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Aerobic exercise training increases circulating insulin-like growth factor binding protein–1 concentration, but does not attenuate the reduction in circulating insulin-like growth factor binding protein–1 after a high-fat meal

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ABSTRACT

Insulin-like growth factor binding protein–1 (IGFBP-1) has metabolic effects throughout the body, and its expression is regulated in part by insulin. Circulating IGFBP-1 predicts development of cardiometabolic diseases in longitudinal studies, and low IGFBP-1 concentrations are associated with insulin resistance and consumption of a high-fat diet. Because of the favorable metabolic effects of regular aerobic exercise, we hypothesized that aerobic exercise training would increase plasma IGFBP-1 concentrations and attenuate the reduction in IGFBP-1 after a high-fat meal. Ten overweight (body mass index = 28.7 ± 0.9 kg/m^2), older (61 ± 2 years) men and women underwent high-fat feeding and oral glucose tolerance tests at baseline and after 6 months of aerobic exercise training. In response to aerobic exercise training, subjects increased cardiorespiratory fitness by 13% ($P < .05$) and insulin sensitivity index by 28% ($P < .05$). Basal plasma concentrations of IGFBP-1 increased by 41% after aerobic exercise training ($P < .05$). The insulin response to an oral glucose tolerance test was a significant predictor of fasting plasma IGFBP-1 concentrations at baseline and after exercise training ($P = .02$). In response to the high-fat meal at baseline, plasma IGFBP-1 concentrations decreased by 58% ($P < .001$); a 61% decrease to similar postprandial concentrations was observed after exercise training ($P < .001$). Plasma insulin response to the high-fat meal was inversely associated with postprandial IGFBP-1 concentrations at baseline and after exercise training ($P = .06$ and $P < .05$, respectively). Although aerobic exercise training did not attenuate the response to a high-fat meal, the increase in IGFBP-1 concentrations after exercise training may be one mechanism by which exercise reduces risk for cardiometabolic diseases in older adults.

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Institutional approval: This study was approved by the Institutional Review Boards at the University of Maryland College Park and the University of Maryland School of Medicine.

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1. Introduction

The insulin-like growth factor binding proteins (IGFBPs) are a family of proteins that bind insulin-like growth factors (IGFs) [1] and affect metabolism through both IGF-dependent and IGF-independent actions [2]. Circulating IGFBP-1 concentration has been proposed as a marker of insulin resistance, and circulating IGFBP-1 concentrations directly correlate with measures of insulin sensitivity in older subjects with a range of glucose tolerance and diabetes [3-6]. Furthermore, low IGFBP-1 concentrations are also associated with increased prevalence of cardiovascular disease risk factors and metabolic syndrome [6-10]; therefore, IGFBP-1 may be a marker for cardiometabolic disease risk.

In older adults, circulating IGFBP-1 concentrations may be influenced by lifestyle habits. A sedentary lifestyle is an established risk factor for obesity and cardiometabolic diseases; and initiating a program of exercise training in older, previously sedentary adults can reduce this risk. Aerobic exercise training has been shown to improve insulin sensitivity and reduce insulin levels [11,12] and, therefore, may increase circulating IGFBP-1 concentration. Acute aerobic exercise has been shown to increase circulating IGFBP-1 concentrations [13-16]; but to date, few studies have examined the effects of an exercise training intervention on IGFBP-1. One study shows increases in circulating IGFBP-1 after intensive training in previously trained competitive cyclists [17], whereas another study showed no change in IGFBP-1 concentrations after 8 weeks of combined aerobic and resistance training in young women [18]. Consumption of a high-fat diet is also associated with a heightened risk for cardiometabolic diseases, and 2 cross-sectional studies reported that high dietary fat consumption is associated with low circulating IGFBP-1 concentrations in a range of young to older adults [7,19]. To our knowledge, the acute effect of a high-fat meal on IGFBP-1 concentration has not been reported.

