Adiponectin and 8-epi-PGF2α as intermediate influence factors in weight reduction after legumes consumption: a 12-week randomized controlled trial

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Research

Keywords: legumes, obesity, body weight, adiponectin, 8-epi-PGF2α, insulin resistance

Posted Date: July 27th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-46032/v1

Abstract

Background and Aims:

The current nutritional intervention study was designed to determine the effect of legume on body weight in obese subjects.

Methods

Randomized controlled study of 12 weeks with 383 participants (body mass index $\geq$ 25 kg/m^2) was enrolled for the study. The intervention program consisted of replacing 1/3 refined rice intake with legumes three times per day as a carbohydrate source in high fat diet group. In contrast, low fat diet group was recommended to eat as their usual diet.

Results

In high fat diet group, intake of energy and carbohydrate were lower, while the intake of fat and protein were higher. Mean weight loss at 12 weeks was 2.87 ± 0.21 kg and 0.17 ± 0.11 kg in the high fat diet group and low fat diet group, respectively, and was significantly different between groups (P< 0.001). HDL-cholesterol and adiponectin were increased, while glucose, insulin, triglyceride, HOMA-IR index, and 8-epi-$PGF_{2\alpha}$ were decreased at 12 weeks in the high fat diet group compared with baseline.

Conclusions

The conclusion is that the consumption of legumes may accelerate weight loss accompanied by regulation of adiponectin and 8-epi-$PGF_{2\alpha}$ in obese subjects. Also, increases in plasma adiponectin induced by a larger amount of weight loss may relate to greater activation of insulin resistance.

Trial registrations:

NCT04392882 (Registered 19 May 2020 - Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT04392882?cond=NCT04392882&draw=2&rank=1)

Background

Obesity has been considered as one of the most serious health problems in Korea. As the prevalence of obesity, including severe obesity, has been increasing in Korea, a change of Asians' diagnostic standard for obesity seems to be needed.[1] Obesity is a significant risk factor for many metabolic diseases like cardiovascular diseases (CVD), diabetes, and certain types of cancer, also associated with higher mortality.

Numerous data have shown a negative relationship between the consumption of legumes and obesity and metabolic syndrome.[2–4] Alizadeh et al., indicated that consumption of a legumes-rich hypocaloric diet for six weeks reduced waist, hip, triceps, biceps, subscapular, and skinfold thicknesses among healthy premenopausal women with central obesity.[5] Several cross-sectional and prospective studies have also supported the inverse association of legume consumption with obesity and CVD.[6,7] Besides the beneficial effects of non-soy legumes, a large body of documents is available regarding the impact of soy consumption on controlling and preventing cardiometabolic risks, improving features of the metabolic syndrome following a short-term period of soy consumption.[8,9] Weight reducing effect of soy intake[10] and favorable outcomes for type II diabetes,[11,12] are some aspects of these beneficial effects. Several investigations have confirmed that chronic non-communicable conditions such as insulin resistance, diabetes, and CVD have a close link to obesity.[13]

For a long time, legumes are nutritionally recognized for their high protein content as well as for their soluble-fiber and other bioactive compounds.[14] According to a study with an LC-MS-metabolomic approach, 43 compounds showed differences between the three different legumes (chickpea, lentil, white bean). Among them, 30 compounds were kind of polyphenols, mainly flavonol or flavanol, and others are α-galactosides, fatty acyls, prenol lipids, nucleoside, and organic compounds.[15] Like this, there are various bioactive compounds in legumes. While the effects of dietary fiber on serum lipoproteins have received much attention, other bio-functional components in legumes could likely be involved in the cardioprotective results.[16] Dietary soy protein's beneficial effects on lipid profiles are well documented, and several studies have suggested that soy intake aids against oxidative stress with antioxidant capacity.[17,18]

Here, we designed a nutritional intervention study to determine whether a diet enriched in legumes could accelerate weight loss accompanied by regulation of adiponectin and 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$).

