Resistance Exercise in Already-Active Diabetic Individuals (READI): Study Rationale, Design and Methods for a Randomized Controlled Trial of Resistance and Aerobic Exercise in Type 1 Diabetes

Jane E. Yardley[a,b,c], Glen P. Kenny[c,d], Bruce A. Perkins[e], Michael C. Riddell[f], Gary S. Goldfield[g], Lois Donovan[i], Stasia Hadjiyannakis[g], George A. Wells[d,h] , Penny Phillips[d] and Ronald J. Sigal[i] on behalf of the READI trial investigators

[a]University of Alberta, Augustana Campus, Camrose, AB, T4V 2R3 Canada
[b]Manitoba Institute of Child Health, University of Manitoba, Winnipeg, MB,R3E 3P4, Canada
[c]School of Human Kinetics, University of Ottawa, Ottawa, ON, K1N 6N5, Canada
[d]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON K1H 8L6, Canada
[e]Mount Sinai Hospital and Lunenfeld Tanenbaum Research Institute, University of Toronto, Toronto, ONM5G 2M9, Canada
[f]School of Kinesiology and Health Science, York University, Toronto, ON M3J 1P3, Canada
[g]Healthy Active Living & Obesity Research Group, Children's Hospital of Eastern Ontario Research Institute, Ottawa, ONK1H 8L1, Canada
[h]Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Ottawa, ON K1Y4W7., Canada
[i]Departments of Medicine, Cardiac Sciences and Community Health Sciences, Cumming School of Medicine, Faculties of Medicine and Kinesiology, University of Calgary, Calgary, AB T2T 5C7, Canada.

Address for correspondence:

Ronald J. Sigal, MD, MPH
Division of Endocrinology and Metabolism, RRDTC
1820 Richmond Road SW, Room 1898
Calgary, AlbertaT2T 5C7
Canada

e-mail: rsigal@ucalgary.ca
phone: 403-955-8327
fax: 403-955-8249

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ABSTRACT

The Resistance Exercise in Already Active Diabetic Individuals (READI) trial aimed to examine whether adding a 6-month resistance training program would improve glycemic control (as reflected in reduced HbA_{1c}) in individuals with type 1 diabetes who were already engaged in aerobic exercise compared to aerobic training alone. After a 5-week run-in period including optimization of diabetes care and low-intensity exercise, 131 physically active adults with type 1 diabetes were randomized to two groups for 22 weeks: resistance training three times weekly, or waiting-list control. Both groups maintained the same volume, duration and intensity of aerobic exercise throughout the study as they did at baseline. HbA_{1c}, body composition, frequency of hypoglycemia, lipids, blood pressure, apolipoproteins B and A-1 (ApoB and ApoA1), the ApoB-ApoA1 ratio, urinary albumin excretion, serum C-reactive protein, free fatty acids, total daily insulin dose, health-related quality of life, cardiorespiratory fitness and musculoskeletal fitness were recorded at baseline, 3 (for some variables), and 6 months. To our knowledge, READI is the only trial to date assessing the incremental health-related impact of the adding resistance training for individuals with type 1 diabetes who are already aerobically active. Few exercise trials have been completed in this population, and even fewer have assessed resistance exercise. With recent improvements in the quality of diabetes care, the READI study will provide conclusive evidence to support or refute a major clinically relevant effect of exercise type in the recommendations for physical activity in patients with type 1 diabetes.

Keywords: resistance exercise, type 1 diabetes, randomized controlled trial, HbA_{1c}

1. Introduction

Type 1 diabetes mellitus (T1DM) is characterized by absence or near-absence of insulin secretion. Long-term complication risk is comparable to similarly-aged individuals with type 2 diabetes mellitus (T2DM) (1, 2), even though those with T1DM usually have fewer additional cardiovascular risk factors. Hemoglobin A_{1c} (HbA_{1c}) reflects average glucose concentrations over the previous 2-3 months. A 1% higher HbA_{1c} is associated with a 37% higher risk of developing advanced diabetes microvascular complications (3). While aerobic exercise clearly improves glycemic (blood glucose) control in T2DM (4, 5), aerobic exercise interventions in T1DM have generally not found significant effects on HbA_{1c} (6, 7), despite reduced insulin requirements (8-10), and improved insulin sensitivity (11, 12). In a cross-sectional study of 1,030 people with T1DM, physical activity explained *none* of the HbA_{1c}variance in men, and less than 2% in women (13). This may be because those with T1DM are at higher risk of hypoglycemia and tend to overcompensate with carbohydrate intake (and reduced insulin administration) to avoid exercise-induced drops in glucose, negating potential benefits on HbA_{1c}. It may also be that aerobic training has little impact on HbA_{1c} in T1DM, and HbA_{1c} is impacted primarily by other factors (diet, insulin regimen and other behavioural/physiological processes).

Resistance exercise produces slower glucose declines than aerobic exercise (14), and might offer other exercise-related metabolic benefits with less hypoglycemia risk. Acutely, there is less glucose instability after a bout of resistance exercise versus aerobic exercise (14). Small studies suggested resistance training reduced HbA_{1c} in T1DM. Durak et al. (15) studied eight males using a crossover design, and found that HbA_{1c} averaged 6.9% following rest and 5.8% following resistance training (3-4 sets of 14 exercises three days/week) was performed. Mosher et al. (16) found that a 12-week combined aerobic and resistance exercise program decreased HbA_{1c} (7.72% to 6.76%, n=10). Similarly, Ramalho et al. (17) found a non-statistically significant decline in HbA_{1c} (8.2±2.9% to 7.6±1.6%) after a 12-week resistance exercise program (three times/week, n=13).

Earlier studies could not capitalize on recent advances in T1DM care. Rapid-acting insulin analogues have decreased the risk of hypoglycemia and consequently the need for excessive exercise-related carbohydrate consumption. Small, light-weight, rapid-acting glucose meters have made capillary glucose testing more convenient. Few published exercise intervention studies incorporated background diabetes care that would meet current guidelines (18), and none possessed the methodological rigour currently expected in clinical trials (19).

