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Impact of short-term exercise training intensity on β-cell function in older obese adults with prediabetes

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Abstract

The effect of work-matched exercise intensity on β-cell function is unknown in people with prediabetes before clinical weight loss. We determined if short-term moderate continuous (CONT) vs. high-intensity interval (INT) exercise increased β-cell function. Thirty-one subjects (age: 61.4 ± 2.5 yr; body mass index: 32.1 ± 1.0 kg/m^2) with prediabetes [American Diabetes Association criteria, 75-g oral glucose tolerance test (OGTT)] were randomized to work-matched CONT (70% HR_{peak}) or INT (3 min 90% HR_{peak} and 3 min 50% HR_{peak}) exercise for 60 min/day over 2 wk. A 75-g 2-h OGTT was conducted after an overnight fast, and plasma glucose, insulin, C-peptide, and free fatty acids were determined for calculations of skeletal muscle [oral minimal model (OMM)], hepatic (homeostatic model of insulin resistance), and adipose (Adipose-IR) insulin sensitivity. β-Cell function was defined from glucose-stimulated insulin secretion (GSIS, deconvolution modeling) and the disposition index (DI). Glucagon-like polypeptide-1 [GLP-1(active)] and glucose-dependent insulinotropic polypeptide (GIP) were also measured during the OGTT, along with peak oxygen consumption and body composition. CONT and INT increased skeletal muscle- but not hepatic- or adipose-derived DI ($P < 0.05$). Although both treatments tended to reduce fasting GLP-1(active) ($P = 0.08$), early phase GLP-1(active) increased post-CONT and INT training ($P < 0.001$). Interestingly, CONT exercise increased fasting GIP compared with decreases in INT ($P = 0.02$). Early and total-phase skeletal muscle DI correlated with decreased total glucose area under the curve ($r = -0.52$, $P = 0.002$ and $r = -0.50$, $P = 0.003$, respectively). Independent of intensity, short-term training increased pancreatic function adjusted to skeletal muscle in relation to improved glucose tolerance in adults with prediabetes. Exercise also uniquely affected GIP and GLP-1(active). Further work is needed to elucidate the dose-dependent mechanism(s) by which exercise impacts glycemia.

NEW & NOTEWORTHY Exercise is cornerstone for reducing blood glucose, but whether high-intensity interval training is better than moderate continuous exercise is unclear in people with prediabetes before weight loss. We show that 2 wk of exercise training, independent of intensity, increased pancreatic function in relation to elevated glucagon-like polypeptide-1 secretion. Furthermore, β-cell function, but not insulin sensitivity, was also correlated with improved glucose tolerance. These data suggest that β-cell function is a strong predictor of glycemia regardless of exercise intensity.

Keywords

training, exercise, short-term, impact, prediabetes, adults, obese, older, function, β-cell, intensity

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Title: Impact of Short-Term Exercise Training Intensity on β-cell Function in Older Obese Adults with Prediabetes

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ABSTRACT

The effect of work-matched exercise intensity on β-cell function is unknown in people with prediabetes prior to clinical weight loss. We determined if short-term moderate continuous (CONT) versus high intensity interval (INT) exercise increased β-cell function. Thirty-one subjects (Age: 61.4±2.5 yr; BMI: 32.1±1.0 kg/m^2) with prediabetes (ADA criteria, 75g OGTT) were randomized to work-matched CONT (70% HRpeak) or INT (3 min 90% HRpeak and 3 min 50% HRpeak) exercise for 60min/d over 2-weeks. A 75g 2 hr OGTT was conducted after an overnight fast, and plasma glucose, insulin, C-peptide and FFA were determined for calculations of skeletal muscle (Oral Minimal Model; OMM), hepatic (HOMA-IR), and adipose (Adipose-IR) insulin sensitivity. β-cell function was defined from glucose-stimulated insulin secretion (GSIS, deconvolution modeling) and the disposition index (DI). GLP-1(active) and GIP were also measured during the OGTT, along with VO2peak and body composition. CONT and INT increased skeletal muscle, but not hepatic or adipose, derived DI (P<0.05). Although both treatments tended to reduce fasting GLP-1(active) (P=0.08), early phase GLP-1(active) increased post-CONT and INT training (P<0.001). Interestingly, CONT exercise increased fasting GIP compared with decreases in INT (P=0.02). Early and total phase skeletal muscle DI correlated with decreased total glucose area under the curve (r=-0.52, P=0.002 and r=-0.50, P=0.003, respectively). Independent of intensity, short-term training increased pancreatic function adjusted to skeletal muscle in relation to improved glucose tolerance in adults with prediabetes. Exercise also uniquely affected GIP and GLP-1(active). Further work is needed to elucidate the dose-dependent mechanism(s) by which exercise impacts glycemia.

KEY WORDS: pancreatic function, insulin sensitivity, glucose tolerance, type 2 diabetes, high intensity interval training

NEW & NOTEWORTHY

Exercise is cornerstone for reducing blood glucose, but whether high intensity interval training is better than moderate continuous exercise is unclear in people with prediabetes prior to weight loss. We show that 2-weeks of exercise training, independent of intensity, increased pancreatic function in relation to elevated GLP-1 secretion. Further, β-cell function, but not insulin sensitivity, was also correlated with improved glucose tolerance. These data suggest that β-cell function is a strong predictor of glycemia regardless of exercise intensity.

INTRODUCTION

Maintaining the capacity of β-cells to secrete adequate amounts of insulin in response to low multi-organ insulin sensitivity is paramount to preventing the progression from prediabetes to type 2 diabetes (6). Habitual exercise is established to reduce oral glucose-stimulated insulin secretion (GSIS) and preserve pancreatic function (3, 7, 16, 20, 34). However, GSIS is influenced by the prevailing level of multi-organ insulin sensitivity. This is clinically important because the product of GSIS and insulin sensitivity (i.e. disposition index) is considered a better predictor of future diabetes development than insulin sensitivity alone (1, 27, 38). Thus, work is required to determine how to optimize β-cell function.

