timeline of the physical activity day. Insulin doses for breakfast and lunch were administered according to the ongoing insulin plan. Insulin adjustments 30 minutes before the exercise were personalized according to the ongoing insulin regimen and glucose level as reported in the study procedures.*



PG, plasma blood glucose; CG, capillary blood glucose; isCGM, intermittently scanned continuous glucose monitoring.

Data and Outcomes

Primary outcome was to test the performance of isCGM values during exercise against temporally matched (within ± 5 min) plasma and capillary BG. Thus, each of the 8 time points of the exercise session (before exercise, +15 min, +30 min, +45 min during the workout and 30, 60, 90, 120 min after exercise, during the recovery period) consisted of three glucose levels: plasma BG, capillary BG and isCGM reading.

Secondary outcome was to evaluate the accuracy of isCGM against capillary BG during the 14-days study period out of the exercise session.

Data on safety of isCGM system were also analyzed.

Statistical methods

Several parameters were used to assess the accuracy outcomes, including sensor bias (SB), absolute difference (AD) and absolute relative difference (ARD), the percentage of isCGM vs plasma/capillary BG readings that meet the International Organization for Standardization (ISO) 2013 standards (which means within ± 0.83 mmol/L for plasma glucose value < 5.55 mmol/L and within ± 15% for plasma glucose values ≥ 5.55 mmol/L) [17]. To test the clinical safety of the isCGM values, Clarke's error grid analysis (Consensus Error Grid, CEG) was performed comparing isCGM reading against the corresponding plasma or capillary BG value. Values in zones A and B were considered clinically acceptable [18]. For the accuracy outcome, a sample of 20 participants has been calculated to obtain a 95% CI around an estimate of the percentage of results in zone A of the CEG of 5%. Continuous variables are expressed as mean (SD) or median (IQR), categorical variables are expressed as percentages. Two-sided Wilcoxon rank sum test was used to assess comparison of median ARDs between different time points. All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Participants

A total of 20 youth with T1D were enrolled, two subjects did not complete the study due to the sensor break off, one patient suspended physical activity performance 30 minutes after the start due to the occurrence of hypoglycemia. Therefore 17 youth were included in the analyses, 53% male, aged 13.7±3.8 years, with T1D for 5.4±3.8 years. The majority of them were pump users (81%) and the mean HbA1c was 7.4±1.0% [57±11 mmol/mol] (Table 1).

Table 1. *Participants characteristics.*

Variable	**Mean±SD or %**
Age (years)	13.7±3.8
Gender (% male)	53
z-BMI (kg/m^2)	0.6 ± 0.9
Duration of diabetes (years)	5.4 ± 3.8
Insulin dose (Units/kg/day)	0.8±0.3
BG monitoring (times/day)	5.1±2.6
Pump therapy (%)	81
Hemoglobin A1c (%)	7.4±1.0
Hemoglobin A1c (mmol/mol)	57±11
$VO_{2\ max}$ (mL/(kg*min)	33.2 ± 6.2
HR peak (bpm)	170 ± 19

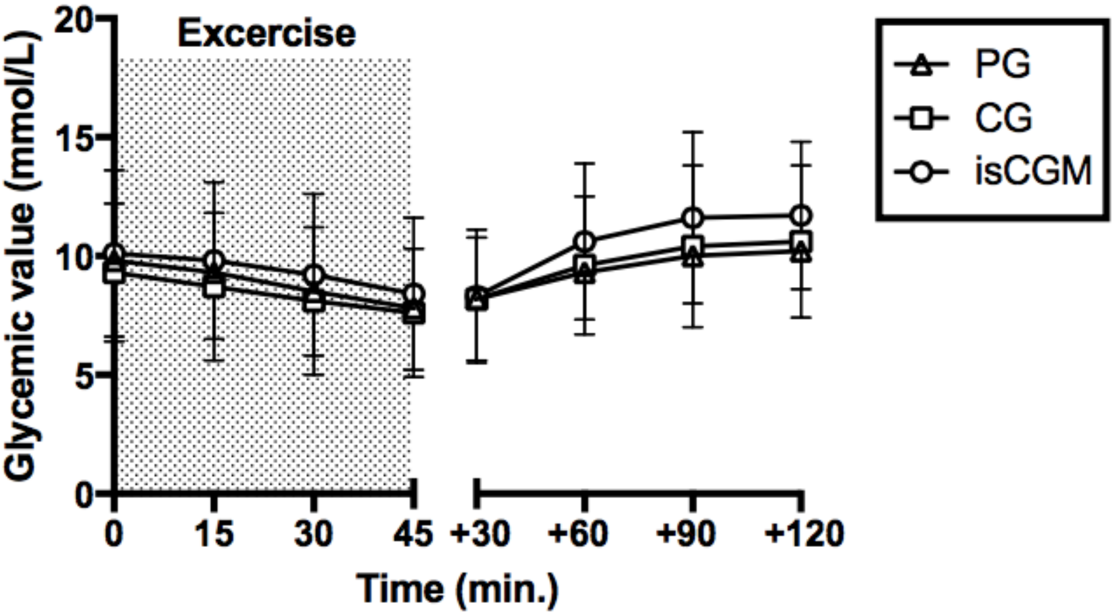
HbA1c, haemoglobin A1c; BG, blood glucose; BMI, body mass index; VO_2, maximal aerobic capacity; HR, heart rate. Data are presented as percentages or mean ± SD.

