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Original Research Article

The Dose-Response Relationship between High-Intensity Functional Training and Insulin Resistance in a Metabolic Syndrome Cohort

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ABSTRACT

Literature supports exercise training as a remarkable mechanism for insulin resistance mitigation. Regarding the exercise prescription within a clinical population, greater improvements in insulin sensitivity will follow greater dose of exercise. However, the optimal dosage of high intensity functional training (HIFT) for an insulin resistance population has not been established. **Purpose**: To study the effect of different frequencies of HIFT on insulin resistance in a metabolic syndrome (MetS) cohort. **Methods:** This randomized trial recruited both men and women (n=25) categorized with MetS. Participants were randomized into one of three exercise frequency groups: 1x/week, 2x/week, 3x/week. A twelve-week HIFT exercise training intervention was prescribed to each individual across all three frequency groups. Baseline and post-program measures were taken regarding insulin resistance parameters, body composition, cardiorespiratory fitness, and metabolic blood measures. **Results:** Following the exercise training intervention, although there was no significant difference ($p > .05$), there were favorable reductions in HOMA-IR and insulin (IU) across all three groups: HOMA-IR 1x/week 36.1% decrease, HOMA-IR 2x/week 44.4% decrease, HOMA-IR 3x/week 9.7% decrease, insulin (IU) 1x/week 27.0 % decrease, insulin (IU) 2x/week 46.2 % decrease, and insulin (IU) 3x/week 6.0 % decrease. **Conclusion:** Within an insulin resistance population, low frequency HIFT was more effective (1x and 2x/week) than higher frequency HIFT (3x/week) in improving insulin resistance.

KEYWORDS: Diabetes, Group Exercise, Energy Expenditure, Exercise Intensity.

Introduction

Metabolic Syndrome (MetS) is a collection of cardiovascular risk factors predisposing an individual to atherosclerotic cardiovascular disease (ASCVD) – the leading cause of death in the United States[1]. Individuals with MetS have a two-fold increased risk for developing ASCVD[2]. This increased heart disease burden is concerning, for by the year 2030, it is projected nearly half of American adults will develop ASCVD in their lifetime[3]. Insulin resistance is a common feature of metabolic and

cardiovascular disorders[4-5]. A glucolipotoxic environment occurs when glucose is chronically elevated in the blood stream and negatively impacts pancreatic beta-cell function[5]. If this occurs chronically in response to elevated plasma glucose, beta-cell function diminishes despite increased insulin concentration[6]. Insulin resistance occurs when insulin is secreted in greater portions, but followed by a weakened biological response[6]. The primary mechanism of glucose uptake is regulated by glucose transporters, most commonly GLUT-4. GLUT-4 requires insulin for activation and translocation[7]. However, with reduced insulin sensitivity in clinical populations, the function of GLUT-4 is impaired[8]. It has been well-established in the literature that exercise aids in insulin sensitivity improvements, and the improvements are a result of enhanced GLUT-4 expression[8-9]. Previous research has shown exercise training elicits favorable changes in glucose tolerance, uptake, and disposal throughout the entirety of the body[8,10]. Regarding modality of exercise, both cardiorespiratory and muscular training have been widely recognized as a useful intervention for mitigating metabolic syndrome and heart disease risk[11]. Physiologically, aerobic exercise increases insulin sensitivity while anaerobic exercise increases glucose uptake with hypertrophy and GLUT-4 mechanisms[12].

Overall, it has been established that exercise provides substantial benefits for a MetS population; however, multiple adherence barriers exist to regular exercise[13-15]. Indeed, less than 25% of adults participate in adequate exercise despite ample evidence demonstrating its health benefits[13]. According to the World Health Organization, 1.4 billion adults are insufficiently active[15]. Physical inactivity is influenced by multiple factors including “lack of time”, “fear of injury”, “convenience/access”, “cost”, “lack of knowledge”, and “lack of self-discipline”[14]. Regardless of the number of obstacles present, it is clear a proper, individualized modality of exercise for a MetS population is needed.

High intensity functional training (HIFT) is an exercise modality implementing foundational and everyday movements based on real-world situation, creating a novel training prescription with numerous constantly varying movements of both aerobic and anaerobic nature[16-17]. It has been demonstrated that HIFT is an effective exercise intervention for the improvement of musculoskeletal fitness, energy expenditure, fat mass, blood pressure, blood lipid profile, insulin sensitivity, body composition and adherence[16, 18-22]. HIFT training combines two extremely effective modalities of exercise to initiate favorable physiological changes while maintaining adherence. However, dosage of HIFT prescription in a MetS population, in relation to insulin resistance changes, is still an unexplored area of research.

Furthermore, literature has established a dose-response relationship with exercise and numerous health outcomes including cardiovascular disease risk, all cause-mortality, obesity, and type two diabetes mellitus (T2DM)[23]. However, the exercise prescription and dosage required to elicit favorable benefit to cardiovascular disease risk is still understudied[23-24]. The dosage of exercise is a concept in exercise prescription associated with the prescription or “amount” of exercise related to health benefits—encompassing dosage is frequency, duration, time and modality[23, 25]. Regarding insulin sensitivity and glucose uptake there is a positive correlation with dosage of exercise in relation to amount of time prescribed. Indeed, it has been demonstrated that greater volumes of

exercise elicit greater improvements in insulin sensitivity[26]. Exercise is not a one size fits all program, for each individual participating in exercise has a personalized goal, expectation, time frame, and health characteristics that needs to be addressed for proper exercise prescription[25]. Exercise physiologists continue to seek the optimal dosage of exercise to elicit favorable insulin sensitivity responses and regular exercise adherence. Therefore, the purpose of this study was to investigate the dose-response relationship of HIFT frequency and insulin resistance in a MetS cohort. It was hypothesized that greater frequencies of HIFT would elicit increased risk mitigation.