Although IGFBP-1 may serve as a marker for insulin resistance, it may have more direct effects on insulin resistance and glucose metabolism through IGF-independent mechanisms. Because of the IGF-independent actions of IGFBP-1 on glucose metabolism and the potential effects of chronic exercise and high-fat feeding on IGFBP-1, we sought to determine the effects of 6-month aerobic exercise training and an acute high-fat meal on circulating IGFBP-1 concentrations in older men and women. We hypothesized that plasma IGFBP-1 concentrations would decrease in response to the high-fat meal and that regular aerobic exercise training would increase basal plasma IGFBP-1 concentrations and attenuate the response to the high-fat meal.

2. Methods

2.1. Subjects

Men and postmenopausal women were originally recruited to participate in studies examining the effects of gene polymorphisms on responses to aerobic exercise training. Subjects were required to (1) be sedentary (exercise less than 20 minutes, 2×/wk), (2) be 50 to 75 years of age, (3) not be taking glucose-lowering medication, (4) have no recent history of smoking tobacco, (5) have no previous diagnosis of diabetes mellitus or cardiovascular disease, and (6) not have any other medical condition that would preclude aerobic exercise. Five men and 5 women (mean age = 60 ± 2 years) from the larger studies who participated in the high-fat meal test and for whom plasma samples were available were randomly chosen for inclusion in this report. The research protocols were approved by the Institutional Review Boards at the University of Maryland College Park and the University of Maryland School of Medicine. All subjects provided written informed consent.

2.2. Aerobic exercise training intervention

After baseline testing, subjects underwent 24 weeks of standardized aerobic exercise training, supervised by exercise physiologists and conducted on treadmills, elliptical trainers, and cycle ergometers. Subjects began at a training volume of 3 weekly sessions of 20 minutes at 50% of heart rate reserve and gradually increased to 3 weekly sessions of 40 minutes at 70% of heart rate reserve, a level maintained for the final 14 weeks of the intervention. Subjects also added 1 weekly, independent walking session during this time. For inclusion in the analyses, subjects were required to have completed at least 80% of the scheduled exercise sessions.

Before baseline testing, all subjects underwent 6 weeks of instruction on the American Heart Association dietary guidelines [20]. Subjects were counseled to consume an isocaloric diet, following the dietary guidelines (<30% total energy intake derived from fat, <10% from saturated fat, and <300 mg cholesterol per day), and were weight stable for at least 3 weeks before baseline testing. Throughout the study, subjects maintained this isocaloric diet and remained weight stable to eliminate potentially confounding effects of weight loss and differing dietary intake.

2.3. Oral glucose tolerance test

Subjects underwent a 2-hour oral glucose tolerance test (OGTT) after a 12-hour overnight fast. The OGTTs were started between 6:30 AM and 9:00 AM, and subjects consumed more than 250 g of dietary carbohydrate for 3 days before the test. During final testing, the OGTT was conducted 24 to 36 hours after the last bout of exercise. A catheter was placed in an antecubital vein; and blood samples were drawn into tubes containing 15% potassium EDTA before and 30, 60, 90, and 120 minutes after the ingestion of a 75-g glucose solution for measurement of plasma glucose and insulin. Glucose and insulin incremental areas under the curve (AUCs) were calculated using the trapezoidal method. The insulin sensitivity index (ISI_M) was calculated using the method of Matsuda and DeFronzo [21], and the homeostatic model assessments for insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were calculated as described by Matthews et al [22].

