RESEARCH ARTICLE

Whole-grain intake favorably affects markers of systemic inflammation in obese children: A randomized controlled crossover clinical trial

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Scope: Whole-grain foods have been reported to affect serum levels of inflammatory cytokines. However, we are aware of no study examining the effect of whole-grain intake on inflammatory biomarkers among children. The present study aimed to determine the effect of whole-grain intake on serum levels of inflammatory biomarkers in overweight or obese children.

Methods and results: In this randomized crossover clinical trial, 44 overweight or obese girls aged 8–15 years participated. After a 2-week run-in period, subjects were randomly assigned to either whole-grain or control groups. Subjects in the whole-grain group were given a list of whole-grain foods and were asked to obtain half of their needed servings of grains from whole-grain foods each day for 6 weeks. Individuals in the control group were also given a list of whole-grain foods and were asked not to consume any of these foods during the intervention phase of the study. A 4-week washout period was applied following which subjects were crossed over to the alternate arm for an additional 6 weeks. Fasting blood samples were taken before and after each phase of the study to quantify markers of systemic inflammation. Mean age, weight, and BMI of study participants were 11.2 ± 1.49 years, 51.2 ± 10.2 kg, and 23.5 ± 2.5 kg/m^2, respectively. No significant effect of whole-grain intake on weight and BMI was seen compared with the control group. We found a significant effect of whole-grain intake on serum levels of high-sensitive C-reactive protein (−21.8 versus +12.1%, $p = 0.03$), soluble intercellular adhesion molecule-1 (−28.4 versus +6.3%, $p = 0.02$), serum amyloid A (−17.4 versus +9.9%, $p = 0.02$), and leptin (−9.7 versus +39.2%, $p = 0.02$) after 6 weeks. A trend toward the significant effect of whole-grain intake on serum levels of soluble vascular cell adhesion molecule-1 (−36.2% versus −7.8%, $p = 0.07$) was also observed.

Conclusion: This study provides evidence supporting the beneficial effects of whole-grain foods on biomarkers of systemic inflammation in obese children.

Keywords:
Children / Obesity / Systemic inflammation / Whole grain

1 Introduction

Obesity has been defined as an excess body fat [1]. Childhood obesity is a major threat for global health in both developed and developing countries [2]. In United States, 16% of children are obese [3]. Data from national studies have reported that 16% of Iranian girls and 13% of boys are overweight or obese [4]. Obesity is associated with increased inflammation and oxidative stress, which in turn lead to metabolic dysfunction [2]. It has been shown that obese children have

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Abbreviations: hs-CRP, high-sensitive C-reactive protein; **SAA**, serum amyloid A; **sICAM-1**, soluble intercellular adhesion molecule-1; **sVCAM-1**, soluble vascular cell adhesion molecule-1

higher levels of inflammatory cytokines that make them susceptible to hypertension, dyslipidemia, cardiovascular disease, metabolic syndrome, and other chronic diseases [2].

Several dietary factors have been reported to affect serum levels of inflammatory cytokines. For instance, adherence to the Mediterranean-style diet has been associated with reduced levels of inflammatory biomarkers and lower risk of metabolic syndrome in adults [5]. Consumption of meat has been associated with elevated inflammation in children [6]. The effect of dairy and fish intake [7, 8] as well as nutrients such as zinc, iron, and mercury [9–11] on inflammation among children has been indicated in earlier studies. Although consumption of whole-grain foods has received particular attention in adults, the evidence about their beneficial effects on health in children is limited [12]. Whole-grain foods contain several bioactive compounds, such as vitamins B, E, magnesium, selenium, zinc, fiber, and phytoesterogenes, which might attenuate inflammation [13]. In terms of their effect on inflammation, several investigations in adults have reported that consumption of whole grains has been inversely associated with serum levels of high-sensitive C-reactive protein (hs-CRP), tumor necrosis factor-receptor 2, and risk of obesity and type 2 diabetes [14, 15]. On the contrary, consumption of refined grains has been related to a higher risk of chronic diseases [12]. Such findings have been reported from both developed and developing countries [16, 17]. However, in a recent review that summarized findings from earlier intervention studies in adults, it has been concluded that available data could not indicate a clear effect of whole-grain intake on inflammation in adults [18]. de Punder and Pruimboom [18] have even claimed that whole grains may be partly responsible for chronic inflammation. Among children, consumption of whole grains (three servings per day) has been linked to a lower BMI and central obesity [19], but it is not clear whether the beneficial effects of whole grains on chronic diseases are mediated through their effect on systemic inflammation. The present study was conducted to determine the effect of whole-grain intake on serum levels of inflammatory biomarkers in overweight or obese children.

