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Dose-Response Effects of Exercise on Insulin among Colon Cancer Survivors

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ABSTRACT

Physical activity is associated with a lower risk of disease recurrence among colon cancer survivors. The pathways through which physical activity may alter disease outcomes are unknown, but may include changes in metabolic growth factors, such as insulin. Methods: Between January 2015 and August 2015, 39 stage I-III colon cancer survivors were randomized to one of three groups: usual-care control, 150 min·wk^{-1} of aerobic exercise (low-dose), and 300 min·wk^{-1} of aerobic exercise (high-dose) for six months. The pre-specified key metabolic growth factor outcome was fasting insulin. Insulin resistance was quantified using the homeostatic model assessment. Results: Mean age was 56.5±10.0 years, 51% had stage III disease, 72% were treated with chemotherapy, and the mean time since finishing treatment was 10.9±6.1 months. Over six months, the low-dose group completed 141.5±9.9 min·wk^{-1} of aerobic exercise, and the high-dose group completed 247.2±10.7 min·wk^{-1} of aerobic exercise. Fasting insulin concentrations decreased 7.4±9.4 pmol/L in the control group, 28.0±8.3 pmol/L in the low-dose group, and 20.7±9.3 pmol/L in the high-dose group (nonlinear P_{trend}=0.042). Insulin resistance decreased 0.11±0.20 in the control group, 0.63±0.17 in the low-dose group, and 0.43±0.19 in the high-dose group (nonlinear P_{trend}=0.012). Discussion: Aerobic exercise reduces insulin concentrations and insulin resistance among patients with stage I-III colon cancer. Prescribing 150 min·wk^{-1} of aerobic exercise may be sufficient for reducing insulin concentrations and insulin resistance, which may partially mediate the relationship between physical activity and colon cancer prognosis.

INTRODUCTION

Each year more than 103,000 people are diagnosed with colon cancer in the United States (Siegel, et al. 2016). Three-quarters of patients will be diagnosed with disease that is localized to the colon (stage I-II) or spread to regional lymph nodes (stage III). Despite surgical resection, either alone or in combination with chemotherapy, up to one-half of patients with stage I-III colon cancer will experience disease recurrence (Siegel, et al. 2014). Consequently, there exists a need to identify additional therapies that reduce the risk of recurrent disease in this population.

The prescription of physical activity or exercise is a potential therapy that has been reported in observational studies to be associated with a lower risk of recurrence and death among colon cancer survivors (Je, et al. 2013). The relationship between physical activity and disease outcomes is independent of known prognostic factors, and occurs in a dose-response fashion, such that higher volumes of physical activity or exercise, up to 300 minutes per week ($min \cdot wk^{-1}$), are associated with more favorable disease outcomes (Schmid and Leitzmann 2014).

The biologic or biobehavioral pathways through which exercise may favorably alter colon cancer outcomes have not been elucidated, but may include exercise-induced alterations in metabolic growth factors, such as insulin, C-peptide, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor-binding protein-3 (IGFBP-3). Colon cancer cells have insulin/IGF-1 receptors on their surface (Belfiore and Malaguarnera 2011), and insulin/IGF-1 promote colon cancer cell proliferation and inhibit apoptosis (Koenuma, et al. 1989). *In vitro* studies demonstrate that states of hyperinsulinemia increase colon cancer cell resistance to 5-fluorouracil (Chen, et al. 2011b) and oxaliplatin chemotherapy (Chen, et al. 2011a; Volkova, et al. 2014). Preclinical models demonstrate that exposure to insulin promotes colonic tumor multiplicity (Tran, et al. 1996), and IGF-1 promotes a pro-metastatic hepatic microenvironment for colon cancer cells (Fernandez, et al. 2016). In the general population, hyperinsulinemia is associated with an

increased risk of cancer-specific mortality (Wargny, et al. 2017). Among men and women with stage I-III colon cancer, elevated concentrations of C-peptide and lower concentrations of IGFBP-3 are associated with a higher risk of mortality (Haydon, et al. 2006; Wolpin, et al. 2009). Genetic variants within insulin-related genes are associated with colon cancer risk, recurrence, and survival (Fu, et al. 2016; Simons, et al. 2015). Together, this evidence supports the hypothesis that insulin/IGF-1 may be important mediators of the relationship between exercise and disease outcomes among colon cancer survivors.