It is critical to determine the optimal dose at which exercise affects pancreatic function in people with prediabetes since they have lost upwards of 80% of their β-cell function (2, 13, 27, 29). While exercise confers insulin sensitizing and cardiometabolic benefit (e.g. lower total cholesterol and/or blood pressure), few studies have specifically been designed to determine the dose of exercise required to optimize β-cell function (5, 21, 29). Prior work by some (3, 20), but not all (28), suggests that exercise volume is more important than intensity for pancreatic function in subjects at risk for type 2 diabetes, despite some individuals having a blunted insulin secretion adaptation (7, 32, 35). Nonetheless, high intensity interval exercise training (INT) improves β-cell function when adjusted to changes in skeletal muscle insulin resistance in adults with obesity (11) and type 2 diabetes (18, 26), and it may yield greater benefit than continuous (CONT) exercise (18). However, training studies to date examining the effect of INT versus CONT exercise on insulin secretion have been confounded by significant weight/fat loss (18, 33), thereby making it difficult to determine the impact of exercise intensity per se on pancreatic function. A recent study by Heiskansen et al. compared a 2-week sprint interval versus moderate continuous training program in adults with

prediabetes/type 2 diabetes and reported no difference between exercise intensities on enhancing pancreatic function (15). A limitation of this prior work though was that the workloads were not work-matched, only early phase insulin secretion was tested and no assessment of incretin hormones (i.e. glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like polypeptide-1 (GLP-1)) were made. Thus, there is a major knowledge gap in determining whether INT exercise enhances both early and total phase pancreatic function to a greater extent than CONT exercise when matched on energy expenditure. This is germane in individuals with prediabetes because they have disturbances in both phases of insulin secretion (17). Based on a recent study we conducted demonstrating that 2-weeks of work-matched CONT and INT exercise improved glucose tolerance comparably, but did not relate to insulin sensitivity, in people with prediabetes (12), we tested the hypothesis that INT and CONT would induce similar benefit to early and total phase β-cell function in relation to glucose tolerance. We also hypothesized that this increase in β-cell function would relate to the incretins GIP and GLP-1 following training.

METHODS

Subjects: These older, obese subjects (Age: 61.4±2.5 yr; BMI: 32.1±1.0 kg/m^2) were the same individuals that were previously reported in our prior randomized-controlled study on glucose tolerance and metabolic flexibility (12). Subjects were recruited via flyers and/or newspaper advertisements from the local community. All subjects underwent a 75g oral glucose tolerance test (OGTT) to determine prediabetes status according to the American Diabetes Association (ADA), which was defined as either a fasting plasma glucose between 100-125 mg/dl and/or 2 hr glucose between 140-199 mg/dl (12). Subjects were non-smoking and sedentary (exercise < 60 min/wk) and underwent medical history and physical examination that included a resting and exercise stress test with 12-lead electrocardiogram. Blood and urine chemistry analyses were also conducted to exclude people with known disease (e.g. type 2 diabetes, liver disease, cardiac dysfunction, etc.). Subjects

were excluded if taking medications considered to impact glycemia (e.g. biguanides, GLP-1 agonists, etc.). All subjects provided written signed and verbal informed consent as approved by the University of Virginia Institutional Review Board.

Body Composition and Aerobic Fitness: Weight was assessed on a digital scale and height was recorded with a stadiometer to determine body mass index (BMI). Body fat, skeletal muscle mass (i.e. fat-free mass minus total body water) and visceral fat were measured by bioelectrical impedance (InBody 770 Analyzer, Cerritos, CA) (8). Subjects completed a continuous incremental peak oxygen consumption (VO2peak) test using cycle ergometer with indirect calorimetry (Carefusion, Vmax Encore, Yorba Linda, CA) and heart rate (HR) peak was used to prescribe submaximal exercise.

Metabolic Control: Subjects were instructed to consume a diet containing about 250 g of carbohydrates during the 24 hr period prior to the pre-intervention testing. This dietary pattern was recorded and replicated on the day before post- testing. Three-day food logs, including two weekdays and one weekend day, were used to assess *ad libitum* food intake before and after training (ESHA Research, Version 11.1, Salem, OR). Subjects were also instructed to refrain from alcohol, caffeine, medication and strenuous physical activity for 24 hr prior to each study visit. Post-intervention assessments were obtained approximately 24 hr after the last training session.

Exercise Training: Subjects were randomly assigned to 12, 60 minute/d work-matched bouts of CONT or INT cycle ergometry exercise over 13 days. A rest day was provided on day 7. CONT exercise was performed at a constant intensity of 70% HRpeak, whereas INT exercise involved alternating 3 minute intervals at 90% HRpeak followed by 50% HRpeak. Subsequently, both interventions were designed to exercise at approximately 70% HRpeak. HR (Polar Electro, Inc. Woodbury, NY) and rating of perceived exertion (RPE) were monitored throughout training to

ensure intensity. Exercise energy expenditure was calculated using HR-VO2 regression analysis with correction for O2 consumption during CONT (n=3) and INT (n=4) from a subset of our group as previously performed (29).