2 Materials and methods

2.1 Participants

This randomized crossover clinical trial was performed in Isfahan, Iran between July 2012 to December 2012. Totally, 44 overweight or obese (BMI $\geq$ 85th percentile for age and sex, Table 1) girls aged 8–15 years who did not lose weight significantly (>5%) through weight reduction diets in the last 6 months were included in this study. Individuals with a history of chronic diseases and medication use were not included. All participants were recruited from a private clinic of a pediatrician (private clinic of M.H.). Sample size for the study was calculated based on suggested formula for crossover trials. We considered type 1 error of 5%, type 2 error of 20% (power = 80%), and serum hs-CRP levels among children as a key variable and reached the sample size of 31 participants for the whole intervention [20]. Considering the high dropouts in crossover trials, we enrolled 44 children based on the above-mentioned inclusion criteria for this study. Participants were randomly assigned to whole-grain or control groups for 6 weeks in a crossover design (Fig. 1). Random assignment was done by the use of computer-generated random numbers. During the intervention, nine children were dropped out due to fear of blood sampling or personal reasons. The study was performed according to the guidelines laid down in the Declaration of Helsinki. The study was approved by the Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran. Oral assent was obtained from all participants, and informed written consents from their parents. This study was registered at Iranian website for registry of clinical trials (IRCT201305191485N10).

Table 1. Cut-off points of BMI ($\geq$ 85th percentile for age and sex) used to recruit subjects in the study[a)]

Age (years)	Overweight or obese
8	$\geq$17.8
9	$\geq$18.4
10	$\geq$19.1
11	$\geq$20.0
12	$\geq$20.9
13	$\geq$21.9
14	$\geq$22.9
15	$\geq$23.7

a) Based on the World Health Organization criteria.

2.2 Study design

To obtain detailed information about the lifestyle characteristics of study participants as well as to assess the compliance of study participants to whole grains, all subjects were placed on a 2-week run-in period. A dietitian met individually with each participant at this period to discuss the dietary whole grain; she also provided educational materials to facilitate understanding and adherence. Subjects were asked to continue their habitual diet and physical activity and to consume one serving per day of whole grains during this period to prepare them for whole-grain intake and increase their compliance throughout the study. Two dietary records (nonconsecutive days) as well as a 2-day physical activity record were obtained from each participant in the run-in period. At the end of this period (study baseline), all measurements were done. Then, participants were randomly assigned to whole grain and control groups, each for 6 weeks. After the first phase of intervention, a 4-week washout period was applied following which participants were crossed over to the alternative group for an additional 6 weeks. During the washout period, subjects were asked to avoid whole-grain intake that they were consuming during the intervention. Participants

