

Interval Training in Men at Risk for Insulin Resistance

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Key words

- exercise
- insulin resistance
- insulin sensitivity
- glucose control
- diabetes

Abstract

▼ We compared 3 months of eucaloric (12 kcal/kg/wk) steady state aerobic training (AER) to interval training (INT) in men at risk for insulin resistance. Primary outcomes included oral glucose tolerance testing (OGTT) and HOMA-IR 24 h and 72 h after each participants last exercise session. Secondary outcomes were $\text{VO}_{2\text{max}}$, anthropometry, and metabolic syndrome expressed as a summed z-score (zMS). We also performed a sub-analysis for participants entering the trial above and below the HOMA-IR study median. Mean (95% CI) AER (–12.81 mg/dl; –24.7, –1.0) and INT (–14.26 mg/dl; –24.9, –3.6) significantly improved 24h OGTT. HOMA-IR did not

improve for AER, but did for INT 24h and 72h post-exercise. $\text{VO}_{2\text{max}}$ improved similarly for both groups. Changes in body mass for INT (–2.29 kg; –3.51, –1.14), AER, (–1.32 kg; –2.62, 0.58)] and percent body fat [INT, –0.83%; –1.62, –0.03], AER (–0.17%; –1.07, 0.06)] were only significant for INT. When examined as a full cohort, zMS improved for both groups. Upon HOMA-IR stratification, only high HOMA-IR AER showed significant improvements, while both low and high INT HOMA-IR participants demonstrated significant reductions ($P < 0.05$). Eucaloric AER and INT appear to affect fasting glucose, OGTT and $\text{VO}_{2\text{max}}$ similarly, while INT may have a greater impact on HOMA-IR and zMS.

Introduction

▼ Insulin resistance is an important underlying factor for diabetes and the metabolic syndrome [39]. As a whole, insulin resistance represents an eroding physiologic system compounded by poor lifestyle habits such as physical inactivity and nutrition choices resulting in a reduced capacity to metabolize glucose. In men, risk factors associated with insulin resistance include a higher BMI, waist circumference, and waist-to-hip ratio than normal glucose tolerant men [25]. Baring a change in lifestyle habitus, the likelihood of developing insulin resistance increases over time where the development of type 2 diabetes now affects 8–10% of American adults and pre-diabetes, or those individuals whose fasting blood glucose is abnormal but not yet considered diabetes, affects approximately 23% of Americans [7,17,20,37]. Fortunately, regular exercise positively affects the mechanisms of action associated with the physiologic deterioration and transition from normal glycaemia to type 2 diabetes. While most exercise policy guidelines recommend exercise

be performed within an intensity ranging of 40–85% of $\text{VO}_{2\text{max}}$ more recent guidelines emphasize the need to explore the effects of intensity [4,22,45].

Evolving research suggests that interval training (INT) produces greater changes in maximal cardiorespiratory capacity (i.e., $\text{VO}_{2\text{max}}$) than aerobic (AER) training [10,12,26,48]. Interval training also shows greater improvements in sub-maximal and maximal exercise capacity, body anthropometry, improved glucose metabolism, muscle respiratory capacity, mitochondrial biogenesis and respiratory chain activity, β -oxidation, and GLUT4 expression and peroxisome proliferator activator protein- γ co-activator1 α (PGC-1 α) than obtained with traditional steady state training, all of which deteriorate in the presence of insulin resistance and type 2 diabetes [10,11,12,16,26,45,48].

Given that insulin resistance is the resultant combination of impaired glucose uptake at the muscle and insulin signaling, and that exercise, and more specifically, INT, may affect various signaling pathways more so than traditional AER

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training, we hypothesized that INT would provide a more potent exercise stimulus for improving a number of metabolic factors in male individuals at risk for insulin resistance. Accordingly, we performed a randomized clinical trial to test this hypothesis.

Methods

The Insulin Sensitivity of Aerobic Interval Conditioning (ISAIC) trial was an NIH funded pre-clinical feasibility trial designed to compare traditional AER to INT in sedentary, overweight/obese men at risk for insulin resistance. Our study was approved by the ethical review committee at Pennington Biomedical Research Center (Baton Rouge, LA USA), conducted in accordance with the Declaration of Helsinki, and ethical standards of IJSM [21]. All study participants gave their written informed consent outlining the study before initiating the trial.

Study participants

We recruited and randomized 42 male participants between the ages of 30–60 years. In brief, participants participated in a 12 week exercise training period divided into (a) a 6-week ramp up and steady state period of traditional AER guidelines followed by, (b) the randomization to INT or continued AER training for 6 more weeks at the eucaloric energy expenditure of 12 kcal/kg/week. As our study was based on an “at risk” population, we recruited participants who were previously sedentary, had a BMI ≥ 25 , but less than 36 kg/m², a waist circumference ≥ 38 ” and a waist-to-hip ratio >0.95 as research suggests that these parameters are predictive of impaired glucose tolerance (IGT), which is used clinically to diagnose a pre-diabetic condition [34,35]. Sedentary was defined as not being physically active ≥ 3 d/week for 20 or more minutes or actively engaged in regular resistance exercise for the previous 6 months [22]. Our rationale to include only men was based on the pilot nature of the study whereby the limited ability to recruit participants would not allow us to make gender distinctions.

