Spring 2013

Effects of moderate to vigorous-intensity physical activity on nocturnal and next day hypoglycemia in adolescents with Type 1 Diabetes

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EFFECTS OF MODERATE TO VIGOROUS-INTENSITY PHYSICAL ACTIVITY ON NOCTURNAL AND NEXT DAY HYPOGLYCEMIA IN ADOLESCENTS WITH TYPE 1 DIABETES

by

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A thesis submitted in partial fulfillment
of the requirements for the Master of
Science degree in Health and Human Physiology
in the Graduate College of
The University of Iowa

May 2013

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MASTER'S THESIS

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ACKNOWLEDGMENTS

I would like to offer my special thanks to Dr. Kathleen Janz for her guidance and encouragement throughout the research project. I would also like to thank the other members of my thesis committee, Dr. Gary Pierce and Dr. Eva Tsalikian for their assistance and feedback throughout the project.

I also wish to thank the participants, as well as Ajay Singvhi, Cathy Chenard, Harold Winnike and the ICTS staff for their work with the participants. I would like to offer a very special thanks to Dr. Dale Esliger, who helped me organize and analyze the research data.

Finally, I wish to thank my family for their support and encouragement throughout the research project.

ABSTRACT

Physical activity (PA) provides many benefits to adolescents with type 1 diabetes (T1DM); however, adolescents with T1DM tend to have lower fitness and PA levels than their disease-free counterparts. One reason adolescents with T1DM engage in less PA is due to a fear of hypoglycemia. Most studies examining PA in relation to glycemic control measure PA through self-report, thus introducing bias. The purpose of this study was to objectively monitor PA and glucose in adolescents with T1DM to examine the temporal associations between moderate-to-vigorous intensity physical activity (MVPA) and hypoglycemia.

Twenty participants (14 to 19 yr, n=10 females and 10 males) with a clinical diagnosis of T1DM ≥ 1 year duration were recruited. Participant fitness was evaluated via indirect calorimetry (Parvo Medics, Sandy, UT) during a maximal treadmill exercise test, and body composition was measured using air displacement plethysmography (BOD POD Model 2007A, COSMED USA, Inc., Concord, CA). An accelerometer (GENEActiv, Activinsights Ltd, Kimbolton, UK) was worn on the wrist continuously for 3-5 days and the acceleration data were used to estimate MVPA in min/d. Blood glucose values were simultaneously tracked using continuous glucose monitoring (DexCom SEVEN PLUS, San Diego, CA). After controlling for sex, percent body fat (%BF), fitness, and next-day MVPA, the likelihood of hypoglycemia (≤ 70 mg/dl) at nighttime or the next day due to MVPA was examined using logistic regression.

Participants were of average fitness (females: 43.9 ml/kg/min; males: 49.8 ml/kg/min) and fatness (females: 26.2%; males: 19.2%), and 63.2% of participants met the US federal guideline of accumulating 60 min/d of MVPA. Hypoglycemia was 38% more likely in those who had 30 min/d more MVPA in the afternoon than those with less (95% CI: 1.13, 1.69; p=0.002).

The results indicate that participating in MVPA increases the risk of hypoglycemia later on. The relationship is independent of sex, %BF, fitness and next-day MVPA. While promoting PA as a healthy behavior, it is important to educate adolescents with T1DM on prevention of hypoglycemia following PA.

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CHAPTER 1 - SIGNIFICANCE

There are many known benefits of physical activity (PA) in adolescents. PA is associated with improved blood lipid profiles, cardiorespiratory fitness, bone health, self-esteem and psychological wellbeing. It is also negatively associated with levels of adiposity and stress. Not only are these health outcomes beneficial to adolescents, but the health outcomes and physically active behavior track into adulthood, further increasing the importance of regular participation in PA (Loprinzi, Cardinal, Loprinzi, & Lee, 2012). The US Department of Health and Human Services established guidelines for PA based on the number of minutes of moderate-to-vigorous intensity physical activity (MVPA) needed to realize positive health outcomes. The *2008 Physical Activity Guidelines for Americans* recommends a minimum of 60 minutes of MVPA daily for children and adolescents, citing the need for vigorous intensity activity, as well as muscle- and bone-strengthening activities to be a part of the 60 minutes. MVPA is characterized as any activity greater than or equal to 3 METs, or any activity eliciting a rating of at least 5 on a 0 to 10 point Rating of Perceived Exertion scale (US Department of Health and Human Services, 2008). Activities qualifying as MVPA include brisk walking, bike riding, running, and lap swimming. Regardless of the benefits of PA, the latest data from the 2011 Centers for Disease Control and Prevention (CDC) Youth Risk Behavior Surveillance System indicate that only 28.7% of high school students, nationwide, are meeting the federal guideline of accumulating 60 minutes of MVPA daily. Additionally, 13.8% of high school students did not participate in 60 minutes of MVPA on any days of the week (CDC, 2012). Research indicates that these numbers may be even lower for individuals with chronic diseases, including type 1 diabetes (T1DM) (Lukács et al., 2012; Maggio et al., 2010).

T1DM is an autoimmune disease characterized by lack of insulin production of the pancreas (Bar-Or & Rowland, 2004). In healthy individuals, there is a reduction in

insulin secretion and an increase in glucose counter-regulatory hormones, which facilitate an increase in liver glucose production to match that taken up by skeletal muscle during exercise. In individuals with T1DM, however, the counter-regulation system does not function properly, as insulin levels are not managed by the pancreas; thus, hypoglycemia can result from bouts of exercise because insulin levels either stay the same or increase (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008).

PA is important among adolescents with T1DM. It promotes weight control, decreases cardiovascular disease risk, increases sense of wellbeing, and increases bone density (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). These are important benefits, as cardiovascular disease is the leading cause of mortality among individuals with T1DM. While some studies have shown no benefit of PA on glycemic control, others have shown that PA can reduce insulin requirements by 6-15% (Chimen et al., 2012). Furthermore, participating in post-meal PA can aid in decreasing postprandial glucose spikes (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). Although PA can benefit individuals with T1DM, fitness and PA levels tend to be lower in these individuals than those with type 2 diabetes and individuals without disease (Chimen et al., 2012).

While PA is an important aspect of disease management for individuals with T1DM, along with nutrition and insulin therapy, it is often lacking. The problem of hypoglycemia may contribute to this lack of PA (Bernardini et al., 2004; Brazeau, Rabasa-lhoret, Strychar, & Mircescu, 2008). Episodes of hypoglycemia have been shown in children and adolescents participating in prolonged moderate PA greater than 60 minutes (The Diabetes Research in Children Network (DirecNet) Study Group, 2005). Moderate PA tends to illicit the greatest decreases in blood glucose levels both during and post-exercise, while the effects are blunted when participating in intermittent high intensity PA (Guelfi et al., 2005). Factors that affect the glycemic response to exercise of an individual with T1DM include exercise duration, intensity, familiarity with type of

activity, metabolic control, blood glucose levels, type and timing of insulin injections, type and timing of food intake, insulin absorption, muscle-mass required for activity, conditioning, degree of stress, and timing of activity. However, Robertson and colleagues also note that given consistent timing of exercise, amount of insulin and pre-exercise meal, the response to 60 minutes of intermittent exercise can be reproducible (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). In addition to increased bouts of hypoglycemia, individuals with T1DM have been shown to report a higher Rating of Perceived Exertion (RPE) at the same workload than their disease free peers (Bar-Or & Rowland, 2004). Fear of hypoglycemia and increased RPE may contribute to the lack of PA participation among this population.

Many studies have looked at PA and its effect on glycemic control, but most have used questionnaires or other forms of self-report to assess daily PA participation (Åman et al., 2009; Herbst, Bachran, Kapellen, & Holl, 2006; Schweiger, Klingensmith, & Snell-Bergeon, 2010; The Diabetes Research in Children Network (DirecNet) Study Group, 2005). While questionnaires are a valid, cost- and time-effective tool for assessing habitual PA, accelerometers are a more accurate measure of total PA level and energy expenditure. Additionally, accelerometers allow viewing of daily activity patterns (Westerterp, 2009). Although accelerometry is one of the best ways to assess habitual PA in free living situations, there are drawbacks to their use. Accelerometers can be more burdensome on the participants, many citing issues with the looks and comfort of waist-worn accelerometers, as well as fear of losing or breaking them (Audrey, Bell, Hughes, & Campbell, 2012).

PA has been shown to increase cardiorespiratory fitness in individuals with T1DM, decrease their risk for cardiovascular disease and depression, and decrease reliance on insulin (Chimen et al., 2012). Regardless of these benefits, physical fitness and activity levels are consistently lower in these individuals than in their disease free counterparts. Research has shown VO_2max values to be 3-10 ml/kg/min lower in

adolescents with T1DM than in healthy adolescents (Komatsu et al., 2005; Lukács et al., 2012). Additionally, research has shown that adolescents with T1DM spend about 17 fewer minutes in MVPA daily than healthy adolescents (Maggio et al., 2010). More research is needed to better assess these relationships, as well as to better understand the barriers to PA in this population. One commonly attributed barrier is fear of hypoglycemia. The aim of this study is to further analyze the relationship between MVPA and hypoglycemia through the assessment of their acute, temporal associations. Specific study aims include looking at the glycemic response, specifically bouts of hypoglycemia, to differing amounts of MVPA in adolescents with T1DM. Our specific research questions were: 1) What are the acute, temporal associations between MVPA and hypoglycemia in adolescents with T1DM? 2) Are these associations moderated by sex, fitness or adiposity?

CHAPTER 2 – LITERATURE REVIEW

Physical Activity

The benefits of PA are many; however, many children and adolescents still do not accumulate the recommended 60 minutes of MVPA per day. The 2008 US Physical Activity Guidelines recommend that children and adolescents accumulate at least 60 minutes of MVPA daily. The 60 minutes should include both moderate and vigorous intensity activity, and should also include muscle and bone strengthening activities (US Department of Health and Human Services, 2008). In a review of the literature completed by Loprinzi, Cardinal, Loprinzi and Lee (2012), they found that PA during childhood and adolescents has a beneficial effect on adiposity, bone health, psychological health and cardiorespiratory fitness. Additionally, they found that PA in childhood and adolescence tends to track into adulthood, which can further increase the benefits seen from PA, by seeing further improvements in cardiometabolic risk profile (Loprinzi, Cardinal, Loprinzi, & Lee, 2012). Despite the apparent benefits of PA, only 28.7% of high school students are currently meeting these guidelines (CDC, 2012). The relationship between PA, physical fitness and adiposity can be puzzling; this chapter aims to review the literature surrounding these complex relationships, as well as discuss T1DM, hypoglycemia and their relationship with PA.

In a cross-sectional review of 1075 adolescents, age 9-15, from the Swedish arm of the European Youth Heart Study, Ortega, Ruiz, Hurtig-Wennlof, Vicente-Rodriguez, Rizzo, Castillo and Sjostrom (2010) studied the interactions between physical fitness, PA levels and abdominal adiposity. The purpose of the study was to assess the relationship between PA and abdominal adiposity in adolescents, and to see if this relationship is modified by cardiorespiratory fitness (CRF). The researches collected anthropometry information including height and weight, to calculate BMI, waist circumference, and percent body fat, calculated from skinfolds. PA was objectively measured using the MTI

model WAM 7164 activity monitor worn at the hip, and reported as average time per day spent in MVPA. CRF was measured using a maximal exercise test on a cycle ergometer. Associations between these variables were assessed using multiple regression analyses. The researchers found that boys spent more time in both moderate (14%) and vigorous (46%) intensity PA than did girls. In assessing the relationship between fitness, fatness and level of PA, the researchers found that while CRF was negatively associated with waist circumference, this relationship was not affected by PA level, and there was no significant association between waist circumference and PA. When all factors were put into the model, however, positive associations were seen between PA level and abdominal adiposity. A positive association between MVPA and waist circumference was seen in adolescents with high cardiorespiratory fitness. These results were tested for possible confounders, but associations were not affected. This relationship is unexplainable, and should be further analyzed in a longitudinal study. It is possible that the measuring abdominal adiposity via waist circumference, rather than directly measuring adiposity affected the results. Additional confounding factors such as genetics and dietary intakes should be considered. In looking at adolescents with low CRF, vigorous PA was inversely associated with waist circumference These results suggest that cardiorespiratory fitness modifies the associations between PA and abdominal adiposity, but further study is needed to adequately understand the relationships (Ortega et al., 2010).

