The Impact of a Low Glycemic Index Diet on Inflammatory Markers and Serum Adiponectin Concentration in Adolescent Overweight and Obese Girls: A Randomized Clinical Trial

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Key words
- low glycemic index
- insulin resistance
- inflammation
- female

Abstract

Although the effects of dietary glycemic index (GI) on insulin resistance are well documented in adults, the complex interaction among glucose intolerance, inflammatory markers, and adipokine concentration has not been well studied, especially among adolescents. We investigated the effect of a low glycemic index (LGI) diet on insulin concentration, fasting blood sugar (FBS), inflammatory markers, and serum adiponectin concentration among healthy obese/overweight adolescent females. In this parallel randomized clinical trial, 2 different diets, an LGI diet and a healthy nutritional recommendation diet (HNRD) with similar macronutrient composition were prescribed to 50 obese and overweight adolescent girls with the same pubertal status. Biochemical markers FBS, serum insulin concentration, high sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), and adiponectin were measured before and after a 10 week intervention. Using an intention-to-treat analysis, data from 50 subjects were analyzed. According to a dietary assessment, GI in the LGI group was 43.22 ± 0.54. While the mean for FBS, serum insulin concentration, the homeostasis model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI), and adiponectin concentration did not differ significantly within each group, the average hs-CRP and IL-6 decreased significantly in the LGI diet group after the 10 week intervention ($p = 0.009$ and $p = 0.001$; respectively). Comparing percent changes, we found a marginally significant decrease in hs-CRP in the LGI group compared with the HNRD group after adjusting for confounders. Compliance with an LGI diet may have favorable effect on inflammation among overweight and obese adolescent girls.

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Abbreviations

FBS	Fasting blood sugar
GI	Glycemic index
HGI	High glycemic index
HNRD	Healthy nutritional recommendation diet
hs-CRP	High sensitivity C-reactive protein
IL-6	Interleukin 6
LGI	Low glycemic index
QUICKI	Quantitative insulin sensitivity check index

Introduction

Insulin resistance, a major cause of diabetes mellitus and metabolic syndrome [1,2], is usually associated with obesity [3]. It is also closely associated with serum adiponectin concentration [4–6] and inflammatory cytokines such as high sensitivity C-reactive protein (hs-CRP) [1]. This relationship between blood glucose, insulin resistance, and inflammatory cytokines, however, does not appear to depend on obesity status [7,8]. Previous studies show that serum adiponectin concentration has an inverse correlation with obesity [9] and concentration of inflammatory markers [e.g., interleukin 6 (IL-6) and hs-CRP] [4]. Obesity usually results in chronic inflammation [10]. The association between low-grade inflammation and obesity has also been observed among adolescents living in developing countries [11]. Therefore, it is important to identify effective nutritional interventions to improve insulin resistance and inflammation in overweight and obese adolescents in such populations.

Although it is well established that adiponectin concentration, insulin resistance, and inflammatory markers are influenced by environmental

conditions, particularly diet [12–14], the role of carbohydrate quality has not been emphasized. The potential of different foods to increase postprandial blood sugar has been defined as the glycemic index (GI). Previous studies reported that dietary GI may affekt insulin resistance-related factors such as, insulin concentration, fasting blood sugar (FBS) [15], and inflammatory markers [16,17] in adults. An inverse association between GI and adiponectin has been reported among the elderly [18]. The effekt of dietary GI on insulin concentration and FBS has previously been examined among adolescents [19–22]. Although some of these studies measured changes in inflammatory markers [23,24], variations in adiponectin in adolescents have not been assessed following a dietary GI intervention. Few studies have examined the effekt of GI on insulin resistance related factors simultaneously, such as inflammatory markers and adiponectin among adolescents. Furthermore, prior studies have been conducted with both sexes combined and, therefore, physiological sex differences may have confounding role. Moreover, the prevalence of obesity among females is quite concerning [25]. Limited evidence has been reported regarding inflammation and adiponectin in adolescents. Therefore, the aim of the current study was to examine the effekt of a low glycemic index (LGI) diet on insulin concentration, FBS, inflammatory markers and adiponectin among healthy overweight and obese adolescent girls.

