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Exercise Dose and Insulin Sensitivity: Relevance for Diabetes Prevention

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Abstract

Purpose—Exercise improves insulin resistance and is a first line for the prevention and treatment of type 2 diabetes. The extent, however, to which these response are dose-dependent is not known. The purpose of this study was to examine whether or not exercise dose was associated with improvements in insulin sensitivity following four months of exercise training in previously sedentary adults.

Methods—Fifty-five healthy volunteers participated in a 16-week supervised endurance exercise intervention with a pre/post intervention design. Insulin sensitivity was assessed by euglycemic hyperinsulinemic clamp, peak oxygen uptake by a graded exercise test and body composition by DXA. The exercise intervention consisted of 3 to 5 sessions/week with a minimum of 3 sessions supervised. A ramped exercise prescription protocol was used to achieve 75% of peak HR for 45 minutes/session. Exercise dose, expressed as average kcal expended per week, was computed as the product of exercise intensity, duration and frequency.

Results—Improved insulin sensitivity was significantly related to exercise dose in a graded dose-response relationship. No evidence of threshold or maximal dose-response effect was observed. Age and gender did not influence this dose-response relationship. Exercise intensity was also significantly related to improvements in insulin sensitivity, while frequency was not.

Conclusion—This study identifies a graded dose-response relationship between exercise dose and improvements in insulin sensitivity. The implication of this observation is of importance for the adaptation of exercise prescription in clinical situations.

Keywords

Exercise dose-response; insulin resistance; obesity; type 2 diabetes; exercise prescription

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CONFLICT OF INTEREST

The authors have nothing to disclose. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

INTRODUCTION

Insulin resistance (IR) is a key contributor to the development of type 2 diabetes and is associated with obesity and physical inactivity. Epidemiological studies support the evidence that physical activity is related to the incidence of type 2 diabetes (22, 33) and that chronic physical activity prevents or delays the development of type 2 diabetes (19). Thus, chronic exercise, i.e. regular exercise training, is one of the first lines of diabetes prevention.

Cross-sectional (2) and prospective intervention (10, 16, 28) studies have demonstrated the beneficial effect of endurance exercise interventions on the improvement of insulin sensitivity. This has been shown in healthy volunteers (8) and in 'pre-diabetic' states such as in impaired glucose tolerant obese volunteers (11). This observation is not universal; some studies report no effect of exercise training on insulin sensitivity (31) while others report the effect of exercise only if performed at relatively high intensity (30). The relationship between exercise intensity and the improvement in insulin sensitivity has already been investigated with partly contradictory results. While two studies (6, 9) found a gradual positive effect of exercise intensity on insulin sensitivity, another one (18) did not find any difference between groups exercising at different intensities.

The dose of exercise needed to bring about a particular response can be defined by the characteristics of type of activity, frequency, duration and intensity. The product of frequency, duration and intensity allows an estimate of total energy expenditure and is a measure of the dose (or volume) of exercise (20). A dose-response effect of the total energy expended while exercising, thus taking into account exercise intensity, frequency and duration, could help explain why an exercise training effect has not been more consistently observed. The purpose of this study was to examine the dose-response effect of exercise dose on improvements in insulin sensitivity during exercise training in previously sedentary adults.

METHODS

Study Design, Subjects and Intervention

All subjects included in this analysis were enrolled in our clinical trial from 2005 to 2008 and completed a 16-week exercise intervention. Men and women aged 25–75 years were included if they were in good health, without recent illnesses, currently not engaged in a regular exercise program (1≤day/week of continuous physical activity), non-smoker, normal weight to obese (BMI 20–38 kg/m^2) and weight stable (±3 kg) for at least 6 months before the study. Subjects were excluded if they had a history of type 2 diabetes and/or they were taking chronic medications known to affect glucose homeostasis. The University of Pittsburgh Institutional Review Board approved the protocol and all volunteers gave written informed consent.