Colon cancer survivors have fasting insulin concentrations that are 58% higher than healthy persons without a history of colon cancer (Jiang, et al. 2014). A study of 17 colon cancer survivors demonstrated that a three-month prescription of exercise reduced insulin and IGFBP-3 concentrations (Lee, et al. 2013). However, no studies have examined the dose-response effects of exercise on these metabolic growth factors among colon cancer survivors.

These observations provided the scientific rationale for the COURAGE trial, a randomized controlled trial investigating the safety, feasibility, and biological efficacy of 150 and 300 $min \cdot wk^{-1}$ of aerobic exercise versus usual care control over six months among men and women recently-treated for stage I-III colon cancer (Brown, et al. 2016). We have previously reported that exercise was safe, feasible, and led to reductions in serum intercellular adhesion molecule-1 (Brown, et al. 2017a) and visceral adipose tissue (Brown, et al. 2017b). Here we report metabolic growth factor outcomes. Fasting insulin was pre-specified as the key growth factor of interest. As an exploratory aim of this report, we characterize the relationship between changes in visceral adipose tissue with changes in fasting insulin. Our hypotheses were that: 1) exercise would reduce fasting insulin concentrations in a dose-response fashion; and 2) reductions in visceral adipose tissue would correlate with reductions in fasting insulin.

MATERIALS and METHODS

Participants

Study methods of the COURAGE trial were published (Brown et al. 2016). Participants were eligible if they: 1) were diagnosed with histologically-proven stage I-III colon cancer; 2) completed surgical resection and post-operative chemotherapy within 36 months of entering the study; 3) self-reported participating in ≤150 min·wk^{-1} of moderate or vigorous intensity physical activity using the Paffenbarger Physical Activity Questionnaire (Paffenbarger, et al. 1978); 4) were of age ≥18 years; 5) provided written physician approval; 6) had no additional surgery planned within the six-month intervention period (including colostomy reversal); and 7) had the ability to walk unassisted for six minutes. Participants were ineligible if they: 1) had a history of another primary cancer (other than non-melanoma skin-cancer); 2) had evidence of metastatic cancer; 3) were pregnant or breast feeding; 4) were unable to provide a baseline blood sample; 5) had a myocardial infarction or coronary revascularization procedure within the past three months; 6) had uncontrolled hypertension, defined as a systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 mm Hg; 7) had high-risk or uncontrolled heart arrhythmias (not including atrial fibrillation); 8) had clinically significant heart valve disease; 9) had decompensated heart failure; 10) had a known aortic aneurysm; or 11) had any other condition which, in the opinion of the investigator, may impede testing of the study hypothesis or make it unsafe to engage in the exercise program.

Participants were stratified by cancer stage (AJCC 7th Edition: I *vs* II *vs* III) and randomized to one of three groups: low-dose aerobic exercise (150 min·wk^{-1}), high-dose aerobic exercise (300 min·wk^{-1}), or usual care control. This study was approved by the University of Pennsylvania Institutional Review Board and registered on clinicaltrials.gov as NCT02250053. All participants

provided written informed consent and written approval from their physician prior to participation in any study-related activities.

Intervention

Detailed methods of the exercise intervention are published (Brown et al. 2016). Participants randomized to the low-dose or high-dose exercise groups were provided with an in-home treadmill (LifeSpan Fitness, TR1200i, Salt Lake City, UT) and heart rate monitor (Polar Electro, RS400, Kempele Finland). Exercise intensity was prescribed at 50–70% of the age-predicted maximum heart rate [equivalent to 3–6 METs; (Ainsworth, et al. 2000)]. The low-dose and high-dose groups progressed towards of the goal of 150 or 300 $min \cdot wk^{-1}$ of exercise, respectively. Participants met with a certified clinical exercise physiologist to introduce the exercise prescription, and familiarize the participant with use of the treadmill, completion of exercise logs, use of a heart rate monitor, appropriate warm-up and cool-down, stretches, and proper footwear for aerobic exercise. The exercise physiologist provided ongoing behavioral and clinical support and monitored exercise adherence to the study protocol throughout the duration of the study.