Subjects and Methods

Subjects

Eligible participants for this parallel randomized clinical trial were identified using recruitment flyers and Isfahanian student health booklets. An introductory meeting was held in which a detailed explanation was given to the volunteers' parents, and informed written consent was obtained. The study was conducted in Isfahan, Iran in 2011. Adolescents were eligible to participate if they were female, between 12 and 18 years old, overweight or obese, menstruating and not on medication. Low compliance with recommendations and use of medications that interact with inflammatory responses or insulin function were exclusion criteria. Based on WHO body mass index (BMI) definitions [26], overweight and obesity were defined as between 85th and 95th percentile and greater than the 95th percentile, respectively. Information on age, menstrual status and medication use were collected orally. Fifty adolescent participants were recruited for the study. The required sample size was calculated by $N=2[(Z_{1-\alpha/2}+Z_{1-\beta})^2\times S^2]/d^2$ [27] where $\alpha=0.05$ (Type I error) and $\beta=0.20$ (Type II error). The main outcome variable was hs-CRP. Variance of hs-CRP was 0.9 [23] and the difference in its mean was 1. The formula estimated that 13 subjects were required for each group. This study was approved by the Research Council and Ethical Committee of the School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran and the Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. This randomized clinical trial was registered at IRCT.ir (IRCT201109272839N4).

Study procedure

Participants were randomly assigned to an LGI or healthy nutritional recommendation diet (HNRD) using a random number table. Study duration was 10 weeks. Although the biochemical laboratory staffs were blinded, we could not blind the participants to the intervention type because it was a dietary intervention. In this study, there were 3 important variables (age, sex, and pubertal status) that were matched by restricting our inclusion of participants to: subjects who were female, menstruating, and between 12–18 years old. Clinical visits were scheduled each 2.5 weeks. Therefore, 4 sessions were conducted before the end of the study.

Dietary intervention

According to the US Institutes of Medicine formula [28], total energy expenditure was estimated for each participant. A moderate caloric restriction (200 kcal) was given only to adolescents with BMI > 95th percentile. Recommended macronutrient distribution was similar between the 2 groups (53–56% carbohydrate, 16–18% proteins and 27–30% fat). LGI and high glycemic index (HGI) were defined as GI < 50 and GI ≥ 50, respectively. The LGI diet group was instructed to select carbohydrate containing foods from a list of LGI grains, fruits, vegetables, and dairy, which was provided by the study researchers. Moreover, a list of prohibited HGI foods was given to LGI group members. We used a food exchange list to select foods in the meat and fat groups. We used several nutritional recommendations that emphasized limiting foods rich in fat, fast foods, French fries, fried foods, industrial beverages, and unhealthy fats. Participants were also recommended to drink 1.5–2 liters of water per day, consume a variety of fruits and vegetables and eat low-fat dairy and whole grains. The HNRD group's diet was based on these guidelines. All participants were asked to fill out a one-day food diary and a one-day physical activity record for 3 work days and one weekend day. The completed records were reviewed by trained staff. The participants were asked to complete food diaries based on household portion sizes. We converted quantities reported using household measures (e.g., a cup of milk) to grams [29]. Grams of foods were analyzed by Nutritionist IV to obtain the nutrient and energy content of the foods reported. Comparisons between macronutrient distribution as a percentage of energy in the prescribed diets and reported food records were used to check compliance in the HNRD group. The criterion for compliance in the LGI group was GI < 50, calculated from the food diaries.

To extract GI values, we referred to the Iranian GI table [30]. The international table of GI [31] was used for GI values not reported on the Iranian-specific table. The GI for foods not included in the Iranian or the international table was estimated using the GI for the most similar food. To calculate the mean GI for diet, we used the reported formula [32].

Biochemical measurements

One blood sample was taken after 12 h of fasting in the early morning. After coagulation, we centrifuged blood samples at 3000 × g for 10 min to separate the serum. FBS was measured by an enzymatic colorimetric method based on glucose oxidase activity (Pars Azmoon, Tehran, Iran). Insulin was assessed by enzyme-linked immunosorbent assay (ELISA) (Monobind Inc, Costa Mesa, CA, USA). Standard sandwich ELISA technology was used for measuring adiponectin and IL-6 (Boster Biological Technology, USA). Intra- and interassay variations for IL-6 were less than 6 and 8%, respectively. The Immunoturbidimetry method was used to measure hs-CRP with a polyclonal antibody (Pars Azmoon Inc). For hs-CRP, the interassay and intra-assay variation was 5.1–10.0% and 4.3–6.1%, respectively. To estimate insu-

Table 1 Percent changes of fasting blood sugar, insulin, adiponectin, and inflammatory factors among adolescents in the low glycemic index (LGI) and healthy nutrition recommendations diet (HNRD) groups following a 10 week intervention.