3.2 isCGM performance during exercise

During exercise, a total of 136 isCGM and paired plasma glucose (PG) values and capillary (CG) values were collected. At the start of exercise, the mean glucose value (PG) was 9.7±3.5 mmol/L, probably as the breakfast was administered about 2 hours before and possibly still influencing the glycemic profile (Table 4). Neither glycemic values below 5.0 mmol/L nor above 15.0 mmol/L requiring adjustments occurred before the exercise. Glycemic profile during the activity resulted pretty stable until the end of the sport session (PG values: median=8.6, IQR= 7.3-10.9 mmol/L), while a trend toward hyperglycemia has been reported starting from one hour after the end of the session, probably due to the exercise protocol and, later, to the occurrence of the lunch (Figure 2). As previously mentioned, one participant only reported hypoglycemia below 3.9 mmol/L about 30 minutes after the exercise started. The session was stopped as hypoglycemic symptoms occurred (CG 3.7 mmol/L; isCGM 3.6 mmol/L) and the participant asked to drop out from the study.

During the overall exercise period (0,15,30,45 and +30, +60, +90, +120) the isCGM bias means/medians were 0.78/0.67 mmol/L versus PG values and 0.89/0.72 mmol/L versus CG values. The isCGM ARDs means/medians were 12.5/9.4% versus PG and 15.4/10.8% versus CG (Table 2).

Figure 2. *Rates of change of glucose values during and right after the physical activity. The plotted data are means of glycemic values at each time point and SD (error bars.)*



PG, plasma blood glucose; CG, capillary blood glucose; isCGM, intermittently scanned continuous glucose monitoring.

Table 2. *Accuracy of isCGM system during exercise and during the overall 14-days study period.*

	Exercise session		**14-days**
Period	**isCGM vs PG**	**isCGM vs CG**	**isCGM vs CG**
Mean SB (SD) mmol/L	0.78 (1.04)	0.89 (1.37)	0.58 (1.99)
Median SB (IQR) mmol/L	0.67 (0.11 to 1.33)	0.72 (-0.11 to 1.72)	0.44 (-0.50 to 1.55)
Mean ARD (SD) %	12.5 (11.9)	15.4 (14.5)	16.6 (18.6)
Median ARD (IQR) %	9.41 (4.05 to 16.18)	10.79 (5.14 to 21.42)	12.03 (5.71 to 22.41)
Results in zone A of CEG (%)	84	73	71
Results in zones A and B of CEG (%)	100	98	97

SB, sensor bias; ARD, absolute relative difference; SD, standard deviation; IQR, interquartile range; isCGM, intermittently scanned continuous glucose monitoring; PG, plasma blood glucose; CG, capillary blood glucose; CEG, Consensus Error Grid.

When compared against CG, the percentage of isCGM readings within the Consensus Error Grid Zone A and zones A+B was 73% and 98% respectively, during exercise (Table 2, Figure 3a). The percentage of readings meeting the ISO criteria was 62% (10/16) for CG levels <5.55 mmol/L and 64% (77/120) for CG levels ≥5.55 mmol/L during exercise (Table 3).

Figure 3a. *Consensus error grid analysis of sensor glucose results during exercise compared to plasma blood glucose readings. The analysis showed that 100% (n = 136) of the values were in zone A + B and 0% (n = 0) in zone C, D and E.*