2.4. High-fat meal

Subjects reported to our laboratory between 6:30 AM and 9:00 AM after a 12-hour overnight fast with no ethanol consumption for 24 hours. During final testing, the high-fat meal test was

conducted 24 to 36 hours after the last bout of exercise. Subjects consumed a standard liquid high-fat meal [23] within 3 minutes, and blood samples were drawn just before consumption of the meal (0 minute) and every 30 minutes thereafter until 4 hours after consumption (240 minutes). This abbreviated 4-hour high-fat meal test is a valid and reproducible surrogate for the more common 8-hour tests [24]. The size of the fat meal was adjusted for body size and administered at a dose of 386 g (1362 kcal) per 2 m^2 of body surface area. Of the 1362 kcal, approximately 84% was derived from fat (53% of which was saturated fat), 13.7% from carbohydrates, and 2.7% from protein. Triglyceride and insulin incremental AUCs were calculated using the trapezoidal method.

2.5. Body composition and cardiorespiratory fitness

Fat mass and lean body mass were measured using dual-energy x-ray absorptiometry (DPX-L; Lunar, Madison, WI). Computed tomography (General Electric Hi-Light Scanner, Fairfield, CT) was used to measure cross-sectional areas of visceral adipose tissue (VAT) and subcutaneous abdominal adipose tissue at L_4-L_5. Cardiorespiratory fitness was measured as maximal oxygen consumption (Vo_{2max}) during a graded exercise test on a treadmill to maximal effort as determined by standard physiological criteria. The Vo_2 was measured continuously using a validated indirect calorimetry system consisting of a mixing chamber, bidirectional turbine, and mass spectrometer. The test consisted of a continuous series of 2-minute stages, where speed was fixed and treadmill grade was increased 2% in each stage. Values of VO_2 were averaged in 30-second increments, and Vo_{2max} was defined as the highest oxygen consumption value obtained for a full 30-second increment.

2.6. Blood analyses

Blood samples were collected in tubes containing 15% potassium EDTA and centrifuged. Plasma was removed and stored at –80°C so that all samples from a given subject were analyzed in the same assay. The IGFBP-1 concentrations were measured in samples from the high-fat meal test (0 and 240 minutes) using enzyme-linked immunosorbent assay plates from MesoScale Discovery (Gaithersburg, MD). All samples were run in duplicate in the same assay; the intraassay coefficient of variation was less than 9%. Plasma triglyceride levels were determined by a 2-step colorometric assay (kit 337-B; Sigma Diagnostics, St Louis, MO). Plasma insulin levels were determined by radioimmunoassay (Linco Research, St Charles, MO). Plasma glucose levels were analyzed with a glucose analyzer (2300 STAT Plus; YSI, Yellow Springs, OH).

2.7. Statistical analyses

Data are presented as mean ± SEM. Repeated-measures analysis of variance was used to detect differences in plasma IGFBP-1 concentrations in response to a high-fat meal at baseline and after aerobic exercise training. Paired Student *t* tests were used to detect changes in weight, lean body mass, fat mass, Vo_{2max}, insulin, glucose, and triglycerides at baseline and after aerobic exercise training. Data for HOMA-IR and ISI_M were not normally distributed and were therefore analyzed using the Wilcoxon signed rank test and Spearman correlation analyses. Bivariate Pearson correlation analyses were used to test for correlations between plasma IGFBP-1 concentrations and glucose, insulin, and triglyceride levels.

3. Results

3.1. Effects of the intervention on cardiorespiratory fitness and body composition

All subjects completed 6 months of aerobic exercise training with greater than 80% compliance. After aerobic exercise training, Vo_{2max} increased by 13% (2.03 ± 0.19 vs 2.31 ± 0.19 L/min, $P = .001$). There was no significant change in body weight

Table 1 – Metabolic characteristics of subjects at baseline and after 6 months of aerobic exercise training (n = 10)