Variables	Low glycemic index (LGI) group[1] (n = 25)	Healthy nutrition recommendations diet (HNRD) group[2] (n = 25)	p[3]	Model 1[4]	Model 2[5]
Fasting blood sugar	5.54 ± 2.45[6]	4.24 ± 2.20	0.69	0.81	0.97
Serum insulin	1.59 ± 1.95	1.67 ± 2.03	0.96	0.37	0.32
HOMA	2.54 ± 1.98	2.25 ± 2.08	0.90	0.83	0.33
QUICKI	−0.00 ± 1.26	−0.75 ± 1.96	0.74	0.57	0.43
Serum adiponectin	22.04 ± 24.45	46.30 ± 24.31	0.48	0.25	0.29
hs-CRP	−16.21 ± 8.48	27.96 ± 24.16	0.09	0.04	0.08
IL-6	−74.87 ± 6.14	−70.27 ± 6.92	0.62	0.84	0.48

HOMA: Homeostasis model assessment; QUICKI: Quantitative insulin sensitivity check index; hs-CRP: high sensitivity C-reactive protein; IL-6: Interleukin 6

[1] GI < 50 was considered LGI

[2] Healthy nutritional recommendations included avoidance of foods rich in fat, fast foods, French fries, fried foods, industrial beverages and unhealthy fats as well as advice to drink 1.5–2 liters of water, consume more amount of diverse fruits and vegetables, and eat low-fat dairy and whole grains

[3] p-values show percent changes between the 2 groups (independent samples *t*-tests were used for calculating p-values)

[4] Adjusted for age

[5] Adjusted for age, physical activity, weight change, and the distribution of obese subjects in the 2 groups

[6] Variables are presented as mean ± SEM except for insulin and HOMA, which are presented as geometric mean ± SEM

lin resistance, homeostasis model assessment (HOMA) and the quantitative insulin sensitivity check index (QUICKI) were calculated with reported formulas [32].

Statistical analysis

The Kolmogorov-Smirnov test and histogram curves were used to test if the variables were normally distributed. Results showed that the distribution of adiponectin, IL-6 and percent changes of insulin, HOMA, hs-CRP, and IL-6 were not normal. Therefore, the geometric mean was used for these variables. Means of nutrient intake, baseline values, final values and percent changes were compared between the 2 groups with the Student's *t*-test. We used the following formula to calculate percent changes: [(E-B)/B] × 100 where baseline and final values were represented by B and E; respectively. Within group comparisons between baseline and final values were calculated with paired *t*-tests. We also used repeated measures ANOVA to calculate p_{time}, p_{group}, $p_{time \times group}$ and $p_{time \times age}$. An intention-to-treat analysis was also performed. All variables are presented as mean ± SEM. All analyses were carried out using SPSS 20 (SPSS Inc) statistical software.

Results

The study procedure is presented in **Fig. 1S**. Among 50 enrolled adolescents, 9 subjects withdrew due to poor compliance, change in phone number, or other reasons. Finally, 41 remained in the study. Using an intention-to-treat analysis, we included the data for all 50 subjects in the statistical analysis. As mentioned, the comparison between macronutrient distribution as a percentage of energy in the prescribed diets and reported food records were used as a compliance check in the HNRD group. No differences were observed between macronutrient composition between the prescribed and the consumed diets. A glycemic index of less than 50 was used as the compliance criterion in the LGI group. Analysis of food records demonstrated that the mean ± SEM of GI in the LGI group was 42.67 ± 0.67.

Baseline characteristics for adolescents in the LGI group and the HNRD group are displayed in **Table 1S**. Mean age in the LGI group was lower than in the HNRD group (p = 0.03). There was no significant difference in physical activity level between the 2 groups (p = 0.43).Moreover, the percent of overweight subjects in the HNRD group was significantly higher than in the LGI group. Although weight decreased in both groups, changes were not different between the 2 groups. Analysis of food diaries showed that nutrient intake including energy intake, carbohydrate, protein, fat, fiber, zinc, vitamin E, vitamin B_3, folate, vitamin C, vitamin B_6, and vitamin D were not significantly different between the 2 groups (**Table 1**). Furthermore, dietary GI in the LGI group was lower than 42.67 ± 0.067. According to physical activity records, there was not a significant difference in physical activity levels between the 2 groups (p = 0.43). We observed significant weight reduction in both groups (p < 0.001 for both).

