Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Effects of Dietary Weight Loss and Exercise on Insulin-Like Growth Factor-I and Insulin-Like Growth Factor-Binding Protein-3 in Postmenopausal Women: A Randomized Controlled Trial

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Abstract

High levels of insulin-like growth factor (IGF)-I may increase the risk of common cancers in humans. We hypothesized that weight loss induced by diet and/or exercise would reduce IGF-I in postmenopausal women. Four hundred and thirty nine overweight or obese [body mass index (BMI) $\geq 25\ kg/m^2$] women (50–75 years) were randomly assigned to: (i) exercise ($N = 117$), (ii) dietary weight loss ($N = 118$), (iii) diet + exercise ($N = 117$), or (iv) control ($N = 87$). The diet intervention was a group-based program with a 10% weight loss goal. The exercise intervention was 45 minutes/day, 5 days/week of moderate-to-vigorous intensity activity. Fasting serum IGF-I and IGF-binding protein (IGFBP)-3 were measured at baseline and 12 months by radioimmunoassay. Higher baseline BMI was associated with lower IGF-I and IGF-I/IGFBP-3 molar ratio. Although no significant changes in either IGF-I or IGFBP-3 were detected in any intervention arm compared with control, the IGF-I/IGFBP-3 ratio increased significantly in the diet (+5.0%, $P < 0.01$) and diet + exercise (+5.4%, $P < 0.01$) groups compared with control. Greater weight loss was positively associated with change in both IGF-I ($P_{trend} = 0.017$) and IGF-I/IGFBP-3 ratio ($P_{trend} < 0.001$) in the diet group, but inversely with change in IGFBP-3 in the diet + exercise group ($P_{trend} = 0.01$). No consistent interaction effects with baseline BMI were detected. Modified IGF-I bioavailability is unlikely to be a mechanism through which caloric restriction reduces cancer risk in postmenopausal women. *Cancer Epidemiol Biomarkers Prev; 22(8); 1457–63. ©2013 AACR.*

Introduction

Biologic and epidemiologic evidence suggests that high levels of insulin-like growth factor (IGF)-I may increase risk for several common cancers (1, 2). IGF-I has mitogenic and antiapoptotic properties that are modulated through IGF-binding proteins (IGFBP; ref. 1). Most circulating IGF-I is bound to one of six IGFBPs, the most abundant being IGFBP-3, whereas a small amount remains unbound and biologically active. Modifications in IGF-I bioavailability have been proposed as a mechanism linking obesity and cancer risk (3, 4), whereas animal studies suggest that alterations in IGF-I, as well as other cytokines and inflammatory factors, may mediate the antiproliferative, proapoptotic, and anticancer effects of negative energy balance (5).

Calorie restriction in rodents and other animal models decreases serum IGF-I concentrations up to 40% (6, 7) but the effects in humans are equivocal (8–10). One explanation may be that, unlike insulin, human IGF-I does not appear elevated in obese individuals, but peaks in persons with body mass index (BMI) values of 24 to 27 kg/m^2 (11). Alternately, caloric restriction models in animals may not be relevant to humans because they are typically initiated in young ages, thereby preventing obesity, whereas calorie restriction has been tested in humans who are already obese. It is postulated that obesity-related hyperinsulinemia inhibits IGFBP production and results in elevated levels of free IGF-I. In turn, this exerts a negative feedback on growth hormone secretion, thereby lowering IGF-I (12). Few studies examining the interrelationships between energy balance, IGF-I, and cancer risk factors have considered differential effects according to baseline weight or body composition.

The purpose of this study was to investigate the independent and combined effects of 12 months of dietary

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weight loss and/or aerobic exercise on IGF-I, IGFBP-3, and the 1GF-I/IGFBP-3 molar ratio as a proxy for free IGF-I (13) in overweight and obese postmenopausal women. A secondary purpose was to examine the degree to which any intervention effects were moderated by baseline adiposity. We hypothesized that IGF-I and the IGF-I/IGFBP-3 molar ratio would be significantly decreased in women randomized to diet and diet + exercise, but that this effect would be stronger among women with baseline BMI less than 28 kg/m^2.

