Final Project

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Introduction

According to the Center for Disease Control and Prevention (CDC)[1], 34.2 million people in the United States have been diagnosed with diabetes, 90-95% of those cases being type 2 diabetes. Furthermore, 88 million people are prediabetic, which is defined by elevated fasting blood glucose levels of 100-125 mg/dL or glycated hemoglobin levels of 5.7-6.4%[1]. Untreated, diabetes can cause seizures, cardiovascular disease, organ failure, coma, or even death[1].

Type 2 diabetes is characterized by hyperglycemia, or high levels of blood glucose, which results from impaired insulin production and sensitivity. The two main risk factors for type 2 diabetes are physical inactivity and obesity[2,3], which contribute to the development of the disease through three main pathways: increased hepatic glucose production, decreased insulin sensitivity of the muscle cells, and decreased beta-cell function in the pancreas[2]. The negative feedback loop that functions to maintain stable blood glucose levels in healthy individuals gets disrupted by these three main pathologies, leading to pathological hyperglycemia and ultimately type 2 diabetes[2,4,5].

Even though type 2 diabetes is diagnosed with fasting glucose or Hemoglobin A1C levels, researchers have become increasingly aware of the importance of non-steady state glucose levels throughout the day. Glucose variability refers to the deviance of blood glucose levels from a steady state[6]. It is important to note that a small degree of variance in blood glucose is normal in healthy individuals throughout the day, after, and between meals. For individuals with pathological glucose variability, studies suggest that high glycemic variability has more detrimental effects on the body than chronic hyperglycemia does[7–9]. Highly variable blood glucose increases oxidative stress by impacting the cell's ability to get rid of free radicals[7–9]. Excess oxidative stress has detrimental effects on endothelial function and has a strong

correlation to cardiovascular disease due to the increased cell injury and death caused by free radicals[7,8]. This amount of oxidative stress on the body may contribute to the development or worsening of type 2 diabetes as it has been linked to an increase in systemic inflammation, nephropathy, retinopathy, and cardiomyopathy[7,10,11].

Many studies have shown that exercise helps decrease the risk of developing type 2 diabetes in many different ways, including improving the liver's ability to metabolize glucose[2,3], decreasing lipotoxicity and glucotoxicity[2], improving peripheral insulin sensitivity[12-14], and repairing beta cell function in the pancreas[2,15]. Individuals at risk for type 2 diabetes could lower their risk by 50% with lifestyle changes such as exercise and a healthier diet. [2,16]. Various studies have compared the effects of high intensity interval training (HIIT) and moderate-intensity continuous training (MICT) on glucose variability in individuals with type 2 diabetes or at risk for developing type 2 diabetes[17–26]. In general, the results of these studies show that an acute bout of HIIT causes a decrease in blood glucose levels for about 30 minutes post-exercise and could provide more lasting effects on glycemic variability compared to MICT[19,21,23,25,27]. There are very few studies that have measured the chronic effects of a training period on glycemic variability, yet the results are varied. Some show that HIIT may be better for improving variability[26], whereas others show similar or even better effects from continuous exercise[17,22,24]. Although it is well known that exercise is beneficial in decreasing glucose variability, it is still unknown which type of training elicits the best results.

This study aims to compare the effects of high intensity interval training (HIIT) and moderate intensity continuous training (MICT) on blood glucose regulation in sedentary, obese subjects. By using continuous glucose monitoring (CGM) there will be more insight into the 24-hour glucose variability in subjects after exercise training. These results will lead to better

understanding of what kind of training would optimize exercise prescription for the prevention of type 2 diabetes and its complications.

Methods

Subjects

A total of 22 obese but otherwise healthy individuals between ages 18-55 were enrolled in this study. Subjects were screened with the Physical Activity Readiness Questionnaire (PAR-Q) and were excluded from the study for any "yes" answers. All subjects completed a telephone or email screening followed by a one-hour screening in the laboratory. During the screening, the subjects signed an informed consent form, answered the PAR-Q, and spoke to one of the researchers about the study. Then, each subject had their height and weight measured to verify a BMI of 30 kg/m^2.

Testing Overview

Baseline testing was done on each participant on the first day of the study. Subjects did not perform any vigorous exercise for 48 hours prior to testing and abstained from alcohol and caffeine for 24 hours before testing. Female subjects performed testing during the follicular phase of their menstrual cycle. Testing was also performed after the eight-week training period, about 72 hours after exercise training was over. About 36 hours before pre-training and post-training testing began, subjects were given prepared meals to consume over the 24 hours before testing and were asked to record the time and quantity of each food item consumed. After the controlled diet period, subjects fasted for at least 10 hours before testing began. Testing included

anthropometric measurements, including height, weight, and waist circumference, dual-energy X-ray absorptiometry (DXA), fasting blood draw, and the maximal exercise test.