The exercise training protocol consisted of 16-weeks of moderate intensity aerobic exercise as described elsewhere(3). Subjects were asked to engage in 3 to 5 sessions per week with at least 3 sessions supervised in our facility. Supervised exercise modes included mostly stationary bicycling and treadmill walking, some running and rowing. The intensity and duration of the exercise session, both supervised and unsupervised, was monitored by the use of heart rate (HR) monitors (Polar Electro Oy, Finland). Exercise prescription was ramped as follows: for the first 4 weeks, the intensity was 60–70% of peak HR for duration of 30 minutes. In weeks 5 to 8, intensity was kept similar and exercise duration was increased to 40 minutes. During weeks 9 to 16, intensity was increased to 75% of peak HR and the duration to 45 minutes. The exercise prescription was based on the subject's individual peak HR achieved during a graded exercise test conducted at baseline and

adapted at the mid-point of the intervention with a submaximal ergometer test (3). HR monitors, recall of mean heart rate and duration, were used for the unsupervised sessions to quantify exercise. This was done on the next supervised session, thus allowing accurate record of the unsupervised sessions and limiting self-reporting error. Subjects were instructed not to change their dietary habits for the duration of the intervention.

Outcome Measures

Insulin sensitivity was determined by the glucose infusion rate (GIR) of the last 30 minutes of steady state from a 4-hour hyperinsulinemic (40 $mU/m^2/min$) euglycemic clamp (12). On the evening before the clamp, subjects were admitted to the Clinical & Translational Research Center. They received a standard dinner (7.5 Kcal/kg of body weight; 50% carbohydrate, 30% fat, 20% protein) and then fasted until completion of the glucose clamp. For the post intervention assessment, the clamp was performed 36–48 hours following the last exercise session to avoid the acute effects of exercise on insulin sensitivity. The GIR reflects mostly skeletal muscle insulin sensitivity as it is assumed that hepatic glucose production is nearly completely suppressed at this insulin infusion rate (1).

Weight was measured on a calibrated medical digital scale (BWB-800, Tanita Corporation, Japan) in undergarments. Height was measured at the same time with a wall-mounted stadiometer. Body mass index (BMI, kg/m^2) was calculated as weight (kg) divided by square height (m). Fat mass (kg) and fat free mass (kg) were assessed by dual-energy X-ray absorptiometry (Lunar, GE Lunar Prodigy and Encore 2005 software version 9.30).

Physical fitness was determined by the peak aerobic capacity (VO_2peak) measured using a graded exercise protocol on an electronically braked cycle ergometer (Ergoline 800S, Sensormedics, Yorba Linda, CA) (29). Heart rate, blood pressure and electrocardiogram were recorded before, during and after the exercise test. Oxygen consumption was computed by indirect calorimetry (Moxus, AEI Technologies, Pittsburgh). All of the outcome measures were performed at baseline and after the 16-week exercise intervention under weight stable conditions. The 8^{th} week submaximal test, performed to extrapolate changes in HRmax and thus to determine appropriate workload adjustments, was similar to the graded exercise test used to assess peak aerobic capacity but was stopped when the subject reached 60% of baseline VO_2peak (3).

Adherence to the exercise program was evaluated using the duration of the exercise sessions, the average HR per session and the number of sessions per week. Linear regressions of VO_2 as a function of HR were performed at three distinct time points using the baseline maximal graded test, the 8^{th} week submaximal graded test and the post-intervention maximal graded test. These regression equations allowed us to compute the average oxygen consumption in l/min for each session based on the average HR obtained at that particular session. The average oxygen uptake was then converted into energy units (1 liter of O_2 = 5 kcal) to obtain the energy expended per minute for each session. The product of the average kcal/min with the duration of the session, allowed for a kcal expended per session computation. These were then summed to obtain the kcal expended per week. The fact that we used the baseline regression equation for the first 8 weeks of the intervention, followed by the mid-point regression equation for the following 4 weeks and finally the post-intervention regression equation for the last 4 weeks of intervention allowed us to account for the individual changes in fitness of each volunteer. We report ‘exercise dose’ as the average kcal expended per week (kcal/week), ‘intensity’ as the average kcal expended per minute (kcal/min) and ‘frequency’ as the average number of sessions per week.