For our primary outcomes we selected all indices related to an oral glucose tolerance testing (OGTT), which include fasting glucose and the 2 h postprandial response to a 75 g glucose load, and insulin resistance as determined by the homeostatic model (HOMA-IR). While pre-diabetes is defined as having a fasting glucose level of 100–125 mg/dL (5.6–6.9 mmol/L) or a 2 h OGTT response of 140–199 mg/dL (7.8–11.0 mmol/L), it is possible to have impaired HOMA-IR in at risk patients who have normal glucose levels [34,35]. As secondary outcomes we examined maximal cardiorespiratory fitness (VO_{2max}), anthropometry indices, and metabolic syndrome expressed as a summed z-score (zMS; see below).

Volunteers were excluded from study participation for a number of reasons including: having a resting blood pressure $\geq 160/100$ mm Hg, triglycerides >500 mg/dl or factors that may have limited their adherence to intervention or affect conduct of the trial such as lack of time, amount of travel, and/or work or family stressors. Volunteers were also excluded from participation based on medical and behavioral considerations, hospitalized for depression in the last 6 months, consumed more >14 alcoholic beverages per week, presented with a diagnosis of schizophrenia, other psychotic disorders, or bipolar disorder, had a history of bariatric surgery within last 3 years, cancers requiring treatment in the past 5 years, self-report HIV or tuberculosis, a

history or evidence of serious arrhythmias, cardiomyopathy, congestive heart failure, aortic aneurysm, or heart transplantation, chronic obstructive lung disease, peripheral vascular disease or angina that limited their ability to follow exercise protocol, advanced neuropathy or retinopathy, the presence of renal disease, or any other medical, psychiatric, or behavioral limitations that in the view of our medical personnel would interfere with study participation.

Study procedures

All participants were asked to complete their visits in the order they are presented in **Fig. 1**.

Orientation and educational run-ins

All participants initiated the study by attending an orientation meeting explaining the study procedures. Within 2 weeks of the orientation each participant attended 2 educational run-in visits providing an opportunity to meet study staff and view slide-show presentations on the risks and benefits associated with exercise in individuals at risk for insulin resistance. During these visits participants were asked to complete a series of questionnaires detailing their medical history, eating habits, and medication use. In addition, we performed measurements of height, weight, a medical exam, and a resting electrocardiogram. We also used these visits to gauge a participant's potential compliance to our study procedures.

Clinical Testing

The formal testing phase of our study included 2 visits at baseline and 3 visits at follow-up.

Insulin sensitivity

All participants performed their OGTT during the first clinic visit following an overnight fast (≥ 10 h). Additional blood was also collected during this blood draw to determine basic blood chemistries. The OGTT was performed by consuming 75 g of glucose and then partaking a second blood draw 2 h later. During the follow-up clinic visits we performed the OGTT on 2 occasions. The first test took place 24 h post exercise to examine the acute effects of exercise on mechanisms surrounding glucose control. The second test was performed 72 h following exercise to determine the more chronic effects of the intervention as prior exercise does have an acute effect on glucose control, whereby those effects should be abolished by 72 h [24]. Though we realize that more sensitive analyses are available to examine insulin resistance, we chose the OGTT and homeostatic model assessment for insulin resistance (HOMA-IR) methods, as they were both clinically relevant and fell within the budgetary limitations associated with our pre-clinical pilot grant. Accordingly, HOMA-IR was calculated from the following equation [31]: $HOMA-IR = (FPI * FPG) / 22.5$, where FPI and FPG are fasting plasma insulin and glucose, respectively. Trained personnel drew all blood samples from an antecubital site on either arm into vacutainer tubes according to standard OSHA guidelines. We performed our glucose assays on a Beckman Coulter Synchron CX7 (Fullerton, CA) using a glucose oxidase electrode. Insulin was assayed using a Diagnostic Products Corp. 2000 (Los Angeles, CA) immunoassay with chemiluminescent detection system. The (Institution removed) laboratory participates in and meets quality control standards of the U.S. Centers for Disease Control and Prevention Lipid Standardization Program.