In a randomized, controlled trial, Kriemler, Zahner, Schindler, Meyer, Hartmann, Hebestreit, Brunner-La Rocca, van Mechelen, and Puder (2010) sought to improve aerobic fitness, PA, and quality of life, while decreasing body fat and cardiovascular risk profile through a school based PA intervention in 2 provinces in Switzerland. The intervention involved adding two additional physical education lessons per week, for a total of 5, incorporating 3-5 activity breaks into academic lessons each day, and assigning 10 minutes of PA homework each evening. Outcomes measured included body fat, BMI,

aerobic fitness, PA, quality of life, and a cardiovascular risk score of all metabolic syndrome components. Body fat was measured using skinfolds, aerobic fitness was measured via the 20 meter shuttle run test, PA was measured via accelerometry and quality of life was measured using questionnaires. The researchers observed a smaller increase in skin folds, BMI and most cardiovascular risk factors in the intervention group than in the control group. Additionally, the intervention group had a significantly greater increase in physical fitness and total minutes of MVPA. No differences were seen between the intervention and control groups in quality of life. The results of this study indicate that an intervention aimed at increasing PA level in children is associated with a favorable effect on body composition, aerobic fitness and cardiovascular risk profile (Kriemler et al., 2010).

Strengths of this study include its design of a randomized, controlled trial. The researchers also used high quality data collection procedures via the cardiovascular risk profile and the use of accelerometry to assess PA levels. The measure of cardiorespiratory fitness, however, was problematic. On the other hand, given the large cohort, performing the 20 meter shuttle run may have been the only feasible option. Much of the PA completed during the intervention was completed while school was in session; a long-term follow-up would be helpful, to see if increases in PA were sustained outside of school, and over the summer break.

Physical Activity Levels, Aerobic Capacity and Type I Diabetes

Levels of PA tend to be lower in adolescents with T1DM, when compared to their disease-free peers. In the following text, I will review the literature examining PA in children and adolescents with T1DM. Bernardini, Vanelli, Chiari, Iovane, Gelmetti, Vitale, and Errico (2004) investigated exercise adherence, time spent exercising and risk reduction measures in 91 adolescents with T1DM in a cross-sectional study. The

participants were aged 10-18 yr, and were recruited from outpatient clinics for the study. Demographic, anthropometric and diabetes marker information were collected on all participants; they completed a questionnaire concerning their time spent weekly in PA. PA participation was categorized as either "activities in spare time" or "competitive sports." Linear correlation coefficients were used to assess the relationship between metabolic control and time spent in PA. Participants reported spending 438 minutes per week in exercise, with no difference seen between boys and girls for duration. Sex differences in activity type did exist, with boys participating in competitive sports for 71 more minutes than did girls. Participants were asked to evaluate their PA levels before being diagnosed with T1DM and after. Interestingly, 81% of participants reported no change in their exercise patterns since diagnosis (Bernardini et al., 2004).

The researchers found glycemic control, as measured by HbA_{1c}, to be significantly correlated with the amount of activity accumulated throughout the week, with the highest values seen in participants exercising less than 60 minutes per week (HbA_{1c}: 8.9%). Participants who exercised 120-360 minutes per week had mean HbA_{1c} values of 8.3%, and those exercising 360-480 minutes per week had mean HbA_{1c} values of 8.0%. Lower values for HbA_{1c} are indicative of better glycemic control. Children and adolescents who participated in competitive sports showed better glycemic control than their active peers, whose activity was mostly spare time leisure activities. Contrary to other studies of children and adolescents with T1D, the researchers found that 60% of participants reported spending the recommended 60 minutes per day exercising (Bernardini et al., 2004). However, a limitation of this study was that usual weekly PA was measured using an administered questionnaire.

Using a cross-sectional study design, Schweiger, Klingensmith, and Snell-Bergeon (2010) examined the amount of PA acquired by adolescents with T1DM, as well as the relationship between amount of PA and glycemic control. They limited their analyses to female adolescents, studying 203 adolescent females with T1DM, age 11-19

yr. Past-week PA and habitual PA were measured via a PA questionnaire. The questionnaire found that participants were physically active for at least 60 minutes per day on average 2.6 days over the past week, and 3.1 days in a typical week. Additionally, only 4.7% of study participants met the federal guideline for PA of 60 minutes of MVPA daily. Level of PA decreased with age among participants, and non-Hispanic white females were most active. Additionally, more active females had lower HbA_{1c} values, indicating better glycemic control. Females who participated in PA ≥5 days per week had a mean HbA_{1c} value of 8.9, compared with 9.6 in those who participated in PA on ≤1 day per week (Schweiger, Klingensmith, & Snell-Bergeon, 2010).

While this study sampled a large population of adolescent females, it also had some limitations. Limitations included using self-report questionnaires to assess both past week PA and habitual PA. Additionally, there were no healthy controls included in this study to compare PA levels to. It has long been understood that PA levels decline in females throughout adolescence, so it would have been interesting to see how healthy adolescent females compare to those with T1DM.

In a cross-sectional study of 209 children and adolescents aged 4 to 18, Maggio, Hofer, Martin, Marchand, Beghetti and Farpour-Lambert (2010) compared PA and physical fitness levels in healthy children with levels in children with chronic diseases included T1DM, obesity and juvenile idiopathic arthritis. Participants underwent anthropometry assessments using BMI, cardiorespiratory fitness assessment using direct gas analysis during a maximal treadmill test and PA assessment, measured using ActiGraph accelerometers. Univariate linear regression analysis and Pearson correlation coefficient were used to assess significant relationships. An inverse relationship between age and PA was seen across all groups, which is consistent with the literature. After adjusting for age, daily PA intensity was lower among those with T1DM than their healthy counterparts (497 counts per minute vs. 668 counts per minute). Interestingly, daily PA values were also lower in participants with T1DM than those in the other

disease groups, including juvenile idiopathic arthritis and obesity. The researchers also looked at time spent MVPA per day in minutes. While the results were not significant between healthy children and those with T1DM, there was a visible difference, with healthy children participating in MVPA on average 17.3 minutes more per day. Maggio and colleagues also found that only 60.4% of healthy children met the recommended 60 minutes of MVPA per day; furthermore, only 38.5% of children with T1DM met the recommended amount of PA. Additionally, no significant difference was seen in cardiorespiratory fitness between the healthy participants and those with T1DM. There was no association seen between time spent in PA and level of cardiorespiratory fitness in participants with T1DM (Maggio et al., 2010).

This study had major limitations, however, in its data collection procedures. PA data was collected and analyzed on only 120 of the 209 participants, including only 13 individuals with T1DM, due to monitor failure. While this study had data collection issues, its findings were similar to other studies of PA levels in adolescents with T1DM.

With the aim of assessing PA and fitness levels in adolescents with T1DM, Cuenca-Garcia, Jago, Shield and Burren (2012) studied adolescents with T1DM, in comparison to their disease-free siblings in a case-control, cross-sectional study design. The researchers recruited children and adolescents from pediatric diabetes clinics, and asked about siblings who could be potential controls for the study. Anthropometric measures were taken, along with pubertal assessment and measures of PA and physical fitness. PA was measured for 7 days using the ActiGraph GT1M, and physical fitness was measured as physical work capacity at a heart rate of 170 bpm. Contrary to other studies, the researchers did not observe a difference in either level of PA or physical fitness between the adolescents with T1DM and their disease-free siblings. They did, however, find an association between PA and glycemic control; lower, more favorable HbA_{1c} values were associated with increased levels of MVPA. Results on the association between MVPA and glucose regulation are mixed, however, this study found a strong

correlation with MVPA predicting 30-37% of HbA_{1c} variance (R^2 = 0.295-0.374) (Cuenca-Garcia, Jago, Shield, & Burren, 2012).

A major strength of this study was their use of accelerometry to assess PA levels; the use of objective monitoring provides valid PA measures. Another study strength was the case-control design, using adolescents with T1DM and their siblings. The ability to compare results between individuals with T1DM to those without is extremely valuable. Using the siblings of the adolescents with T1DM controls for some potential confounding factors, such as genetics and household culture. A limitation of the study was their use of physical work capacity at 170 bpm to assess fitness. Using a maximal protocol could have provided more accurate fitness values.

Lukacs, Mayer, Juhasz, Varga, Fodor and Barkai (2012) also assessed physical fitness levels in children and adolescents with T1DM in a cross-sectional study. One hundred six children and adolescents with T1DM, and 130 healthy children and adolescents, aged 8 to 18, participated in fitness testing using the Eurofit physical fitness test. The Eurofit physical fitness test measures motor performance and cardiorespiratory fitness, with tests looking at balance, upper limb speed and coordination, flexibility, explosive strength of legs, static strength of hand and forearm, abdominal strength, upper body strength, running speed and agility, and VO_2max. VO_2max was predicted using the 20 meter endurance shuttle run. Additionally, anthropometric measures were taken, including a 4-site skin fold and BMI assessment. Participants also filled out either the Physical Activity Question for Older Children (PAQ-C) or the Physical Activity Questionnaire for Adolescents (PAQ-A). Results of each of these tests were compared with HbA_{1c} values, and correlations assessed using Spearman's correlation coefficients.

The researchers found that adolescent males and females with T1DM had lower VO_2max values than their age-matched controls, however, activity levels did not differ significantly, according to the PAQ-A results. The Eurofit testing battery also revealed that VO_2max and abdominal strength were significantly associated with HbA_{1c}. VO_2max

was the single best predictor, with higher values being associated with a more favorable HbA_{1c} value, indicating better long-term metabolic control. The researchers did not find BMI and skinfolds to be significantly associated with HbA_{1c} values, nor did these values differ significantly between the healthy participants and those with T1DM (Lukács et al., 2012).

Komatsu, Gabbay, Castro, Saraiva, Chacro, De Barros Neto, and Dib (2005) also compared aerobic exercise capacity in healthy adolescents to those with T1DM in a cross-sectional study. 72 adolescents with T1DM and 46 healthy adolescents, age 9-20 were recruited. Body composition was assessed using both BMI and dual energy X-ray absorptiometry. Aerobic capacity was determined using direct gas analysis during a maximal treadmill test. Correlation between the measured variables and diabetes markers was assessed using the chi-square test.

Similar to the previously discussed article, participants with T1DM showed no statistical differences when compared to the controls in anthropometric measures. The only differences seen were higher HbA_{1c} values in those with T1DM, which was to be expected. Significant differences were seen, however, in performance on the maximal $V0_2$ test. Individuals with T1DM showed a lower maximal heart rate, shorter time to exhaustion, lower peak VE, and lower peak VO_2 (Komatsu et al., 2005).

Nadeau, Regensteiner, Bauer, Brown, Dorosz, Hull, Zeitler, Draznin, and Reusch (2010) sought to analyze the relationship between insulin resistance in individuals with T1DM and cardiovascular fitness, as measured by VO_2max. Twelve adolescents with T1DM were compared with 12 healthy controls in a cross-sectional study to assess differences in cardiovascular fitness. Habitual PA was estimated using a 3-day PA recall questionnaire. VO_2max was also determined via a maximal graded exercise test using a cycle ergometer. Other measures include completion of an electrocardiogram as well as body composition determined by dual-energy x-ray absorptiometry.

The 3-day PA recall found no significant differences in amount of habitual PA between healthy participants and those with T1DM. However, despite similar reported levels of PA and similar maximal effort during VO_2max testing, the adolescents with T1DM had significantly lower VO_2max values than controls. Insulin sensitivity was shown to be a significant predictor of VO_2max. Other notable relationships were seen between VO_2max and LDL-cholesterol, as well as forearm blood flow. HbA_{1c} correlated with VO_2max in univariate analysis, but not when using multivariate analysis. This finding was different than in other studies reviewed that compared HbA_{1c} values with VO_2max. These findings indicate that the decrease in VO_2max may be more than simply an issue with glycemic control (Nadeau et al., 2010).

The strengths of this study include the data collection measures, including fasting laboratory testing, dual-energy x-ray absorptiometry, ECG, and maximal VO_2 testing via a cycle ergometer. Also, the use of healthy controls was a study strength. While the collection techniques for fitness and laboratory data were strengths of this study, measurement of habitual PA was a limitation. The researchers estimated habitual PA using a 3-day PA recall.

While other studies assessed cardiovascular fitness in adolescents with T1DM, Margeirsdottir, Larsen, Brunborg, Overby, and Dahl-Jorgensen (2008) assessed the prevalence of cardiovascular risk factors, using a cohort of children and adolescents already being followed via the population-based study, the Norwegian Childhood Diabetes and Quality (NCDQ) project. 576 children and adolescents with T1DM completed questionnaires to evaluate the prevalence of cardiovascular risk factors, as well as to assess PA and sedentary behaviors. The PA questionnaire included questions on school time and leisure time PA and sedentary behaviors, and provides information regarding activity patterns, activity time and activity intensity. All of this information was used to calculated total energy expenditure as an outcome value. Pearson's chi-square

tests were completed on categorical variables, while independent sample t tests were completed for continuous variables.