Pancreatic β-cell Function: Following an approximate 10 hr fast subjects reported to our Clinical Research Unit. Subjects rested in a semi-supine position while an intravenous line was placed in the antecubital vein for blood collection. Blood samples were obtained for the determination of plasma glucose, insulin, and C-peptide at 0, 30, 60, 90, and 120 minutes. GLP-1(active) and GIP were collected at 0, 30 and 60 minutes to characterize incretin responses. Fasting free fatty acids (FFA) was also obtained. Total area under the curve (AUC) during the OGTT was calculated using the trapezoidal rule as previously performed for GSIS adjustments to multi-organ insulin sensitivity by our group and others (4, 9, 29, 30). Skeletal muscle insulin sensitivity was calculated using the oral minimal model (OMM) and hepatic and adipose insulin resistance were estimated by multiplying fasting glucose and FFA by fasting insulin, respectively (30). Pre-hepatic insulin secretion rate (ISR) was reconstructed by deconvolution from plasma C-peptide (39). Glucose-stimulated insulin secretion (GSIS) was calculated as ISR AUC divided by glucose AUC during the OGTT. The early (0-30 min) and total phase (0-120 minute) disposition index was used to calculate β-cell function relative to skeletal muscle as AUC of ISR/glucose divided by 1/OMM. β-cell function adjusted for hepatic and adipose insulin resistance was also calculated as AUC of ISR/glucose divided by homeostatic model of insulin resistance (HOMA-IR) or Adipose-IR. Hepatic insulin extraction was calculated as AUC of C-peptide divided by insulin during the OGTT.

Biochemical Analysis: Plasma glucose was analyzed by a glucose oxidase assay (YSI Instruments 2700, Yellow Springs, OH). Remaining samples were centrifuged at 4°C for 10 min at 3000 RPM, and stored at -80°C until later batched-analyzed in duplicate to minimize variance within conditions.

Insulin, C-peptide, and FFA vacutainers contained aprotonin, while GLP-1(active) and GIP vacutainers contained aprotonin and dipeptidyl peptidase-4 (DPP-IV). Insulin, C-peptide, GLP-1(active) (i.e. 7-36 and 7-37 amide) and GIP were measured using an ELISA (Millipore, Billerica, MA). Plasma FFAs were determined by a colorimetric assay (Wako Chemicals, Richmond, VA).

Statistical Analysis: Given the relevance of fitness, body composition, glucose, FFA and insulin to understanding of pancreatic function, these data are reported in text for clarity (12). Data were analyzed using R (The R Foundation, Vienna, Austria 2013). Skewed data were log transformed for statistical analysis to meet normality. Unfortunately, due to technical difficulty some GIP (n=2, 1 Female and 1 Male) and GLP-1 (n=1, Male) data were lost within the CONT treatment. Baseline data were compared with independent, two-tailed *t*-tests. Intervention data were compared using a 2-way (group x test) or 3-way (group x test x time) ANOVA with test as the repeated measures when appropriate. Pre-test total phase GSIS as well as early and total phase adipose disposition index and Adipose-IR were different between groups. Thus, these data were used as co-variates when performing ANOVA. Pearson's correlation was used to determine associations. Significance was set at $P \leq 0.05$, and data are expressed as mean ± SEM.

RESULTS

Subject Characteristics: Both CONT and INT exercise reduced body weight (-0.3 ± 0.2 vs. -1.0 ± 0.2kg, $P<0.01$) and skeletal muscle mass (-0.4 ± 0.1 vs. -0.4 ± 0.1kg, $P<0.01$) (12). However, there was no difference following CONT or INT training in body fat (0.1 ± 0.1 vs. 0.3 ± 0.2kg, $P=0.18$; (12)) or visceral fat (1.1 ± 0.2 vs. 1.1 ± 1.5 cm^2, $P=0.26$). VO2peak increased following both CONT and INT (0.4 ± 0.2 vs. 0.5 ± 0.2 ml/kg/min; $P<0.05$). Although submaximal HR was approximately 73 ± 1% and 79 ± 1% for CONT and INT, respectively ($P<0.01$), subjects had similar RPE (12.8 ±

0.3 vs. 12.2 ± 0.5 a.u.; *P*=0.23) (12) and exercise energy expenditure (388.3±14.8 vs. 384.5±18.8 kcal/session, *P*=0.87). There were no dietary intake differences post-training (data not shown) (12).

Glucose, FFA, and Insulin Metabolism: CONT and INT training had no effect on fasting (1.0 ± 1.7 vs. -2.1 ± 2.1 mg/dl, *P*=0.70) or early phase glucose tolerance (***Figure 1)***. However, training reduced time series glucose levels, as evident by decreased total phase glucose AUC (*P*=0.03; ***Figure 1***). Fasting FFA (0.03 ± 0.7 vs. 0.05 ± 0.04 mEq/ml, *P*=0.15) and insulin levels (-0.4 ± 1.5 vs. 0.1 ± 1.1 μU/ml, *P*=0.89) were not statistically different following CONT or INT (12), although training reduced early and total-phase insulin AUC following both exercise treatments (*P*<0.05, ***Table 1***).

Insulin Sensitivity: Skeletal muscle insulin sensitivity increased following both CONT and INT (*P*=0.01, ***Table 2***). Neither hepatic or adipose insulin resistance were altered after the intervention.

Pancreatic β*-cell Function:* CONT and INT training had no effect on fasting (*P*=0.17) or early phase C-peptide levels, although it did lower total phase AUC (*P*<0.01, ***Table 1 and Figure 1***). Early and total phase ISR were also unaltered following CONT and INT treatment. Early phase GSIS was additionally not significantly changed following either exercise intensity, although CONT training increased total phase GSIS compared to a slight decrease after INT exercise (*P*=0.02). Hepatic and adipose disposition index was not altered following CONT or INT training (***Figure 2***). However, both CONT and INT exercise increased early and total phase skeletal muscle disposition index (*P*<0.001, ***Figure 1)***. Both treatments increased early phase hepatic insulin extraction (*P*=0.01), although CONT training decreased clearance during the total phase versus INT exercise (*P*=0.05, ***Table 1***)

Incretins: Although both interventions tended to reduce fasting GLP-1(active) (P=0.08), training raised early phase GLP-1(active) in response to the OGTT (P<0.01, ***Table 1***). CONT exercise increased fasting GIP compared with INT (P=0.05), and there was no effect of training on post-prandial GIP (***Table 1***).

