

Effect of daidzein-low-calorie diet on body weight, serum levels of glucose, resistin, and high sensitive C-reactive protein in high fat, high calorie diet induced rats

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ABSTRACT

الأهداف: تقييم مدى تأثير تقييد السعرات الحرارية باستخدام الديدزين أو بدون استخدامه وذلك على الوزن، ومستويات الغلوكوز، ومؤشرات الالتهاب الحيوية لدى الجرذان المصابة بالسمنة.

الطريقة: أُجريت هذه الدراسة في جامعة جوندشاپور، أهواز، إيران وذلك خلال الفترة من سبتمبر 2010م إلى يناير 2011م. لقد قمنا بتحفيز السمنة لدى 30 جردي ذكر من نوع ويسترن (140-160، 6-8 أسابيع) وذلك على مدى 6 أسابيع بإطعامهم حمية عالية الدهون. لقد قُسم الجرذان إلى 3 مجموعات وهي: مجموعة الجرذان السمنة التي عولجت بحمية قليلة السعرات الحرارية وتحتوي على الديدزين بمقدار 50 ملغ/كغ (العدد: 10)، ومجموعة الجرذان السمنة التي عولجت بحمية قليلة السعرات الحرارية وتحتوي على ديميثيل سولفوكسيد بمقدار (العدد: 10)، ومجموعة الشاهد التي كان لها الحرية في الأكل (العدد: 10). لقد قمنا بجمع عينات الدم بعد مرور 4 أسابيع وذلك من أجل تحليل مستويات الغلوكوز، والريسيستين، وبروتين سي التفاعلي.

النتائج: أشارت نتائج الدراسة إلى أن تقييد السعرات الحرارية قد أدى إلى خفض مستويات الغلوكوز ($p=0.002$)، ومستويات بروتين سي التفاعلي ($p=0.000$)، بالمقابل لم يكن لها تأثير واضح من الناحية الإحصائية على مستويات الريسيستين. ولم يكن لإعطاء الديدزين تأثير واضح على الوزن، ومستويات الغلوكوز، والريسيستين، وبروتين سي التفاعلي.

خاتمة: أثبتت هذه الدراسة بأن تقييد السعرات الحرارية قد أثر تأثيراً كبيراً من الناحية الإحصائية على الوزن، ومستويات الغلوكوز، والمؤشرات الحيوية للالتهاب من الدرجة الدنيا وهذا بدوره غطى على تأثير الديدزين.

Objectives: To assess the effect of restricting calories with or without daidzein on weight, serum levels of glucose, and inflammatory markers in obese rats.

Methods: This experimental study was carried out in Jundishapur University, Ahvaz, Iran, from September 2010 to January 2011. Obesity was induced in 30 male Wistar rats (140-160, 6-8 weeks age) after 6 weeks by feeding them a high-fat diet. Then, the rats were divided into 3 groups: obese rats treated with low-calorie diet containing 50 mg/kg daidzein ($n=10$); obese rats treated with low-calorie diet containing dimethyl sulfoxide ($n=10$); and obese rats that were given ad libitum access to food as the control group ($n=10$). After 4 weeks, blood samples were collected in order to analyze the levels of glucose, resistin, and high sensitive C-reactive protein (CRP).

Results: Restriction of calories resulted in decreased blood glucose ($p=0.002$), and decreased levels of high sensitive CRP ($p=0.000$), but had no significant effect on resistin level. Daidzein administration had no significant effect on body weight, serum glucose, levels of resistin, and high sensitive CRP.

Conclusion: Calorie restriction significantly affected body weight, serum glucose, low-grade inflammation biomarkers, and masked the effect of daidzein.