The means of the insulin resistance indices, adiponectin and inflammatory factors, before and after the 10 weeks of the intervention are illustrated in **Table 2**. Although average hs-CRP in the LGI group (p = 0.002) and IL-6 in both groups (p < 0.001 for both) decreased significantly after the 10 week intervention, other variables did not differ significantly within each group. The comparison between baseline and final values failed to show a significant difference between the 2 groups. Analyses did not demonstrate significant interactions except for a time × age interaction for serum adiponectin concentration (p < 0.001).

Percent changes in insulin resistance indices, serum adiponectin concentration, and inflammatory factors are presented in **Table 1**. We compared percent changes in 2 different statistical models. In model 1 (adjusted for age), a significant reduction in hs-CRP was observed (p = 0.04). We did not observe any significant differences in other variables. In model 2 (adjusted for age, physical activity, weight change and the distribution of obese subjects in the 2 groups), a marginal decrease was observed in hs-CRP (p = 0.08). Differences were not significant for the other variables.

Discussion

As our results show, although changes in insulin resistance indices and adiponectin were not significantly different between the 2 groups, a marginally significant decrease in hs-CRP was observed in the LGI group compared to the HNRD group after adjusting for confounding variables. To our knowledge, this is

Table 2 Fasting blood sugar, insulin, serum adiponectin concentration, and inflammatory factors among adolescents in the low glycemic index (LGI) and healthy nutrition recommendations diet (HNRD) groups following a 10-week intervention.

Variables	Low glycemic index (LGI) group[1] (n=25)	Healthy nutrition recommendation diet (HNRD) group[2] (n=25)	p overall[3]	P_{time}[4]	P_{group}[5]	$P_{time \times group254}$[6]	$P_{time \times age}$[7]
Fasting blood sugar (mg/dl)							
Before	89.88 ± 1.91	91.86 ± 1.67	0.44	0.58	0.24	0.94	0.70
After	93.63 ± 0.98	94.99 ± 1.35	0.41				
p[8]	0.07	0.11	–				
Serum insulin (μIU/ml)							
Before	20.30 ± 2.31	16.50 ± 1.48	0.17	0.30	0.26	0.22	0.26
After	18.03 ± 1.43	15.93 ± 1.59	0.33				
p[8]	0.10	0.66	–				
HOMA							
Before	4.55 ± 0.54	3.77 ± 0.34	0.23	0.28	0.36	0.29	0.25
After	4.20 ± 0.35	3.77 ± 0.40	0.42				
p[8]	0.29	0.99					
QUICKI							
Before	0.31 ± 0.00	0.32 ± 0.01	0.31	0.50	0.31	0.48	0.53
After	0.31 ± 0.00	0.32 ± 0.00	0.20				
p[8]	0.46	0.41					
Serum adiponectin (ng/ml)							
Before	5.86 ± 1.15	3.98 ± 1.14	0.06	<0.001	0.04	0.03	<0.001
After	3.95 ± 1.16	3.81 ± 1.16	0.86				
p[8]	0.08	0.81	–				
hs-CRP (mg/l)							
Before	3.97 ± 0.35	3.48 ± 0.39	0.36	0.67	0.79	0.19	0.53
After	2.62 ± 0.23	2.89 ± 0.31	0.49				
p[8]	0.002	0.25	–				
IL-6 (pg/ml)							
Before	74.44 ± 1.33	60.86 ± 1.26	0.59	0.09	0.33	0.37	0. 21
After	10.21 ± 1.27	8.38 ± 1.28	0.57				
p[8]	<0.001	<0.001	–				

HOMA-IR: Homeostasis model assessment; QUICKI: Quantitative insulin sensitivity check index; hs-CRP: high sensitivity C-reactive protein; IL-6: Interleukin 6

[1] GI<50 was considered LGI

[2] Healthy nutritional recommendations included avoidance of foods rich in fat, fast foods, French fries, fried foods, industrial beverages, and unhealthy fats as well as advice to drink 1.5–2 liters of water, consume higher quantities of diverse fruits and vegetables, and eat low-fat dairy and whole grains