Materials and Methods

The Nutrition and Exercise in Women (NEW) study was a 12-month randomized controlled trial testing caloric restriction and exercise on circulating hormones and other outcomes. Study procedures were reviewed and approved by the Fred Hutchinson Cancer Research Center Institutional Review Board in Seattle, WA. All participants provided informed written consent.

Participants and interventions

The study methods have been previously described (14). Briefly, participants were postmenopausal women (50–75 years) with a BMI of 25.0 or more ($\geq$23.0 kg/m^2 if Asian-American), recruited through media and mass mailings. Exclusion criteria included: >100 minutes/week of moderate physical activity; diagnosed diabetes or fasting blood glucose $\geq$126 mg/dL; serious medical condition (s); postmenopausal hormone use; >2 alcoholic drinks/day; current smoking; participation in another structured weight loss program; contraindication to participation (e.g., abnormal exercise tolerance test).

Eligible women were randomized to one of: (i) reduced-calorie dietary modification ($N = 118$), (ii) moderate-to-vigorous intensity aerobic exercise ($N = 117$), (iii) combined diet and exercise ($N = 117$), or (iv) control (no intervention; $N = 87$). Computerized random assignment, using permuted blocks randomization to achieve a proportionally smaller control group, was stratified according to BMI ($\geq$ or <30 kg/m^2) and race/ethnicity.

The dietary intervention was a modification of the Diabetes Prevention Program (15) and Look AHEAD (Action for Health in Diabetes; ref. 16) lifestyle behavior change programs with goals of: 1,200 to 2,000 kcal/day, less than 30% daily calories from fat, and 10% weight loss. The exercise intervention goal was 45 minutes of moderate-to-vigorous ($\geq$4 metabolic equivalents) intensity exercise at a target heart rate of 70% to 85% observed maximum, 5 days/week. Participants attended 3 facility-based supervised sessions/week, and exercised 2 days/week at home.

Measures

All study measures were obtained and analyzed by trained personnel who were blinded to participants' randomization status.

At baseline (prerandomization) and 12 months, demographic information, height, weight, medical history, dietary intake, supplement use, and physical activity data were collected (14). Body composition was measured by dual x-ray absorptiometry (DXA) whole-body scanner (GE Lunar).

Twelve-hour fasting venous blood (50 mL) was collected during clinic visits (no exercise within 24 hours, no alcohol within 48 hours). Blood was processed within 1 hour and samples were stored at −70°C. Blood samples were analyzed in batches such that each participant's samples were assayed simultaneously, the number of samples from each group were approximately equal, participant randomization dates were similar, and sample order was random.

IGF-I and IGFBP-3 assays were conducted at the Jewish General Hospital (Montreal, Canada) using reagents from the Diagnostic Systems Laboratory, Beckman Coulter. The intra-assay coefficients of variation (CV) were 4.2% and 3.8% for IGF-I and IGFBP-3, respectively; interassay CVs were 5.4% and 4.9% for IGF-I and IGFBP-3, respectively. The molar ratio of IGF-I/IGFBP-3 was calculated as a proxy for free IGF-I: [IGF-I (ng/mL) $\times$ 0.130]/[IGFBP-3 (ng/mL) $\times$ 0.036; ref. 13].

Statistical analysis

For the primary analysis, no change from baseline was assumed in cases of missing data. Age-adjusted partial correlation coefficients were conducted between baseline measures. The mean 12-month change in IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio in each intervention group was compared with controls using the generalized estimating equations (GEE) modification of linear regression to account for intraindividual correlation over time. Assuming 80% power to make 3 primary pairwise comparisons (diet + exercise vs. exercise; diet + exercise vs. diet; and diet vs. exercise), the minimum detectable differences in IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio were estimated at 14.36, 305, and 0.009, respectively (type I error = 0.05). Bonferroni adjustment for multiple comparisons was made (two-sided $\alpha = 0.05/3 = 0.016$). Intervention effects were examined on the basis of assigned treatment at randomization, regardless of adherence or study retention (i.e., intent-to-treat).