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Approximately 1.7 billion people throughout the world are obese.¹ Obesity is one of the most widespread metabolic disorders in the modern world. It is closely associated with cardiovascular risk factors, including altered levels of inflammatory markers, and adipocytokines. Obesity is characterized as a low-grade inflammation. The major reason for this view is that there is an increased circulating level of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), Interleukin-6 (IL-6), leptin, resistin, and other adipocytokines in subjects with obesity.¹ Resistin (a 12-kDa protein) is one of the adipocytokines. In rodents, it is expressed and secreted by mature adipocytes.² In humans, however, resistin is expressed at higher levels in monocytes and macrophages than in adipocytes.³ Some studies showed that increased levels of serum resistin are related to insulin resistance,^{2,4} but other studies did not show this effect.^{5,6} Therefore, the role of resistin in insulin resistance is not yet conclusive. Several studies in obese animals and humans suggested that phytoestrogens have significant antiobesity effects.^{7,8} Phytoestrogens are a group of bioactive plant compounds with a chemical structure similar to estradiol; an endogenous estrogen. Three major classes of phytoestrogens are: lignans, isoflavones, and coumestans.⁹ The main bioactive isoflavones are genistein and daidzein, which are abundant in soybean and soy products. Epidemiologic studies in humans indicate that increased soy consumption could be cardioprotective. This may be because of the ability of the isoflavones, which are found in soy products, to act as antioxidant and anti-inflammatory agents,¹⁰ but which isoflavone is responsible for the cardioprotective effect is yet to be determined. It has been demonstrated that genistein can significantly reduce body fat mass in rodents.¹¹ Other studies also showed that genistein is beneficial in correcting hyperglycemia in diabetic rats,¹² besides its antioxidant and anti-inflammatory properties.¹³ However, so far, there is little evidence that daidzein has the same effect.¹⁴ Whether soy and its daidzein could moderate complications of obesity by reducing resistin and high sensitive CRP levels is not yet determined. Therefore, in the present study, we investigated the effect of a daidzein-low-calorie diet on weight, serum levels of glucose and inflammatory markers including resistin and high sensitive CRP in obese rats.

Disclosure. The authors declare no competing financial interests. Funding was received from Jundishapur University, Ahvaz, Iran.

Methods. This experimental study was carried out in Jundishapur University, Ahvaz, Iran, from September 2010 to January 2011.

Animals. Male Wistar rats (140-160 g), aged 6-8 weeks, were obtained from the Physiology Research Center of Ahvaz Jundishapur University of Medical Sciences. The animals were housed under standard environmental conditions ($22\pm 3^{\circ}\text{C}$, $55\pm 5\%$ humidity, and a 12-h light/dark cycle), and maintained with free access to water and ad libitum standard laboratory diet. The study was conducted in accordance with the ethical procedures and policies approved by the Animal Care and Use Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

High fat, high calorie induced obesity. The obesity model was established by feeding the rats a high fat, high calorie diet for 6 weeks.¹⁴ This diet contained 40% of calories from fat, 40% from carbohydrates, and 20% from proteins (Table 1). After combining the ingredients, we gave the diet to the rats as pellets, so they could eat easily. Each gram of this diet contained 19.3 KJ (4.6 kcal). The body weight of the rats, and weight of the consumed food were measured once a week during this period. After 6 weeks of feeding with the high fat, high calorie diet, a significant weight gain in high fat diet (HFD) group as compared with the control group was observed (252 ± 24 g versus 197 ± 8 g; $p=0.000$).

Experimental design. Thirty obese rats were divided randomly into 3 groups ($n=10$), and treated as follows: obese rats taking daidzein-low-calorie diet (daidzein dissolved in dimethyl sulfoxide [DMSO], Sigma Aldrich, St. Louis, Missouri, USA) (50 mg/kg) (daidzein group); obese rats taking DMSO-low-calorie diet (50 mg/kg) (DMSO group); and obese rats taking ad libitum standard laboratory chow diet (control

Table 1 - Composition of the high fat, high calorie diet fed to the study rats.

Ingredients	g/kg diet
Casein (Merck, Germany)	200
D-L methionine (Merck, Germany)	3
Corn starch (Alborz, Iran)	111
Sucrose	370
Wheat bran	50
Corn oil	30
Butter	170
Mineral mixture* (MP Biomedicals, USA)	40
Vitamin mixture† (MP Biomedicals, USA)	12
Cholin bitartrate	2
Percentage of Fats	40%
Total energy, KJ/Kg diet	19315

*Mineral mixture for American Institute of Nutrition (AIN)-76A rodent diet, †vitamin mixture for AIN-76A rodent diet

group). Standard chow diet was composed of 3% fats, 21% proteins, 70% carbohydrates, and 2.75 kcal/gr. Daidzein (LC Lab, Woburn, Massachusetts, USA) and DMSO were given by oral gavage and the treatments lasted for 4 consecutive weeks. Food intake and body weight were monitored daily. During calorie restriction, rats in the daidzein group (22.63 ± 5.00 kcal/day), and the DMSO group (23.45 ± 6.01 kcal/day) ate (as standard chow diet) only 40% of the energy available to their respective ad libitum controls (54.36 ± 7.05 kcal/day). Woods et al¹⁵ showed that 60% restriction of calories would cause rapid and reliable weight loss in rats in a short interval. The means of food and calorie intake in the experimental groups are shown in Table 2.