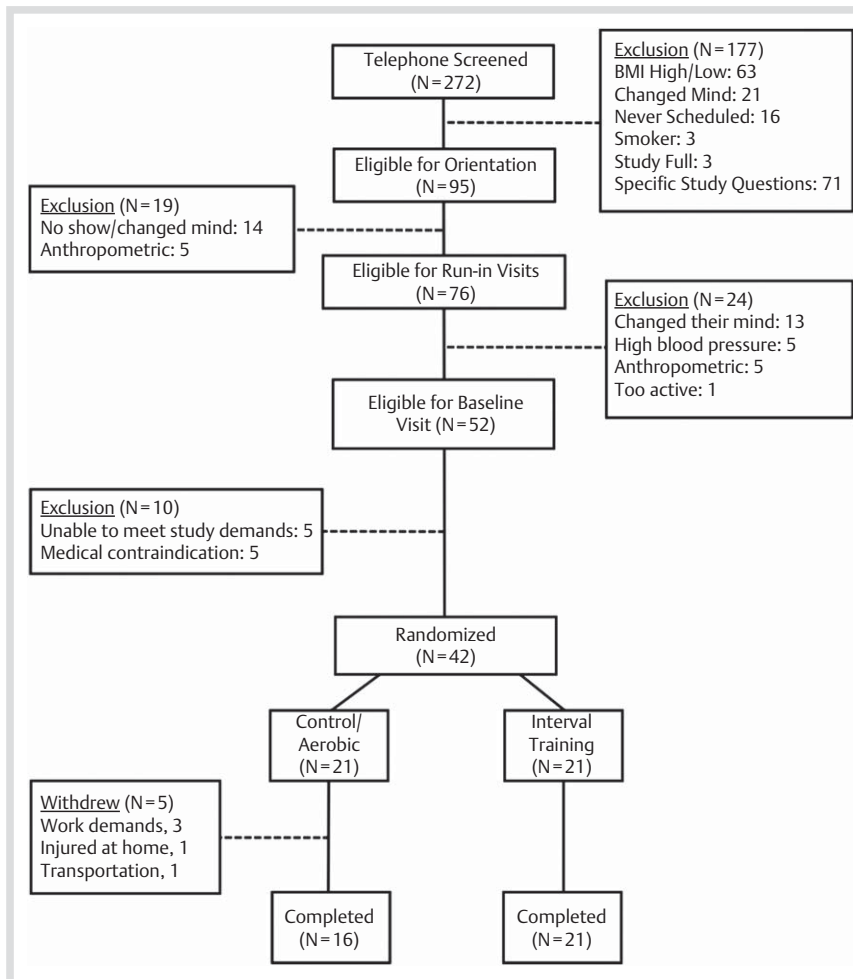


Fig. 1 CONSORT schematic representing study procedures.

Anthropometry

During their second clinic visit each participant was examined by a DXA whole body scan (Hologic QDR 4500a) to determine percent body fat, fat mass and lean body mass. To ensure the accuracy of the DXA assessment we performed daily quality control scans with a lumbar spine phantom, a manufacturer provided whole body step phantom, and a specially designed whole body phantom detailing tissue densities and percentages for fat mass, percent fat, lean body mass, and percent lean body mass. We measured waist and hip circumference using the recommendations of the Airlie Conference using a Gulick tape measure (Gays Mills, WI).

Cardiorespiratory testing

During the second clinic visit we also performed an ECG monitored maximal cardiorespiratory exercise test to determine maximal oxygen consumption ($\text{VO}_{2\text{max}}$) and maximal heart rate so as to rule out the presence of potential underlying cardiovascular disease and to establish the exercise intensities that each person would work at during the course of the exercise intervention portion of the study. We performed all exercise testing using a standardized graded exercise testing protocol administered on a treadmill (Trackmaster 425, Newton, KS), ECG monitoring using a Q-Max (Quinton Instruments, Seattle, WA), and oxygen consumption using a Parvomedics True Max 2400 Metabolic Measurement Cart (Salt Lake City, UT).

Dietary assessment

We monitored dietary changes using the Block Food Frequency Questionnaire. This questionnaire collects information about an individual's eating habits over a 12 month period. The Block Food Frequency Questionnaire contains ~105 items grouped by categories for frequency, consumption and portion size. The Block Food Frequency Questionnaire is also scannable with coding and file locations of the variables set by the DIETSYS technical support staff of the National Cancer Institute in conjunction with National Computer Systems, Inc. (NCS). The questionnaire estimates daily intake values for selected nutrients and provides information on food group servings.

Treatment assignment and exercise intervention

After their second clinic visit eligible participants were randomly assigned in a blinded fashion to either AER or INT training that was monitored and performed in the Pennington Fitness and Wellness Center. Treatment assignments were known only to the one research study coordinator (jt) and 2 exercise intervention staff (el, hc), but were blinded to the principal investigator (cpe) and all other personnel involved in the study. All groups began with a preparatory phase followed by a more formalized treatment phase (see below). We did not use a sedentary control group as we considered the AER group a standard-of-care health recommendation. All exercise was performed on a treadmill. With regard to exercise dose we considered several options. The recommendation that individuals with pre-diabetes and type 2 diabetes obtain 30 min of moderate intensity physical activity

on most days represents a consensus for recent reports [3]. We used these recommendations as the basis for determining the specific exercise dose used in our study.

As we were concerned that 5 days a week of exercise might pose an excessive burden to participants undertaking our supervised exercise sessions and the observation that the frequency of exercise sessions show little difference in physiological changes for exercise frequencies performed 3 or more days per week, provided the total weekly exercise doses are held constant we sought to have participants exercise 3–4 sessions per week [22]. In 3 sessions, this would be 336 kcal of expenditure per exercise session and in 4 sessions this would be 252 kcal per exercise session. The total length of the intervention was 12 weeks.

Preparatory training phase: Weeks 1–6

To initiate our study we used a 6-week preparatory phase of training to bring all participants up their 12 kcal/kg/wk goal. To accomplish this, all participants began their exercise program at a self-selected intensity set at a heart corresponding to 50–70% of $\text{VO}_{2\text{max}}$ and a frequency of 3–4 times per week. We started each preparatory period using an exercise dose of 6 kcal/kg/wk, which was progressively increased 2 kcal/kg/wk until week 4, where they then stayed at 12 kcal/kg/wk through 6 week. Prior to each exercise session we obtained the participants weight to determine weekly energy expenditure to achieve their target of 12 kcal/kg/wk. We expected that the gradual increase in total energy expenditure would minimize fatigue, soreness, injuries, and attrition. Each exercise session began with a 3 min warm-up period using a lower intensity (~40% $\text{VO}_{2\text{max}}$), followed by exercise at the participants target dose. Before terminating the exercise session we reduced the speed of the treadmill to allow for a 3–5 min cool down period. This approach has worked in several other exercise interventions performed by our group with few adverse musculoskeletal events [14]. After the first 6 weeks those assigned to the AER group continued to exercise for an additional 6 weeks at the same steady state level while those assigned to INT initiated a progressive protocol that also provided a ramp-up period before initiating our desired work levels.

