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Review Article

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Type 1 Diabetes and Physical Activity in Children and Adolescents

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Abstract

The diagnosis of type 1 diabetes (T1D) often occurs in childhood; age and maturation of that patient come with elevated risk of developing microvacular complications and cardiac disease. Insulin treatment, diet control and physical activity are incorporated in T1D treatment, and childhood should be a time at which good diabetes control habits should be developed. Exercise clearly offers many health and psychological benefits, improves body composition, insulin sensitivity, glycemic control and quality of life. Unfortunately, T1D adolescents often do not achieve the recommended physical activity level and are sometimes less active than healthy adolescents. A clear statement about expected beneficial effects is required in order to encourage and to provide opportunities for engaging in physical activity since childhood fosters the maintenance of an active lifestyle in adulthood. This review highlights the beneficial effects of physical activity in T1D children and adolescents and provides some guidance on how physical activity should be managed in this patient population.

Keywords: Exercise; Type 1 diabetes; Children; Adolescents; Adherence; Barriers; Exercise intensity

Abbreviations: PA: Physical Activity; ATP: Adenosine Triphosphate; T1D: Type 1 Diabetes or Type 1 Diabetes Patient; GLUT 4: Glucose Transporters; HbA_{1c}: A1c Glycated hemoglobin; HDL-C: High-Density-Lipoprotein-Cholesterol; LDL-C: Low Density Lipoprotein-Cholesterol; PWC_{170}: Physical Working Capacity 170; VO_2: Oxygen consumption

Introduction

Type 1 diabetes (T1D) is a form of diabetes that results from autoimmune destruction of insulin-producing beta cells of the pancreas. This insulin deficiency once quickly caused death in children, but technological advances in insulin therapy and diabetes management tools now allow for a near full life expectancy with dramatically improved patient quality of life. Nonetheless, poor diabetes management can lead to diabetes-related complications and childhood should be a time in which good diabetes control habits should be developed. Since the diagnosis of type 1 diabetes (T1D) often occurs in childhood, age and maturation of that patient brings elevated risk of developing microvacular (diabetic retinopathy, nephropathy, and neuropathy) and macrovascular complications. Therefore, childhood represents a very good timeframe to focus on the prevention of micro- and macrovascular disease through good diabetes management.

Type 1 diabetes treatment is based on exogenous insulin injection, diet control and regular physical activity. A basal insulin concentration is needed throughout the day, but insulin boluses are also required at mealtimes and for corrections for hyperglycemia. However, other parameters, such as physical activity, illness and stress levels have to be constantly monitored to determine the appropriate insulin dosage. It is generally well accepted that regular activity along with a good diet are helpful in maintaining glycemic control, since very sedentary behavior is associated with poor control [1].

Diet recommendations are relatively straight forward for children and adolescents with T1D, and are similar to the general dietary guidelines for healthy children [2]. When respected, this helps to avoid unbalanced and irregular carbohydrate intake. The aim of regular physical activity for youth with type 1 diabetes is to improve quality of life and to enhance both short-term and long-term health. Due to the possibility of worsening metabolic control during exercise (resulting in either hypoglycemia or hyperglycemia), guidelines regarding metabolic control, blood glucose monitoring and food intake for physical activity must be followed. Some review papers have focused on glycemic variations with exercise and on practical considerations for the clinical management of type 1 diabetes in athletic youth [1,3-7]. Other reviews previously presented exercise training induced benefits on glycemic control in both adulthood and childhood [8,9] but not on different other important health related parameters. The purpose of this review is to focus on the short- and long-term effects of different training models in youth with T1D and to understand which mechanisms are involved. This review will also focus on physical activity rate in young T1D and analyze what would limit their adherence, in order to improve its promotion.

Beneficial Effects of a Regular Physical Activity

In T1D management, physical activity, glycemic control, insulin treatment and diet control represent the three cornerstones of care. Physical activity by itself induces health-related beneficial effects and improves patient quality of life.

Beneficial effects of regular exercise in young patients with T1D

A number of studies of TD1 children or adolescent have shown that pure endurance or mixed (endurance and strength exercise) training have beneficial effects in type 1 diabetes. After 3 to 9 months, training has beneficial effects on quality of life (assessed using a questionnaire) [10-13], endurance capacity (4 to 34% improvement) [11,14-24],

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body composition – fat to muscle mass ratio [10,15,16,21,22,25], lipid profile – fraction of 'good' (HDL-C) and 'bad' cholesterol (LDL-C) [10,21,26,27], tissue insulin sensitivity – insulin receptor efficiency [22], and finally, but not universally observed, glycemic control (as reflected by improvement of long term indicator HbA_{1c}, or short and middle term indicators such as fructosamine, glycemia/glycosuria) [16,18,20,21,26-30] (Table 1 data included as supplementary). It is worth noting that lipid profile and fructosamine improvement can be observed after only 2 weeks of intensive physical activity in youth with T1D [27].