The effect of weight loss on IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio was examined using a stratified analysis (<5%, 5%–10%, and >10% weight loss) conducted within each arm, without imputation for missing values. These analyses were repeated after stratification by baseline BMI (<28 vs. $\geq$28 kg/m^2) using the cut-point around which IGF-I peaks in humans (11). The potential moderating effect by baseline BMI was tested by including an appropriate interaction term in each model.

All statistical analyses were conducted using SAS software version 9.2 (SAS Institute).

Results

At 12 months, 399 participants completed a physical exam, a DXA scan, and provided a blood sample; 40

did not complete the study. Participant characteristics, intervention adherence, 12-month weight and body composition changes have been previously published (14). Mean age and BMI were 58.0 years and 30.9 kg/m^2. Most women (65%) were college graduates and 85% were non-Hispanic White. Mean weight changes were −2.4% ($P = 0.03$) in the exercise group, −8.5% ($P < 0.001$) in the diet group, and −10.8% ($P < 0.001$) in the diet + exercise group, compared with −0.8% among controls.

Exercise groups participated in moderate-to-vigorous activity for a mean (SD) 163.3 (70.6) minutes/week (exercise), and 171.5 (62.9) minutes/week (diet + exercise). Both groups significantly increased average pedometer steps per day (+2,416 and +3,471 steps/day, respectively) compared with baseline. In both diet groups, women attended an average of 27 diet counseling sessions (86%).

Baseline associations

The age-adjusted partial correlations between BMI and IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 ratio at baseline are shown in Fig. 1. Both IGF-1 and the IGF-1/IGFBP-3 molar ratio were inversely associated with BMI, whereas IGBP-3 showed no association. In addition to age (−0.13, $P = 0.008$), baseline IGF-I concentrations were also significantly inversely associated with waist circumference (−0.25, $P < 0.0001$), and percentage (%) body fat mass (−0.20, $P < 0.0001$). IGFBP-3 was significantly inversely associated with% body fat (−0.11, $P = 0.02$). The IGF-I/IGBP-3 molar ratio was significantly inversely associated

