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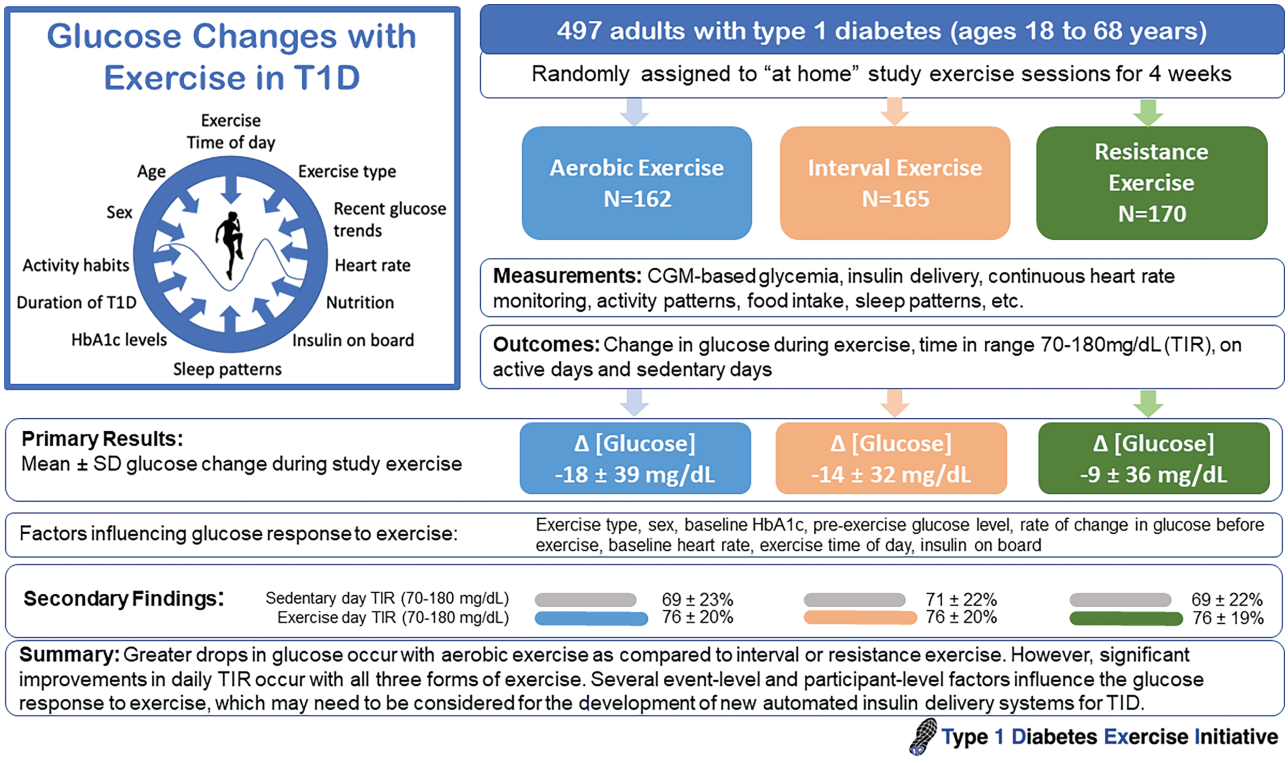

ARTICLE HIGHLIGHTS

- Glucose drop during structured at-home exercise was greatest with aerobic exercise, followed by high-intensity interval exercise and resistance exercise, in adults with type 1 diabetes.
- In addition to exercise type, factors that influenced glucose change during exercise included pre-exercise glucose concentration, sex, baseline HbA_{1c} level, pre-exercise heart rate, exercise time of day, and on-board insulin level.
- Structured aerobic, interval, and resistance exercise increased daily time in range by 6% in adults with type 1 diabetes who had good glycemic control, but they also increased 24-h time below range, even in those using hybrid closed-loop insulin delivery systems.

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Examining the Acute Glycemic Effects of Different Types of Structured Exercise Sessions in Type 1 Diabetes in a Real-World Setting: The Type 1 Diabetes and Exercise Initiative (T1DEXI)

https://doi.org/10.2337/dc22-1721

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OBJECTIVE

Maintenance of glycemic control during and after exercise remains a major challenge for individuals with type 1 diabetes. Glycemic responses to exercise may differ by exercise type (aerobic, interval, or resistance), and the effect of activity type on glycemic control after exercise remains unclear.

RESEARCH DESIGN AND METHODS

The Type 1 Diabetes Exercise Initiative (T1DEXI) was a real-world study of at-home exercise. Adult participants were randomly assigned to complete six structured aerobic, interval, or resistance exercise sessions over 4 weeks. Participants self-reported study and nonstudy exercise, food intake, and insulin dosing (multiple daily injection [MDI] users) using a custom smart phone application and provided pump (pump users), heart rate, and continuous glucose monitoring data.

RESULTS

A total of 497 adults with type 1 diabetes (mean age ± SD 37 ± 14 years; mean HbA_{1c} ± SD 6.6 ± 0.8% [49 ± 8.7 mmol/mol]) assigned to structured aerobic (n = 162), interval (n = 165), or resistance (n = 170) exercise were analyzed. The mean (± SD) change in glucose during assigned exercise was −18 ± 39, −14 ± 32, and −9 ± 36 mg/dL for aerobic, interval, and resistance, respectively ($P < 0.001$), with similar results for closed-loop, standard pump, and MDI users. Time in range 70–180 mg/dL (3.9–10.0 mmol/L) was higher during the 24 h after study exercise when compared with days without exercise (mean ± SD 76 ± 20% vs. 70 ± 23%; $P < 0.001$).

CONCLUSIONS

Adults with type 1 diabetes experienced the largest drop in glucose level with aerobic exercise, followed by interval and resistance exercise, regardless of insulin delivery modality. Even in adults with well-controlled type 1 diabetes, days with structured exercise sessions contributed to clinically meaningful improvement in glucose time in range but may have slightly increased time below range.

Regular exercise is recommended for adults living with type 1 diabetes for a variety of health and fitness reasons (1,2). However, only ∼30% of adults with type 1 diabetes

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*A complete list of the T1DEXI Study Group can be found in the Supplementary Material online.

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achieve the recommended 150 min per week of accumulated moderate- to vigorous-intensity exercise (3), with hypoglycemia identified as one of several barriers to engagement (4).