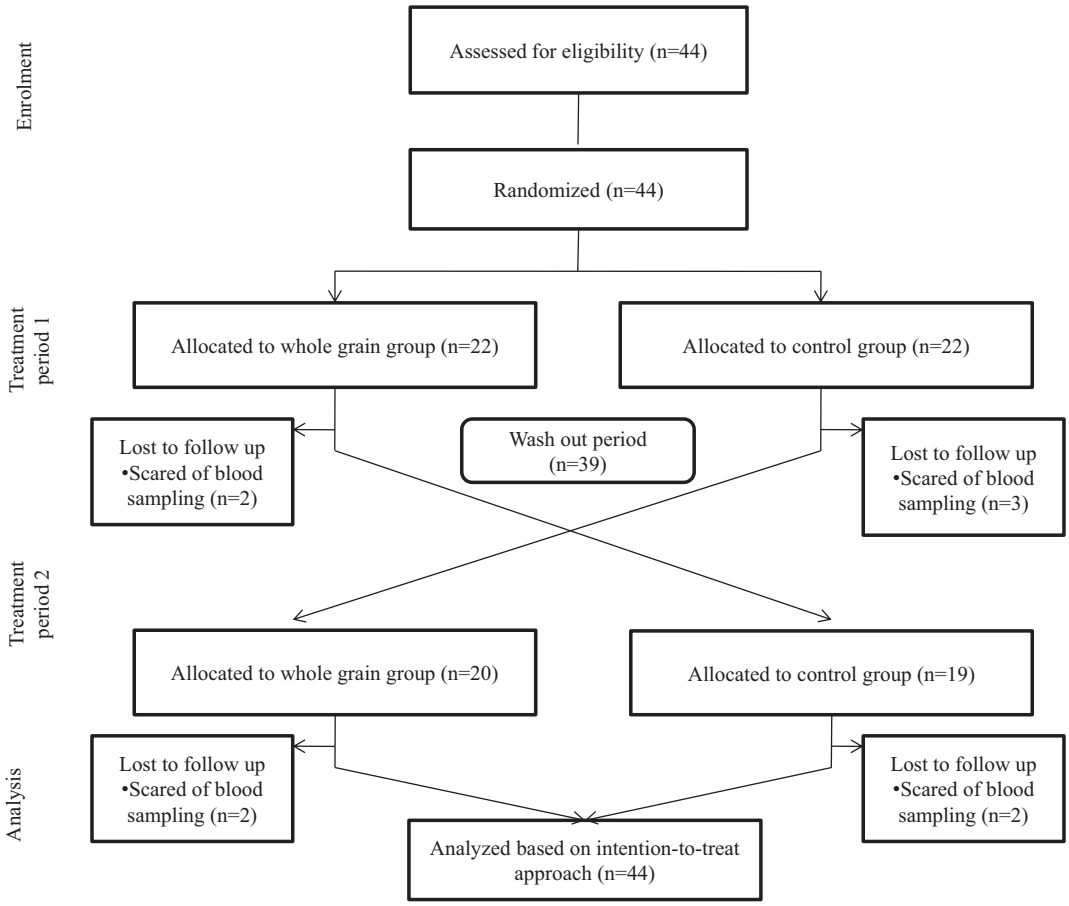

Figure 1. Study flow diagram.

were asked not to alter their routine physical activity or usual diets throughout the study and not to consume any supplements. All measurements were completed at the beginning and end of each phase. Compliance with the consumption of whole grains was monitored once a week through phone interviews. During the study, all participants provided dietary and physical activity records once every 2 weeks. Therefore, each participant had 3 days of dietary and physical activity records in each phase (two weekdays and one weekend day). The dietary records were based on estimated values in household measurements.

2.3 Interventions

In the current study, we did not provide menu cycles to the participants. First, individual energy requirements for each participant were calculated based on recommendations of the Institute of Medicine [21]. Then based on the macronutrient composition of 53% of energy from carbohydrates, 30% from dietary fats, and 17% from dietary proteins, we computed the total servings of grains (and also other food groups) needed for each participant. Then, the number of servings of grain products needed for each individual was given to the participants. Subjects in the whole-grain group were given a list of whole-grain foods (dark breads [sangak, barbari], brown rice, barley bread, cornflakes, bulgur, popcorn, wheat germ, bran, whole meal biscuits) and were asked to obtain half of their total grain servings from whole-grain foods each day. Individuals in the control group were also given a list of whole-grain foods and were asked not to consume any of these foods during the whole-grain phase of the study.