Importantly, some studies in young patients with T1D report training-induced improvement in bone mineral density [25], vascular function (vasomotricity) [14] and antioxidant capacity [31].

These results from longitudinal studies are in accordance with cross-sectional studies, which underline significant correlations between different health indicators and the amount of physical activity performed as assessed by accelerometer and/or questionnaires [32-44].

However, since the beneficial effects of exercise training are not systematically observed (Table 1 data included as supplementary), it seems relevant to examine further the underlying mechanisms involved in order to adapt and optimize the training prescription.

Physical fitness improvement and underlying mechanisms: All studies except two, show that aerobic fitness, evaluated with maximal oxygen uptake (VO_2max) or PWC_{170} (power output corresponding to 170 bpm during an incremental test), is improved when the training lasts for at least 3 months and is supervised [28,45]. The aerobic capacity improvement could be linked to different parameters like heart volume [19] and muscle mass improvement [10] following training. The increase of muscle aerobic enzyme maximal activity could also be involved, but to date, data are just available in the adult T1D population [46-48].

Insulin sensitivity and underlying mechanisms: Only a few papers have focused on the effects of regular exercise on tissue insulin sensitivity in T1D children, but results are encouraging [22,24]. Training-induced improvements in insulin sensitivity may be particularly important in children and adolescents, since puberty is known to increase insulin resistance, especially in girls [49,50]. The stimulating effect of insulin on glucose metabolism, measured during hyperinsulinemic euglycemic clamp, is reduced by 33 to 42% in T1D adolescent compared to prepubescent and adult T1D [49]. It is also worth noting that in T1D, 2 weeks of intense activity decreases circulating ghrelin levels [51], while more prolonged training (6 months) attenuates the puberty induced increase in leptin levels [10]. Ghrelin and leptin are both insulin resistance indicators/factors.

There are likely multiple underlying mechanisms for training induced improvements in insulin sensitivity in youth with T1D. A first explanation could be the training-induced improvement in body composition. The training-induced lean mass gain observed in youth with T1D [10,21,22,25] is likely representative of muscle mass gain, which may be linked to improvement in peripheral insulin sensitivity. Indeed, skeletal muscle represents the main insulin stimulated glucose utilization site, even at rest (consumption of 54.4 kJ/kg/j vs. 18.8 kJ/kg/j for adipose tissue) [52-54]. In addition, muscle is quantitatively the main tissue involved in lipid metabolism [55,56]. Muscle energy expenditure during each training session could lead to fat mass decrease [57], that has already been observed in a few studies of youth with T1D [15,21] (Table 1 data included as supplementary). The fat mass decrease could induce improvement in insulin resistance since when adipose tissue mass is in excess, it secretes more molecules (adipocytokines) like leptin, that increases insulin resistance [58]. A 6-month combined training (aerobic and muscle strength) was able to limit fat mass increase, and also leptin levels, in T1D adolescents who were in their later stages of puberty [10]. In this context, it seems reasonable to combine different training models that would at the same time, also help to avoid monotony and keep young T1D patients motivated. As such, the exercise prescription could be as follows:

Muscle strength training activities [10,21], such as weight bearing, weight activities, like jumping, push-up and sit-ups, step climbing machines, rope climbing, and rock climbing [10,25] are all favorable for muscle mass gain [59], which should promote increased insulin sensitivity.

Aerobic exercise activities like running or swimming [15], which promote increased energy expenditure, increase aerobic fitness and increase lipid oxidation – they can be planed as continuous and moderate intensity (example : 30min at 50% VO_2 peak), or as high intensity intermittent exercise (example : 30sec at 100%VO_2 peak/30sec recovery). This kind of intermittent activity has been shown to improve insulin sensitivity in healthy subjects [60]. Moreover, intermittent exercise is comparable to continuous exercise (at the same total mechanic work) according to the total energy expenditure during exercise and lipid oxidation level during recovery [61]. Intermittent exercise also tends to represent the type of activities that children prefer according to Bailey et al. [62].

