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A high-legume low-glycemic index diet reduces fasting plasma leptin in middle-aged insulin-resistant and -sensitive men

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Abstract

Fasting leptin and ghrelin levels were measured in 36 insulin-sensitive (IS) and 28 insulin-resistant (IR) men who consumed a legume-enriched low-glycemic index (LG) diet or healthy American (HA) diet in a randomly ordered cross-over feeding study consisting of two 4-week periods. Weight remained stable over the entire study. Fasting plasma leptin was significantly reduced from pre-study levels by both the LG (18.8%, $P<0.001$) and HA (16.1%, $P<0.001$) diets, whereas fasting ghrelin did not change. By subgroup analysis according to prestudy insulin status, leptin was reduced in IR subjects after both the LG (17.1%, $P<0.01$) and the HA (33.3%, $P<0.001$) diets, whereas IS subjects responded only after the LG diet (23.1%, $P<0.01$). Thus, a legume-rich LG index diet may be a beneficial strategy for reducing circulating leptin concentrations, even under conditions of weight maintenance.

Keywords

ghrelin; insulin resistance; legume-enriched diet; leptin

Introduction

Leptin, a 16-kDa protein encoded by the *obese* (*ob*) gene, is produced primarily by the adipose tissues and is thought to have a key role in weight maintenance. In a well-known animal experiment, leptin administration to leptin-deficient *ob/ob* mice led to reduced food intake, weight loss and increased energy expenditure (Halaas *et al.*, 1995; Pelleymounter *et al.*, 1995). Grelin, a 28-amino-acid peptide, is a gut hormone primarily produced by the endocrine cells of the stomach. Ghrelin administration stimulates food intake in humans through increasing appetite and gastrointestinal motility (Karhunen *et al.*, 2008).

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Conflict of interest
The authors declare no conflict of interest.

Epidemiological and clinical studies have shown that increased dietary fiber consumption is associated with a lower risk for heart disease (Kushi *et al.*, 1999; Bazzano *et al.*, 2001), type 2 diabetes (Ylonen *et al.*, 2003), and obesity (Ludwig *et al.*, 1999; Liu *et al.*, 2003). Metabolic studies suggest that fiber may contribute to postprandial satiety via changes in gut hormones, such as leptin and ghrelin (Chearskul *et al.*, 2009). To date, a number of animal studies have evaluated the long-term effect of fiber consumption on these hormones (Wang *et al.*, 2007; Maurer *et al.*, 2009); the studies showed that increasing fiber consumption in daily diets significantly lowered fasting leptin and ghrelin concentrations. Despite promising animal data, human feeding investigations are limited.

The Legume Inflammation Feeding Experiment Study was a randomized controlled cross-over feeding study designed to determine the effects of a legume-enriched low-glycemic index diet on biomarkers of inflammation and insulin resistance in men at high risk for colorectal cancer. An important secondary objective of the Legume Inflammation Feeding Experiment Study was to evaluate the effects of the dietary intervention on fasting plasma leptin and ghrelin. To our knowledge, this was the first randomized controlled cross-over feeding study to evaluate the effects of mixture of legumes (pinto, navy, kidney, lima and black beans) constituting a LG diet, on changes in these hormones under conditions of weight maintenance.

Subjects and methods

All aspects of this study were approved by the Institutional Review Boards of the Pennsylvania State University and the National Cancer Institute. A detailed explanation of inclusion criteria was published previously (Hartman *et al.*, 2010). Briefly, we recruited 64 non-smoking men (35–75 yrs), who had undergone colonoscopies within the previous 2 years. Subjects had no history of inflammatory bowel disease, stroke, diabetes, colorectal or any cancers. They were not using vitamin, herbal, fiber or other nutritional supplements or any medications known to affect cholesterol, inflammation or glucose. Insulin resistance status was ascertained by homeostasis model assessment index level (Matthews *et al.*, 1985). Subjects were defined as insulin-resistant (IR) if their homeostasis model assessment index values were higher than 2.6 (Gazzaruso *et al.*, 2006). Eligible subjects had a resting metabolic rate test and three random 24-h telephone diet recalls (two weekdays and one weekend) to estimate energy requirements.