Methods

Participants

This randomized dose response trial recruited both men and women (n=25) categorized with MetS. Participants were separated into two cohorts (n=13 and n=12). Inclusionary criteria included physically inactive individuals (less than 30 minutes per day, 3 times per week, for three months) between 35-65 years of age and possessing at least three of the five metabolic syndrome components, 1) waist circumference ≥ 102 cm for males and ≥ 88 cm for females 2) resting blood pressure ≥ 130/85 mmHg 3) high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL for males and ≤ 50 mg/dL for females 4) fasting triglycerides ≥ 150 mg/dL 5) fasting blood glucose ≥ 100mg/dL. Exclusionary criteria included any medical diagnosis of or taking medication for heart, lung, kidney, liver, or neurological diseases as well as a medical orthopedic condition preventing one from performing exercises. This research study was approved by the Human Research Committee of Western Colorado University (WCU) [HRC2020-01-01-R04].

Experimental Design

This dose response trial examined the relationship between metabolic risk factors and insulin resistance. Potential participants were recruited via word of mouth and flyers, and once completing eligibility screening qualifications and tests, they were randomized into one of three exercise dose groups. Pre-testing followed eligibility screening where participants underwent endothelial function testing, lipoprotein metabolism profile (LPMP), dual-energy x-ray absorptiometry (DEXA) scans, and a graded maximal-exercise test. Participants then partook in three weeks of exercise familiarization, twelve weeks of the high intensity functional training (HIFT) protocol, followed by a week of post testing. Post testing procedure was identical to pre-testing procedure (see Figure 1).

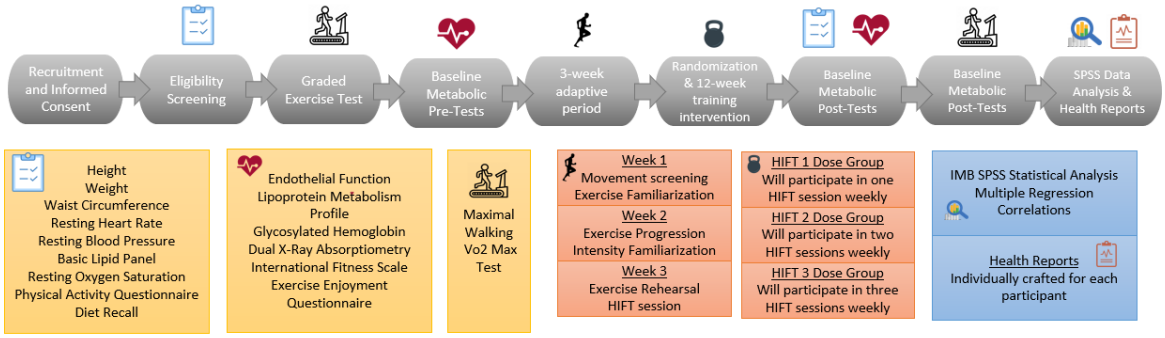

Figure 1. Experimental Flowchart.

Procedures

Eligibility Screening

Following recruitment, potential participants visited Western Colorado University's High Altitude Performance Laboratory (HAP Lab) for an eligibility screening. Each participant signed an informed consent document and was asked to complete a series of paperwork and questionnaires: physical activity questionnaire, diet recall, menstrual cycle history questionnaire, simple lifestyle indicator questionnaire, Medial History questionnaire, and exercise participant information sheet. Eligibility screening consisted of resting blood pressure and resting heart rate, as well as resting oxygen saturation. Height and weight were also collected. Additionally, waist circumference and abdominal height were measured using a cloth tape measure with a spring-loaded handle in cm and located below the xiphoid process and above the umbilicus (narrowest part of the sternum). The Cholestech LDX Analyzer was utilized to gather 40 µL of capillary blood via finger prick. Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), and fasting blood glucose (FBG) were measured. TG/HDL ratio was calculated once Cholestech results become available. Once it was determined that a participant satisfied inclusionary criteria, they were randomized into of one three HIFT frequency groups: 1) one exercise session per week, 2) two exercise sessions per week, or 3) three exercise sessions per week.

Pre-test Protocol: Blood Work

On the same day, participants were escorted to Gunnison Valley Health Hospital. Trained phlebotomist drew blood from the participant via the antecubital vein. The LMPP included Apolipoprotein B (ApoB), lipoprotein a (lp(a)), TG, HDL-C, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), very low-density lipoprotein triglyceride (VLDL-T), low density lipoprotein triglyceride (LDL-T), and Hemoglobin A1c (HbA1c). Hemostatic Model Assessment for Insulin Resistance (HOMA IR) and TG/HDL ratio were calculated.

Pre-test Protocol: DEXA

Participants were instructed to meet at GVH Hospital for their DEXA scan. Participants were escorted to the correct region of the hospital, where they received their body composition test.