Training induced structural and functional skeletal muscle adaptations could be responsible for the enhancement of peripheral insulin sensitivity. For example, it has been shown in healthy adults and in adults with Type 2 diabetes that physical training improves glucose delivery to muscle via an enhanced muscle vascularization (increased muscle capillaries number, and increased local blood flow) [63]. It also has been shown that maximal capacity for glucose utilization is improved via increased glucose transporter (GLUT4) number [63] and/or maximal activity of the enzymes involved in blood glucose catabolism (i.e. hexokinase), or muscle glucose disposal (i.e. glycogen synthase) [63]. In T1D adult, the same improvement is observed for muscle capillarization [46,47] and maximal activity of enzymes involved in aerobic glucose disposal (citrate synthase) [46,48] (Succinate dehydrogenase) [47,48] after 2 to 4 months of aerobic training.

Glycemic control improvement and underlying mechanisms: In general, regular exercise improves insulin sensitivity in youth with T1D. However, it should be noted that the putative improvement in exercise-induced peripheral insulin sensitivity in young patients with T1D [22,24] is not always coincidental with the improvement of the following parameters (usually linked to improved insulin sensitivity) : daily insulin dose decrease [10,11,22,24,51,64] and glycemic control improvement [10-12,17,22-24,31,51,64,65] (Table 1 data included as supplementary). This could be linked to a difficult management of exercise glycemic variations influenced by multiple factors (delay between last meal and insulin injection, insulin absorption, initial glycemia, time of the day, etc.) [1]. Because of these glycemic variations and the fear of hypoglycemia, patients might consume carbohydrates in excess [66] or they may decrease their insulin dose far too aggressively, thereby eliminating the potential improvements in glucose disposal. This can explain why several studies show significant decrements in total daily insulin dose but no improvement in glycemic control [13,45]. This behavior might induce hyperglycemia, and hence even impair glycemic control [17,45].

On the contrary, when young patients with T1D benefit from recommendations about diet control, insulin therapy and glucose monitoring in addition to the training program, glycemic control (HbA_{1c} or fructosamine) can significantly improve [20] and this even after only two weeks of high intensity physical activity [27,29].

The effects of chronic exercise on glycemic control in patients (age from 8 to 48 years old) with T1D have been recently studied in a meta-analysis by Tonoli [8]. In prepubescent children (average age 12.1 years old) [17,65], this meta-analysis does not highlight any glycemic improvement with aerobic training. However, chronic aerobic exercise significantly decreased HbA_{1c} levels in a group of 61 adolescents (average age 13.8 years old) with a poor glycemic control (from studies : [16,20,28-30]). Combined training (aerobic and muscle strength exercise) (based on [10,13,21,67]) slightly decreased HbA_{1c} levels (Best improvement: from 7.72 to 6.76) in T1D adolescents (average age 17.2 years old). When both young and adult T1D results were analyzed together, beneficial effects were found: exercise training-induced glycemic control improvement could be observed when training lasted at least 3 months, including 1 to 3 sessions a week, and when diet control and insulin therapy recommendations were added. Glycemic control improved more after training when initial glycemic control was poor ($HbA_{1c} \geq 8\%$).

Lipid profile improvement and underlying mechanisms: According to the studies in table 1 (Data included as supplementary), lipid profile (especially HDL-C / LDL-C ratio) improves more when training session frequency is increased [26], and when the glycemic control is improved at the same time [21,26,27]. When glycemic control is not improved with training, most studies [10,24,31,45,64], except one [68], do not detect any improvement in LDL-C and/or HDL-C. This result is in accordance with the fact that glycemic control and lipid profile are often highly correlated health parameters in T1D [69-74]. The link between lipid profile and glycemic control, and their parallel improvement induced by exercise training, could be explained by the negative impact of insulin deficiency and excessive glycosylation (observed in case of high HbA_{1c} level) on LDL degradation and removal, hence increasing LDL-C levels [75]. Moreover, lipolysis, also accentuated in case of insulin deficiency and insulin resistance, increases free fatty acid and serum glycerol, which could in turn impair glucose metabolism through the Randle cycle [2].

Training induced beneficial effects on lipid profile and glycemic control, could eventually diminish the chances to develop vascular complications. According to Kriska et al. [76], an improved spontaneous physical activity between 14 and 17 years old lowers nephropathy and neuropathy prevalence in adults T1D.

Finally, and perhaps most importantly, physical exercise is also very important for enhancing the quality of life (QOL) in young T1D [10-13], especially during psychological instable periods such as puberty.