2.4 Anthropometric assessment

Measurement of height was done using a tape measure in standing position without wearing shoes while shoulders were relaxed. Weight was measured to the nearest 100 g using a digital scale in light clothing (Seca, Hamburg, Germany). BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the smallest circumference, and hip circumference was measured at the maximum level using an un-stretched tape measure. To avoid subjective error, all measurements were made by the same person. Obesity was defined as BMI $\geq$ 85th percentile for age and sex; the relevant cut-off points are given in Table 1.

2.5 Assessment of biomarkers

Fasting blood samples (10 mL) were taken at baseline and after 6-week intervention at Milad laboratory (which is under external quality control of the National Reference Laboratory). Blood samples were immediately centrifuged (Hettich D-78532, Tuttlingen, Germany) at 1465 × *g* for 10 min to separate serum. Then, the samples were stored at −70°C before analysis. Serum hs-CRP was quantified using ultrasensitive latex-enhanced immunoturbidimetric assay (Bionik, Tehran, Iran). Concentrations of serum amyloid A (SAA), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured by commercially available ELISA kits and standards (Glory Science, Del Rio, USA). Serum concentrations of leptin were also quantified using ELISA method (Boster, Fremont, USA). The inter- and intraassay CVs for all biochemical indicators were <10%. All biochemical measurements were done in a blinded fashion, in duplicate, in pairs (before/after intervention) at the same time, in the same analytical run, and in a random order to reduce systematic error and interassay variability.

2.6 Statistical methods

To ensure the normal distribution of variables, we applied Kolmogrov–Smirnov test. Log transformation was applied for nonnormally distributed variables. The analyses were done based on intention-to-treat analysis. Missing values were treated based on Last-Observation-Carried-Forward method. Descriptive statistics (means, SEMs or SD, and range) for general characteristics of the study participants were reported. Data on dietary intakes and physical activity were compared by paired *t*-test. To determine the effects of whole-grain intake on biomarkers of systemic inflammation, we used one-way repeated measures analysis of variance. In this analysis, the treatment (whole grain versus refined grain) was regarded as between-subject factor and time with two time points (baseline and week 6 of intervention) was considered as within-subject factor. We also assessed if the carry-over effect was significant. The carry-over effect was tested for by computing the average of the end-of-trial values of each variable for the two treatments (two different groups) and comparing the two treatment orders using *t*-test. *p* Values <0.05 were considered significant.

3 Results

Baseline characteristics of the study participants are shown in Table 2. Mean age, weight, BMI, and waist circumference of study participants were 11.2 ± 1.49 years, 51.2 ± 10.2 kg, 23.5 ± 2.5 kg/m^2, and 80.6 ± 7.9 cm, respectively.

Dietary intakes of participants during intervention period are provided in Table 3. Individuals in the whole-grain group consumed 175 kcal higher energy than those in control group; however, the difference was not significant. There were no significant differences between the two groups in terms of macronutrients intakes, except for carbohydrate intake which was significantly higher in the whole-grain group than that in control group (231 versus 203 g/day, $p = 0.03$). No significant differences in dietary intakes of saturated fatty acids

Table 2. Baseline characteristics of participants[a] ($n = 44$)

	Mean	SD	Range
Age (years)	11.22	1.49	8.00–14.00
Weight (kg)	51.26	10.27	30.50–78.00
Height (cm)	146.72	9.28	128.00–172.50
BMI (kg/m^2)	23.57	2.51	18.27–28.60
Waist circumference (cm)	80.69	7.96	62.00–102.00
Hip circumference (cm)	92.19	7.51	76.00–106.00

Table 3. Dietary intakes of participants, obtained from 3 days of dietary records, throughout the study[a]

