Complete Title of Protocol: Exercise Snacks and Glutamine to Improve Glucose Control in Adolescents with Type 1 Diabetes

NCT: NCT03199638

Date: April 24, 2015

RESEARCH PLAN

I. Specific Aims : To determine whether the sustained use of short bouts of exercise ('exercise snacks'), with or without the administration of the amino acid glutamine results in diminished glycemic variability and/or improved glucose control in adolescent with T1 diabetes.

II. Background and Significance: Puberty is associated with a physiological decline in insulin sensitivity [1,2] and such a decline leads to increased difficulty in achieving glycemic control in adolescents with T1D [3,4]. Designing innovative ways to improve diabetes control in adolescents is a highly desirable and challenging goal. Exercise increases glucose uptake by skeletal muscle [5,6], through an insulin-independent mechanism [7,8], and exercise training increases mitochondrial biogenesis and therefore muscle respiratory capacity and the expression of GLUT-4, the main glucose transporter in skeletal muscle [9]. Literature suggests exercise improves glucose tolerance in healthy individuals [10], and increases insulin sensitivity as measured by the euglycemic clamp in adolescents with T1D [11]. A recent meta-analysis concluded that regular aerobic training improves HbA1c in patients with T1D [13]. Nutritional supplements are critical for conditions of malnutrition caused by either decreased intake or chronic medical illnesses. Diabetes, especially when poorly controlled, is a state of relative malnutrition with impaired glucose transport and relatively decreased amino acid flux. We have previously shown that oral supplementation with glutamine, a non essential amino acid dietary supplement given prior to exercise decreases overnight post-exercise blood glucose in adolescents with long-standing T1D who do not retain residual insulin secretion [17,18]. These data suggest that a simple dietary supplement may be beneficial improving diabetes control. Using hyperinsulinemic euglycemic clamps we further examined whether this effect of glutamine was secondary to increased insulin sensitivity in adolescents with T1D (Torres-Santiago, et al, manuscript to be submitted). Lack of time is the most commonly perceived reason preventing the performance of exercise in both healthy and diabetic subjects [14,15]. Recently, John Hawley, an Australian scientist who will serve as a consultant in this grant and colleagues, showed that performing 6 bouts of just x1 min of intense exercise (90% maximal heart rate; termed 'exercise snacks') 30 min before meals, improved glycemic control in obese adults with impaired glucose tolerance [16]. This novel approach is partciularly attractive due to its simplicity and low cost,but this has never been investigated in adolescents with T1D previously.

III. Preliminary Studies/Progress Report *(Not to exceed 3 pages.)*

a). Pilot studies on the effect of glutamine and exercise in adolescents with T1D [17]. Mauras, et al, Diabetes Care 2011.

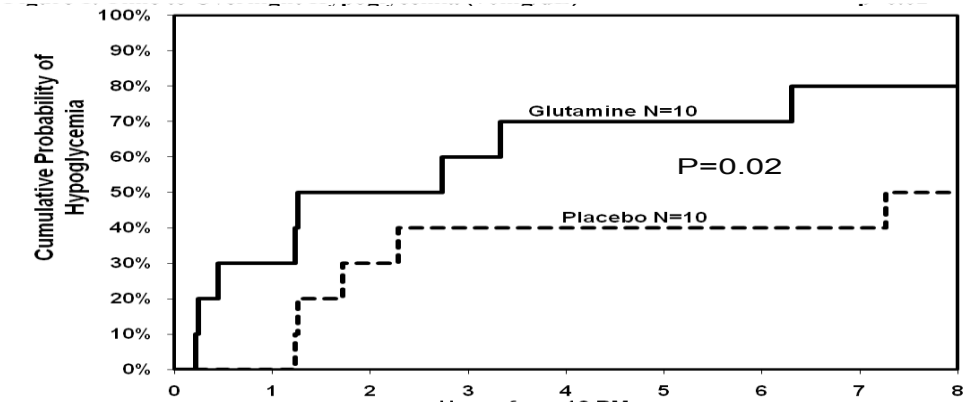
Post-exercise hypoglycemia is a common problem in youth with T1D. Approximately 20% of endogenous glucose production comes from gluconeogenesis via amino acid (AA) precursors, particularly GLN and AA depletion occurs in insulin-induced hypoglycemia. As GLN is a major contributor to gluconeogenesis, we studied the effects of GLN on glucose concentrations during afternoon exercise as well as overnight post exercise. We studied ten adolescents with uncomplicated T1D (mean age 15±1 yr-old, 5M, 5F) who had been diabetic for 6.2±3.3 years and wore insulin pumps, with a mean HbA1c of 6.9±0.9%, and a normal BMI (between the 10^{th} and 85^{th} percentiles). They were on no chronic medications.