Biochemical analysis. At the end of the study, fasting blood samples were collected directly from the heart under light ether anesthesia. Sera were obtained by centrifuging the blood at 3000 rpm for 15 minutes at 4°C, and then stored in -80°C until assayed. Glucose levels were determined enzymatically using standard methods by autoAnalyser SA1000 (Skalar, Breda, Netherlands). Serum resistin and high sensitive CRP concentrations were assayed by ELISA technique using commercially available kits (BioVendor, Brno, Czech Republic) in accordance with the manufacturer's instructions.

Statistical analysis. Statistical analyses were carried out using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) program for windows version 17. Data were expressed as mean±SD. Statistical analysis was performed by one way ANOVA, independent sample t-test, and paired sample t-test with 95% confidence intervals. Differences were considered to be statistically significant at $p < 0.05$.

Results. The initial and final body weights in the control and treatment groups are summarized in Table 3. The results showed that initial body weight was not significantly different between the groups ($p=0.98$), but the mean value of final body weight in both obese treatment rats, taking low-calorie diet with daidzein

or DMSO, were significantly lower than those of the non-treatment control rats ($p=0.000$). The changes of body weight during the intervention (4 weeks) in the 2 experimental groups are presented in Figure 1. There was no significant difference between the weight of daidzein and DMSO groups at the end of the study ($p=0.998$). The effects of daidzein-low-calorie diet, and DMSO-low-calorie diet on serum levels of glucose, resistin and high sensitive CRP are shown in Table 4. As shown, the daidzein-low-calorie diet ($p=0.003$), or DMSO-low-calorie diet ($p=0.002$) caused a significant decrease in glucose levels in comparison with the control obese rats. The difference between serum glucose concentrations of daidzein and DMSO groups was not statistically significant ($p=0.999$). The present data also indicated that low-calorie diet caused a significant decrease in serum high sensitive CRP levels of the treated obese animals compared with the obese control rats ($p=0.000$). However, there was no significant difference in high sensitive CRP levels between daidzein and DMSO groups ($p=0.493$).

Table 3 - Means of body weight in experimental groups at the beginning and end of study (N=30).

Groups	Initial body weight (g)	Final body weight (g)
Control obese rats (n=10)	252±17	276±38
Low calorie diet + daidzein (50mg/kg) (n=10)	251±24	188±14 [†]
Low calorie diet + DMSO (50 mg/kg) (n=10)	255±20	190±18 [†]

All values are expressed as mean±SD, *indicates $p=0.000$ versus initial body weight (paired sample t-test with confidence interval 95%), [†]indicates $p=0.000$ versus control obese group (independent sample t-test with confidence interval 95%), DMSO- dimethyl sulphoxide

Table 2 - Means of total food and calorie intake in the experimental rat groups (N=30).

Groups	Total food intake (g/day)	Total calorie intake (kcal/day)
Control obese rats (n=10)	19.67±2.21	54.36±7.05
Low calorie diet + Daidzein (50mg/kg) (n=10)	8.05±1.00*	22.63±5.00*
Low calorie diet + DMSO (50 mg/kg) (n=10)	8.30±1.05*	23.45±6.01*

All values are expressed as mean±SD, *indicates $p=0.000$ versus control obese group (independent sample t-test with confidence interval 95%), DMSO- dimethyl sulphoxide