	Whole grain[b] ($n = 44$)	Control[c] ($n = 44$)	p[d]
Macronutrients			
Energy (kcal/day)	1629 ± 434	1454 ± 445	0.27
Carbohydrate (g/day)	231 ± 64	203 ± 67	0.03
Protein (g/day)	61 ± 21	53 ± 20	0.12
Fat (g/day)	55 ± 20	51 ± 19	0.34
Micronutrients (per day)			
Saturated fat (g)	16 ± 6	14 ± 6	0.18
PUFA (g)	17 ± 8	17 ± 10	0.87
Potassium (mg)	2191 ± 782	2142 ± 656	0.72
Calcium (mg)	664 ± 342	613 ± 318	0.42
Magnesium (mg)	205 ± 54	184 ± 65	0.09
Folate (μg)	181 ± 69	216 ± 112	0.17
Vitamin C (mg)	91 ± 88	83 ± 34	0.67
Dietary fiber (g)	13 ± 6	13 ± 4	0.95
Vitamin A (μg)	999 ± 741	796 ± 684	0.17
Vitamin E (mg)	10.5 ± 6.1	8.4 ± 5.8	0.20
Vitamin D (μg)	2.2 ± 2.1	0.8 ± 1.1	0.04
Zinc (mg)	8.9 ± 3.1	6.6 ± 3.4	0.09
Iron (mg)	14 ± 5	13 ± 7	0.48
Copper (mg)	1.3 ± 0.1	0.7 ± 0.1	0.03
Selenium (μg)	81.4 ± 20.1	60.8 ± 20.1	0.04
Food groups (g/day)			
Fruits	221 ± 85	243 ± 95	0.21
Vegetables	161 ± 71	153 ± 82	0.36
Whole grains	98 ± 25	11 ± 19	0.01
Refined grains	112 ± 66	208 ± 79	0.02
Dairy products	288 ± 154	297 ± 129	0.41
Meats	84 ± 39	81 ± 31	0.55
Legumes	34 ± 21	38 ± 17	0.44
Fats and oils	34 ± 19	39 ± 22	0.23

a) All values are means ± SD.
b) Whole-grain group: consumed half of their needed servings of grains from whole-grain foods each day.
c) Individuals in the control group were also given a list of whole-grain foods and were asked not to consume any of these foods during the whole-grain phase of the study.
d) By paired *t*-test.

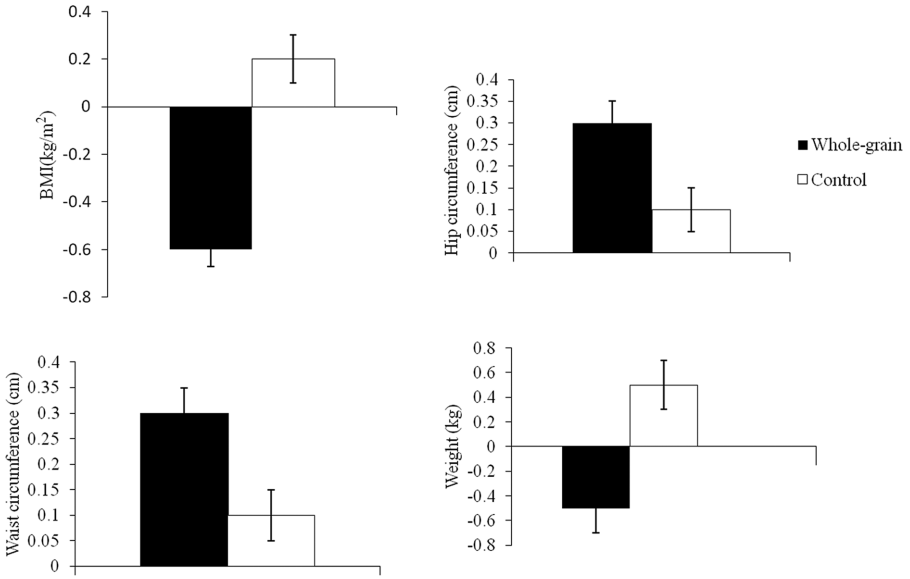

Figure 2. Changes in anthropometric measures after intervention. Whole-grain group: participants in this group consumed half of their needed servings of grains from whole-grain foods each day. Individuals in the control group were also given a list of whole-grain foods and were asked not to consume any of these foods during the whole-grain phase of the study.