Subjects were studied twice in the Clinical Research Center CRC during 1-h exercise session starting at 3PM. Mean blood glucose was in the mid 100 mg/dL range prior to exercise. Sessions consisted of 4, 15-min treadmill exercise (heart rate 140 bpm) with 5-min rest breaks interspersed. Blood glucose was continuously monitored during exercise and overnight. Basal insulin rates were continued during the study. Subjects were randomized to receive a drink containing either glutamine (before exercise and at bedtime (0.5 g/kg per dose), or a calorie- and nitrogen-free placebo. Studies were repeated within 3 weeks, and in randomized order. Plasma GLN concentrations measured 16 h post exercise the following morning were higher during the GLN study day than after placebo (316 vs. 200 μmol/L, $p<0.001$).

However, regardless of the dietary supplement received prior to exercise, plasma GLN concentrations measured in the postabsorptive state the following day, were below normal as compared to healthy, age-matched controls measured at rest ($p<0.001$) [33]. In earlier studies performed under resting conditions and using the same assay, we consistently observed that adolescents with T1D had plasma GLN concentrations in the normal range at rest as normal age-matched controls (484±25 *vs.* 513±29 μmol/L, NS) [33]. This suggests that intense exercise likely depletes plasma GLN in adolescents with T1D, as it does in healthy adults. Blood

glucose was similar at baseline on both study days (143±31 and 162±54 mg/dL on the GLN and placebo study day, respectively; p=0.44), and blood glucose dropped comparably (52±15% vs. 52±9% on the GLN and placebo study day, respectively; p=0.84) during exercise on both days. Yet overnight, post-exercise low blood glucose levels (defined as either <70 mg/dL or <60 mg/dL) were significantly more frequent (P=0.03, and 0.05, respectively) after GLN than after placebo. The cumulative probability of overnight hypoglycemia was increased on the GLN day (80%) compared with placebo (60%, p=0.02, Fig 4). We concluded that GLN supplementation increases the incidence of post exercise nighttime hypoglycemia. [17]. Taken in aggregate, our preliminary studies suggest that, in adolescents with T1D performing heavy exercise, plasma GLN is low after exercise; and GLN supplementation increases the likelihood of hypoglycemia after exercise.
As the patients studied presumably had no residual endogenous insulin secretion, our findings suggest that GLN may enhance glucose uptake and/or increase insulin sensitivity. These data, in addition to the data reviewed from other studies suggest that GLN supplementation may affect insulin sensitivity either at the peripheral or hepatic level in T1D. If proven true, these results could have important implications to improve glycemic control in T1D.

Fig.4 Time to post-exercise, nocturnal hypoglycemia (defined as first drop below 70mg/dL) in adolescents with T1DM after oral ingestion o glutamine or placebo [17]



b). Glucose-lowering Effects of Glutamine in Adolescents with Type I Diabetes [18] Torres, et, al (manuscript to be submitted for publication)
Thirteen pubertal adolescents (15.96±1.6 years [SD], 8M; 5F; BMI 69th ±16 centiles 6, HbA1C 8.2 ±0.5%, T1D: 7.5±4 yrs) on insulin pumps were randomized to receive a drink with GLN or placebo pre-exercise, bedtime and early morning (0.25 g/kg/dose) in a double-blind crossover design over 4 weeks. Exercise session (3pm) consisted of four 15-min treadmill/5-min rest cycles. Blood glucose (BG) was monitored during exercise and overnight. The following morning, a 5-hr primed, continuous infusion of D-[6, 6-$^2H_2$] glucose was administered, during a 2-dose hyperinsulinemic, euglycemic clamp (low dose: 8 mU/m^2/min; high dose: 80 mU/m^2/min) in the post absorptive state. BG levels dropped comparably during exercise on both days. However, the total number of nocturnal hypoglycemic events (17 vs. 7, p=0.045) and the cumulative probability of overnight hypoglycemia (50% vs. 33%, (p=0.02) were higher on the glutamine day than on the placebo day. During clamp, glucose infusion rate did not differ between days (7.7 ±1 mg/kg/min vs. 7.0 ± 1; glutamine vs. placebo; p=0.4). A correlation was noted between nocturnal hypoglycemic events and S_I on the glutamine day.
Our findings confirm our previous observations that glutamine has glucose-lowering effects in adolescents with type 1 diabetes after exercise no consistent change in insulin sensitivity was observed. Although a correlation was noted between nocturnal hypoglycemic events and insulin sensitivity on the glutamine day. The mechanisms mediating the effect of glutamine remain to be elucidated.