Of the participants, 86% had at least one risk factor for CVD, 45% had two or more, 15% had three or more, and 2% had four or more risk factors. The most common CVD risk factors were elevated HbA_{1c}, high LDL-cholesterol, family history of type 2 diabetes, family history of CVD and a blood pressure value greater than the 90^{th} percentile. However, the number of participants with elevated BP matches what would be expected in the general population. Physical inactivity was another prevalent risk factor for CVD, as only 48.1% of the participants who participated in the PA arm of the study met the recommended guidelines of participating in 60 minutes of MVPA per day (Margeirsdottir, Larsen, Brunborg, Øverby, & Dahl-Jørgensen, 2008).

The size of the study population and depth of data are definite strengths of this study. This research was completed as a part of the Norwegian Childhood Diabetes and Quality project, which includes all children and adolescents with T1DM in Norway. While this particular arm of the study had only a 35% participation rate, this still equated to 576 children and adolescents. While elevated LDL-cholesterol levels were found to be a prevalent CVD risk factor, the cholesterol values were not taken in a fasting state, which is a limitation to the study. Another limitation is that there is no control group; thus any comparisons that were made to non-diabetic adolescents were based upon data gathered in other research settings, under differing methods.

In an observational, cross sectional study of 100 adults with T1DM, Brazeau, Rabasa-Lhoret, Strychar and Mircescu (2008) sought to determine the most common barriers to PA in this population. The researchers administered a 44-item questionnaire to the Canadian participants during a routine office visit. The questionnaire required participants to rate how likely a barrier would keep them from engaging in PA over the next 6 months. The questionnaire also looked at social support and encouragement for PA. Additionally, participants self-reported severe hypoglycemic events over the past

year and what measures were taken to prevent them. HbA_{1c} was obtained from the participants' medical chart. The researchers found the greatest barriers to PA to be fear of hypoglycemia, work schedule, loss of control over diabetes and low levels of fitness. Knowledge of insulin pharmacokinetics and strategies to prevent hypoglycemia were related to the number of perceived barriers. Having someone to perform PA with was also associated with fewer perceived barriers (Brazeau, Rabasa-lhoret, Strychar, & Mircescu, 2008). While this information is not specific to adolescents, and there may be certain age-specific barriers, such as work schedule that do not apply to adolescents, this information is useful in understanding PA barriers in individuals with T1DM. The results also suggest ways to work with individuals in this population to overcome these barriers. The research suggests that fear of hypoglycemia is the most common barrier, but increasing knowledge around prevention strategies and individuals having others to be active with may lessen the severity of this perceived barrier.

Physical Activity and Hypoglycemia

Hypoglycemia occurs when blood glucose levels fall below a set value. Much of the research uses either 60 mg/dL or 70 mg/dL as the cutoff point for hypoglycemia; symptoms include hunger, fatigue, headaches, cognitive dysfunction, dizziness, blurred vision and aggressive behavior. Cases of severe hypoglycemia can lead to convulsions, seizures and even coma (Bar-Or & Rowland, 2004). Hypoglycemia is a common response to prolonged exercise in individuals with T1DM. While it can occur during or immediately following exercise, several hours post exercise is also recognized as a high risk time for hypoglycemia to occur. Bar-Or and Rowland discuss the inability of many children and adolescents with T1DM to correctly identify when they are having a hypoglycemic episode. This inability may lead to improper treatment of a hypoglycemic episode, and thus worse outcomes. Prevention of an exercise-induced hypoglycemic event involves both an increase in carbohydrate intake, as well as a reduction in insulin

dose prior to exercise (Bar-Or & Rowland, 2004). Hypoglycemia can have serious outcomes, and has been cited as a major barrier to PA among individuals with T1DM (Brazeau, Rabasa-lhoret, Strychar, & Mircescu, 2008). The study discussed below addresses the prevalence of hypoglycemia in adolescents with T1DM.

Using a cross-sectional design, Ahmet, Dagenais, Barrowman, Collins and Lawson (2011) studied the prevalence of nocturnal hypoglycemia in children and adolescents with T1DM. Participants wore a CGM for three consecutive days and continued with their usual insulin doses and routine diabetes care. Based upon a hypoglycemia definition of blood glucose of <70 mg/dL, for greater than 15 minutes, this study found that 68% of patients had at least one hypoglycemic episode, with an episode rate of 33.3% of patient-nights (Ahmet, Dagenais, Barrowman, Collins, & Lawson, 2011). This study shows the high prevalence of nocturnal hypoglycemia in children and adolescents with T1DM. It also suggests the value in using CGM to assess glucose levels, as some of these bouts of nocturnal hypoglycemia may go unnoticed if individuals are asymptomatic.

In an observational, cross sectional study across 19 countries, Aman, Skinner, de Beaufort, Swift, Aanstoot and Cameron (2009) investigated the effects of PA on glycemic control and psychological well-being in adolescents, age 11-18 yr, with T1DM. The researchers assessed glycemic control via HbA_{1c}, frequency of severe hypoglycemic events and diabetic ketoacidosis (DKA). PA data were collected via questionnaires, while diabetic information was collected via case report forms and capillary blood samples. In the 2093 participants analyzed, boys reported being physically active for at least 60 minutes on 4.2 days per week, while girls reported being physically active for at least 60 minutes on 3.6 days per week. The researchers found no association between level of PA and HbA_{1c}, hypoglycemia or DKA. They did, however, find PA to be positively associated with markers of psychological health, including well-being, less worry, greater perception of health, fewer symptoms and general improved quality of life (Åman et al.,

2009). The results of this study are consistent with others that fail to show an association between level of PA and metabolic control.

Strengths of this study include a large sample of adolescents with T1DM, from a wide array of study locations. The study also assessed sedentary behaviors, in addition to PA. While sedentary behavior is not the focus of this paper, it is an important aspect of health that is separate from PA. Additionally, the researchers looked at other benefits of PA, including markers of psychological well-being. A limitation of this study is their choice to measure PA and sedentary behavior via a 5 question questionnaire, limiting the data. It also would have been beneficial to follow this cohort longitudinally, rather than just compare their self-reported days of PA to case reports.

In a multi-center, cross-sectional analysis of over 19,000 children and adolescents with T1DM, Herbst, Bachran, Kapellen and Holl (2006) studied the effect of regular PA on frequency of severe hypoglycemia and HbA_{1c}. Regular physical activity (RPA) was measured as the number of times per week PA was performed for at least 30 minutes, with the exclusion of organized sport. Participants were grouped by RPA frequencies of none, 1-2 times per week, and 3 or more times per week. Hypoglycemia was split between severe hypoglycemia needing assistance from another person, and hypoglycemia with the occurrence of seizure or loss of consciousness. Results of the study indicate that RPA was one of the most important factors influencing HbA_{1c}, with children and adolescents with the highest levels of RPA having lower HbA_{1c} values. While the present study did not assess the relationship between RPA and mild hypoglycemia, there was no association between RPA and severe hypoglycemia. The results suggest that PA has a positive effect on glycemic control in individuals with T1DM, without increasing risk for severe hypoglycemia (Herbst, Bachran, Kapellen, & Holl, 2006).

Strengths of this study include a large sample size, and their outcome measures of severe hypoglycemia and HbA_{1c}. A limitation of this study is their method for assessing level of PA. They not only use a self-report measure, they only ask about PA of 30

minutes or more, while not specifying the total amount of activity for a given day. Additionally, organized sport is not included in this assessment, which may be a large portion of the activity accumulated by this age group.

The Diabetes Research in Children Network (DirecNet) Study Group (2005) has completed much research on the physiological outcomes of PA among children and adolescents with T1DM. In the paper "Impact of exercise on overnight glycemic control in children with type 1 diabetes mellitus" the researchers assessed the relationship between exercise and overnight hypoglycemia. 50 participants, age 10-18 yr, were assessed during two separate inpatient stays. Glucose was monitored during activity and throughout the following night. During the first visit, participants completed a 75 minute exercise session in the late afternoon, while there was no exercise during the second visit. The exercise session consisted of four 15 minute walking periods at a speed that would produce an exercise heart rate of 140 bpm. The walking periods were alternated with 5 minute rest periods. Blood glucose values were tracked during and post exercise, as well as every 30 minutes throughout sleep via an intravenous catheter. Hypoglycemia was defined as a glucose level of ≤60 mg/dL, and a hypoglycemia index was calculated for each subject to characterize the cumulative magnitude of hypoglycemia that occurred over night. Multivariate analysis was completed to compare overnight hypoglycemia between the exercise and non-exercise sessions.

Glucose values taken after the exercise session and throughout the night following exercise were significantly lower than the blood glucose values taken on the non-exercise day, even though blood glucose values were similar at the 4 p.m. reading directly before the exercise session. Additionally, the number of hypoglycemic events was greater on the exercise day, as was the hypoglycemia index, than on the non-exercise days. The risk of hypoglycemia was independent of glycemic control, as measured by HbA_{1c}. Additionally, participants who exercised more frequently at home, measured as the number of days in which the participant reported accumulating one hour of PA during a typical week, were

at a greater risk of nocturnal hypoglycemia. Another predictor of nocturnal hypoglycemia was the pre-bedtime snack glucose values. This was seen on both the exercise and non-exercise days, although a stronger predictor on the non-exercise day (The Diabetes Research in Children Network (DirecNet) Study Group, 2005).

Strengths of this study include direct measure of glucose after a controlled exercise session, where exercise and rest periods were regulated. It also looked at habitual PA, to see if there were any confounding effects. Additionally, the time of day that the exercise session was completed coincides with the timing of after school activities. This is beneficial in understanding glucose regulation in the hours following those activities. However, some limitations of the study include using self-reported usual PA as the measure for habitual PA. Also, completing an exercise session of 75 minutes of treadmill walking may not be indicative of true activity patterns in adolescents.

The DirecNet Study Group (2006) wrote a second paper based on the data collected in the study discussed above, titled "The effects of aerobic exercise on glucose and counterregulatory hormone concentrations in children with T1DM." In addition to the methods described above, blood samples were taken before, during and following the exercise session to assess concentrations of growth hormone, norepinephrine, cortisol and glucagon. ANCOVA was used to compare how these hormones differed between participants who experienced hypoglycemia during exercise versus those who did not. During and immediately following the exercise session blood glucose values dropped and were consistently lower than those taken at the same times during the non-exercise day. Blood glucose values dropped, on average, about 40% of baseline values. The strongest predictor of hypoglycemia was baseline blood glucose. Because of this, the researchers recommend achieving a baseline blood glucose value of at least 120 mg/dL prior to starting exercise. Additionally, a rise in circulating growth hormone concentration and norepinephrine was seen with exercise; however, the response seen was normal given the exercise load, and the response did not prevent hypoglycemia. Individuals who

experienced a hypoglycemic event had higher levels of circulating growth hormone and norepinephrine (The Diabetes Research in Children Network (DirecNet) Study Group, 2006a).

Guelfi, Jones, and Fournier (2005) sought to analyze the differences in blood glucose responses to different intensities of exercise in a cross-sectional study. Seven physically active participants with T1DM participated in two separate exercise sessions to assess the difference in glucose control given moderate intensity activity versus intermittent high intensity activity. Anthropometric and VO_2max data were collected at an initial visit, followed by two separate exercise sessions. During the moderate intensity exercise session, participants performed 30 minutes of activity on a cycle ergometer at 40% VO_2max. The intermittent high intensity exercise (IHE) session involved the same cycling exercise at 40% VO_2max, however, 4 second maximal effort sprints were incorporated every 2 minutes. This was done to simulate team sports that most adolescents participate in, where high intensity activity is interspersed within light and moderate intensity activity. Two-way repeated-measures ANOVA was completed to assess differences in the two exercise sessions. A decrease in blood glucose was seen during both exercise sessions, however, interestingly, the decline in blood glucose levels was less on the IHE day, than with the continuous moderate intensity activity. Additionally, blood glucose leveled off during the hour following IHE, while it continued to drop following moderate intensity activity. Interestingly, a greater amount of work was performed during the IHE protocol than during the moderate activity protocol, and higher heart rates were achieved, yet the hypoglycemic response was still blunted (Guelfi et al., 2005).