New research examining effects of resistance exercise on glycemic control in the context of modern diabetes care is necessary. Most previous exercise trials enrolled only previously inactive subjects (6, 7). However, people who already perform aerobic exercise regularly may be more likely than sedentary individuals to begin, and maintain, resistance exercise. We therefore undertook the Resistance Exercise in Already-active Diabetic Individuals (READI) clinical trial to evaluate the impact of resistance exercise on metabolic control in people with T1DM who were already aerobically active. Herein we describe the READI trial methods; trial results will be submitted for publication separately.

2. METHODS

2.1 Design

READI was a four-centre randomized parallel-group controlled trial in individuals with T1DM already performing aerobic activity regularly. Prior to randomization, participants entered a five-week stabilization/run-in period, including assessment and optimization of participant diet and insulin therapy and, starting in the second week, low-volume moderate-intensity resistance exercise. Those previously on only two insulin injections per day were encouraged to switch to a basal-bolus regimen using NPH, insulin glargine or insulin detemir as basal insulin and insulin lispro or aspart prior to meals. Starting in week 2 of the run-in period, participants were asked to attend three weekly supervised sessions of low-volume moderate-intensity resistance exercise. Upon successful completion of the run-in phase, participants were randomized in equal numbers to Resistance Training (**R**) or waiting-list control (**C**).

We assessed 1641 individuals for eligibility to participate in the study. Of these, 282 entered screening, where a further 128 were excluded, resulting in 154 participants entering the run-in phase of the study. Finally, 131 aerobically active individuals with T1DM were randomized to participate in the trial. The CONSORT diagram outlining the details of the screening, run-in and randomization phases of the study and reasons for participant exclusion can be found in Figure 1. The study was reviewed and approved by the Research Ethics Board at each site, and all participants provided written informed consent. The first screening visit occurred on August 10, 2007. The first person was randomized on October 15, 2007, and the last patient visit took place on March 21, 2012. Participants were recruited through advertising, referrals from physicians and diabetes educators, and word of mouth. Interested participants contacted the Research Coordinator for more information and to be screened for inclusion. The Coordinator ensured that potential participants were aware of the study protocol and met the inclusion/exclusion criteria (Table 1) before obtaining informed consent according to the Tri-Council Policy Statement Guidelines (20). To take part in the study, participants were required to be 16 years of age or older, have HbA_{1c} between 6.6 and 9.9%, to have T1DM as defined by the Canadian Diabetes Association (CDA) guidelines (21), requiring insulin therapy within one year of diagnosis and continually thereafter, and to partake regularly in moderate to vigorous aerobic activity (Table 1). It was also required that participants be willing to undertake a regimen of intensive diabetes therapy including glucose monitoring at least four times daily, intensive insulin therapy and carbohydrate counting.

2.2 Baseline Assessment

Potential participants were assessed for inclusion by the Research Coordinator. Table 2 contains a complete list of measurements taken at baseline and at various time points throughout the study. Complete medical, drug, and exercise histories (including history of hypoglycemia) were taken. A structured physical examination was also performed to ensure that no conditions that would make vigorous, weight-bearing activity hazardous were present (e.g. skin breakdown, severe peripheral neuropathy). Insulin injection sites

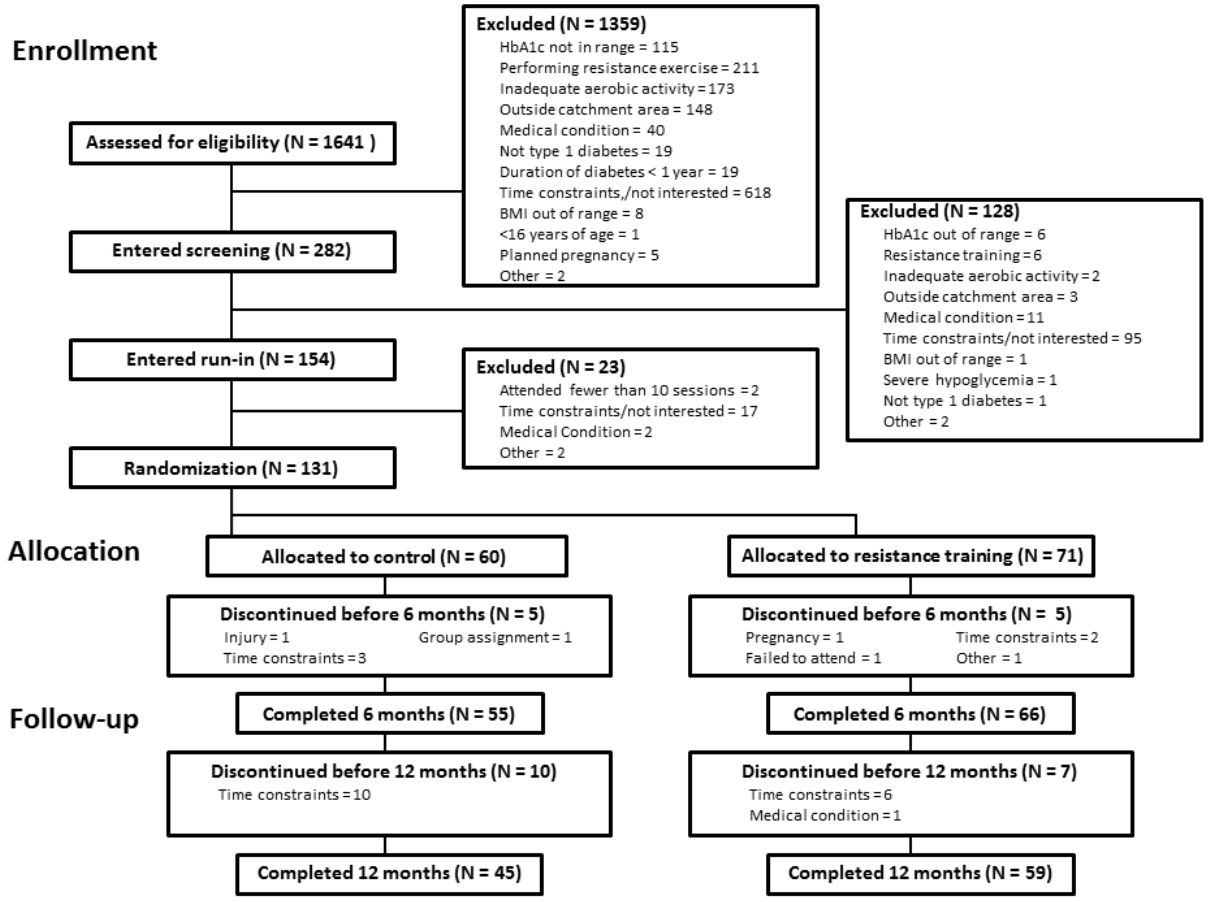

Figure 1 - READI study CONSORT diagram

were also inspected for evidence of lipohypertrophy. The Research Coordinator took anthropometric measurements and fasting blood tests, and administered psychological questionnaires. An assessment of diabetes self-care was also performed in order to determine the participants' knowledge and skill pertaining to blood glucose monitoring, carbohydrate counting, hypoglycemia awareness and diet/insulin adjustments for physical activity.