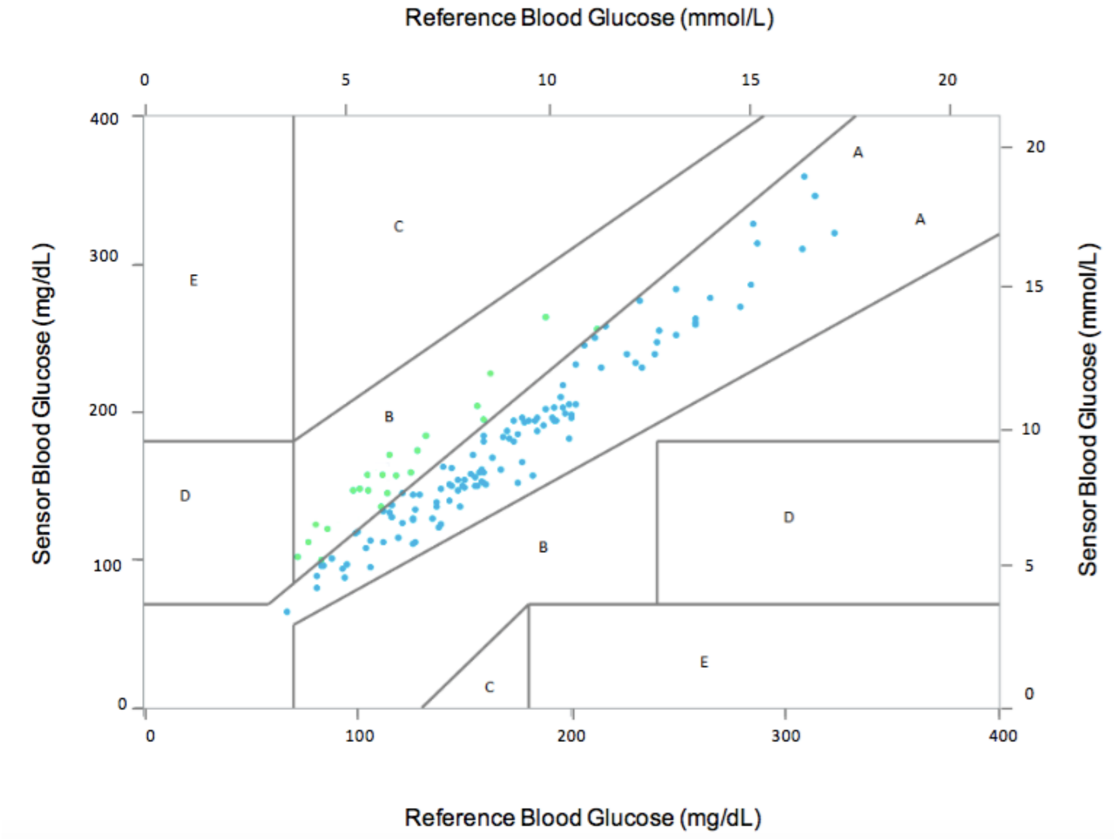


Table 3. *Frequency of isCGM readings meeting the ISO standard criteria (15197:2013) during exercise and over the 14-days study period.*

Accuracy Measure	Exercise session (isCGM vs PG)	Exercise session (isCGM vs CG)	14-days (isCGM vs CG)
CG <5.55 mmol/L (Within ±0.83 mmol/L)	78% (11/14)	62% (10/16)	53% (68/129)
CG ≥5.55 mmol/L (Within ±15%)	76% (93/122)	64% (77/120)	60% (425/703)

ISO, *International Organization for Standardization; PG, plasma glucose; CG, capillary glucose*

Table 4 reports mean PG values and MARD of each of the 8 time points during the exercise period, including the workout and the recovery period. The detailed analyses show a decreasing in isCGM accuracy during the overall exercise period, with the lowest median ARD of 5.5% at the beginning of the training session increasing to the maximum of 14.3% at minute 30 of the workout period, but not reach the statistical significance, probably due to the small sample size (n=17, p=0.1). During the recovery period, the median ARD slightly decreased, even if a peak of MARD (12.1%) was registered 60 minutes after the exercise, when also the lunch occurred. ARD means/medians for the workout period (0,15, 30, 45 minutes) and the recovery period (+30, +60, +90, +120 minutes) were 12.2/6.4% and 12.8/11.0% respectively (p=0.2).

Table 4. *Glycemic values (PG) and isCGM accuracy at each time point during workout period and during post-exercise period.*

	Workout period				Post-exercise recovery period			
	0	15	30	45	+30	+60	+90	+120
PG (SD) (mmol/L)	9.7 (3.5)	9.3 (3.2)	8.5 (3.3)	7.8 (2.9)	8.2 (2.4)	9.3 (2.7)	10.0 (3.1)	10.2 (3.4)
ARD (%) Mean (SD) median (IQR)	8.9 (11.7) 5.5 (1.9-10.8)	12.5 (15.6) 4.8 (3.0-18.5)	15.8 (14.7) 14.3 (4.5-20.8)	11.5 (11.5) 8.8 (4.4-15.7)	11.3 (6.3) 10.8 (6.2-16.4)	14.6 (10.7) 12.1 (8.9-14.8)	12.2 (10.3) 9.8 (5.2-16.2)	13.4 (13.2) 7.7 (3.6-18.1)

PG, plasma *blood glucose; ARD, absolute relative difference; SD, standard deviation; IQR, interquartile range.*