Statistical Analysis

Descriptive statistics for continuous variables are presented as mean±SD. Changes between the pre- and post-measures were computed as post-intervention values minus pre-intervention values. Paired T-tests were used to explore significant differences with intervention. Spearman correlations were performed to assess the relationships between these changes. To examine the relationship between dose of exercise and the difference in insulin sensitivity, we used a regression model with the difference of insulin sensitivity as the response variable and the amount of exercise (expressed as exercise dose, intensity or frequency) as explanatory variable. To account for a possible 'regression to the mean' effect, baseline insulin sensitivity was entered in the model. As fat free mass accounts for about 80% of the whole body insulin sensitivity (7), fat free mass was entered into the model. This allowed for an estimation of the expected difference in insulin sensitivity as a function of exercise for a given baseline value of insulin sensitivity and a given fat free mass. In another model, age and gender were entered to further investigate the significance of these predictors. To facilitate comparison between the models and between the sizes of the effects of the various predictors, all continuous variables have been expressed as a number of standard deviations above or below the average value at baseline. For all analyses, the alpha level was set *a priori* at 0.05. All analyses were performed in a 2-tailed approach using Stata for Mac, version 10.1 (StataCorp, College Station, TX).

RESULTS

Clinical characteristics

Among the 55 volunteers, 38% were men (n=21) and 62% women (n=34). According to their BMI, 20% of volunteers had a class II obesity, 35% class I obesity, 33% were overweight and 13% were in the normal range. The distribution of the GIR before and after intervention is presented in figure 1 panel A. All other characteristics are presented in table 1.

Exercise adherence

During the 16-week intervention, subjects expended, on average, 1094.3±518.6 kcal per week (range 407.5–2623.3). Mean exercise intensity was 6.40±2.26 kcal per minute (range 2.29–14.65). The average number of weekly sessions achieved was 3.91±0.85 sessions per week (range 2.29–6).

Changes with intervention

Insulin sensitivity significantly improved with intervention (table 1, figure 1 panel A and B). Further analyses revealed that this change was significantly related to the average kcal expended per week (figure 1 panel C) and to the average kcal expended per minute (figure 1 panel D), but not of the amount of sessions per week (table 2). From figure 1 (panel C and D), it can be seen that these relationships are approximately linear and that there is no evidence of threshold or maximal effect.

VO_2peak followed the same pattern with a significant improvement following the intervention (table 1), which was significantly related to the average kcal expended per week and per minute of exercise, but not with the number of sessions (table 2). BMI and fat mass were also significantly improved by intervention and these changes were significantly related to the average kcal expended per week, per minute and the amount of sessions per week (table 1 and 2). Fat free mass did not change with intervention (table 1).

Multivariate analyses

After controlling for baseline insulin sensitivity and fat free mass, the improvement in insulin sensitivity remained significantly related to the average kcal expended per week (table 3 panel A). In this model, the intercept was estimated to be 0.716, meaning that an average hypothetical subject (with respect to all predictors entered in the model) would achieve a GIR gain corresponding to 0.716 standard deviations (i.e. a gain of 0.716*111.8=80 mg/min), which is clinically relevant.

The fact that the estimated coefficient for the factor baseline insulin sensitivity was −0.197 indicates that the expected GIR gain would still correspond to 0.716−0.197=0.519 standard deviations (i.e. to 0.519*111.8=58 mg/min) for a subject with a baseline GIR value 1 standard deviation above average, whereas the expected GIR gain would attain 0.716+0.197=1.633 standard deviations (i.e. 1.633*111.8=183 mg/min) for a subject with a baseline GIR value 1 standard deviation below average. Thus, the model accounts for the fact that the expected GIR gain will be higher for those subjects starting with a lower GIR value.

The estimated coefficient for the factor of interest, exercise dose expressed in kcal/week, was 0.275. Thus, the expected GIR gain would be increased another 0.275 standard deviations (i.e. of another 0.275*111.8=31 mg/min) for those subjects expending one standard deviation above the mean of kcal/week (i.e. 1094+519=1613 kcal/week).

Finally for this first model, the estimated coefficient for the factor fat free mass was 0.258, which was comparable with the coefficient for kcal/week, meaning that the expected GIR gain would increase another 0.258 standard deviations (i.e. another 0.258*111.8=29 mg/min) for those subjects with a fat mass of 1 standard deviation above average.

When introducing baseline VO_2peak in the model instead of fat free mass, we obtained similar results, although fat free mass was more significant than VO_2peak at baseline. In subsequent models with kcal/week as explanatory variable (not shown), we entered age and gender, none of which were significant.

