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Comparison of Essential Fatty Acid Intakes and Serum Levels of Inflammatory Factors between Asthmatic and Healthy Adults: A Case- Control Study

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ABSTRACT

Dietary fatty acids play a critical role in modulation of airway inflammation in asthma. This study was conducted to compare dietary intakes of essential fatty acids and serum levels of inflammatory factors in asthmatic and healthy adults, and to examine the potential relationship between inflammatory markers and dietary fatty acids.

In this case-control study, 47 asthmatic patients (26 males and 21 females) were compared with 47 controls (24 males and 23 females). Blood samples were taken from case and control groups and tumor necrosis factor-α (TNF-α), high sensitive C-reactive protein (hs-CRP), leptin and adiponectin were determined. Dietary intakes were assessed by semi-quantitative food frequency questionnaire (FFQ).

Dietary intakes of omega-3 fatty acids were significantly lower in asthmatic patients compared to controls ($p<0.05$). Serum concentrations of TNF-α, hs-CRP and leptin were significantly higher in asthmatic patients. There was a significant negative relationship between adiponectin levels and saturated fatty acid intakes in both groups, but the relationship between adiponectin and mono-unsaturated fatty acid intakes was positive and significant only in asthmatic group. No significant correlation between other inflammatory factors and dietary intakes was found in this study.

Higher intake of omega-3 and lower levels of inflammatory factors in the healthy control group compared to asthmatic group may explain the protective role of essential fatty acids in asthma. Further studies with larger sample size are needed in this regard.

Keywords: Adiponectin; Asthma; Fatty acid; hs-CRP; Leptin; TNF-α

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by episodes of reversible breathing problems due to airway narrowing and obstruction.[1,2] According to estimates by World Health Organization (WHO), more than 300 million peoples globally have been diagnosed with asthma in 2009.[3] It is estimated that the number of people with asthma will grow by more than 100 million by 2025.[4] Despite progress in treatment and control, asthma has still remained a dominant illness in mortality, affection and cost.[5] Genetic, immunologic and environmental factors have been associated with the occurrence of asthma outbreaks.[6] Dietary factors and nutrients with a potentially protective role in inflammatory response have also been implicated in the genesis or evolution of asthma.[7] Recent studies suggest that the amount and type of dietary fatty acids play a critical role in modulation of airway inflammation and bronchodilator recovery in asthma.[4,8] The omega (ω)-6 fatty acids such as arachidonic acid have inflammatory effects, whereas ω-3 fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have anti-inflammatory effects, and these two types of fatty acids compete in the production of inflammatory lipid mediators.[3,5] The results of the Barkhordari et al. study in rats showed a significant direct relationship between the serum levels of arachidonic acid and IL-6. They also demonstrated a significant decrease in the level of IL-6 due to the increase in serum DHA and monounsaturated fatty acid (MUFA).[9] According to the results of the study carried out by Battle et al. in patients with stable chronic obstructive pulmonary disease (COPD), the more intakes of ω -3 fatty acids alpha-linolenic acid (ALA) and ω -6 fatty acids (AA) were related to the lower levels of tumor necrosis factor-alpha (TNF-α) and the higher levels of IL-6 and C-reactive protein (CRP), respectively.[10] The result of the study conducted by Kalogeropoulos in healthy men and women also indicated a significant positive correlation between plasma ω -6/ ω -3 ratio and inflammatory markers high sensitive-CRP (hs-CRP), IL-6, TNF-α, fibrinogen and homocysteine.[11]

Recent literatures suggest that there is an association between higher levels of inflammatory factors and increased airway inflammation and complication of asthma.[12,13] On the other hand, some studies have demonstrated that low intake of essential fatty acid (EFA) increased the levels of inflammatory markers.[9-11] However, most of the studies in this topic focused on other chronic inflammatory diseases rather than asthma, and also the effectiveness of different types of EFA are controversial.[10,14] Therefore, the present study was planned to compare the levels of inflammatory factors and dietary intakes of EFAs in asthmatic and healthy adults, and to examine the potential relationship between inflammatory markers and dietary intakes of EFA.