Pre-test Protocol: Graded Exercise Test

Participants returned to the lab on separate occasions, well rested and prepared to complete a maximal graded exercise test. Gas exchange data was collected and processed using the metabolic cart PARVO system (ParvoMedics TrueOne Metabolic System). Upon arrival, heart rate monitors were placed upon the Xiphoid of the sternum. The Balke VO_2max protocol was utilized. Participants determined a challenging walking pace, establishing their set speed for the remainder of the test. Beginning at zero percent, percent grade was increased every minute. The participant walked until volitional exhaustion. A twenty-minute rest period followed the graded exercise test. During this rest, two forms were completed: "Testing the Simple Lifestyle Indicator Questionnaire" and "Self-reported Physical Fitness" After a twenty-minute rest period, the participant performed a verification test at peak metabolic equivalents (METS)x1.05. The verification test included the same termination criteria as the previous maximal exercise test—until volitional exhaustion. This test generally lasted between 2 to 4 minutes. A cool down of 2 mph for five minutes proceeded the verification test. Ventilatory Thresholds (VT1

and VT2) were determined by experienced exercise physiologists from VO_2max data plots to individualize exercise prescription intensities.

Exercise Intervention

Three-week Adaptive Period

Participants initially completed two weeks of familiarization to properly master the three basic stability skills and fundamental movements of the exercise intervention. The first session consisted of instruction and practice of transverse abdominus bracing, scapular retraction/depression, and Glute Medius activation. The second session of familiarization included practice and instruction of the hinge, step-up, push, plank, squat, press, pull, and rotation movements. The next sessions incorporated all fundamental movements and stability skills when participants were introduced to the HIFT exercise program. Over the course of the adaptive period, heavier weights were incorporated and time length was increased. The adaptive period was completed when all participants mastered the movements safely and completed the HIFT intervention completely.

Twelve-week Exercise Intervention

Each participant performed the exercise intervention according to the frequency group to which they were randomized: 1x/wk, 2x/wk, or 3x/wk. Heart rate monitors were worn for all workouts. (Polar Wear Link Coded, model 1W). Instructors led a sufficient warm up targeting all major muscle groups in the upper and lower extremities. Once participants were properly warmed up, time was allotted to explain new exercises and answer questions. When the participants were prepared, a timer was set for six minutes and the HIFT program began. The six minute as-many-reps-as-possible (AMRAP) round occurred four times with three-minute rests. Heart rate, rated perceived exertion (RPE), and number of rounds were collected immediately at the beginning of the rest. VT1 and VT2 determined from pre-testing VO_2max data plots were used to individually prescribe exercise intensity for each participant. Target intensity for each participant was the heart rate (± 5 beats per minute) corresponding to VT2. Throughout the duration of the intervention, the HIFT instructors were monitoring movement, interjecting with cues, instruction and encouragement. Once the four rounds were complete, a cool down was led by the instructors to properly stretch all major muscles.

The intervention was separated into three phases of 4 weeks each, with progressive overload throughout three weeks and a deload week. However, the training structure remained the same throughout phases: 20 repetitions of a cardio exercise, followed by six repetitions of a lower body exercise, 8 repetitions of an upper body exercise, and finishing off the set with a core exercise. Cardio exercises included jumping jacks, butt-kickers, skaters, or high knees. Upper body exercises included different variations of the TRX strap and the dumbbell (DB) push press. Leg- focused exercises included step ups, goblet squats, box jumps, barbell (BB) deadlift, BB Romanian dead lift, BB front squat, DB rear lunge, and wall sits. The core exercises included different plank variations, hollow holds, and Russian twists.

Post Test Protocol: Blood work, DEXA, and graded exercise test

All participants signed up for two post-testing appointments. On day one, participants arrived well rested and fasted as well as free from caffeine for 12 hours. Participants were escorted to GVH hospital for a phlebotomy appointment, collecting the same LMPP data as pre-testing. The DEXA scan followed. The second post-testing

appointment required participants to come well-rested, well-hydrated and fueled for their graded exercise test—following the same protocol as pre-testing. Height, weight, waist circumference, and abdominal height were also collected.

Statistical Analysis

All analyses were performed using SPSS Version 28.0 (IBM Corporation, New York, NY USA). Measures of centrality and spread are presented as mean ± SD. Mean differences in primary outcome variables between baseline and post program across HIFT frequency groups were assessed with one-way analysis of variance (ANOVA). Where appropriate, Tukey's post hoc tests were performed to determine differences between HIFT frequency groups. The probability of making a Type I error was set at $p < 0.05$ for all statistical analyses. Cohen's d effect size was calculated to quantify the effect meaningfulness. Effect size was considered either small (d= 0.2), medium (d=0.5), or large (d=0.8) according to Cohen's d effect size thresholds. Additionally, to determine the practical assessment of this exercise intervention, magnitude-based inferences were utilized to determine percent benefit, triviality, and harm[27]. A 90% confidence interval was used to express the uncertainty in effect and the clinical meaningfulness (beneficial or detrimental) of this intervention on a metabolic syndrome population. The magnitude-based inference spreadsheet was derived from published literature[27].

Results

Of the original 25 participants, 21 participants successfully completed the training intervention. The intervention was well tolerated and 84% of participants finished the study. Those who withdrew from the study experienced one of the following: COVID-19 complications (n=1), pulmonary concern (n=1), kidney stones (n=1), and family emergency (n=1). Attrition was 16%. As for the participants who successfully completed the study, an 80% adherence minimum to the protocol was maintained and intensity was controlled for by careful regulation of exercise mechanics and heart rate. All 21 participants successfully adhered to the 80% minimum adherence threshold. Adherence was calculated per exercise dose group, and an allotted cushion of missed training sessions provided accordingly. Participants randomized to the 3x/week group were permitted a maximum of five missed sessions throughout the 12-week training study, while the 2x/week group could miss three sessions, and the 1/week could only be absent for one session to ensure continued participation in the training study.