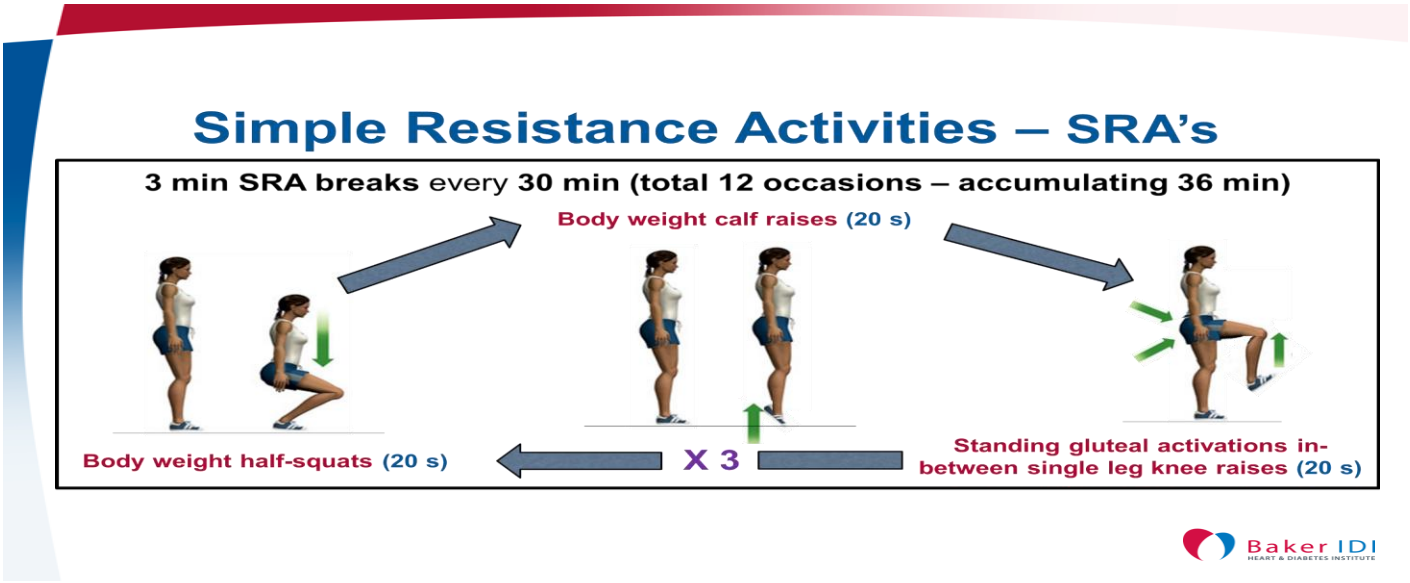
C). 'Exercise snacks' before meals to improve glycemic control in individuals with insulin resistance [16]. Francois, et al, Diabetologia, 2014

This study investigated whether small doses of intense exercise before each main meal ('exercise snacks') would result in better blood glucose control than a single bout of prolonged, continuous, moderate intensity exercise in individuals with insulin resistance. Nine adults with impaired glucose tolerance or type 2 diabetes completed three exercise interventions in randomized order. Measures were recorded across 3 days with exercise performed on the middle day, as either: 1) traditional continuous exercise (CONT), comprising 30 min moderate-intensity (60% of maximal heart rate [HRmax]) incline walking before dinner; (2) exercise snacking (ES), consisting of 6×1 min intense (90% HRmax) incline walking intervals 30 min before each meal; or (3) composite exercise snacking (CES), encompassing 6×1 min intervals alternating between walking and resistance-based exercise,30 min before meals. Meal timing and composition were controlled within participants for exercise interventions. Results: ES attenuated mean 3 h postprandial glucose concentration following breakfast (by 1.4±1.5 mmol/l, p=0.02) but not lunch (0.4±1.0 mmol/l, p=0.22), and was more effective than CONT following dinner (0.7±1.5 mmol/l below CONT; p=0.04). ES also reduced 24 h mean glucose concentration by 0.7±0.6 mmol/l (p=0.01) and this reduction persisted for the subsequent 24 h (lower by 0.6±0.4 mmol/l vs CONT, relative to their baselines; p=0.01). CES was just as effective as ES (p>0.05 for all glycemic variables) at improving glycemic control. Conclusions/interpretation dosing exercise as brief, intense exercise snacks before main meals is a time-efficient and effective approach to improve glycemic control in individuals with insulin resistance. **The effect of exercise snacks on glycemic control has not been addressed in adolescents with T1D.**

d). Interrupting Prolonged Sitting Modulates Glycemic Control in Adults with Type 2 Diabetes [David Dunstan and John Hawley to be presented at ADA meeting in 2015]