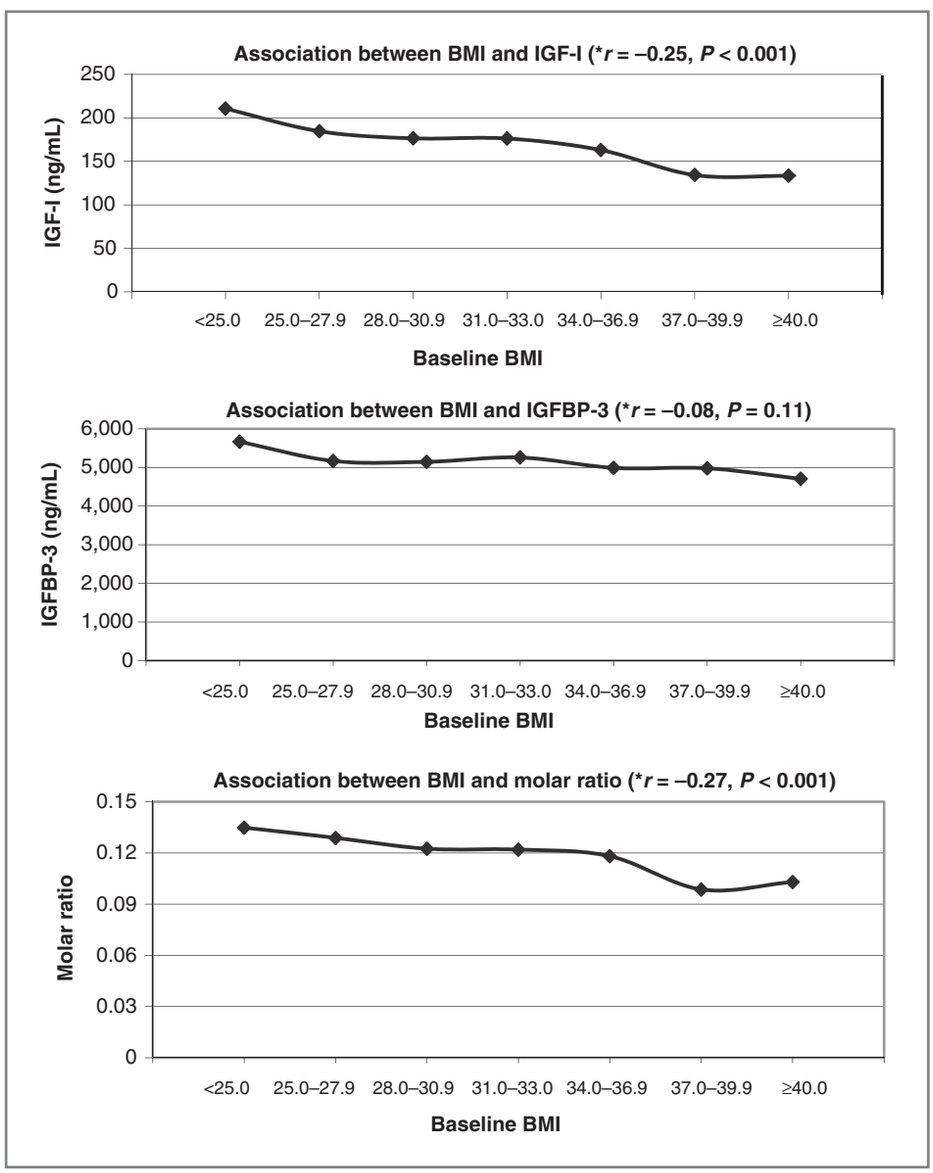

Figure 1. Associations between IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 molar ratio with BMI at baseline among overweight or obese postmenopausal women. *r, age-adjusted partial correlation coefficient.

Table 1. Baseline, 12-month (mean, SD), and change in serum IGF-I, IGFBP-3, and IGF-I/IGFBP-3 molar ratio, stratified by intervention arm

	Mean (SD)				
	Baseline	12 month	Change	Change %	*P*
Control					
IGF-I, ng/mL	178.7 (53.4)	174.0 (53.1)	−4.7	−2.6	Ref.
IGFBP-3, ng/mL	5,214 (1,102)	5,110 (1,240)	−104	−2.0	Ref.
Molar ratio[a]	0.124 (0.028)	0.123 (0.027)	−0.001	−0.4	Ref.
Exercise					
IGF-I, ng/mL	172.8 (47.3)	169.0 (46.2)	−3.8	−2.2	0.81
IGFBP-3, ng/mL	5,137 (943)	4,991 (958)	−146	−2.8	0.63
Molar ratio[a]	0.121 (0.025)	0.122 (0.024)	0.001	0.8	0.53
Diet					
IGF-I, ng/mL	167.9 (46.0)	170.3 (45.5)	2.4	1.4	0.06
IGFBP-3, ng/mL	5,081 (951)	4,921 (1,022)	−160	−3.2	0.56
Molar ratio[a]	0.119 (0.024)	0.125 (0.024)	0.006	5.0	0.008
Diet + exercise					
IGF-I, ng/mL	177.1 (57.3)	179.6 (58.5)	2.6	1.4	0.06
IGFBP-3, ng/mL	5,165 (1051)	4,969 (929)	−197	−3.8	0.31
Molar ratio[a]	0.123 (0.026)	0.130 (0.028)	0.007	5.4	0.004

Results from GEE model, comparing change from baseline to 12 months between each intervention group and controls.
[a]Molar ratio = [IGF-I (ng/mL) × 0.130]/[IGFBP-3 (ng/mL) × 0.036].

with age (−0.10, $P = 0.04$), waist circumference (−0.33, $P < 0.0001$), and% body fat (−0.17, $P < 0.001$).

Intervention effects

Compared with controls, neither IGF-I nor IGFBP-3 changed significantly in either group receiving dietary intervention (Table 1). The IGF-I/IGFBP-3 molar ratio increased significantly in the diet group ($P = 0.008$) and in the diet + exercise group ($P = 0.004$). No significant change in IGF-I, IGFBP-3, or their molar ratio was detected among exercisers compared with controls.