Correlational Analysis: Baseline fasting and 2-hr glucose tended to correlate with changes in total phase β-cell function (r=0.29, P=0.11 and r=0.32, P=0.07, respectively). Enhanced early and total phase skeletal muscle disposition index was not related to weight loss (r=0.21, P=0.23 and r=0.18, P=0.32) or increases in VO2peak (r=-0.20, P=0.26 and r=-0.26, P=0.14). Reduced glucose AUC at 120 minutes correlated with increased early (r=-0.52, P=0.002) and total (r=-0.50, P=0.003) phase skeletal muscle disposition index following short-term training (***Figure 3***). There was no relation between glucose AUC at 120 minutes and insulin sensitivity derived from the OMM (r=-0.28, P=0.12) or early (r=-0.20, P=0.27) and total phase GSIS (r=-0.14, P=0.42). Decreased fasting GIP correlated with lower fasting C-peptide (r=0.41, P=0.02) and plasma insulin (r=0.50, P=0.005).

DISCUSSION

This study demonstrates that short-term exercise training increases β-cell function adjusted for skeletal muscle insulin sensitivity in adults with prediabetes, independent of intensity. Further, only CONT exercise raised fasting GIP, whereas both CONT and INT increased early phase GLP-1 during the OGTT. The increase in pancreatic function is clinically important as it was directly related to improved glucose tolerance. Together, these data suggest that exercise promotes unique compensatory mechanisms between skeletal muscle, gut and pancreas to reduce ambient glucose concentrations. Although our data confirm the use of high intensity INT exercise to improve glucose regulation (18, 32), the present data do not support prior work (5, 29, 34) suggesting greater intensities of exercise training enhance β-cell function above that of lower exercise doses in

overweight people. In fact, our findings not only support moderate intensity exercise as an effective program to increase GSIS and induce pancreatic function (34), but also we confirm recent work in adults with prediabetes and type 2 diabetes that 2 weeks of sprint interval or continuous moderate intensity exercise induced similar beneficial effects on pancreatic function (21). However, this prior work was not work-matched between intensities, nor was insulin secretion measured in the early and total phase adjusted for different indexes of insulin sensitivity to elucidate how multiple organs may impact glucose disposal. Herein we expand on this prior work and show that when high intensity INT exercise is calorically matched to moderate CONT training there is a similar rise in early and total phase pancreatic function when adjusted to skeletal muscle, but not hepatic or adipose, insulin sensitivity. This is physiologically relevant as the inverse of GSIS and tissue-specific insulin sensitivity provides an integrated view for whole-body glucose disposal (4, 9, 16, 30).

Prior work by our group demonstrated that β-cell function was a stronger predictor of glycemic control benefit following CONT exercise training than insulin sensitivity (35). We confirm these findings in the present study, and expand upon our recent exercise intensity work (12), by showing that the capacity to secrete insulin following CONT or INT exercise training may be more important for glycemic regulation than insulin sensitivity. Importantly, although associations do not equal causation, improved glucose tolerance was correlated with increased early and total phase β-cell function. This is consistent with recent work we published showing that INT exercise adds to the benefit of caloric restriction on glucose tolerance in obese adults through a pancreatic function-skeletal muscle mechanism (11). To that extent, it is recognized that the disposition index is the product of GSIS and insulin sensitivity. If one of these outcomes related to glucose tolerance, it may confound the ability to confirm that β-cell function is independently driving glycemic control. Interestingly, GSIS nor insulin sensitivity correlated with improved glucose tolerance in this report, thereby highlighting that it is the coordinated capacity to secrete insulin relative to the level of insulin

sensitivity that is critical for glucose control. Indeed, recent work has postulated that functional high intensity exercise training (32) or high intensity INT exercise (33), but not moderate intensity exercise with weight lifting (41), increases the efficiency by which insulin is synthesized in people with type 2 diabetes and/or metabolic syndrome. We did not design the current study to test the mechanism by which exercise increases pancreatic function per se, but the present data do support that in as little as 2 weeks training increases the ability of the pancreas to release of the readily available pool of insulin (i.e. early phase) and synthesize insulin in response to ambient glucose (i.e. total phase) in people with prediabetes. Moreover, we note no change in hepatic and/or adipose disposition index. This is in contrast to prior work by our group showing that a single bout of high intensity exercise reduces GSIS when adjusted to hepatic and adipose insulin resistance to support glucose control in the immediate post-exercise period (30). Subjects in the current study, however, were studied approximately 24 hr following the last exercise bout in order to minimize effects of the residual exercise bout. As such, our findings suggest that tissues involved in insulin-mediated glucose regulation play distinct roles to maintain glucose homeostasis over time.

GLP-1 and GIP are collectively referred to as incretins and regulate nearly 60% of post-prandial insulin secretion (42). Few exercise training studies have examined gut incretin responses, and none have tested the effect of intensity in people with prediabetes prior to clinically meaningful weight loss. Interestingly, prior work using CONT exercise and diet-induced weight loss report increased pancreatic function in relation to GIP in older, obese adults with prediabetes or type 2 diabetes (19, 36). This is consistent with a recent 7-day CONT high intensity exercise intervention in obese adults resulting in reduced fasting GLP-1(active) and increased early phase GLP-1(active) in response to an OGTT (23). We report herein that fasting GLP-1(active) tended to decrease following both CONT and INT training, but only CONT exercise increased fasting GIP. Furthermore, we noted marked increases in GLP-1(active) during the early phase of the OGTT following both exercise treatments

(***Table 2***). Our findings are consistent with this prior work (23) as well as cross-sectional work showing that trained individuals have lower fasting GLP-1 compared with untrained counterparts (24). In contrast, others have reported no change in fasting GLP-1 (25) or GLP-1 and GIP response to glucose-stimulation (25, 32, 43). Collectively, the rise in fasting GIP from CONT exercise, coupled with the rise in early phase GLP-1 active after both CONT and INT exercise herein, is consistent with our observation for the preservation of GSIS in the presence of increased insulin sensitivity as well as elevated pancreatic function following both treatments in people with prediabetes. Indeed, we report that the change in fasting GIP was associated with tracking fasting circulating C-peptide and insulin. The mechanism by which CONT exercise raised GIP versus INT is beyond the scope of this study, but it may relate to reductions in DPP-IV (28) and/or altered incretin-pancreas sensitivity (37, 43) since we detected no difference in body/visceral fat or aerobic fitness following exercise. Additional work is warranted to elucidate the mechanism(s) by which exercise dose acts on the pancreas for precision treatment of glucose control.