To examine the existence of a possible threshold, we entered a binary variable based on the physical activity guidelines of 900 kcal/week; thus in this model the intercept and the slope were allowed to change above or bellow 900 kcal/week. Subsequently, after the observation of figure 1 panel C where it can be seen that a small number of subjects exercising above 1500 kcal/week may have modified the regression, we performed the same model but with a binary variable of 1500 kcal/week. No significant improvements were found compared to the simpler model (table 1 panel A) with just one intercept and one slope for exercise dose (p=0.93 and p=0.89 respectively for 900 kcal/week and 1500 kcal/week). The same was true when only allowing the intercept to change (keeping the same slope above and below the threshold). Thus, we did not find any evidence for the existence of a threshold. Our results are suggesting a graded relationship between exercise dose and the improvement in insulin sensitivity as illustrated in figure 1 panel C.

As exercise intensity and frequency are key components of exercise dose, we explored in ancillary models, their relationship with insulin sensitivity. Table 3 panel B presents the model with intensity as explanatory variable; table 3 panel C represents frequency as explanatory variable and table 3 panel D is the combination of both variables in the same model. It can be seen that the average kcal per minute of exercise expended significantly predicted the change in GIR, although in this model, the baseline GIR was not found to be significant. In contrast, the amount of sessions per week was not significantly related to the change in GIR. The last model including both intensity and frequency, allows observing that

the directions are maintained but that the coefficients (corresponding to the effects) are smaller and non-significant. Thus we have not proven statistically that these two components are independent predictors on the change in insulin sensitivity.

DISCUSSION

The primary finding of this study is the positive dose-response relationship between the dose of exercise performed and the improvements in insulin sensitivity. Although exercise is encouraged for the prevention and treatment of type 2 diabetes (14, 17, 32), dose-response studies are warranted (34).

The dose-response effect observed in this study was graded. We did not evidence a threshold, neither in the lower nor on the higher end of the spectrum of the exercise volume performed by previously sedentary adult women and men with a wide range of age and BMI. Notably, even an exercise dose of ~400 kcal/week (about 40–50% of the guidelines for physical activity) was associated with a significant improvement in insulin sensitivity. This is an important finding from a clinical point of view.

The present observation of the shape of the relationship between exercise dose and direct assessments of peripheral insulin sensitivity is in accord with previous studies that used indirect measures of insulin sensitivity and self-reported exercise data (24) or exercise prescription resulting in groups of different exercise dose (16).

Similarly to this graded dose-response relationship, Church et al.(5) observed a graded dose-response relationship between exercise dose and improvements in cardiorespiratory fitness. In agreement with others (4), we believe that the largely prescribed common dose of 150 min/week of moderate intensity physical activity, based on epidemiological data, is based on insufficient evidence, particularly in regards to the cardiometabolic risk outcomes, including insulin resistance. Therefore, this may not necessarily be the best cut-off point for exercise prescription. To examine the relevance for the guidelines promoting physical activity for health (27), we entered in the regression model a dichotomous variable based on a weekly volume of 900 kcal/week (~150 minutes/week at a moderate intensity). We found no statistical evidence that the relationship between the amount of exercise and the improvement of insulin sensitivity was different for those subjects above or below a weekly volume of 900 kcal/week.

Interestingly, our data show that for the same volume of physical activity, a person with a lower baseline insulin sensitivity improves to a greater degree than an individual with relatively higher insulin sensitivity values. A further increase in exercise volume promotes additional improvement in insulin sensitivity. Baseline muscle mass and physical capacity was also positively related to the improvement in insulin sensitivity. Taken together these data corroborate the notion that one exercise prescription does not fit all clinical circumstances and that a little is better than nothing.

It is important to differentiate the acute effect of exercise (25) from the chronic effect of training (26). A single bout of moderate intensity exercise increases insulin sensitivity for 12–48 hours; Magkos et al.(23) reported a curvilinear dose-response relationship between exercise energy expenditure and insulin sensitivity assessed by the $HOMA_{IR}$ score. A threshold of approximately 900 kcal (~60–90 min of exercise at 60% VO_2peak) was suggested to improve insulin sensitivity in healthy untrained individuals. Dela et al.(8) observed that the effect of training on insulin sensitivity was an adaptation of repeated exercise and not the consequence of the last exercise bout. The molecular mechanisms by which acute and chronic exercise improve insulin sensitivity have been extensively

studied(15, 35), but have not yet been fully elucidated(13), and are beyond the scope of this project.

