Functional High Intensity Training Improves Pancreatic β-cell Function in Adults with Type 2 Diabetes

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Running Title: Functional-HIT Improves β-cell Function in T2D

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Type 2 diabetes (T2D) is characterized by reductions in β-cell function and insulin secretion on the background of elevated insulin resistance. Aerobic exercise has been shown to improve β-cell function, despite a subset of T2D patients displaying “exercise resistance”. Further investigations into the effectiveness of alternate forms of exercise on β-cell function in the T2D patient population are needed. We examined the effect of a novel 6-week CrossFit™ Functional High Intensity Training (F-HIT) intervention on β-cell function in 12 sedentary adults with clinically diagnosed T2D (54±2 years, 166±16 mg/dL fasting glucose). Supervised training was completed 3 days a week, comprising of functional movements performed at a high intensity in a variety of 10-20 minute sessions. All subjects completed an oral glucose tolerance test and anthropometric measures at baseline and following the intervention. The mean Disposition Index (DI), a validated measure of β-cell function, was significantly increased (PRE: 8.4±3.1, POST: 11.5±3.5, P=0.02) after the intervention. Insulin processing inefficiency in the β-cell, expressed as the fasting proinsulin-to-insulin ratio, was also reduced (PRE: 2.40±0.37, POST: 1.78±0.30, P=0.04). Increased β-cell function during the early-phase response to glucose correlated significantly with reductions in abdominal body fat (R²=0.56, P=0.005) and fasting plasma alkaline phosphatase (R²=0.55, P=0.006). Mean total body fat percentage decreased significantly (Δ: -1.17 0.30%, P=0.003), while lean body mass was preserved (Δ: +0.05±0.68kg, P=0.94). We conclude that F-HIT is an effective exercise strategy for improving β-cell function in adults with T2D.

Keywords: Pancreas, insulin secretion, exercise, type 2 diabetes, obesity
INTRODUCTION

Insulin is an essential glucoregulatory hormone. In the presence of insulin resistance, this pancreatic β-cell secreted hormone has a diminished ability to drive plasma glucose into peripheral tissues. The subsequent glycemic dysregulation is overcome by β-cell compensation via insulin hyper-secretion. In a subset of individuals, however, the β-cell is unable to sustain this compensatory state and eventually undergoes failure. This progression underlies the pathogenesis of type 2 diabetes (T2D) and is the topic of several in-depth reviews (8, 12, 15). Investigating therapies that target recovery of β-cell function in the T2D patient population is of paramount clinical importance, as 21 million American adults have already been diagnosed with the disease (7).

Several groups have demonstrated that exercise has a profound effect on insulin secretion and β-cell function (16, 29), in addition to its already established influence on insulin sensitivity (17, 28). The specific effects of exercise on β-cell function appear to be dependent on metabolic status and the mode of exercise implemented. We have shown that a twelve-week aerobic exercise intervention improved β-cell function in adults with T2D (31). The same intervention also suppressed insulin hyper-secretion in healthy overweight adults. We further demonstrated that exercise-driven improvements in glycemic control were better predicted by insulin secretion rather than sensitivity (32). Specifically, participants with greater pre-intervention pancreatic secretory function also had the greatest improvements in glycemic control. When comparing responses to physical training in T2D patients with moderate versus low secretory capacity, Dela et al. reached a similar conclusion, showing that only the moderate secretors responded favorably to exercise training (9). From these findings there appears to be a response dichotomy to exercise in the T2D population, specifically dependent on residual β-cell secretory capacity.
The aforementioned studies employed only aerobic exercise training. A recently published study of 8-67 weeks of High Intensity Interval Training (HIIT), which has risen in popularity in both the exercise science field and society at large, in adults with T2D showed improvements in β-cell function, despite no changes in insulin secretion or sensitivity (21). The combination of aerobic and resistance training in the STRRIDE-AT/RT randomized trial resulted in increased β-cell function to a greater extent than either training mode alone, in sedentary, obese, non-diabetic adults (1). Combination training or high intensity training may be able to overcome the apparent resistance to exercise seen in some individuals in aerobic training only studies, but this has yet to be investigated.