Prior to being admitted to the run-in phase of the trial, participants were also asked to attend a series of baseline visits for the measurement of body composition, an assessment of physical activity levels, and the completion of quality of life questionnaires, as well as to perform a resting and exercise stress test electrocardiogram. Blood samples were drawn to determine complete blood count, alanine aminotransferase (**ALT**), thyroid stimulating hormone (**TSH**), and urine was taken for albumin/creatinine

Table 1 – Study inclusion and exclusion criteria

Inclusion Criteria

1. Type 1 diabetes as defined by the 2008 Canadian Diabetes Association guidelines (21) with duration ≥ one year requiring insulin therapy starting within one year of diagnosis and continuously thereafter.
2. Male or female, age ≥ 16 years (Tanner stage ≥ IV).
3. HbA_{1C} between 6.6% and 9.9%.
4. Habitual performance during the previous four months of exercise ≥three times per week, including at least 90 minutes per week of vigorous aerobic exercise (of sufficient intensity to cause sweating; e.g. jogging, soccer, basketball, racquet sports), and/or ≥150 minutes per week of aerobic exercise of at least moderate intensity (e.g. brisk walking, moderate-paced bicycling) but no resistance training.
5. Willingness and ability to work closely with the study physicians, nurse and dietitian and follow their recommendations for insulin therapy and adjustments for diet.

Exclusion Criteria

1. Participation during the previous four months in any resistance training.
2. Severe hypoglycemia requiring assistance from another person within the previous 3 months, or hypoglycemia unawareness
3. "Brittle" diabetes, characterized by frequent and unpredictable hyperglycemia and hypoglycemia (even if not requiring assistance from others).
4. Restrictions in physical activity due to disease: severe peripheral neuropathy, severe arthritis, active proliferative retinopathy, intermittent claudication, unstable cardiac or pulmonary disease, disabling stroke, etc.
5. Clinically significant gastroparesis (known or suspected).
6. Body mass index ≥35 kg/m^2 or weight > 147 kg (exceeding capacity of the Dual Energy X-ray Absorptiometry or Computed Tomography scanners)
7. Fasting serum c-peptide ≥0.2 nmol/l (0.6 ng/mL).
8. Increase or decrease of ≥5% of body weight during the previous two months.
9. An expected requirement within the subsequent 6 months for medications (other than insulin) that will affect glucose metabolism (e.g. corticosteroids).
10. If age < 18 yrs, linear growth of ≥1cm during the previous year.
11. Significant renal disease: serum creatinine ≥200 mEq/l (2.26 mg/dL) or proteinuria >1 g/24 hours.
12. Uncontrolled hypertension: systolic blood pressure >150 mm Hg systolic or diastolic blood pressure >95 mm Hg while seated.
13. Other illness, judged by the participant or investigators to make participation in this study inadvisable.
14. Cognitive deficit resulting in inability to understand or comply with instructions.
15. Pregnancy at the start of the study, or intention to become pregnant in the next year.
16. Inability to communicate in English or French.
17. Ischemic ECG changes during baseline maximal cardiopulmonary stress test, unless subsequently cleared for participation by a cardiologist after appropriate investigation.
18. Unwillingness to sign informed consent.

ratio, to identify individuals with anemia, liver or thyroid dysfunction or renal insufficiency that might require further investigation and, where appropriate, further treatment before taking part in the study. Serum total cholesterol, high density lipoprotein-C (**HDL-C**), triglycerides, low-density lipoprotein C (**LDL-C**), cholesterol/HDL cholesterol ratio, apolipoproteins A-1 and B (**ApoA1** and **ApoB**), free fatty acids (**FFA**), C-peptide and C-reactive protein were also measured at baseline along with HbA_{1c} and fasting plasma glucose (Table 2).

2.3 Study Protocol

2.3.1 Run-in phase (weeks 1-5)

Participants were asked to complete a five-week run-in period for study staff to ensure that diabetes management met current standards, that participants were familiarized with the exercise protocols prior to randomization, and to ascertain whether or not participants would be sufficiently adherent with the prescribed intervention. During this period, the details of their diabetes management were reviewed with the diabetes nurse-educator, including all aspects of capillary glucose monitoring, recognition and management of hypoglycemia and insulin/carbohydrate adjustments for physical activity. Participants who were not already on multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) were switched to a basal bolus regimen with NPH insulin, insulin detemir or insulin glargine as basal insulin, and insulin aspart, glulisine or lispro prior to meals (or at least prior to breakfast and supper).

All participants met with a dietitian who prescribed a diet with an energy distribution of 55% carbohydrate, 15-20% protein and 25-30% fat (18) and encouraged participants to consume low glycemic index foods, legumes, barley and whole intact grains. Carbohydrate counting was reviewed in detail, and participants were provided with carbohydrate counting tools. In keeping with the current CDA guidelines (18) participants were provided with target capillary blood glucose ranges of 4-7 mmol/l pre-meal, and 5-10 mmol/l 1-2 hours postprandial. Participants were able to interact with study endocrinologists, diabetes nurse-educators and dietitians by phone, fax, or e-mail so that insulin and diet therapy could be optimized.