In this randomized crossover study, overweight/obese/ inactive adults with type 2 diabetes were included to study the effects of brief bouts of light intensity walking or simple resistance activities on lowering postprandial plasma glucose and improve glycemic control in TD patients. Eucaloric diet was consumed over 22 h (9am – 7am) while wearing a continuous glucose monitor system for 3 x 8 h conditions (6-day washout).

There were 3 groups 1) SIT: uninterrupted sitting (control); 2) LW: sitting + 3 min bouts of light-intensity walking at 3.2 km/h every 30 min; and 3) SRA: sitting + 3 min bouts of simple resistance activities (alternating half-squats, calf raises, brief gluteal contractions and knee raises) every 30 min (see below).



Over 22 h, both LW and SRA significantly reduced mean [interstitial] glucose, time in hyperglycemia and glycemic variability (quantified via the SD of mean glucose and mean amplitude of glycemic excursions) relative to uninterrupted sitting (Table). These simple interruptions to sitting significantly reduced the time in hyperglycemia, mean glucose and glycemic variability in adults with T2D. **This approach has not been studied yet in adolescents with type 1 diabetes.**

Table (A) Participant Characteristics and (B) Effects of the Three Trial Conditions on Glycemic Control

(A) Participant characteristics

Characteristic	*N or mean (95% CI)*
Number of study participants	14 M 10 F
Age (yr)	62.3 (64.8, 59.8)
BMI (kg/m^2)	33 (34.4, 31.7)
HbA1c (%)	7.2 (7.5, 7)

Note: All participants were Metformin/diet controlled individuals with type 2 diabetes.

(B) Effects of the three trial conditions on measures of glycemic control over 22 h

Measure of glycemic control	*SIT (control)*	*LW*	*SRA*
Time in hyperglycemia (%)	60.3 (49.2, 71.3)	37.5 (26.5, 48.6)**	26.5 (15.5, 37.6)**
Time in hyperglycemia (hr)	13.3 (10.8, 15.7)	8.3 (5.8, 10.7)**	5.8 (3.4, 8.3)**
Mean interstitial glucose (mg/dl)	11 (10.2, 11.8)	9.4 (8.5, 10.2)**	8.6 (7.8, 9.4)**
SD of mean interstitial glucose	2.2 (2, 2.5)	1.9 (1.7, 2.2)**	1.7 (1.5, 2)**
MAGE (mg/dl)	104.94 (92.11, 117.78)	85.5 (72.66, 98.34)**	76.18 (63.35, 89.02)**

SD=standard deviation; MAGE=mean amplitude of glycemic excursions.
*difference from SIT ($P < 0.05$);
**difference from SIT ($P < 0.001$);
Analysed using multi-level mixed models, controlling for age and BMI. Data are mean (95% CI).

IV. Research Design and Methods

In this protocol we will determine whether 'exercise snacks', alone or in combination with dietary glutamine supplementation over a period of 3 months improve glycemic control in adolescents with type 1 diabetes.

Inclusion/Exclusion Criteria:

Twenty-four adolescents with T1D for at least 12 months, between 13-19 yr-old will be recruited after informed written consent from their parents and the youngsters themselves. We will strive to recruit patients with comparable phenotype in both groups. They will be of normal weight (BMI between 10th and <85th percentile) and will be in puberty (at least Tanner stage III breast or genitalia) with a HbA1 between 7.5 and 9%. Subjects will be on either multiple daily injections (MDI) or insulin pump therapy. They will be recruited among the ~1,000 patients with T1D followed at Nemours Children's Clinic Jacksonville. We will exclude subjects with biopsy proven celiac disease, cystic fibrosis, chronic steroid therapy, mental retardation, microalbuminuria or evidence of other diabetic complications. Subjects involved in an active exercise program or in an organized sport team will be excluded. Studies will be conducted at least 2 weeks after resolution of any intercurrent infection.