A benefit to this study is the focus on replicating sports that adolescents participate in, in terms of intensity. Many activities that children and adolescents participate are intermittent in nature, including organized and free-time activities. A downfall may be that cycling is most likely not the mode of exercise that most

adolescents participate in. Another benefit is the randomized cross-over design, where all participants take part in both exercise sessions, and efforts were taken to make the days as identical as possible. The study could be improved by following the participants' blood glucose values for a longer period of time post exercise to see the response. Hypoglycemia is often seen over night following exercise, it would be interesting to see the effects of IHE versus moderate activity on nocturnal glycemia levels. It would also be beneficial to complete this research in bouts of IHE greater than 30 minutes, as many sporting events and practices can last 60 to 90 minutes.

A third analysis completed by the DirecNet Study Group (2006) titled, "Prevention of hypoglycemia during exercise in children with T1DM by suspending basal insulin" aimed to assess the effectiveness of stopping basal insulin dosages on decreasing the frequency of hypoglycemia during exercise. In this study, 49 children and adolescents with T1DM using insulin pumps, aged 8 to17, were recruited and put through two days of exercise testing. The same exercise session was completed at both visits; the protocol was the same as that followed in previously discussed studies by the DirecNet Study Group. Basal insulin remained constant during one exercise session, while it was stopped for 2 hours during and following the exercise session during the other visit. Blood glucose concentrations were measured before, during and after the exercise session to assess the effectiveness of discontinuing basal insulin by pump during exercise on hypoglycemia. Hypoglycemia occurred in more participants during the exercise session where basal-insulin was given than in the exercise session where basal-insulin was stopped. Additionally, more hypoglycemic events were seen post-exercise in the basal-continued group. Given a hypoglycemic event, blood glucose values returned to normal quicker when basal-insulin was stopped. However, hyperglycemia was more commonly seen when basal-insulin was stopped (The Diabetes Research in Children Network (DirecNet) Study Group, 2006b).

Strategies for preventing exercise-induced hypoglycemia were also studied by Riddell and Milliken (2011). Twenty-five participants attending a diabetes specific youth sports camp were recruited to test a carbohydrate intake algorithm, wearing a CGM, while participating in the youth sports camp activities. The carbohydrate algorithm was designed to offer a recommended dose of fast-acting oral carbohydrate based upon current blood glucose level and the trend picked up by the CGM. The purpose being to find a way to keep blood glucose levels stable during sport and activity, without having to stop participation. The researchers found that using the CGM in conjunction with the algorithm was successful at maintaining glycemic control during and 1 hour post activity (Riddell & Milliken, 2011).

The ability to successfully maintain euglycemia during PA, without having the adolescents stop PA was a strength of this study. They also used standardized recommendations for fast-acting glucose that were not individualized to the participants, making the results easier to apply in other situations. Additionally, this occurred in a structured environment, where diabetes trained counselors were present to assist in making judgments regarding glucose supplementation. One limitation to the study was the absence of a controlled environment. Activity levels of the participants were unknown, as analysis was done during a sports camp. Although this could be considered a strength as well, as it may more closely match after school activities of adolescents with T1DM. Additionally, monitoring of blood glucose stopped after 1 hour post exercise. It would be beneficial to continue tracking of glucose values for a longer duration post-exercise, as this is a time when adolescents are at a higher risk of a hypoglycemic event.

Continuous Glucose Monitoring

Continuous glucose monitoring systems (CGMs) are needle-like sensors that are inserted subcutaneously to measure subcutaneous interstitial glucose levels. The sensors measure glucose every 10 seconds, and send 5-minute average glucose information to a

pocked-sized monitor to be read by the individual. The frequency of measurement can provide a deeper look into glucose fluctuations than measuring blood glucose levels (Adolfsson, Nilsson, & Lindblad, 2011). Bode and Battelino (2010) completed an analysis of multiple randomized control trials completed to assess the efficacy of using real time-CGM monitors in the routine care of individuals with T1DM. Their review showed that CGM is effective, and is becoming the standard in self-management of glucose monitoring in T1DM. More research, however, is needed to assess its impact on hypoglycemia (Bode & Battelino, 2010).

Bettelino, Phillip, Bratina, Nimri, Oskarsson and Bolinder (2011) sought to assess the effect of wearing a CGM on hypoglycemia in children and adults with T1DM. The researchers recruited 120 participants from local diabetes registries to participate in a randomized, controlled, multicenter trial. Participants were randomized to a control group of blood glucose monitoring with a masked CGM to be worn every second week, or an intervention group with real-time CGM for 26 weeks. Outcomes assessed included time spent in hypoglycemia and HbA_{1c}. Time spent in hypoglycemia was significantly lower in the CGM group, than in the control group; this outcome was seen during the first month of intervention, and was sustained throughout the duration of the intervention. Additionally, the CGM group saw significant decreases in HbA_{1c} values, indicating better glycemic control. While this study could not be blinded, it was a strong study design, as it was a randomized, controlled trial. This study showed a significant benefit on glycemic control of wearing a CGM (Battelino et al., 2011).

In a cross-sectional study of 58 adolescents, age 14-19, Adolfsson, Nilsson and Lindblad (2011) evaluated the efficacy of using CGMs during different intensity levels of PA to assess glucose levels. The researchers recruited the adolescents to participate in two-day sports camps, where they participated in differing levels of PA, including soccer, floorball, cross-country skiing, and golf. Blood glucose was measured by health care professionals before and after meals, immediately before, during and after exercise and

once overnight. Additional measures were taken if participants experienced symptoms of hyperglycemia or hypoglycemia. Participants wore a Medtronic CGM to concurrently measure subcutaneous interstitial glucose; values were reviewed each evening. Mean absolute relative difference (MARD) was calculated between the CGM and blood glucose readings. An overall correlation coefficient of 0.87 was seen between CGMs and blood glucose measurements. This correlation varied with glucose level; MARD was higher when glucose values were in the hypoglycemic range, and were lower in the hyperglycemic range, with the CGMs detecting more episodes of both hypo- and hyperglycemia. This increase in detection occurred both during PA and during subsequent hours, including overnight. Ultimately, Adolfsson and colleagues found CGMs to be an adequate method of collecting glucose data on individuals with T1DM during PA, as well as following activity, while decreasing the burden of self-measurement. An additional benefit of CGMs is the frequency of readings, which can increase detection of hypo- and hyperglycemic events that may have otherwise gone unnoticed (Adolfsson, Nilsson, & Lindblad, 2011).

Physical Activity Tracking and Accelerometry

Many studies assess the relationships between PA and health outcomes. A common method for measuring levels of PA is self-report. Diabetes research is no different; the majority of PA studies completed in individuals with T1DM use self-report methods. Self-report methods include PA diaries, interviewer-administered questionnaires, self-administered questionnaires and proxy questionnaires (Dale, Welk, & Matthews, 2002). While self-report methods have been shown to have adequate reliability and validity, there are some limitations to using this method, including difficulty with participants recalling physical activities, misinterpretation of the questions, and difficulty assessing all aspects of PA, including frequency, type, intensity and duration. In addition, issues with social desirability may arise in how questionnaires

are responded to (Dale, Welk, & Matthews, 2002). Other, less common methods for assessing free-living PA include heart rate monitors, pedometers, indirect calorimetry, and doubly-labeled water. While heart rate monitors can provide valuable information on duration and intensity of exercise, they do not account for non-exercise induced increases in heart rate. They can also be very uncomfortable for long-term wear. Pedometers are devices that assess the number of steps taken in a given time period, and the distance covered. They can be useful in assessing walking behavior, but miss other physical activities, such as cycling. Additionally, pedometers cannot provide information on time and intensity of movement, can miscalculate distances based on stride-length differences, and if they have an output screen, have the ability to change the behavior of the individual wearing it. Lastly, indirect calorimetry and doubly-labeled water are two of the most valid ways to assess energy expenditure. They do not, however, provide contextual information regarding participant PA patterns. They are also expensive, and indirect calorimetry is extremely invasive on the participants (Dale, Welk, & Matthews, 2002). Because of the measurement and cost issues associated with other measures of PA, accelerometers have become a popular method for collecting PA in free-living situations. The benefits of using accelerometry include their ability to objectively measure body movement in free-living situations, they provide information on frequency, intensity and duration of activity, they are easy to use and are fairly non-invasive to participants. While there are benefits to accelerometry, it has its drawbacks as well; this includes higher cost than other popular methods, their inability to measure certain activities with less hip-acceleration, including cycling, and their inability to detect incline or carrying a load (Dale, Welk, & Matthews, 2002). Additionally, many accelerometers are worn at the hip, which can be uncomfortable for participants. Drawbacks and benefits of different types of accelerometers are discussed in more detail below.

Klaas Westerterp (2009) published a review of PA assessment methods. For PA monitoring to be successful, the method of measurement must be objective and reliable.

For collected information to be useful, it should span multiple days so that it is representative of habitual PA. For this reason, the method of data collection must be tolerable and provide minimal discomfort to the participants. Methods of measuring PA range from behavioral observation and questionnaires to more physiological methods, including calorimetry and using motion sensors. While calorimetry is the gold standard for assessing total energy expenditure, it is not always the most feasible or accessible way to measure PA patterns. The use of motion sensors, more specifically, accelerometers, is a good alternative to tracking PA. Many accelerometers have been validated against doubly-labeled water, to validate their ability to measure total energy expenditure. Additionally, they have the ability to store PA data to study patterns of PA, including frequency, intensity and duration. Westerterp found the best method for assessing habitual PA to be accelerometry, more specifically an accelerometer that has been validated using doubly-labeled water (Westerterp, 2009).

In a cross-sectional study of 492 adolescents, age 12-16, Machado-Rodrigues, Coelho-E-Silva, Mota, Cyrino, Cumming, Riddoch, Beunen and Malina (2011) compared self-reported and objective estimates of activity energy expenditure using 3-day diaries and accelerometry. The researchers acknowledged that there are no PA measures that can accurately reflect all aspects of PA. Self-report methods of PA measurement, such as questionnaires and diaries can be a cost-effective method, and are beneficial in large studies, however, they rely on the participants ability to recall the information, and can often be biased based upon social desirability. Accelerometry is a valid and reliable measure of the frequency, intensity and duration of activity, but is often more expensive than self-report methods, and can be more invasive for the subject. The researchers in this study sought to evaluate objective and subjective measures of PA in adolescents, and to review the effect of sex, age and weight on these measures. Participants wore an ActiGraph GT1M accelerometer, as well as kept a 3-day activity diary to assess levels of PA. The researchers found the activity diary to underestimate activity energy

expenditure, and the correlation between the diary and accelerometry was only moderate (Machado-Rodrigues et al., 2011).

Objective monitoring of PA, using accelerometry has been shown to be the best way to assess daily PA levels of study participants. As was shown in the literature reviewed above, many studies do not objectively monitor PA levels, but rather rely on less valid methods, such as PA questionnaires. Some reasons for this may include cost and ease of data collection. While these barriers relate to the researchers, Audrey, Bell, Hughes and Campbell (2012) sought to assess participant views on accelerometer use. Throughout the Activity and Healthy Eating in Adolescence (AHEAD) study, Audrey and colleagues assessed adolescent views on accelerometer use after wearing the ActiGraph GT1M accelerometer for seven days during two separate phases of the study. Throughout the study, focus groups were conducted to discuss feelings about the accelerometers. Additionally, information regarding the accelerometers was collected via questionnaires post intervention. The main reasons found for not wearing an accelerometer were absenteeism on the day the accelerometers were distributed and worry about losing or breaking the monitor. The researchers showed that participants who were compliant in wearing the monitors were also concerned about losing or breaking the monitors, which may have affected their decision to wear it in certain circumstances. Other findings included that participants thought the monitors were uncomfortable to wear, that they got in the way while trying to be active, and that they did not like the belts that the accelerometers were worn on. While both sexes had an issue about belt appearance, this seemed to be a greater issue for the girls when they were wearing nice clothes. This may have affected wear time during non-school hours, especially over the weekends. An issue also arose with making it clear that the accelerometers should be worn during a typical week, when there are not special activities planned that may affect habitual levels of PA (Audrey, Bell, Hughes, & Campbell, 2012).