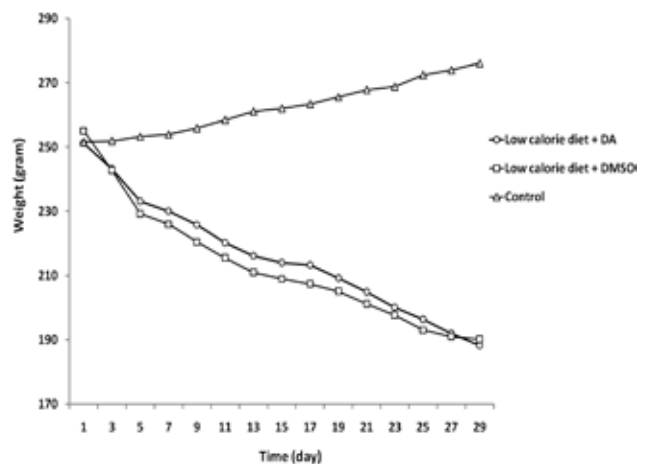
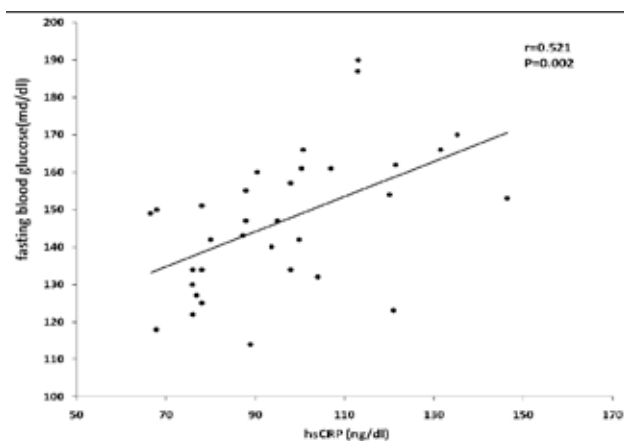
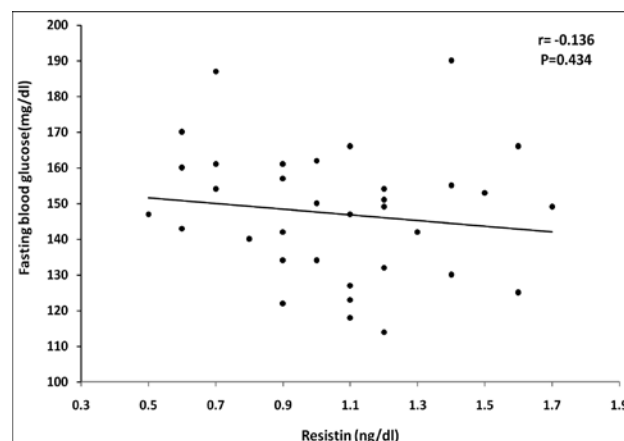


Figure 1 - Effect of daidzein-low-calorie diet on body weight changes. DA- Daidzein (50 mg/kg), DMSO- dimethyl sulphoxide (50 mg/kg).

Table 4 - Effect of daidzein-low-calorie diet on serum levels of glucose, resistin, and high sensitive CRP (N=30).

Groups	Glucose (mg/dl)	Resistin (ng/dl)	High sensitive CRP (ng/dl)
Control obese rats (n=10)	168±14	1.17±0.33	122±13
Low calorie diet + daidzein (50mg/kg) (n=10)	142±13*	1.06±0.29	84±14**
Low calorie diet + DMSO (50 mg/kg) (n=10)	141±14†	1.01±0.33	93±14**

All values are expressed as mean±SD, *indicates $p=0.003$, †indicates $p=0.002$, and **indicates $p=0.000$ versus control obese rats (independent sample t-test with confidence interval 95%), DMSO- dimethyl sulphoxide, CRP - C-reactive protein

**Figure 2** - Correlation between serum high sensitive CRP and fasting blood glucose levels. HsCRP- high sensitive C-reactive protein.**Figure 3** - Correlation between serum resistin and fasting blood glucose levels.

In addition, the results of this study showed that restricting the calories in the daidzein and DMSO groups resulted in no significant decrease in resistin level when compared with the obese control group. Additionally, daidzein had no effect on resistin levels in comparison with the DMSO group ($p=0.538$). The results also showed a significant positive correlation between high sensitive CRP and glucose levels ($r=0.52$, $p=0.002$) (Figure 2). A negative correlation between resistin and glucose concentrations also existed, but it was not statistically significant ($r= -0.136$, $p=0.434$) (Figure 3).