Participants randomized to the usual-care control group were asked to maintain their pre-study levels of physical activity or follow the recommendations provided by their physician. After completing six month measures, control group participants were provided with an in-home treadmill and individualized exercise program, like that prescribed to the two exercise groups. Upon completion of study-related activities, all participants could keep their study-provided treadmills.

Measurements

Baseline and follow-up measurements were obtained by trained staff members who were blinded to treatment assignment. Demographic characteristics including age, sex, and race

were self-reported. Daily caloric intake and the proportion of calories from carbohydrate sources were quantified using three-day diet records that were analyzed using the Nutrition Data System for Research software (v.2014) by a registered dietitian who was blinded to study group. Moderate to vigorous intensity physical activity was quantified using an accelerometer [ActiGraph GT3X+; (Troiano, et al. 2008)]. Clinical information including cancer stage and treatment with chemotherapy were obtained from the cancer registry, pathology reports, and physician records. Body mass index (BMI; kg/m^2) was calculated using standard anthropometric measures [weight (kg) and height (m)], and dual-energy x-ray absorptiometry was used to quantify visceral adipose tissue (Brown et al. 2017b). Comorbid health conditions were self-reported.

Metabolic Growth Factor Outcomes

All study participants underwent a fasting blood draw at baseline and follow-up. EDTA-preserved plasma was stored at −80°C. Insulin and C-peptide concentrations were quantified using a radioimmunoassay (EMD Millipore, Billerica, MA). IGF-1, IGFBP-3, and fructosamine concentrations were quantified using an enzyme-linked immunosorbent assay (DSL, Webster, TX). Glucose concentrations were quantified spectrophotometrically (Roche, Indianapolis, IN). Baseline and follow-up plasma samples were assayed simultaneously and in duplicate at the end of the study. Coefficients of variation for all samples were ≤10%. The homeostatic model assessment (HOMA) was used to quantify insulin resistance (Levy, et al. 1998).

Statistical Analysis

Descriptive statistics presented for baseline variables include counts and proportions for categorical variables and medians with interquartile [25–75%] ranges for continuous variables. Categorical baseline characteristics were compared among the three groups using Fisher's exact test, and continuous baseline characteristics were compared among the three study

groups using the Kruskal-Wallis test. This trial was statistically powered to detect changes in the co-primary study endpoints soluble intercellular adhesion molecule-1 and soluble vascular adhesion molecule-1 (Brown et al. 2016; Brown et al. 2017a). However, the study had adequate statistical power to examine changes in fasting insulin concentrations. Based on prior research (Houmard, et al. 2004), over six months we estimated a mean change in fasting insulin concentrations of +6.6 pmol/L in the control group, −3.3 pmol/L in the low-dose group, and −5.9 pmol/L in the high-dose group with a pooled standard deviation of ±4.6 pmol/L. Against the hypothesis of a dose-response relationship, 39 participants provided 80% power with a type I error rate of 5% (α=0.05). All inferential analyses were conducted on an intention-to-treat basis. Dependent variables were log transformed in the inferential analysis to improve distributional normality and back transformed to facilitate interpretation. Changes were evaluated from baseline to follow-up in the three groups using repeated-measures mixed-effects regression models. This statistical approach includes all available data and accounts for the correlation between repeated measures. The baseline value of the dependent variable and cancer stage (randomization stratification factor) were included as covariates in the regression models (Fitzmaurice, et al. 2012). Group-by-time interaction terms were included as fixed-effects in the regression model. Model fit was assessed using graphical techniques. Results from the repeated-measures mixed-effects regression models are presented as least-square means ± standard error or 95% confidence intervals. To evaluate the presence of a dose-response relationship across randomized groups, a test of trend was conducted by examining linear and nonlinear (quadratic) contrasts. Linear regression models were used to characterize changes in visceral adipose tissue with changes in growth factor concentrations from baseline to six months (Schousboe, et al. 2017).

