Low-fat diet with omega-3 fatty acids increases plasma insulin-like growth factor concentration in healthy postmenopausal women

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Abstract

The insulin-like growth factor pathway plays a central role in the normal and abnormal growth of tissues; however, nutritional determinants of insulin-like growth factor I (IGF-I) and its binding proteins in healthy individuals are not well defined. Three test diets—high-fat diet (40% energy as fat), low-fat diet (LF; 20% energy as fat), and a diet with low fat and high omega-3 fatty acid (LFn3; 23% energy as fat)—were tested in a randomized crossover designed controlled feeding trial in healthy postmenopausal women. Plasma IGF-I, IGF binding protein-3 (IGFBP-3), insulin, glucose, and ratio of IGF-I/IGFBP-3 concentrations were measured in response to diets. Insulin sensitivity was calculated using the homeostatic model assessment of insulin resistance. We hypothesized that IGF-I, insulin, and glucose concentrations would decrease and IGFBP-3 concentration would increase in response to the low-fat diets. Eight weeks of the LFn3 diet increased circulating IGF-I (P < .001) and IGFBP-3 (P = .01), and the LF diet increased IGFBP-3 (P = .04), resulting in trends toward an increased IGF-I/IGFBP-3 ratio with the LFn3 diet and a decreased IGF-I/IGFBP-3 ratio with the LF diet (P = .13 for both comparisons). No statistically significant differences were detected between treatments at baseline or 8 weeks for IGF-1, IGFBP-3, or the ratio of IGF-1/IGFBP-3. Insulin, glucose, and the homeostatic model assessment of insulin resistance were not altered by the interventions. Low-fat diet with high n-3 fatty acids may increase circulating IGF-I concentrations without adversely affecting insulin sensitivity in healthy individuals.

Keywords: Diet, Dietary fat, Omega-3 fatty acids, Insulin-like growth factor I (IGF-I), IGF binding protein-3 (IGFBP-3), Insulin, Glucose

1. Introduction

Insulin-like growth factor I (IGF-I) is a peptide hormone predominantly secreted by the liver in response to pituitary-derived growth hormone (GH) [1]. Insulin-like growth factor I is generated, to a lesser degree, in peripheral tissues and acts in an autocrine and paracrine fashion in these tissues [2]. In the blood, approximately 90% of IGF-I is complexed with insulin-like growth factor binding protein-3 (IGFBP-3; 1 of 6 IGF binding proteins) and acid labile subunit in a 1:1:1 ratio, which

Abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor I; IGFBP-3, IGF binding protein-3; HOMA-IR, homeostatic model assessment—insulin resistance (fasting insulin [mUL] × fasting glucose [mmol/L] 22.5).

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0271-5317/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.nutres.2013.04.011
increases the half-life of IGF-1 [3]. Insulin-like growth factor I is involved in both the normal and neoplastic growth of tissues via mediation of cell proliferation, cell-cycle progression, and programmed cell death [1,2,4], and inhibition of the IGF signaling pathway is a target for cancer therapy [5]. In contrast, aging is associated with decreased GH and IGF-I concentrations accompanied by decreased bone mineral density, decreased lean body tissue, and increased adiposity, along with a higher risk vascular profile associated with increased cardiovascular mortality and morbidity [6].

Insulin-like growth factor I levels are markedly reduced in postmenopausal women [27] and protein and calorie restriction [9] in cancer cachexia [10]; however, the nutritional determinants of IGF-I and its binding proteins are less well defined in healthy, adequately fed individuals. Cross-sectional studies have shown associations between concentrations of IGF-I and IGFBP-3 and dietary fat intake, as assessed by food frequency questionnaire [11–13], although all studies did not report an association [14–16]. Vegans who reportedly consumed significantly more polyunsaturated fat than meat eaters and vegetarians had reduced concentrations of IGF-I [17], whereas intake of omega-3 (n-3) fatty acids was associated with increased concentrations of IGFBP-3 [13].

Insulin modulates the bioavailability of IGF-1 by reducing levels of IGF binding proteins, modulating GH receptor density on liver cells, and stimulating hepatic IGF-1 synthesis [3,18]. High total fat intake was positively associated with fasting insulin concentrations [19,20] and negatively associated with insulin sensitivity [21] in cross-sectional studies in nondiabetic individuals. Low-fat/high-carbohydrate diets improved insulin sensitivity [22–24] and fasting insulin concentrations [22,25,26] in several intervention studies relative to a high-fat [23,24] or habitual [22,25,26] diets in healthy individuals.