Adherence and limits to physical activity in young patients with T1D

Because of the numerous beneficial effects on physical and psychological health (see section 1), exercise is clearly highly recommended in young T1D. Nonetheless, some evidence exists to suggest that participation in exercise and physical activity is often suboptimal.

Physical activity engagement in young patients with T1D

As shown in table 2, T1D adolescents often do not achieve the recommended physical activity level (often set at 60 min a day and including moderate to high intensity exercise) and they are often even less active than their non-diabetic healthy peers. This relative inactivity is especially observed in girls and this gender difference is observed in early childhood (i.e. as early as 6-7 years of age [77].

In order to motivate patients who are not involved in physical activity, it is important to know why they choose not to participate in regular activity. A study by Faulkner et al. [12] showed that adolescents with T1D exercising more than 10 min a day don't have any negative or limiting feelings about physical activity (PA) (evaluated with Diabetes Social Support Questionnaire-Family Version, DSSQ-Family). Also, the frequency of exercise sessions, longer than 30 min, is correlated to the feeling of important family support [12,78].

A Canadian investigation from Quebec [79] conducted in 100 T1D adults showed that the 4 main limitations for exercising were : fear of hypoglycemia (the highest barrier), work schedule, loss of control over diabetes and low levels of fitness. However, further studies are needed in large samples of children and adolescents with T1D in order to determine what are the main barriers to physical activity participation in this age group. It is possible that, like in adults, a fear of hypoglycemia and low levels of fitness could represent strong barriers.

Two possible barriers to physical activity in youth with T1D: Exercise-induced hypoglycemia and low fitness levels

Exercise induced hypoglycemia: Most studies about T1D children and adolescents acknowledge the fact that blood glucose levels decrease during moderate intensity continuous exercise (Table 3). Thus, the fear of hypoglycemia could become a major barrier to physical activity participation in this population. However, when T1D children and adolescents stop their insulin pump basal rate altogether [80], or decrease it by 20% [81] or 50% [82] during a moderate intensity continuous exercise, hypoglycemia occurrence risk is lowered during the activity [80], but also during the following night [81]. Importantly, if exercise is performed at the same time as peak insulin (fast acting) action or during insulin bolus action, it is recommended to anticipate the activity and to decrease the insulin dose at the meal before exercise from 30 to 100%, depending on the duration and intensity of the activity [83,84]. However, the reduction in basal insulin delivery could also enhance hyperglycemia events in early recovery [80] and during the subsequent evening [81] (Table 3). The timing of basal insulin reduction should be about 60-90 minutes before the start of exercise to allow for circulating insulin levels to already be diminished by the time exercise starts [85] .

An alternative to insulin modification, to prevent hypoglycemia, is to vary the type of exercise performed (duration, intensity, modality). It has been shown in T1D adults that the addition of sprints before (45 min muscle strength exercise [86]), during (sprint: 4 sec every 2 min [87,88], or 15 sec every 2 min [89]) or after (10 sec once [90]) moderate intensity endurance exercise (40 to 60 % of maximal aerobic power during 20 to 45 min) attenuates the drop in blood glucose, or the occurrence of subsequent hypoglycemia, compared to when just moderate intensity exercise is performed. In young patients with T1D, only one study compared the effects of high intensity intermittent exercise (6 times 3 min at 70% of maximal aerobic power with 1.5 min recovery) with moderate intensity exercise (60 min at 40% of maximal aerobic power) [91]. The authors found that the former exercise protects against late-onset hypoglycemia (Table 3). This positive effect of adding sprints or high-intensity exercise might be the result of increased stress hormones secreted (epinephrine or cortisol) [91].