RESULTS

Between January 2015 and August 2015, 39 colon cancer survivors were recruited and randomized with data collection ending in February 2016. Baseline characteristics study participants have been described (Brown et al. 2017a), and are briefly presented in **Table 1**. Age ranged from 35–81 years. BMI ranged from 20–43 kg/m^2; 31% of participants were overweight (BMI 25.0–29.9 kg/m^2) and 51% were obese (BMI ≥30 kg/m^2). Visceral adipose tissue ranged from 34.2–257.9 cm^2. Time since finishing cancer directed treatment ranged from 1–21 months. Five participants had type 2 diabetes mellitus at baseline, all were diagnosed ≥3 years prior to study enrollment, and all were using metformin (one as monotherapy, four as combination therapy with a sulfonylurea or dipeptidyl peptidase-4 inhibitor).

Exercise prescription program variables have been described in detail (Brown et al. 2017a). Over six months, the average exercise volumes in the low-dose and high-dose groups were 141.5±9.92 min·wk^{-1} (92.8±2.44% of prescribed dose) and 247.2±10.71 min·wk^{-1} (89.0±2.64% of prescribed dose), respectively. Daily caloric intake (group-by-time interaction P=0.743) and the proportion of daily calories from carbohydrate sources (group-by-time interaction P=0.645) were not significantly different from baseline to six months in any of the groups.

Metabolic growth factor concentrations are presented in **Table 2**. Fasting insulin concentration, the pre-specified key growth factor outcome, decreased 7.4±9.4 pmol/L in the control group, 28.0±8.3 pmol/L in the low-dose group, and 20.7±9.3 pmol/L in the high-dose group (nonlinear P_{trend}=0.042; **Figure 1**). Similarly, insulin resistance decreased 0.11±0.20 in the control group, 0.63±0.17 in the low-dose group, and 0.43±0.19 in the high-dose group (nonlinear P_{trend}=0.012). Fasting glucose concentration decreased in the low-dose group, whereas no difference was observed high-dose and control groups (nonlinear P_{trend}=0.004). IGF-1, IGFBP-3, fructosamine, and C-peptide did not change in any of the study groups. Adjustment for type 2 diabetes mellitus as a covariate in the regression models did not substantively alter the above-described

findings. No serious (grade ≥3) adverse events occurred. Non-serious (grade 1-2) adverse events occurred at similar rates among the three groups (Brown et al. 2017a).

We previously reported that exercise reduced visceral adipose tissue in a dose-response fashion (linear P_{trend}=0.008), such that each 60 min·wk^{-1} increase in exercise volume predicted a –2.7±1.4 cm^2 reduction in visceral adipose tissue (Brown et al. 2017b). For each 1 cm^2 reduction in visceral adipose tissue, fasting insulin concentrations were lowered by 0.96±0.41 pmol/L (P=0.025; **Table 3, Figure 2**); changes in visceral adipose tissue accounted for 13.5% of the shared variance of changes in fasting insulin concentrations. Changes in visceral adipose tissue were also correlated with changes in fasting glucose and insulin resistance. Adjustment for visceral adipose tissue did not alter the relationship between exercise dose and fasting insulin concentrations (nonlinear P_{trend}=0.042) or insulin resistance (nonlinear P_{trend}=0.010).

DISCUSSION

A six-month moderate-intensity aerobic exercise program among stage I-III colon cancer survivors reduced fasting insulin concentrations and insulin resistance in a predominately overweight and obese population. The findings from this randomized trial support the hypothesis that the relationship between physical activity and colon cancer prognosis may be mediated, in part, by changes in fasting insulin concentrations or insulin resistance.

The reductions in fasting insulin concentrations and insulin resistance with exercise are similar to those observed in a prior dose-response study in overweight and obese adults (Ross, et al. 2015). This prior study demonstrated that fasting insulin concentrations and insulin resistance may be lowered to a similar magnitude across distinct doses of exercise (Ross et al. 2015). However, the absolute magnitude of reduction in fasting insulin concentrations in our study was larger than that of others (Houmard et al. 2004; Ross et al. 2015). This may be the result of our sample having higher baseline fasting insulin concentrations [111 pmol/L in the current study vs

49 pmol/L (Houmard et al. 2004) and 67.5 pmol/L (Ross et al. 2015)], which is consistent with the observation that colon cancer survivors have significantly higher fasting insulin concentrations than healthy persons (Jiang et al. 2014). Our findings are similar to studies in breast cancer survivors that exercise reduces fasting insulin concentrations (Irwin, et al. 2009; Ligibel, et al. 2008).