The exercise approach that was developed by CrossFit, Inc.™, differs significantly from the exercise protocols used in studies to date, and may be described as a Functional High Intensity Training (F-HIT) protocol. This type of supervised training is defined by constantly varied, functional movements performed at a high intensity, and combines resistance training, gymnastics (body weight), and aerobic exercise. Importantly, workouts only require 10 to 20 minutes per session and are only performed 3 times per week (30). To date, there are no published studies that have assessed β-cell function in F-HIT or resistance training within the T2D patient population. We hypothesized that this novel F-HIT intervention program would increase β-cell function in adults with T2D.

METHODS

Subjects. This pilot, proof-of-principle study, involved twelve adults with clinically diagnosed T2D (8 women, 4 men, HbA1c 8.6±0.7%, 53 ± 2 years), recruited from the Cleveland Metropolitan Area. All participants were receiving standard of care treatment including metformin and diet/exercise education, but none were taking insulin to control their diabetes. Exclusion criteria included heart, kidney, liver, thyroid, intestinal, and pulmonary diseases or medications known to affect the outcome
variables of the study. All participants underwent medical history, physical exam, and clinical blood-work prior to entering the study. Participants were sedentary (less than 1 hour of exercise a week) and weight stable (±5 lbs.) for the prior 6 months. Study design and procedures were approved by the Cleveland Clinic Institutional Review Board, and all participants provided written informed consent.

**Intervention.** Exercise comprised of 6-weeks of F-HIT (CrossFit™) training, performed at an established gym (Great Lakes CrossFit, Bedford Heights, Ohio, USA) under the instruction of a certified CrossFit™ trainer. Groups of 2-4 participants performed three exercise training sessions per week, which included one high-intensity workout (> 85% HR maximum) ranging in duration from 10-20 minutes. Over the course of 6 weeks, participants were exposed to an array of functional weightlifting, gymnastics, and endurance movements in various combinations. More information about the individual movements and exercises may be found at [https://www.crossfit.com/exercisedemos/](https://www.crossfit.com/exercisedemos/). Post-testing commenced within 36 hours after the final exercise bout.

**Oral Glucose Tolerance Test (OGTT).** Participants were provided a standardized mixed meal dinner (55% carbohydrate, 30% fat, 15% protein) the night before testing. The meal made up 33% of their daily energy requirements based upon the Harris-Benedict Equation (13). Medications were withheld 24 hours prior to testing, and the participants also refrained from structured exercise during that time. Following an overnight (~12 hours) fast, a baseline blood sample (5 mL) was drawn from an antecubital vein. A 75 gram glucose beverage was then consumed within 5 minutes. Additional blood samples were drawn at 30, 60, 90, 120, and 180 minutes after the glucose was consumed. Aprotinin, EDTA, and DPP-IV inhibitors were included in sub-aliquots of plasma and serum according to manufacturer recommendations.
Blood Analysis. The following clinical blood measures were determined on an automated platform (Roche Modular Diagnostics, Indianapolis, IN): alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), plasma glucose, total triglycerides, total cholesterol, VLDL cholesterol, LDL cholesterol, and HDL cholesterol. Free fatty acids (FFA) were measured on serum samples collected at 0 and 120 minutes of the OGTT using a non-esterified fatty acid enzymatic colorimetric quantification assay (Wako Diagnostics, Richmond, Virginia, USA). FFA suppression was calculated as the percent reduction in serum FFA from the 0 to 120-minute time points (14). Insulin and C-peptide were measured for all OGTT samples via radioimmunoassay (EMD Millipore, Billerica, Massachusetts, USA) and counted on a Beckman Gamma 4000 Counter (Beckman Coulter, Brea, California, USA). Intact proinsulin was measured by ELISA (Mercodia, Uppsala, Sweden), with <0.03% and <0.006% specificity for insulin and C-peptide, respectively. Plasma glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) were measured on baseline, 30, and 60 minute samples using an enzyme-linked immunosorbent assay (ELISA) (EMD Millipore, Billerica, Massachusetts, USA). Insulin processing was calculated as the ratio of proinsulin to insulin (6). The early-phase C-peptide secretory response (Secretory Index), an established predictor of early-phase insulin secretion, was calculated as the ratio of the change in plasma C-peptide and glucose concentrations between baseline (0 minute) and 30 minute samples during the OGTT (26). Late-phase insulin secretion was calculated as the ratio of the total area under the curve (tAUC) for plasma C-peptide and glucose measures from 30 to 180 minutes of the OGTT. An Insulin Sensitivity Index (ISI) was calculated using the validated Stumvoll equation (37). β-cell function (Disposition Index, or DI) was individually calculated as the product of the Secretory Index and ISI multiplied by $10^3$ (2). Unless stated otherwise, secretion and β-cell function here refer to the early-phase Secretion Index and Disposition Index, respectively.
Body Composition. Body composition measures were obtained prior to and after completion of the intervention. Body weight was determined using standard procedures to the nearest 0.1 kg averaged over three independent measures. Dual energy x-ray absorptiometry (DXA) was used to determine total and depot specific body fat, as well as lean mass, with the Lunar iDXA model scanner and software (GE Healthcare, Madison, Wisconsin).