This study was focused on the effect on insulin sensitivity of the total exercise dose per week of training, i.e. de product of the mean exercise intensity, mean duration and frequency. Our objective was not to imply that any of the three components is more important then the others. Previous studies looking at exercise intensity reported changes in insulin sensitivity with higher intensity training (80–75% of VO_2max) but not with moderate intensity (65–50% of VO_2max) while controlling for energy expenditure, thus with the same exercise dose in all groups (6, 9). In another study controlling for energy expenditure, Hughes et al.(18) found similar improvement in insulin sensitivity in groups exercising at high or moderate intensity. In this study, we found a stronger and more significant relationship with the improvement in insulin sensitivity when considering exercise dose than when considering only one of its components. When taken alone exercise intensity was still significantly related to an improvement of insulin sensitivity. In fact when we add exercise intensity to the multivariate model including exercise dose (data not shown), the regression coefficient for exercise dose remained similar (0.258 instead of 0.275), while the coefficient of intensity became almost zero. This result would suggest that for a fixed amount of exercise dose, an increase of exercise intensity (and thus a decrease of exercise frequency and/or duration) would not affect the change of insulin sensitivity in the context of this population and for the range of exercise intensity and exercise dose observed in our study. Furthermore, this supports the fact that exercise dose is a good summary measure, allowing us to get a higher statistical power than when considering exercise intensity alone.

Only the subjects that finished the exercise intervention were included. Another limitation of this study is that only sedentary volunteers were studied, thus the same magnitude of improved insulin sensitivity may not be transposable to long-term active lifestyle individuals. Regarding the mode of training, the primary mode of activity of this intervention was stationary cycling and walking, with some running and rowing. To our knowledge, there are no data to support the hypothesis that a particular endurance-training exercise mode improves insulin sensitivity more than another.

In this diverse group of subjects, in terms of BMI and adiposity, weight loss was not a goal *per se*, thus we instructed our subjects not to modify their dietary patterns. For this reason and the fact that weight loss could not be taken as predictive values at the start of intervention, we chose *a priori* not to enter the difference in BMI, weight or adiposity in the regression model. Indeed, for a given patient, this would be a rather confusing and complex message, ‘if you lose X amount of weight, you will increase your insulin sensitivity by X amount’. It is important to note that a recent study has shown improvements of insulin sensitivity with exercise independently of weight loss(21). Moreover, an epidemiological study reported an independent association of low cardiorespiratory fitness and high BMI with the incidence of type 2 diabetes(33).

In summary, in previously sedentary adults, diverse in terms of BMI, age and gender, there is evidence for a graded exercise dose-response change in insulin sensitivity. This observation is relevant for clinical settings and particularly diabetes prevention programs. These data reinforce the concept that more insulin resistant individuals at greater risk for developing type 2 diabetes and cardiovascular disease can attain greater benefit by performing more exercise, but that there is no obvious exercise volume threshold for these benefits. It appears that, in term of improving insulin sensitivity, more is likely better than a little, and a little is better than nothing.

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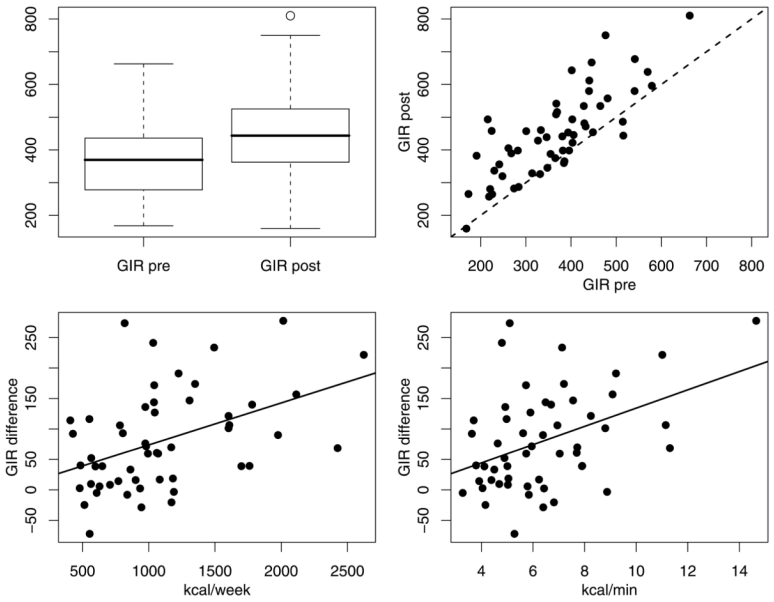