Methods

Subjects and study design

A 12-week weight reduction program conducted by the National Leading Research Laboratory of Clinical Nutrigenetics/Nutrigenomics at Yonsei University. 400 subjects with a body mass index (BMI) of 25 kg/m^2 or higher based on Asia-Pacific guideline[19] were recruited at the health promotion center of the National Health Insurance Corporation Ilsan Hospital in Goyang, Korea between March 2011 and December 2012. Based on personal health, medical history questionnaire, people who had a history of type 2 diabetes, CVD, psychiatric problems, thyroid disorders, liver or kidney disease, and/or use of any medications (antihypertensive, lipid-lowering, antiplatelet, antidiabetic, etc.) were excluded. The paper-based informed consent forms were obtained and the Institutional Review Board of the Yonsei University approved the study protocol, which complied with the Declaration of Helsinki.

Weight loss protocol and calorie intake

One week before starting the 12-week program, the enrolled subjects' usual diet information was obtained using both a 24-h recall method and a semi-quantitative food frequency questionnaire. Registered dietitian gave written and verbal instructions on completion of a 3-day (2 weekdays and one weekend) dietary record.

After a week, the intervention started. Individually-planned diets for each subject were provided based on their dietary data previously obatained before, and Korean Recommended Dietary Allowance (Korean RDA, Korean Nutrition Society, Seoul, Korea). The intervention program consisted of replacing 1/3 refined rice intake with legumes three times per day as a carbohydrate source in high-fat diet group (HFD) while low-fat diet group (LFD) were recommended to eat as their usual diet and increased vegetable intake to at least six units (30–70 g/unit) per day. The subjects were assigned physical activity consisting of a regular 30-min walk after dinner each day, also instructed to record their physical activity for 24-h every four weeks.

Participants' compliance was checked by the dietician, interviewing them biweekly by telephone. They were interviewed whether they were following the program well, including dietary intake and physical activity. Dietary energy values and nutrient content were calculated using the Computer-Aided Nutritional analysis program (CAN-pro 2.0, Korean Nutrition Society, Seoul, Korea) based on 3-day food records. Basal metabolic rate, physical activity for 24-h, and specific dynamic action of food were considered for total energy expenditure (kcal/day) of each subject.

Anthropometric parameters, blood pressure, and blood collection

Body weights and heights were measured for BMI (kilograms per square meter) calculating. Blood pressure (BP) was measured in the left arm of seated patients with an automatic BP monitor (TM-2654; A&D, Tokyo, Japan) after resting. After 12-h fast, venous blood specimens were collected in EDTA-treated or untreated tubes. Separated plasma and serum were stored at − 70 °C until used in further analysis.

Serum glucose, insulin, lipid profiles, serum high sensitivity C-reactive protein, and urinary 8-epi-prostaglandin $F_{2\alpha}$

Detailed information about assessments of fasting glucose, insulin, serum high sensitivity C-reactive protein (hs-CRP) was described in our previous study[20]. Analysis of triglycerides and total-cholesterol performed using a Hitachi 7150 Autoanalyzer (Hitachi Ltd., Tokyo, Japan). HDL-cholesterol separated from participated apoB-containing lipoproteins with dextran sulfate-magnesium was measured

Loading [MathJax]/jax/output/CommonHTML/jax.js ed using the Fridewald formula in serum triglyceride $\leq$ 400 mg/dL subjects. The compound 8-epi-$PGF_{2α}$ was measured in urine using an enzyme immunoassay (BIOXYTECH urinary 8-epi-$PGF_{2α}$ TM Assay kit, OXIS International Inc., Portland, OR).

Homeostasis-model assessment of insulin resistance and adiponectin

Insulin resistance (IR) was calculated by the homeostasis-model assessment (HOMA): [fasting insulin (μIU/mL) × fasting glucose (mmol/L)] /22.5. Plasma adiponectin concentration was measured by an enzyme immunoassay (Human Adiponectin ELISA kit, B-Bridge International Inc., CA, USA) and Victor2 (Perkin Elmer Life Sciences, Turku, Finland).