DXA scans were performed to record percent body fat, regional fat distributions, and visceral fat (Lunar iDXA GE Healthcare, Little Chalfont, UK). Women took a urine pregnancy test before DXA measurements and a negative test was required before the test was performed. All scans were performed by a radiology technician.

The maximal exercise test was performed on an electronically braked cycle ergometer (VIAsprint 150P; Ergoline, Bitz, Germany) before training, after 4 weeks, and after 8 weeks of training. Pulmonary ventilation and gas exchange were measured with a Parvo Medics TrueOne 2400 (Parvo Medics, Sandy, UT). Heart rate was measured with a Polar heart rate monitor (Polar, Lake Success, NY). After resting for two minutes, subjects warmed up for five minutes at a cadence chosen by the subject between 50 and 90 rpm at 50 W for men or 25 W for women. The cadence chosen was maintained for the rest of the test. After the five minutes of warmup, power was increased by 30 W/min for men or 15 W/min for women until exhaustion. Subjects then cooled down for 5 minutes at the same cadence and power as the warm up. After cool down, subjects performed a verification phase test at a constant power of 100% of the peak power attained during the ramp test. Subjects were told to pedal for as long as possible above 50 rpm. The VO_{2max} was calculated as the mean of the two highest consecutive 15 second VO_2 averages. This data was used to prescribe training at the beginning and the 4-week maximal exercise test was used to adjust exercise prescription.

Exercise Training

Exercise training was completed three times a week for eight weeks, totaling 24 sessions overall. Each session was supervised and performed in the lab. Subjects were randomly placed into the HIIT group or the MICT group. Exercises were performed on cycle ergometers and the maximum heart rate achieved during the maximal exercise test was used for intensity prescription. Heart rate was monitored continuously by Polar heart rate monitors and recorded by research technicians. Both groups started each session with a five-minute warm up at 50-60% of $HR_{max.}$ Then, the HIIT group performed 10 one-minute interval at 90-95% of HR_{max} with one minute of low-intensity cycling between each interval. The MICT group performed 30 minutes of cycling at 70-75% of HR_{max}. Both groups ended their sessions with a cooldown consisting of five minutes of cycling at 50-60% HR_{max}. The time per session was 29 minutes for the HIIT group and 40 minutes for the MICT group.

Continuous Glucose Monitoring

Continuous glucose monitoring was conducted using Medtronic iPro2 continuous glucose monitors (CGM; Medtronic, Northridge, CA) for 24 hours pre- and post-intervention. The CGM consisted of a small micro-dialysis catheter inserted subcutaneously in the abdomen via a spring-loaded insertion device. The devices were calibrated using a standard glucometer (One-Touch, Ultra 2, Lifescan, Inc., Milpitas, CA) 4 times throughout each 24-hour period. Subjects recorded their glucose values and time of each reading in a provided glucose log.

Statistical Analysis

Linear mixed models were used to detect differences between groups over time in glucose values measured by the CGMs. Linear mixed models were used due to their superior ability to deal with unequal groups and their lack of reliance on sphericity, equal variance and

covariance assumptions[28,29]. Glucose area under the curve (Gluc AUC) was calculated using the trapezoidal method. The trapezoidal method consists of dividing the glucose concentration-time curves into multiple trapezoids and calculating the area under the curve by adding together the areas of the trapezoids. This provides a value for overall glucose exposure. A two-way ANOVA was used to test for differences for each descriptive and anthropometric measurement, each variability measurement, and glucose AUC between groups (HIIT/MICT), time (pre-training/post-training), and group x time interaction. All P values were two-tailed and values of <0.05 were considered to indicate statistical significance. All statistical procedures were performed by using SPSS 26 (IBM, Armonk, NY). The independent variables included in the two-way ANOVA were time (pre/post training) and training group (MICT/HIIT). The dependent variables were area under the curve and variability measurements: glucose area under the curve (Gluc AUC), mean amplitude of glycemic excursions (MAGE), J-index (JINDEX), continuous overall net glycemic action (CONGA), high blood glucose index (HGBI), and M-Value (MValue).