Figure 1. Changes in insulin sensitivity with exercise intervention

Panel A. Box plot of GIR before and after exercise intervention

Panel B. GIR pre vs. GIR post

Panel C. Average kcal expended per week vs. the difference in GIR (post-pre)

Panel D. Average kcal expended per minute vs. the difference in GIR (post-pre)

GIR is glucose infusion rate in mg/min. Dotted line is the equivalence line. Black line is a simple regression line. Correlation coefficients: panel B r=0.79 (P<0.001), panel C r=0.44 (P<0.001), panel D r=0.42 (P=0.002)

Table 1

Subject characteristics

	Pre	Post	Paired T-test (two sided-P value)
age (years)	53.9±14.8 (25–74.3)		
gender	21 men/34 women		
weight (kg)	86.9±14.8 (61.3–119.1)	84.4±12.7 (59.6–115.6)	<0.0001
BMI (kg/m^2)	30.5±4.4 (20.6–38.9)	29.5±3.9 (21.3–38.1)	<0.0001
fat mass (kg)	34.1±9.5 (16.2–65.0)	30.9±8.4 (16.5–50.4)	<0.0001
fat free mass (kg)	53.0±11.9 (33.7–85.8)	52.6±10.8 (35.8–82.6)	0.098
VO_2peak (ml/min)	1939.7±635.1 (873–4005)	2180.2±743.7 (967–4469)	<0.0001
GIR (mg/min)	367.2±111.8 (168.2–662.7)	449.8±130.4 (160.0–810.0)	<0.0001

Caption: Results are mean±SD (min–max), GIR=glucose infusion rate at steady state at the end of glucose clamp.

Table 2

Correlation matrix

	dGIR	dVO$_2$peak	dBMI	dfatmass	kcal/week	kcal/min	sessions
dGIR	1						
dVO$_2$peak	0.354**	1					
dBMI	−0.630***	−0.162	1				
dfatmass	−0.635***	−0.154	0.958***	1			
kcal/week	0.442**	0.222**	−0.391**	−0.419**	1		
kcal/min	0.419**	0.168**	−0.457**	−0.501***	0.821***	1	
sessions	0.283*	0.206**	−0.362**	−0.386***	0.637***	0.393**	1

Caption: Spearman correlation factors,

* P≤0.05,

** P<0.01,

*** P<0.001. d= difference computed as post-intervention values minus pre-intervention values, GIR=glucose infusion rate (mg/min), VO2peak=peak oxygen consumption (ml/min), fatmass= fat mass (kg).

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Table 3

Multivariate regression

Panel A				
	Estimate	**Std. Error**	**t value**	**P value**
(Intercept)	0.716	0.083	8.650	<0.001
Standardized baseline GIR	−0.197	0.090	−2.180	0.034
Standardized baseline FFM	0.258	0.093	2.783	0.008
Standardized kcal/week	0.275	0.091	3.035	0.004
Panel B				
	Estimate	**Std. Error**	**t value**	**P value**
(Intercept)	0.720	0.085	8.461	<0.001
Standardized baseline GIR	−0.144	0.090	−1.590	0.118
Standardized baseline FFM	0.283	0.094	3.004	0.004
Standardized kcal/min	0.222	0.090	2.472	0.017
Panel C				
	Estimate	**Std. Error**	**t value**	**P value**
(Intercept)	0.771	0.092	8.412	<0.001
Standardized baseline GIR	−0.217	0.095	−2.274	0.028
Standardized baseline FFM	0.354	0.094	3.765	0.001
Standardized sessions	0.149	0.095	1.566	0.125
Panel D				
	Estimate	**Std. Error**	**t value**	**P value**
(Intercept)	0.757	0.090	8.457	<0.001
Standardized baseline GIR	−0.248	0.100	−2.493	0.017
Standardized baseline FFM	0.279	0.098	2.841	0.007
Standardized kcal/min	0.189	0.095	1.982	0.054
Standardized sessions	0.111	0.102	1.086	0.284

Caption: Change in insulin sensitivity as a function of volume (panel A), intensity (panel B), frequency (panel C) and both intensity and frequency (panel D), after accounting for baseline insulin sensitivity (GIR) and fat free mass (FFM). All variables are standardized.