Authors	T1D subjects	Healthy population comparison	Physical level evaluation methods	Physical activity level of young T1D
[101]	6-20 yo	Yes	Physical activity evaluation by the mother according to 3 levels	Physical activity decrease with age, more important in T1D compared to healthy subjects.
[102]	Children and adolescents	No	Behaviour questionnaire	Behaviour with physical activity more negative in T1D adolescents compared to T1D children.
[103]	10-15 yo	Yes	Descriptive questionnaire. Not quantitative	T1D are more involved in light intensity activities compared to control who prefer competition.
[104]	6-18 yo	Yes	Descriptive questionnaire. Not quantitative	T1D have better adherence to physical activity in gym compared to healthy subjects (40% vs. 27%).
[11]				Patients with the best adherence to training program are the youngest, with a better glycemic control.
[105]	♂ 10.2-16.5yo	Yes	Physical activity evaluation by the parents according to 5 levels	No significant difference compared to healthy controls.
[106]	N=142; 6 -18 yo	Yes (n=97 BMI matched)	No indication about the Questionnaire used	No difference for the time dedicated to sport at school or in competition. No difference for the type of physical activity during free time (ball games very present, but time dedicated to them > inT1D (6.8 h/week vs. 4.6 h/week), in ♀or ♂. Total time spent in a week for physical activity > in T1D.
[107]	Children and adolescent <18yo	No	Descriptive questionnaire. Not quantitative filled out by parents	33% are involved in 3 different physical activities or more in a week, 31% in only one, and 15% are sedentary.
[108]	♀ 12-19 yo (Tanner stage 2 -5)	Yes	Uniaxisaccelerometer	T1D are less involved in physical activity (464 ± 123 vs. 523 ± 138 counts.min^{-1}.j^{-1}, P = 0.06) and are more sedentary (443 ± 60 vs. 390 ± 73 min.j^{-1}, P< 0.005) vs. healthy.
[90]	N=17 ♂ prepubescent; 8.5-13yo	Yes	Questionnaire	No quantitative difference of weekly physical activity (gym, leisure, school) between T1D and healthy.
[27]	N=23251; 3-18 yo	No	Questionnaire about physical activity (> 30min) frequence a week	Physical activity frequency in a week represented 0 to 9 times /week 44.7% of patients are inactive, 37% are involved 1-2 times/week, and 18.3% >3 times/week. Increased frequency in older subjects, and in ♂compared to ♀
[35]	N=138 children and adolescents (5.9-20yo)	Yes	Questionnaire	Physical activity score in moderate and high intensity < in T1D vs. healthy Level and frequency of physical activity in moderate to high intensity, frequency of PA < in ♀ vs. ♂
[29]	N=2269; 11-18 yo	No	Questionnaire	Older patients and ♀ have less physical activity.
[109]	N=240 children 6-10 yo and 483 T1D adolescents from 11 to 19 yo	No	Questionnaire	54% of patients don't follow recommendations of 60min/day of moderate to high intensity physical activity. ♀ less active than ♂ during childhood and adolescence
[110]	N=37 children and adolescents	No	HR recordings	Moderate to high intensity cumulated physical activity = 53.6 min/day in average (< recommendations of 60min/day) Only a few high intensity physical activity (8.3 min/day in average) Physical activities are mostly ≤5min
[37]	N=32; 6-17 yo	Yes	Accelerometer	Total amount of physical activity (Counts) at moderate to high intensity < in T1D vs. healthy
[32]	N=203 ♀ 11-19 yo	No	Questionnaire	Physical activity for at least 60min/day for only 2.7 days in average during the last week, and 3.1 days in average during an usual week.
[111]	N=384; 10-20 yo	Yes (healthy and T2D)	Week-to-a-page diary of physical activity and electronic monitoring over 3 days (report of sessions >30min of physical activity)	No difference (slight decrease) of physical activity between T1D and healthy. 60% (in average) of T1D have < 1 session of 30min of high intensity physical activity /day and 20% have < 2 sessions of moderate to high intensity /day (whereas international recommendations are 2 sessions of moderate to high intensity of physical activity a day).
[112]	N=48; 5-18 ans	Yes	Accelerometer	Total physical activity decreased in T1D vs. healthy. Only 38.5% of T1D and 60.4% of healthy matched recommendations of 60min/day of moderate to high intensity physical activity.
[113]	N=129; children	Yes	Questionnaire by phone	Physical activity comparable between T1D and healthy. T1D more involved in team sport.
[31]	N=19 ♀; <18.5 yo; Tanner stages 4-5	Yes	Questionnaire	Tendancy (NS) for a lower physical activity in gym in T1D (0.7h/week in average) vs. healthy (1.4h/week in average).
[34]	N=60; 8-16 yo	Yes	Accelerometer	No difference in physical activity nor intensity between T1D and healthy.
[72]	N=24 children < 7 yo	Yes	Accelerometer and HR recording	T1D less active than healthy, present 16min less in moderate to high intensity physical activity. Total physical activity (counts/day and min/day) and time spent in moderate to high intensity physical activity < in ♀ vs. ♂.
[98]	N=35 children prepubescent/peri-pubescent	Yes	Accelerometer and questionnaire	Total physical activity measured with accelerometer < in T1D vs. healthy whereas physical activity estimated with questionnaire comparable in both groups.
[91]	N=106; 8-18 yo	Yes	Questionnaire	No difference between T1D and healthy.