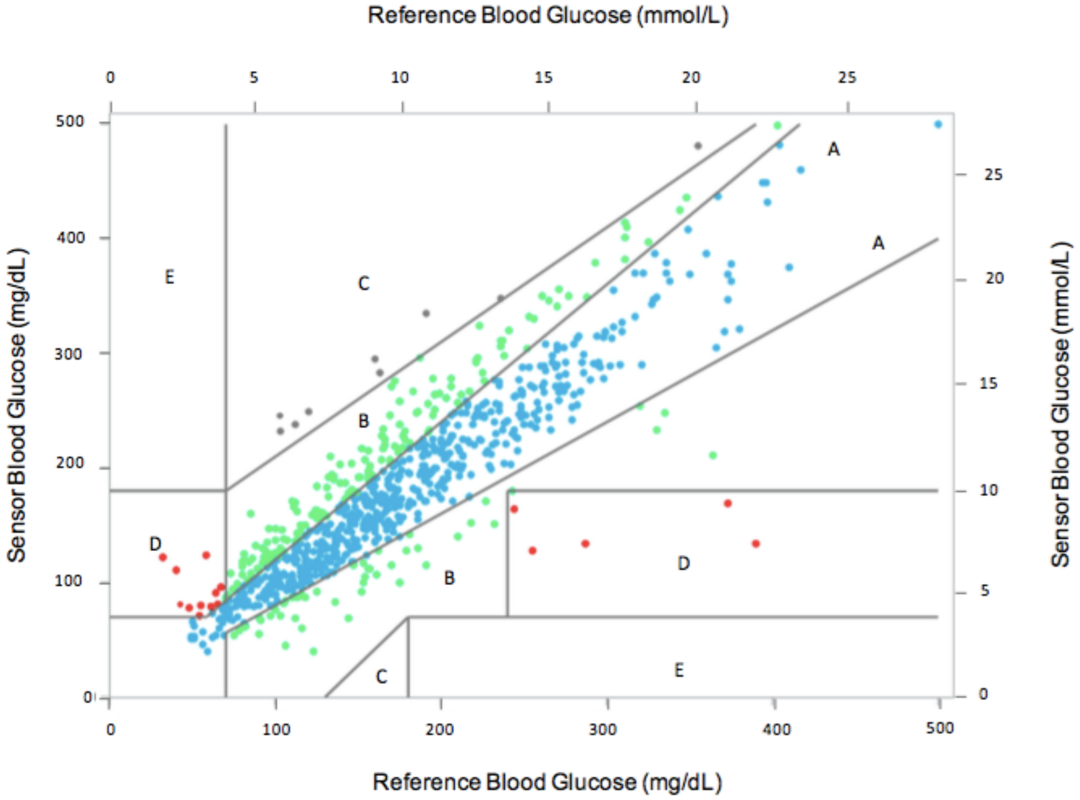
isCGM ***performance during the follow up period***

During the 14-days study period, a total of 832 isCGM and paired CG values were collected. No severe hypo/hyper-glycemic event occurred.

During the follow up period, as well as during the exercise session, isCGM readings reported a similar pattern, modestly higher compared to CG. Indeed, for the overall period, the isCGM bias means/median were 0.58/0.44 mmol/L versus CG and ARDs means/medians were 16.6/12.0% (Table2). When considered separately, ARDs means/medians for days 1 to 2 were 19.1/12.1% (IQR 6.0-25.3) and for days 3 to 14 were 16.3/12.1% (IQR 5.6-22.2).

The percentage of isCGM readings during the 14-days within the Consensus Error Grid Zone A and zones A+B was 71% and 97% respectively (Table 2, Figure 3b). Percentage of reading meeting the ISO criteria for CG levels <5.55 mmol/L was 53% (68/129) during rest; for CG levels≥5.55 mmol/L was 60% (425/703) during rest. (Table 3).

Figure 3b. *Consensus error grid analysis of sensor glucose results during 14 days compared to capillary blood glucose readings. The analysis showed that 97% (n = 807) of the values were in zone A + B, 1.1% (n = 9) in zone C, 1.9% (n = 16) in zone D and 0% (n = 0) in zone E.*



Safety

None of the participants reported adverse events or device-related adverse events for either the exercise day or the follow up period. About adverse events, only one participant reported itching symptoms in the adhesive area during the second week of sensor wear, but the grade of disturb was mild and the subject did not ask to interrupt the study.

Sensor site inspection performed at each study visit did not report any adverse reaction associated with sensor insertion and application, including erythema, oedema, haematoma, soreness, pain. At the last study visit, when the sensor was removed, a mild skin irritation was observed in the adhesive area of the participant who have reported itching symptoms during the second week of sensor wear.