Following the exercise training intervention, there was no significance ($p > 0.05$) found in the dose-response relationship with insulin resistance measures across all dose groups and participants; however, according to percent change calculations, there were some promising results. Insulin resistance was measured via insulin (IU), HOMA-IR, and fasting blood glucose (FBG) (mg/dL). All variables within the three dosage groups elicited favorable responses. A few notable highlights include: HOMA-IR 1x/week 36.1% decrease, HOMA-IR 2x/week 44.4% decrease, insulin (IU) 1x/week 27.0 % decrease, insulin (IU) 2x/week 46.2 % decrease. See Table 1 for baseline and post program participant characteristics according to dose groups. Mean and individual values at baseline and post-program for each frequency group for HOMA-IR, Insulin (IU), and FBG are presented in Figures 2-4. Across all frequency dose groups and variables, the HIFT intervention elicited favorable reductions; however, less HIFT frequency generally elicited greater beneficial responses

Clinical Practical Assessment

Batterham and Hopkins state the p value alone does not provide researchers with adequate information about direction or size of the effect; and insignificant results, as seen in this research ($p > 0.05$), do not necessarily imply there is "no worthwhile effect"[27]. Instead of just saying the results are significant/insignificant, magnitude-based inferences can be interpreted and applied saying, the effect is "likely beneficial/trivial/harmful". With this information, researchers are provided adequate information for how to proceed[27].

According to magnitude-based inferences, HOMA-IR HIFT 1x and 2x/week were practically assessed as likely beneficial at 86.9 and 88.9% (a large effect). Insulin (IU) HIFT 1x and 2x/week were practically assessed as likely beneficial also at 86.9 and 88.9% (a large effect). Fasting blood glucose HIFT1x week was practically assessed as likely beneficial with 87.5%, and HIFT 2x/week as very likely beneficial at 98.6% (a large effect). For all three dependent variables of HOMA-IR, Insulin, and fasting blood glucose, the lesser frequency (1x and 2x weekly HIFT intervention) was at minimum "likely beneficial," opposing the higher frequency (3x a week), being "possibly beneficial". See Table 2 for magnitude-based inference results. According to the data, a dose-response relationship with HIFT and insulin sensitivity does not occur. All calculations were completed via a published magnitude-based inference spread sheet[27]

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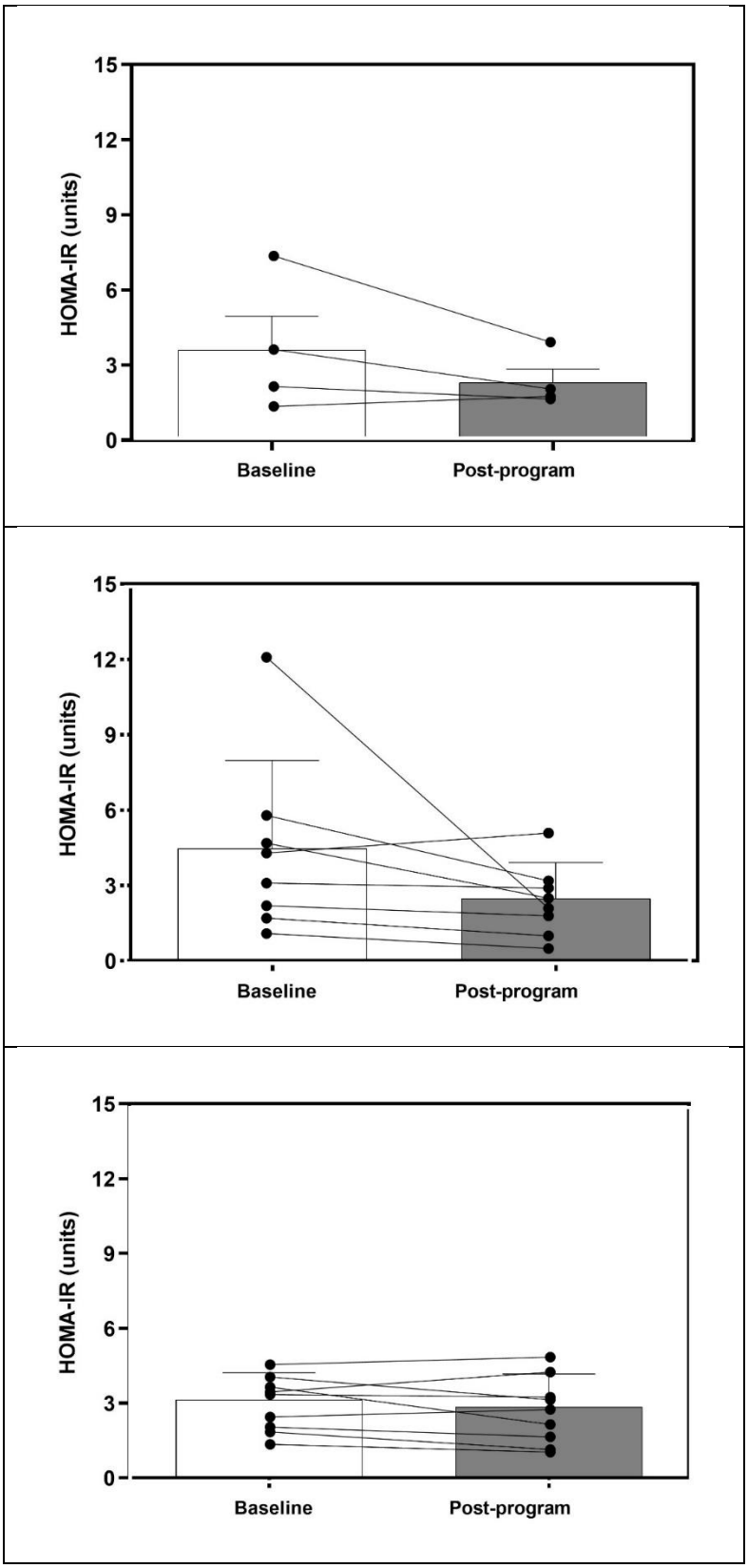

Figure 2. HOMA-IR depicted baseline to post program for 1x/week (upper panel), 2x/week (middle panel), and 3x/week (lower panel) for 12 weeks groups, respectively.