Physical Performance. All participants underwent a screening 12-lead electrocardiogram submaximal exercise stress test (SensorMedics, CareFusion, San Diego, CA) to assess healthy heart function and safety to exercise. The test was performed on a treadmill at constant speed while the grade was increased in two minute stages until the individual reached 80-85% of their age-predicted heart rate max. Blood pressure was also recorded during every 2-minute stage of the test. A second incremental graded treadmill exercise test was administered on a separate day and was performed before and after the exercise intervention to measure maximal oxygen consumption ($\text{VO}_{2\text{max}}$; Jaeger Oxycon Pro, Viasys, Yorba Linda, CA) (17). The test was deemed maximal if there is a plateau of VO$_2$ despite increased work load and at least two of the following additional criteria were satisfied: volitional fatigue, heart-rate greater than age-predicted maximum, and RER of ≥1.10. Blood pressure and heart rate were also monitored during the test. Performance during each exercise training session was recorded by the CrossFit™ trainer. Days 2 and 18 (final session) consisted of the same sets of exercises with total repetitions recorded: 5 sets of 1 minute of rowing, 1 minute of sit-ups, 1 minute of squats (no weight), and 1 minute of rest. One subject did not complete a post-intervention VO$_2$$_{\text{max}}$ test due to equipment failure, and another subject did not have the number of repetitions recorded for their final exercise training session.
Statistics. Data are presented as means ± standard error of the mean. Statistical analyses were performed using GraphPad Prism 5. Data sets were tested for normality using the Shapiro-Wilk test. Non-normal data were natural log transformed to approach normality, which was subsequently confirmed using the Shapiro-Wilk test. PRE- to POST-intervention statistical comparisons were analyzed with a paired two-tailed Student’s t-test. Linear regression analyses between study variables (Δ vs. Δ) were also performed in GraphPad Prism 5, using the Pearson test for correlations. Non-normally distribute Δ data sets were also natural log transformed to approach normality. The accepted P value for significance for each two-tailed test and Pearson correlation was set a priori at less than 0.05.