A single bout of exercise can promote a drop or rise in glucose level (5), although considerable interindividual variation in the acute glucose responses to aerobic (6,7) or anaerobic (8) exercise exists, even when exercise conditions are standardized in a laboratory environment. There are likely many factors that influence glycemic responses to exercise, such as exercise type, carbohydrate intake, onboard insulin level, and counterregulatory hormone levels. Our understanding of the magnitude of effect of these and other variables, such as sex, fitness level, insulin delivery modality, and recent glycemic control, remains unclear (9).

To provide needed data for developing new adult-specific type 1 diabetes exercise management guidelines and informing automated insulin delivery system algorithms, we conducted a large at-home observational study to examine acute effects of structured aerobic, high-intensity interval, and resistance exercise on glycemia, as measured by continuous glucose monitoring (CGM), across a range of patient characteristics.

RESEARCH DESIGN AND METHODS

Study Design and Population

Participants learned of this study through social media, diabetes interest groups, and endocrinology centers. An institutional review board approved the study, and electronic informed consent was obtained from each participant. Participants were U.S. residents age ≥18 years with type 1 diabetes for at least 2 years who were using a commercially approved hybrid closed-loop (HCL) system, a standard insulin pump, or multiple daily injections (MDIs) to administer insulin. Detailed eligibility criteria are listed in Supplementary Table 1.

Participants self-reported their diabetes history (recent HbA_{1c}, insulin delivery modality, and so on), hypoglycemia awareness (Clarke Hypoglycemia Awareness Questionnaire), sleep quality (Pittsburgh Sleep Quality Index), and physical activity patterns (International Physical Activity Questionnaire) via an online portal. Participants then completed a virtual visit to review the study protocol and set up study devices and smart phone applications.

Participants were randomly assigned to complete one of three video-guided exercises (aerobic, interval, or resistance) at home for a total of at least six sessions throughout a 4-week observational period. Study exercise assignment was stratified by insulin administration method (HCL, standard pump, or MDI), age group (18–25, 26–44, or 45–70 years), and sex. Study videos were 30 min in duration, including warm-up and cool-down periods that lasted ∼3 min each, and were designed to elicit a target heart rate based on exercise type: 70–80% of the age-predicted maximal heart rate (aerobic), up to 80–90% of age-predicted maximal (interval), or major muscle group fatigue after three sets of eight resistance-band repetitions (resistance). Participants were asked to complete study exercise sessions each week, with no restrictions on the time of day for exercise or frequency of sessions completed. Participants were also encouraged to continue their usual regimens of activity, nutrition, and insulin dosing for exercise and achieve ≥150 min of weekly physical activity, inclusive of the study exercise video sessions.

Participants used a study-developed, cloud-connected smartphone application (T1DEXI app) to enter information about study exercise and other personal physical activities, including work and chores (6). Activity entries included time, duration, activity type, self-reported exercise intensity rating, if activity was competitive, and timing since last meal. Self-reported food intake through the T1DEXI app included carbohydrate content and categorical (low/small, typical, or high/large) estimates of fat and protein content as well as meal size.

Participants used their personal Dexcom G6 CGM (San Diego, CA), or a blinded Dexcom G6 CGM if they did not use a personal Dexcom G6 CGM, as well as a Verily Study Watch (South San Francisco, CA) to collect continuous heart rate data. During study exercise, participants were asked to wear a Polar H10 chest strap heart rate system (Polar Electro Oy, Kempele, Finland) to gauge their relative exercise intensity.

Statistical Analyses and Outcomes

The primary analysis assessed the mean change in glucose level during study exercise sessions by assigned exercise type and by insulin delivery modality using a mixed-effects linear model, adjusted for baseline glucose, age, and sex as fixed effects and a random participant effect. A sample size of 660 was calculated such that the margin of error of a 95% CI on the adjusted mean change in glucose during exercise was at most 5 mg/dL for each exercise type and for each insulin modality stratum. Inclusion in the primary analysis required a study exercise session with duration ≥10 min, a CGM reading in the 10 min before the exercise session, and a CGM reading in the 10 min after the end of the exercise session.

Secondary analyses compared glycemic outcomes on study exercise days with those on sedentary days. A study exercise day was defined as a 24-h period after the end of a study exercise session, whereas a sedentary day was defined as a 24-h period without any exercise (study or personal) in the current or past 24 h. In the pilot T1DEXI study (10), the effect of exercise on glycemia seemed to last 12–16 h, so for this study, a sedentary day could start 24 h after an exercise session. Outcomes were summarized as means and SDs or summary statistics appropriate to the distribution. Exploratory analyses assessed the impact of different event- and participant-level factors on change in glucose during study exercise and overall glycemia on study exercise and sedentary days. Multiple comparisons were corrected using the Benjamini-Hochberg adaptive false discovery rate correction procedure (11). Additional details of the statistical methods are described in Supplementary Table 2.

RESULTS

Study Participants

A total of 561 adults with type 1 diabetes enrolled, and 497 had sufficient CGM data for at least one study exercise event in the 4-week observational period for inclusion in the analyses (n = 162 were assigned to study aerobic exercise, n = 165 to interval exercise, and n = 170 to resistance exercise) (Supplementary Fig. 1). For HCL and standard-pump groups, the margin of error of the 95% CI on the adjusted mean change in glucose during exercise was between 4 and 5 mg/dL for the three exercise types, whereas for the MDI group, the margin of error was between 6 and 7 mg/dL for the three exercise types. Sufficient CGM data were

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available for 398 participants for the secondary analyses.

Participants had a mean (range) age of 37 (18–70) years, mean ± SD HbA_{1c} of 6.6 ± 0.8% (49 ± 8.7 mmol/mol), and mean ± SD disease duration of 18 ± 13 years, and they reported a median of 2,319 weekly MET minutes of physical activity before study initiation. Ninety-five percent were current CGM users (89% Dexcom, 9% Medtronic, and 3% Abbott). Insulin delivery was by HCL in 45% (84% Tandem and 16% Medtronic), standard pump in 37%, and MDIs in 18%. Other baseline characteristics are listed in Supplementary Table 3.

Ninety-seven percent of the 497 participants completed the full 28-day observation period. Eighty-nine percent of the 497 participants completed the target of at least six study exercise sessions during their 4-week study period, with an additional 6% completing five study exercise sessions. The median time between study exercise sessions was 4.0 days (interquartile range [IQR] 2.1–6.0 days). The median duration of all study exercise sessions was 30 min (IQR 22–30 min). Overall, participants were physically active for a median (IQR) of 4.3 (3.0–6.2) hours per week; the prescribed exercise video sessions accounted for 0.7 (0.6–0.8) of these hours per week. The median (IQR) daily step count was 7,991 (6,200–10,487) (Supplementary Table 4). Overall, a total of 2,756 study video exercise sessions (905 aerobic, 903 interval, and 948 resistance) were logged that met criteria for primary analyses.