Newer monitors on the market, such as the GENEA accelerometer, attempt to fix the barriers seen by most study participants. The GENEA accelerometer is a waterproof, wrist-worm accelerometer; this allows participants to wear the accelerometer 24 hours per day, and attempts to lessen the burden by allowing it to be worn on the wrist, as opposed to an elastic belt at the hip. Esliger, Rowlands, Hurst, Catt, Murray, and Eston (2011) were the first to study these accelerometers. Esliger and colleagues examined the technical reliability and validity of the GENEA accelerometer and compare it to other popular accelerometers on the market. Additionally, they sought to set value thresholds for light, moderate and vigorous intensity PA in adults. The researchers measured technical reliability and validity using a Multi-Axis Shaking Table. While the shaking table was designed to mimic spatial motion in three-dimensions, this study only validated vertical motion. The researchers found the GENEA accelerometers to have good intra-instrument and inter-instrument reliability, 1.8% and 2.4% respectively. They also showed excellent validity (r=0.97).

The study also sought to compare the GENEA accelerometer (now called GENEActiv) against the ActiGraph GT1M and RT3 accelerometers, and set intensity threshold cutpoints. To complete this arm of the study, the researchers recruited 60 adults (age 40-65 yr) for a single visit. Participants wore three GENEA accelerometers, one on each wrist and one positioned over the right hip, in addition to the other two accelerometers, also placed over the right hip adjacent to the GENEA. While wearing the 5 accelerometers, participants were asked to complete 10-12 semi-structured activities, such as lying, seated work, treadmill walking and free-living walking. Indirect calorimetry data was simultaneously collected. When compared to VO_2, as measured using indirect calorimetry, the GENEA showed excellent criterion validity across all activities and wear locations (left wrist, r=0.86; right wrist, r=0.83; waist, r=0.87), and when worn at the wrist, showed similar criterion validity to both the ActiGraph GT1M (r=0.86) and the RT3 (r=0.88). Additionally, researchers used receiver operating

characteristic (ROC) curve analysis to create intensity cutpoints for sedentary, light, moderate and vigorous activity given each of the three wear locations (Esliger et al., 2011).

Strengths of this study were their comparison of the GENEA accelerometers to both a mechanical shaker table, as well as more activity specific criterion, such as indirect calorimetry and 2 commonly used accelerometers. Additionally, the development of cutpoints for activity intensity using the ROC curve was a useful aside. Some limitations of the study include only validating the vertical axis with the shaker table, and not comparing the GENEA to the more widely used triaxial ActiGraph GT3x+.

Following the validation paper by Esliger and colleagues, Phillips, Parfitt, and Rowlands (2012) sought to validate the GENEA accelerometer in children and adolescents, and create PA intensity cutpoints specifically for children. To achieve this, the researchers recruited 44 children and adolescents aged 8-14 to wear the GENEA accelerometers at multiple wear locations (both wrists and right hip), along with the ActiGraph GT1M at the hip, and a gas analyzer while completing 7 activities of daily living, such as lying, watching a DVD, playing active computer games and walking and running at various speeds. Mixed model ANOVA was used to assess differences between accelerometers and wear locations, and Pearson's r values were calculated to assess validity at all wear locations. The GENEA accelerometers showed good criterion and concurrent validity at each wrist, however, the validity was excellent at the waist, and showed similar values to that of the ActiGraph GT1M.

Similar to Esliger and colleagues, the researchers used ROC curve analysis to create PA intensity cutpoints. Age-specific values were used to convert VO_2 values into METs, and the standard MET cutoff values (3 METs for moderate-intensity, 6 METs for vigorous-intensity) were used. This different from the approach of Esliger and colleagues, who used elevated MET cutpoints of 4 METs and 7 METs for moderate- and vigorous-intensity activity, respectively. The wrist worn GENEA accelerometers were

best able to classify sedentary activities, while they had the lowest sensitivity and specificity values for moderate intensity activity, when compared with the other intensities. The researchers did, however, acknowledge that the lower validity values of the wrist worn monitors is only a small compromise if the comfort of wear location increases wear compliance in the study population. Ultimately, the researchers developed intensity cutpoints for each wear location that appeared to be valid for the entire age range analyzed in the study. The GENEA accelerometer was shown to be a valid tool for use in children for PA studies (Phillips, Parfitt, & Rowlands, 2012).

The previous literature review shows the importance of PA and physical fitness as important aspects of daily living for adolescents with T1DM. What is still unclear, however, are the nuances of the relationship between PA, physical fitness and its effect on blood glucose levels in adolescents with T1DM. While PA provides many benefits to the cardiovascular well-being of these adolescents, there is a warranted fear of hypoglycemia during and following activity in this population. Because of this, we often see lower levels of PA and lower fitness levels in adolescents with T1DM, than in their disease-free peers. A better understanding of the relationship between PA and hypoglycemia is necessary to provide more education and promotion of PA to adolescents in this population. My present study aims to further clarify the relationship between PA and T1DM using new technologies. Through the use of CGM and accelerometry, this study aims to understand the temporal relationship between PA and glucose regulation. If the relationships between PA and hypoglycemia can be clarified, adolescents can be provided with the tools necessary to participate in PA while managing blood glucose values, and avoiding bouts of hypoglycemia.

CHAPTER 3 – RESEARCH PAPER

Abstract

Physical activity (PA) provides many benefits to adolescents with type 1 diabetes (T1DM); however, adolescents with T1DM tend to have lower fitness and PA levels than their disease-free counterparts. One reason adolescents with T1DM engage in less PA is due to a fear of hypoglycemia. Most studies examining PA in relation to glycemic control measure PA through self-report, thus introducing bias. The purpose of this study was to objectively monitor PA and glucose in adolescents with T1DM to examine the temporal associations between moderate-to-vigorous intensity physical activity (MVPA) and hypoglycemia.

Twenty participants (14 to 19 yr, n=10 females and 10 males) with a clinical diagnosis of T1DM ≥ 1 year duration were recruited. Participant fitness was evaluated via indirect calorimetry (Parvo Medics, Sandy, UT) during a maximal treadmill exercise test, and body composition was measured using air displacement plethysmography (BOD POD Model 2007A, COSMED USA, Inc., Concord, CA). An accelerometer (GENEActiv, Activinsights Ltd, Kimbolton, UK) was worn on the wrist continuously for 3-5 days and the acceleration data were used to estimate MVPA in min/d. Blood glucose values were simultaneously tracked using continuous glucose monitoring (DexCom SEVEN PLUS, San Diego, CA). After controlling for sex, percent body fat (%BF), fitness, and next day MVPA, the likelihood of hypoglycemia (≤ 70 mg/dL) at nighttime or the next day due to MVPA was examined using logistic regression.

Participants were of average fitness (females: 43.9 ml/kg/min; males: 49.8 ml/kg/min) and fatness (females: 26.2%; males: 19.2%), and 63.2% of participants met the US federal guideline of accumulating 60 min/d of MVPA. Hypoglycemia was 38% more likely in those who had 30 min/d more MVPA in the afternoon than those with less (95% CI: 1.13, 1.69; p=0.002).

The results indicate that participating in MVPA increases the risk of hypoglycemia later on. The relationship is independent of sex, %BF, fitness and next-day MVPA. While promoting PA as a healthy behavior, it is important to educate adolescents with T1DM on prevention of hypoglycemia following PA.

Funding

This work was supported by a grant from the Doris Duke Charitable Foundation and the National Center for Advancing Translational Sciences, and the National Institutes of Health (NIH), through Grant 2 UL1 TR000442-06 for the Institute for Clinical and Translational Sciences.

Background

There are many known benefits of physical activity (PA) in adolescents. PA is associated with improved blood lipid profiles, cardiorespiratory fitness, bone health, self-esteem and psychological wellbeing. It is also negatively associated with levels of adiposity and stress. Not only are these health outcomes beneficial to adolescents, but the health outcomes and physically active behavior track into adulthood, further increasing the importance of regular participation in PA (Loprinzi, Cardinal, Loprinzi, & Lee, 2012). The US Department of Health and Human Services established guidelines for PA based on the number of minutes of moderate- to vigorous-intensity physical activity (MVPA) needed to realize positive health outcomes. The *2008 Physical Activity Guidelines for Americans* recommends a minimum of 60 minutes of MVPA daily for children and adolescents, citing the need for vigorous intensity activity, as well as muscle- and bone-strengthening activities to be a part of the 60 minutes. MVPA is characterized as any activity greater than or equal to 3 METs, or any activity eliciting a rating of at least 5 on a 0 to 10 point Rating of Perceived Exertion scale (US Department of Health and Human Services, 2008). Activities qualifying as MVPA include brisk walking, bike riding, running, and lap swimming. Regardless of the benefits of PA, the

latest data from the 2011 Centers for Disease Control and Prevention (CDC) Youth Risk Behavior Surveillance System indicate that only 28.7% of high school students, nationwide, are meeting the federal guideline of accumulating 60 minutes of MVPA daily. Additionally, 13.8% of high school students did not participate in 60 minutes of MVPA on any days of the week (CDC, 2012). Research indicates that these numbers may be even lower for individuals with chronic diseases, including type 1 diabetes (T1DM) (Lukács et al., 2012; Maggio et al., 2010).

While counter-regulatory systems that keep insulin levels in check do not function properly in individuals with T1DM, increasing the risk of exercise induced hypoglycemia, PA is still important. It promotes weight control, decreases cardiovascular disease risk, increases a sense of wellbeing, and increases bone density (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). These are important benefits, as cardiovascular disease is the leading cause of mortality among individuals with T1DM. Some studies have shown no benefit of PA on glycemic control, as measured by $HbA_{1C.}$ Others, however, have shown that PA can reduce insulin requirements by 6-15% (Chimen et al., 2012). Furthermore, participating in post-meal PA can aid in decreasing postprandial glucose spikes (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). Although PA can benefit individuals with T1DM, fitness and PA levels tend to be lower in these individuals than those with type 2 diabetes and individuals without disease (Chimen et al., 2012).

The relationship between PA and glycemic control may be moderated by certain factors. Research regarding the association between VO_2max and HbA_{1c} has been inconclusive. While some research has shown VO_2max to be inversely associated with HbA_{1c}, citing it to be the single best predictor of long-term metabolic control (Lukács et al., 2012), other studies have failed to show an association (Cuenca-Garcia, Jago, Shield, & Burren, 2012; Nadeau et al., 2010). Additionally, research on the relationship between adiposity and HbA_{1c} has shown mixed results. Research has shown BMI and adiposity to

be positively associated with HbA_{1c} (Herbst, Bachran, Kapellen, & Holl, 2006), however, others have failed to show a significant association (Lukács et al., 2012; The Diabetes Research in Children Network (DirecNet) Study Group, 2005). Sex may be another important modifier in the relationship between PA and glycemic control. Some research shows a lack of association (The Diabetes Research in Children Network (DirecNet) Study Group, 2005), while others cite sex as being an important predictor to HbA_{1c}, indicating that males have more favorable HbA_{1c} values than females (Herbst, Bachran, Kapellen, & Holl, 2006).

PA is an important aspect of disease management for individuals with T1DM, along with nutrition and insulin therapy, however, it is often lacking. The problem of hypoglycemia may contribute to the lack of PA (Bernardini et al., 2004; Brazeau, Rabasa-lhoret, Strychar, & Mircescu, 2008). Episodes of hypoglycemia have been shown in children and adolescents participating in prolonged moderate PA greater than 60 minutes (The Diabetes Research in Children Network (DirecNet) Study Group, 2005). Factors that affect the glycemic response to exercise of an individual with T1DM include exercise duration, intensity, familiarity with type of activity, metabolic control, blood glucose levels, type and timing of insulin injections, type and timing of food intake, insulin absorption, muscle-mass required for activity, conditioning, degree of stress, and timing of activity. However, Robertson and colleagues note that given consistent timing of exercise, amount of insulin and pre-exercise meal, the response to 60 minutes of intermittent exercise can be reproducible (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). In addition to increased bouts of hypoglycemia, individuals with T1DM have been shown to report a higher Rating of Perceived Exertion (RPE) at the same workload than their disease free peers (Bar-Or & Rowland, 2004). Fear of hypoglycemia and increased RPE may contribute to the lack of PA participation among this population.

Many studies have looked at PA and its effect on glycemic control, but most have used questionnaires or other forms of self-report to assess daily PA participation (Åman

et al., 2009; Herbst, Bachran, Kapellen, & Holl, 2006; Schweiger, Klingensmith, & Snell-Bergeon, 2010; The Diabetes Research in Children Network (DirecNet) Study Group, 2005). While questionnaires are a valid, cost- and time-effective tool for assessing habitual PA, accelerometers are a more accurate measure of total PA level and energy expenditure. Additionally, accelerometers allow viewing of daily activity patterns (Westerterp, 2009). Although accelerometry is one of the best ways to assess habitual PA in free living situations, there are drawbacks to their use. Accelerometers can be more burdensome on the participants, many citing issues with the looks and comfort of waist-worn accelerometers, as well as fear of losing or breaking them (Audrey, Bell, Hughes, & Campbell, 2012).