Subjects received both a 4-week legume-enriched diet (LG; with approximately 1.5 cups of cooked bean mixture per 2000 kcal) and a 4-week isocaloric healthy American (HA) diet in random order, separated by a 2–4-week compliance break. Both the HA and the LG diets were well tolerated. Calorie intake was adjusted by study dietitians in order to maintain participants' body weights throughout the study. Fasting blood samples (12-hour overnight) were collected at the beginning and end of each dietary period. All of each subject's samples were grouped together for analysis in the same batch. Plasma leptin was measured using a human enzyme-linked immuno sorbent assay (EZHL-80SK, Linco, Billerica, MA, USA). Plasma ghrelin was measured using ghrelin (total) radioimmunoassay (GHRT-89HK, Linco).

Statistical analysis

Baseline characteristics stratified by subjects' insulin resistance status were compared using one-way ANOVA. General linear mixed models were used to test for the effects of diet, period and their interactions for all continuous outcomes using Proc Mixed in SAS. The analyses were also conducted by IR stratification. There was no evidence that adenoma status was an important effect modifier (Hartman *et al.*, 2010). Calculations were performed

using SAS version 9.1 (SAS Institute, Cary, NC, USA). The results are reported as least square means (95% confidence interval (CI)). Significance was set at $P<0.05$.

Results

Subjects' baseline characteristics of other endpoints were published previously (Hartman *et al.*, 2010). IR subjects had higher leptin (11.1 ng/ml (95% CI): 8.7–13.4 vs 5.2 ng/ml (95% CI: 3.6–6.8), $P<0.001$) and lower ghrelin (578 pg/ml (95% CI: 470–685) vs 742 pg/ml (95% CI : 653–832), $P = 0.02$) levels than insulin-sensitive (IS) subjects (Table 2).

Diet-related changes in fasting leptin and ghrelin levels are presented in Table 1. Fasting leptin was reduced 18.8%, $P<0.001$ and 16.1%, $P<0.001$, respectively, in the LG and HA groups, and without between-diet difference. There was no effect of diet on fasting ghrelin concentrations.

Changes in fasting leptin and ghrelin according to IR and IS status at entry into the study are shown in Table 2. The LG diet led to significant reductions in fasting leptin concentration in both IR and IS subjects (IR, 17.1%, $P<0.01$; IS, 23.1%, $P<0.001$); however, the difference between reductions of IR and IS subjects were not statistically significant. On the HA diet, fasting leptin concentration was reduced significantly in IR subjects (33.3%, $P<0.001$), but not in IS subjects. Compared with IS subjects, IR subjects showed a greater reduction in fasting leptin concentration ($P<0.01$) after the HA diet.

Discussion

In the Legume Inflammation Feeding Experiment Study under conditions of weight maintenance, both the LG and the HA diets favorably decreased fasting plasma leptin concentrations. We compared the differences of the major nutrients and food profiles and observed that both the LG and HA test diets were more healthful than the subjects' pre-study diets (Hartman *et al.*, 2010). Thus, the HA diet, used as our control, provided an improved diet compared with the subject's habitual diet. Additionally, compared with the HA diet, the LG diet had significantly lower glycemic index and glycemic load and included more dietary fiber. Possibly, this healthy dietary regimen shifted metabolism in the IR subjects thus, improving their fasting leptin concentrations.

The Legume Inflammation Feeding Experiment study found that a 4-week high-legume low-glycemic index diet had no effects on fasting total ghrelin values. Perhaps intervention duration was not sufficiently long, or the assay of total ghrelin may have missed an effect of acylated ghrelin, which is believed to function as the active form, whereas desacylated ghrelin is considered an antagonist (Asakawa *et al.*, 2005; Chen *et al.*, 2005).