In prior cross-sectional analyses, fasting insulin concentrations were higher with larger areas of visceral adipose tissue, an effect that is attributable to increased insulin resistance (Goodpaster, et al. 2003). We demonstrated that changes in visceral adipose tissue accounted for 13.5% of the shared variance in insulin concentration, which is similar to studies in obese men that estimated the shared variance to be 16–22% (Borel, et al. 2017; Rice, et al. 1999). These data suggest that the effects of exercise to lower fasting insulin may include mechanisms beyond that of changes in visceral adipose tissue. We hypothesize that alterations in skeletal muscle insulin resistance and free fatty acid (FFA) metabolism may help to further explain this effect (Abdul-Ghani and DeFronzo 2010; DeFronzo and Tripathy 2009). Insulin resistance in skeletal muscle is associated with hyperinsulinemia (Abdul-Ghani and DeFronzo 2010; DeFronzo and Tripathy 2009) and the inability to lower FFA in the postprandial state (Jensen 2008). Skeletal muscle preferentially oxidizes FFA (Randle, et al. 1963), suppressing insulin-stimulated glucose uptake into the muscle (Boden, et al. 1994; Dresner, et al. 1999). Exercise improves the insulin suppression of FFA release (Shadid and Jensen 2006), corrects the mismatch between FFA uptake and FFA oxidation (Turcotte and Fisher 2008), and promotes insulin-stimulated glucose uptake into skeletal muscle (Hayashi, et al. 1997).

The biologic or biobehavioral pathways through which exercise may alter cancer outcomes are unknown. States of hyperinsulinemia activate the PI3K-Akt-mTOR pathway (McCurdy and Klemm 2013). In preclinical experiments, activation of the PI3K-Akt-mTOR pathway promotes the growth of colon cancer metastases (Gulhati, et al. 2011), and inhibition of this pathway

induces cell-cycle arrest and apoptosis (Zhang, et al. 2009). Insulin receptor substrate 1 (IRS1) is a mediator of glucose homeostasis, and the down regulation of IRS1 is associated with insulin resistance (Karlsson and Zierath 2007). Colonic tumor expression of IRS1 and physical activity interact to influence colon cancer outcomes (Hanyuda, et al. 2016). Among patients with decreased expression of IRS1, physical activity is associated with a significantly lower risk of colon cancer-specific mortality (P_{trend}=0.005), whereas no relationship is observed with IRS2. IRS1 is associated with insulin metabolism in skeletal muscle, whereas IRS2 is associated with insulin metabolism in the liver (Karlsson and Zierath 2007). These observational data provide additional support to the hypothesis that exercise may have an insulin sensitizing effect that is produced through skeletal muscle contractions, and this insulin sensitization may influence disease outcomes.

There are several limitations to this trial. The main limitation is the small sample size which limits the generalizability of our findings. We have previously reported that participants in this trial were younger than the population from which they were recruited (Brown et al. 2016). Because of the small sample size, we observed numeric differences at baseline in select metabolic growth factor concentrations. Our analyses plan pre-specified that the baseline value of the dependent variable would be included in the model to account for baseline differences, however we cannot rule out that the observed differences may be partly due to regression to the mean. The small sample size precluded our ability to undertake formal mediation analysis to explore the relationships among exercise dose, visceral adipose tissue, and insulin concentrations (Friedenreich, et al. 2011). The small sample size also limited our statistical power to examine other metabolic growth factors such as IGF-1. Additional randomized studies with larger sample sizes are needed to confirm our findings. It is not known if the relationship between exercise dose and change in insulin concentrations are linear at the population level. If a linear relationship does exist, there may be a several reasons why we did not identify such a

relationship. Our study was only six months in duration. It is unknown if the observed improvements in outcomes would be sustained or improved upon over a longer time horizon. Participants were not recruited based on having hyperinsulinemia; however, 82% of our study sample was overweight or obese, consequently hyperinsulinemia was common. We examined two distinct volumes of moderate-intensity aerobic exercise, but we did not examine the effects of light- or vigorous-intensity aerobic exercise (McGarrah, et al. 2016) or resistance exercise (either as a single modality or prescribed in combination with aerobic exercise).