Implementation of interval training

The overall goal for the INT group was to perform exercise sessions in a 1-to-1 work-to-recovery ratio with each work and rest interval lasting 2 min using repeated 120 s cycles for each. Similar to the preparatory-training period we initiated the INT at a lower dose and increased the number of intervals performed each session. To accomplish this all INT participants began with 2 intervals in week 6 and then progressed by adding 2 intervals per week until they were able to complete 8 intervals during their exercise session (week 9). During each exercise session, we had participants adhere to the 12 kcal/kg/wk energy expenditure format. The exercise prescription we used was established from the participants baseline exercise test and corresponded to a speed and grade associated with an upper intensity working level of 90–95% $\text{VO}_{2\text{max}}$ followed by recovery level of 50% $\text{VO}_{2\text{max}}$.

Monitoring daily activity and weight

During the intervention portion of the ISAIC study, we monitored routine daily energy expenditure in all participants by obtaining objective data on physical activity with step counters. It has been suggested that individuals who start a new exercise program may become more sedentary during the rest of the day, although we have not observed changes in daily steps in our

other studies providing an exercise intervention [14]. Overall, however, this monitoring allowed us to evaluate the issue of changes in other physical activities and adjust if necessary. We have used this same strategy in other large clinical exercise trials and find that exercise training does not demonstrate a compensatory effect on physical activity patterns outside the actual clinical exercise intervention [8,13]. As we do in all current ongoing exercise studies, we measured weight once a week prior to the first exercise session of each week.

Statistical analysis

We compared baseline characteristics between exercise groups using t-tests or chi-square tests when appropriate. Normality was determined via the Shapiro-Wilkes test. The primary aim for our current study was to examine fasting glucose, the subsequent response of participants to a standardized 2 h OGTT, and HOMA-IR following the exercise intervention. Given the possibility that acute and chronic adaptations are present with exercise training, we performed 2 post-intervention measures for the OGTT and HOMA-IR: one 24 h and the other 72 h following the participants last exercise session. As a sub-group analysis, we examined those individuals presenting to the study with fasting HOMA-IR above or below the median cohort value. Though we contemplated using fasting glucose as our criteria for this sub-group analysis, we reasoned that we were examining participants at risk for insulin resistance, not with a diabetic condition [34]. Thus, it is conceivable their fasting glucose and OGTT may not be impaired. It is, however, quite possible to have impaired HOMA without impaired fasting glucose or OGTT due to high insulin concentrations [34]. To determine the extent of these relationships and weight of relationships between various anthropometric variables, fasting plasma glucose, fasting insulin, and corresponding OGTT responses, to HOMA-IR, we performed a correlation and stepwise regression analysis, respectively.

The secondary aim of our current study was to examine the effectiveness of AER vs. INT on $\text{VO}_{2\text{max}}$ and metabolic syndrome as the etiology surrounding the onset of pre-diabetic state is similar to metabolic syndrome. We performed an exploratory analysis by using a standardized continuous Z score (zMS) for sum of metabolic syndrome scores defined by the Report of the National Heart, Lung, and Blood Institute/American Heart Association Conference [19]. This variable was determined by standardizing and then summing each index of the individual metabolic syndrome score to form a composite score or zMS. We accomplished this by taking each participant's individual score and subtracting the cohort's baseline mean value. The resultant value was then divided by the cohort's standard deviation for that score (Equation 2) [9].

Equation 2. $\text{zMS} = \sum \text{of the individual Z-scores} / \text{the number of composite scores}$, where, $\text{Individual Scores} = ([\text{Ind Metabolic syndrome score} - \text{cohort mean at baseline}] / \text{cohort SD at baseline})$.

We explored our analyses as both an intent-to-treat and per protocol analysis. As the results of these analyses did not differ, we herein present our findings as per protocol findings. Decisions for statistical significance were based significant on mixed linear model analyses with appropriate covariance components and mean (95% CI) changes from baseline to follow-up. To explore significant in-between differences we used a Tukey post hoc assessment. All descriptive data are presented as mean and standard deviation (SD). Changes from baseline to post-test

	All		Aerobic Conditioning (n = 16)		Interval Training (n = 21)	
	Mean	SD	Mean	SD	Mean	SD
age (years)	48	9	49	9	48	9
systolic BP (mm Hg)	119	10	123	8	116	11
diastolic BP (mm Hg)	79	9	83	6	76	7
lipids						
total cholesterol (mg/dl)	194.73	34.5	203.30	35.2	188.19	33.3
triglycerides (mg/dl)	143.46	89.3	165.20	122.6	126.90	49.0
HDL-C (mg/dl)	44.14	9.3	44.10	8.5	44.19	10.1
LDL-C (mg/dl)	121.81	28.2	126.50	29.4	118.47	27.5
glucose, insulin, and indices of glucose control						
glucose (mg/dl)	99.08	9.3	100.70	11.2	97.86	7.7
glucose 120 (mg/dl)	109.78	31.7	111.40	35.9	108.52	28.9
insulin (uU/ml)	11.11	7.6	10.10	6.8	11.86	8.2
insulin 120 (uU/ml)	72.45	42.4	67.90	43.1	75.88	42.7
HOMA-IR	2.73	2.0	2.54	1.9	2.87	2.1
cardiorespiratory capacity						
VO _{2max} (L/min)	2.80	0.5	2.77	0.6	2.83	0.4
VO _{2max} (ml/kg/min)	29.00	3.7	28.32	4.5	29.51	2.9
HR _{max} (b/min)	173	14	170	18	176	8
RER _{max}	1.19	0.1	1.18	0.1	1.21	0.1