Heart Rate at Baseline and During Study Exercise

Baseline heart rate (mean ± SD) was 74 ± 11, 74 ± 10, and 74 ± 10 bpm in the aerobic, interval, and resistance exercise video sessions, respectively, increasing to a peak of 145 ± 16, 134 ± 17, and 129 ± 17 bpm, respectively, or 65 ± 15%, 56 ± 18%, and 52 ± 15% of age-predicted maximal heart rate, respectively.

Changes in Glucose Concentration by Exercise Type

The mean ± SD baseline (pre-exercise) glucose level was 149 ± 52 mg/dL and was similar among the three exercise types and insulin delivery modalities. The mean ± SD change in glucose was −18 ± 39 mg/dL during aerobic compared with −14 ± 32 mg/dL during interval (adjusted difference −4 mg/dL; 95% CI −8 to −1 mg/dL; $P = 0.02$) and −9 ± 36 mg/dL during resistance exercise (adjusted difference −10 mg/dL; 95% CI −13 to −6 mg/dL; $P < 0.001$). The adjusted difference between interval and resistance exercise was −5 mg/dL (95% CI −9 to −2 mg/dL; $P = 0.003$). Aerobic exercise resulted in a larger drop in glucose compared with interval and resistance exercise, regardless of the insulin delivery modality (Fig. 1). Similarly, the median (IQR) change in glucose during exercise, as measured from baseline to nadir, was −14 (−33 to −1), −10 (−26 to 0), and −8 (−26 to 0) mg/dL in the aerobic, interval, and resistance sessions, and this was similar among the insulin delivery modalities (Supplementary Table 5). Reproducibility in response to study exercise glucose change within each study participant was variable within each study exercise type (overall intraclass correlation coefficient 0.12).

Temporary basal rates and/or periods of basal rate suspensions were strategies used during study exercise; suspensions were more common for those using automated insulin delivery (Supplementary Table 6). Carbohydrate intake in the hour before exercise occurred in 23% of all sessions, whereas carbohydrate intake during exercise was infrequent (6% of sessions); it was similar across the three insulin treatment modalities. Average total daily basal insulin delivery was similar between exercise days and sedentary days, across all insulin modalities.

Other Factors Influencing Glucose Change During Study Exercise

Exercise sessions performed by men were associated with a greater drop in glucose compared with sessions performed by women, even after predefined adjustment for insulin modality, baseline HbA_{1c}, baseline glucose, and baseline age ($P = 0.009$) (Table 1). The sex effect was no longer significant after post hoc adjustment for additional potential confounders, including insulin on board during exercise (higher for men) and mean heart rate before exercise (higher for women). Baseline HbA_{1c} also influenced the change in glucose level during exercise ($P = 0.004$), with sessions performed by those with lower HbA_{1c} levels (<7%) having greater drops in glucose during exercise. For event-level factors, measured at or before the start of exercise, a greater decline in glucose during exercise was associated with a higher baseline glucose ($P < 0.001$), a declining glucose immediately before exercise ($P < 0.001$), a greater percent time <70 mg/dL in the 24-h preceding start of exercise ($P = 0.03$), a lower baseline heart rate ($P = 0.02$), afternoon/evening exercise ($P < 0.001$),

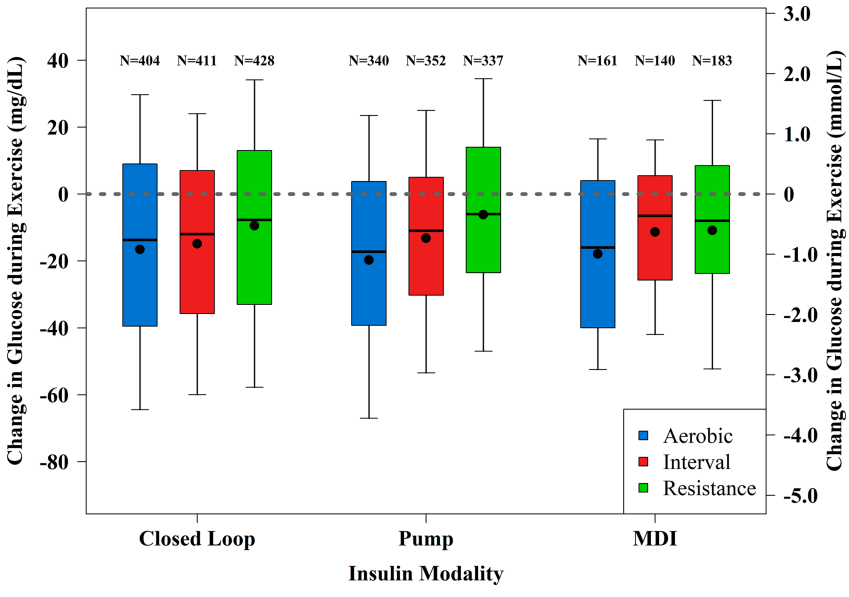

Figure 1—Boxplots of change in glucose during study exercise by exercise type and insulin modality ($N = 2,756$ exercise sessions from 497 participants). Black lines in the middle of colored boxes represent medians; solid black dots in the middle of boxes represent means. Whiskers outside of the colored boxes represent the 10th and 90th percentiles. The number above each box indicates the number of exercise sessions.