Statistical analyses

We performed statistical analyses using SPSS ver 25.0 (SPSS Inc., Chicago, IL, USA). Before statistical analyses, the skewed variables were logarithmically-transformed. To evaluate differences of clinical variables levels between two groups, independent t-tests were used. For analyzing differences between baseline/12-week follow-up time scale, paired t-tests were used. Pearson's correlation coefficients were used to investigate the relationships between variables over time.

Results

Among the enrolled subjects (n=400), 17 dropped out, 8 dropped out in HFD group and 9 dropped out in LFD group by the end of the 12-week dietary intervention for personal reasons or poor compliance, leaving 383 subjects.

Clinical characteristics and nutrient intake before and after dietary intervention

After 12-week follow-up in HFD group, weight (P<0.001), systolic blood pressure (SBP) (P=0.037), diastolic blood pressure (DBP) (P=0.001), and daily nutrient intake, especially, energy intake (P<0.001) and carbohydrate intake (P<0.001) were decreased (Table 1). However, total energy expenditure (TEE) (P<0.001), protein (P=0.027), fat (P<0.001), and fiber (P=0.003) intake were increased. These result patterns were not showed in the LFD group after the intervention, except TEE (P<0.001) and fiber intake (P=0.037) were increased. Between HFD and LFD group, weight, BMI, energy intake, carbohydrate, and fat intake showed significant after 12-week follow-up and changed values (difference from baseline), while SBP showed significant only in 12-week (Table 1).

Serum glucose, insulin, lipid profiles, hs-CRP, and 8-epi-$PGF_{2α}$

In HFD group, glucose (P<0.001), insulin (P<0.001), and 8-epi-$PGF_{2α}$ (P=0.021) had decreased after the 12-

0.001) had significantly increased (Table 2). Unlike HFD group, there were no changes and significant differences shown in LFD group. Compared with HFD and LFD groups, HDL-cholesterol (*P*=0.003), fasting glucose (*P*=0.039), and insulin (*P*<0.001) were significantly different at the end of the 12-week intervention period. Besides, the changed value of insulin (*P*=0.020) was significantly different between the two groups; also, 8-epi-$PGF_{2\alpha}$ tended to different after the 12-week intervention period (Table 2).

Triglyceride, HOMA-IR index, and adiponectin

Triglyceride (*P*<0.001) and HOMA-IR index (*P*<0.001) significantly decreased, and adiponectin (*P*<0.001) increased at the end of the 12-week follow-up in HFD group, while LFD group had not shown any differences after a dietary intervention (Figure 1). Between HFD and LFD group, the HOMA-IR index was significantly different at follow-up (*P*<0.001) and difference from baseline (*P*=0.016), as similar to adiponectin change was significantly different at follow-up (*P*<0.001) and difference from baseline (*P*<0.001). In the case of triglyceride, only at the end of the 12-week follow-up tended to differentiate between two groups (Figure 1).

Correlations among changes in BMI, HDL-cholesterol, HOMA-IR index, and adiponectin

In total, 383 subjects, changes in BMI and HDL-cholesterol (r=-0.146, *P*=0.004), and changes in BMI and adiponectin negatively correlated (r=-0.314, *P*<0.001) in a linear manner (Figure 2). Changes in BMI positively correlated with changes HOMA-IR index (r=0.154, *P*=0.003). In HFD group, only changes in BMI negatively correlated with changes in adiponectin (r=-0.271, *P*=0.003). In the case of LFD group, changes BMI and HDL-cholesterol negatively correlated (r=-0.161, P=0.016), while changes BMI tended positively associated with changes HOMA-IR index and negatively correlated with changes adiponectin (Figure 2).