OGTT	Baseline	After training	*P* values
Fasting plasma glucose (mmol/L)	5.1 ± 0.2	5.2 ± 0.2	.58
2-h OGTT glucose (mmol/L)	6.9 ± 0.6	6.8 ± 06	.90
Glucose incremental AUC (mmol/[L 120 min])	172 ± 57	160 ± 53	.51
Fasting plasma insulin (pmol/L)	88 ± 7	77 ± 6	***.047***
2-h plasma insulin (pmol/L)	523 ± 75	344 ± 47	***.010***
Insulin incremental AUC (pmol/[L 120 min])	53 238 ± 7429	44 356 ± 4027	.10
HOMA-β	166 ± 17	154 ± 34	.75
HOMA-IR	3.0 ± 0.3	2.3 ± 0.2	***.038***
ISI_M	2.5 ± 0.2	3.2 ± 0.3	***.025***
High-fat meal	**Baseline**	**After training**	***P* values**
Fasting TG (mmol/L) (n = 8)[a]	1.50 ± 0.29	1.26 ± 27	.45
TG incremental AUC (mg/[dL 240 min]) (n = 8)[a]	156 ± 30	156 ± 37	.99
Insulin incremental AUC (pmol/[L 240 min]) (n = 8)[a]	21 566 ± 7625	14 411 ± 5095	.09

Data are means ± SEM. TG indicates triglyceride. *P*-values in bold, italic font denote statistical significance ($P < .05$).
[a] Triglyceride and insulin data during the oral fat load were unavailable for 2 subjects.

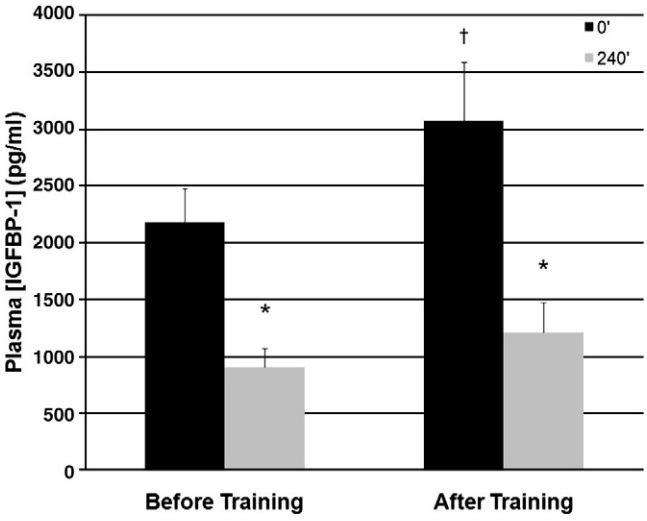

Fig. 1 – Plasma IGFBP-1 response to a high-fat meal at baseline and after 6 months of aerobic exercise training (n = 10). Data are means ± SEM. *Significant difference compared with 0′ ($P < .001$). †Significant difference compared with baseline ($P < .05$).

(81.3 ± 3.2 vs 80.3 ± 3.4 kg, $P = .21$); however, we did detect small changes in body composition, as lean body mass increased (47.2 ± 2.9 vs 48.2 ± 2.9 kg, $P = .008$) and fat mass decreased (37.2 ± 3.0 vs 35.5 ± 3.1 kg, $P = .01$) after the intervention. There were no significant changes in visceral adipose tissue (131 ± 8 vs 128 ± 10 cm^2, $P = .33$) or subcutaneous abdominal adipose tissue (346 ± 36 vs 328 ± 34 cm^2, $P = .85$) after aerobic exercise training.

3.2. *Effects of the intervention on metabolic variables*

At baseline, subjects had normal fasting plasma glucose levels and normal glucose tolerance in response to an OGTT. After aerobic exercise training, there were no statistically significant improvements in plasma glucose variables. Fasting plasma insulin decreased significantly after 6 months of aerobic exercise training (Table 1, $P < .05$), as did 2-hour plasma insulin levels during the OGTT (Table 1, $P = .01$). The HOMA-IR and ISI_M improved significantly after aerobic exercise training in these subjects (Table 1, $P < .05$); the HOMA-β was not significantly different after aerobic exercise training (Table 1). During the high-fat meal, plasma triglycerides and insulin increased significantly as expected at baseline and after aerobic exercise training (Table 1, $P \leq .01$ for all). No statistically significant decrease was observed in the response of triglycerides to a high-fat meal after aerobic exercise training. The insulin response to the high-fat meal tended to decrease by approximately 33% after aerobic exercise training (Table 1, $P = .09$). Aerobic exercise training–induced changes in glucose and insulin responses to the OGTT or high-fat meal were not associated with changes in fat mass or lean body mass.