MATERIALS AND METHODS

Subjects

From September 2012 to March 2013, 47 cases with physician-diagnosed asthma according to American Thoracic Society (ATS) definition[15] were identified from asthma clinic of Ahvaz, Iran. 47 non-asthmatic controls of similar sex, age and body mass index (BMI) were randomly selected from the patient' entourages that satisfied the study base principles. To minimize bias due to seasonal variation, we tried to study matched cases and controls as closely as possible in time. Asthma severity was classified into four categories based on the combined assessments of symptoms, lung function and activity restrictions.[16] Cases and controls were informed that the researchers were interested in 'asthma and nutrition'. The exclusion criteria for both cases and controls were a diagnosis of diabetes, cardiovascular diseases, other metabolic or inflammatory disorders, acute and chronic pulmonary diseases (e.g. pneumonia, bronchitis and cystic fibrosis), autoimmune and infectious diseases, usage of dietary supplements, cholesterol-lowering or nonsteroidal anti-inflammatory drugs, pregnancy or current breastfeeding. The current study was approved by the Research Ethic Committee of Ahvaz Jundishapur University of Medical Sciences, Iran (B-9116). A written consent was obtained from all subjects. Anthropometric indices (weight, height, waist circumference (WC) and hip circumference (HC)) were measured and then waist-to-hip ratio (WHR) and BMI were determined. The body adiposity index (BAI) was also calculated using the equation BAI= ((hip circumference)/(height) $^{1.5}$) - 18). Dietary intakes were assessed by interviewing complete semi-quantitative food frequency questionnaire (FFQ) including 168 items which had previously been validated and adapted to assess intakes of the main nutrients and food groups.[17] Nutritionist IV (N4) program was used to estimate dietary intake of patients in this study.

Biochemical Analysis

Fasting venous blood samples were obtained and sera were separated and maintained at -70°C until assay. For controlling hormone variation, blood samples were not collected during the menstrual period in women. TNF-α, hs-CRP, leptin and adiponectin were measured by using an enzyme-linked immunosorbent assay method and with commercial reagents (Orgenium laboratories-Finland for TNF-α, leptin and adiponectin, and Labor Diagnostika Nord for hs-CRP) according to the manufacturer's specifications.

Statistical Analysis

All data were presented as mean±SD. Normal distribution of all variables was checked with the Kolmogorov-Smirnov test. We compared absolute intake of dietary fatty acids and levels of inflammatory factors between cases and controls with Independent sample t test, and adjusted for covariates by ANCOVA. The correlations between variables were controlled for the effects of confounders by partial correlation. The differences with *p* values less than 0.05 were considered as significant. All statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA) Program version 18.0 for windows.

RESULTS

In total, 94 adults with 33.18±6.10 years of age were included in the study. Cases were 47 adults (26 males, 21 females) with asthma and controls were 47 healthy adults (24 males, 23 females). Table 1 summarizes the demographic and anthropometric characteristics of the participants in this study. Cases and controls were similar, with no statistically significant differences in weight, height, BMI, WC and HC, WHR and BAI ($p>0.05$).

Dietary intakes of participants are presented in Table 2. No significant differences were observed regarding the amount of calorie, protein and carbohydrate intake between asthmatic and healthy subjects. However, dietary intakes of total fat, saturated fatty acids (SFAs), MUFAs, poly unsaturated fatty acids (PUFAs), total ω-3, ALA, EPA, DHA and cholesterol were significantly higher in control group compared to asthmatic patients ($p<0.05$). However, the ω-6/ω-3 ratio was significantly higher in asthmatic group compared to controls ($p<0.05$).

As presented in Table 3, there were significant differences between two groups regarding the serum levels of inflammatory biomarkers. As serum concentrations of TNF-α, hs-CRP and leptin were significantly higher in the asthmatic group than in the control group ($p=0.000$, $p=0.018$ and $p=0.000$, respectively). This significance remained even after adjusting for sex, age, energy intake, BAI and WHR. In the adjusted model, the asthmatic group also showed significant lower concentrations of adiponectin than the control group ($p=0.049$).

Table 1. Demographic and anthropometric characteristics of asthmatic patients and healthy controls

Variables	Asthmatics (n=47) Mean ± SD	Controls (n=47) Mean ± SD	P*
Age (years)	31.28±7.33	35.08±4.87	0.054
Asthma severity			
Step 1 n (%)	11 (23.4)	-	
Step 2 n (%)	15 (31.9)	-	
Step 3 n (%)	12 (25.5)	-	
Step 4 n (%)	9 (19.1)	-	
Weight (kg)	68.97±9.26	71.26±10.32	0.261
BMI (kg/m^2)	24.55±2.80	24.57±2.63	0.967
WC (cm)	84.94±7.58	84.27±8.52	0.688
HC (cm)	100.60±6.04	100.97±5.65	0.758
WHR	0.84±0.06	0.83±0.05	0.377
BAI	28.56±4.53	27.74±4.47	0.383

*: Independent sample t test. BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; BAI: body adiposity index.