DISCUSSION

In the present study we tested the performance of the isCGM system during both an interval exercise and a daily life period in pediatric patients. Previous reports have assessed the accuracy of isCGM in everyday life, both in adults [5;19-21] and in pediatric patients [6-7;22], but data on its performance during exercise in youth with T1D are lacked. The rapid change of blood glucose levels during physical activity continues to be a challenging situation and it is also expected to affect the performance of sensor systems, including isCGM. This study is the first evaluating isCGM performance in different conditions, including rest and exercise in the pediatric age. Results from the study demonstrated that isCGM performed similarly during the interval physical activity and the rest period. The overall accuracy during interval exercise was good, with 84% of the paired isCGM-PG readings falling within the Consensus Error Grid (CEG) zone A and 100% of readings within zones A and B. During the 14 days' period a similar pattern of accuracy was shown. Furthermore, no statistically significant differences were detected in MARD between the first two days of sensor wear and the days 3 to 14, suggesting a stable performance of the sensor during the period. Similarly, no significant differences in MARD have been demonstrated over the 14-day sensor life in the study of Aberer F et al. [23], while in the study of Bailey T et al. only the first day reported a lower accuracy [19]. In the study by Hansen et al, the difference in MARD for the first 24 hours (16.8±14.1%) vs the MARD of the following days (16.7%±16.6%) was not significant (P =0.90) [24].

When considering the results in the CEG areas, isCGM resulted clinically safe both during the interval exercise and the rest period. These data seem to corroborate the reliability of isCGM in pediatric patients with T1D during sport.

Nevertheless, when MARD value is considered, isCGM performed less accurately. As expected, the isCGM MARD during exercise resulted higher compared to the MARD of the glucometer (12.5 vs 5.7%). Interesting, during the workout session, there was an increase of the MARD value (from 5.5% at the beginning of the session to 15,8% at 30 minutes) suggesting a possible degradation of MARD during the training session, even if the variation did not result statistically significant, probably for the small size of the sample. The trend of the MARD values slightly decreased during the recovery period, with a final value of 7.7% two hours after the workout period. These results did not allow any conclusive speculation as the sample is small, but further studies may investigate the impact of different types, intensities and duration of exercise on isCGM performance. In a recent study, a similar pattern of accuracy has been reported for CGM sensors during aerobic exercise, with a 73% increment in MARD during the training session, followed by a progressive decrease few hours later. In the present study, the interval workout characterized by acute bouts of exercise may produce rapid changes in redistribution in body fluid between the interstitium, lymphatics, and bloodstream, conditioning continuous adjustments to facilitate glucose provision to the exercising tissues [25-26].

When considering traditional ISO standard goals for system accuracy, criteria were not fully met by isCGM readings during exercise for both values <5.55 mmol/L (77.8% compared to the 95% recommended) and ≥5.55 mmol/L (76.2% compared to the 95% recommended).

However, specific tools for the evaluation of sensor accuracy beside the traditional ones should be considered for future implementation. In a recent report, Leelarathna et al. suggested that the classical parameters such as the ARD, the ISO criteria, and the CEG analysis may not accurately reflect the performance of the sensor systems as they may fail to assess the incidence of individual sensor discrepancies [22]. This is even more crucial for isCGM, as Libre data can be used in place of self-monitoring blood glucose for insulin adjustments and not as adjunctive to fingersticks.

Data from this study are similar to those previously reported: in the study of Edge J. et al in pediatric patients in free-living conditions, isCGM reported a MARD against CG of 13.9% and a percentage of results in zone A and B of the consensus grid of 99.4% [6]. Similarly results have been reported by Massa et al in 67 youth wearing the sensor for 14 days: the overall MARD was 16.7%, and 98.7% of the data pairs were in zone A and B of the consensus error grid [27].

In a similar study in adults, isCGM MARD against CG was 13.9% and percentage of results isCGM in zone A and B of CEG was 99.7% [19].

When considering the performance of isCGM in conditions of intense physical activity, as during summer camps, results are slightly different. The pediatric studies by Szadkowska et al achieved an overall MARD of 13.5±12.9% using the Contour Plus One glucometer in a camp setting, with a significantly higher computed MARD values of isCGM during rapid fall flag (22.6% ± 18.6%) than in stable glycemic conditions (11.4% ± 10.4%), allowing authors to suggest that physical activity could significantly impact on sensor accuracy [28]. Similarly, Adolfsson et al showed the MARD of a CGM system was positively associated with higher activity intensity among adolescents attending sports camps [29]. In the study by Hansen et al in sixty-six youth with T1DM participating in a 7-day summer camp, isCGM overall MARD was 16.7%±16.1%, similar to that of the current study [24].