Table 2 – Study timeline

	Baseline Assessments							Randomization		Intervention	
Testing Variables	Phone Screening	Screening visit 1	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Run-in† (5 wks)	Pre-randomization	3 month	6 month
Inclusion/Exclusion criteria	X										
Informed consent form		X									
Medical history		X								X	X
Physical examination		X									
Waist/hip circumference		X		X				X	X	X	X
Height, weight& blood pressure		X		X				X	X	X	X
Complete Blood Count (CBC)			X								
Thyroid Stimulating Hormone (TSH)			X								
Urine microalbumin/creatinine ratio			X						X	X	X
Liver Enzymes			X								
Serum Creatinine			X								
C-peptide			X								
Serum fructosamine			X						X	X	X
Fasting plasma glucose,			X						X	X	X
HbA_{1c} (central lab)			X						X	X	X
HbA_{1c} (local lab)			X						X	X	X
Fasting plasma lipid profile			X						X	X	X
C-peptide									X		
Serum total cholesterol									X		
High sensitivity C-reactive protein									X		X
HDL-C, LDL-C									X		X
Apolipoprotein B (frozen)									X		X
Apolipoprotein A-1 (frozen)									X		X
Free fatty acids (frozen)									X		X
Samples for future testing									X	X	X
Quality of Life (QOL) Questionnaires			X							X	X
Pedometer 7-day log			X							X	X
Review activity log			X							X	X
DXA scan					X						X
Abdominal CT scan						X					X
Thigh CT scan						X					X
Resting Electrocardiogram							X				
Cardiopulmonary Stress test							X				X
Dietary assessment				X				X	X	X	X
Diabetes Education (Nurse Educator)				X				X	X	X	X
Strength Test								X*	X	X	X
Exercise Education								X			X
Exercise Prescription								X			C
Orientation to gym								X			C
Supervision of exercise sessions								X		E	E
Exercise logs								X		E	X

† Exercise orientation and supervision began in week 2 of run-in and lasted four weeks

* Strength testing took place during the first exercise session and again during the last exercise session of run-in

X = all participants, C = control only, E = resistance exercise group; DXA = dual X-ray absorptiometry; CT = computerized tomography, HDL = high density lipoprotein, LDL = low density lipoprotein

During weeks 2-5 of run-in, participants took part in supervised low-volume moderate intensity resistance training at community-based fitness facilities three times per week. This served to familiarize participants with the exercise protocols as well as to assess adherence, and to provide a week for optimization of care before introducing a novel exercise routine. Each session consisted of one to two sets of light weight, high repetition (15 repetitions) resistance exercises. Each week, two of the sessions were supervised by exercise specialists so that exercises were performed safely and correctly. An initial strength test was performed during the first gym visit. Strength was then assessed again at the end of the run-in period. Table 3 contains a list of all exercises performed and their progression throughout the study. Participants were also asked to maintain their regular frequency and volume of aerobic exercise.

Participants were expected to meet the following criteria during run-in in order to qualify for randomization: 1) attend at least 10 of the 12 scheduled exercise sessions, 2) perform a total of at least 80 capillary glucose tests during weeks 2 to 5, including tests before and after exercise sessions at least twice per week, 3) a written record of insulin doses, capillary glucoses, and activity (with written capillary glucose records matching the numbers downloaded from the meter and 4) no episodes of severe hypoglycemia during weeks 2 to 5 of run-in. The option of extending run-in up to three weeks (with decisions made one week at a time) was provided if the participant fell short of the criteria but was expected to meet them with additional short-term support. Participants attended a pre-randomization visit at the end of the run-in period, where they were re-evaluated by the Research Coordinator, Nurse-Educator and Dietitian, and all measures were repeated (Table 2).

If run-in was completed successfully, participants were randomized to one of two groups (resistance exercise or waiting-list control) using central telephone randomization (Pronexus VB voice randomization software) with allocation concealment prior to randomization. Randomization was done in blocks randomly varying in size from four to six, stratified by centre (Ottawa, Calgary, Toronto or Winnipeg), sex, and use or non-use of insulin pump therapy. All participants were asked to continue performing aerobic exercise at the same volume, duration and intensity as they did at baseline. Participants could not be blinded as to group assignment after randomization, but the main study

outcomes were measured by blinded individuals (lab technologists) using objective methods. Participants randomized to waiting-list control had the option to begin a supervised resistance training program after all six-month measures were completed.

2.3.2 Intervention phase (weeks 6-26)

2.3.2.1 Diet & medical management (common to both groups)

Diabetes-related medical and dietary management was performed with the assistance of study staff throughout the intervention period (beginning of run-in to end of six months). In order to minimize the number of changes and adjustments necessary after randomization, a great deal of effort was put into optimizing diabetes management during the run-in period. After randomization, the contact with study personnel was similar to the contact that individuals with type 1 diabetes would have with regular health care team: in-person visits with the nurse and dietitian at three and six months, with phone, fax and/or e-mail contact when initiated by patients. Participants were asked to contact study staff in the event of any episode of hypoglycemia requiring assistance from others, if they encountered more than three instances per week where capillary glucose was less than 2.8 mmol/L (even if not requiring assistance from others), or if they encountered more than two episodes of hypoglycemia at the same time of day within one week. After randomization, efforts were made to minimize changes to daily insulin dose and carbohydrate intake so that the possibility of the effects of exercise being washed out by changes in diet and insulin were small. However, where necessary, changes were made to reduce the risk of hypoglycemia. Participants were given instruction cards to guide insulin adjustment (Appendix 1). Participants were asked to complete three-day food diaries, including details of capillary glucose and insulin dosage when they met with the diabetes nurse-educator and dietitian at baseline and prior to each subsequent visit. Food and activity logs were reviewed and coded by the dietitian in order to assess habitual nutrient intake. Instruction on carbohydrate counting provided at the initial visit was reviewed and reinforced during subsequent visits.

Table 3 – Resistance Exercise training program

		Resistance Training Progression				Exercises	
Week Number	**Intervention Phase**	**Number of Sets**	**Repetitions**	**Weight (RM*)**	**Frequency (Sessions/week)**	**Group A****	**Group B****
2-3	Run-in	1	15	15	3	Leg press (quadriceps, gluteals)	Leg press (quadriceps, gluteals)
4-5	Run-in	2	15	15	3	Supine bench press (chest)	Sitting chest press (chest)
6-7	Intervention	3	8	8	3	Leg extensions (quadriceps)	Leg curls (hamstrings)
8-9	Intervention	3	8	8	3	Shoulder press (shoulders/neck)	Upright row (shoulders /neck)
10-11	Intervention	3	8	8	3	Seated row (back)	Latpulldown (back)
12-13	Intervention	3	8	8	3	Seated bicep curls	Triceps pushdown
14-16	Intervention	3	8	8	3	Abdominal crunches	Abdominal crunches
17-19	Intervention	3	8	8	3		
20-26	Intervention	3	8	8	3		

Note - During week 1 there is no resistance exercise. During weeks 2-5 all subjects participated in light resistance training in addition to their regular aerobic regime.