Relationship among adiponectin, hs-CRP, 8-epi-$PGF_{2\alpha}$, anthropometric, and biochemical markers before and after 12-week intervention

All subjects in baseline, though adiponectin negatively correlated with weight (r=-0.150, *P*=0.009), triglyceride (r=-0.202, *P*<0.001), glucose (r=-0.140, *P*=0.015), insulin (r=-0.115, *P*=0.048), HOMA-IR index (r=-0.150, *P*=0.010), and hs-CRP (r=-0.129, *P*=0.026), positively correlated with HDL-cholesterol (r=0.162, *P*<0.001) and LDL-cholesterol (r=0.162, *P*=0.005). At the end of the 12-week intervention, adiponectin negatively correlated with triglyceride (r=-0.349, *P*<0.001), HDL-cholesterol (r=0.189, *P*=0.042), insulin (r=-0.236, *P*=0.012), and HOMA-IR (r=-0.215, *P*=0.022) in HFD group. However, in LFD group, adiponectin negatively correlated with triglyceride and glucose (r=-0.193, *P*=0.029; r=0.204, *P*=0.021, respectively), and positively correlated with HDL-cholesterol (r=0.352, *P*<0.001) after follow-up. In case of hs-CRP, insulin [illegible]015), and 8-epi-$PGF_{2\alpha}$ (r=0.431, *P*<0.001) were positively correlated, and positively tended to correlated with triglyceride in HFD group at 12-week period. These result patterns were shown in LFD group as similar as HFD group after intervention. Furthermore, 8-epi-$PGF_{2\alpha}$ was positively correlated with glucose, insulin, and HOMA-IR (r=0.264, P=0.002; r=0.219, P=0.010; r=0.264, P=0.002, respectively) in HFD group at the end of the 12-week intervention, also, these relationships were shown in LFD group likewise HFD group.

Discussion

The present study suggests that a 12-week legume enriched-diet may improve clinical variables in obese subjects. After 12 weeks, legume enriched-diet groups had significant reductions in body weight and BMI. However, the significant differences were not observed in the control group who intake the usual diet with increased vegetable. According to the Korea Health Statistics 2011: Korea National Health and Nutrition Examination Survey (KNHANES V-2), populations who live in cities consume approximately 19.6% of total calories from fat. Based on this data, our results showed significantly different between HFD and LFD group after a 12-week intervention (22.0 ± 0.29 vs. 19.7 ± 0.21).

Our results are partly following some clinical studies.[21] Papanikolaou and Fulgoni[22] reported a relationship between bean consumption and obesity risk in about 8000 adult participants in the NHANES 1999–2002 using data obtained by the 24-h dietary recall. They found that people who had consumed a variety of beans or baked beans presented significantly low body weight compared with those who had not consumed beans. Also, the odds of being obese (BMI > 30 kg/m^2) was significantly lower in variety bean and baked bean consumers, (odds ratio = 0.78 and 0.77, respectively). Venn et al. showed a slightly different result. This has shown that the incorporation of pulses and whole grain foods into a weight loss program resulted in an essential reduction in waist circumference compared to the control diet, although weight loss was no difference between groups.[23] Also, no relationship between legume consumption and the odds of metabolic syndrome is reported in a recent meta-analysis study.[24]

Adiponectin identified as an adipocytokine in the human adipose tissue has antiatherosclerotic and antidiabetic properties. Blood levels of adiponectin are low in metabolic syndrome including obesity, diabetes, and CVD. Several studies have reported that weight loss in massively obese subjects is associated with serum adiponectin concentration increase.[26,27] The present study demonstrated that a decrease in BMI correlated with an increase in adiponectin at an obese subject. Yannakoulia et al. noted that whole grain intake has an association with high adiponectin levels. In a cross-sectional study of 220 healthy Mediterranean women, adherence to a dietary pattern characterized by high consumption of legumes, whole grain cereals, and low-fat dairy products was positively associated with adiponectin levels after controlling potential confounders.[25] Adiponectin activates peroxisome proliferator-activated receptor (PPAR)-α and activated protein kinases (AMPK). PPAR-α and AMPK increase the utilization of fatty acids, glucose in skeletal muscle. Their control of gluconeogenesis, glycogenolysis, and lipid content in the liver can lower insulin resistance. Our results showed plasma adiponectin levels has a negative correlation with body weight, HOMA-IR, and hs-CRP and positive relationship with HDL-cholesterol, which is the same as previous studies.[28,29] Also, the HFD group had significant decreases in HOMA-IR and significant increases in adiponectin levels after the 12-week intervention. These data suggest that a more substantial amount of weight loss could affect increases in plasma adiponectin which may control insulin and glucose metabolism normally.