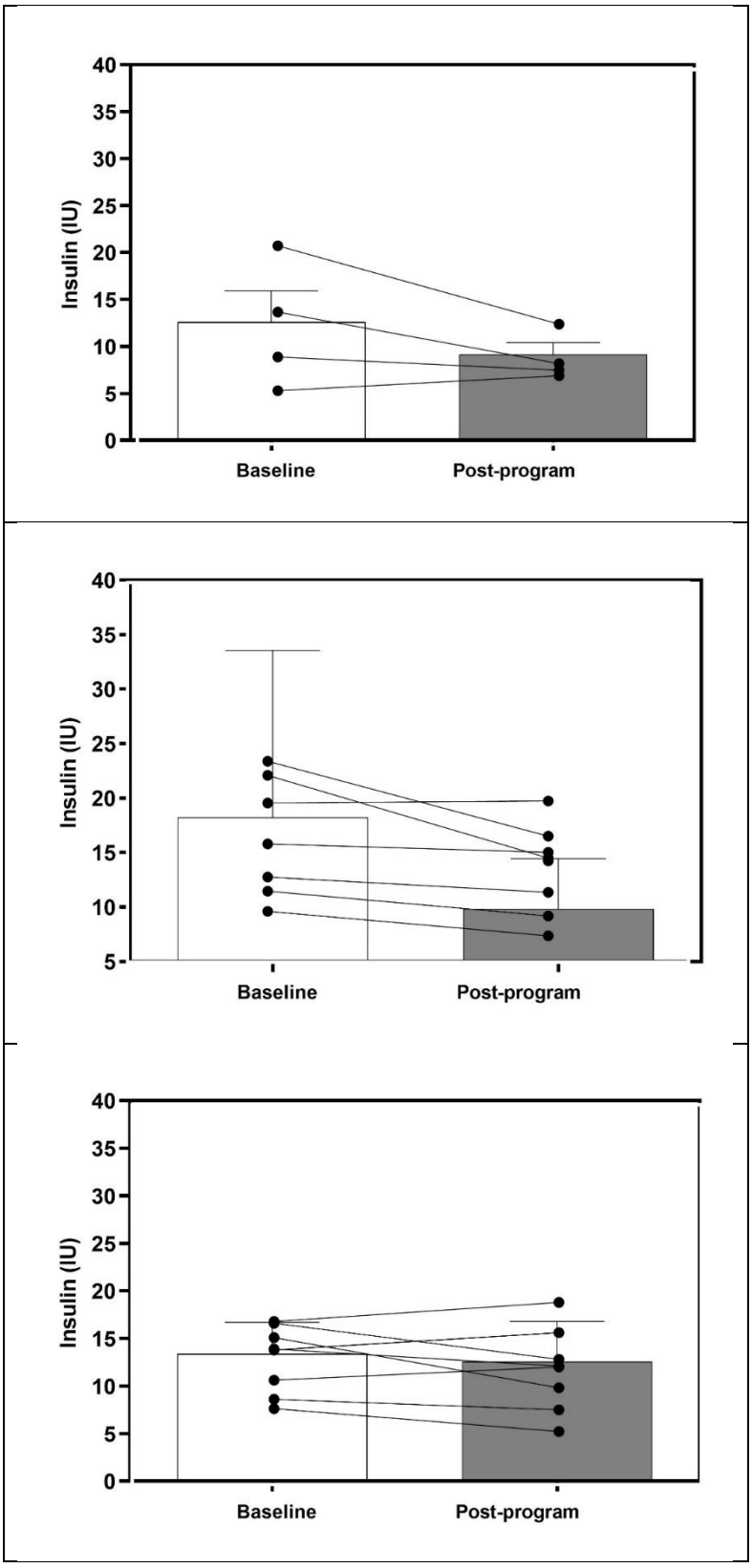

Figure 3. Insulin (IU) depicted baseline to post program for 1x/week (upper panel), 2x/week (middle panel), and 3x/week (lower panel) for 12 weeks groups, respectively.