People with prediabetes (29, 34) and type 2 diabetes (7, 36) have been documented to increase β-cell function following habitual physical activity. In fact, prior work suggests that individuals with low pre-treatment β-cell function are likely to increase β-cell function following exercise training (29, 34). This later point is clinically relevant, as even small amounts of exercise could benefit β-cell function (29, 34). However, some have postulated that adults with chronic hyperglycemia or type 2 diabetes have blunted responses to habitual exercise training (7, 22, 35). Herein we show that baseline fasting and 2-hr glucose levels tended to relate to increased total phase β-cell function after training. This is consistent with some work by our group (12) and others (40) showing that people with hyperglycemia derive gluco-regulatory benefit from exercise. Nonetheless, additional work is required to elucidate how exercise regulates glucose control in different obese phenotypes as well as

consider the mechanism by which nutrition and/or pharmaceutical intervention alters the exercise effect on pancreatic function (10, 14, 31).

Our interpretations may be affected by the limitations of this study. This is a relatively small sample size without a lean control group. Therefore, it is unclear if our intervention would impact obese adults with prediabetes across age or have differential training responses to healthy controls. Individuals undergoing INT exercise had slightly higher percent heart rates during training on average than CONT exercise. The reason for this likely resides in slowed recovery between high and low intervals. Nonetheless, this is unlikely to impact our results given comparable energy expenditures between treatments. Further, we used the OGTT to assess pancreatic function, and it is possible that this approach did not detect comparable changes in insulin secretion when compared with intravenous glucose methods. However, use of the OGTT increases the physiologic relevance of our study and provide "real-world" findings that allows simultaneous assessment of incretins. We acknowledge use of surrogate measures of liver and adipose insulin resistance may also underestimate true changes in multi-organ insulin action. However, HOMA-IR and Adipose-IR are valid approaches to estimate hepatic and adipose insulin resistance, respectively, and have been previously used by our group and others (4, 9, 30). Nevertheless, we recognize that further work using stable isotopes to more directly assess skeletal muscle glucose uptake, hepatic glucose production and lipolytic rate is needed to tease out the role of distinct tissues on pancreatic function. Early phase hepatic insulin extraction increased during the OGTT, suggesting that circulating insulin more efficiently cleared following CONT and INT training. However, CONT exercise decreased total phase hepatic insulin extraction compared with INT. While these differences in insulin and C-peptide may influence calculations of insulin metabolism, the relevance of this observation is unclear as both exercise treatments reduced total phase glucose, insulin and C-peptide during the OGTT and pancreatic function was modeled using C-peptide deconvolution. Nonetheless, it highlights that

exercise likely acts in dose-dependent manner to support glycemia and further work investigating hepatic insulin extraction is required to understand insulin metabolism post-exercise.

In conclusion, short-term exercise training increases GSIS when adjusted to skeletal muscle, but not hepatic or adipose, insulin sensitivity. Independent of intensity, repeated bouts of exercise over 2 weeks increased post-prandial GLP-1(active). However, only CONT exercise increased fasting GIP. Together, these data indicate that exercise adjusts pancreatic function uniquely between glucose regulatory tissues to support glycemic control in people with prediabetes. Further work is warranted to understand the cross-talk between insulin sensitive tissues and the pancreatic β-cells to optimize treatments that prevent, treat and/or delay the onset of type 2 diabetes.

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TABLE LEGENDS

Table 1. Early and Total Phase Insulin Secretion and Incretin Responses before and after training. Data are expressed as mean ± SEM. ^Data log-transformed for statistical analysis. CONT = continuous exercise. INT = interval exercise. PG = plasma glucose. C-pep = plasma C-peptide. AUC = total area under the curve. ISR = insulin secretion rate derived from deconvolution of plasma C-peptide. GSIS = glucose-stimulated insulin secretion rate (AUC of ISR divided by Glucose). HIE = hepatic insulin extraction.

Table 2. Insulin Sensitivity before and after exercise training. Data are expressed as mean ± SEM. OMM = oral minimal model was calculated from plasma glucose and insulin to measure skeletal muscle insulin resistance. Homeostatic model of insulin resistance (HOMA-IR) was calculated as fasting PG x fasting PI then divided by 405 to depict hepatic insulin resistance. Adipose-IR was calculated as fasting FFA x fasting PI to determine adipose insulin resistance.

Table 1. Early and Total Phase Insulin Secretion and Incretin Responses before and after training.