♀: Girls; ♂: Boys; NS: Not Significant

Table 2: Physical activity level in young T1D.

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Authors	T1D subjects included	Exercise description	Exercise time (vs. meal & insulin)	Glucose evolution during exercise	Glucose evolution during recovery
Maximal graded exercise					
Continuous moderate intensity exercise					
[77]	N=10 ; 10-19 yo Age : 15.7 ± 3 years HbA1c : < 10% With insulin pump	Continuous moderate intensity exercise, 40 to 45 min at 60% VO_2 max on ergocycle 2 exercise conditions, in randomized order, staggered by 7days : with basal insulin rate reduced by 50% with the pump suspended basal. Back to normal basal rate 5min after exercise No physical activity in the previous 24h	2h after standardized breakfast and usual insulin bolus, not reduced (in order to mimic conditions of an unplaned exercise) Glucide intake (20g) before exercise and 15 min after exercise. Glycemia before exercise between 1 and 3 g/L, with no ketosis	↓ glycemia in average of 29% (2 hypoglycemia i.e. <70mg/dL) and 35.5% (2 hypoglycemia) for exercise with 50% basal rate, and exercise with suspended basal rate (no significant difference between both conditions) (and no significant difference in cortisol, GH, NE) Insulin concentration ↑ at the beginning of exercise (until 20min) then ↓ back to initial values at the end of exercise, and continues to ↓ until 45min recovery (no significant difference between both conditions) Subjects with hypoglycemia during exercise started it with <glycemia level and > insulin concentration vs. other subjects	Glycemia goes back to initial values after 45min recovery Data from continuous glucose sensor : Every subject had 1 to 3 delayed hypoglycemia 1h after each exercise (after 2.5h to 12h), not always symptomatic. 9 and 6 delayed hypoglycemia after 50% basal rate and suspended basal rate respectively (no difference)
[114] [115]	N=50; 11-17yo	Exercise : 4 sessions of 15 min exercise on treadmill at 140 bpm, with 5min recovery in between (140bpm ≈ 55%VO_2 max) Comparison between a sedentary and exercising day staggered by 1 to 4 weeks in randomized order (with meal and same insulin dose)	Exercise at 4pm-5pm Same insulin treatment as usual Glycemia before exercise between 1 and 2g/L If glycemia< 0.60 g/L during exercise or during the night →glucide intake	22% of patients had a hypoglycemic episode	Averaged glycemia from 10pm to 6am < after the afternoon with exercise vs. sedentary Nocturnal hypoglycemia occurrence frequency > the next night after exercise vs. sedentary No nocturnal hypoglycemia the sedentary day when glycemia before bedtime >1.30g/L No significant difference related to counterregulatory hormones (GH, E, NE, Cortisol, Glucagon) during the night after exercise vs. sedentary
[75]	N=49 ; 8-17 yo ; with insulin pump	2 days of exercise including one with suspended insulin basal rate during exercise and the 45min recovery, staggered by 6 to 36days in randomized order (with the same meal)	Glycemia before exercise between 1.2 and 2g/L	Hypoglycemia (<0.7g/L) during exercise are less frequent when basal insulin rate is suspended (16% vs. 43%) ↓ glycemia during exercise < when basal rate suspended (-28% vs -41%)	After 45min of recovery : Hyperglycemia (↑20% compared to value at the end of exercise, or > 2g/L) more frequent when insulin basal rate is suspended (27% vs. 4%) No abnormal ketonemia
[116]	N=10 adolescents; 15.2 yo in average ; 6.9% HbA1c in average		Exercise at around 3pm Basal insulin rate maintained during exercise	Averaged glycemia before exercise : 1.62g/L Glycemia ↓ by 52% in average during exercise	
[76]	N=16 ; 10-17yo ; HbA1c<10% ; average =7.5% ; with insulin pump	3 conditions (randomized order) : 2.5mg oral Terbutaline at bedtime ; 20% basal insulin rate reduction ; no modification of usual treatment (=control) Staggered by at least 72h	Standardized lunch and normal insulin bolus Exercise at 4pm (glycemia before exercise between 1.2 and 2g/L) Suspended basal insulin rate during exercise then decreased by 50% during the next 45min after exercise Glucide snack if glycemia< 0.7g/L during the 5 min recovery periods and during the following recovery		Averaged glycemia at midnight : 1.88g/L after terbutaline ; 1.72g/L after basal insulin reduction < vs. 1.27g/L control Terbutaline : No more nocturnal hypoglycemia but more frequent hyperglycemia >2.5g/L vs. control Basal insulin rate decrease : less glycemia <0.8 and 0.7 g/L but more >2.5g/L vs. control