(SFA), poly unsaturated fatty acids (PUFA), potassium, calcium, vitamin C, and folate were observed between the two groups. However, individuals in the whole-grain group consumed higher amounts of vitamin D (2.2 versus 0.8 μg/day, $p = 0.04$), copper (1.3 versus 0.7 mg/day, $p = 0.03$), and selenium (1.4 versus 0.8 mg/day, $p = 0.04$) than those in the control group. Magnesium (205 versus 184 mg/day, $p = 0.09$) and zinc intake (8.9 versus 6.6 mg/day, $p = 0.09$) tended to be higher among those in the whole-grain group than that in the control group.

There was no significant difference in changes of anthropometric measures between the two groups (Fig. 2). The effects of whole-grain intake on serum levels of inflammatory biomarkers and adipocytokines are presented in Table 4. Whole-grain intake led to a significant reduction in serum levels of hs-CRP compared with the control group (−21.8 versus +12.1%, $p = 0.03$). Greater reductions in sICAM-1 (−28.4 versus +6.3%, $p = 0.02$) and SAA (−17.4 versus +9.9%, $p = 0.02$) were found in the whole-grain group than those in the control group. Significant changes in serum leptin levels were also seen following whole-grain intake than that in the control group (−9.7 versus +39.2%, $p = 0.02$). Individuals in the whole-grain group tended to have greater reductions in serum sVCAM-1 concentrations than those in the control group (−36.2 versus −7.8%, $p = 0.07$). The effects of time were significant for sICAM-1, SAA, and leptin. The time × group interaction was significant for sVCAM-1 and serum leptin concentrations.

4 Discussion

In this crossover randomized clinical trial in overweight children, we observed that consumption of whole-grain foods for 6 weeks could significantly reduce serum levels of inflammatory biomarkers and adipocytocines. To the best of our knowledge, the present study was the first examining the effects of whole-grain intake on inflammation among overweight children.

Inflammation is thought to play a central role in the pathogenesis of metabolic disease, including obesity, metabolic syndrome, and type 2 diabetes [22–24]. Although recent observational studies have reported the inverse association between intakes of fruit, vegetables [25], soya [26] and dietary fiber and serum levels of inflammatory biomarkers, few interventions have examined the effects of diet on markers of systemic inflammation, especially in children. This is particularly relevant for whole grains where we are aware of just five reports that assessed the effect of whole grains on inflammation in adults [27–31]. In the present study, we found a significant effect of whole-grain consumption on serum levels of hs-CRP, sICAM-1, sVCAM-1, SAA, and leptin in overweight children. This finding is in line with an earlier study in adults, where whole-grain consumption for 12 weeks favorably influenced inflammatory biomarkers among obese adults with metabolic syndrome [27]. In contrast, some studies did not confirm the significant effect of whole-grain intake on systemic inflammation. Andersson et al. [28] indicated that replacing whole grain for refined grain for 6 weeks among apparently healthy overweight adults did not affect inflammation. Similar results were observed in another 16-week comprehensive trial in overweight adults [29]. Different between-study findings could be explained by the discrepancy in recruited subjects in terms of their health conditions, age, and gender. Type and dosage of whole grains used as intervention along with duration of intervention might also explain some differences. Earlier studies have mostly used wheat and oat, while our study used a variety of whole grains. Furthermore, the amount of whole grains used in previous studies was in the range of 60–180 g/day. In the current study, we requested participants to

Table 4. The effects of whole-grain intake on serum levels of inflammatory biomarkers and adipocytokines in obese children[a)]

	Whole grain[b)] ($n = 44$)		Control[c)] ($n = 44$)		p[d)]		
	Baseline	6th week	Baseline	6th week	Time	Group	Time × group
hs-CRP[e)](mg/L)	2.52 ± 1.96	1.97 ± 1.80	1.65 ± 1.43	1.85 ± 1.91	0.14	0.03	0.26
sICAM-1[f)](μg/L)	426 ± 270	305 ± 169	362 ± 201	385 ± 246	0.04	0.02	0.14
sVCAM-1[g)](μg/L)	458 ± 202	292 ± 175	410 ± 239	378 ± 247	0.11	0.07	0.02
SAA[h)](mg/L)	3.38 ± 2.77	2.79 ± 2.48	3.21 ± 2.22	3.53 ± 2.62	0.04	0.02	0.37
Leptin (ng/L)	118.5 ± 101	107.0 ± 55.2	93.7 ± 71.1	130.5 ± 85.8	0.02	0.02	0.02