Although comparisons between devices not tested simultaneously in the same trial should be considered with caution, results of isCGM performance in this study are similar to those of other CGM sensors previously tested during interval exercise sessions. In a recent paper comparing the Dexcom Platinum G4 with the Medtronic Veo Enlite during an interval exercise training, the ISO criteria were met by 48.2% versus 53.9% of data points for Dexcom and Enlite, respectively (Table 5) [30]. However, as in the meantime the new Dexcom G5 system has been launched by Dexcom, it would be interesting to compare the isCGM Libre with the Dexcom G5, as it is the first CGM device approved by the U.S. Food and Drug Administration (FDA) for non-adjunctive use as well.

Strength areas of our study included, in addition to the evaluation of isCGM in rigorous exercise training, the use of plasma glucose values as the reference standard during exercise unlike to other studies that relied on capillary blood glucose measurements. Furthermore, the study was carried out in a well-controlled research environment and standardized conditions in regard to meals and exercise sessions. The insertion of the isCGM system was performed by a trained staff in clinic 1 week before the exercise was performed, allowing to avoid the potential lower accuracy of the sensor previously reported during the first two days of sensor use [19]. Additionally, the study was performed independent from the sensor manufacture.

We, nevertheless, acknowledge some limitations. First, the sample size was relatively small and restricted to pediatric patients in the age suitable for performing the exercise protocol. Additionally, data of the patient who dropped out from the study due to the occurrence of hypoglycemia during exercise were not included in the analyses, as the participant asked to exit from any study procedure, including attending visits for data download. Second, glycemic profile during the exercise session was relatively stable, as the protocol was designed to maintaining a safe glycemic profile during the exercise period in the pediatric participants [11]. The occurance of breakfast and lunch relatively close to the exercise session have made the glycemic trend higher than it was expected for both the workout and the recovery periods. Based on this experience, it would probably worthy to test a lower or shorter reduction in temporary basal rate in CSII participants or lower CHO intakes in MDI participants during intense interval exercise when high carbohydrates meals occur close to the training session. However, the aim of the present study was not to analyze isCGM accuracy in different glucose ranges, as it has already been investigated [5], but to test isCGM in different common conditions. Indeed, multiple challenges can affect the accuracy of sensor systems during physical activities, including changes in subcutaneous blood circulation, impacting on the glucose kinetics and equilibration between blood and interstitial fluid compartments, as well as skin temperature changes, resulting in a shift of 4% of the sensor readings degree Celsius change [31-32].

Furthermore, other limitations were due to the exclusion criteria: subjects with previous episodes of severe hypoglycemia were not included in the protocol. Indeed, as this was not the aim of the current study, participants were dismissed from the hospital few hours after the exercise ended and no admission to the hospital was planned by the protocol. It has been suggested that other CGM systems are likely to be superior to the isCGM in reducing hypoglycemic events, also because the FreeStyle Libre sensor does not have alarms for hypoglycemia [5]. Thus, it would be of interest to target patients at high risk for hypoglycemia in a further, tailored trial.

In conclusion, in the present study isCGM showed a reasonable accuracy both during physical activity and daily-life setting in youth with T1D. However, further investigations on the accuracy of the system during rapid glycemic fluctuations in a larger sample size are needed, and patients should be encouraged to observe not only the values displayed by their sensor during exercise but also the trend of glucose changes in anticipation of hypoglycemia.

Management of physical activity remain challenging in pediatric patients, due to the fear of hypoglycemic events. Sensor technologies may contribute in implementing physical activity among the youngest with T1D by increasing the time-in range periods and allowing timely interventions to either prevent or rapidly recognize and treat hypoglycemic episodes.

Table 5. *Accuracy of isCGM compared to other sensors previously tested during an interval exercise (PG was used as reference to evaluate the accuracy of all the systems tested) [13].*

Period	**isCGM**	**DEXCOM G4***	**ENLITE***
Mean SB (SD) mmol/L	0.78 (1.04)	-0.44 (1.80)	-0.30 (0.88)
Median SB (IQR) mmol/L	0.67 (0.11 to 1.33)	0.002 (-0.78 to 0.56)	-0.32 (-0.78 to 0.58)
Mean ARD (SD) %	12.5 (11.9)	17.70 (15.29)	12.70 (6.96)
Median ARD (IQR) %	9.41 (4.05 to 16.18)	10.91 (6.14 to 22.46)	11.27 (8.03 to 14.67)
Results in zones A and B of CEG (%)	100	97.10	98
ISO criteria (%)	76.2	48.20	53.9

SB, sensor bias; ARD, absolute relative difference; SD, standard deviation; IQR, interquartile range; isCGM, intermittently scanned continuous glucose monitoring; PG, plasma blood glucose; CEG, Consensus Error Grid; ISO, International Organization for Standardization.