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[117]	N=9 ; 16 yo in average ; average HbA$_{1c}$ 7.8%	1 exercise day (45min at 95% of second lactic threshold = 54.9 ± 2.8% VO$_2$ peak on ergocycle) and 1 sedentary day, staggered by 4 weeks, in a randomized order	Exercise at 4pm Morning : usual breakfast and usual rapid acting insulin injection, but no intermediate/long acting. From 11am : iv insulin infusion at an usual basal rate (=50% of total insulin dose /day) At noon : standardized meal + usual insulin bolus Comparable insulin concentration between both days Comparable previous 24h diet 48h before : no hypoglycemia ; 24h before : no exercise ♀ : in the middle of menstrual cycle follicular phase	iv infused glucose in order to maintain euglycemia (during 18h) : glucose infusion rate in order to maintain glycemia> during exercise	Glucose infusion rate in order to maintain glycemia > at the beginning of recovery after exercise (90min recovery) and again 7-11h after exercise (=early or delayed hypoglycemia risk) No difference in counterregulatory hormones level between exercise and sedentary days except during early recovery : peaks E, NE, GH, Cortisol > (→ compromised nocturnal hypoglycemia counterregulatory response after exercise)
High intensity intermittent exercise					
[118]	N=12 ; 12.2-15.8 yo ; Tanner stages 2-4; HbA1c 6.5-10.5%	10 bouts of 2min at 80% VO$_2$ peak with 1 minute recovery between each (on ergocycle)	In the norning, after light breakfast Glycemia maintained between 0.9 and 1.10 g/L during 90min before exercise by infusing insulin (clamp) then insulin rate infusion maintained at the same level during exercise.	Glucose iv infusion in order to maintain euglycemia during exercise : average infusion rate = 1.5 mg/kg/min for 90 min before exercise, 1.7 mg/kg/min at the end of exercise, and 1.7 mg/kg/min after 30min recovery	
Moderate intensity continuous vs. High intensity intermittent exercise					
[86]	N=12 ; 14-19 yo, Tanner stages 4-5 ; (♀ and ♂) HbA$_{1c}$ 6.6-9.6% Actives 2 adolescents excluded from the analysis because of a nocturnal hypoglycemia the night before continuous exercise	Maximal graded test on ergocycle	2h in average after breakfast Insulin dose according to subject's habits 3 exercises performed on 3 consecutive days, always in the same order : graded test, continuous, and intermittent	↓ glycemia (-1,5 mM in average) (final value = 11.2 mM in average) *No hypoglycemic episode* ↑↑E (*10) and NE (*8)	
		Continuous 60min at 40% of VO$_2$ max on ergocyle		↓↓ glycemia (-4,1 mM in average) (final value = 11.2 mM in average) *No hypoglycemic episode* ↑E (*5) et NE (*3)	
		Intermittent exercise on ergocycle : 5min warm-up, and 6 times 3min at 70% of VO$_2$ max interspersed with 1.5min active recovery (light resistance cycling), and 5 min resting time		↓ glycemia (-2.7 mM in average) (final value = 11.4 mM in average) *No hypoglycemic episode* ↑↑E (*8) and NE (*7) ↑ more important for cortisol vs. Other exercises	
Everyday life exercises					
[119]	n=30 ; 12-18 yo; HbA1c < 12%	Parallel between accelerometer data and continuous intersticial glucose concentration measurement (subcutaneous sensor)		Hyperglycemia rebound after exercise induced glycemia decrease. Hypothesis : This rebound could be linked to : SNS effect during physical activity, a strategy before physical activity in order to prevent exercise induced hypoglycemia, or an excessive treatment for low glycemia.	

↓: Significant Decrease ; ↑: Significant Increase ; Δ: Significant Variation; ♀: Girl; ♂: Boy ; E: Epinephrine; NE: Norepinephrine GH: Growth Hormone ; VO$_2$: Oxygen Comsumption; HbA1c: A1 Glycated Hemoglobin ; NS: Not Significant

In blue: studies about the effect of insulin dose variation on exercise glycemia; In green: results about the effect of glycemia variation on performance; in orange: associated hormones response

Table 3: Evolution of blood and plasma glucose concentration in T1D according to different exercise type.

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It is important to note that hypoglycemia is not the only concern with exercise for patients with T1D. Indeed, hyperglycemia can occur, particularly if blood insulin levels are insufficient during the activity, or if very high intensity exercise is performed [82,92,93].