RESULTS

Physiological and Metabolic Adaptations. F-HIT intervention effects on subject anthropometrics and fasting plasma measures are listed in Table 1. Body composition changed significantly, with a mean reduction in total body fat percentage (Δ: -1.1 ± 0.3 %, P = 0.002) along with trending total body weight loss (Δ: -1.8 ± 1.0 kg, P = 0.09). Exercise capacity was significantly greater after training, with increases in both VO2max (Δ: 0.38 ± 0.08 L/min, P = 0.001) and total repetitions completed for standardized training sessions (Δ: 59 ± 8, P < 0.001). Mean fasting plasma measures of glucose, insulin, C-peptide, proinsulin, and free fatty acids, which are of general clinical importance to patients with T2D, did not change significantly. Measures of liver enzyme levels in the plasma (ALP, AST, ALT) were significantly, or tended, to be reduced. First-phase (0-30min) and late-phase (30-180min) plasma glucose, insulin, C-peptide, and proinsulin remained unchanged as well (Table 1).

Insulin Secretion. The early-phase DI was significantly improved following the intervention (PRE: 8.4 ± 3.1, POST: 11.5 ± 3.5, P = 0.02; Fig. 1A). Late-phase DI was not increased (PRE: 15.6 ± 3.1, POST: 16.4 ± 2.5, P = 0.65). There was, however, variability in individual responses to the intervention with regard to
DI (Fig. 1C). Individuals with ΔDI above the mean are indicated as filled circles, with those below the mean with little to no change in DI indicated as crossed circles. Since DI is the product of early-phase secretion and insulin sensitivity, the individual Δ’s for these measures are presented in Figure 1D and 1E. The individual demarcations from Figure 1C are retained in 1D and 1E, to further illustrate the variability in responses to the intervention. These latter data show that improvements in insulin secretion, and not insulin sensitivity, were most likely responsible for the improvement in DI. The proinsulin/insulin ratio, a measure of insulin processing inefficiency, was reduced after the intervention (PRE: 2.40 ± 0.37, POST: 1.78 ± 0.30, P=0.04; Fig. 1B).

Incretin and FFA Responses. Fasting GLP-1 (PRE: 3.32 ± 0.65, POST: 3.46 ± 0.72 ng/mL, P = 0.78) and GIP (PRE: 40.5 ± 7.0, POST: 46.9 ± 7.0 ng/mL, P = 0.14) levels remained unchanged, as well as tAUC for the first 60 minutes of the OGTT: GLP-1 (PRE: 558 ± 98, POST: 477 ± 88 ng/mL*min, P = 0.58), GIP (PRE: 10903 ± 1502, POST: 11645 ± 1257 ng/mL*min, P = 0.38). The intervention did not significantly alter fasting FFA levels (Table 1) or FFA suppression (PRE: -78.4 ± 3.8, POST: -78.5 ± 5.3 %, P = 0.98).

Correlations. Based on correlation analyses, changes in body composition and ALP correlated significantly with β-cell function and secretion. These data are presented in Figure 2, with linear regressions and 95% confidence intervals plotted for each Δ vs. Δ correlation. The individual demarcations from Figure 1 for individual responses in early-phase β-cell function are kept in Figure 2. This representation further emphasizes the significant correlations between changes in β-cell function and insulin secretion, and decreases in abdominal body fat, and lowered fasting serum ALP levels. Individual changes in the fasting proinsulin/insulin ratio, another measure of β-cell function, did not significantly correlate with any study variables.
**Sub-group Analysis.** Figure 2C shows the spread of individual responses to the F-HIT intervention based on the DI derived β-cell function index. Sub-group analyses were performed to compare the individuals demarcated in Figure 1 as filled circles (“responders”, n=5) versus crossed circles (“non-responders”, n=7). Participants in the “responder” sub-group were all female, with no significant differences from the “non-responders” in terms of age or body composition. This “responder” sub-group had higher PRE-intervention fasting plasma ALP levels (92 ± 5 vs. 64 ± 7 U/L, P = 0.008), as well as higher fasting C-peptide levels (4.0 ± 0.3 vs. 2.7 ± 0.5 ng/dL, P = 0.05). This sub-group also had better overall glucose tolerance, as tAUC (0-180 min) glucose was lower for this sub-group PRE- (33603 ± 2228 vs. 44157 ± 4060 mg/dL*min, P=0.05) and POST-intervention (32242 ± 2051 vs. 43290 ± 3502 mg/dL*min, P=0.02). Secretory capacity, expressed as C-peptide tAUC (0-180 min), was also greater in the “responder” sub-group PRE- (792.4 ± 54.0 vs. 550.8 ± 73.9 ng/mL*min, P=0.03) and POST-intervention (787.0 ± 44.5 vs 569.0 ± 75.0 ng/mL*min, P=0.03). Early-phase secretion changes were significantly greater in the “responder” sub-group (0.20 ± 0.06 vs. -0.02 ± 0.01 ng/mL/mM, P = 0.02), which is apparent from the distribution of individual changes in secretion presented in Figure 1D. Congruent with the correlations shown in Figure 2, fasting plasma ALP levels (-18.4 ± 3.3 vs. 0.9 ± 2.6 U/L, P = 0.002) and abdominal fat (-2.6 ± 0.85 vs. 0.40 ± 0.65 %, P = 0.02) were significantly reduced in the “responder” sub-group. Following the intervention, the “responder” sub-group also had lower fasting plasma glucose (126 ± 11 vs. 187 ± 22 mg/dL, P=0.04).

