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.

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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

increases the half-life of IGF-I [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 with malnutrition [7,8] and protein and calorie restriction [9] and 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/m^2 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 isoenergenic 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