Physical fitness impairment in young T1D: It has recently been shown in 304 young T1D that physical activity level and self-perceived physical fitness are significantly related [94]. In addition, literature suggests that aerobic fitness (measured or estimated with maximal incremental test or submaximal test respectively) decreases with age in young T1D. So in T1D prepubescent boys, aerobic fitness is reported to be preserved [95,96] whereas it might already be declined in girls at the same age [96].

In adolescents, aerobic fitness is often impaired in boys [19,96-99] and girls [96,98-100] compared to healthy peers. This impairment in aerobic fitness is even more pronounced when diabetes control is poor [39,50,96,97,101-103]. Only 3 studies [21,50,91] have shown that physical fitness is normal in T1D adolescents, perhaps because physical activity levels were also high. Also, T1D girls presented lower values compared to T1D boys, but this gender difference was not observed in healthy adolescents [50]. This deterioration in the fitness of girls could partly be explained by the fat mass gain that occurs during puberty [37,104,121-125].

Conclusion

Physical activity is challenging for the child with T1D. The child and his or her family member, teacher, coach and friends need to be aware of the basic strategies to prevent hypoglycemia and maintain reasonable glucose control. Initial glycemia, time of the last rapid acting insulin injection, injection site, diet, time of the day, exercise type, etc… are all factors to be considered in order to anticipate the hypoglycemic or hyperglycemic effect of exercise (Figure 2). Moreover, the individual response to exercise can be different for each patient and sometimes even within a patient, thus making general recommendations around exercise and blood glucose management strategies is difficult. Therefore, it would be interesting in future investigations to study different individualized responses to exercise, while taking into consideration the previously shown parameters that are established to influence glucose control. Thus, it could be possible to better anticipate glycemic variations during exercise and recovery. These tests could be taken into consideration in the patient's therapeutic approach.

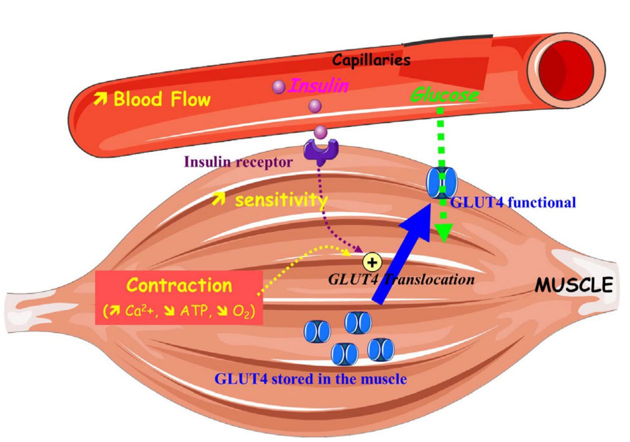

Figure 1: Physiological mechanisms of hypoglycemia during exercise.

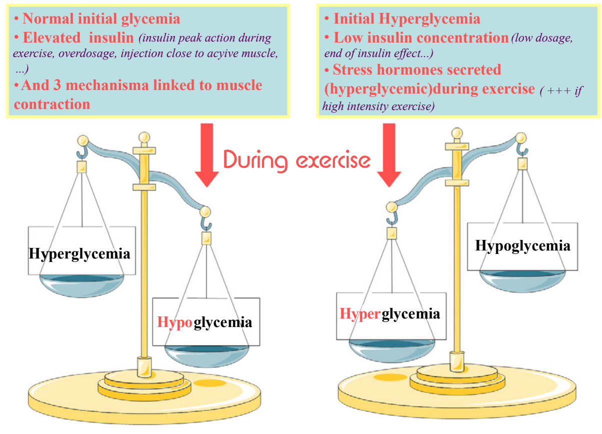

Figure 2: Hypoglycemic or hyperglycemic effect during exercise?

Glycemic variations during exercise do not mean that regular exercise is not beneficial. Indeed after each exercise session, insulin receptor sensitivity improves. Moreover, regular exercise allows for the continued increase muscle mass, and muscle tissue is the single greatest "consumer" of glucose, even at rest. So physical activity, through muscle mass increase can contribute to improve glycemic control. Moreover, exercise clearly offers many health and psychological benefits. Unfortunately, T1D patients do not seem to be involved enough in exercising to reach the daily recommendations. Further studies would help to specify the barriers to physical activity, especially in young T1D girls. This information could be useful to help young patients and their families with improved self-management programs.

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