3.3. *Effects on plasma IGFBP-1 concentrations*

We found significant main effects of aerobic exercise training and a high-fat meal on plasma IGFBP-1 concentrations. After 6-month aerobic exercise training, fasting plasma IGFBP-1 concentrations increased by 41% (Fig. 1, $P < .05$). At baseline, IGFBP-1 concentrations decreased by 58% at 4 hours after a high-fat meal (Fig. 1, $P < .001$). This effect persisted after 6 months of aerobic exercise training, when IGFBP-1 concentration decreased 61% in response to the high-fat meal (Fig. 1, $P < .001$).

3.4. *Relationships between plasma IGFBP-1 and insulin concentrations*

Plasma insulin levels were associated with plasma IGFBP-1 concentrations at baseline and after aerobic exercise training. Plasma insulin responses to an OGTT (insulin incremental

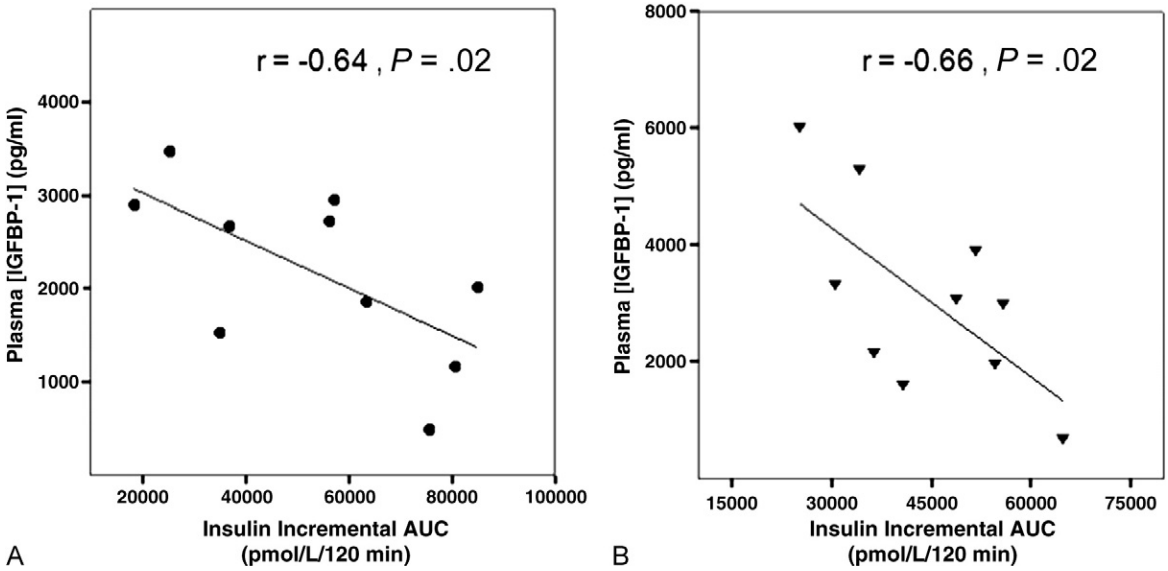

Fig. 2 – Scatter plots depicting the correlation between insulin incremental AUC during the OGTT and plasma IGFBP-1 concentration at baseline (A) and after 6 months of aerobic exercise training (B).

AUC) inversely correlated with fasting plasma IGFBP-1 concentrations at baseline and after aerobic exercise training (Fig. 2, $P = .02$ for both). Neither HOMA-IR nor ISI_M correlated with IGFBP-1 concentrations at baseline or after aerobic exercise training.

