Null Results in Brief

Insulin-Like Growth Factor I, Insulin-Like Growth Factor I Binding Protein 1, Insulin, Glucose, and Leptin Serum Levels Are Not Influenced by a Reduced-Fat, High-Fiber Diet Intervention

Wael K. Al-Delaimy, Loki Natarajan, Cheryl L. Rock, Shelly Sun, Shirley W. Flatt, and John P. Pierce

Cancer Prevention and Control, Moores Cancer Center, University of California, San Diego, La Jolla, California

Introduction

The Women's Healthy Eating and Living study is a dietary intervention aimed at increasing vegetables, fruit, and fiber, and reducing fat intake in breast cancer survivors. In a subsample of this study, we measured five interrelated factors: free circulating insulin-like growth factor I (IGF-I), insulin-like growth factor binding protein (IGFBP-1), insulin, glucose, and leptin, to assess the influence of the intervention on these factors after 12 months of follow-up. Few intervention studies have addressed the influence of a reduced fat-high fiber diet on these factors. Animal models in which energy intake was restricted showed a reduction in IGF-I and leptin levels (1, 2) and some fatty acids were related to a reduction of plasma leptin levels (3, 4). It is believed that the cancer protective role of energy restriction is through the influence of these hormones (5). In one previous study, high vegetable intake (specifically, tomato intake) was related to lower levels of IGF-I among 344 healthy men whereas polyunsaturated fat intake was related to increased IGF-I levels (6), but other smaller intervention and observational studies have failed to find an effect of fruits and vegetables on IGF-I and its binding proteins (7-9).

Materials and Methods

Subjects for this study were a subgroup of women from the Women's Healthy Eating and Living Study. The Women's Healthy Eating and Living study is a multisite randomized control trial of the effect of a diet high in vegetables, fruit, and fiber, and low in fat, on risk for recurrence and survival in breast cancer survivors (10). More than 3,000 women were recruited between 1995 and 2000 and will be followed until 2007. Blood samples, dietary data (24-hour dietary recalls from 2 weekdays and 2 weekend days, collected over a 3-week period), and lifestyle data were collected at enrollment, 12, 24 or 36, 48, and 72 months of follow-up. Participants identified for this substudy were a systematic quota sample of the first 400 women randomized into the Women's Healthy Eating and Living Study. Within each study group (intervention and comparison), we selected the first 100 participants with dietary data who were ≤50 years of age at enrollment and the first 100 women who were >50 years of age. Participants who changed tamoxifen use from baseline to 12 months or used insulin were excluded. The Institutional Review Board for the University of California, San Diego and each participating institution approved the study.

The collection of fasting blood samples and height and weight measurements were done during clinic visits, and body mass index (kg/m^2) was computed. Laboratory analyses of free IGF-I and IGFBP-1 were done by the two-site immunoradiometric assay (IRMA) kit purchased from Diagnostic Systems Laboratories (Webster, TX). For free IGF-I, the lower detection limit was 0.03 ng/mL with intra-assay and interassay coefficient of variance of <11%. The IGFBP-1 lowest detection limit was 0.33 ng/mL, with intra-assay precision of <5.2% and inter-assay precision of <6%. Leptin analyses were done using the leptin human RIA kit from Linco Research (St. Charles, MO), with the lowest detection limit of 0.5 ng/mL, intra-assay precision of <8.3%, and inter-assay precision of <6%. Fasting serum insulin concentration was measured as a surrogate for insulin resistance (11). A double-antibody RIA with <0.2% cross-reactivity with human proinsulin was used for the analysis of insulin (Linco Research). The lowest detection limit was 2 μU/mL, the intra-assay coefficient of variance was <5%, and the interassay coefficient of variance was <6.0%. The glucose analyzer (YSI STAT 2300, Yellow Springs Instruments, Yellow Springs, OH) was used to analyze glucose levels. A total of 7 women had missing serum levels of IGF-I, IGFBP-1, and leptin; 8 women had missing insulin serum levels; and 12 did not have glucose measured and were excluded from the relevant analyses.

Median levels of the factors at baseline and 12 months for the intervention and control groups were examined and nonparametric paired Wilcoxon rank-sum tests were applied for statistical analyses. For the regression analyses, all data were log transformed and mixed-effects repeated measures models were used to assess the influence of confounders on changes in IGF-I. Given 196 women in each group, we can detect a minimum effect size of 0.284 and 0.328 with 80% and 90% power, respectively (α = 0.05).