SI Conversions. To convert total cholesterol, HDL-C, LDL-C to mmol/L multiply by 0.0259. To convert triglycerides to mmol/L multiply by 0.0113. To convert glucose to mmol/L multiply by 0.0555. To convert insulin to pmol/L multiply by 6.945

Table 1 Baseline characteristics of study participants randomized to steady state Aerobic Conditioning or Interval Training.

measures are presented as mean and 95% CI unless otherwise noted. All correlations are presented as the *r*-value for each significant relationship and the corresponding β coefficients of the stepwise analysis inclusive of 95% CI. All reported *P*-values are 2-sided ($P < 0.05$) and statistical analysis was performed using SPSS 19 software (Somers, NY).

Results



Participant and study characteristics

We have presented the baseline characteristics for our study participants in **Table 1, 2**. Overall, we screened 272 people who were interested in the study. Of these individuals, 52 were eligible to initiate the baseline phase of our trial. Following further exclusions, we randomized 42 participants to exercise training. Of those individuals entering the study their age ranged from 32–60 years, weight from 78.7–117.9 kg, BMI from 26.7–36.0 kg/m², and body fat percentage from 21.1–34.2%. No statistical differences were observed between treatment groups for the baseline characteristics reported in this investigation, as well as general medication use including (N, % of cohort): cholesterol (N=13, 35%), blood pressure (N=6, 16%), aspirin (N=5, 13%), pain relief (N=5, 13%) and gastrointestinal relief (N=6, 16%) medications. For our sub-group analysis, 7 participants presented with low HOMA-IR in the AER group and 10 for the INT group. Other than study entry HOMA-IR no other distinguishing differences were noted between the 2 sub-groups. Those individuals completing the study were 100% compliant and adherent to their exercise protocols.

Oral glucose tolerance testing and glucose control

Oral glucose tolerance testing

We observed significant improvements in the OGTT performed 24 h after the last exercise session for both the AER (–12.81 mg/dl, 95% CI, –24.7, –1.0) and INT (–14.26 mg/dl, 95% CI, –24.9, –3.6) groups; however, these improvements did not persist to the 72 h test (**Fig. 2a**). Further analysis of our HOMA-IR determined sub-groups showed that only those individuals in the INT enter-

ing the study with elevated HOMA-IR showed an improvement in the 24 h post exercise OGTT ($P < 0.05$), while no improvements were observed at 72 h post exercise test for either group (**Fig. 2b**). No statistical difference between the 2 groups was noted for either the 24 h or 72 h assessments.

Insulin resistance

We did not observe an improvement in HOMA-IR for the AER group at 24 h [–0.23 (95% CI, –0.77, 0.31)] or 72 h [–0.17 (95% CI, –0.65, 0.31)]. However, we did observe a significant improvement for the INT group both at 24 h [–0.51 (95% CI, –0.99, –0.3)] and 72 h [–0.46 (95% CI, –0.89, –0.2)], **Fig. 3a** following the last exercise session performed in the intervention. Within our sub-group analysis for HOMA-IR stratified participants, we found that high HOMA-IR improved for the AER and INT groups; however, only in the INT group did this improvement in HOMA-IR persist through 72 h post exercise (**Fig. 3b**). Lastly, we did not observe any significant changes in fasting insulin for any time point or treatment group. However, if we set our confidence intervals at 90% we would have observed the same statistical pattern as HOMA-IR.

Overall, we only observed significant correlations between changes in glucose and insulin relative to their effect on HOMA-IR. At follow-up 24 h post exercise testing we found a moderate correlation between glucose changes ($r = 0.41$, $P < 0.01$; $\beta = 0.03$, 95% CI, 0.02, 0.05, $P < 0.0001$) and insulin changes to HOMA-IR ($r = 0.97$, $P < 0.0001$; $\beta = 0.23$, 95% CI, 0.21, 0.25, $P < 0.0001$). For the 72 h post exercise testing, we also observed a moderate correlation between glucose changes ($r = 0.56$, $P < 0.0001$; $\beta = 0.03$, 95% CI, 0.02, 0.04) and insulin changes ($r = 0.97$, $P < 0.0001$; $\beta = 0.23$, 95% CI, 0.22, 0.26) to HOMA-IR.