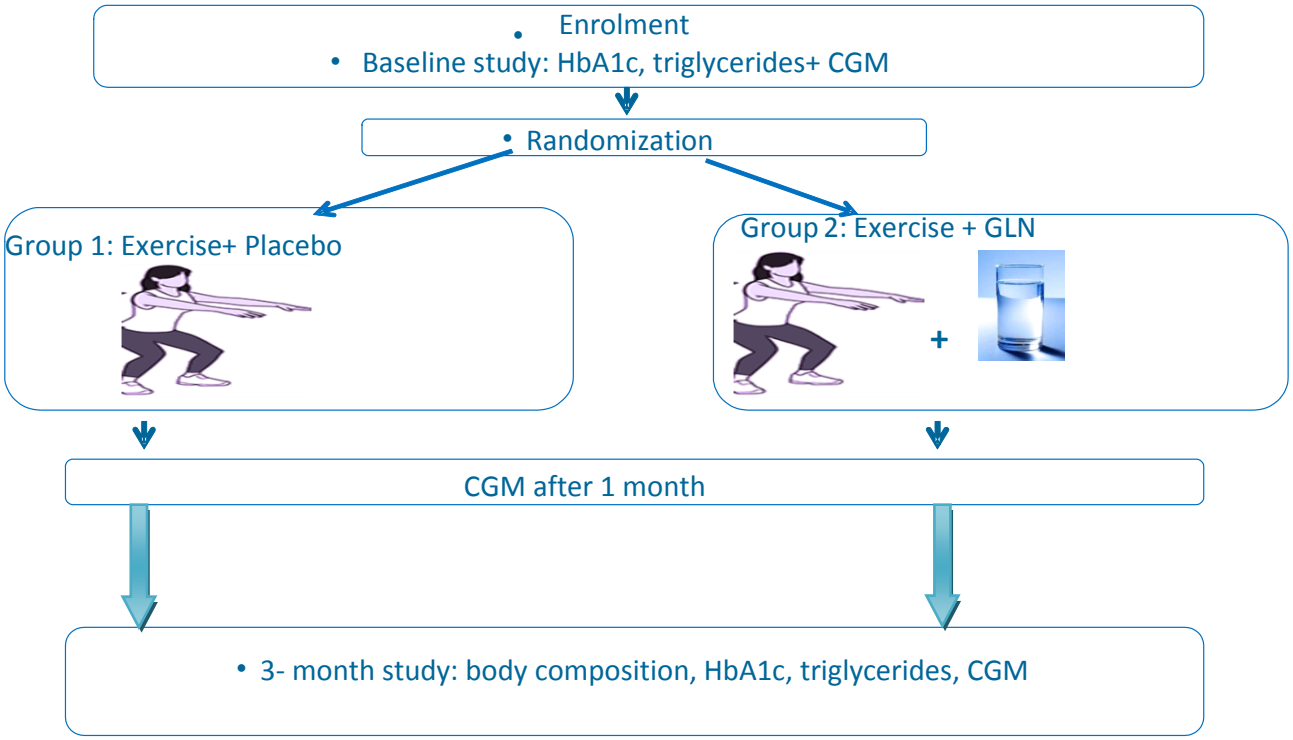
Procedures: All subjects will have a full physical exam including Tanner staging as well as waist circumference measurement. A HbA1c, will be obtained as well as fasting triglycerides. A continuous glucose monitor (CGM IPro®, Medtronic Minimed, or a DexCom ^4) will be worn blindly for 6 days and data downloaded. Subjects will then be randomized to 2 study groups of 12 patients each:

(A) an 'exercise group', in which subjects will perform daily 'exercise snacks' within 30 min before breakfast, lunch, and/or dinner or bedtime snack, along with a placebo drink;

(B) an ‘exercise + glutamine group’, in which subjects will receive a glutamine drink (0.25 g/kg per dose) before meals TID, and perform ‘exercise snacks’ before each meal.
Allocation to the exercise only or the exercise + glutamine group will be tsratified according to HbA1c range (eg, 7.5-7.9%; 8.0-8.4%; 8.5-9.0%), so as to ensure the comparability of groups.
The placebo and glutamine drink will be prepared at home using measuring spoons of glutamine or placebo powder to be mixed in a calorie-free, flavored soft drink tailored to the child’s individual taste. Patients, families and investigators will be blinded as to the contents of the supplement.
Exercise snacks will be designed to be feasible using 6 min worth of simple resistance activities (SRA’s) designed by the exercise physiology consultants, Drs. Churilla and Hawley. These will consist of activities such as alternating half-squats, calf raises, brief gluteal contractions and knee raises. A short video will be created showing the participants how to conduct these exercises and these will be updated periodically in order to keep their interest and compliance. We elected not to use an accelerometer as the data to be gathered from these would be less useful for the study given the short nature of these bouts of exercise. These will be completed 30 min before breakfast, lunch and dinner.