[3] p-values show comparisons of baseline and final values between the 2 groups (independent sample *t*-tests were used for calculating p-values)

[4] p-values show the effekt of time (analysis of covariance was used for calculating p-values)

[5] p-values show the effekt of grouping (analysis of covariance was used for calculating p-values)

[6] p-values show the time * group interaction (analysis of covariance was used for calculating p-values)

[7] p-values show the time * age interaction (analysis of covariance was used for calculating p-values)

[8] p-values show comparisons of baseline and final values within each group (paired sample *t*-tests were used for calculating p-values)

[9] Variables are presented as mean ± SEM except for adiponectin and IL-6, which are presented as geometric mean ± SEM

the first study to examine the effects of an LGI diet on insulin resistance indices, serum adiponectin concentration and inflammatory markers simultaneously in overweight and obese female adolescents.

Although the effekt of GI on insulin resistance has been evaluated previously, reported results have been inconsistent. Several studies reported a beneficial effekt of LGI diets on insulin resistance among adolescents and children [19,22,23]. LGI foods are absorbed and digested slowly and therefore provide a prolonged full state in which free fatty acid release is suppressed. Therefore, improvements observed in glucose tolerance and insulin sensitivity may be observed following an LGI diet [33]. However, this beneficial effekt has also been observed following a hypocaloric HGI diet [24]. Based on those reported results, it is plausible that the effekt of calorie restriction is more important than dietary GI [24]. Because study subjects were adolescents, we prescribed moderate calorie restriction only among obese participants. Therefore, this might be the reason for not detecting a significant improvement in insulin resistance.

The evidence regarding the effects of GI on inflammatory factors among adolescents has been limited. In previous studies, a significant drop in inflammatory markers has been reported for both hypocaloric LGI and hypocaloric HGI diets in children [23,24]. In a longitudinal study conducted with 22 obese girls and boys, hs-CRP decreased after consumption of both hypocaloric LGI (GI=60) and hypocaloric HGI (GI=90) diets [24]. Although we reported a similar reduction in hs-CRP for the LGI group, there are several differences between the aforementioned study and our intervention, including participant gender, the definition of LGI and the degree of caloric restriction. Moreover, we observed a remarkable decrease in IL-6 in the LGI group as well as in hs-CRP in within-group analyses. On the other hand, our results show greater reduction in hs-CRP in the LGI group compared to the HNRD group, independent of age and weight change. This implies that weight change did not mediate the effekt of LGI diet on inflammation. HGI foods induce higher glucose concentration [30]. Glukose has been considered a stimulating factor for the expression of inflammatory markers [34].

Further, the pattern of methylation at promoters of inflammatory genes is permanently changed by a temporary increment in glucose concentration [34].

Although several studies have examined the effects of GI on adiponectin in animals [35–37], limited research has been reported from clinical trials in humans. Mitsuhashi et al. [35] did not observe any difference in adiponectin concentration between LGI and HGI groups in dogs. However, this conclusion was inconsistent with studies by van Schothorst et al. and Pawlak et al. [36,37], which were conducted on mice. In a human study, the comparison between 2 meals with different GI showed that serum adiponectin concentration increased following consumption of an LGI meal [32]. Unlike that study, our intervention focused on the whole diet rather than a single meal. Further, participant age and anthropometric status in the present study were also distinct from that study.

Iranians do not consume HGI foods as staple foods because, as reported in the Iranian native GI table [30], Iranian staple foods (rice and white bread) are not HGI [38,39]. At the same time, for ethical reasons we could not prescribe an HGI diet in a sample of overweight and obese adolescents. Therefore, we could not compare the effects of an LGI diet on insulin resistance and inflammatory markers to an HGI diet in the present study. Another limitation of current study is that there was no biochemical indicator used to assess adherence to the diet. Also, we were unable to measure physical activity using a precise method such as accelerometry. Moreover, we did not match intervention groups for percent of obese subjects.

Statistically sufficient sample size, similarity in age and gender of participants and maintaining the same macro/micro nutrient intake between 2 groups are strengths of the current study.

In conclusion, changes in insulin resistance indices and serum adiponectin concentration were not significantly different between the 2 groups studied. Moreover, compliance with an LGI diet may have favorable effekt on inflammation among overweight and obese adolescent girls.

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Conflict of Interest

The authors declare no conflict of interest.

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