* A weight of 15 RM is the maximum weight that can be lifted 15 times safely and with good technique. A weight of 8 RM is the maximum weight that can be lifted 8 times safely and with good technique.

** Participants performed Group A and Group B exercises on alternate exercise session.

Efforts were made to minimize variability due to co-intervention (dietary or medication). Letters were sent to the physicians of the qualifying participants to inform them of the patients' participation in the study (including specific start and end dates) and to ask that any necessary insulin adjustments during this period be made by the study staff. Non-study physicians were also asked not to make any changes to antihypertensive or lipid-altering medication during this period, unless considered medically necessary. Where changes were deemed to be necessary, both the participant and the physician were encouraged to discuss the details with the study staff.

2.3.2.2 Exercise Protocol Elements Common to all Training Groups

Participants were provided with free memberships at local gyms for the duration of involvement in the study. All participants were asked to attend three exercise sessions weekly during weeks 2-5 of run-in. Training programs were overseen by exercise specialists. During run-in, an exercise specialist supervised at least two of the three weekly sessions. To ensure appropriate progression through the program after randomization, exercise sessions were supervised weekly for the first four weeks, every two weeks for the subsequent two months, then monthly for the remainder of the program. Exercise sessions each began with a 5-10 min warm-up, and ended with a 5-10 min cool-down (light exercises, stretching). Attendance, assessed by exercise logs and electronic scanning of the membership card, and completion of exercise logs, was monitored by the exercise specialist. Participants missing scheduled sessions were contacted by the exercise specialist to ascertain whether barriers to attendance needed to be addressed.

2.3.2.3 Resistance training **(R)**

The resistance exercise intervention took place at community facilities in each participating city. Details of the exercises included in the program and their progression are listed in Table 3. Resistance training took place three times per week, beginning with one to two sets of 15 repetitions of seven exercises at moderate intensity during run-in (weeks 2 to 5) and progressing to three sets, eight repetitions of seven exercises at the participants' 8-repetition maximum (8RM) (weeks 6 to 26). Exercises were

performed on weight machines. Throughout the resistance training program, participants alternated between the exercises of group A and group B listed in Table 3. The weights were increased progressively as strength increased. Participants were also asked to maintain volume, duration and intensity of aerobic exercise consistent with what they were performing prior to enrolling in the study. After the intervention period, participants were provided with a six-month strength training maintenance program.

2.3.2.4 Waiting-list control (C)

Participants in the control group were asked to maintain the same volume, duration and intensity of aerobic activity that they had prior to entry into the study. After the end of the intervention period and completion of all six-month measures, they were provided the option to undertake supervised resistance training.

3. MEASUREMENTS

All measurements and the timing of their collection are listed in Table 2. All participants (exercise and control) met with the diabetes nurse-educator and the dietitian at baseline, one month (immediately pre-randomization), three and six months. Participants were questioned about the following at each visit: episodes of hypoglycemia, smoking, blood glucose monitoring, medication changes and major medical events.

3.1 Primary Outcome

HbA_{1c} was measured using the method employed at the Population Health Research Institute (PHRI) at McMaster University for large international studies. Blood samples were collected in EDTA tubes, and a drop of this blood sufficient to cover the collection area was applied to a filter paper (Roche diagnostics). The filter papers were stored at -20°C at each site, then batch-shipped to the PHRI Laboratory for analysis. A hemolysate was made from the filter papers so that they could be run on the BIORAD Variant II HPLC analyzer (Bio-Rad, Hercules, CA). The inter-assay and intra-assay coefficients

of variation are ≤2%. Stability on filter paper has been demonstrated at room temperature or 4°C for 5-7 days (22), and for up to 3.5 years at -20°C or -70°C (23).

3.2 Secondary Outcomes

3.2.1 Anthropometry

The research coordinator, who was blinded to group assignment, measured height (cm) and weight (kg) using a Health O Meter manual scale (Health O Meter, Continental Scale Corp., Bridgeview, Ill). Body mass index (BMI) was calculated using the equation BMI = weight (kg)/[height (m)]^2. Waist circumference was measured at the middle distance between the iliac crest and the last floating rib using a retractable ergonomic measuring tape (SecaGmBH& Co KG, Hamburg, Germany). Whole-body Dual-energy X-ray Absorptiometry (DXA) scans were performed at baseline and six months in order to determine lean body mass and fat mass (GE Lunar Prodigy, GE Healthcare, Madison, WI). This technique, often considered to be a gold-standard method, classifies body weight into the components of lean soft tissue, fat soft tissue and bone, based on the differential attenuation by tissues of two levels of x-rays. Body composition was also assessed at baseline and six months by computed tomography (CT) imaging, which provides information complementary to that from DXA. CT scan images were analyzed using Slice-O-Matic software, version4.3 (Tomovision, Montreal, Quebec), using standard attenuation ranges to visualize and quantify adipose tissue (-190 to -30 Hounsfield units[HU] and muscle tissue [0–100 HU]). Muscle characteristics were expressed as the cross-sectional area of muscle and were separated into the cross-sectional areas of low-density muscle (0–34 HU) or normal-density muscle (35–100 HU). Abdominal adipose tissue was also measured by CT scan with abdominal visceral fat area being defined as adipose tissue within the area delineated by the muscle wall surrounding the abdominal cavity. The subcutaneous adipose tissue area was defined as the difference between the total abdominal adipose tissue area and the amount of abdominal visceral adipose tissue (24, 25). A single cut CT scan taken midway between the inguinal crease and the proximal border of the patella on the non-dominant leg was used to determine cross-sectional area of bone, muscle and adipose tissue of the mid-thigh (26, 27). In image

analyses, areas of bone, adipose tissue and muscle were measured by selecting the regions of interest, defined by the following attenuation values: ≥200 Hounsfield units for bone, -30 to –190 Hounsfield Units for adipose tissue, and 0-100 Hounsfield units for muscle.