Discussion. Some studies showed that soy-containing foods can have beneficial effects on obesity and energy expenditure.¹⁶ In this study, we found that daidzein has no more favorable effect on the rate of weight loss compared with calorie restriction alone in obese rats. As we can see in Figure 1, the rate of weight loss in daidzein and DMSO groups is the same. As the amount of food ingested daily in these 2 groups was equal, it can be inferred that daidzein has no effect on energy expenditure. Some studies that assessed soy protein isolate (SPI), which is rich in isoflavones, also

proved that SPI has no effect on body weight and food intake.^{17,18} In this study, we also found that treatment groups (daidzein and DMSO groups) with the low-calorie diet had lower serum glucose levels in comparison with the control group. It seems that restricting food intake, and related decrease in body weight is responsible for the low levels of glucose in these groups.¹⁹ Moreover, in our study we found that daidzein had no significant effect on serum glucose levels in the daidzein group in comparison with the DMSO group. Our finding is in concert with Wagner et al,²⁰ who showed that isoflavone supplementation has no effect on blood glucose in rats. Chen et al²¹ also showed that soy isoflavones can reduce resistin, but have no effect on high sensitive CRP levels. In the study, Chen et al²¹ found that soy isoflavones can improve insulin sensitivity by decreasing resistin expression, while we found that daidzein had no effect on serum resistin. Our study differs from the study of Chen et al²¹ in that we imposed calorie restriction with daidzein supplementation. Therefore, one possible reason for no significant effect of daidzein on resistin in our study may be that the calorie restriction has a powerful effect on decreasing resistin level by which the same effect of daidzein is masked. Additionally, in contrast to the study by Chen et al,²¹ in our study

serum resistin levels had no significant correlation with glucose levels. As resistin is produced by macrophages infiltrated in adipose tissue, and presents in areas of inflammation, it has been proposed to be a member of a new class of proinflammatory cytokines, and a link between obesity and inflammation.²²⁻²⁴ In our study, high fat, high calorie diet resulted in increased resistin level in comparison with normal diet. Several studies proved that rats fed with a high fat diet showed higher level of serum resistin.²⁵⁻²⁸ These studies showed that HFD results in obesity, and consequently increases white adipose tissue (WAT). The WAT is the main site of resistin secretion in rodents. Therefore, restriction of calories by losing weight, and consequent decreasing WAT can lead to lower levels of resistin.

The results of the present study exhibited lower levels of high sensitive CRP in obese rats taking low-calorie diet in comparison with the obese control rats. There was also a positive correlation among serum high sensitive CRP concentration, glucose levels, and body weight in our study, which could simply explain that this reduction could be due to the weight loss in the low-calorie diet-treated animals. This finding is in concert with other studies,^{29,30} and may be because of the higher secretion of high sensitive CRP by hepatocytes in obese rats. The level of high sensitive CRP rises in response to inflammation, and a link between obesity and inflammation has been proposed.³¹ Heilbronn et al³¹ showed that CRP has a significant positive correlation with body mass index (BMI). It has been proposed that in as much as 60% of people with BMI greater than 30, the CRP level is high.²⁴ They also showed that caloric restriction and weight loss lowered IL-6, and subsequently high sensitive CRP levels, and may beneficially suppress the immune response.³² This may be of pathogenic significance as high sensitive CRP stimulates the uptake of low-density lipoprotein (LDL) particles by macrophages, induces activation, which may cause cellular damage in the arteries, and increases monocyte production of tissue factor, consequently enhancing the risk of thrombosis.³⁰ The results of this study showed that weight loss may be an effective non-pharmacologic strategy for lowering high sensitive CRP level. Like resistin levels, the serum concentrations of high sensitive CRP did not change with daidzein administration in comparison with DMSO. Similar to our study, Jenkins et al³³ showed that high isoflavone diet for one month has no effect on high sensitive CRP levels in hypercholesterolemic middle aged men and postmenopausal women.

In conclusion, we demonstrated that treatment of obesity with daidzein in obese rats did not significantly reduce weight, also had no significant effect on serum

levels of glucose, resistin, and high sensitive CRP. But, the restriction of calories and therefore resultant weight loss had a significant effect on these biochemical profiles. Therefore, it seems that caloric restriction may still be the best way for weight reduction, and treating obesity related low-grade inflammation. Our study also showed that daidzein is less effective when it is administered with low-calorie diet, and it includes less favorable effects. In this study, we used only one dose of daidzein, and higher doses of daidzein could have favorable effects on these parameters, and therefore should be evaluated in future studies.

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