The plasma insulin response to a high-fat meal (insulin incremental AUC) tended to be inversely associated with plasma IGFBP-1 concentration after the high-fat meal at baseline ($r = –0.58$, $P = .06$) and was significantly and inversely associated with plasma IGFBP-1 concentrations after the high-fat meal after aerobic exercise training ($r = –0.71$, $P = .02$). Plasma triglycerides did not correlate with plasma IGFBP-1 concentrations in the fasting state ($r = 0.22$-0.24, $P > .57$) or in response to the high-fat meal ($r = –0.12$ to 0.22, $P > .6$).

4. Discussion

The major findings of the present report are that (*a*) a 6-month aerobic training program significantly increases circulating IGFBP-1 concentrations in overweight, normoglycemic (and normal glucose-tolerant), middle-aged to older adults and (*b*) a high-fat meal induces a large, acute reduction in circulating IGFBP-1 concentrations at baseline and after aerobic exercise training. The increase in IGFBP-1 after aerobic exercise training may be related to improvements in fasting and postprandial insulin levels in older adults. Interestingly, despite the observed metabolic improvements and lower insulinemia after aerobic exercise training, the response of IGFBP-1 to a high-fat meal was not attenuated by regular aerobic exercise training.

To our knowledge, this is the first study to investigate IGFBP-1 responses to a high-fat meal and to long-term, standardized exercise training; however, there are previous reports of the effects of exercise and diet on IGFBPs. Several studies show increases in circulating IGFBP-1 concentrations after acute aerobic exercise [13-16], but all studies have not reached the same conclusion [25]. Manetta et al [26] show that serum IGFBP-1 concentrations (as determined ~72 hours after the last exercise bout) are approximately 50% higher in trained middle-aged cyclists compared with their sedentary counterparts. Together with our results, this supports an effect of aerobic exercise training on IGFBP-1 concentration. Studies showing an increase in IGFBP-1 concentrations after acute exercise are in agreement that concentrations return to baseline 12 to 24 hours after exercise [13,15,16]. As our measurements were obtained 24 to 36 hours after the last bout of exercise, the increase in IGFBP-1 in our subjects is not likely attributable to the final bout of exercise, but to a chronic effect of exercise training. Future studies will be necessary to address the duration of the effect of chronic aerobic exercise on IGFBP-1 concentrations in older subjects. In contrast to our data, one study involving 8 weeks of aerobic and resistance exercise training in a group of young women showed no change in serum IGFBP-1 concentrations as measured more than 48 hours after the most recent exercise bout [18]. Although this appears discordant with our findings, differences between this and the present report may be due to the use of a different training regimen or a sample of relatively lean younger women.

In contrast to regular aerobic exercise, Heald et al [19,27] report that high dietary fat intake is associated with low fasting circulating IGFBP-1 concentrations in cross-sectional studies of 2 large cohorts. Consistent with these reports, we find that an acute high-fat meal reduced plasma IGFBP-1 concentrations regardless of exercise training status. Although the exact duration of this suppression is not yet established, it is possible that the summation of repeated meals high in fat content acts to chronically reduce IGFBP-1 concentrations.

Two previous studies reported the effect of combined diet and exercise on IGFBP-1 concentrations [28,29]. Foster et al [29] reported that acute aerobic exercise increases IGFBP-1 concentration in young men and that this is partially reduced by postexercise carbohydrate consumption with a corresponding increase in circulating insulin level; however, the effect of exercise on diet-induced changes in IGFBP-1 was not studied as in the present report. Ngo et al [28] reported that 11 days of daily aerobic exercise with a low-fat (<10%) and high-carbohydrate (70%-75%) diet increased serum IGFBP-1 concentrations by 53%. It is unclear whether the effects of this intervention are due to aerobic exercise, dietary composition, weight loss, or some combination of these. In the present report, subjects were stabilized on a low-fat diet before baseline testing and maintained this isocaloric diet throughout the intervention. Thus, it is quite likely that the effects we observe are due to the aerobic exercise training regimen and not diet or weight loss. We have previously shown that aerobic exercise training independently increases insulin sensitivity and reduces insulin responses to OGTT; however, the addition of weight loss may result in greater benefit [30,31]. Future prospective studies will be necessary to address the interactive effects of regular aerobic exercise and chronic dietary habits (both macronutrient composition and caloric intake) on IGFBP-1 concentrations.