Patients will keep a record of their dietary intake and physical activity for 2 days while CGM is placed (one weekday+ one weekend day) at baseline, and at 1,and 3 months during the study. If the family has a smart phone, a free application will be installed which is “My diet diary calorie count “ for better assesment of total caloric intake during this study. Otherwise, a log book would be used. Compliance will be monitored by weekly contact with the study subjects either via phone call or text messaging or via MyNemours. A system of rewards will be implemented with a $10 gift card given per week with at least 50% compliance with study program, with an extra $25 for succesful wearing and downloading of the CGM at baseline and 3 months ($10x12w=$120, +$25x3=$75, Total=$195 per subject).

At one month visit after the enrollement, CGM will be placed again for 6 days, then all baseline studies, including CGM, HbA1c and triglycerides will be repeated at 3 months. Every patient will undergo a body composition analysis using a dual X-ray absorptiometry (DEXA) at the end of the study.Total insulin dosing will be carefully recorded as units/kg/day during the study.



- Assays – HbA1C will be measured using a DCA 2000 in clinic [17,18]. Triglycerides (TG) will be performed using an Olympus AU400e Chemistry.

-Calculations - An insulin sensitivity score (ISS) will be calculated as previously described using the SEARCH ISS model: $\log_e IS = 4.64725 – 0.02032$ (waist, cm) – 0.09779(HbA1c, %) – 0.00235(TG, mg/dl) (R^2=0.74 in the initial SEARCH model) [34-35]. This has been validated using the hyperinsulinemic euglycemic clamp, considered the gold standard for insulin sensitivity measures [34,35]. CGM data will be downloaded and used to calculate % blood glucose (BG) at, below or above target and the mean amplitude of glycemic excursions using a SAS program (MAGE) as previously described [17,21,22].

-Statistical Analysis and Statistical Power.

To determine whether short bouts of exercise and/or glutamine improve glycemic variability and diabetes control, we will compare the following parameters between baseline and 3 months:

a) Changes in HbA1C
b) Changes in MAGE
c) Changes in % BG at target (70-180), below target (<70), above target (>180)
d) Changes in ISS
e) Changes in total insulin dosing (units/kg/day)

A mixed effects models and/or generalized estimating equations (GEE), which ever appropriat ill be used within and between subjects and groups comparisons. Model assumptions will be checked be analyses. Significance will be established at $p<0.05$.

-Sample Size Justification: A sample size of 24 patients is planned assuming no more than 10% attrition rate. The main judgment criterion will be the mean amplitude of glycemic excursion (MAGE, measured using CGM). In the Australian study by Dunstan et al. [36]–described above in the Preliminary results section of this application– performed in adults with type 2 diabetes, MAGE was 104.9±12.8 mg/dl (mean ±SD) in the sedentary group of patients with type 2 diabetes, vs. 76.2±12.8 mg/dl—*i.e.*, a drop by 28.7–in the group performing short bouts of resistance exercise. To the best of our knowledge, there is no earlier study of such type of exercise in adolescents with T1D published in literature. Assuming 'exercise snacks' will decrease MAGE to the same extent in our population of children with T1D as in adults with T2D, such reduction will amount to an effect size of $\delta/\sigma=28.7/12.8\approx2.24$, where δ is the expected change in MAGE (104.9-76.2=28.7), and σ^2 the estimated variance of MAGE (σ=12.8, calculated based on John Hawley et al's data). Using equations for unpaired studies, the number (n) of subjects per group needed to detect such difference with an α risk<0.05, and a statistical power(1-β) of 80% can be estimated as: $n= 2 \times (Z_\alpha + Z_\beta)^2 / (\delta^2/\sigma^2)$ [37], where Z_α=1.96, and Z_β=0.84, therefore $n=2 \times (1.96 + 0.84)^2 / (2.24)^2 = 2 \times 7.84/5.02=3.1$. The enrolment of 12 patients per group therefore should be amply sufficient to test our hypothesis, even if we take into account a putative 25% attrition rate.

- Future Directions: These simple and short resistance activities as it was shown in previous studies [16, 36] have significantly reduced the time in hyperglycemia, mean glucose and glycemic variability in adults with T2D. With the ubiquity of sedentary behaviors and the low adherence to structured exercise, this approach has the potential to be beneficial and practical. This interesting approach has not been studied yet with combination of glutamine in patients with type 1 diabetes.