3.2.2 Background physical activity

In order to assess background physical activity levels and to ensure that baseline levels of aerobic activity were maintained in both groups, participants were asked to wear pedometers (Yamax DIGIWALKER SW-700, Yamax Corporation, Tokyo, Japan) for one week at a time (except when showering and sleeping) at baseline, 3 months, and 6 months. Leisure time physical activity was defined as the mean number of steps taken per day. Steps that took place during scheduled exercise sessions were excluded. Participants were also asked to fill out activity logs at baseline, 3 months and 6 months, which were reviewed by the exercise specialist.

3.2.3 Energy intake

Three-day food diaries were used to assess food intake. These were also used by the dietitian to guide discussions on carbohydrate counting and nutrition. The logs were analyzed using food composition analysis software (The Food Processor SQL 2006, ESHA Research, Salem, OR) to determine intake of carbohydrate, protein and fat for each participant, as well as total energy intake.

3.2.4 Cardiorespiratory fitness

Participants who met the inclusion and exclusion criteria, and who signed the informed consent, were asked to return for a separate visit in order to perform a resting electrocardiogram and a cardiopulmonary treadmill stress test. This served to screen for ischemic heart disease, assess peak oxygen consumption (VO_{2peak}) and to determine the heart rates corresponding to different percentages of VO_{2peak}. Prior to the stress tests, participants were monitored by 12-lead electrocardiogram while resting quietly. This was followed by a stress test, where continuous breath-by-breath analysis of inspired and

expired oxygen and carbon dioxide was performed during a ramp protocol to volitional fatigue, also while being monitored by 12-lead electrocardiogram. If any light-headedness, chest discomfort, arrhythmia or significant ST depression or elevation occurred during the stress test, participants were referred for appropriate cardiac investigation. Entry into the study was delayed until medically cleared after investigation.

3.2.5 Strength testing

Strength testing was performed at the initial gym visit, and again at the end of the run-in period (just prior to randomization at the end of week 5) and at 3 and 6 months. Subjects were instructed on proper breathing technique for resistance exercises, avoiding Valsalva manoeuvres and the associated large rise in blood pressure. For each weight machine used in strength training (Table 3), the maximum weight which could be lifted eight times while maintaining good technique (8RM) was determined at the first session (28). This testing was performed as a baseline measure and to establish appropriate starting weights for participants later allocated to resistance training.

3.2.6 Musculoskeletal fitness

The following additional tests were conducted in consecutive order: grip strength, push-ups, sit and reach, partial curl-up and vertical jump. These tests are designed to assess muscular strength, muscular endurance and flexibility. The protocols for the tests have been established by the Canadian Society for Exercise Physiology (28).

3.2.7 Laboratory measurements

Blood samples were taken under fasting conditions. Participants were asked to refrain from taking anti-inflammatory drugs and to avoid vigorous physical activity for 24 hours before phlebotomy. Triglyceride levels, total cholesterol, and high-density lipoprotein (HDL) were determined using enzymatic methods on a Beckman-Coulter LX20 analyzer (Beckman Instruments, Brea, California). Low-

density lipoprotein (LDL) was calculated using the Friedewald equation (29). Immunoturbidimetric assays (Beckman Coulter Unicel®DxC600 Synchron® Clinical System and Beckman reagents, Beck Coulter, Inc., Brea, California) were used to measure apolipoproteins A-1 and B. The Beckman Coulter Unicel®DxC600 Synchron® Clinical System was also used in measuring non-esterified fatty acid (NEFA) concentration using an enzymatic colorimetric method (Randox Laboratories, Antrim, UK). High-sensitivity C-reactive protein (CRP) levels were assessed using highly sensitive Near Infrared Particle Immunoassay rate methodology (Beckman Coulter Unicel®DxC600 Synchron® Clinical System and Beckman reagents, Beck Coulter, Inc., Brea, California).

3.2.8 Hypoglycaemia

Hypoglycemia was defined in this study as a capillary glucose under 3.8 mmol/L, or symptoms of hypoglycaemia that were corrected by carbohydrate consumption. Hypoglycemia was considered "severe" if it required intervention by a person other than the patient.

3.2.9 Health-related quality of life

Health-related quality of life were assessed by questionnaire [SF-36 (30) and Diabetes-Specific Quality-of-Life Scale (DSQOLS) (31) EQ-5D (32)] at baseline, three and six months. The SF-36 (30) is the most widely-used and extensively-validated generic measure of health-related quality-of-life. It has also been validated in studies of participants with diabetes (33). The DSQOLS (31) was designed to assess physical complaints, social relations, leisure time flexibility, diet restrictions, worries about the future and daily hassles. It was designed for and validated in patients with type 1 diabetes and has excellent psychometric properties (31). Finally, the EQ-5D questionnaire involves single questions for five core domains of quality of life (mobility, self-care, ability to conduct usual activities, pain and discomfort, and anxiety and depression) as well as a simple visual analogue scale (32). This questionnaire has been extensively validated and has strong reliability (34-36).

4. BIOSTATISTICAL CONSIDERATIONS

4.1 Sample size calculation

In the controlled trial of resistance exercise in individuals with type 1 diabetes by Durak (15), the absolute HbA_{1c} difference between resistance exercise and control was 1.1% with SD 0.9%. We polled 10 academic endocrinologists and 10 diabetes educators, and they unanimously felt that a HbA_{1c} difference as low as 0.5% would be clinically significant, given the strong relationship between HbA_{1c} and the risks of both microvascular (37) and macrovascular disease (38, 39). This difference would be slightly less than the 0.66% overall effect on HbA_{1c} of aerobic exercise in type 2 diabetic patients in our meta-analysis (4). For 80% power to detect a 0.5% absolute difference in HbA_{1c} change between groups, assuming SD of 0.9% (same as the intergroup difference in the Durak trial), with α=0.05, the required number in each group would be 52 (104 participants altogether). If we assumed a 10% post-randomization dropout rate and applied the sample inflation factor $1/(1\text{-}D)^2$ where D is the expected dropout rate, we would have needed to randomize 128 individuals. We randomized 131 participants, and retention rates were good with121/131 (92.4%) completing the intervention (Figure 1).

4.2 Statistical analyses

The primary analysis will be on an intention-to-treat basis. The distributional properties of all outcome variables will be examined and transformations will be performed, as necessary. Residual plots will be investigated and leverage statistics calculated to verify the required assumptions. Transformations (log or square root) will be considered if they improve on the approximate normality of the residuals. Analyses will be performed using SAS software.