Our findings demonstrate that 40 g of dietary fiber consumption from a mixture of 1.5 cups of navy, pinto, kidney, lima and black beans in our LG diet lowered fasting leptin levels during weight maintenance, but had no effect on fasting ghrelin concentrations. Our study thus suggests that a dietary improvement that includes high-legume consumption may be effective in reducing plasma leptin in men regardless of insulin resistance status.

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Table 1

Effects of diets on study endpoints[a]

Variable	*Study entry*[b]	*ΔLG*[c]	P-*value*	*ΔHA*[d]	P-*value*	*ΔLG–Δ HA*[e]	P-*value*
Leptin, ng/ml[f]	7.8 (6.3, 9.3)	−1.5 (−2.1, −0.8) (18.8%)	<0.001	−1.3 (−1.9, −0.6) (16.1%)	<0.001	−0.2 (−1.1, 0.6)	0.15
Ghrelin, pg/ml	670 (600, 741)	−15 (−49, 18) (2.3%)	0.36	19 (−20, 58) (2.9%)	0.33	−34 (−80, 11)	0.14

[a] Values are reported as mean (95% confidence interval); $n = 64$.

[b] Baseline values at study entry.

[c] ΔLG = change over the legume-enriched diet.

[d] ΔHA = change over the isocaloric healthy American diet.

[e] ΔLG–ΔHA = change between the two diets.

[f] Data were log-transformed for the analysis.

Table 2

Effects of diets on leptin and ghrelin among subjects stratified by IR status[a]

Variable	*IR* (n = *28*)			*IS* (n = *36*)			*Difference between IR and IS*[b]	
LG Diet **(n = *64*)**	***Study entry***[c]	***Change over the LG diet***	**P-*value***	***Study entry***[d]	***Change over the LG diet***	**P-*value***	***IR–IS***	**P-*value***
Leptin, ng/ml[e]	11.1 (8.7, 13.4)[f]	−1.9 (−2.9, −0.9) (17.1%)	<0.01	5.2 (3.6, 6.8)[f]	−1.2 (−2.1, −0.2) (23.1%)	<0.01	−0.7 (−2.1, 0.6)	0.76
Ghrelin, pg/ml	578 (470, 685)[g]	−2 (−52, 49) (0.3%)	0.95	742 (653, 832)[g]	−26 (−71, 19) (3.5%)	0.25	24 (−44, 92)	0.48
HA diet (n = *64*)	*Study entry*[c]	*Change over the HA diet*	P-*value*	*Study entry*[d]	*Change over the HA diet*	P-*value*	IR – IS	P-*value*
Leptin, ng/ml[e]	11.1 (8.7, 13.4)[f]	−2.6 (−3.4, −1.7) (33.3%)	<0.001	5.2 (3.6, 6.8)[f]	−0.2 (−1.0, 0.5) (3.9%)	0.22	−2.3 (−3.5, −1.1)	<0.01
Ghrelin, pg/ml	578 (470, 685)[g]	43 (−17, 102) (6.4%)	0.15	742 (653, 832)[g]	1 (−52, 53) (0.1%)	0.98	42 (−37, 122)	0.29

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; HA diet, healthy American diet; IR, insulin resistant; IS, insulin sensitive; LG diet, low-glycemic diet.

[a] Values are reported as mean (95% CI).

[b] IR–IS = difference in changes between IR and IS subjects.

[c] Plasma leptin and ghrelin at study entry among IR subjects.

[d] Plasma leptin and ghrelin at study entry among IS subjects.

[e] Data were log-transformed for the analysis.

[f] Leptin values at study entry were stratified by subjects' IR status; difference between IR and IS subjects was significant based on one-way ANOVA (11.1 vs 5.2 ng/ml, $P<0.001$).

[g] Ghrelin values at study entry were stratified by subjects' IR status; difference between IR and IS subjects was significant based on one-way ANOVA (578 vs 742pg/ml, $P = 0.02$).