PA has been shown to increase cardiorespiratory fitness in individuals with T1DM, decrease their risk for cardiovascular disease and depression, and decrease reliance on insulin (Chimen et al., 2012). Regardless of these benefits, physical fitness and activity levels are consistently lower in these individuals than in their disease free counterparts. Research has shown VO_2max values to be 3-10 ml/kg/min lower in adolescents with T1DM than in healthy adolescents (Komatsu et al., 2005; Lukács et al., 2012). Additionally, research has shown that adolescents with T1DM spend about 17 fewer minutes in MVPA daily than healthy adolescents (Maggio et al., 2010). More research is needed to better assess these relationships, as well as to better understand the barriers to PA in this population. One commonly attributed barrier is fear of hypoglycemia. The aim of this study is to further analyze the relationship between MVPA and hypoglycemia through the assessment of their acute, temporal associations. Specific study aims include looking at the glycemic response, specifically bouts of hypoglycemia, to differing amounts of MVPA in adolescents with T1DM. Our specific research questions were: 1) What are the acute, temporal associations between MVPA and hypoglycemia in adolescents with T1DM? 2) Are these associations moderated by sex, fitness or adiposity?

Methods

Consent Procedures

The Institutional Review Board at the University of Iowa approved the study protocol and consent form. A parent or guardian provided written consent for all participants less than 18 years old, and participants provided assent. Participants 18-19 years old provided their own consent.

Eligibility Criteria and Assessment

To be eligible for the study, the participant had to 1) be between ages 14 and 19 years of age, post-menarche or at least Tanner stage III for girls and at least Tanner stage III for boys, 2) have a clinical diagnosis of T1DM of ≥ 1 year duration, 3) have a stable insulin regimen using an insulin pump or multiple daily injections for at least 12 months prior, 4) have a $HbA_{1c} \leq 10.0\%$ in the past 3 months measured with the DCA 2000 (Bayer Diagnostics, Tarrytown, NY), 5) have a BMI between the 5th and 95th percentile for age and sex, 6) have normal TSH in the past 12 months, 7) be willing and able to complete exercise protocols and all study requirements. Participants were not eligible if they 1) were hospitalized in the past month, 2) used systemic glucocorticoids in the past month, 3) had a musculoskeletal problem or physical or mental illness that may affect exercise performance, or 4) had a medical condition or were using a medication that, in the judgment of the investigator, could affect completion of the exercise protocol.

Study Procedures

The study consisted of two visits to the Clinical Research Unit of the Institute for Clinical and Translational Science at the University of Iowa (ICTS) separated by 3-5 days. During the first visit the CGM was calibrated and inserted subcutaneously and the participant was instructed in its use. Anthropometric measures were taken, and an

accelerometer was placed on the left-wrist. VO_2 max testing was performed. Participants wore the CGM and accelerometer until they returned for the second study visit.

Glucose

Glucose values were measured in mg/dL using CGM (DexCom SEVEN PLUS® CGM, San Diego, CA). Glucose was checked during the initial visit using a home glucose meter at 2:00, 3:00 and 4:00 p.m. and these values were used to calibrate the CGM. The CGM was placed subcutaneously during the initial visit to the ICTS, and was removed upon completion of a second visit to the ICTS 3-5 days later. The CGM collected glucose readings every 5 minutes, 24 hours per day. Data from the CGM were downloaded during the second visit, and glucose values were used to calculate the proportion of readings qualified as a hypoglycemic event. A hypoglycemic event was defined as any CGM reading ≤70 mg/dL.

Anthropometry

Height (cm) was measured using a wall-mounted stadiometer to the nearest 0.1 centimeter, and weight (kg) was measured on a calibrated beam balance platform scale to the nearest 0.1 kilogram.

Adiposity

Body fat was measured using air displacement plethysmography via the BOD POD® *Gold Standard* Body Composition Tracking System (Model 2007A, COSMED USA, Inc., Concord, CA). The BOD POD uses body mass and body volume to calculate body density in g/mL. Body mass is measured using a platform scale connected to the BOD POD, and body volume is measured using air displacement. Body density is then used to calculate percent body fat (%BF) using the Lohman density equation. The BOD POD has excellent validity when compared with dual energy x-ray absorptiometry (DXA) in young females, with an intraclass correlation coefficient of 0.92 (Maddalozzo,

Cardinal, & Snow, 2002). In adolescent males, the BOD POD has a correlation coefficient of 0.90 when compared to hydrostatic weighing (Moon et al., 2008).

Cardiovascular Fitness

Cardiovascular fitness (VO_2max) was measured via maximal exercise testing to volitional fatigue by open circuit spirometry using a metabolic cart (Parvo Medics, Sandy, UT). Participants were fitted with a heart rate chest strap (Polar USA, Lake Success, New York) before completing a modified Balke treadmill protocol. Immediately before testing, participants were seated for 5 minutes after which resting heart rate and blood pressure were measured. Individuals then practiced walking on the treadmill while being given instructions on proper treadmill walking technique (e.g. not holding onto bars and minimizing trunk flexion). Participants then self-selected a brisk but comfortable walking pace, speeds ranged from 3.0 to 4.0 mph at 0% grade, for an initial 4-minute warm-up. While keeping the speed constant, the grade was then increased to 5% for 4 minutes. Speed was increased by 0.5 mph for two minutes, after which the grade was increased by 2% each minute until exhaustion (Nemeth et al., 2009). During the test, measures of gas exchange and heart rate were recorded. RPE was assessed using Borg's 15-point scale during each stage. Participants were considered to have reached their maximal effort when 2 of the following criteria were met: 1) heart rate ≥ 200; 2) respiratory exchange ratio > 1.0; 3) ≤ 2 ml/kg/min change in VO_2 in final 60 seconds of test. VO_2max in ml/kg/min was used in analysis.

Physical Activity

Prior to fitness testing, a GENEActiv accelerometer (Device Model 1.1, GENEActiv, Activinsights Ltd, Kimbolton, UK) was placed on the left wrist, to be worn between the two clinic visits for 3-5 days. The GENEActiv has excellent criterion validity in both adults (r=0.86) and children (0.91) when worn at the left wrist (Esliger et al., 2011; Phillips, Parfitt, & Rowlands, 2012). Accelerometers were programmed to

collect data, starting on the initial visit day, at a frequency of 75.00 Hz. Participants were instructed to wear the monitor 24 hours per day, including while sleeping and during water activities. Accelerometers were removed at the completion of the participants' second visit to the ICTS and data were downloaded. MVPA (min/day) was calculated for each participant-day using the raw acceleration output, converted to 60 second epochs using the GENEActiv Post-Processing PC Software (Version 2.2, GENEActiv, Activinsights Ltd, Kimbolton, UK). Sixty second epoch data was entered into an Excel macro which used the magnitude of acceleration data to classify activity as sedentary, light, moderate or vigorous intensity. Validated acceleration magnitude cutpoints from Esliger and colleagues were used to classify activity intensity (Esliger et al., 2011). KineSoft software (Version 3.3.75, KineSoft, Loughborough, UK) was used to produce a series of standardized accelerometry outcome variables following procedures similar to those described by Esliger and colleagues (Esliger & Tremblay, 2007; Esliger et al., 2010). KineSoft was also used to produce heat maps, which show the amount of time spent in each activity intensity each day. Hours of the day were split in two for analysis: daytime PA, defined as 6:00 a.m. through 3:00 p.m.; and after school/evening PA, defined as the post-school day activity hours of 3:00 p.m. through going to bed.

Statistical Analysis

Descriptive statistics, including mean, standard deviation and range, were calculated for MVPA (min/day), VO_2 max (ml/kg/min), adiposity (%BF), and number of hypoglycemic events. Sex-specific differences were evaluated using independent sample t-tests. Hypoglycemia was represented by the proportion of hypoglycemic events occurring overnight and the next day following activity. Analysis of the association between MVPA and hypoglycemic events was completed using individual days of data collection, rather than participants. A timeline of the analyses can be viewed in Figure A1. Statistically significant associations between MVPA and bouts of hypoglycemia

were assessed using logistic regression. In this analysis, MVPA was analyzed using 30 minute increments and was compared with bouts of hypoglycemia. From the logistic regression, odds ratio and 95% confidence intervals were calculated. All models were adjusted for sex, VO_2max, percent body fat, and total next-day MVPA. P-values of less than 0.05 were considered to be statistically significant. All statistical analyses were performed using SAS (SAS Version 9.3, SAS, Cary, NC).

Results

Twenty adolescents participated in the study, however analyses are based on 67 days of data on 19 participants, as one participant was lost to non-compliance with study procedures. Average age of participants was 16.6 ± 1.6 yr; 53% were female. Participants were of average fitness with an average VO_2max of 43.8 ml/kg/min for females (SD = 6.8), and 49.8 ml/kg/min for males (SD = 6.8) (Shvartz & Reibold, 1990). Participants also had average levels of adiposity with the average percent body fat in females of 26.1% (SD = 4.8), while males had an average of 19.1% (SD = 9.3) (Ogden, Li, Freedman, Borrud, & Flegal, 2011). Sixty-three percent of participants met the US federal guideline for adolescents of accumulating 60 minutes per day of MVPA (US Department of Health and Human Services, 2008). Descriptive statistics for participants are shown in Table A1. The average minutes of MVPA per day was 108.9 ± 56.2 minutes in males and 114.6 ± 48.6 minutes in females. Descriptive statistics for MVPA and hypoglycemia are shown in Table A2. There were no statistically significant differences between male and female participants. A heat map of average time spent in sedentary, light, moderate and vigorous physical activities by all participants is shown in Figure A2. The figure shows that participants spent the majority of morning and during-school hours in sedentary and light activity, and MVPA levels increased in the early afternoon hours.

Of the 19 participants, 18 experienced at least one bout of hypoglycemia over the 67 participant-days analyzed. The median number of hypoglycemic readings was 3 (range = 0, 53). The mean proportion of CGM readings with a hypoglycemic event was 4.67% for overnight (11 p.m. to 6 a.m.) and 5.01% for the day following activity (6 a.m. to 11 p.m.).

Overnight and Next Day Hypoglycemia

Risk of hypoglycemia, given increased MVPA, was calculated using logistic regression (n=52); adjusted and unadjusted results are presented in Table A3. Odds ratios were adjusted for sex, VO_2max, % body fat and next day MVPA. Total MVPA was significantly associated with overnight and next day hypoglycemia (OR: 1.25; 95% CI: 1.07, 1.45; p = 0.005). In the adjusted model, for every 30 min/day increase in MVPA, overnight and next-day hypoglycemia risk increases by 25%. MVPA accumulated during the daytime hours, defined as 6:00 a.m. through 3:00 p.m., did not have a statistically significant effect on overnight and next day hypoglycemia (OR: 1.10; 95% CI: 0.83, 1.44; p = 0.496). In the adjusted model, accumulating an additional 30 min/day of MVPA in the after school/evening hours, defined as 3:00 p.m. through going to bed, had a statistically significant odds ratio of 1.38 (95% CI: 1.13, 1.69; p = 0.002) for events of overnight and next day hypoglycemia. The full adjusted model is shown in Table A4 and Table A5. Sex was significant in the adjusted model for afternoon MVPA.

Overnight Hypoglycemia

Risk of hypoglycemia occurring overnight (11 p.m. – 6 a.m.) was calculated using logistic regression (n=67); adjusted and unadjusted results are presented in Table A3. In the adjusted model, total MVPA was not significantly associated with bouts of hypoglycemia overnight (OR: 1.25; 95% CI: 0.90, 1.75; p = 0.182). MVPA accumulated during the daytime hours did not have a statistically significant effect on overnight

hypoglycemia (OR: 1.36; 95% CI: 0.74, 2.51; p = 0.314), nor did MVPA accumulated during the after school/evening hours (OR: 1.26; 95% CI: 0.82, 1.93; p = 0.275).

Next Day Hypoglycemia

Risk of hypoglycemia occurring the next day following activity (6 a.m. – 11 p.m.) was calculated using logistic regression (n=50); adjusted and unadjusted results are presented in Table A3. In the adjusted model, total MVPA was significantly associated with next day hypoglycemia (OR: 1.26; 95% CI: 1.06, 1.49; p = 0.010). Increasing total MVPA by 30 min/day significantly increased risk of next day hypoglycemia by 26% when adjusting for next day MVPA. MVPA accumulated during the daytime hours did not have a statistically significant effect on next day hypoglycemia (OR: 0.98; 95% CI: 0.73, 1.32; p = 0.878). In the adjusted model, accumulating an additional 30 min/day of MVPA in the after school/evening hours, defined as 3:00 p.m. through going to bed, had a statistically significant odds ratio of 1.40 (95% CI: 1.14, 1.73; p = 0.002) for next day hypoglycemia. VO_2max was significant in the adjusted model for afternoon MVPA.