**DISCUSSION**

Determining β-cell function in humans poses specific challenges, as only indirect plasma metabolite measures are generally possible. The OGTT has emerged as an efficient and effective method for assessing pancreatic insulin secretion (36). However, insulin secretion is tied directly to insulin sensitivity, in a classic hyperbolic relationship (4). The Disposition Index or DI, which is the mathematical...
product of secretion and sensitivity, has thus been clinically accepted and validated as a measure of β-
cell function in humans (33). Here we show that exercise at high intensity for as little as 10-20 mins/day,
3 days/wk for 6-weeks improves β-cell function in adults with T2D (Fig. 1A). The fasting
proinsulin/insulin ratio, representing the processing inefficiency of insulin within the β-cell, was also
significantly reduced following the intervention (Fig. 1B), providing further evidence for improved β-cell
function.

Despite achieving mean improvements in β-cell function, overall glucose tolerance was not significantly
changed. Following a more traditional 3-month aerobic exercise intervention in T2D patients, Dela et al.
used a sub-group analysis to show that only participants with residual β-cell secretory capacity (defined
as “moderate secretors”) had significantly improved β-cell function, despite no changes in glucose
tolerance (9). We also found variability in individual changes in DI, where some participants had limited
changes and even reductions in DI in response to the intervention. Therefore, we used a similar sub-
group analysis approach to delineate possible factors that might contribute to these differences. This
analysis revealed that the “responder” sub-group did indeed show improved glucose tolerance, lower
glucose tAUC and fasting glucose POST-intervention, following the intervention in contrast to the “non-
responder” sub-group. These data highlight that participants who did not appreciably improve their β-
cell function also do not experience improvements in glucose tolerance.

Resistance to the beneficial effects of exercise could be due to under-performance or compensatory
lifestyle changes, as some research groups have suggested (20, 24, 35). This variability in response to
lifestyle intervention has been noted before (5). In this study two measures of physical performance
improved very significantly in response to the intervention (Table 1), but neither β-cell function nor
secretion significantly correlated with either of these measures. Within the sub-group analysis, there
were also no differences between “training volume”, or the total number of repetitions in comparative sessions, between either of the two sub-groups. As a result we cannot attribute response variability specifically to differences in training effort. Instead, as our previously published (32) and currently presented data suggest, residual β-cell secretory capacity is required for exercise (independent of mode) to effectively improve β-cell function and glycemic control. Longer exercise interventions, combined with strict dietary guidelines, may be able to drive improvements in β-cell function in patients with more severe T2D who display resistance to the exercise modes studied to date (25). However, if non-response is driven by genetic factors, as Stephens et al. (34) and Lessard et al. (20) suggest, modifying lifestyle only, may not be a sufficient therapeutic approach.