There are several strengths to this trial. The use of two intervention groups, each prescribed a distinct dose of exercise allowed us to examine changes in fasting insulin along the exercise dose curve. The exercise program, which emphasized home-based treadmill walking, promoted good intervention adherence that was confirmed with objective heart rate monitor measures. Most participants (97%) completed the study.

In summary, the findings from this phase II randomized dose-response trial demonstrate that moderate-intensity aerobic exercise reduces fasting insulin concentrations and insulin resistance among patients with stage I-III colon cancer. The findings from this randomized trial may be useful to help guide exercise prescriptions in this population. The relationship between physical activity and colon cancer prognosis may be mediated, in part, by changes in insulin concentrations or insulin resistance. Continued research to examine this hypothesis is warranted.

Declaration of Interest

The authors declare no conflicts of interest.

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Author Contributions

All authors were involved in the study design. JCB, ABT, BK, and KHS collected and analyzed the data in conjunction with the authors. The manuscript was written by JCB, and was reviewed, modified, and approved in its final version by all the authors. All authors vouch for the accuracy and completeness of the data reported and the fidelity of the study to the protocol.

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Figure 1. Between group changes in fasting insulin concentration from baseline to six months

Figure 2. Relationship between changes in visceral adipose tissue area and changes in fasting insulin concentration from baseline to six months

Table 1. Baseline characteristics of the participants

Characteristic	Total (*n*=39)	Control (*n*=13)	Low-Dose (*n*=14)	High-Dose (*n*=12)	*P*
Age, years	56.5 [49.1-63.3]	56.5 [51.0-60.9]	59.1 [54.3-66.4]	54.6 [45.0-62.0]	0.493
Sex, %					
Male	15 (38%)	4 (31%)	7 (50%)	4 (33%)	0.601
Female	24 (62%)	9 (69%)	7 (50%)	8 (67%)	
Race, %					
White	31 (80%)	8 (62%)	12 (86%)	11 (92%)	0.332
Black	6 (15%)	3 (23%)	2 (14%)	1 (8%)	
Other	2 (5%)	2 (15%)	0 (0%)	0 (0%)	
Caloric Consumption, $kcal \cdot d^{-1}$	1735 [1270-1962]	1800 [1233-2110]	1776 [1483-2111]	1632 [1196-1739]	0.725
Calories from Carbohydrate, %	46.8 [39.7-51.3]	43.5 [36.9-49.4]	48.7 [46.0-54.8]	37.7 [45.1-51.3]	0.261
Moderate or Vigorous Physical Activity, $min \cdot d^{-1}$	15.7±8.7	12.2±8.1	18.8±9.6	15.7±7.3	0.174
Body Mass Index, $kg \cdot m^{-2}$	30.3 [25.3-35.3]	29.0 [25.0-33.5]	30.4 [27.1-32.1]	33.6 [25.6-37.7]	0.408
Waist Circumference, cm	102 [91-110]	94 [90-107]	99 [91-107]	109 [110-114]	0.154
Visceral Adipose Tissue, cm^2	130.8 [82.2-168.8]	116.7 [61.4-150.3]	133.0 [82.2-162.1]	138.8 [117.4-206.6]	0.227
Cancer Stage, %					
I	5 (13%)	1 (8%)	2 (14%)	2 (17%)	0.999
II	14 (36%)	5 (38%)	5 (36%)	4 (33%)	
III	20 (51%)	7 (54%)	7 (50%)	6 (50%)	
Chemotherapy, %	28 (72%)	10 (77%)	10 (71%)	8 (67%)	0.906
Time Since Treatment, Months	10 [5-16]	12 [8-16]	7.5 [4-13]	10 [6-17]	0.417
Comorbid Conditions, %					
Hypertension	13 (33%)	4 (31%)	6 (43%)	3 (25%)	0.695
Hyperlipidemia	6 (15%)	1 (8%)	2 (14%)	3 (25%)	0.480
Type 2 Diabetes	5 (13%)	1 (8%)	1 (7%)	3 (25%)	0.409
Cardiovascular Disease	4 (10%)	2 (15%)	1 (7%)	1 (8%)	0.827

P values are from the overall test of group differences. Data are median [interquartile range], or counts with percentages.