For more information on the methods of this study, please refer to "Effects of high-intensity interval training and moderate-intensity continuous training on endothelial function and cardiometabolic risk markers in obese adults" by Sawyer, et al.[30]

Results

Fifteen subjects finished the study (n=15), eight in the MICT group (n=8) and seven in the HIIT group (n=7). The anthropometric and descriptive measurements for each group are shown in Table 1. The 2-way ANOVA showed a significant difference between pre-training and post-training in VO_{2max} and body fat percentage, but no group x time interactions, and no other significant differences.

Table 1: Subject characteristics and pre-training and post-training anthropometrics for MICT and HIIT groups

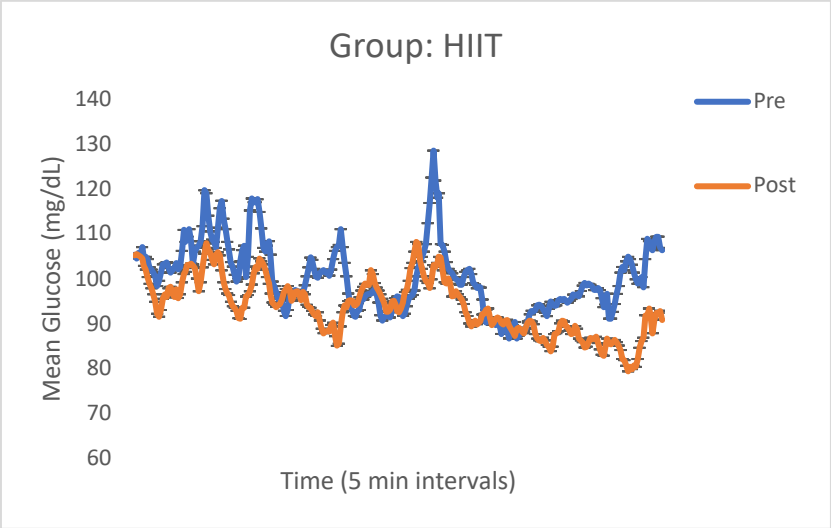
	MICT		HIIT			
	Pre-training	Post-training	Pre-Training	Post-Training	Time P value	Group*Time P Value
Weight (kg)	99.3 ± 11.5	99.5 ± 12.2	118.7 ± 27.3	118.6 ± 26.6	0.805	0.503
Body Fat %	46.4 ± 7.7	46.0 ± 7.7	46.3 ± 4.9	45.8± 4.9	0.013	0.552
VO_{2max} (L/min)	2.23 ± 0.51	2.54 ± 0.65	2.37 ± 0.69	2.7 ± 0.95	0.002	0.375
BMI	34.6 ± 3.4	34.7 ± 3.7	38.7 ± 6.4	38.7 ± 6.2	0.894	0.552
Height (cm)	169.5 ± 8.6		174.4 ± 11.4			
Age (years)	34.0 ± 7.9		34.0 ± 9.2			

The mixed model results showed significant group ($P < 0.001$), time ($P < 0.001$), and group x time interaction ($P = 0.002$) effects (See Glucose Values in Table 2 for the averages by group and time). The graphs shown in Figures 1 and 2 show the pre- and post-24-hour CGM tracings before and after training in each group. As seen in Figure 1, the HIIT group's pre-testing glucose levels were more variable than the MICT group's pre-testing levels and the HIIT group

	MICT (n=8)		HIIT (n=7)				
	Pre-Training	Post-Training	Pre-Training	Post-Training	Group P value	Time P value	Group*Time P value
Glucose* (mg/dL)	102. ± 16	101 ± 17	100 ± 18	97 ± 19	< 0.001	<0.001	0.002
Gluc AUC	136863 ± 13005	137874 ± 17079	143995 ± 12585	136515 ± 20326	0.626	0.585	0.451
MAGE (mg/dL)	34 ± 16	38 ± 16	38 ± 16	32 ± 8	0.845	0.845	0.386
CONGA (SD)	91 ± 10	91 ± 10	93 ± 6	88 ± 14	0.941	0.502	0.530
JINDEX (mg/dL)	4208 ± 840	4267 ± 926	4539 ± 668	4099 ± 1167	0.809	0.574	0.462
HBGI (mg/dL)	276 ± 19	277 ± 22	285 ± 13	272 ± 32	0.817	0.490	0.439
MVALUE	1618 ± 167	1625 ± 191	1690 ± 115	1588 ± 268	0.807	0.503	0.447

saw more improvement in glucose control. The MICT group's CGM data did not show much improvement over the training period.