Greater weight loss was associated with an increase in IGF-I and the IGF-I/IGFBP-3 molar ratio among women randomized to diet alone (Table 2), whereas we observed an inverse trend greater between weight loss and IGFBP-3 in the diet + exercise group.

In the stratified analysis (BMI ≥28 vs. <28), the IGF-I/IGFBP-3 ratio was significantly increased among women with BMIs 28 kg/m^2 or more randomized to diet + exercise compared with controls. No significant differences were detected in women with BMIs less than 28 kg/m^2. A greater decrease in IGFBP-3 was observed among women with BMI ≥28 vs.<28 in the diet + exercise group ($P_{interaction} = 0.005$; Supplementary Table).

Discussion

No significant changes in IGF-I or its main binding protein, IGFBP-3, were detected in any intervention arm compared with control; however, the IGF-I/IGFBP-3 molar ratio increased significantly in the diet and diet + exercise groups. This suggests that lifestyle-based weight loss of 8% to 10% may increase IGF-I bioavailability in overweight and obese postmenopausal women; an effect that is counter intuitive to the anticipated effect of weight loss on cancer risk, and opposite to the effects consistently observed in animal models (5). However, as noted above, the majority of published animal studies have not tested caloric restriction weight loss in already obese animals, and therefore do not serve as true models for overweight/obese persons undergoing weight loss. Furthermore, by comparison with animal models in which caloric restriction does alter IGF-I and impede tumor growth, the degree of change in energy balance was relatively modest in this study (17, 18). Equivalently severe exercise and/or caloric restriction may not be practical in most human populations.

The equivocal effect of dietary weight loss on IGF-I in our trial is consistent with a limited number of other studies in women and men (19–23). In the only other study of exclusively postmenopausal women ($n = 99$, mean BMI 26.9 kg/m^2), 5 months of dietary intervention yielding a mean BMI decrease of 1.62 kg/m^2 did not significantly alter serum IGF-I compared with weight-stable controls, although IGFBP-1 and -2 were increased (22); IGFBP-3 was not measured. In another 6-month trial comparing intermittent versus continuous caloric restriction in premenopausal women (mean BMI 30.6 ± 5.1 kg/m^2), negligible changes in total and free IGF-I were observed in response to mean weight changes of −6.4 and −5.6 kg in each group, respectively (23). However, both groups experienced similar significant increases in IGFBP-1 and -2.

Table 2. Baseline and 12 months (Mean, SD), and % change in IGF-I, IGFBP-3, and the IGF-I/IGFBP-3 molar ratio, stratified by weight loss