Table 2. Metabolic growth factor outcomes at baseline and change during six months

Outcome	Baseline (Mean ± SD)	Δ Baseline to Month 6 (LS Mean ± SE)	Δ from Control (LS Mean [95% CI])
Insulin, pmol/L			
Control	99.2±60.5	−7.36±9.41	—
Low-Dose	101.8±40.5	−28.02±8.35[a]	−20.66 [−45.32, 3.99]
High-Dose	135.1±87.1	−20.70±9.35[a]	−13.34 [−39.33, 12.6]
Test for trend		Linear, *P*=0.170; Nonlinear, *P*=0.042	
Glucose, mmol/L			
Control	5.3±1.0	0.01±0.16	—
Low-Dose	5.3±0.8	−0.39±0.15[a]	−0.39 [−0.83, 0.05]
High-Dose	6.1±2.3	−0.09±0.17	−0.09 [−0.56, 0.38]
Test for trend		Linear, *P*=0.931; Nonlinear, *P*=0.004	
Insulin Resistance (HOMA)			
Control	2.2±1.3	−0.11±0.20	—
Low-Dose	2.2±0.9	−0.63±0.17[a]	−0.52 [−1.03, −0.01][b]
High-Dose	2.9±2.0	−0.43±0.19[a]	−0.32 [−0.86, 0.22]
Test for trend		Linear, *P*=0.125; Nonlinear, *P*=0.012	
IGF-1, nmol/L			
Control	58.0±15.9	−4.57±3.23	—
Low-Dose	59.8±13.2	−0.94±3.21	3.63 [−5.29, 12.56]
High-Dose	64.7±17.5	1.62±3.57	6.19 [−3.25, 15.62]
Test for trend		Linear, *P*=0.054; Nonlinear, *P*=0.850	
IGFBP-3, nmol/L			
Control	1765.1±446.8	−103.71±69.15	—
Low-Dose	1925.7±449.5	−30.01±68.04	73.69 [−116.96, 264.34]
High-Dose	2290.0±748.2	−154.28±71.97[a]	−50.58 [−246.83, 145.68]
Test for trend		Linear, *P*=0.685; Nonlinear, *P*=0.093	
C-Peptide, nmol/L			
Control	0.64±0.4	0.007±0.033	—
Low-Dose	0.58±0.3	−0.003±0.032	−0.010 [−0.10, 0.08]
High-Dose	0.75±0.3	−0.013±0.035	−0.020 [−0.11, 0.07]
Test for trend		Linear, *P*=0.701; Nonlinear, *P*=0.934	
Fructosamine, mmol/L			
Control	201.4±20.5	2.60±16.82	—
Low-Dose	183.0±51.2	22.91±15.84	20.31 [−24.98, 65.60]
High-Dose	204.1±28.6	−12.65±16.96	−15.26 [−62.08, 31.57]
Test for trend		Linear, *P*=0.380; Nonlinear, *P*=0.382	

SD, standard deviation; LS Mean, least squares mean; SE, standard error; CI, confidence interval; HOMA, homeostatic model assessment. [a]Signifcantly different from baseline (within-group), $P \leq 0.05$. [b]Significantly different from control, $P \leq 0.05$.

Changes in outcomes are estimated using a linear mixed-effects regression model that adjusted for the baseline value of the dependent variable and cancer stage (randomization stratification factor).

Table 3. Relationship between change in visceral adipose tissue (per 1 cm^2 reduction) and change in metabolic growth factor concentration during six months

Outcome	Δ in Metabolic Growth Factor Concentration (LS Mean ± SE)	R^2	*P*
Insulin, pmol/L	−0.96±0.41	13.5%	0.025
Glucose, mmol/L	−0.03±0.01	21.9%	0.004
Insulin Resistance (HOMA)	−0.024±0.009	16.5%	0.013
IGF-1, nmol/L	−0.22±0.13	7.6%	0.098
IGFBP-3, nmol/L	−1.22±3.16	0.4%	0.701
C-Peptide, mmol/L	0.0007±0.001	0.6%	0.650
Fructosamine, mmol/L	−0.16±0.47	0.3%	0.736

LS Mean, least squares mean; SE, standard error; R^2, proportion of variability of change in metabolic growth factor concentration explained by change in visceral adipose tissue.