Table 2: Averages and standard deviations of variability measurements of each group pre-training and post-training, including all subjects. The p-value that resulted from a 2-way ANOVA analysis is included. Acronyms Defined: glucose area under the curve (Gluc AUC), mean amplitude of glycemic excursions (MAGE), J-index (JINDEX), continuous overall net glycemic action (CONGA), high blood glucose index (HGBI), and M-Value (MValue). *Analyzed with mixed model analysis



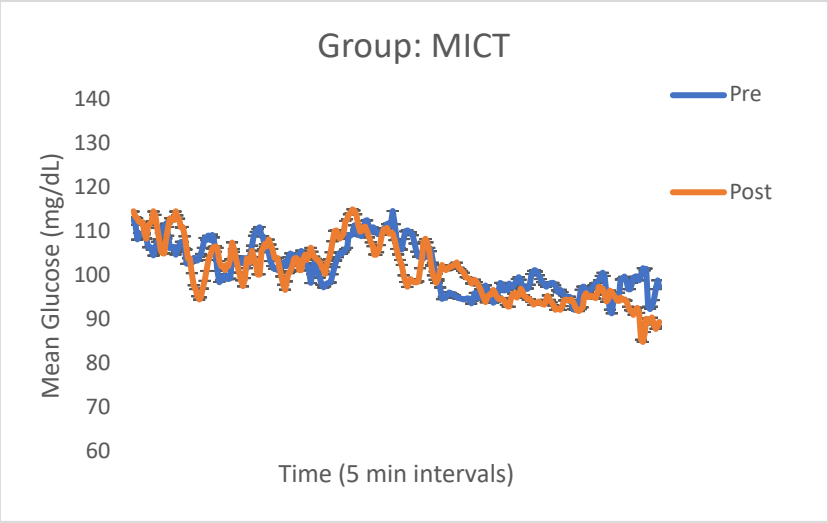


Figure 1&2: Graphs of the 24-hour CGM data pre and post training for HIIT group (Figure 1) and MICT group (Figure 2).

Because the p-values obtained from the two-way ANOVA were greater than the pre-determined alpha level of 0.05, it was determined that there were no statistically significant differences between groups or time for variability measurements when all subjects were included. This data is represented in Table 2.

However, when the two-way ANOVA was run including only subjects with a baseline average 24-hour glucose level above 100 mg/dL, there were significant differences *($p < 0.05$)* found between pre-training and post-training, but not between training groups (See Table 3). The p-values met the pre-determined criteria for significance, so the decreases between pre-training and post-training in the following variability measurements were considered significant in subjects with a average 24-hour glucose level above 100 mg/dL: CONGA, JINDEX, HBGI, and MValue. Furthermore, when the mixed model analysis was done with this subset of subjects the group, time, and group x time interaction effects achieved greater levels of significance (all *P* values < 0.001; see Glucose variable below in table 3).

Table 3: Averages and standard deviations of variability measurements of each group pre-training and post-training, including only subjects with a starting baseline blood glucose level of over 100 mg/dL. The p-values that resulted from a 2-way ANOVA analysis. *Analyzed using mixed model analysis

	MICT		HIIT				
	Pre-Training	Post-Training	Pre-Training	Post-Training	Group P value	Time P value	Group*Time P value
Glucose* (mg/dL)	108.6 ± 15.7	98.0 ± 14.7	106.3 ± 16.8	89.2 ± 16.2	< 0.001	< 0.001	< 0.001
Gluc AUC	145926 ± 9807.5	134055 ± 11870.3	148802 ± 10713.4	132245 ± 23183	0.943	0.072	0.753
MAGE (mg/dL)	34.8 ± 21.4	38 ± 17	40.5 ± 17.8	30 ± 5	0.88	0.654	0.384
CONGA (SD)	100.1 ± 3.3	89.3 ± 6	95 ± 6.5	85 ± 15.7	0.336	0.04	0.931
JINDEX (mg/dL)	4808.7 ± 740	4106.5 ± 336	4783.8 ± 623.4	3766.3 ± 1134	0.633	0.037	0.679
HBGI (mg/dL)	292 ± 9.6	273.7 ± 12.8	289.8 ± 11.3	264.8 ± 34.4	0.578	0.044	0.746
MVALUE	1757 ± 87	1593 ± 107	1737 ± 100	1521 ± 287	0.587	0.038	0.761

Discussion

The primary findings of this study show that both HIIT and MICT can improve glycemic control with a potentially more powerful effect in response to HIIT. The improvement in glycemic control in response to both HIIT and MICT was more pronounced in individuals who started with a higher 24-hour average blood glucose. Likewise, the superiority of HIIT was also more pronounced in that subgroup. This implies that if individuals who are farther in the progression of type 2 diabetes, HIIT may provide an efficient way to reduce glycemic control and slow the progression of disease more than MICT would.