REFERENCES

1. Ajjan RA, Cummings MH, Jennings P, et al. Accuracy of flash glucose monitoring and continuous glucose monitoring technologies: implications for clinical practice. Diab Vasc Dis Res 2018;15(3):175-184.
2. Olafsdottir AF, Attvall S, Sandgren U, et al. A Clinical Trial of the Accuracy and Treatment Experience of the Flash Glucose Monitor FreeStyle Libre in Adults with Type 1 Diabetes. Diabetes Technol Ther 2017;19: 164–172.
3. Dover AR, Stimson RH, Zammitt NN, et al. Flash Glucose Monitoring Improves Outcomes in a Type 1 Diabetes Clinic. J Diabetes Sci Technol 2017;11(2):442–443.
4. McKnight JA, Gibb FW. Flash Glucose Monitoring is associated with improved glycaemic control but use is largely limited to more affluent people in a UK diabetes centre. Diabet Med 2017;34(5):732.
5. Leelarathna L, Wilmot EG. Flash forward: a review of flash glucose monitoring. Diabet Med. 2018 Apr;35(4):472-482.
6. Edge J, Acerini C, Campbell F, et al. An alternative sensor-based method for glucose monitoring in children and young people with diabetes. Arch Dis Child 2017;0:1-7.
7. Campbell F, Kordonouri O, Murphy N, et al. FreeStyle Libre Use for Self-Management of Diabetes in Children and Adolescents. Diabetes 2017;66(Suppl. 1A):LB28–LB28.
8. McPhater A, Gardiner M, Modgil G. The impact of the Libre device for families and children with Type 1 diabetes. Diabetic Med 2017;34:104–104.

9. Jabbour G1, Henderson M1, Mathieu ME2. Barriers to Active Lifestyles in Children with Type 1 Diabetes. Can J Diabetes. 2016 Apr;40(2):170-2.
10. Giani E, Scaramuzza AE, Zuccotti GV. Impact of new technologies on diabetes care. World J Diabetes. 2015 Jul 25;6(8):999-1004.
11. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol. 2017 May;5(5):377-390.
12. Davey RJ, Low C, Jones TW, et al. Contribution of an intrinsic lag of continuous glucose monitoring systems to differences in measured and actual glucose concentrations changing at variable rates in vitro. J Diabetes Sci Technol 2010;4:1393–99.
13. Bally L, Zueger T, Pasi N, et al. Accuracy of continuous glucose monitoring during differing exercise conditions. Diabetes Res Clin Pract 2016;112:1–5.
14. Harmer AR, Chisholm DJ, McKenna MJ, et al. Sprint training increases muscle oxidative metabolism during high-intensity exercise in patients with type 1 diabetes. Diabetes Care 2008;31:2097–102.
15. Rebel A, Rice MA, Fahy BG. Accuracy of point-of-care glucose measurements. J Diabetes Sci Technol 2012;6(2):396–411.
16. Dovc K, Macedoni M, Bratina N, et al. Closed-loop glucose control in young people with type 1 diabetes during and after unannounced physical activity: a randomized controlled crossover trial. Diabetologia. 2017;60(11):2157-2167.
17. International Organization for Standardization: in vitro diagnostic test systems. Requirements for blood-glucose monitoring systems for self-

testing in managing diabetes mellitus. Geneva Int Organ Stand ISO 151972013.

18. Clarke WL, Cox D, Gonder-Frederick LA, et al. Evaluating clinical accuracy of systems for self- monitoring of blood glucose. Diabetes Care 1987;10:622– 628.
19. Bailey T, Bode BW, Christiansen MP, et al. The performance and usability of a factor-calibrated flash glucose monitoring system. Diabet Technol Ther 2015;17:787-94.
20. Reddy M, Jugnee N, El Laboudi A, et al. A randomized controlled pilot study of continuous glucose monitoring and flash glucose monitoring in people with Type 1 diabetes and impaired awareness of hypoglycaemia. Diabet Med 2018; 35: 483–490.
21. Haak T, Hanaire H, Ajjan R, et al. Use of Flash Glucose-Sensing Technology for 12 months as a Replacement for Blood Glucose Monitoring in Insulin-treated Type 2 Diabetes. Diabetes Ther 2017; 8: 573–586.
22. Leelarathna L, Nodale M, Allen JM, et al. Evaluating the accuracy and large inaccuracy of two continuous glucose monitoring systems. Diabetes Technol Ther 2013;15:143–149.

23. Aberer F, Hajnsek M, Rumpler M, et al. Evaluation of subcutaneous glucose monitoring systems under routine environmental conditions in patients with type 1 diabetes. Diabetes Obes Metab 2017;1-5.

24. Hansen EA, Klee P, Dirlewanger M, et al. Accuracy, satisfaction and usability of a flash glucose monitoring system among children and

adolescents with type 1 diabetes attending a summer camp. Pediatr Diabetes. 2018;1-9.