The intervention was quite effective at reducing total body fat, with trending reductions in body weight. Notably, lean mass was preserved (Δ: 0.05 ± 0.68 kg, P = 0.94) indicating that any changes in body weight were due to reductions in fat mass. We also found that reductions in abdominal fat correlated significantly with changes in both β-cell function (R² = 0.56, P = 0.005) and secretion (R² = 0.41, P = 0.02) (Fig. 2). Accumulation of adipose tissue in the abdominal region has been linked to increased insulin resistance (18), and correlates closely with increased β-cell dysfunction (40), highlighting the negative role of fat in this region on metabolic function. Potential mechanisms include increased plasma FFAs driving lipotoxicity of the β-cell (3). However, we did not see any significant statistical association between change in FFAs and β-cell function. We recognize that fasting levels of FFAs do not adequately represent the dynamic regulation of lipolysis (38). However, the percent suppression of plasma FFAs from minute 0 to minute 120 of the OGTT also remained unchanged after the intervention. We have previously reported that exercise and diet intervention-induced improvements in β-cell function among adults with T2D were significantly correlated with changes in GIP (31). However, the incretin hormone
levels of GLP-1 and GIP remained unchanged in this study, suggesting that some other mechanism is
driving improved β-cell function after this type of intervention.

Many patients with T2D also have accompanying non-alcoholic fatty liver disease (NAFLD) and
hepatocyte apoptosis, which we (10) and others (27) have shown can be reduced by exercise (aerobic
and resistance training). Mean plasma AST and ALT levels, which are clinical measures of liver
hepatocyte apoptosis, were significantly reduced following the intervention (Table 1), suggesting overall
improvements in liver function (11). Fasting ALP also tended to decrease. The correlations in Figure 2
and our sub-group analyses reveal that in the “responder” sub-group, ALP levels were significantly
elevated PRE-intervention, but markedly reduced POST-intervention. Cross-sectional analysis of plasma
ALP levels show that there appears to be no link to sex (41), despite the sex differences between the
two sub-groups. The source of circulating ALP, which may be of liver, bone, or intestinal origin, was not
specifically identified in the clinical assay performed. As a result, we are unable to conclude whether ALP
levels were indicative of changes in liver, gut, or bone function. The limited available literature on the
topic of ALP in T2D is conflicting. One study determined that bone is the predominant source of
elevated ALP in T2D (23), although this is not a consistent observation (39). In a mouse model, a high fat
diet increases serum ALP levels, but ALP was unaffected by exercise training despite protecting the mice
from liver steatosis and loss of β-cell function (22). Our data are contrary to these animal model findings,
highlighting the need to further investigate the role of this enzyme in diabetes and exercise, especially
as it relates to β-cell function.

This was a pilot proof-of-principle study investigating the efficacy of a 6-week F-HIT lifestyle intervention
in adults with T2D, and hence limitations of this study include the relatively small sample size and lack of
comparative groups, in the form of a control group or groups participating in alternative forms of
exercise. Instead, we designed the study using an internal validity paradigm, where each participant’s PRE-intervention served as the control for the POST-intervention testing results. Second, we note that from a technical perspective, the use of the hyperglycemic clamp technique would have provided a more in-depth determination of pancreatic function.

There is little scientific doubt that exercise is beneficial, yet adults with T2D may find it difficult to adhere to a strict exercise regimen, citing “lack of time” as one of their primary barriers (19). F-HIT programs like CrossFit™ may address this barrier by providing structure, supervision, and accountability, with a minimal time commitment (10-20 min/session 3 times per week). Additionally, no adverse events or injuries were reported by participants throughout the course of the study. Therefore, we conclude that F-HIT is a safe and effective exercise approach by which adults with T2D may improve their β-cell secretory function, given that residual β-cell secretory capacity is preserved. Here we have identified that changes in plasma ALP levels and abdominal adiposity appear to be additional delineating factors in determining the efficacy of exercise mediated improvements in β-cell function. Larger training studies may shed important insight into the variability in responses to exercise observed in the T2D patient population and to subsequently develop the most effective exercise treatment options for these patients.
AUTHOR DISCLOSURES