There are very few studies that have compared the chronic effects of HIIT and MICT on individuals with prediabetes, with most assessing only acute effects of exercise or use subjects who have already been diagnosed with type 2 diabetes[17–27,31,32]. Of those that studied acute bouts of exercise, many found that HIIT improved glycemic control and insulin sensitivity more effectively and for a longer amount of time than MICT did in subjects with type 2 diabetes[18,19,23,25]. The current study showed similar results as other studies with subjects at risk for developing type 2 diabetes and a long-term training plan[24,26,31,32]. Many found no significant difference between HIIT and MICT on glycemic control or insulin sensitivity in individuals with prediabetes, which is consistent with our results. HIIT showed to be superior if we consider only the over 100 mg/dl subgroup..

A study published in 2016 by Kong et al. investigated the physiological effects of 5-week training plans of HIIT and MICT on obese and overweight women without type 2 diabetes[24]. The training interventions in Kong's study were comparable to those of ours. The results show that fasting blood glucose levels decreased significantly in both interventions with no difference between the groups[24]. A 12-week training intervention by Rowan et al in 2017 found the same results when comparing HIIT and MICT in individuals with prediabetes[32]. There was an overall

improvement in anthropometric measurements and fasting blood glucose levels, but no significant difference between the training groups[32]. Our study generally supports these findings as the data show no significant difference between training groups for variability measurements, but there was a group x time interaction when the data was analyzed with the mixed models where all CGM time points could be utilized. Due to the large number of time points used in this analysis we were able to detect a small but significantly stronger effect of the HIIT compared to the MICT.

Winding et al. tested an 11-week training plan of either HIIT or endurance (END) training on glycemic control in subjects with type 2 diabetes[26]. Glycemic variability was measured using CGM and the training protocol was comparable to ours. The CGM data from this study show a reduction in glycemic variability in the HIIT group, but a lower mean glucose concentration in the END group[26]. The conclusion of Winding's study is relevant to our study because the subjects already had type 2 diabetes before starting training. This is consistent with our findings that HIIT had a greater effect on subjects who were closer to disease. Due to the more harmful effects of glycemic variability compared to continuously high glucose levels, this indicates that HIIT may be the better option for exercise prescription in individuals who are closer to development or who already have type 2 diabetes[26]. Our CGM data is consistent with these results when only subjects with a baseline glucose level over 100 mg/dL are accounted for. The HIIT group had a greater overall stabilization in glucose levels throughout the day post-training than the MICT group did.

The mechanism by which HIIT may improve glycemic variability more than MICT in prediabetic people is still unknown. One potential explanation could be that higher intensity exercise relies mainly on glucose as fuel while lower intensity exercise utilizes more fat[33]. As

seen in multiple studies that examine the acute effects of HIIT and MICT on individuals with type 2 diabetes, HIIT is able to acutely effect glycemic control to a higher degree than MICT is [2,3,34]. With multiple bouts of exercise each week over multiple weeks, maybe the body becomes more sensitive to insulin due to the chronic reduction from exercise. Exercise may also lead to decreased hepatic fat content, which would improve the liver's ability to metabolize glucose and slow the rate of gluconeogenesis [2,3,34]. It may also reduce the glucotoxicity of the pancreas over time, which could potentially improve beta-cell function and allow for glucose sensitivity and more appropriate insulin release[2]. Whether HIIT is able to accomplish this to a greater degree is still unknown and requires further research..

One limitation to this study is the small sample size of 15 subjects, resulting in eight subjects in the MICT group and seven in the HIIT group. When the sample was reduced to include only those whose baseline glucose levels were above 100 mg/dL, the sample size was even smaller, with only nine subjects: four in MICT and five in HIIT. The limited number of subjects limits the generalizability of our results. For clearer results in future studies, it would be beneficial to have a larger sample size. It would also be helpful to only include subjects who are pre-diabetic in order to be able to see this trend more clearly. Furthermore, our subjects in the HIIT group may have started out with slightly more impairments in glucose regulation compared to the MICT group. This is seen by higher glucose excursions in the HIIT group compared to the MICT group (See Figures 1 and 2) before training.

In summary, the results of this study show that 8-weeks of HIIT or MICT can improve glycemic control with potentially more pronounced effects in response to HIIT. These results were especially true in subjects who started with higher 24-hour average glucose.

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