		IGF-I				IGFBP-3				Molar ratio[a]			
	N	Baseline	12 months	% Change	*P*	Baseline	12 months	% Change	*P*	Baseline	12 months	% Change	*P*
Control													
Weight loss <5%	67	181.0 (52.5)	172.5 (50.9)	−4.7	Ref.	5,262 (1,064)	5,126 (1,159)	−2.6	Ref.	0.124 (0.027)	0.122 (0.026)	−2.0	Ref.
5%–10%	9	174.1 (57.6)	187.0 (69.7)	7.4	0.008	5,029 (1,205)	4,855 (1,164)	−3.5	0.84	0.125 (0.036)	0.137 (0.037)	9.6	0.0003
>10%	4	173.7 (66.3)	183.8 (52.9)	5.8	0.45	5,628 (1,180)	6,026 (2,340)	7.1	0.55	0.110 (0.024)	0.114 (0.16)	3.4	0.36
					$P_{trend} = 0.13$				$P_{trend} = 0.59$				$\mathbf{P_{trend} = 0.03}$
Exercise													
Weight loss <5%	75	172.9 (48.8)	167.0 (46.6)	−3.4	Ref.	5,242 (983)	5055 (1,007)	−3.6	Ref.	0.119 (0.024)	0.119 (0.022)	0.2	Ref.
5%–10%	26	181.0 (45.7)	182.8 (49.2)	1.0	0.33	5086 (837)	5,041 (850)	−0.9	0.23	0.129 (0.027)	0.131 (0.029)	2.0	0.63
>10%	4	189.8 (57.4)	167.3 (46.7)	−11.8	0.03	5,166 (918)	4,665 (1,103)	−9.7	0.13	0.132 (0.027)	0.130 (0.022)	−1.1	0.81
					$P_{trend} = 0.88$				$P_{trend} = 0.89$				$P_{trend} = 0.77$
Diet													
Weight loss <5%	28	167.2 (48.9)	163.3 (50.6)	−2.3	Ref.	5,065 (955)	5,044 (1,286)	−0.4	Ref.	0.119 (0.026)	0.118 (0.029)	−0.9	Ref.
5%–10%	27	175.9 (49.1)	172.2 (39.5)	−2.1	0.97	5,190 (962)	4,997 (761)	−3.7	0.4	0.122 (0.026)	0.125 (0.023)	1.9	0.43
>10%	49	161.0 (41.8)	171.8 (45.1)	6.7	0.03	5,030 (837)	4,767 (871)	−5.2	0.22	0.116 (0.023)	0.130 (0.022)	12.3	<0.001
					$P_{trend} = 0.017$				$P_{trend} = 0.22$				$P_{trend} < 0.001$
Diet + exercise													
Weight loss <5%	18	158.2 (47.9)	163.2 (50.1)	3.2	Ref.	4,962 (973)	4,983 (979)	0.4	Ref.	0.115 (0.027)	0.118 (0.027)	2.8	Ref.
5%–10%	21	167.7 (53.8)	173.7 (46.2)	3.6	0.93	4,702 (985)	4,708 (890)	0.1	0.95	0.129 (0.028)	0.134 (0.025)	3.9	0.75
>10%	69	188.6 (60.1)	189.8 (64.2)	0.7	0.68	5,342 (1,072)	5,004 (938)	−6.3	0.04	0.127 (0.025)	0.136 (0.027)	7.1	0.19
					$P_{trend} = 0.59$				$P_{trend} = 0.01$				$P_{trend} = 0.16$

[a]Molar ratio = [IGF-I (ng/mL) × 0.130]/[IGFBP-3 (ng/mL) × 0.036].

In contrast, IGF-I increased significantly after a mean 9.7 ± 4.3% weight loss in obese women with a mean BMI of 37.2 kg/m^2 (19). Likewise, IGF-I increased significantly in a sample of obese men and women (mean BMI 32.6 kg/m^2) during a 6-month weight loss period, and levels continued to increase despite partial weight regain during the subsequent 6 months (20). In another sample of premenopausal women (mean BMI of 29.2 ± 6.2 kg/m^2), intentional weight loss 5% or more body weight (vs. weight stable/gain) was associated with a significant increase in serum total IGF-I, whereas free IGF-I and IGFBP-3 remained unchanged (21).

Strengths of our study include its large sample and adequate power to examine changes in IGF-I and IGFBP-3 in 3 separate lifestyle interventions compared with controls. However, the IGF-I axis is complex, and circulating levels may not reflect local tissue levels, which we were unable to assess. Furthermore, we relied on the IGF-I/IGFBP-3 molar ratio as a surrogate of bioactive IGF-I. Although this ratio is a reasonable approximation of free IGF-I under normal physiologic conditions (13), free IGF-I is also influenced by levels of other IGFBPs (24). Finally, IGF-I and IGFBP-3 levels are affected by multiple factors, including gender and race/ethnicity (25); therefore, these results may not be generalizable to men or to populations that are not predominantly Caucasian.

The findings of the current study, plus those of previous studies, suggest that animal models of caloric restriction on IGF-I and IGFBP-3 are not confirmed with caloric restriction and weight loss in overweight/obese women. They also suggest that modified IGF-I bioavailability is unlikely to represent a major mechanistic link through which caloric restriction impacts obesity-associated cancer risk in humans.

Disclosure of Potential Conflicts of Interest

A. McTiernan is a consultant/advisory board member of Metagenics. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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