Table 2. Dietary intakes of asthmatic patients and healthy controls

Variables	Asthmatics (n=47) Mean ± SD	Controls (n=47) Mean ± SD	*P* *
Energy (Kcal)	2495 ± 487.90	2574 ± 558.10	0.466
Protein (gr)	97.58 ± 26.37	104.79 ± 26.86	0.192
Carbohydrate (gr)	329.28 ± 72.51	319.77 ± 75.98	0.536
Total fat (gr)	77.80 ± 20.77	84.45 ± 20.19	0.019
Cholesterol (mg)	225.73 ± 93.54	285.13 ± 129.93	0.013
SFA (gr)	22.06 ± 5.91	26.28 ± 7.07	0.002
MUFAs (gr)	27.37 ± 7.85	30.71 ± 8.08	0.045
PUFAs (gr)	25.68 ± 5.58	28.18 ± 5.41	0.030
Total omega-6 (gr)	24.41 ± 5.34	26.21 ±5.34	0.104
Total omega-3 (gr)	1.28 ±0.86	1.97 ±0 .98	0.000
Omega-6 / Omega-3	29.20 ± 20.53	18.13 ± 11.93	0.002
Oleic acid (gr)	23.22 ± 7.73	24.87 ± 6.61	0.270
Linoleic acid (gr)	22.31 ± 5.42	23.10 ± 5.37	0.476
ALA (mg)	828 ± 416	1070 ± 554	0.018
EPA(mg)	222 ± 312	438 ± 367	0.003
DHA(mg)	224 ± 312	454 ± 375	0.002

*: Independent sample t test. SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; ALA: alphalinolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

Table 3. Serum levels of inflammatory markers in asthmatic patients and healthy controls

Variables	Asthmatics (n=47) Mean ± SD	Controls (n=47) Mean ± SD	P_1	P_2
TNF-α (pg/ml)	15.00±4.18	4.21±1.63	0.000	0.000
hs-CRP (mg/l)	3.30±1.82	2.50±1.13	0.018	0.002
Leptin (ng/ml)	1.41±0.50	0.59±0.19	0.000	0.000
Adiponectin (ng/ml)	6.68±2.07	7.55±2.10	0.052	0.049

P_1 =Independent sample t test. P_2 = Adjusted for sex, age, energy intake, BAI and WHR by ANCOVA.

Table 4. Correlation between serum levels of inflammatory factors and anthropometric indices in asthmatic patients and healthy controls [1]

Variables		Adiponectin (ng/ml)		Leptin (ng/ml)		TNF-α (pg/ml)		hs-CRP (mg/l)	
		Asthmatics	Controls	Asthmatics	Controls	Asthmatics	Controls	Asthmatics	Controls
Weight (kg)	r	0.009	-0.231	0.117	0.429	-0.003	0.039	0.111	-0.067
	P	0.956	0.128	0.444	0.004	0.984	0.794	0.242	0.669
BMI ($kg/m^{2)}$	r	-0.009	-0.128	-0.026	0.260	0.018	-0.042	0.064	-0.167
	P	0.952	0.403	0.866	0.092	0.910	0.781	0.345	0.284
WC (cm)	r	-0.183	-0.245	0.062	0.426	-0.109	0.102	0.152	-0.165
	P	0.228	0.105	0.685	0.004	0.480	0.494	0.168	0.291
HC (cm)	r	-0.116	-0.081	-0.063	0.249	-0.008	-0.096	0.082	0.006
	P	0.449	0.598	0.679	0.108	0.958	0.521	0.302	0.969
WHR	r	-0.133	-0.284	0.134	0.385	-0.122	0.234	0.120	-0.228
	P	0.383	0.059	0.381	0.011	0.430	0.113	0.224	0.141
BAI	R	-0.990	0.142	-0.194	-0.132	0.006	-0.151	0.005	-0.065
	P	0.516	0.352	0.201	0.399	0.969	0.310	0.973	0.679

[1] Controlling for the effects of sex, age and energy intake by partial correlation;
BMI: body mass index; WC: waist circumference; HC: hip circumference; WHR: waist to hip ratio; BAI: body adiposity index.