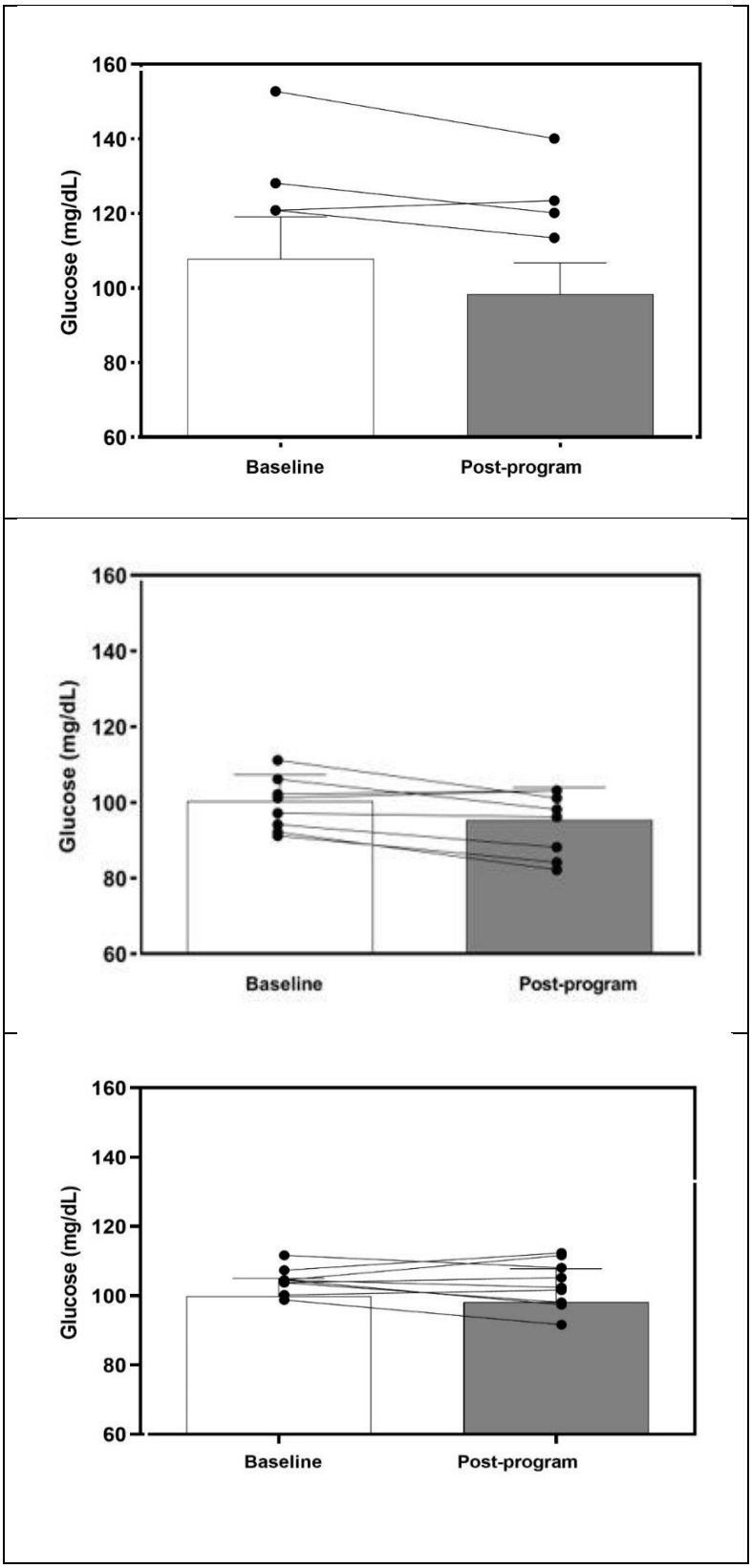

Figure 4. Fasting blood glucose (mg/dL) depicted baseline to post program for 1x/week (upper panel), 2x/week (middle panel), and 3x/week (lower panel) for 12 weeks groups, respectively.

Table. 1 Participant Characteristics at Baseline and Post Program for 1x/week, 2x/week, and 3x/week HIFT groups, (Mean ± SD).

Dosage	1x/ week (n=4)			2x/ week (n=8)			3x/ week (n=9)		
	Baseline	Post-program	Cohen's d (95% CI)	Baseline	Post-program	Cohen's d (95% CI)	Baseline	Post-program	Cohen's d (95% CI)
Height (cm)	175 ± 5.2	---	---	172 ± 2.4	---	---	170.8 ± 4.2	---	---
Sex	Male n=3 Female n=1	---	---	Male n=5 Female n=3	---	---	Male n=3 Female n=6	---	---
Age (years)	55.2 ± 3.8	---	---	52.1 ± 4.3	---	---	56.4 ± 3.1	---	---
Mass (kg)	98.8 ±9.1	97.1 ± 8.9	---	87.4 ± 5.6	85.9 ± 5.4	---	92.6 ±8.6	93.1 ± 8.7	---
Waist circumference (cm)	112.5 ± 4.5	108.4 ± 3.9	---	109.7 ± 6.2	104.2 ± 4.8	---	112.1 ± 5.7	111.4 ± 5.8	---
Abdominal height (cm)	23.9 ± 1.6	23.1 ± 1.6	---	23.1 ± 2.0	22.2 ± 1.7	---	23.8 ± 1.4	23.5 ± 1.6	---
Lean mass (%)	61.9 ± 1.7	61.9 ± 1.7	---	61.9 ± 2.5	63.1 ± 1.9	---	55.2 ± 6.0	56.0 ± 5.7	---
Body fat (%)	34.8 ± 1.9	35.0 ± 2.0	---	32.1 ± 2.7	32.4 ± 2.3	---	41.8 ± 2.1 *	41.1 ± 2.0	---
VO_2max (mL/kg/min)	30.6 ± 1.0	33.9 ± .9	---	31.2 ± 3.0	31.8 ± 3.3	---	25.8 ± 1.5	24.2 ± 1.5	---
HbA1c (%)	5.8 ± .1	5.7 ± .09	.39 (-.7, 1.4)	5.5 ± .09	5.5 ± .08	.23 (-.5, .9)	5.8 ± .1	5.7 ± .08	.20 (-.5, .9)
HOMA-IR (unit)	3.6 ± 1.4	2.3 ± .5	.77 (-.4, 1.9)	4.5 ± 1.3	2.5 ± .5	.58 (- .2, 1.3)	3.1 ± .4	2.8 ± .4	.40 (- .3, 1.1)
Fasting Blood Glucose (mg/dL)	107.8 ± 11.4	98.3 ± 8.5	.98 (-.3, 2.2)	100.3 ±2.5	95.4 ± 3.0	1.0 (.1, 1.8)	99.8 ±1.7	98.1 ±3.2	.23 (-.4, .9)
Insulin (IU)	12.6 ±3.4	9.2 ±1.2	.78 (-.4, 1.9)	18.2 ±5.4	9.8 ±1.6	.58 (-.2, 1.3)	13.4 ±1.1	12.6 ±1.4	.30 (-.4, 1.0)