Cardiorespiratory fitness

We observed that both the AER and INT groups increased their relative VO_{2max} in a similar fashion after 12 w of exercise conditioning. Specifically, the AER group improved by 3.10 ml/kg/min (95% CI, 1.0, 5.1) and the INT group by 2.94 ml/kg/min (95% CI, 1.1, 4.7). When we expressed maximal aerobic capacity as time to exhaustion, both the AER [2.8 (95% CI, 1.2, 4.4 min)] and INT

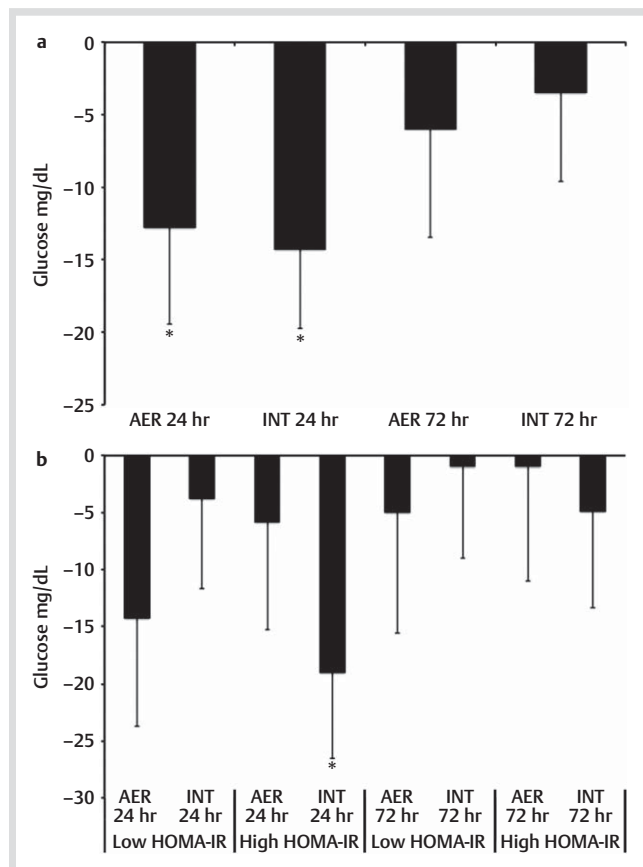


Fig. 2 The data presented represent mean (95% CI) post-test change for 24 h and 72 h OGTT after the participants final exercise session measurements for the cohort (panel a) and sub-group stratification by HOMA-IR at study entry (panel b). Significance is $P < 0.05$ (*).

group [3.1 (95% CI, 1.8, 4.5 min)] showed similar improvements to our treadmill protocol. However, when expressed in absolute terms (L/min) we observed no significant improvement for either group: AER [0.25 L/min (95% CI, -0.2, 0.54)], INT [0.13 L/min (95% CI, -0.1, 0.37)]. Therefore, the improvements observed in $\text{VO}_{2\text{max}}$ were derived from a reduction in body mass (see below).

Anthropometry

At follow-up we observed a significant reduction in body mass only within the INT group (Table 2). Though the change in body mass was not significantly different from the placebo group, the net reduction in body mass almost 2-fold higher in the INT group. The reduction in total body mass in the INT group was matched by a significant reduction in percent body fat, fat mass and lean mass. Lastly, we observed similar and significant reductions in waist circumference for the AER and INT groups, alike.

Dietary assessment

We observed no significant difference in total dietary energy intake macronutrient partitioning for carbohydrates, fat, or protein at baseline. Moreover, we observed no significant change in any dietary factor within or between groups at baseline (Table 2).

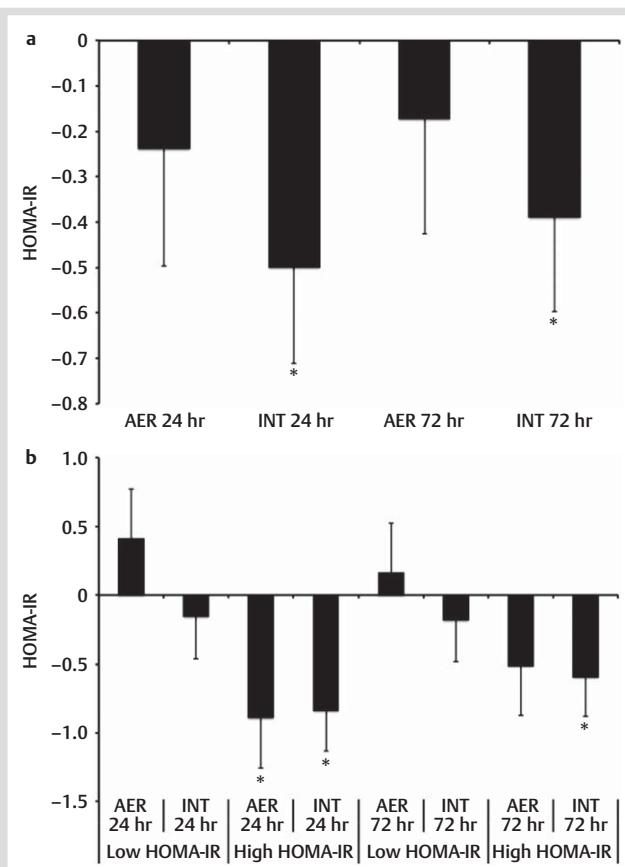


Fig. 3 The data presented represent mean (95% CI) post-test change for 24 h and 72 h HOMA-IR after the participants final exercise session measurements for the cohort (panel a) and sub-group stratification by HOMA-IR at study entry (panel b). Significance is $P < 0.05$ (*).