Discussion

While PA provides many benefits to adolescents with T1DM, including improvements in cardiovascular risk profile, cardiorespiratory fitness, bone health, and adiposity, there is a risk of hypoglycemia in the hours and day following activity. The results of the present study indicate that 30 minute increases in MVPA increase the risk of hypoglycemia the next day following activity by 40%, indicative of a dose response. When analysis was further broken down, it was revealed that the increased risk is throughout the next day following activity. This relationship is independent of sex, fitness and adiposity, and was stronger when adjusting for next day MVPA.

This study found that increasing the amount of MVPA accumulated in a given day increases the likelihood of experiencing a bout of hypoglycemia throughout the next day following activity. The risk was shown to be even greater for hypoglycemia if PA is

done in the afternoon hours, as opposed to in the morning or during school hours. This may, however, be due to the fact that participants accumulated more MVPA during the after school/evening hours than during the daytime hours. Data were also collected on weekend days. Analysis was completed on all days and weekdays only, however the results were not affected by removing weekend days from analysis. Final analysis includes all days of the week.

Overall, sex, fitness and adiposity did not have an effect on hypoglycemic events. Sex, however, was significant in the relationship between afternoon/evening MVPA and overnight and next day hypoglycemia. Previous literature on the relationship between these covariates and hypoglycemia has been mixed. While other studies have shown cardiovascular fitness to be associated with glycemic control, there was no association seen in our study (Lukács et al., 2012; Nadeau et al., 2010). This suggests that PA effects glycemic control, independent of fitness. Fitness was, however, significant in the relationship between afternoon/evening MVPA and next day hypoglycemia. Participants in our study were of average fitness; these results are in disagreement with much of the previous literature, which indicates that adolescents with T1DM have lower levels of fitness. Adiposity was also insignificant in its effect on hypoglycemia. While hypoglycemia is an acute response to exercise, adiposity and fitness are stable traits. Additionally, participants were of average adiposity levels. Participant adiposity levels and the lack of variability may contribute to why there is no statistically significant association seen.

The average PA pattern of all participants is shown in Figure A2. The heat map represents all 19 participants, for each day that they wore the accelerometer, and shows the time spent in each intensity of PA in minutes per hour throughout each day. The heat map allows patterns of average activity to be seen across the entire week. The majority of each hour is spent in sedentary and light-intensity activity, with the highest amounts of MVPA occurring in the late afternoon and early evening hours. We did not analyze

sedentary and light-intensity PA. Due to small sample size, our a priori analysis was between MVPA and hypoglycemia, as informed by the literature (The Diabetes Research in Children Network (DirecNet) Study Group, 2005). The participants in our study, on average, accumulated more daily MVPA than has been reported in previous studies (Cuenca-Garcia, Jago, Shield, & Burren, 2012; Maggio et al., 2010). Average MVPA was 108.9 ± 56.2 for males and 114.6 ± 48.6 for females. Because of study requirements of completing exercise testing, more active and fit individuals may have volunteered.

MVPA was assessed as total daily minutes of MVPA, and also by splitting the day in two portions; daytime hours and after school/evening hours. This divide was made to assess the effect of MVPA accumulated during after school hours, which was the most common time to participate in MVPA, and is also the time of many practices for organized athletics. Figure A3 shows the average PA pattern of all participants across a weekday. When looking at total MVPA, there was a significantly increased risk of next day hypoglycemia, as well as overnight and next day combined. The present study did not find a statistically significant increase in risk of hypoglycemia when looking solely at the overnight hours following activity. This is inconsistent with previous research completed by the DirecNet Study Group that found an increased risk of nocturnal hypoglycemia (The Diabetes Research in Children Network (DirecNet) Study Group, 2005). This extended risk of hypoglycemia may be due to increased glucose transport into skeletal muscle. Glucose transport is stimulated not only by insulin, but also by muscle contractions occurring during activity; these effects can be seen for many hours post exercise (Goodyear & Kahn, 1998; Koistinen & Zierath, 2002).

Assessing the temporal associations of MVPA and hypoglycemia furthers the research in this area and is a novel analysis. Previous research has found an increased risk of nocturnal hypoglycemia following PA (The Diabetes Research in Children Network (DirecNet) Study Group, 2005), however, the analysis ends after overnight hours. Other studies assessed physical activity patterns using HbA_{1c}, rather than looking at acute

glucose effects (Bernardini et al., 2004; Cuenca-Garcia, Jago, Shield, & Burren, 2012; Schweiger, Klingensmith, & Snell-Bergeon, 2010). This study assessed acute effects of MVPA, and continued analysis into the following day, finding an increased window of time where adolescents are at continued risk of hypoglycemia. It provides a warning that an active day may trigger a hypoglycemic event up to 32 hours post activity.

Promoting PA in adolescents with T1DM is an important aspect in their disease management process. This research suggests the importance of including education on the prevention of hypoglycemia following PA in health promotion efforts. Studies have cited fear of hypoglycemia as a main barrier to PA in this group, thus providing education and tools to avoid hypoglycemia is of the utmost importance (Brazeau, Rabasa-lhoret, Strychar, & Mircescu, 2008). Other studies, however, have noted that given consistent timing of exercise, amount of insulin and pre-exercise meal, the response to 60 minutes of intermittent exercise can be reproducible (Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2008). This is important to emphasize when educating adolescents with T1DM about disease management.

Strengths of the current study include the use of valid measures to obtain study values. This includes the measurement of VO_2max using indirect calorimetry during a maximal exercise test to volitional fatigue, as well as using air displacement plethysmography to assess percent body fat. Another strength was the use of new technologies, including CGM and 24-hour accelerometry to assess the temporal relationships between MVPA and hypoglycemia. The use of CGM allowed for glucose measurements to be taken round the clock, while the use of the GENEActiv accelerometer allowed for 24-hour monitoring of PA. Additionally, much of the research in PA and adolescents with T1DM has been completed in a controlled laboratory setting. The use of CGM and accelerometry allowed for the analysis of the PA and hypoglycemia relationship in a free-living setting, permitting the measurement of normal daily activity for study participants.

Use of the GENEActiv accelerometer is a strength of this study; it was used to decrease monitor compliance issues seen with other accelerometers. The accelerometer was worn at the wrist, and is waterproof, ensuring participants are able to comfortably wear the accelerometer 24 hours per day, resulting in full-day data collection. Because the CGM was worn at the waist, it was important to use an accelerometer worn elsewhere, to ensure participant comfort. The excellent accelerometer compliance of 92% seen in this study was likely due to the wrist-worn model being more comfortable to participants than an accelerometer worn at the hip on an elastic belt. Accelerometer compliance was measured as the percentage of days with at least 600 minutes of wear time. Another benefit of the GENEActiv is that data is collected in units of raw acceleration (Esliger et al., 2011). While many commonly used accelerometers use proprietary movement counts, the use of raw acceleration counts allows for more meaningful data output. To my knowledge, this is the first time the GENEActiv accelerometer has been used in a study assessing free-living daily PA patterns.

Limitations of the present study include a small, convenience sample size and few data collection days. Including more days in our analysis would have provided a stronger measure of usual MVPA, however, we were analyzing the acute effects of MVPA on hypoglycemia and characterizing usual activity was not a main focus. Additionally, there were no dietary measures collected. Diet is an important aspect of glycemic control, and could affect hypoglycemic events. Lastly, the adolescents' willingness to participate in the study may bias the results. Maximal exercise testing was required of all participants, which may have attracted more active individuals. This may be why our participants had higher fitness and MVPA levels than studies of similar populations.

The present study provides a novel look at the temporal associations between PA and hypoglycemia in a free-living environment. This is the first study, to my knowledge, to assess this temporal pattern using 24 hour tracking of glucose via CGM, and PA via wrist-worn accelerometry. The study results reveal an increased risk of hypoglycemia

during the next day following activity seen with increasing afternoon MVPA. Future analyses should be completed to assess next day glucose values by time of day, rather than the whole day. This will allow us to determine a time of highest risk of hypoglycemia. Additional research should be completed to duplicate these findings with a larger sample size and having participants wear the CGM and accelerometer for a longer time period. Work should also be completed to assess the barriers to PA in this population, and interventions to help them overcome those barriers and find methods to avoid hypoglycemia.

APPENDIX

Table A1. Participant Characteristics

	Males (n = 9)	**Females (n = 10)**
Age (yr)	16.7 ± 1.9	16.5 ± 1.3
Height (m)	1.7 ± 0.1	1.6 ± 0.1
Weight (kg)	65.2 ± 12.7	60.5 ± 7.9
% BF[a]	19.2 ± 9.4	26.2 ± 4.8
VO_2max[b]	49.8 ± 6.8	43.9 ± 6.4

Values are presented as mean ± SD

SD, standard deviation

[a] Percentage of body fat determined by air displacement plethysmography

[b] VO_2max measured using indirect calorimetry in a maximal exercise test

Table A2. Descriptive Statistics for Participant MVPA and Hypoglycemia Events

	Males (n = 9)[a]	**Females (n = 10)[a]**
MVPA Total (min)[b]	108.9 ± 56.2	114.6 ± 48.6
MVPA 6:00 a.m. – 2:59 p.m. (min)	46.4 ± 36.9	52.5 ± 28.8
MVPA 3:00 p.m. – Bedtime[c] (min)	62.5 ± 34.3	62.1 ± 39.8
Overnight/Next Day Hypoglycemia (%)[d]	6.0 (4.0, 9.0)	3.7 (2.3, 6.1)
Overnight Hypoglycemia (%)[e]	4.9 (2.2, 10.8)	4.5 (2.1, 9.5)
Next Day Hypoglycemia (%)[f]	6.8 (4.4, 10.5)	3.4 (1.8, 6.2)

Values are presented as mean ± SD

SD, standard deviation

[a] Data were collected for 33 days for males and 34 days for females

[b] Moderate to vigorous-intensity physical activity

[c] Bedtime varied by participant. Times ranged from 8:00 p.m. to 3:00 a.m., with an average bedtime of 11:18 p.m.

[d] Proportion of readings with hypoglycemic event (glucose ≤ 70 mg/dL). Values presented as proportion (95% CI)

[e] 11:00 p.m. – 6:00 a.m.

[f] 6:00 a.m. – 11:00 p.m. following day

Table A3. Odds Ratios for Temporal Associations Between Daily MVPA and Hypoglycemia

	Unadjusted OR (95% CI)	Adjusted[a] OR (95% CI)
CGM reading ≤70 during sleep/next-day[b]		
MVPA Total (min)[c]	1.17 (1.00, 1.36)	1.25 (1.07, 1.45)*
MVPA 6:00 a.m. – 2:59 p.m. (min)	1.10 (0.83, 1.44)	1.10 (0.83, 1.44)
MVPA 3:00 p.m. – Bedtime (min)	1.23 (1.01, 1.49)*	1.38 (1.13, 1.69)*
CGM reading ≤70 during sleep[d]		
MVPA Total (min)	1.17 (0.86, 1.58)	1.25 (0.90, 1.75)
MVPA 6:00 a.m. – 2:59 p.m. (min)	1.17 (0.67, 2.05)	1.36 (0.74, 2.51)
MVPA 3:00 p.m. – Bedtime (min)	1.18 (0.82, 1.69)	1.26 (0.82, 1.93)
CGM reading ≤70 during next-day[e]		
MVPA Total (min)	1.17 (0.98, 1.41)	1.26 (1.06, 1.49)*
MVPA 6:00 a.m. – 2:59 p.m. (min)	1.04 (0.75, 1.44)	0.98 (0.73, 1.32)
MVPA 3:00 p.m. – Bedtime (min)	1.26 (1.01, 1.59)*	1.40 (1.14, 1.73)*

[a] Odds ratios are calculated based on days of data collection, and are adjusted for sex, VO_2max, % BF and next-day MVPA

[b] 11:00 p.m. – 11:00 p.m. following day (n = 52)

[c] OR is for an additional 30 minutes of MVPA per day

[d] 11:00 p.m. – 6:00 a.m. (n = 64). Sleep odds ratios are adjusted for sex, VO_2max and % BF