Notes: HbA1c (Hemoglobin A1c), HOMA-IR (Homeostatic Model Assessment of Insulin Resistance), CI (confidence interval)

*denotes statistically different baseline value compared to 2x/week dose group.

Table 2. Effect of High Intensity Functional Training (HIFT) on mean changes in HOMA-IR, HbA1c, Insulin, and Fasting Blood Glucose.

			Chances that the true effect has substantial…			
	Mean Difference	**± 90% Confidence Limits**	**Benefit (%)**	**Trivial (%)**	**Harm (%)**	**Practical Assessment**
HOMA-IR +HIFT (relative to baseline)						
Once a week	1.3	1.3, ± 1.3	86.9	10.9	2.2	Likely beneficial, +ive
Twice a week	1.9	1.9, ± 1.7	88.9	10.0	1.2	Likely beneficial, +ive
Thrice a week	.28	.28, ± .31	63.9	35.2	.9	Possibly beneficial, +ive
HbA1c +HIFT (relative to baseline)						
Once a week	.05	.05, ± .082	69.6	25.1	5.3	Unclear
Twice a week	.05	.05, ± .079	50.0	47.6	2.4	Possibly beneficial, +ive
Thrice a week	.03	.03, ± .048	8.1	91.6	.2	Likely trivial
Insulin +HIFT (relative to baseline)						
Once a week	3.4	3.4, ± 3.6	86.9	10.5	2.6	Likely beneficial, +ive
Twice a week	8.4	8.4, ± 7.4	88.9	9.9	1.1	Likely beneficial, +ive
Thrice a week	.82	.82, ± 1.1	60.6	37.7	1.7	Possibly beneficial, +ive
Fasting Blood Glucose +HIFT (relative to baseline)						
Once a week	9.5	9.5, ± 8.2	87.5	11.1	1.4	Likely beneficial, +ive
Twice a week	4.9	4.9. ± 2.8	98.6	1.1	.3	Very likely beneficial, +ive
Thrice a week	1.7	1.7, ± 2.6	67.6	28.2	4.2	Possibly beneficial, +ive

If chances of benefit and harm both > 5% the true effect was deemed unclear (could be beneficial or harmful).
Otherwise, chances of benefit or harm were assessed in the following manner: <1%, almost certainly not, 1-5%, very unlikely; 5-25%, unlikely; 25-75%, possibly; 75-95%, likely; 95-99%, very likely; >99%, almost certain.

Discussion

Within a MetS cohort, low frequency HIFT was more effective (1x and 2x/week) than higher frequency HIFT (3x/week) at improving insulin and glucose control. There were favorable reductions in HOMA-IR, FBG, and insulin across all three groups, with lower frequency HIFT eliciting greater effects. These findings provide critical preliminary evidence on the effectiveness of a HIFT training intervention in a clinical population regarding glucose control and insulin sensitivity.

According to literature, high intensity exercise elicits favorable changes in insulin sensitivity, and related improvements in B-cell secretory capacity glucose control[16, 20-21]. However, according to the analysis of this current data, there is not a dose response relationship with the exercise training HIFT intervention. This is contrary to literature stating greater volumes of high intensity interval exercise elicited greater magnitudes of change in insulin and glucose dependent variables[18]. HIFT and exercise dosage in relation to insulin resistance is unexplored, in contrary to exercise dosage exploration and other high intensity exercise interventions. According to a study by Houmard and colleagues[26], there is a direct relationship between exercise dosage in relation to time and insulin resistance. Those within the experimental group completing 170 minutes of exercise a week (frequency 3 to 4 sessions weekly) had greater improvements in insulin sensitivity (+83%) when compared to those completing 115 minutes of exercise per week (3 sessions weekly) with less prominent insulin sensitivity improvements (+38%). Those within the sedentary control group had decreases in insulin sensitivity (-4%). Similarly, Dube and colleagues[28] found a significant dose response relationship with high intensity exercise dosage and insulin sensitivity, as following high intensity exercise, glucose disposal rate was increased more significantly with increased exercise dose. There was no obvious exercise threshold for the insulin sensitivity benefits. As for research in agreement with results from the present study, Ramos et al. studied 99 metabolic syndrome participants, finding a greater magnitude of HOMA-IR reduction with low volume HIIT (51 minutes/week) (-15%) as opposed to greater volume HIIT (114 minutes/week) (-10%)[29].