Metabolic syndrome

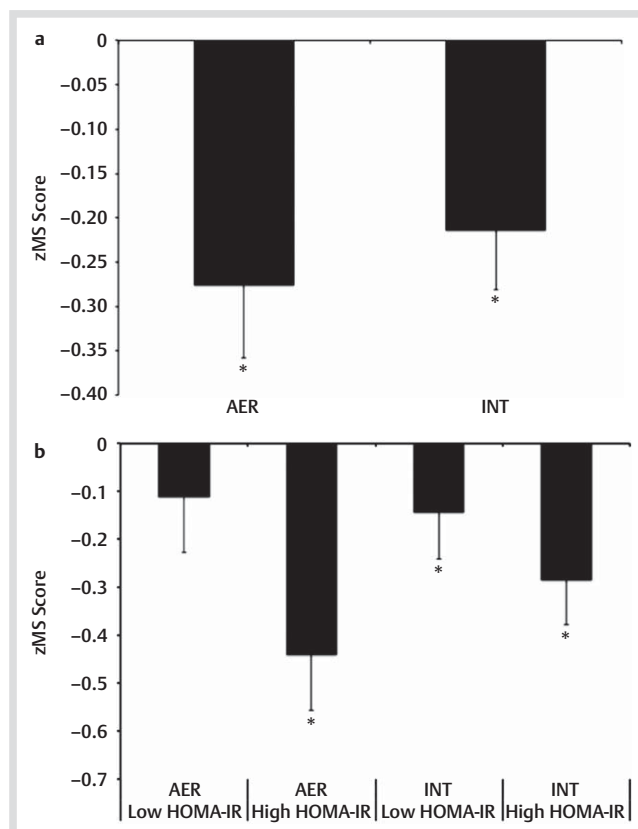
Lastly, we observed a significant decrease in zMS for both the AER and the INT group ($P < 0.05$, Fig. 4a). In our sub-group analysis based on HOMA-IR at trial entry, we observed that those individuals in the AER and INT group with high HOMA-IR at trial entry significantly reduced their zMS ($P < 0.05$; Fig. 4b). Interestingly, while those individuals with low HOMA-IR at trial entry did not show a significant reduction in zMS for the AER group, those individuals with low HOMA-IR undertaking INT did ($P < 0.05$, Fig. 4b).

Discussion

In our current trial, we examined the effects of the eucaloric administration of AER vs. INT exercise training. Our primary findings show that AER and INT improved fasting glucose, insulin, and the 2 h response to an OGTT similarly 24 h following the participants last exercise session. However, only those partaking in INT training significantly improved HOMA-IR. When we further examined our cohort based on individuals above and below the baseline HOMA-IR median, we observed that while fasting glucose only improved in high HOMA-IR INT participants 24 h post exercise, HOMA-IR improved with both AER and INT for those entering the study with high HOMA-IR values. Of particular interest is that those individuals presenting with high HOMA-IR at baseline and subsequently participating in INT also showed

Table 2 Body Composition, anthropometry, and dietary characteristics at baseline and follow-up.

	All		Aerobic Conditioning				Interval Training			
	Baseline		Baseline		Follow-Up		Baseline		Follow-Up	
	Mean	SD	Mean	SD	Mean	95% CI	Mean	SD	Mean	95% CI
body mass (kg)	95.59	11.1	98.94	12.7	-1.32	(-2.62, 0.58)	93.85	9.6	-2.29	(-3.51, -1.14)
body composition (DXA)										
body fat (%)	29.16	3.8	28.79	4.1	-0.17	(-1.07, 0.06)	29.22	3.8	-0.83	(-1.62, -0.03)
fat mass (kg)	27.62	7.1	28.33	7.1	-0.57	(-1.56, 0.53)	27.47	4.9	-1.39	(-2.36, -0.51)
lean mass (kg)	65.47	7.0	70.11	6.8	-0.75	(-1.60, 0.18)	66.38	7.2	-0.90	(-1.72, -0.15)
anthropometry										
body mass index (m/kg ²)	30.86	2.8	31.43	3.4	-0.96	(-1.73, 0.19)	30.42	2.3	-0.66	(-0.94, 0.17)
waist circumference (cm)	107.62	6.8	109.26	8.8	-3.84	(-6.04, -1.68)	106.38	4.6	-3.94	(-5.86, -2.00)
energy intake										
total energy (Kcals)	1 646	1 141	1 806	1 561	-106	(-331, 306)	1 518	658	200	(-159, 410)
carbohydrate (g)	165	105	181	143	3	(-20, 40)	151	60	25	(-8, 46)
fat (g)	69	47	72	60	-5	(-0.3, 33)	67	35	9	(-0.3, 11)
protein (g)	78	74	90	106	-14	(-21, 12)	69	32	5	(-17, 12)

**Fig. 4** The data presented represent mean (95% CI) post-test change for zMS for the cohort (panel **a**) and sub-group stratification by HOMA-IR at study entry (panel **b**). Significance is $P < 0.05$ (*).

a significant improvement in HOMA-IR 72h following their last exercise session. These findings are important to those at risk for insulin resistance as they generally share common risk factors to other non-communicable diseases such as increased visceral fat, greater BMI, and low cardiorespiratory fitness [35]. Collectively, these factors represent an eroding physiologic system associated with insulin resistance.