Results

As shown in Table 1, there was no significant difference in any of the variables between the intervention and control groups at baseline. Intakes of carbohydrates, fiber, and fat were significantly different between the intervention and control groups after 12 months of the intervention. The

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Requests for reprints: Wael K. Al-Delaimy, Cancer Prevention and Control, Moores Cancer Center, 3855 Health Sciences Drive #0901, La Jolla, CA 92093-0901. Phone: 858-822-6515; Fax: 858-822-2399; E-mail: wael@ucsd.edu

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Table 1. Median serum concentrations of free IGF-I, IGFBP-1, leptin, insulin, and glucose and macronutrient intakes for the intervention and control groups at baseline and 12 months and the corresponding *P* values (Wilcoxon rank-sum test for the difference between intervention and controls at baseline and 12 months of follow-up)

	Baseline			12 mo		
	Control	Intervention	*P*	Control	Intervention	*P*
Free IGF-I (ng/mL)	1.24	1.08	0.4	1.09	0.93*	0.2
IGFBP-1 (ng/mL)	38.9	44.5	0.7	40.03	45.4	0.6
Leptin (ng/mL)	18.9	20.2	0.5	18.2	19.3	0.6
Insulin (μU/mL)	12.0	13.0	0.4	12.0	12.0	0.2
Glucose (mg/dL)	83.2	82.2	0.5	84.2*	84.3*	0.5
Dietary fat intake(g/d)	53.2	53.4	0.6	47.3*	37.4*	0.0001
Dietary carbohydrate intake (g/d)	245.5	241.0	0.8	228.8*	261.3*	0.0001
Dietary fiber intake (g/d)	20.3	19.7	0.4	20.2	29.0*	0.0001
Dietary protein intake (g/d)	65.5	66.7	0.3	65.8	65.8	0.8
Body mass index	25.8	25.7	0.4	26.0*	25.9	0.5

*Significant difference ($P < 0.05$) within the intervention or control group at 12 months compared with baseline.

intervention was successful in significantly increasing carbohydrate and fiber intake in the intervention group, but there was no change in protein intake. Dietary fat intake was significantly decreased in both groups but the decline was substantially greater by 19% in the intervention group. Within each group and at 12 months of follow-up, there was no significant change for serum concentrations of IGFBP-1, leptin, or insulin. Free IGF-I levels were not different between the intervention and control groups at 12 months but decreased significantly in the intervention group at 12 months compared with baseline ($P < 0.0001$). Body mass index was increased in the control group but there was no significant difference between the intervention and control groups at 12 months.

To further delineate the significant change of free IGF-I in the intervention over 12 months, we used mixed-effects model with IGF-I at baseline and 12 months as the outcome. We found both age and change in body mass index to be significantly inversely predictive of change in IGF-I, but the intervention group status, change in animal protein intake, and change in energy intake (both of which are related to IGF-I levels) were not predictive of change in free IGF-I concentration in this population.

Conclusions

Although there was a significant decrease in serum-free IGF-I concentration in the intervention group after 12 months on the diet intervention, this change was not statistically different from the decrease in the control group and would seem to be unrelated to the change in dietary intakes. Further, the reduction seems to be explained by older age and higher body mass index, a finding supported by a recent study (12). Serum leptin, insulin, and IGFBP-1 concentrations did not change appreciably in response to the intervention, although there was a significant change in dietary intakes of carbohydrate, fiber, and fat as a result of the intervention. These hormones and growth factors do not seem to be influenced by a high-fiber, reduced-fat diet intervention among these women. Our results suggest that future studies involving the relationship between serum IGF-I, IGFBP-1, and leptin concentration and cancer outcomes should be less concerned about the influence of dietary modification on these relationships.

Appendix A

The Women's Healthy Eating and Living Study Group: *University of California, San Diego, Cancer Prevention and Control Program, San Diego, CA:* John P. Pierce, Ph.D. (principal investigator); Wael K. Al-Delaimy, M.D., Ph.D.; Cheryl L. Rock, Ph.D., R.D.; Susan Faerber, B.A.; Vicky A. Newman, M.S., R.D.; Shirley W. Flatt, M.S.; Sheila Kealey, M.P.H.; Loki Natarajan, Ph.D.; Barbara Parker, M.D.; Lisa Madlensky, Ph.D.; Wayne A. Bardwell, Ph.D. *Center for Health Research, Portland, OR:* Njeri Karanja, Ph.D.; Mark Rarick, M.D. *Kaiser Permanente Northern California, Oakland, CA*: Bette J. Caan, D.P.H.; Lou Ferenbacher, M.D. *Stanford University/University of California, San Francisco, Palo Alto, CA*: Marcia L. Stefanick, Ph.D.; Robert Carlson, M.D. *University of Arizona, Tucson & Phoenix, AZ:* James R. Marshall, Ph.D.; Cynthia A. Thomson, Ph.D., R.D.; James Warnecke, M.D. *University of California, Davis, Davis, CA:* Ellen B. Gold, Ph.D.; Sidney Scudder, M.D. *University of California, San Diego Cancer Center, San Diego, CA*: Linda Wasserman, M.D., Ph.D.; Kathryn A. Hollenbach, Ph.D. *The University of Texas M.D. Anderson Cancer Center, Houston, TX:* Lovell A. Jones, Ph.D.; Richard Theriault, D.O.

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