a) All data are geometric means ± SD.
b) Whole-grain group: consumed half of their needed servings of grains from whole-grain foods each day.
c) Individuals in the control group were also given a list of whole-grain foods and were asked not to consume any of these foods during the whole-grain phase of the study.
d) Results of repeated measures ANOVA.
e) hs-CRP: high-sensitive C-reactive protein.
f) sICAM-1: soluble intercellular adhesion molecule-1.
g) sVCAM-1: soluble vascular cell adhesion molecule-1.
h) SAA: serum amyloid A.

consume half of their needed servings of grains from whole grains. In reality, mean consumption of whole grains was 98 g/day in whole-grain group versus 11 g/day in control group in this study. Duration of intervention in previous studies was between 3 and 12 weeks. As both short- and long-term studies did not find significant effects of whole-grain intake on inflammation, duration of intervention cannot explain the significant effects. However, it must be kept in mind that all previous studies have been done in adults, not in children. Lack of control for some confounders such as physical activity or baseline values of adipocytokines can also help interpreting the discrepancies.

The mechanisms through which whole-grain intake might affect systemic inflammation remain to be understood. Whole-grain products are important dietary sources of vitamins, minerals, dietary fiber, phytoesterogens, and antioxidants, which may moderate their beneficial effects on inflammatory markers [32]. Earlier studies have shown the beneficial effects of dietary fiber on body weight regulation and lipids oxidation, which may reduce oxidative stress and inflammation [33, 34]. The favorable effect of whole grains on inflammation might also be mediated through their beneficial effects on glycemic status [35]. Previous studies have indicated that the abnormal glucose homeostasis could result in elevated levels of inflammatory biomarkers [36, 37]. Furthermore, whole-grain products are a rich source of magnesium, which has been shown to reduce inflammatory cytokines [38].

Some limitations need to be considered in the interpretation of our findings. Subjects were asked to consume the recommended amounts of whole grains at home and conducting a feeding trial was impossible for us. However, the adherence to the whole grains was assessed through dietary records. Based on the average of dietary intakes from these dietary records, it seems that the adherence of participants was relatively good. Although, concentrations of alkyl resorcinol in human plasma have been suggested to be biomarkers of dietary whole-grain intake, we could not measure this biomarker in the current study because of the budget limitations. Individuals in the whole-grain group consumed higher energy during the whole-grain phase than did subjects in control group; however, the difference was not significant. Slightly higher energy intake in the whole-grain group might contribute to lack of finding its favorable effect on some outcome variables. In addition, the limitations typically associated with crossover studies may make it difficult to detect the effects of whole grains on inflammatory markers. For instance, four subjects were dropped out during the intervention and we used their last available data for other periods based on the Last-Observation-Carried-Forward method. This might be a source of bias as patients randomized may complete the first period, but randomization typically does not occur at the second period. Also, there may be a residual or carry-over effect of treatments across study periods, which could potentially distort the results. Although, we did not find any evidence for carry-over effect in the current study, the effect of residual confounding cannot be excluded. Furthermore, there might be a "learning" effect in crossover trials. This is particularly of relevance to dietary whole grains. Although the current study has adequate power to detect the significant effects, further studies with longer duration of interventions might be needed to confirm the long-term health benefits of whole grains in children. Finally, it must be noted that sICAM, sVCAM, and SAA are not true inflammatory markers; all these biomarkers are adhesion molecules. Although there are some studies that label these indicators as inflammatory biomarkers [39, 40], it is better for future investigations to examine the effect of whole grains on more relevant inflammatory markers such as IL6, TNF-α, IL1 β, which are more direct markers of inflammation.

In conclusion, we found evidence indicating the favorable effects of whole-grain intake on serum levels of inflammatory biomarkers and adipocytokines in overweight children and adolescents.

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