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Table 1—Factors affecting change in glucose during study exercise

Characteristic	*N* of participants	*N* of exercise sessions	Mean (SD) Baseline glucose before exercise, mg/dL	Mean (SD) Unadjusted change in glucose during exercise, mg/dL	Mean (95% CI) Adjusted change in glucose during exercise, mg/dL*	*P**
Overall	497	2,756	149 (52)	−13 (36)	−14 (−16 to −12)	
Participant level						
Age, years						0.16
18–25	109	552	158 (59)	−15 (38)	−14 (−17 to −10)	
26–44	253	1,417	148 (51)	−13 (37)	−14 (−16 to −11)	
≥45	135	787	145 (46)	−13 (32)	−15 (−18 to −12)	
Assigned exercise type						<0.001
Aerobic	162	905	150 (51)	−18 (39)	−19 (−22 to −16)	
Interval	165	903	149 (51)	−14 (32)	−15 (−18 to −12)	
Resistance	170	948	149 (53)	−9 (36)	−9 (−12 to −7)	
Sex						0.009†
Female	363	2,022	152 (52)	−13 (36)	−12 (−14 to −10)	
Male	134	734	142 (50)	−15 (35)	−16 (−19 to −13)	
Type 1 diabetes duration, years						0.47
<5	60	318	137 (47)	−6 (33)	−10 (−15 to −6)	
5 to <10	81	447	152 (55)	−13 (35)	−14 (−18 to −10)	
≥10	356	1,991	151 (51)	−14 (36)	−15 (−17 to −13)	
Baseline HbA_{1c}, % (mmol/mol)						0.004
<6.0 (<42)	89	493	132 (43)	−10 (33)	−17 (−20 to −13)	
6.0 to <6.5 (42 to <48)	126	701	141 (46)	−13 (36)	−16 (−19 to −13)	
6.5 to <7.0 (48 to <53)	126	715	148 (46)	−12 (35)	−13 (−16 to −10)	
7.0 to <7.5 (53 to <58)	86	486	162 (54)	−17 (36)	−15 (−18 to −11)	
7.5 to <8.0 (58 to <64)	42	219	173 (65)	−16 (39)	−10 (−16 to −4)	
≥8.0 (≥64)	28	142	177 (65)	−17 (37)	−8 (−15 to −1)	
Baseline BMI, kg/m^2						0.11
<25.0	274	1,518	148 (51)	−11 (37)	−12 (−14 to −9)	
25.0 to <30.0	159	881	152 (51)	−17 (35)	−17 (−20 to −14)	
≥30.0	64	357	146 (54)	−14 (31)	−15 (−20 to −11)	
Insulin modality						0.80
Closed loop	223	1,243	149 (48)	−14 (37)	−14 (−17 to −12)	
Pump	186	1,029	148 (54)	−13 (35)	−15 (−17 to −12)	
MDIs	88	484	152 (56)	−13 (34)	−13 (−17 to −9)	
IPAQ, MET minutes per week						0.35
<1,500	138	789	147 (48)	−13 (34)	−15 (−18 to −12)	
1,500 to <3,000	158	852	146 (51)	−13 (36)	−14 (−17 to −11)	
≥3,000	173	955	155 (56)	−15 (37)	−14 (−16 to −11)	
Pittsburgh Sleep Index, hours asleep per day						0.07
<8	151	851	147 (52)	−15 (36)	−16 (−18 to −13)	
8 to <9	227	1,256	148 (52)	−12 (36)	−13 (−15 to −11)	
≥9	119	649	153 (50)	−13 (36)	−14 (−17 to −10)	
Event level						
Baseline glucose 10 min before exercise, mg/dL						<0.001
<100	252	422	87 (12)	11 (27)	11 (8, 15)	

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Table 1—Continued

Characteristic	*N* of participants	*N* of exercise sessions	Mean (SD) Baseline glucose before exercise, mg/dL	Mean (SD) Unadjusted change in glucose during exercise, mg/dL	Mean (95% CI) Adjusted change in glucose during exercise, mg/dL*	*P**
100 to <150	449	1,190	125 (14)	−7 (29)	−8 (−10 to −6)	
≥150	429	1,144	197 (42)	−29 (38)	−31 (−33 to −28)	
Rate of change of glucose 15 min before exercise, mg/dL/min						<0.001
Decreasing by >1.0	263	396	160 (50)	−43 (36)	−41 (−44 to −38)	
Decreasing by >0.5 to 1.0	297	418	151 (53)	−25 (32)	−25 (−28 to −22)	
Approximately stable (decrease of 0.5 to increase of 0.5)	459	1,257	144 (50)	−8 (29)	−11 (−13 to −9)	
Increasing by >0.5 to 1.0	209	275	149 (56)	−4 (36)	−5 (−8 to −1)	
Increasing by >1.0	252	375	153 (50)	7 (38)	7 (4 to 10)	
TIR 70–180 mg/dL 24 h before exercise, %						0.30
<60	218	444	185 (63)	−21 (39)	−13 (−17 to −9)	
60 to <80	351	681	153 (49)	−17 (37)	−17 (−19 to −14)	
≥80	385	1,078	133 (37)	−10 (32)	−14 (−17 to −12)	
Time <70 mg/dL 24 h before exercise, %						0.03
<1	401	1,002	158 (53)	−14 (35)	−13 (−15 to −10)	
1 to <5	378	736	145 (46)	−13 (35)	−15 (−17 to −12)	
≥5	246	465	138 (51)	−15 (37)	−18 (−21 to −15)	
Hours since last exercise						0.15
<10	324	775	148 (52)	−16 (37)	−16 (−19 to −13)	
10 to <30	405	1,003	147 (48)	−12 (33)	−14 (−16 to −11)	
≥30	333	641	155 (57)	−15 (37)	−14 (−16 to −11)	
Verily-measured heart rate 15 min before exercise, bpm						0.02
<70	195	390	146 (48)	−16 (35)	−16 (−19 to −12)	
70 to <90	460	1,414	150 (50)	−14 (35)	−15 (−17 to −13)	
≥90	333	774	150 (56)	−10 (38)	−11 (−14 to −8)	
Exercise time of day						<0.001
Morning (3 A.M. to <noon)	299	847	144 (45)	−6 (32)	−7 (−10 to −5)	
Afternoon (noon to <6 P.M.)	374	1,017	149 (51)	−14 (37)	−15 (−18 to −13)	
Evening (6 P.M. to <9 P.M.)	265	614	150 (54)	−18 (36)	−18 (−21 to −15)	
Night (9 P.M. to <3 A.M.)	132	278	163 (63)	−22 (37)	−19 (−23 to −15)	
Insulin on board at start of exercise, units						<0.001
0	294	568	136 (50)	2 (29)	−2 (−5 to 1)	
>0 to <1.0	318	631	138 (45)	−6 (29)	−10 (−13 to −7)	
1.0 to <2.0	304	523	149 (47)	−15 (35)	−16 (−19 to −13)	
≥2.0	351	891	167 (55)	−29 (39)	−26 (−28 to −23)	
Menstrual cycle day (women only)						0.27
<10	212	429	150 (55)	−11 (35)	−12 (−16 to −9)	
10 to 20	213	432	158 (52)	−15 (37)	−14 (−18 to −11)	
≥20	209	351	154 (54)	−14 (39)	−14 (−18 to −11)	

To convert from mg/dL to mmol/L for glucose, divide mg/dL value by 18. IPAQ, International Physical Activity Questionnaire. *Adjusted mean change in glucose, CIs, and *P* values computed from a mixed-effects linear regression model adjusting for insulin modality, baseline glucose, age, baseline HbA_{1c}, and sex as fixed effects with a random participant effect. Multiple comparisons were adjusted using the Benjamini-Hochberg adaptive false discovery rate correction method. †Post hoc analysis considered full mixed-effects linear regression model adjusting for all factors with a significant *P* value. Sex was the only factor no longer significant after adjusting for assigned exercise type, baseline HbA_{1c}, baseline glucose, baseline rate of change, percent time <70 in prior 24 h, baseline heart rate, exercise time of day, and insulin on board.