JA Foucher has received consulting fees from CrossFit. S Nieuwoudt, CE Fealy, AR Scelsi, SK Malin, M Pagadala, M Rocco, B Burguera, and JP Kirwan have no conflicts of interest relative to this work. CrossFit, Inc™ provided no input to the study design, data analysis, interpretation, or writing of this article.

FUNDING

This research was supported by an investigator-initiated grant from CrossFit, Inc.™ (JPK), Cleveland Clinic research support award RPC 2013-1010, and National Institutes of Health, National Center for Research Resources Grant UL1RR024989.

ACKNOWLEDGEMENTS

We would like to thank Patrick Flannery of the Great Lakes CrossFit™ affiliate gym in Bedford Heights, Ohio, for supervising exercise sessions, ensuring safety, and monitoring participant progress.
REFERENCES


Table 1: Anthropometrics and plasma measures. *P < 0.05

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<th>POST</th>
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<tr>
<td>Age, yr</td>
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<td><strong>Body composition</strong></td>
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<tr>
<td>Body weight, kg</td>
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<td>Total fat, %</td>
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<td>42.5 ± 1.8</td>
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<td>Abdominal fat, %</td>
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<td><strong>Physical performance</strong></td>
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<tr>
<td>VO₂max, L/min</td>
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<td>2.81 ± 0.15</td>
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<td>Session 2 (PRE) vs. 18 (POST), reps</td>
<td>223 ± 12</td>
<td>282 ± 11</td>
<td>59 ± 8</td>
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<td><strong>Fasting plasma</strong></td>
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<td>Glucose, mg/dL</td>
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<td>161 ± 16</td>
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<td>Insulin, μU/mL</td>
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<td>C-peptide, ng/mL</td>
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<td>ΔGlucose (0-30min), mg/dL</td>
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<td>10.9 ± 3.9</td>
<td>11.8 ± 3.4</td>
<td>0.9 ± 3.0</td>
<td>0.77</td>
</tr>
<tr>
<td>Glucose tAUC (30-180min), mg/dL*min</td>
<td>33509 ± 2406</td>
<td>32637 ± 2177</td>
<td>-873 ± 1018</td>
<td>0.41</td>
</tr>
<tr>
<td>Insulin tAUC (30-180min), ng/mL*min</td>
<td>9466 ± 1903</td>
<td>9494 ± 2295</td>
<td>27.8 ± 970</td>
<td>0.98</td>
</tr>
<tr>
<td>C-peptide tAUC (30-180min), μU/mL*min</td>
<td>541 ± 49</td>
<td>550 ± 47</td>
<td>9.36 ± 10.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Proinsulin tAUC (30-180min), pmol/L*min</td>
<td>9784 ± 1807</td>
<td>8186 ± 1239</td>
<td>-1598 ± 835</td>
<td>0.08</td>
</tr>
</tbody>
</table>
**Figure 1.** (A) Early-phase pancreatic β-cell function PRE- to POST-intervention presented as the mean Disposition Index. (B) Insulin processing inefficiency expressed as the ratio between fasting proinsulin and insulin. (C) Individual changes with mean ± S.E.M. DI change, with individuals with changes below the mean indicated with crossed circles. Individual changes in secretion (D) and sensitivity (E), keeping the same individual demarcations used in panel (C). N=12. *P < 0.05.
Figure 2. Correlations of changes Early-phase β-cell function (A, C) and secretion (B, D) versus abdominal fat percentage (A, B) and fasting ALP (C, D). Linear regression is shown with 95% confidence-interval with Pearson correlation coefficient of determination ($R^2$) and significant $P$-value. N=12.