We previously reported the effects of 3 test diets with varying amounts and types of dietary fat on circulating sex hormones [27] in healthy postmenopausal women. As an ancillary analysis to that study, we hypothesized that IGF-I, insulin, and glucose concentrations would decrease and IGFBP-3 concentration would increase in response to low-fat diet interventions with or without omega-3 fatty acids. Insulin sensitivity was assessed using the homeostatic model assessment of insulin resistance (HOMA-IR) [28,29].

2. Methods and materials

2.1. Experimental protocol

This study is part of a trial that was designed to determine the effect of 3 test diets with varying amounts of dietary fat and n-3 fatty acids on plasma sex hormone profile and urinary eicosanoids in postmenopausal women [27]. Each of the 3 controlled diets, high fat (40% energy from fat; HF), low fat (20% energy from fat; LF), and low fat, high n-3 fatty acids (23% energy from fat, 3% of energy from n-3 fatty acids; LFn3) diets were provided to participants in a randomized, crossover design to all participants. The diets were provided for 8 weeks with a washout period of 6 to 12 weeks between diets. During the washout periods, the participants consumed their habitual diets. During the intervention periods, study participants picked up packaged study meals (breakfast, lunch, dinner, and a snack) that were prepared in the metabolic kitchen of the University of Minnesota General Clinical Research Center. Participants recorded any foods that were consumed in addition to the study meals and any foods from the prepared study meals that were not consumed on a daily compliance questionnaire that was monitored by the study staff. At meal pick-up times, participants also recorded their weight.

The University of Minnesota Committee for the Use of Human Subjects in Research and the US Army Medical Research and Materiel Command’s Human Subjects Research Review Board approved the protocol for the study. All participants gave written informed consent before enrollment in the study.

2.2. Participants

Postmenopausal women were recruited from Minneapolis/St Paul, MN, and the surrounding area. Details on study recruitment were detailed previously [27]. Participants were 45 to 70 years old and postmenopausal (1 year since last menstrual period plus a follicle-stimulating hormone concentration of 23 IU/L at screening or 55 years old), had a body mass index of 19 to 32 kg/m² with minimal weight fluctuation in the 6 months before study participation, were willing to refrain from taking nonsteroidal anti-inflammatory drugs and aspirin during the course of the study, and had not taken hormone replacement therapy or fish oil supplements for 2 months before study enrollment. Potential participants were excluded if they were current smokers, had hormone-related cancer in the past, used nonsteroidal anti-inflammatory drugs or prescription medication (excluding high blood pressure medication), had a bilateral oophrectomy (an exclusion criterion pertaining to the larger study on circulating sex hormones in the same study participants), or had diagnosed chronic concurrent disease (eg, diabetes mellitus or inflammatory disease). A medical history screening questionnaire was used to exclude participants with known disease and those taking medications prohibited by the study protocol.

A total of 17 participants completed all aspects of the study (Fig. 1). An additional participant completed 2 diet treatments (missing LF diet period). One participant was excluded from the statistical analysis because of multiple fasting glucose measurements equal to 11.1 mmol/L (indicating the presence of type II diabetes). One participant was excluded from the analysis for the LFn3 diet (missing samples). One participant was excluded from the LFn3 diet statistical analysis for insulin and HOMA-IR because of an inexplicably high insulin value (>5 SDs above the mean) at week 8.

2.3. Dietary treatments

The 3 test diets have been described in detail previously [27]. Briefly, the 3 diets were isoenergetic high-fat (HF; 40% energy from fat, 15% energy from protein, 45% energy from carbohydrate), low-fat (LF; 20% energy from fat, 15% energy from protein, and 65% energy from carbohydrate), and low-fat, high-n-3 (LFn3; 23% energy from fat, 15% energy from protein, and 62% energy from carbohydrate) diets prepared from common, commercially available foods. The HF and LF diets
contained minimal n-3 fatty acids and had similar proportions of saturated to monounsaturated to polyunsaturated fatty acids (1:1:1). The LFn3 diet included 3% of energy from n-3 fatty acids from foods naturally rich in these fats (salmon, flax seed oil, and walnuts). Nutrients in the test diets were determined using nutrient analysis software (Nutritionist V; Axxya Systems, Stafford, TX, USA).

The Harris-Benedict equation \[655.1 + 9.56 \times \text{weight (kg)} + 1.85 \times \text{height (cm)} - 4.68 \times \text{age (years)}\] multiplied by an activity factor (1.4-1.7; mean, 1.6) was used to predict an energy level appropriate for weight maintenance for each participant. The registered dietitian made a clinical assessment of activity level based on reported work and exercise habits [30]. Total energy of the diets was increased or decreased by 840 kJ (200 kcal) if a participant’s weight fluctuated by 1.0 kg. Deviation from the study diets was calculated from the daily compliance questionnaires and was reported previously [27].