	CONT		INT		ANOVA	(*P*-value)
	Pre	**Post**	**Pre**	**Post**	**Test**	**G x T**
Fasting						
C-pep (ng/ml)	2.4 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.1 ± 0.2	0.17	0.73
ISR (pM/min)	207.6 ± 19.4	191.9 ± 19.7	239.3 ± 16.9	232.9 ± 23.4	0.31	0.68
GIP (pg/ml)	58.0 ± 10.2	65.4 ± 15.6	59.5 ± 5.3	46.0 ± 7.0	0.72	0.02
GLP-1(active) (pg/ml)	7.1 ± 2.2	6.7 ± 1.8	8.6 ± 2.9	7.4 ± 2.4	0.08	0.31
Early-Phase Response						
Insulin $_{AUC}$ (μU/ml-30min)	1449.6 ± 154.3	1293.3 ± 142.1	1666.2 ± 182.5	1455.6 ± 206.1	0.01	0.70
C-pep $_{AUC}$ (ng/ml-30min)	135.4 ± 12.6	126.7 ± 11.1	144.7 ± 10.4	140.6 ± 11.2	0.21	0.66
ISR $_{AUC}$ x 10^{-3} (pM/ml-30min)	17.4 ±1.6	16.5 ± 1.6	18.8 ± 1.2	18.7 ± 1.5	0.47	0.59
GSIS (pM/min/mg/dl)^	4.4 ± 0.3	4.3 ± 0.3	4.8 ± 0.3	4.9 ± 0.3	0.88	0.68
HIE (ng/ml/μU/ml-30min)	0.09 ± 0.00	0.11 ± 0.01	0.09 ± 0.01	0.11 ± 0.01	0.01	0.60
GIP $_{AUC}$ (pg/ml-30min)	5302.2 ± 841.3	5529.7 ± 824.0	6222.01 ± 301.3	6031.2 ± 609.4	0.93	0.49
GLP-1(active) $_{AUC}$ (pg/ml-30min)	306.7 ± 75.5	339.9 ± 80.9	406.1 ± 77.7	443.8 ± 75.0	<0.001	0.79
Total-Phase Response						
Insulin $_{AUC}$ (μU/ml-120min)	10200.3 ± 1243.6	9365.7 ± 1208.9	10406.8 ± 1266.4	9288.8 ± 1248.7	0.03	0.75
C-pep $_{AUC}$ (ng/ml-120min)	1156.9 ± 95.0	946.7 ± 86.7	1159.0 ± 88.1	969.7 ± 65.2	<0.001	0.77
ISR $_{AUC}$ x 10^{-3} (pM/ml-120min)	91.3 ± 11.5	104.2 ± 10.7	108.4 ± 7.7	99.1 ± 7.0	0.69	0.13
GSIS (pM/min/mg/dl)	4.9 ± 2.5	5.9 ± 1.8	6.2 ± 1.6^	5.9 ± 1.5	0.06	0.02
HIE (ng/ml/μU/ml-120min)	0.12 ± 0.01	0.10 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	0.05	0.07
GIP $_{AUC}$ (pg/ml-120min)	13797.2 ± 2040.8	14290.4 ± 1949.7	16555.4 ± 846.8	16035.1 ± 1606.7	0.98	0.46
GLP-1(active) $_{AUC}$ (pg/ml-120min)	646.7 ± 156.3	649.3 ± 152.9	850.0 ± 151.9	801.2 ± 139.3	0.52	0.44

Data are expressed as mean ± SEM. CONT = continuous exercise; n = 17 (13 Females) for all outcomes except GIP (n=15, 12 Females) and GLP-1 (n=16, 13 Females). INT = interval exercise; n = 14 (11 Females). GSIS data were log-transformed for statistical analysis. CONT = continuous exercise. INT = interval exercise. PG = plasma glucose. C-pep = plasma C-peptide. AUC = total area under the curve. ISR = insulin secretion rate derived from deconvolution of plasma C-peptide. GSIS = glucose-stimulated insulin secretion rate (AUC of ISR divided by Glucose). HIE = hepatic insulin extraction. ^Pre-test group difference, $P<0.05$.

Table 2. Insulin Sensitivity before and after exercise training.

	CONT		INT		ANOVA (*P*-value)	
	Pre	**Post**	**Pre**	**Post**	**Test**	**G x T**
OMM	0.00044 ± 0.00009	0.00055 ± 0.00008	0.00033 ± 0.00004	0.00051 ± 0.00008	0.01	0.50
HOMA-IR	3.5 ± 0.6	3.6 ± 0.6	3.1 ± 0.5	3.0 ± 0.5	0.98	0.63
Adipose-IR	9.6 ± 1.8	8.6 ±1.9	7.4 ± 2.1^	6.8 ±1.3	0.53	0.99

Data are expressed as mean ± SEM. CONT = continuous exercise; n = 17 (13 Females). INT = interval exercise; n = 14 (11 Females). OMM = oral minimal model was calculated from plasma glucose and insulin to measure skeletal muscle insulin resistance. Homeostatic model of insulin resistance (HOMA-IR) was calculated as fasting PG x fasting PI then divided by 405 to depict hepatic insulin resistance. Adipose-IR was calculated as fasting FFA x fasting PI to determine adipose insulin resistance.

FIGURE LEGENDS

Figure 1. Impact of exercise intensity on circulating glucose during the OGTT. CONT = continuous exercise; n = 17 (13 Females). INT = interval exercise; n = 14 (11 Females). Main effect of Test as well as Time ($P<0.05$) was observed for circulating glucose post-intervention (CONT, A and INT, B). Early phase (C) and total phase (D) glucose tolerance were calculated using total area under the curve (AUC). *Main effect of Test, $P<0.05$.

Figure 2. Effect of exercise intensity on β-cell function adjusted for multi-organ insulin resistance. Data are expressed as mean ± SEM. CONT = continuous exercise; n = 17 (13 Females). INT = interval exercise; n = 14 (11 Females), although 1 subject (Female) was removed from CONT and INT, respectively, for hepatic and adipose DI since they were an outlier (> 2 SD from mean). DI = disposition index and was used to characterize pancreatic β-cell function. Skeletal muscle DI was calculated as AUC of ISR/Glucose divided by 1/OMM. Hepatic DI was estimated as AUC of ISR/Glucose divided by HOMA-IR. Adipose DI was determined as AUC of ISR/Glucose divided by Adipose-IR. All β-cell function data were log-transformed for statistical analysis, but are shown here in raw values. *Main effect of Test, $P<0.05$. ^Pre-test group difference, $P<0.05$.

Figure 3. β-cell Function correlates with Glucose Tolerance. CONT = continuous exercise; n = 17 (13 Females). INT = interval exercise; n = 14 (11 Females). Glucose-stimulated insulin secretion rate (C-peptide deconvolution) AUC was divided by glucose AUC during the OGTT. Early (A; 0-30 min) and total phase (B; 0-120 minute) β-cell function, or disposition index, relative to skeletal muscle was calculated as AUC of ISR/glucose divided by 1/oral minimal model (OMM). Closed circle = CONT and Open circle = INT.