To further assess the effect of the dietary legumes on oxidative stress, urinary excretion of 8-epi-$PGF_{2\alpha}$ was measured.[30,31] As this marker decreased after the intervention, a diet enriched in legumes showed effects by mitigating oxidative stress. Accumulated fat induce production of reactive oxygen species (ROS) and lipid peroxidation by-products. These compounds are closely related to pro-inflammatory state with increasing inflammatory cytokines secretion, and macrophage infiltration. To sum up, our outcome appeared in addition to the recognized beneficial effect associated with weight loss. Another possible contribution to the reduction in oxidative stress is natural antioxidants in legumes. Several studies measured the direct impact of legumes on oxidative stress *in vitro.* Nicola[32] demonstrated lentils' antioxidant capacity using DPPH, ABTS assay, although this effect decreased slightly after the boiling process.

The point that dietary intake information of participants was collected from self-reports is a limitation of our study. However, measurement errors from self-reported nutritional intake and lifestyle variables have been shown to be relatively small.[33]

Conclusions

Our data suggest that legumes enriched diet may help control body weight in overweight and obese subjects with associated with adiponectin and 8-epi-$PGF_{2\alpha}$. Also, increases in plasma adiponectin induced by a more considerable amount of weight loss may relate to greater activation of insulin resistance. Further studies, including more extensive clinical studies with subjects who are extremely obese and have been obese for more extended periods, are needed to confirm the beneficial effects of legume on weight reduction.

Abbreviations

8-epi-$PGF_{2\alpha}$: 8-epi-prostaglandin $F_{2\alpha}$; AMPK: activated protein kinase; BMI: Body mass index; BP: Blood pressure; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; HFD: High fat diet group; HOMA: Homeostasis-model assessment; hs-CRP: High sensitivity C-reactive protein; IR: Insulin resistance; LFD: Low fat diet group; PPAR: peroxisomes proliferator-activated receptor; SBP: Systolic blood pressure; TEE: Total energy expenditure

Declarations

Ethics approval and consent to participate: The Institutional Review Board of the Yonsei University approved the study protocol, which was conducted under the Helsinki Declaration.

Consent for publication: The paper-based informed consent forms, stored in a document system after obtaining the necessary signatures, were used to record the intent and identify the will to join in the research.

Availability of data and materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science and ICT (2012M3A9C4048762 and NRF-2017R1C1B2007195) and Ministry of Education (NRF-2019R1I1A2A01061731).

Authors' contributions: YH, JHL, and MK analyzed data; JHL and MK developed the study protocol and design; all of authors read, commented on, and contributed to the manuscript; JHL and MK provided research funding and developed the study protocol. MK is the guarantor of this work, had full access to all data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments: The authors thank the research volunteers who participated in the studies described in this article.

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Tables

Table 1. Clinical characteristics and macronutrient indices at baseline and at the end of the 12-week dietary intervention period of the participants