The molar ratio of IGF-I/IGFBP-3 was calculated as \((0.130 \times \text{IGF-I concentration [ng/mL]})/(0.036 \times \text{IGFBP-3 concentration [ng/mL]})\) [31]. The HOMA-IR, calculated as \((\text{fasting plasma glucose [mmol/L]} \times \text{fasting plasma insulin [mU/L]})/22.5\), was used as a measure of insulin resistance [28,29].

3. Statistical analyses

A general linear-mixed model (SAS Proc Mixed, SAS 9.2; SAS Institute Inc, 2002-2008, Cary, NC, USA) was fit to the data for each of the primary end points, with correlation between multiple measurements within each participant modeled by a random effect for participant. The mixed model accommodated missing values and was used to assess carryover and period effects. Randomization to diet sequences was unbalanced. Least squares means and their SEs from the mixed model were the basis of pairwise comparisons between diets. Paired \(t\) tests were used for within-diet comparisons. A \(P\) value less than .05 denotes statistical significance.

3. Results

Baseline reported dietary intake and characteristics of the study participants were reported previously [27]. At the study baseline, the participants were 57 ± 6 years of age with a body
The consumption of the LFn3 resulted in increased IGF-I (P < .001; Table 1) and IGFBP-3 (P = .01), whereas consumption of the LF increased IGFBP-3 only (P = .04). Because of these changes, the ratio of IGF-I/IGFBP-3 increased with the LFn3 and decreased with the LF, although the changes in the ratio were not statistically significant (P = .13 for both comparisons). Baseline concentration of IGF-I was lower with the LFn3 (P = .24), which may have contributed to the magnitude of the increase observed. No statistically significant differences were detected between treatments at baseline or 8 weeks for IGF-1, IGFBP-3, or the ratio of IGF-1/IGFBP-3. No changes within or among the diets were observed with insulin, glucose, or HOMA-IR. As previously published [27], the plasma phospholipid n-3 fatty acids in the participants were significantly increased after the LFn3 diet intervention.

### 4. Discussion

The results of this well-controlled dietary feeding study in healthy, nondiabetic postmenopausal women indicate that circulating IGF-I and IGFBP-3 concentrations were increased by a diet low in fat containing 3% of energy from n-3 fatty acids, resulting in a trend toward increased IGF-I/IGFBP-3 ratio. As such, we rejected our research hypothesis that the low-fat diets would reduce IGF, insulin, and glucose. Insulin-like growth factor I binding protein-3 was increased by the low-fat diets, as we hypothesized. Because both IGF-I and IGFBP-3 are GH dependent; these results may indicate a greater effect of the LFn3 diet compared with the LF diet on GH levels. Few data are available regarding the effects of n-3 fatty acids on circulating IGF-I concentrations; however, a cross-sectional study in men and women in Singapore reported an association between increased IGFBP-3 and high intake of n-3 fatty acids [13].

The effects of a low-fat, high-fiber diet on serum IGF-I, IGFBP-3, insulin, and glucose were the focus of an ancillary study involving 750 participants in the Polyp Prevention Trial (PPT) [32]. The investigators observed no significant differences in IGF-I, IGFBP-3, insulin, or glucose concentrations at 1- or 4-year follow-up in the intervention group compared with baseline, or the control group, although the intervention group achieved self-reported reductions in dietary fat from 35% of energy to 22.7% of energy and an increase in fiber intake from 18.9 to 33.6 g/d at 4 years. The diets in the current study were controlled and not self-reported; therefore, the results are not likely affected by reporting errors. There was also no change in IGF-I, IGFBP-3, and IGFBP-3 after a 12-month low-fat/high-fiber dietary intervention in premenopausal women conducted by Gann et al [33]. Neither the PPT authors nor Gann et al addressed n-3 fatty acid composition of the diets. Our low-fat dietary intervention was much shorter in duration than that of both the PPT and Gann et al trial, and it is unknown whether the increase in IGFBP-3 that we observed with the LF diet or the increases in IGF-I and IGFBP-3 that we observed with the LFn3 diet are transitory changes or whether concentrations could be altered in the long term by a diet low in total fat and high in n-3 fatty acids. This point deserves further investigation in a longer-term trial. Others have also shown no association between low-fat diet and omega-3 fatty acids and IGF-I [34,35], although these studies were conducted in men with prostate cancer.