V. Facilities Required/Physical Location of Study

This study will be performed in outpatient settings and will recruit patients who are followed at the deivision of Endocrinology at the Nemours Children's Healthy System in Jacksonville.

VI. **References**

1. Bloch CA, Clemons P, Sperling MA: Puberty decreases insulin sensitivity. J Pediatr 110:481-487, 1987.
2. Caprio S, Cline G, Boulware S, Permanente C, Shulman GI, Sherwin RS, Tamborlane WV: Effects of puberty and diabetes on metabolism of insulin-sensitive fuels. Am J Physiol 266:E885-E891, 1994.
3. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV: Impaired insulin action in puberty. A contributing factor to poor glycemic control in adolescents with diabetes. N Engl J Med 315:215-219, 1986.
4. Arslanian S, Heil BV, Kalhan SC: Hepatic insulin action in adolescents with insulin-dependent diabetes mellitus: relationship with long-term glycemic control. Metabolism 42:283-290, 1993.
5. Richter EA, Hargreaves M. Exercise, GLUT4, and skeletal muscle glucose uptake. Physiol Rev 93:993-1017, 2013.
6. Wahren J, Felig P, Hagenfeldt L. Physical exercise and fuel homeostasis in diabetes mellitus. Diabetologia 14: 213–222, 1978.
7. Goodyear LJ, King PA, Hirshman MF, Thompson CM, Horton ED, Horton ES. Contractile activity increases plasma membrane glucose transporters in absence of insulin. Am J Physiol 258: E667–E672, 1990.
8. Wasserman DH, Geer RJ, Rice DE, Bracy D, Flakoll PJ, Brown LL, Hill JO, Abumrad NN. Interaction of exercise and insulin action in humans. Am J Physiol 260: E37–E45, 1991.
9. Baar K, Wende AR, Jones TE, Marison M, Nolte LA, Chen M, Kelly DP, Holloszy JO. Adaptations of skeletal muscle to exercise: rapid increase in the transcriptionalcoactivator PGC-1. FASEB J 16:1879-1886, 2002.
10. Koopman R, Manders RJ, Zorenc AH, Hul GB, Kuipers H, Keizer HA, van Loon LJ. A single session of resistance exercise enhances insulin sensitivity for at least 24 h in healthy men. Eur J Appl Physiol 94:180-187, 2005.
11. Silveira AP, Bentes CM, Costa PB, Simão R, Silva FC, Silva RP, Novaes JS. Acute effects of different intensities of resistance training on glycemic fluctuations in patients with type 1 diabetes mellitus. Res Sports Med 22:75-87, 2014.
12. Davey RJ, Howe W, Paramalingam N, Ferreira LD, Davis EA, Fournier PA, Jones TW. The effect of midday moderate-intensity exercise on postexercise hypoglycemia risk in individuals with type 1 diabetes. J Clin Endocrinol Metab 98:2908-2914, 2013.
13. Tonoli C, Heyman E, Roelands B, Buyse L, Cheung SS, Berthoin S, Meeusen R. Effects of different types of acute and chronic (training) exercise on glycaemic control in type 1 diabetes mellitus: a meta-analysis. Sports Med 42:1059-1080, 2012.
14. Egan AM, Mahmood WA, Fenton R, Redziniak N, Kyaw Tun T, Sreenan S, McDermott JH. Barriers to exercise in obese patients with type 2 diabetes. QJM 106:635-638, 2013.
15. Bautista L, Reininger B, Gay JL, Barroso CS, McCormick JB. Perceived barriers to exercise in Hispanic adults by level of activity. J Phys Act Health 8:916-925, 2011.
16. Francois ME, Baldi JC, Manning PJ, Lucas SJ, Hawley JA, Williams MJ, Cotter JD. 'Exercise snacks' before meals: a novel strategy to improve glycaemic control in individuals with insulin resistance. Diabetologia 57:1437-1445, 2014
17. Mauras N, Xing D, Fox LA, Englert K, Darmaun D. Effects of glutamine on glycemic control during and after exercise in adolescents with type 1 diabetes mellitus (T1DM): a pilot study. Diabetes Care 33:1951-1953, 2010.
18. Torres-Santiago L, Mauras N, Jobayer H, Weltman AL, Darmaun D. Glucose-lowering effects of glutamine in adolescents with type I diabetes are via insulin-independent mechanisms. Submitted for publication, 2014.
19. Camera DM, West DW, Phillips SM, Rerecich T, Stellingwerff T, Hawley JA, Coffey VG. Protein Ingestion Increases Myofibrillar Protein Synthesis after Concurrent Exercise. Med Sci Sports Exerc. 2014 May 27. [Epub ahead of print].
20. Stephenson EJ, Lessard SJ, Rivas DA, Watt MJ, Yaspelkis BB 3rd, Koch LG, Britton SL, Hawley JA. Exercise training enhances white adipose tissuemetabolism in rats selectively bred for low- or high-endurance running capacity. Am J Physiol 305:E429-438, 2013.
21. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359:1464-1476.
22. Mauras N, Beck R, Xing D, Ruedy K, Buckingham B, Tansey M, White NH, Weinzimer SA, Tamborlane W, Kollman C; Diabetes Research in Children Network (DirecNet) Study Group. A randomized clinical trial to

assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care 2012;35:204-210.
23. Vilsboll T, Holst JJ. Incretins, insulin secretion and type 2 diabetes mellitus. Diabetologia 47:357–66, 2004.
24. Samson SL, Garber A. GLP-1R agonist therapy for diabetes: benefits and potential risks. Curr Opin Endocrinol Diabetes Obes 2013 20:87-97, 2013.
25. Weissman PN, Carr MC, Ye J, Cirkel DT, Stewart M, Perry C, Pratley R. HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea. Diabetologia 57:2475-2484, 2014.
26. Ahrén B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, Feinglos MN; HARMONY 3 Study Group. HARMONY 3: 104-week randomized, double-blind, placebo- andactive-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. Diabetes Care 37:2141-2148, 2014.
27. Rosenstock J, Fonseca VA, Gross JL, Ratner RE, Ahrén B, Chow FC, Yang F, Miller D, Johnson SL, Stewart MW, Leiter LA; Harmony 6 Study Group. Advancing basal insulin replacement in type 2 diabetes inadequately controlled with insulin glargine plus oral agents: a comparison of adding albiglutide, a weekly GLP-1 receptor agonist, versus thrice-daily prandial insulin lispro. Diabetes Care 37:2317-2325, 2014.
28. Derosa G, Maffioli P. Safety and efficacy of albiglutide results from two trials. Nat Rev Endocrinol 10 :514–516, 2014.
29. Prigeon RL, Quddusi S, Paty B, D'Alessio DA. Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. Am J Physiol 285:E701–E707, 2003.
30. Parlevliet ET, de Leeuw van Weenen JE, Romijn JA, Pijl H. GLP-1 treatment reduces endogenous insulin resistance via activation of central GLP-1 receptors in mice fed a high-fat diet. Am J Physiol 299:E318-324, 2010.
31. Greenfield JR, Farooqi IS, Keogh JM, Henning E, Habib AM, Blackwood A, Reimann F, Holst JJ, Gribble FM. Oral glutamine increases circulating glucagon-like peptide 1, glucagon, and insulin concentrations in lean, obese, and type 2 diabetic subjects. Am J Clin Nutr 89:106-113, 2009.
32. Sherr J, Tsalikian E, Fox L, Buckingham B, Weinzimer S, Tamborlane WV, White NH, Arbelaez AM, Kollman C, Ruedy KJ, Cheng P, Beck RW, Diabetes Research in Children Network. Evolution of abnormal plasma glucagon responses to mixed-meal feedings in youth with type 1 diabetes during the first 2 years after diagnosis. Diabetes Care 37:1741–1744, 2014.
33. Hankard RG, Haymond MW, Darmaun D: Role of glutamine as a glucose precursor in fasting humans. *Diabetes* 46:1535-1541, 1997
34. Dabelea D[1], D'Agostino RB Jr, Mason CC, West N, Hamman RF, Mayer-Davis EJ, Maahs D, Klingensmith G, Knowler WC, Nadeau K.: Development, validation and use of an insulin sensitivity score in youths with diabetes: the SEARCH for Diabetes in Youth study. Diabetologia. 2011 Jan;54(1):78-86.
35. Specht BG, Wadwa RP, Snell-Bergeon JK, Nadeau KJ, Bishop FK, Maahs DM: Estimated Insulin Sensitivity and Cardiovascular Disease Risk Factors in Adolescents with and without Type 1 Diabetes J Pediatr. 2013 Feb;162(2):297-301.
36. Dunstan D, Hawely J: Interrupting Prolonged Sitting Modulates Glycemic Control in Adults with Type 2 Diabetes (An abstract would be presented at ADA, 2015)