	High fat diet (n=160)	Low fat diet (n=223)	*P*-value
Male/female (%)	42.5 / 57.5	41.7 / 58.3	0.876
Age (year)	49.4±1.12	48.5±0.85	0.530
Weight (kg)			
Before	74.5±0.85	74.1±0.69	0.758
After	71.6±0.85***	74.0±0.68	0.029
Change	-2.87±0.21	-0.17±0.11	<0.001
Body mass index (kg/m^2)			
Before	27.6±0.21	27.4±0.16	0.329
After	26.5±0.21***	27.3±0.16	0.003
Change	-1.09±0.08	-0.06±0.04	<0.001
Systolic BP (mmHg)			
Before	125.2±1.30	128.6±1.21	0.067
After	122.8±1.23*	128.3±1.05	0.001
Change	-2.41±1.14	-0.21±0.98	0.145
Diastolic BP (mmHg)			
Before	79.5±0.85	79.9±0.77	0.720
After	76.8±0.80**	78.6±0.77	0.096
Change	-2.63±0.77	-1.29±0.66	0.187
Total energy expenditure (kcal/d)			
Before	2218.5±29.6	2192.1±23.4	0.479
After	2308.1±31.2***	2265.3±24.2***	0.273
Change	89.6±12.8	73.3±12.3	0.366
Estimates of daily nutrient intake			
Energy intake (kcal)			
Before	2389.5±27.9	2380.0±29.8	0.824
After	2147.1±39.1***	2333.2±30.7	<0.001
Change	-242.4±42.5	-52.1±34.6	0.001
Carbohydrate (%)			
Before	60.1±0.47	60.6±0.32	0.363
After	57.7±0.41***	59.9±0.40	<0.001
Change	-2.35±0.52	-0.69±0.51	0.027
Protein (%)			
Before	20.5±0.39	20.3±0.25	0.699
After	21.5±0.38*	21.3±0.51	0.820
Change	0.99±0.44	1.03±0.56	0.968
Fat (%)			
Before	19.5±0.41	19.7±0.27	0.729
After	22.0±0.29***	19.7±0.21	<0.001
Change	2.47±0.43	-0.04±0.32	<0.001
Fiber (g)			
Before$^{\oint}$	11.8±0.52	12.1±0.60	0.176
After$^{\oint}$	14.5±0.69**	14.1±0.65*	0.120
Change	2.77±0.72	2.05±0.58	0.431

Means ± SEM.$^{\oint}$tested by logarithmic transformation, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared with baseline values in each diet group tested by paired *t*-test. *P*-values derived from independent *t*-test.

Table 2. Effects of dietary intervention on lipid profiles, glucose, insulin, hs-CRP, and 8-epi-$PGF_{2\alpha}$ at baseline and 12-week follow-up

	High fat diet (n=160)	Low fat diet (n=223)	*P*-value
LDL-cholesterol (mg/dL)			
Before$^{\oint}$	111..0±2.44	114.6±2.60	0.918
After$^{\oint}$	108.0±2.61	113.1±2.50	0.196
Change	-2.99±2.03	-1.50±2.17	0.616
HDL-cholesterol (mg/dL)			
Before$^{\oint}$	45.6±0.98	43.7±0.78	0.165
After$^{\oint}$	48.1±0.88***	44.8±0.80	0.003
Change	2.48±0.76	1.55±0.63	0.342
Glucose (mg/dL)			
Before$^{\oint}$	97.4±1.82	99.3±1.78	0.531
After$^{\oint}$	93.8±2.65***	97.9±1.99	0.039
Change	-3.59±1.94	-1.41±1.63	0.388
Insulin (uIU/mL)			
Before$^{\oint}$	11.8±0.54	10.8±0.36	0.446
After$^{\oint}$	9.17±1.07***	10.6±0.52	<0.001
Change	-2.58±0.96	-0.17±0.53	0.020
Free fatty acid (uEq/L)			
Before$^{\oint}$	532.4±1.8.0	524.9±17.3	0.572
After$^{\oint}$	507.5±20.1	503.0±16.3	0.952
Change	-24.8±18.8	-21.9±17.7	0.911
[1]hs-CRP (mg/dL)			
Before$^{\oint}$	1.97±0.08	2.09±0.09	0.707
After$^{\oint}$	1.89±0.09	2.09±0.11	0.854
Change	-0.19±0.07	0.00±0.10	0.132
8-epi-$PGF_{2\alpha}$ (pg/mg creatinine)			
Before$^{\oint}$	1330.5±81.9	1346.4±66.7	0.504
After$^{\oint}$	1216.6±80.7*	1299.2±65.5	0.077
Change	-56.3±75.7	-36.7±65.9	0.844

Means ± SEM.$^{\oint}$tested by logarithmic transformation, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ compared with baseline values in each diet group tested by paired *t*-test. *P*-values derived from independent *t*-test. [1]hs-CRP = high sensitivity C-reactive protein.