Mechanistically, there are several potential explanations for the present findings. Mitochondrial biogenesis and increased cardiorespiratory fitness occur with high intensity exercise, and according to research[29], low-volume high intensity exercise is a robust stimulus for increasing protein content and translocation for GLUT-4, thus increasing mitochondrial oxidative enzymes, and reducing glucose concentration (CRF). The master regulator of mitochondrial biogenesis, peroxisome proliferator activated receptor gamma coactivator 1-alpha (PGC-1α), is activated through high intensity exercise, in turn increasing mitochondria production and upregulated manufacturing, and thereby quickly increasing the mitochondrial density within the cell[30]. More mitochondria availability increases energy production within the body. PGC-1α contributes to insulin sensitivity by favorably impacting oxidative capacity, glucose uptake, and anti-inflammatory pathways[29]. Low volume, high intensity exercise has been shown to elicit changes in cardiorespiratory fitness levels similar to high volume. Indeed, according to Ramos and colleagues[29], a modest dose of high intensity is only necessary to upregulate mitochondrial biogenesis. PGC-1α was not a measure included in this present study; however, it is hypothesized PGC-1α levels were similar across groups, for

there may not be a dose response relationship with exercise frequency and PCG-1α production. Therefore, the amount of mitochondrial biogenesis is also not dose-dependent hence, it is speculative that cardiorespiratory fitness does not increase with exercise frequency. This is seen in the results on Table 1. Brief and practical exercise interventions, for example HIFT, are associated with increased cardiorespiratory fitness[31]. This addresses the concern of lack of time in an exercise participation barrier for those within a clinical population[31].

Regarding the present research, it can be speculated that inflammation impacted training adaptations in the greater frequency dose groups. Indeed, the lack of a meaningful dose response relationship may be explained by inflammatory markers that can be present in overtraining. The cytokine hypothesis of overtraining states repetitive trauma is due to high intensity or volume of training along with a lack of recovery time/rest[32]. Counteracting favorable benefits of exercise, excessive stress and muscle trauma may result in the appearance of elevated pro-inflammatory cytokines. According to Smith, muscle injury can interfere with glucose disposal[32]. Large volumes of exercise can elicit systemic inflammation and local muscle membrane injury affecting the availability of GLUT-4; hence, negatively impacting glucose control in the body[32]. Furthermore, capacity for improvement may have impacted the final outcome in the present study due to baseline values differing among dose frequency groups[29]. Those with high HOMA-IR had more pronounced changes in all experimental groups in comparison to participants with low baseline HOMA-IR, creating a varying window of improvement. See Table 1 for baseline HOMA-IR values across differing dose groups.

Regarding clinical and practical application of this research, the minimum clinically important difference (MCID) is "offered as a standard for determining effectiveness of a given treatment and describing patient satisfaction in reference to that treatment"[33]. This value is found in literature and is used to determine "the smallest improvement considered worthwhile by a patient"[33]. In relation to the dependent variables analyzed, the MCID for HOMA-IR is half of the standard deviation of each outcome at baseline[34], with the MCID equating to 0.7, 0.65, and 0.2 for 1x/week, 2x/week, and 3x/week, respectively. Comparing the percent difference baseline to post program, the MCID was surpassed by all dose groups—verifying all exercise frequencies of HIFT can be considered worthwhile by a patient in a clinical setting regarding HOMA-IR responses. As for insulin, the MCID was identified as 0.7 mU/l based on the literature[34]. The percent differences across all three frequency groups also surpassed MCID values. Unfortunately, fasting blood glucose does not have a conclusive value found in the literature[35]. Although fasting blood glucose does not have an MCID, looking at the practical assessment through the magnitude-based inferences, glucose control was positively impacted through this intervention as well.

A study by Khalili and colleagues researched the efficacy and legitimacy of HOMA-IR as a measurement of glucose control and diabetes risk assessment[36]. According to this recent research, HOMA-IR is "positively correlated with diabetes and prediabetes subtypes' incidence"[36]. According to this research, an increase in one SD change in HOMA-IR was associated with a 43% increased risk of impaired fasting glucose and a 92% increased risk of T2DM[36]. According to Song and colleagues, high HOMA-IR was independently and consistently associated with

increased T2DM risk in postmenopausal women[37]. However, HOMA-IR when assessed alone, is not always considered a proper criterion for T2DM risk[36]. As literature has displayed, decreased HOMA-IR has a direct relationship with decreased T2DM risk. This present study displays reductions of HOMA-IR across all exercise dose groups of the intervention, inferring the clinical benefit of a HIFT intervention for all frequency groups; however, the present data does suggest less frequency of HIFT elicits greater risk mitigation for a MetS population. These findings provide critical preliminary evidence on the effectiveness of a HIFT training intervention in a clinical population regarding glucose control and insulin sensitivity.

To our knowledge, this is the first study to examine the effects of different frequencies of HIFT on insulin and glucose regulation in a MetS cohort. The novelty of this study is a strength, as well as the randomized experimental design, supervised exercise sessions, and gold standard nature of measurements. Regarding limitations, this study unfortunately had a low sample size (n=21), which led to low statistical power. However, MBI and effect size were applied in an effort to identify clinical meaningful differences. Additionally, without efforts to completely control rest time and readiness to return to exercise, inflammation is speculated to have possibly interfered with training adaptations. Further research is necessary to determine dose response relationships between insulin and glucose regulation following various degrees of HIFT protocols.

Conclusion

To conclude, less is more regarding frequency of HIFT and insulin resistance in a MetS cohort. Indeed, low frequency HIFT was more effective (1x and 2x/week) than higher frequency HIFT (3x/week) in improving insulin and glucose control. There were favorable reductions in HOMA-IR, glucose (mg/dL), and insulin (IU) across all three groups, with lower frequency eliciting greater effects. These findings provide critical preliminary evidence on the effectiveness of a HIFT training intervention in a clinical population at positively modifying glucose control and insulin sensitivity.

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