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and a greater amount of insulin on board at the start of exercise ($P < 0.001$) (Table 1).

Overall Glycemic Control on Exercise Versus Sedentary Days

Compared with sedentary days (n = 2,470), study exercise days (n = 1,302) had a lower mean glucose level ($P < 0.001$), a higher percent time in range (TIR) ($P < 0.001$), and a lower percent time >180 mg/dL (Table 2). Improvement in TIR on exercise versus sedentary days was consistent across the different exercise modalities (Fig. 2 and Table 2), and more participants achieved a greater average TIR on exercise days compared with sedentary days, regardless of exercise type (Fig. 2). Overall, 40% of participants increased their average TIR by >5% on study exercise days compared with sedentary days, whereas 18% of participants decreased their TIR by >5% on study exercise days compared with sedentary days (Fig. 2).

TIR was higher on both exercise days and sedentary days for those who were older, had shorter diabetes duration, had lower baseline HbA_{1c} level, were using closed-loop systems, and had lower patient-reported baseline physical activity levels (Supplementary Table 7). The increase in TIR on exercise days compared with sedentary days did not differ by any participant characteristic (interaction P values not significant) (Supplementary Table 7). On study exercise days, exercise-specific factors that were significantly associated with greater TIR included lower pre-exercise heart rate and a smaller drop in glucose during exercise (Supplementary Table 8).

Participants had more time <70 mg/dL on exercise days than on sedentary days (median 1.1 vs. 0.4%; $P < 0.001$) (Table 2), although the percent time below range (TBR) was low overall on both exercise and sedentary days. The percentage of participants with ≥1% time <54 mg/dL, which is considered by consensus as excessive (12), was 18% on exercise days vs. 13% on sedentary days (P = 0.03) (Supplementary Fig. 2). The percentage of days with a CGM-measured hypoglycemic event, defined as <54 mg/dL for at least 15 consecutive minutes, was also greater on exercise versus sedentary days (13 vs. 10%; P = 0.01) (Table 2). Participants with longer diabetes duration had a higher proportion of sedentary days with hypoglycemic events compared with participants with shorter diabetes duration (P = 0.03), but the increase in hypoglycemic events on exercise days when compared with sedentary days was present regardless of the participants' baseline characteristics (Supplementary Table 9). Three severe hypoglycemic events were reported, all in the study-assigned aerobic exercise group, none of which occurred on the day of or day after study exercise.

Table 2—Glycemia on exercise versus sedentary days

Metric	Summary statistics		P*
	Exercise day	Sedentary day	
N of participants	398	398	
N of days	1,302	2,470	
Median (IQR) hours of glucose readings	24 (23–24)	24 (23–24)	
Mean (SD) glucose, mg/dL	145 (31)	155 (35)	<0.001
Mean (SD) coefficient of variation, %	29 (9)	29 (9)	0.76
Mean (SD) TIR 70–180 mg/dL, %	76 (20)	70 (23)	<0.001
Median (IQR) time >180 mg/dL, %	17 (5–32)	23 (9–41)	<0.001
Time >250 mg/dL, %			<0.001
Median (IQR)	0.0 (0.0–5.6)	0.7 (0.0–10.1)	
0, n (%)	775 (60)	1,198 (49)	
>0 to <2, n (%)	83 (6)	149 (6)	
2 to <5, n (%)	107 (8)	223 (9)	
5 to <10, n (%)	117 (9)	275 (11)	
≥10, n (%)	220 (17)	625 (25)	
Median (IQR) time <70 mg/dL, %	1.1 (0.0–4.0)	0.4 (0.0–3.1)	<0.001
Mean (SD)	3.1 (5.2)	2.5 (4.6)	
Days with hypoglycemic event <70 mg/dL, n (%)†	611 (47)	976 (40)	<0.001‡
Time <54 mg/dL, %			<0.001
0, n (%)	1,002 (77)	2,030 (82)	
>0 to <0.5, n (%)	40 (3)	56 (2)	
0.5 to <1, n (%)	36 (3)	58 (2)	
1 to <3, n (%)	158 (12)	228 (9)	
3 to <5, n (%)	32 (2)	55 (2)	
≥5, n (%)	34 (3)	43 (2)	
Days with hypoglycemic event <54 mg/dL, n (%)†	167 (13)	246 (10)	0.01‡

To convert from mg/dL to mmol/L for glucose, divide mg/dL value by 18. *CGM metrics tested as a continuous outcome unless otherwise noted. P values computed from a mixed-effects linear model adjusting for insulin modality, assigned exercise type, age, baseline HbA_{1c}, and sex as fixed effects and a random participant effect. Multiple comparisons were adjusted for using the Benjamini-Hochberg adaptive false discovery rate correction method. Because of a skewed distribution, percent time <70, <54, and >250 mg/dL were rank transformed. †A CGM sensor-defined hypoglycemic event <70 mg/dL is defined as at least 15 consecutive minutes <70 mg/dL. The hypo event ends when there is at least 15 consecutive minutes ≥80 mg/dL, at which point the participant becomes eligible for a new hypo event. A CGM sensor-defined hypoglycemic event <54 mg/dL is defined as at least 15 consecutive minutes <54 mg/dL. The hypo event ends when there is at least 15 consecutive minutes ≥70 mg/dL, at which point the participant becomes eligible for a new hypo event. ‡CGM metrics tested as a binary outcome. P values computed from a logistic regression model adjusting for insulin modality, assigned exercise type, age, baseline HbA_{1c}, and sex as fixed effects and a repeated participant effect with a compound symmetry covariance structure. Multiple comparisons were adjusted for using the Benjamini-Hochberg adaptive false discovery rate correction method.