Figures

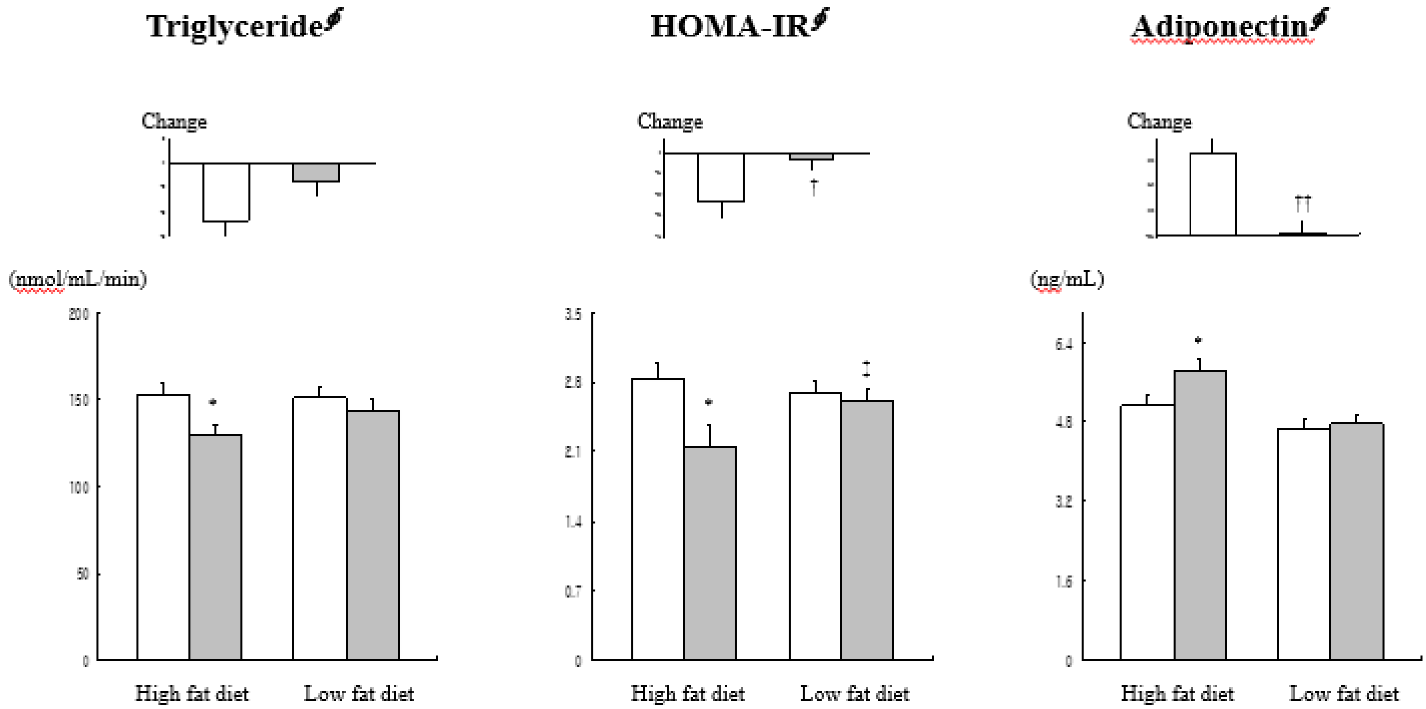

Figure 1

Effects of legume consumption on triglyceride, HOMA-IR index, and adiponectin before (□) and after 12-week (■) dietary intervention Means ± S.E., §Tested by log-transformed. *P<0.001 compared to baseline values in each group tested by paired t-test. P-values derived from independent t-test. P': after adjusting for baseline value. ‡P<0.001 compared between two groups at 12-week follow-up and †P<0.05, ††P<0.001 compared between two groups at changed values tested by independent t-test.