For our assessment of the metabolic syndrome both the AER and INT training groups improved zMS when the cohort was examined as a whole. Yet, in our sub-cohort analysis, we found that

high HOMA-IR participants significantly improved their zMS scores regardless of AER or INT. Interestingly, those individuals with lower HOMA-IR values at study entry also significantly improved zMS when undertaking INT. These observations are important as HOMA-IR, represents the cumulative affect on glucose uptake and insulin signaling [23,25]. While we did not find a pronounced statistical effect on fasting insulin, per se, we did observe that the relationship between the change in HOMA-IR and change in insulin showed a much higher correlation at 24h and 72h post exercise compared to glucose. Thus, INT appears to have a more chronic post exercise affect on HOMA-IR that persists up to 72h post exercise, as well a more robust training effect on metabolic syndrome, and should be strongly considered for future guideline statements regarding exercise participation as a viable compliment to current exercise strategies.

An important consideration for those individuals with or at risk for insulin resistance is the concept that insulin resistance is likely to progress to type 2 diabetes and cardiovascular disease if not targeted early for intervention that includes physical activity [2]. This relationship was well established by the Diabetes Prevention Program Research Group, and other studies of a similar nature [18,28,30]. While physical activity is not the sole reason for the observed changes in these trials, it does support the hypothesis that exercise training contributes to the improvement of those individuals presenting with impaired HOMA-IR. Current exercise recommendations set a goal for individuals with diabetes to accumulate ~1000kcal/week of aerobic exercise training [15]. These recommendations also fall within the range recommended by the Consensus Panel recommendation of the US Surgeon General's report on physical activity [33]. These guidelines appear to work well as Houmard et al. have reported that >150min/week of exercise improves insulin sensitivity more so than exercising ~115min/week [27].

In our current study, INT did not improve the glucose response to an OGTT more so than traditional AER conditioning. Even then, only those individuals in the high HOMA-IR subgroups demonstrated a significant improvement after 12 week of training. Our findings differ from those recently reported by Babraj et al. [6] who recently showed that 2 weeks of INT using 4–6 repetitions of 30-s sprints intervals significantly improved insulin sensitivity after just 2 weeks of training compared to a AER group expending the same amount of calories [6]. Richards et al. have also reported similar findings [40]. Both of these studies

demonstrate the time efficiency and potential superiority of INT; yet, differ from our study in that they were performed at much higher work intensities and in younger, low risk groups. Therefore, a direct comparison between studies is not feasible. Several studies have also shown a greater improvement in VO_{2max} using INT vs. AER training. Our study matched for weekly energy expenditure does not support these findings as we can attribute the changes we observed in relative VO_{2max} to a reduction in body mass. However, similar to other studies, only those partaking in INT demonstrated a significant reduction in body mass [48]. This affect was accompanied by a significant decrease in body fat percentage and waist circumference in the INT group. An interesting finding from our study using DXA compartmentalization to assess body composition is that while both groups lost a similar quantity of fat mass, the INT group also demonstrated a small, yet significant reduction in lean mass. Our findings are similar to those observed by Tjonna et al. [46] who compared AER and INT to risk factors associated with the prognosis of metabolic syndrome. In their study, these investigators found that VO_{2max} increased more in the INT training group than in the AER group and that the INT group also removed 1.9 metabolic syndrome risk factors. However, Tjonna did not use a cumulative zMS score. In this regard, if we examine our data using their criteria we find those in the INT group reduced their risk factors (-1.14 ± 1.15 , $P < 0.05$) vs. the AER group (-1.03 ± 1.68 , $P < 0.05$). We feel, however, that the zMS method is statistically more powerful as traditional metabolic syndrome scores are dichotomous. Consequently, improvement in one risk category that does not meet the criteria of moving into another category is, in essence, treated as “no improvement.” Thus, treating the risk factors associated with the metabolic syndrome as dichotomous attenuates any degree of improvement for the cumulative score. The strength of the zMS score is that it treats each risk factor as a continuous score and is therefore a more powerful tool to assess changes in metabolic syndrome risk.

Strengths and weaknesses

A primary strength of our study is that we compared the eucloric administration of AER to INT energy expenditure. Though we did not measure an interim VO_{2max} , we employed a similar ramp up schema for both groups in order to establish a similar baseline of fitness based on various guideline recommendations before introducing INT. Similarly, we also introduced INT gradually over the second 6 weeks of training. This was done in order to minimize the risk of injury and maximize the rate of adherence and compliance.

Several weaknesses of our study include that the trial was limited to men, all of whom were Caucasian. This homogenous sample therefore limits the generalizability of our study and we cannot apply our results to women and other ethnic groups. Furthermore, we examined insulin sensitivity using an OGTT and did not screen participants entering the study for fasting glucose concentrations. Rather, we relied on a set of anthropometric criteria to identify those individuals at risk for insulin resistance, which introduces a degree of statistical error potentially due to actual fasting glucose concentrations present at baseline. Nonetheless, given the pilot nature of the study, we feel that the information obtained during this trial will serve as a platform for future trials in individuals at risk for developing insulin resistance. Furthermore, we feel that INT was well tolerated by all the individuals in the study. This latter point is reinforced by the

observation that although adherence and compliance were similar between groups for those completing the study, 5 individuals in the AER group dropped out, while all INT group members completed the trial. This observation may assuage critics of INT who argue that it may be too intense or risky or that people will not adhere to such programming [48]. Clearly, our current findings in this study and those examining patients with more medically complex patients suggest otherwise [1,5,29,32,36,38,41–44,47,49,50,51].

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