CONCLUSIONS

Mean declines in glycemia during study-assigned exercise in adults with type 1 diabetes differed by type of activity. The mean drop in glucose was greatest for aerobic exercise, followed by interval and then resistance exercise, with considerable heterogeneity in the glycemic responses within each exercise type. Heterogeneity in change in glucose during exercise seems to be explained, in part, by several participant- and event-level characteristics, including recent HbA_{1c} level, sex, baseline glucose concentration, rate of change in glucose before exercise, time <70 mg/dL

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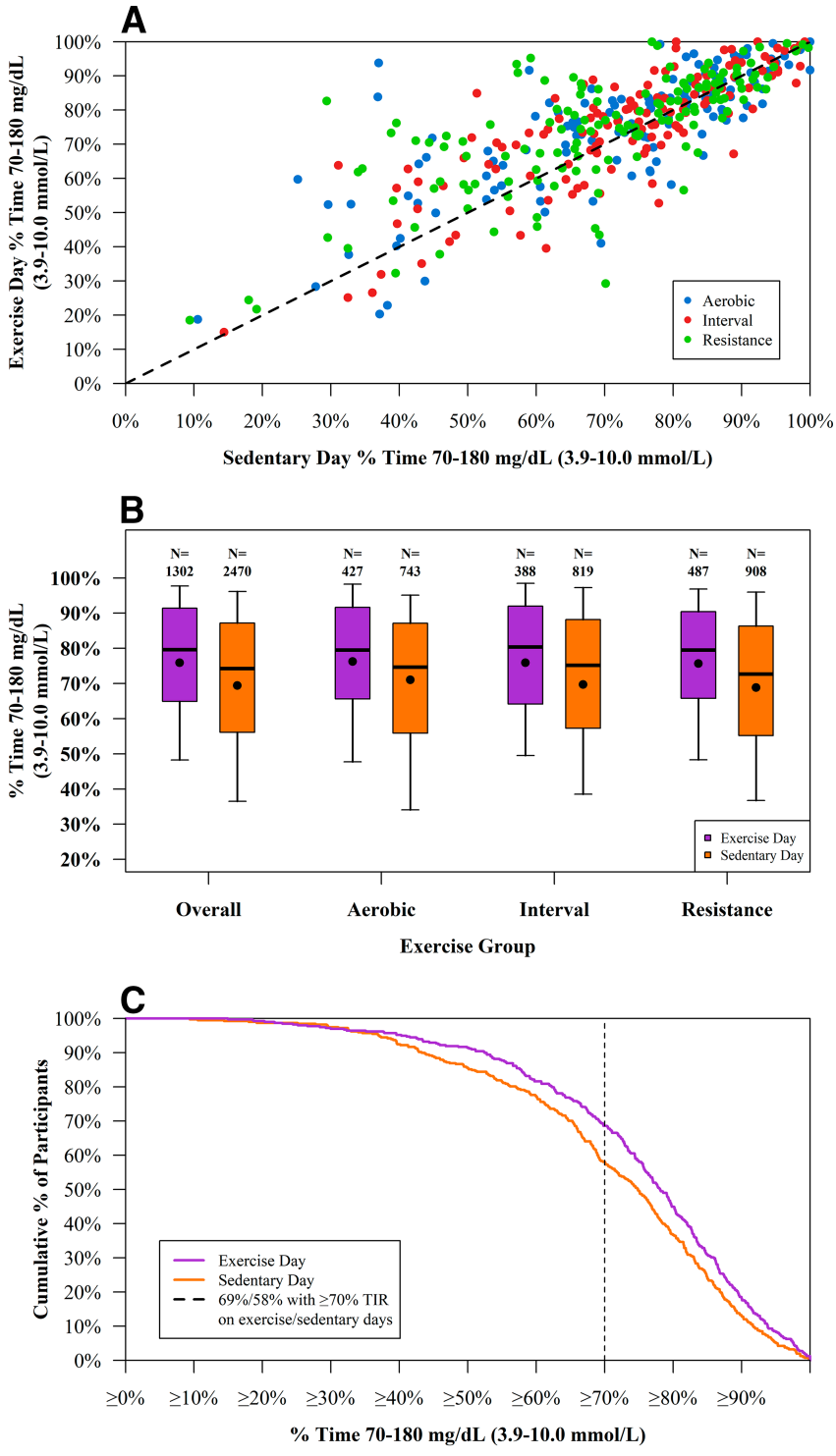

Figure 2—*N* = 398 participants. *A*: Scatterplot of participant-level exercise versus sedentary day percent time 70–180 mg/dL. *B*: Boxplots of day-level percent time in range 70–180 mg/dL on exercise versus sedentary days. Black lines in the middle of colored boxes represent medians; solid black dots in the middle of boxes represent means. Whiskers outside of the colored boxes represent the 10th and 90th percentiles. The number above each box indicates the number of days. *C*: Cumulative distribution of participant-level percent time 70–180 mg/dL on exercise versus sedentary days.

in the 24 h before exercise, time of day of exercise, and estimated insulin on board during the activity. Although the mean decline in glucose differed among the three exercise types, and change in glucose was variable, we also report that TIR generally increased by ∼6% over the next 24 h after the 30-min structured exercise session, regardless of activity type, compared with a day with no reported exercise. The heterogeneity of each participant's glucose change during exercise, as demonstrated by the low intraclass correlation coefficient of 0.12, has been observed in other studies that have also allowed variation in the time of day for exercise and the temporal relationship of exercise timing relative to bolus insulin dosing (13).

Continuous moderate-intensity aerobic exercise is known to promote a decline in glycemia in type 1 diabetes (14), even if HCL systems are used (15,16). The risk of hypoglycemia during aerobic exercise increases as the duration of activity increases, particularly if insulin is not reduced or if the pre-exercise glucose concentration is not elevated (9). In contrast, brief periods of very intense exercise (i.e., >80% peak aerobic capacity) (17), high-intensity interval training, or resistance exercise can cause a rise in glucose level that may require insulin treatment (18,19). In this large real-world study, we found that all three types of home-based exercise resulted in significant declines in mean glucose, with aerobic exercise generating the greatest effect. At-home interval and resistance exercise both promoted a drop in glycemia, rather than the expected rise that has been observed in laboratory-based studies (8,19,20), perhaps because the intensity of effort was lower than expected, according to collected heart rate data, and because the exercise was not restricted to the morning in a fasted state, which is typical of laboratory-based research. Evidence is emerging that prandial state (i.e., fasting vs. postmeal vs. postabsorptive) is a more important determinate of the glucose response to exercise in type 1 diabetes than exercise mode (21). Additional analyses of the T1DEXI nonstudy exercise session data, which include competitive activities that could also influence glycemic responses, with a more detailed examination of the prandial state, should provide further insight into which types and intensities of real-world exercise promote a rise in glycemia.