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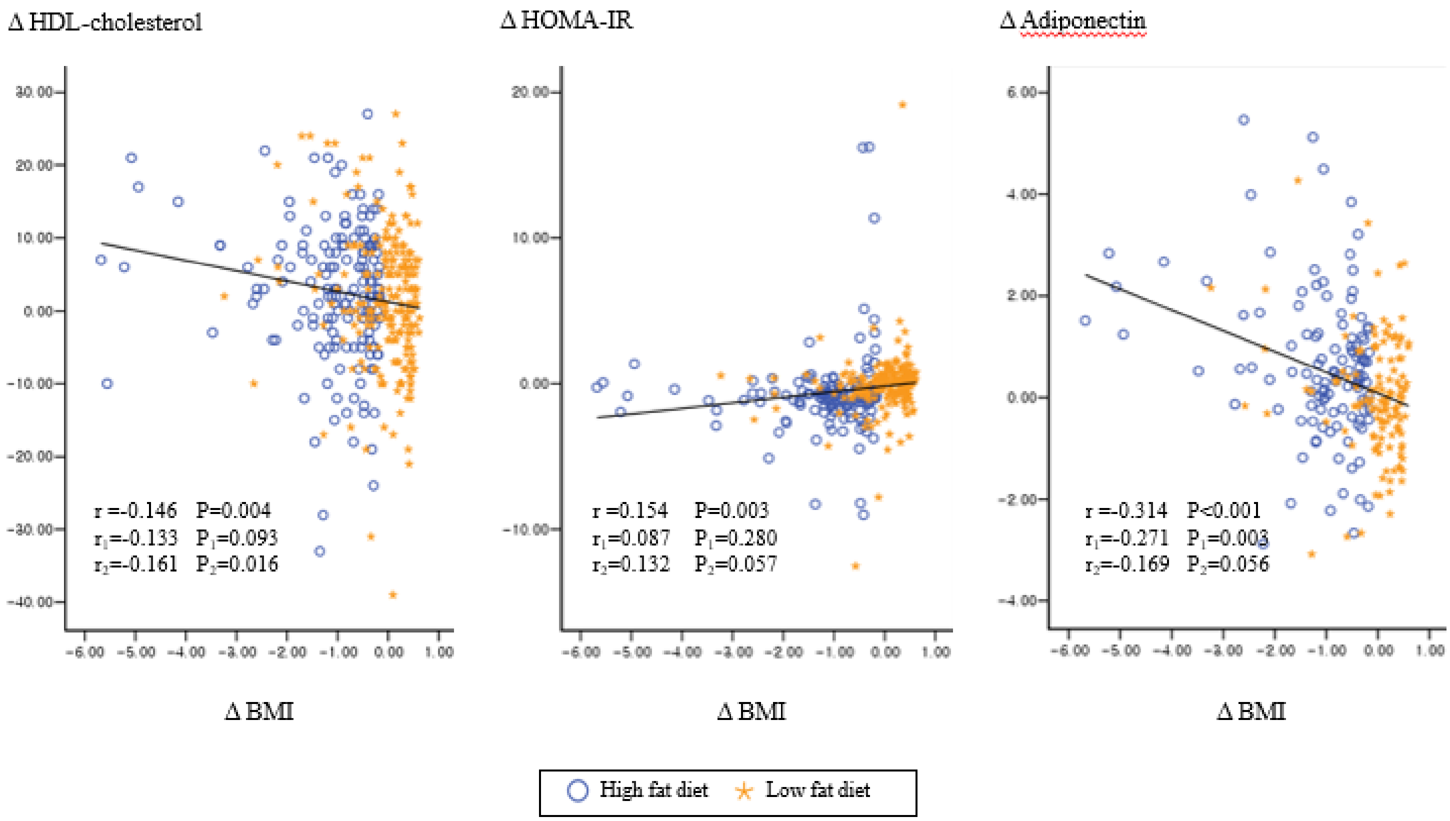

Figure 2

Correlations between changes (difference from baseline) in BMI, HDL-cholesterol, HOMA-IR index, and adiponectin in 383 subjects r: Pearson's correlation coefficients in total subjects. r1: correlation coefficients in HFD group. r2: correlation coefficients in LFD group.

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