4.2.1 Primary analysis

Repeated measures mixed models regression with adjustment for center, age, sex, and baseline BMI will be used to compare the two groups for the primary outcome: change in HbA_{1C} between baseline

and the end of the intervention period (6 months). This method uses all available data points including those from subjects who withdraw before the planned end-of-study, and does not require imputation.

4.2.2 Secondary analyses: For all continuous secondary outcomes, we will use the same procedure as for the primary analysis. The frequency of hypoglycemia over the previous four weeks was treated as a continuous variable. For binary outcomes such as increases or decreases in antihypertensive or lipid-lowering therapy, and occurrence of severe hypoglycemia, Fisher's Exact Test will be used.

4.2.3Multivariable analyses: A multivariate analysis will be performed to assess the extent to which effects of group assignment are moderated by intermediate effects such as proportion of prescribed sessions completed, changes in waist circumference and BMI, diet or medication changes. These covariates will be entered in mixed models singly and in combinations, to elucidate which have the greatest effects.

4.2.4Exploratory subgroup analyses*:* Subgroup analyses will be exploratory and hypothesis-generating rather than hypothesis testing, since statistical power for them will be limited. We will repeat the analyses above, stratifying according to sex, baseline HbA_{1C} (above/below median), use/non-use of insulin pump therapy, degree of exercise adherence, age (above/below median), and BMI (above/below median).

5. DISCUSSION

READI is the first randomized clinical trial to examine the incremental effects of resistance exercise in individuals with type 1 diabetes who already habitually perform aerobic exercise. Most previous trials have either not considered participant activity levels at study entry, or have only involved previously sedentary participants. It is also one of very few exercise studies where background diabetes care meets modern clinical standards. READI trial participation required a significant time commitment. READI trial results will not be generalizable to patients unable or unwilling to travel to a gym, perform resistance

exercise, adhere to carbohydrate counting and carry out frequent capillary glucose monitoring. A well-designed trial like READI is necessary to examine the extent to which the addition of resistance exercise affects HbA_{1c}, physical fitness, and cardiometabolic health in individuals with type 1 diabetes who are already meeting aerobic exercise guidelines. Results of this trial will help clarify the role of resistance training as an adjunctive mode of treatment in this patient population.

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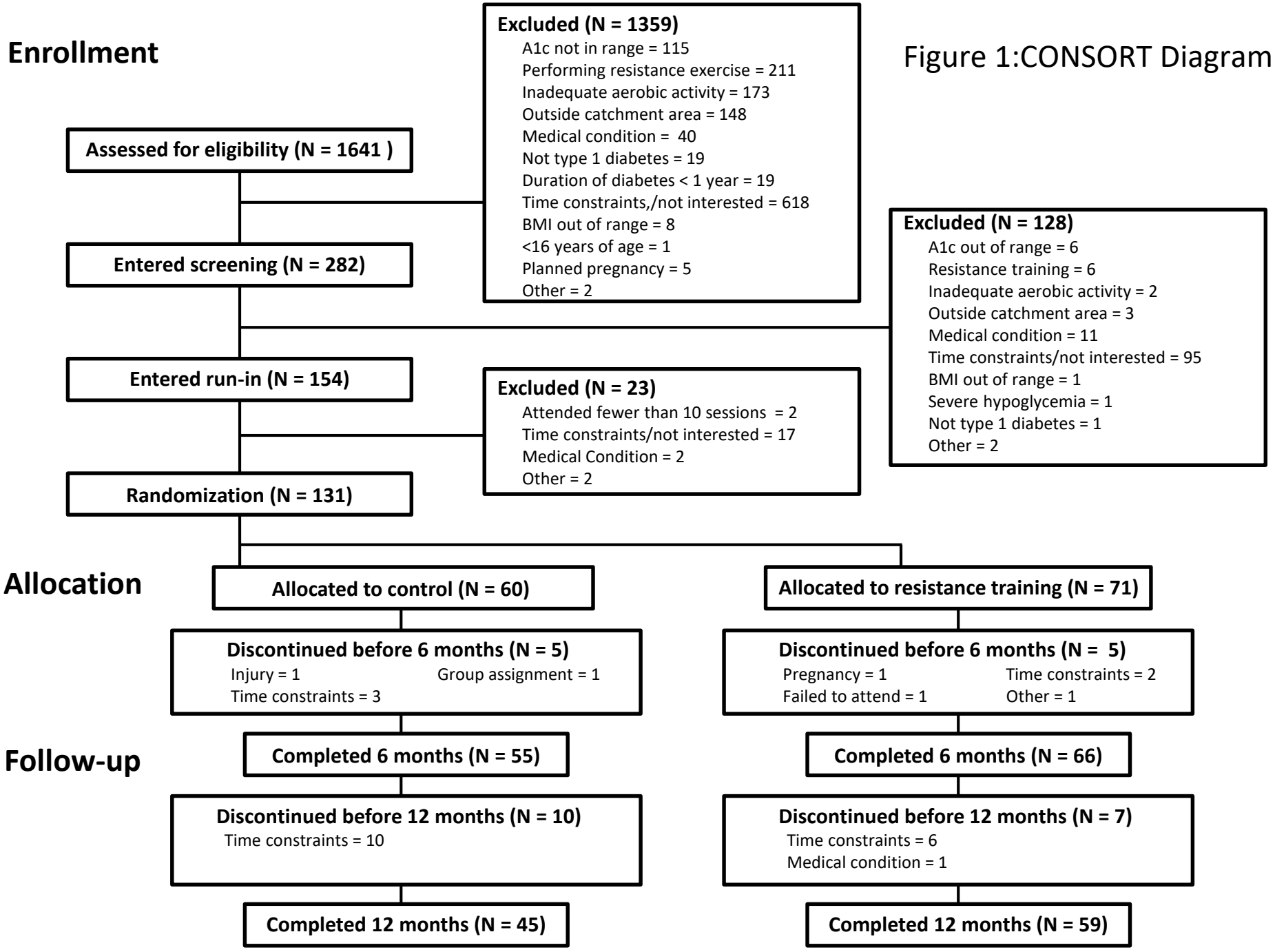

Figure 1:CONSORT Diagram

APPENDIX 1 - INSULIN ADJUSTMENT FOR EXERCISE

General Guidelines:

- These instructions are a starting point for each individual and will be modified for you as needed.
- Please do not make any insulin adjustments on your own: call research staff.
- Please check blood glucose (BG) levels before all meals, before bedtime and at 3 am once weekly.
- On exercise days please check BG before exercise, during (midway) and immediately after exercise.
- Stay hydrated: Drink water starting about 20 minutes before you exercise. Have about one cup of water (250ml) for every 20 minutes of exercise.