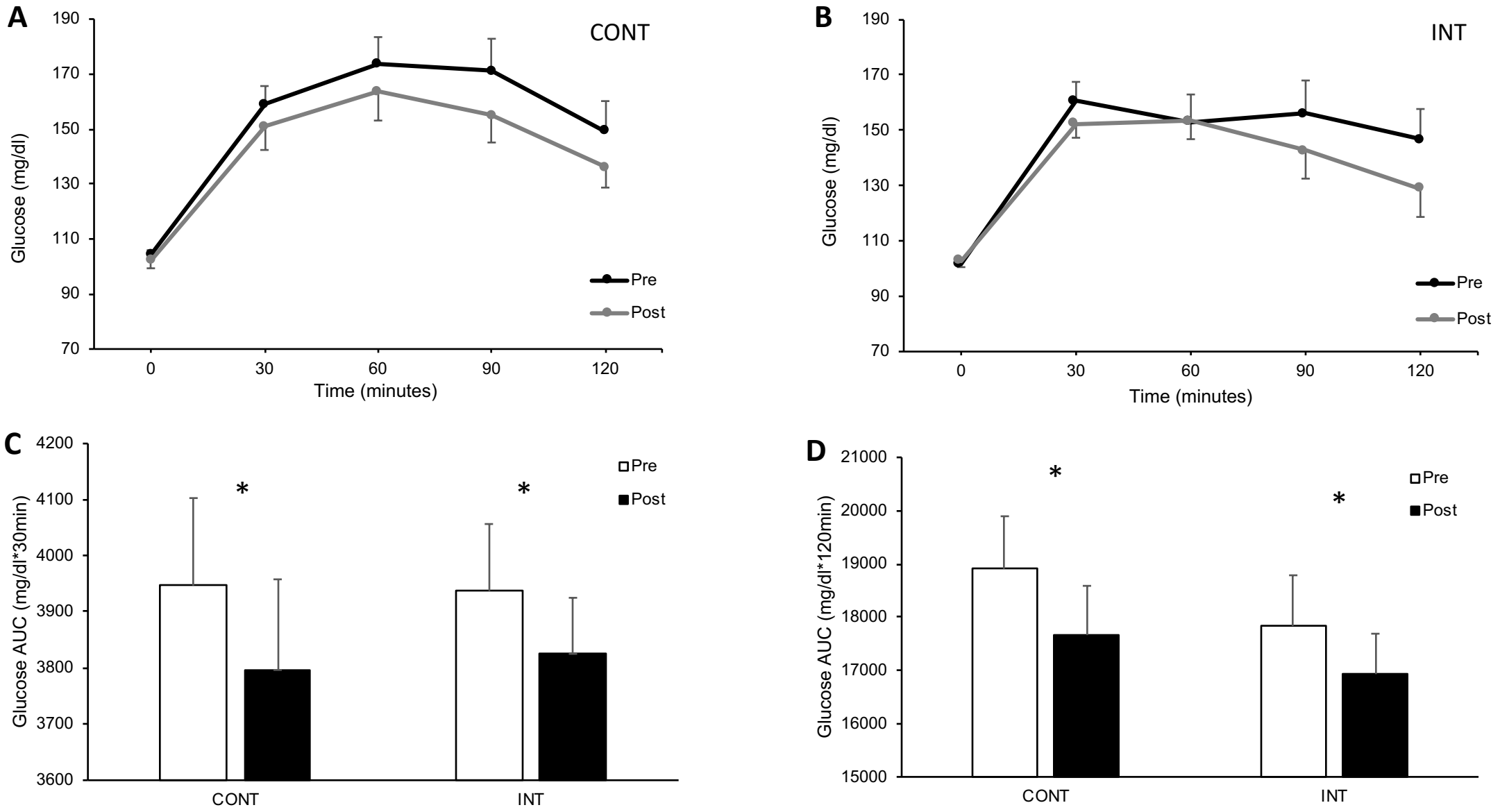
A
CONT
Glucose (mg/dl)
190
170
150
130
110
90
70
0
30
60
90
120
Time (minutes)
Pre
Post
B
INT
Glucose (mg/dl)
Time (minutes)
Pre
Post
C
Glucose AUC (mg/dl*30min)
4200
4100
4000
3900
3800
3700
3600
*
*
Pre
Post
CONT
INT
D
Glucose AUC (mg/dl*120min)
21000
20000
19000
18000
17000
16000
15000
*
*
Pre
Post
CONT
INT