There was no indication that insulin sensitivity was altered by the test diets in this study, although the study participants were healthy, nondiabetic individuals. However, insulin sensitivity-related end points did change after the multifactor intervention of the Diet and Androgens (DIANA) randomized trial [36]. The participants in the DIANA trial intervention group were instructed to alter a number of dietary factors simultaneously and follow a Mediterranean/macrobiotic type...
diet, which, among other aims, intended to reduce animal fat intake and increase n-3 fatty acids intake. After 4 months of the intervention, the participants reported decreased intake of animal protein, total fat (reduced from 37.1% to 30.8% of energy), animal fat, saturated fat, monounsaturated fat, cholesterol, and total energy and increased intake of vegetable protein, vegetable fat, polyunsaturated fat, and carbohydrates [37]. Although IGF-1 and IGFBP-3 concentrations were not altered in the intervention group, concentrations of IGFBP-1 and IGFBP-2 were increased, and C-peptide and fasting glucose decreased. There was no change in fasting insulin with the intervention, although area under the curve of insulin during the oral glucose tolerance test was reduced in the intervention group [36]. Importantly, there was also a significant deficit in energy intake in the DIANA trial intervention group, and significant changes attributed to the intervention were attenuated when adjustments for weight and waist circumference were applied. Therefore, the effects observed with the intervention may be due more to weight loss and the accompanying body composition changes than to the change in dietary composition. Our participants lost a small but statistically significant amount of weight with each dietary treatment; however, the amount of weight lost and mean weights at 8 weeks of each treatment did not differ.

Insulin-like growth factor 1 concentrations decrease with protein and calorie restriction and with malnutrition [38]. Increasing protein intake in adequately fed individuals may also affect IGF-1 and IGF binding protein concentrations. The addition of a soy protein supplement to a low-fat/high-fiber dietary intervention or usual diet reduced IGFBP-3 concentrations and increased IGF-1/IGFBP-3 ratio in premenopausal women [33]. In postmenopausal women, the addition of either a 40-g/d milk protein or soy protein supplement to their usual diets increased circulating IGF-1 concentrations, although the women concomitantly reduced their protein intake from other sources and ended the 3-month study with a similar total protein intake to baseline [39]. Similarly, IGF-1 concentrations were significantly increased by consumption of soy protein supplements in healthy men [40] and patients with prostate cancer [41]. In the present study, the diets were designed so that the percentage of energy from protein was equivalent (15% of energy) among the 3 test diets; therefore, the significant changes that we observed in IGF-1 (LFn3) and IGFBP-3 (LF and LFn3) were not caused by differential protein intake.

Insulin-like growth factor 1 concentrations decrease with age, and the effects of aging (decreased bone mineral density and lean body tissue, increased fat mass, and a high-risk cardiovascular profile) mirror the symptoms of GH deficiency [6]. Increasing the concentration of IGF-1 with pharmacologic GH replacement is accompanied by a number of symptoms related to water retention [42], and therefore, the possibility of raising IGF-1 concentrations with a dietary intervention is desirable. Further studies using the addition of n-3 fatty acids to the diet and assessment of IGF-1 concentrations and effects on the symptoms of aging are warranted.

On the other hand, there have been reports of associations between IGF-1 and breast cancer risk. This association appears to depend on menopausal status, with most studies showing no association between relatively increased IGF-1 concentrations and breast cancer risk in postmenopausal women [43].

Current data do not suggest that the increase in IGF-1 with the LFn3 diet in our postmenopausal female study participants is likely to increase risk of breast cancer.

Strengths of this study include the controlled nature of the study. Participants were provided with all food for each 8-week treatment; therefore, diet was not self-reported. Also, participants crossed over from one treatment to another, and this attributed to increased statistical power for each participant. This study is not without limitations. The results of this trial should be regarded with caution because of the small sample size. Although our study was a crossover trial, imparting stronger statistical power than if each participant had completed only one dietary treatment, the sample size is still regarded as being relatively small and differences in the end points measured may not have been detected because of the high variability and small sample size. Also, as previously mentioned, the length of each dietary intervention was 8 weeks, which may not be long enough to show long-term changes in the analytes.

The results of this controlled dietary intervention in postmenopausal women indicate that the addition of n-3 fatty acids to a low-fat diet increases IGF-1 and IGFBP-3 concentrations, whereas low-fat diet with no additional n-3 fatty acids increases IGFBP-3 only. The effects of increasing IGF-1 concentrations on cancer risk is unknown; however, an increase in circulating IGF-1 may be beneficial in preventing the reduced bone and lean mass associated with aging.

Acknowledgment

We would like to thank the participants for their serious commitment to this study and the General Clinical Research Center staff for their assistance with clinical work and preparation of the study diets. We thank Douglas Yee for his comments and review of the manuscript. Funding for this work was provided by grants from the Department of Defense (WB1XWH-04-1-0448 and W81XWH-06-1-0778) and the National Center for Research Resources, National Institutes of Health (Mo1-RR00400). Salmon of the Americas, Inc, donated salmon fillets for the controlled diets. The authors declare no conflict of interest.

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