ADJUSTMENTS FOR MULTIPLE DAILY INJECTIONS

Time of Day of Planned Exercise	Action
Pre Breakfast	- **<5.6 mmol/L:** Take 30 grams carbohydrate and check BG in 15 minutes. Begin exercise once BG is 7.0 mmol/L or over - **5.7 – 7.0 mmol/L**: Take 15 grams of carbohydrate before exercise
1-2 hours after Breakfast	- Decrease pre-breakfast dose of **rapid** acting insulin (Humalog/Lispro or Novorapid/Aspart) by **50%**
Before Lunch and > 2 hours after Breakfast	- **<5.6 mmol/L:** Take 30 grams carbohydrate and check BG in 15 minutes. Begin exercise when BG 7.0 mmol/L or over - **5.7 – 7.0 mmol/L:** Take 15 grams carbohydrate before exercise
1-2 hours after Lunch	- Decrease pre-lunch dose of **rapid** acting insulin ((Humalog/Lispro or Novorapid/Aspart) by **50%**
Before Supper and >2 hours after Lunch	- Decrease **morning** dose of NPH, N, Glargine/Lantus or Detemir/Levemir by **10%**
Between Supper and Bedtime	- Decrease pre-supper dose of **rapid** acting insulin (Humalog/Lispro or Novorapid/Aspart) by **50%** - If hypoglycemia tends to occur many hours after exercise, decrease **bedtime** Glargine/Lantus, Detemir/Levemir, NPH, N by **10%**
Blood Glucose Before Planned Exercise	
< 4.5 mmol/L	- Take 30 grams carbohydrate, wait 15 minutes, re-check BG, start exercise if BG **5.6 mmol/L** or over. If not, then repeat treatment
4.5 – 5.6 mmol/L	- Take 15 grams carbohydrate before exercise
5.7 – 14.0 mmol/L	- No action required, begin exercise
> 14.0 mmol/L	- If high BG unexplainable, check urine ketones before starting exercise. • If ketones negative, give **30%** of usual **correction** dose of rapid acting insulin only if BG is over **20 mmol/L** and begin exercise • If ketones are present in moderate to large quantities, give correction dose and postpone exercise. Call research staff if you need assistance.
If Exercise is Unplanned	
< 5.6 mmol/L	- Take 30 grams carbohydrate, wait 15 minutes, re-check BG, start exercise if BG is **7.0 mmol/L** or over
5.7 – 6.9 mmol/L	- Take 15 grams of carbohydrate
7.0 – 14.0 mmol/L	- No action required, begin exercise
> 14.0 mmol/L	- If high BG unexplainable, check urine ketones before starting exercise. • If ketones negative, give 30% of usual correction dose of rapid acting insulin only if BG is over 20 mmol/L and begin exercise - If ketones are present in moderate to large quantities, give correction dose and postpone exercise. Call research staff if you need assistance.

Post Exercise:

- Remember to test BG after exercise. If BG is over 14.0 mmol/L after exercise: Give 30% of usual correction and test two hours after the correction.
- Contact research staff if you find BGs are low or high on two occasions after these adjustments; the guidelines will be modified for you.

ADJUSTMENTS FOR INSULIN PUMP USERS

The PUMP is to be WORN during EXERCISE

Planned Exercise	Action
Any time (always)	- Decrease basal rate by **50%**; beginning 1 hour prior to exercise and for one hour following exercise. This will be adjusted up or down at subsequent sessions as needed. - Test BG just before exercising and verify with table below to see if you need additional carbohydrates
1 to 2 hours after a meal	- Decrease basal rate as outlined above - Additionally, decrease meal bolus by **50%** (this includes insulin for food and correction). This will be titrated up or down at subsequent sessions as needed - Test BG before exercising and verify with table below to see if you need additional carbohydrates
Blood Glucose Before Planned Exercise	
< 4.5 mmol/L	- Take 30 grams of carbohydrates; recheck BG in 15 minutes; begin exercise when BG **5.7 mmol/**l or greater
4.5 – 5.6 mmol/L	- Take 15 grams of carbohydrates before starting exercise
5.7 – 14.0 mmol/L	- No action required; begin exercising
> 14.0 mmol/L	- Check urine for ketones if this BG result is not explainable • If ketones negative: give 30% of usual correction bolus ONLY if BG 20 mmol/l or greater. Begin exercise; test BG during and immediately after exercise • If ketones positive in moderate to large quantities: give correction bolus and postpone exercise. Refer to the "sick day guidelines" for insulin adjustment for ketones. Call research staff if need assistance. - Call research staff before next session to discuss pre-exercise dose adjustment
If Exercise is Unplanned	
Any time (always)	- Reduce your basal rate by **50%** as soon as you decide to exercise and keep reduced during exercise and for 1 hour following exercise. Consume extra carbohydrates if necessary based on blood glucose levels.
< 5.6 mmol/l	- Take 30 grams of carbohydrates; recheck BG in 15 minutes; begin exercise when BG **7 mmol/l** or greater
5.6 – 6.9 mmol/l	- Take 15 grams of carbohydrates before starting exercise
7 – 14 mmol/l	- No action required; begin exercising
>14 mmol/l	- If this BG is unexplainable: test ketones • If ketones negative give 30% of usual correction ONLY if BG 20 mmol/l or greater. Begin exercise • If ketones moderate to large: give correction and postpone exercise. Refer to the "sick day guidelines" for insulin adjustment for ketones. Call research staff if need assistance

Post Exercise

- If BG is 14 mmol/l or greater after exercise: give 30% usual correction and test 2 hours after correction
- Keep basal rate reduced for one hour after exercise
- If exercising in evening: also decrease overnight basal rate by 10%
- Call research staff if you find BGs are low or high on two occasions after making these adjustments – the guidelines will be modified