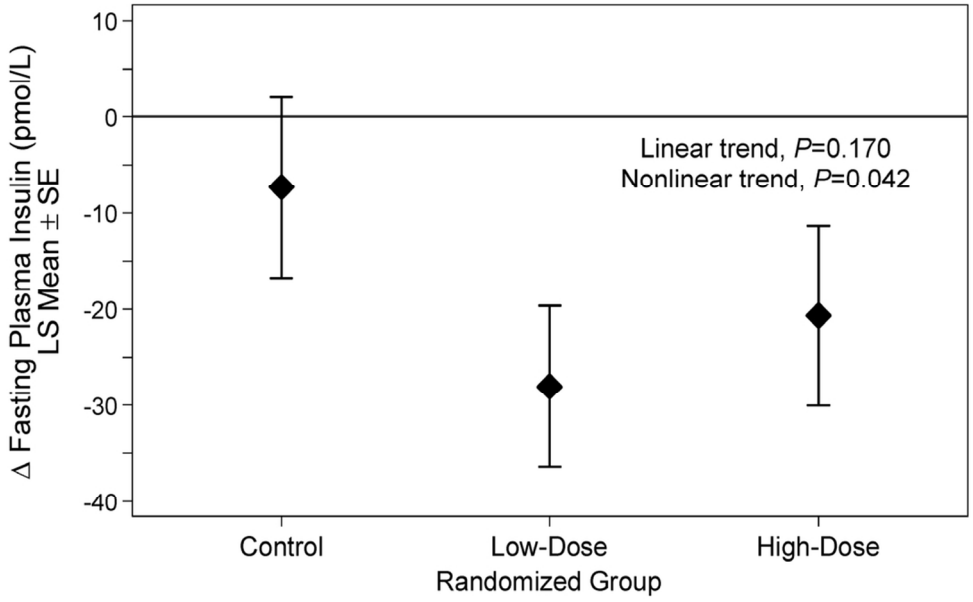

Figure 1

93x58mm (300 x 300 DPI)

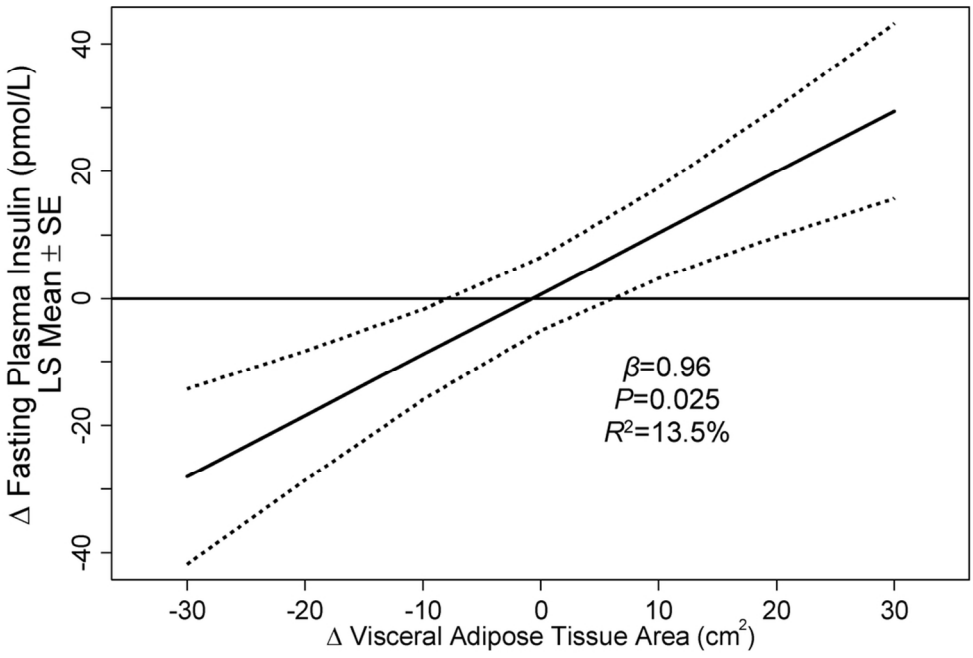

Figure 2

96x67mm (300 x 300 DPI)