There is currently insufficient information to model an HCL system that can predict insulin needs for exercise in individuals with type 1 diabetes. Our analyses identified only two participant-level variables, sex and recent HbA_{1c} level, that influenced the change in glucose during exercise. After adjusting for potential confounders that included insulin modality, baseline glucose, age,

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and baseline HbA_{1c}, men had a greater drop in glycemia during exercise than women; however, sex-related differences in glucose responses to exercise were no longer significant after adjusting for baseline heart rate and insulin on board. Our finding that a greater decrease in glucose during exercise occurred in men than in women is consistent with a recent report on resistance exercise (22) and supports the hypothesis that women may prefer to exercise with less insulin on board to help with weight management and/or reduce requirement for carbohydrate feeding (23). We also found that after correcting for other confounders, particularly pre-exercise glucose concentration, HbA_{1c} level influenced the magnitude of the drop in glucose during study exercise. Specifically, those individuals achieving or exceeding glycemic control targets for HbA_{1c} had greater drops in glucose during exercise compared with those with higher HbA_{1c} levels, after accounting for pre-exercise glucose levels, perhaps because the former have heightened skeletal muscle insulin sensitivity (24) and/or an increased capacity to take up and oxidize glucose (25).

Lower baseline heart rate values were associated with greater declines in glycemia during exercise, which is a novel finding. However, baseline heart rate has a reciprocal relationship to aerobic fitness, at least in individuals without diabetes (26), and individuals with type 1 diabetes who have higher fitness levels are known to have greater decreases in glycemia compared with those who are less fit (13,27). Interestingly, self-reported physical activity levels and sleep duration did not seem to influence the change in glucose levels during exercise.

Greater drops in glucose were found in the exercise sessions with the highest pre-exercise glucose levels, as has previously been noted (7), and in the sessions where glucose levels were already declining before exercise. Greater declines in glucose were also observed in sessions with more TBR in the 24 h before exercise, when exercise occurred in the evening/nighttime compared with morning, and when insulin on board was high at exercise start time. These findings, which are largely confirmatory (9), may be important in further informing next-generation closed-loop systems for exercise.

We observed a near-identical mean drop in glycemia and similar variability within all forms of study exercise among the three distinct insulin delivery modalities (i.e., HCL, standard pump, and MDI). These real-world findings are counter to a recent meta-analysis of clinical trial data suggesting that HCL systems improve glucose control around exercise (28) when temporary target modes are used ~120 min before the start of exercise (16). Some information, such as pump basal rate value, was available for both HCL and standard-pump systems, but data related to proprietary HCL features, such as transition to exercise mode, were not available. Additional analyses of the T1DEXI data may help to determine the optimal timing and setting for the temporary target mode for exercise based on exercise type, time of day, baseline glucose, recent glucose control, and other factors that seem to influence the rate of change in glucose level during exercise.

Like our pilot work (10), we found that an average of 30 min of structured exercise markedly improved TIR over the next 24 h compared with being sedentary. Remarkably, >40% of the participants improved their TIR by >5% on exercise days relative to sedentary days, which is deemed of clinical importance, if sustained, for the prevention of diabetes-related complications (29). This larger data set also allowed us to better determine if any participant- or event-level characteristic influenced the glycemic benefits of the structured exercise sessions. Universally, we observed significant improvements in TIR, with low exposure to TBR, on exercise days versus sedentary days, regardless of age, assigned exercise type, disease duration, baseline HbA_{1c} level, baseline activity level, baseline reported sleep duration, or insulin modality. These findings suggest that regular sessions of structured exercise should be universally recommended for adults living with type 1 diabetes, who are deemed fit for exercise by their health care provider, to improve daily TIR.

A single bout of exercise lasting ≥30 min is known to increase insulin sensitivity and hypoglycemia risk in type 1 diabetes, particularly over the next 12–24 h (30). More prolonged or atypical activity seems to increase hypoglycemia risk over the next 48 h, at least based on epidemiological evidence (31). Consistent with these previous studies, we observed a small but significant increase in TBR on study exercise days compared with sedentary days, along with an increase in hypoglycemic event rates, as defined by an interstitial glucose level <54 mg/dL. TBR was low overall in the cohort, even on active days (i.e., <4%), with level 2 hypoglycemia occurring only on 13% of active days compared with 10% on sedentary days. Thus, this cohort may not be representative of the general type 1 diabetes population, given their high activity level and overall good to excellent glycemic control. None of the participant- or event-level factors that we examined seemed to influence the likelihood of developing postexercise hypoglycemia.

The primary strength of this study is that it presents results from a large cohort demonstrating how three primary exercise types affect glycemia during and after exercise under real-world conditions in adults with type 1 diabetes. The data set will be open access and free for researchers to access and use. Other strengths include randomization by study exercise type and measurement of participant- and event-level factors using exercise wearables, CGM, and a cloud-connected study smartphone application.

The limitations of this study should also be acknowledged. The cohort may not be representative of the general population of adults with type 1 diabetes; participants in the study regularly exercised, had good glycemic control, and used real-time CGM, and individuals using MDIs were underrepresented. Women were overrepresented in the cohort, relative to the typical clinical population. Our analyses comparing exercise versus sedentary days assessed glycemia within participants rather than examining if increased exercise volume improved daily TIR in those initially sedentary. However, we believe the improved TIR would be similar, if not larger, for participants who do not regularly exercise or have lower baseline TIR. The three study-assigned exercise types, although of different forms, may not have differed much in the flux of energy systems or hormonal responses, which can profoundly affect glycemia (32). The peak heart rate achieved during interval exercise was lower than anticipated, and although not measured, lactate concentrations generated using resistance bands may have been lower than those generated with other forms of strength training activity. This was an observational study that measured, but did not manipulate, many of the

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variables thought to influence the glycemic response to exercise in type 1 diabetes, including exercise time of day and insulin dosing (9). Finally, carbohydrate intake data from analyses of food photos were unavailable at the time of these analyses.