Insulin has been the most investigated regulator of IGFBP-1 expression to date because it suppresses IGFBP-1 expression and secretion by the liver [32]. Changes in insulin levels may be partially responsible for the changes we observe in IGFBP-1 concentrations after aerobic exercise training. Fasting insulin levels were reduced by 12% in our subjects after aerobic exercise training, and this may be responsible for the increase in IGFBP-1 concentrations that we observed after exercise training. After the high-fat meal, we found that IGFBP-1 concentrations decreased by 58% and 61% at baseline and after aerobic exercise training, respectively. Given the relatively short (89 minutes) half-life of IGFBP-1 [33], it is possible that insulin suppression of IGFBP-1 expression was primarily responsible for this reduction. Peak insulin levels during the high-fat meal in our subjects were approximately 250 pmol/L, near the concentration found to elicit half-maximal suppression of IGFBP-1 expression [34]. Because plasma insulin levels were approximately 33% lower during the high-fat meal test after exercise training, we would expect an attenuated reduction in IGFBP-1 concentrations if insulin were the sole cause of the reduction in IGFBP-1 concentrations. The similar relative reductions in IGFBP-1 at baseline and after aerobic exercise training suggest that factors other than insulin are at least partially responsible for the reduction in IGFBP-1 concentrations. These mechanisms may be unique to the fat meal; but because IGFBP-1 is higher in the fasted state and

lower in the fed state, they may also be due to high caloric intake in general.

Insulin-like growth factor binding protein–1 concentrations may simply be a marker of metabolic improvements and reduced insulinemia; however, recent research suggests that IGFBP-1 exerts direct metabolic effects. Insulin-like growth factor binding protein–1 binds integrin receptors in skeletal muscle and other tissue [35,36]; and cross talk between integrin receptor and insulin signaling pathways may, in part, increase insulin sensitivity [37]. In a rodent model, overexpression of IGFBP-1 resulted in a reduction in the development of insulin resistance [2]; and longitudinal studies in humans show that low concentrations of IGFBP-1 predict the development of abnormal glucose regulation [38] and heightened cardiovascular disease mortality [6-9]. Although fasting IGFBP-1 concentration correlated with insulin incremental AUC during the OGTT in our subjects, improvements in HOMA-IR and ISI_M did not correlate with plasma IGFBP-1 concentrations. This may be due to our sample being predominately composed of subjects with normal glucose tolerance, or it is possible that a larger number of subjects is necessary to detect any association. It should also be noted that the concentrations of IGF-1 and IGF-2 were not measured in the present study. Because IGFBP-1 may exert IGF-dependent metabolic effects, future studies will be required to determine whether any effect of IGFBP-1 concentration is mediated through IGF-independent or IGF-dependent mechanisms.

5. Conclusion

We conclude that aerobic exercise training has a potentially beneficial effect to increase fasting plasma IGFBP-1 concentrations in previously sedentary middle-aged to older adults. In contrast, ingestion of a meal high in fat has a large and rapid effect to lower circulating IGFBP-1 concentration. Aerobic exercise training did not attenuate the adverse effect of a high-fat meal on plasma IGFBP-1 concentrations. This study begins to shed light on the interaction between diet and exercise effects on IGFBP-1 and may indicate a mechanism by which chronic exercise and diets low in fat confer protection from cardiometabolic diseases with advancing age.

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Conflict of Interest

The authors have no conflict of interest to disclose.

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