[e] 6:00 a.m. – 11:00 p.m. following day (n = 50)

* Results significant at $p \leq 0.05$ level

Table A4. Odds Ratios for Daily MVPA and Hypoglycemia: Adjustment for Next Day MVPA

Variable	Unadjusted for Next Day MVPA OR (95% CI)[a]	Adjusted for Next Day MVPA OR (95% CI)[b]
CGM reading ≤70 during sleep/next-day[c]		
MVPA Total (min)	1.18 (1.02, 1.37)*	1.25 (1.07, 1.45)*
MVPA 6:00 a.m. – 2:59 p.m. (min)	1.10 (0.84, 1.45)	1.10 (0.83, 1.44)
MVPA 3:00 p.m. – Bedtime (min)	1.28 (1.04, 1.57)*	1.38 (1.13, 1.69)*
CGM reading ≤70 during next-day[d]		
MVPA Total (min)	1.16 (0.99, 1.37)	1.26 (1.06, 1.49)*
MVPA 6:00 a.m. – 2:59 p.m. (min)	1.03 (0.78, 1.37)	0.98 (0.73, 1.32)
MVPA 3:00 p.m. – Bedtime (min)	1.30 (1.04, 1.62)*	1.40 (1.14, 1.73)*

[a] Odds ratios adjusted for sex, VO_2max and %BF

[b] Odds ratios adjusted for sex, VO_2max, %BF and next day MVPA

[c] n = 52

[d] n = 50

* Results significant at $p \leq 0.05$ level

Table A5. Full Adjusted Model Odds Ratios for Daily MVPA and Hypoglycemia

Variable	Adjusted OR (95% CI)[a]
CGM reading ≤70 during sleep/next-day[b]	
MVPA Total (min)	
MVPA[c]	1.25 (1.07, 1.45)*
Sex	1.98 (0.97, 4.05)
VO_2max[d]	1.12 (0.79, 1.58)
%BF	1.02 (0.96, 1.08)
MVPA 6:00 a.m. – 2:59 p.m. (min)	
MVPA	1.10 (0.83, 1.44)
Sex	1.75 (0.74, 4.18)
VO_2max	1.21 (0.79, 1.85)
%BF	1.02 (0.95, 1.10)
MVPA 3:00 p.m. – Bedtime (min)	
MVPA	1.38 (1.13, 1.69)*
Sex	2.21 (1.04, 4.68)*
VO_2max	1.18 (0.82, 1.69)
%BF	1.04 (0.98, 1.11)
CGM reading ≤70 during sleep[e]	
MVPA Total (min)	
MVPA	1.25 (0.90, 1.75)
Sex	1.95 (0.46, 8.30)
VO_2max	0.48 (0.20, 1.12)
%BF	0.94 (0.82, 1.07)

Table A5 – continued

MVPA 6:00 a.m. – 2:59 p.m. (min)	
MVPA	1.36 (0.74, 2.51)
Sex	1.52 (0.38, 6.12)
VO_2max	0.48 (0.21, 1.08)
%BF	0.92 (0.80, 1.06)
MVPA 3:00 p.m. – Bedtime (min)	
MVPA	1.26 (0.82, 1.93)
Sex	1.90 (0.44, 8.28)
VO_2max	0.52 (0.23, 1.17)
%BF	0.96 (0.84, 1.09)
CGM reading ≤70 during next-day[f]	
MVPA Total (min)	
MVPA	1.26 (1.06, 1.49)*
Sex	1.58 (0.77, 3.24)
VO_2max	1.39 (0.99, 1.96)
%BF	1.03 (0.96, 1.09)
MVPA 6:00 a.m. – 2:59 p.m. (min)	
MVPA	0.98 (0.73, 1.32)
Sex	1.47 (0.58, 3.72)
VO_2max	1.03 (0.95, 1.12)
%BF	1.02 (0.95, 1.10)

Table A5 – continued

MVPA 3:00 p.m. – Bedtime (min)	
MVPA	1.40 (1.14, 1.73)
Sex	1.72 (0.83, 3.58)
VO_2max	1.48 (1.05, 2.08)*
%BF	1.04 (0.98, 1.11)

[a] Odds ratios are adjusted for sex, VO_2max, % BF and next-day MVPA

[b] n = 52

[c] OR is for an additional 30 minutes of MVPA per day

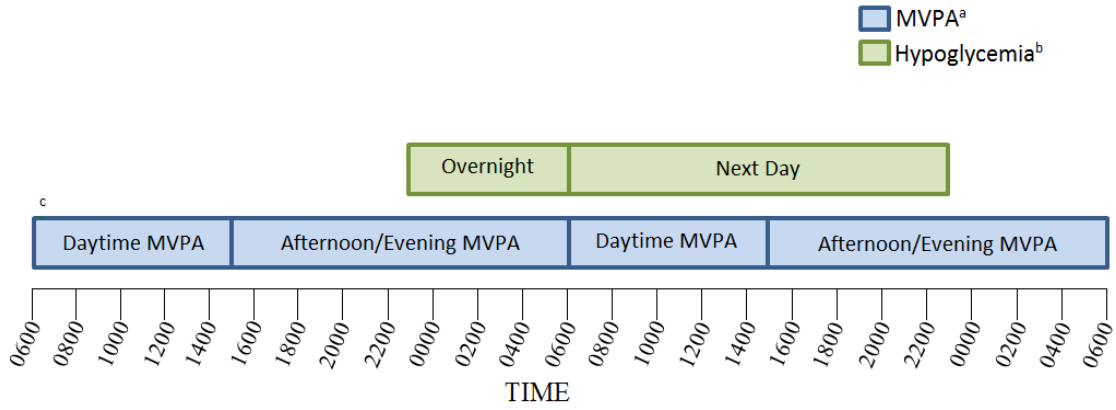
[d] OR is for an increase in VO_2max of 5 ml/kg/min

[e] n = 64

[f] n = 50

* Results significant at $p \leq 0.05$ level

Figure A1. Timeline of Measures of MVPA and Hypoglycemia

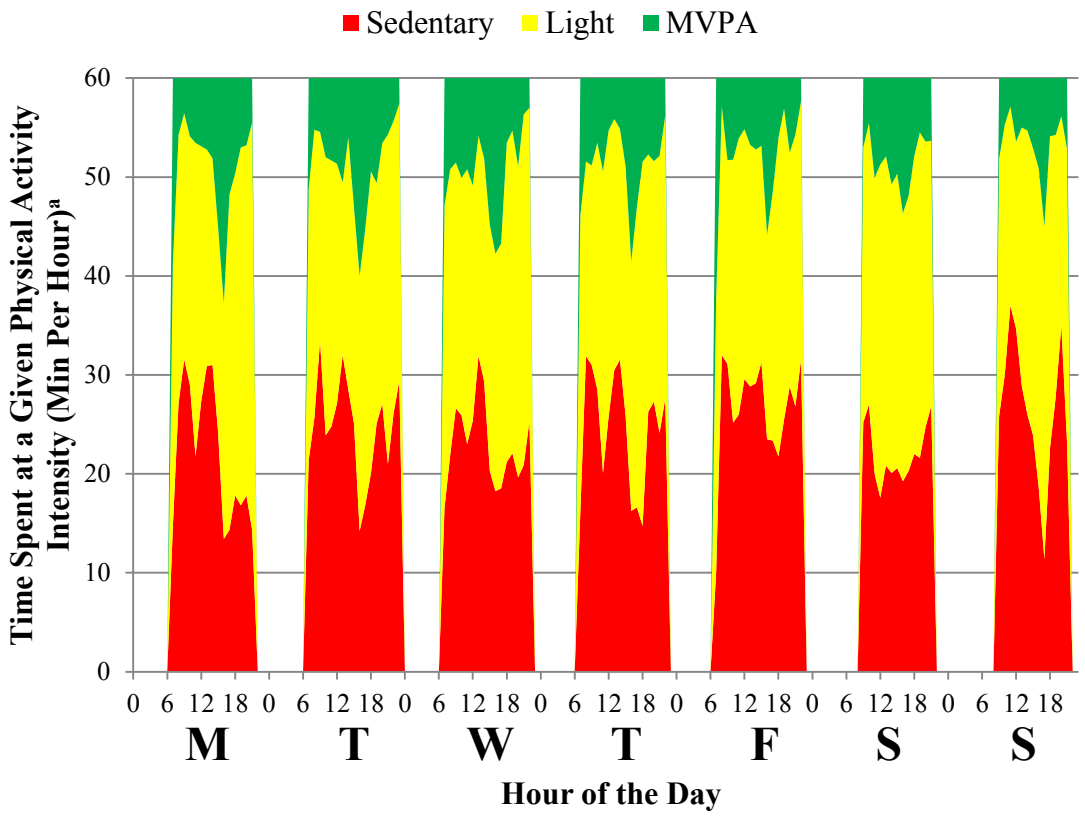


[a] Moderate to vigorous-intensity physical activity

[b] Glucose ≤ 70 mg/dL

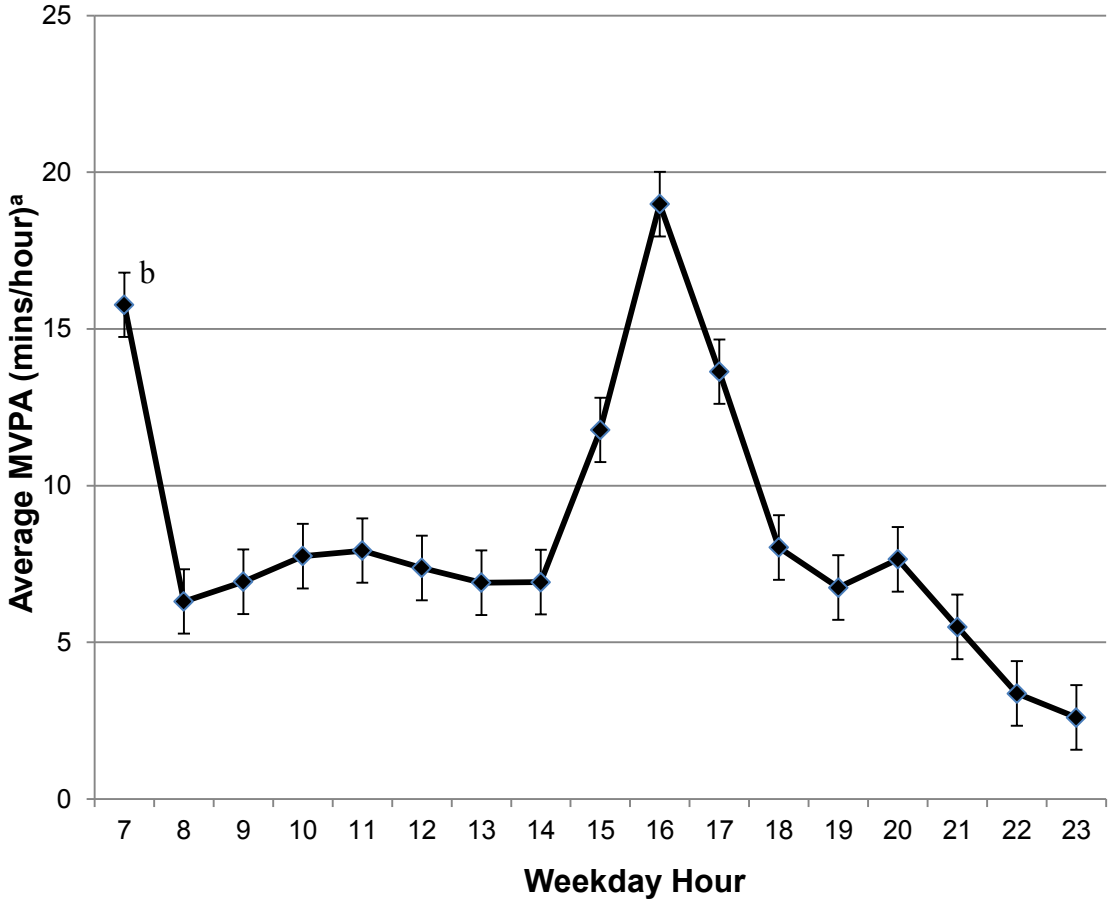
[c] MVPA and hypoglycemia tracked continuously for ≥ 3 days. The figure shows data collection over 2 days.

Figure A2. Heat Map of Average Physical Activity Patterns of All Participants



[a] Times based on average activity of all participants (n = 19)

Figure A3. Average Physical Activity Patterns of All Participants



[a] Average weekday MVPA of all participants (n = 42 days from 19 participants)

[b] Standard error

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