In summary, this real-world study suggests that although glucose response during and after individual exercise events is highly variable, aerobic exercise produces a greater decline in glycemia than high-intensity interval exercise, followed by resistance exercise, in adults with type 1 diabetes. Nonetheless, all three forms of exercise equally increase TIR over the next 24 h, compared with days without exercise. Importantly, the variable change in glucose during an acute exercise session is at least partially related to several quantifiable participant- and event-related characteristics that may be deemed valuable to incorporate into new decision support tools, and potentially HCL insulin delivery systems, to better manage glycemic control during and after exercise in adults living with type 1 diabetes.

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References

1. Colberg SR, Sigal RJ, Yardley JE, et al. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. Diabetes Care 2016;39:2065–2079
2. Wu N, Bredin SSD, Guan Y, et al. Cardiovascular health benefits of exercise training in persons living with type 1 diabetes: a systematic review and meta-analysis. J Clin Med 2019;8:253
3. Bohn B, Herbst A, Pfeifer M, et al.; DPV Initiative. 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;38:1536–1543
4. Keshawarz A, Piropato AR, Brown TL, et al. Lower objectively measured physical activity is linked with perceived risk of hypoglycemia in type 1 diabetes. J Diabetes Complications 2018;32:975–981
5. García-García F, Kumareswaran K, Hovorka R, Hernando ME. Quantifying the acute changes in glucose with exercise in type 1 diabetes: a systematic review and meta-analysis. Sports Med 2015;45:587–599
6. Reddy R, Wittenberg A, Castle JR, et al. Effect of aerobic and resistance exercise on glycemic control in adults with type 1 diabetes. Can J Diabetes 2019;43:406–414.e1
7. Riddell MC, Zaharieva DP, Tansey M, et al. Individual glucose responses to prolonged moderate intensity aerobic exercise in adolescents with type 1 diabetes: the higher they start, the harder they fall. Pediatr Diabetes 2019;20:99–106
8. Riddell MC, Pooni R, Yavelberg L, et al. Reproducibility in the cardiometabolic responses to high-intensity interval exercise in adults with type 1 diabetes. Diabetes Res Clin Pract 2019; 148:137–143
9. Riddell MC, Gallen IW, Smart CE, et al. Exercise management in type 1 diabetes: a consensus statement. Lancet Diabetes Endocrinol 2017;5:377–390
10. Riddell MC, Li Z, Beck RW, et al. More time in glucose range during exercise days than sedentary days in adults living with type 1 diabetes. Diabetes Technol Ther 2021;23:376–383
11. Benjamini Y, Hochberg Y. On the adaptive control of the false discovery rate in multiple testing with independent statistics. J Educ Behav Stat 2000;25:60–83
12. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the International Consensus on Time in Range. Diabetes Care 2019;42:1593–1603
13. Tyler NS, Mosquera-Lopez C, Young GM, El Youssef J, Castle JR, Jacobs PG. Quantifying the impact of physical activity on future glucose trends using machine learning. iScience 2022;25:103888
14. Tuominen JA, Karonen SL, Melamies L, Bolli G, Koivisto VA. Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue. Diabetologia 1995;38:106–111
15. Breton MD, Cherñavvsky DR, Forlenza GP, et al. Closed-loop control during intense prolonged outdoor exercise in adolescents with type 1 diabetes: the Artificial Pancreas Ski study. Diabetes Care 2017;40:1644–1650
16. Paldus B, Morrison D, Zaharieva DP, et al. A randomized crossover trial comparing glucose control during moderate-intensity, high-intensity, and resistance exercise with hybrid closed-loop insulin delivery while profiling potential additional signals in adults with type 1 diabetes. Diabetes Care 2022;45:194–203
17. Shetty VB, Fournier PA, Davey RJ, et al. Effect of exercise intensity on glucose requirements to maintain euglycemia during exercise in type 1 diabetes. J Clin Endocrinol Metab 2016;101:972–980
18. Aronson R, Brown RE, Li A, Riddell MC. Optimal insulin correction factor in post-high-intensity exercise hyperglycemia in adults with type 1 diabetes: the FIT study. Diabetes Care 2019;42:10–16
19. Turner D, Luzio S, Gray BJ, et al. Algorithm that delivers an individualized rapid-acting insulin dose after morning resistance exercise counters post-exercise hyperglycaemia in people with type 1 diabetes. Diabet Med 2016;33:506–510
20. Harmer AR, Chisholm DJ, McKenna MJ, et al. High-intensity training improves plasma glucose and acid-base regulation during intermittent maximal exercise in type 1 diabetes. Diabetes Care 2007;30:1269–1271
21. Yardley JE. Reassessing the evidence: prandial state dictates glycaemic responses to exercise in individuals with type 1 diabetes to a greater extent than intensity. Diabetologia 2022;65:1994–1999
22. Brockman NK, Sigal RJ, Kenny GP, Riddell MC, Perkins BA, Yardley JE. Sex-related differences in blood glucose responses to resistance exercise in adults with type 1 diabetes: a secondary data analysis. Can J Diabetes 2020;44:267–273.e1

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23. Prévost MS, Rabasa-Lhoret R, Talbo MK, Yardley JE, Curry EG, Brazeau AS. Gender differences in strategies to prevent physical activity-related hypoglycemia in patients with type 1 diabetes: a BETTER study. Diabetes Care 2022;45:e51–e53
24. Mao Y, Zhong W. Changes of insulin resistance status and development of complications in type 1 diabetes mellitus: analysis of DCCT/EDIC study. Diabetes Res Clin Pract 2022;184:109211
25. Monaco CMF, Perry CGR, Hawke TJ. Alterations in mitochondrial functions and morphology in muscle and non-muscle tissues in type 1 diabetes: implications for metabolic health. Exp Physiol 2020;105:565–570
26. Aladin AI, Whelton SP, Al-Mallah MH, et al. Relation of resting heart rate to risk for all-cause mortality by gender after considering exercise capacity (the Henry Ford exercise testing project). Am J Cardiol 2014;114:1701–1706
27. Al Khalifah RA, Suppère C, Haidar A, Rabasa-Lhoret R, Ladouceur M, Legault L. Association of aerobic fitness level with exercise-induced hypoglycaemia in type 1 diabetes. Diabet Med 2016;33:1686–1690
28. Eckstein ML, Weilguni B, Tauschmann M, et al. Time in range for closed-loop systems versus standard of care during physical exercise in people with type 1 diabetes: a systematic review and meta-analysis. J Clin Med 2021;10:2445
29. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care 2019;42:400–405
30. 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
31. MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care 1987;10:584–588
32. Riddell MC, Scott SN, Fournier PA, et al. The competitive athlete with type 1 diabetes. Diabetologia 2020;63:1475–1490

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