Figure 1

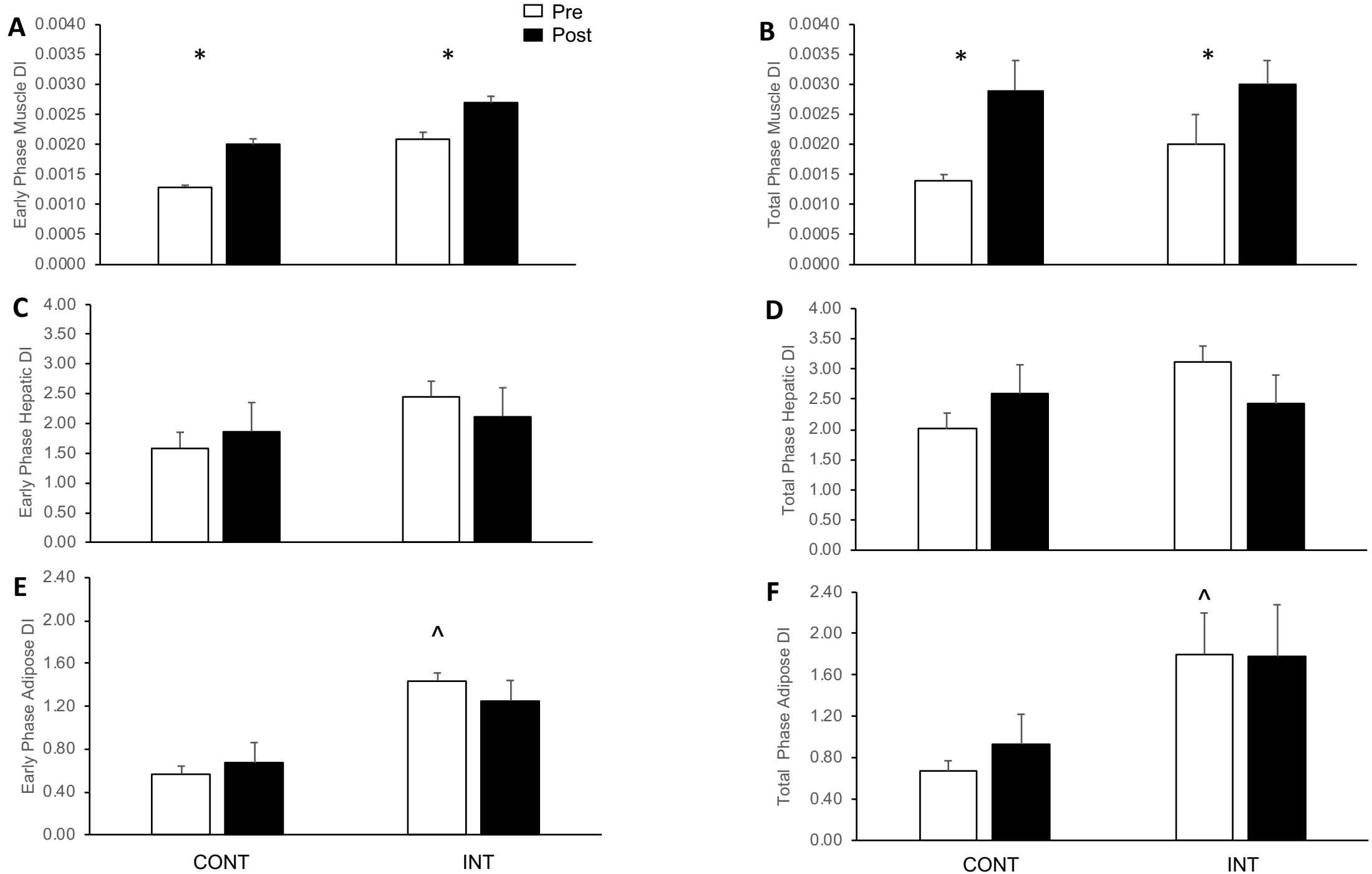
A
Pre
Post
Early Phase Muscle DI
0.0040
0.0035
0.0030
0.0025
0.0020
0.0015
0.0010
0.0005
0.0000
*
*
B
Total Phase Muscle DI
C
Early Phase Hepatic DI
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
D
Total Phase Hepatic DI
E
Early Phase Adipose DI
2.40
2.00
1.60
1.20
0.80
0.40
0.00
^
F
Total Phase Adipose DI
CONT
INT

Figure 2

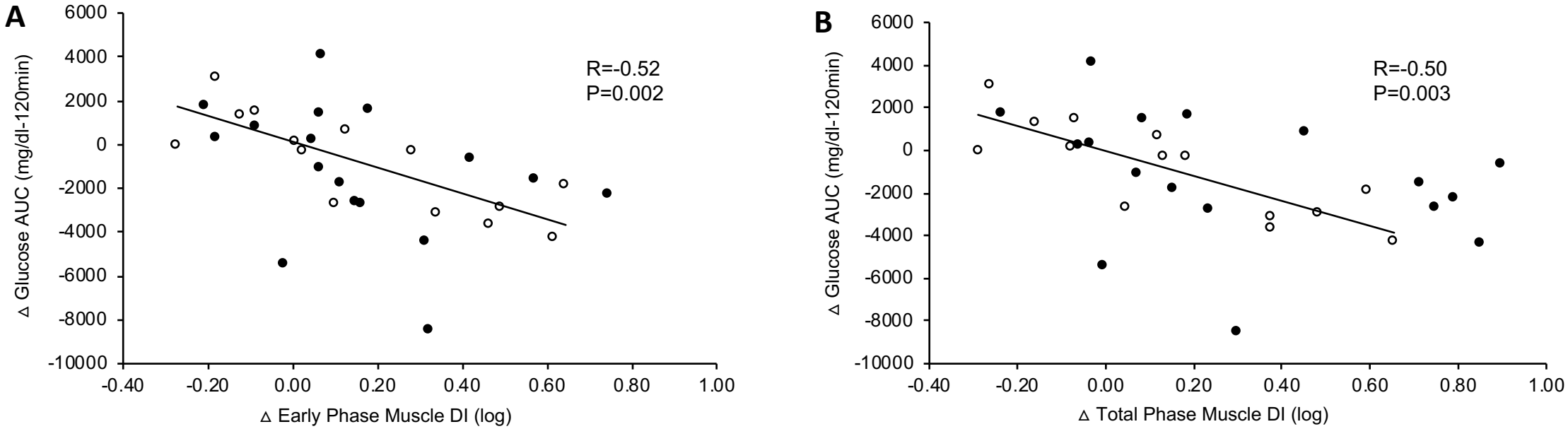
A
6000
4000
2000
0
-2000
-4000
-6000
-8000
-10000
-0.40
-0.20
0.00
0.20
0.40
0.60
0.80
1.00
Δ Glucose AUC (mg/dl-120min)
Δ Early Phase Muscle DI (log)
R=-0.52
P=0.002
B
6000
4000
2000
0
-2000
-4000
-6000
-8000
-10000
-0.40
-0.20
0.00
0.20
0.40
0.60
0.80
1.00
Δ Glucose AUC (mg/dl-120min)
Δ Total Phase Muscle DI (log)
R=-0.50
P=0.003

Figure 3