25. Biagi L, Bertachi A, Quiros C, et al. Accuracy of continuous glucose monitoring before, during and after aerobic and anaerobic exercise in patients with type 1 diabetes mellitus. Biosensors 2018;9:8(1):22.

26. Moser O, Yardley JE, Bracken RM. Interstitial Glucose and Physical Exercise in Type 1 Diabetes: Integrative Physiology, Technology, and the Gap In-Between. Nutrients 2018;15:10(1):93.

27. Massa GG, Gys I, Op 't Eyndt A, et al. Evaluation of the FreeStyle® Libre Flash Glucose Monitoring System in Children and Adolescents with Type 1 Diabetes. Horm Res Paediatr. 2018;89(3):189-199.

28. Szadkowska A, Gawrecki A, Michalak A, et al. Flash Glucose Measurements in Children with Type 1 Diabetes in Real-Life Settings: To Trust or Not to Trust? Diabetes Technol Ther. 2018;20(1):17-24.

29. Adolfsson P, Nilsson S, Lindblad B. Continuous glucose monitoring system during physical exercise in adolescents with type 1 diabetes. Acta Paediatr. 2011;100:1603-1609.

30. Taleb N, Emami A, Suppere C, et al. Comparison of two continuous glucose monitoring systems, Dexcom G4 Platinum and Medtronic Paradigm Veo Enlite System, at rest and during exercise. Diabetes Tech Ther 2016;18:9:561-567.

31. Nerhus K, Rustad P, Sandberg S. Effect of ambient temperature on analytical performance of self-monitoring blood glucose systems. Diabetes Technol Ther. 2011;13:883–892.

32. Ricci F, Caprio F, Poscia A, et al. Toward continuous glucose monitoring with planar modified biosensors, microdialysis. Study of temperature, oxygen dependence and in vivo experiment. Biosens Bioelectron. 2007;22:2032–2039.

CHAPTER 3

General Conclusion

In summary, data from these studies support beneficial effects of exercise on metabolic control, weight management, lipid profile and glycemic excursions in youth with T1D.

In particular, frequency of physical activity on a daily basis resulted superior to the amount of time spent physically active (hours/week) in improving metabolic outcomes. In both the first and the second studies, regular physical activity correlated with a lower A1c level. Moreover, glycemic excursions evaluated by 1,5-anhydroglucitol in the first study and by 3-day masked CGM values in the second study, showed a positive association between regular exercise and lower glycemic fluctuations. Furthermore, in the second study, higher exercise energy expenditure rates were not associated with an incraesed percentage of hypoglycemic events. The fear of hypoglycemic events may induce an excess of snacks and sugars inatke that can interfere with positive effects related to physical activity.

In this study, results on dietary intakes were not different in youth more active: in particular, the percentage of carbs consumed was not higher in youth more physically active compared to their sedentary peers. This findings support the need for tailored approach to exercise management, with diabetes team suggesting personalized advices for insulin therapy and nutrition management.

New technologies like CGM systems may support families, patients and caregivers in optimizing insulin tehrapy to achieve a better metabolic control. In the third study, performance of the Flash Glucose Monitoring (isCGM) was tested in everydaylife and during moderate-intense physical activity. Indeed, glycemic excursion possibly associated with exercise may reduce the accuracy of the system. Results demonstrated a good accuracy of the isCGM both during exercise and everyday life, and no adverse effects occurred during the sensor wear period.

Based on results from these studies and in agreement with previous reports, regular physical activity should be supported starting from childhood, in order to prevent early cardiovascular complications.

Management of physical activity remain challenging in pediatric patients, due to the fear of hypoglycemic events and the need for insulin and dietary modifications. Sensor technologies may contribute in implementing physical activity among the youngest with T1D allowing timely interventions to either prevent or rapidly recognize and treat hypoglycemic episodes.

CONFERENCE PROCEEDING

Study A: Physical activity (PA) in youth with type 1 diabetes (T1D): variable impact on metabolic outcomes, has been accpeted for Oral Poster Tour at the ISPAD Annual Conference, 23-26 October 2016, Valencia.

Study B: Exercise Energy Expendityre in Youth with Type 1 Diabetes Favorably relates to Glycemia, has been accepted as Oral Poster at the Annual ADA Conference, 2017 San Diego.

Study C: Performance of the Flash Glucose Monitoring System during Exercise in Youth with Type 1 Diabetes, has been accepted as Oral Poster at the ISPAD Annual Conference, 18-21 October 2017, Innsbruck and as full paper for publication in the journal Diabetes Research and Clinical Practice.

ACKNOWLEDGMENTS

The author is thankful to all the families for their participation and enthusiasm. The author would like to acknowledge the contributions of the nurses of the pediatric department.