Table 5. Correlation between serum levels of inflammatory factors and dietary intakes in asthmatic patients and healthy controls

		Adiponectin (ng/ml)		Leptin (ng/ml)		TNF-α (pg/ml)		hs-CRP (mg/l)	
		Asthmatics	controls	Asthmatics	controls	Asthmatics	controls	Asthmatics	controls
Total fat (gr)	r	0.263	0.066	0.289	0.331	0.040	0.058	0.150	-0.008
	P	0.081	0.668	0.054	0.030	0.397	0.349	0.172	0.481
SFA (gr)	r	-0.319	-0.356	0.001	0.267	0.171	-0.004	-0.072	-0.173
	P	0.033	0.016	0.995	0.083	0.133	0.489	0.325	0.133
MUFA (gr)	r	0.356	0.111	0.097	0.210	0.166	0.067	0.230	-0.034
	P	0.016	0.466	0.524	0.177	0.141	0.328	0.071	0.413
PUFA (gr)	r	0.264	0.008	0.275	0.215	-0.095	-0.039	0.174	-0.016
	P	0.080	0.959	0.068	0.167	0.269	0.396	0.135	0.460
Total ω-6 (gr)	r	0.266	-0.004	0.293	0.193	-0.095	-0.044	0.174	0.002
	P	0.077	0.981	0.151	0.215	0.537	0.767	0.271	0.987
Total ω-3 (gr)	r	0.063	0.063	-0.024	0.129	-0.023	0.024	0.053	0.101
	P	0.681	0.679	0.874	0.411	0.880	0.874	0.738	0.520
ω-6:ω-3 ratio	r	-0.093	0.037	0.073	-0.001	-0.030	-.072	-0.192	0.202
	P	0.544	0.807	0.634	0.997	0.847	0.630	0.222	0.195
Oleic acid (gr)	r	0.322	0.061	0.075	0.215	0.198	0.049	0.258	-0.056
	P	0.031	0.690	0.623	0.166	0.098	0.371	0.050	0.360
Linoleic acid (gr)	r	0.257	0.000	0.294	0.173	-0.090	-0.048	0.173	0.055
	P	0.089	0.999	0.050	0.169	0.281	0.373	0.136	0.364
ALA (mg)	r	0.101	0.046	-0.082	0.169	0.078	0.024	0.045	-0.045
	P	0.509	0.765	0.592	0.279	0.307	0.436	0.390	0.388
EPA (mg)	r	0.021	0.044	0.021	0.052	-0.071	0.009	0.048	-0.107
	P	0.892	0.773	0.890	0.738	0.324	0.477	0.381	0.247
DHA (mg)	r	0.020	0.056	0.019	0.038	-0.071	0.018	0.049	-0.096
	P	0.894	0.717	0.899	0.808	0.323	0.451	0.379	0.271

[1] Controlling for the effects of sex, age, WHR, BAI and energy intake by partial correlation; SFA: saturated fatty acid; MUFA: monounsaturated fatty acid; PUFA: polyunsaturated fatty acid; ALA: alphalinolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.

In the present study, after controlling for the effects of sex, age and energy intake by partial correlation, leptin concentrations were significantly correlated with weight, WC and WHR in the control group (p=0.004, p=0.004 and p=0.011, respectively). But, this effect was not seen in the asthmatic group (Table 4).

As shown in Table 5, in our study a significant negative correlation between serum adiponectin levels and SFA intake was identified in the asthmatic and control groups (r=-0.319, p=0.033 and r=-0.356, p=0.016, respectively). Moreover, adiponectin concentrations were also positively correlated with dietary intake of MUFAs (r=0.356, p=0.016) and oleic acid (r=0.322, p=0.031) in the asthmatic group. Serum levels of leptin displayed a significant positive correlation with total fat intake in the control group (r=0.331, p=0.030), but no significant correlation between other inflammatory factors and dietary intakes was found in the asthmatic and control groups.

DISCUSSION

The aim of this study was to compare both dietary intakes of essential fatty acids and serum levels of inflammatory factors between asthmatic and healthy adults and to test the possible relationship between these parameters. Our findings were consistent with the hypothesis that ω-3 fatty acids are protective in asthma,[18,19] and indicated that dietary intake of ALA, EPA and DHA were significantly higher in healthy group compared to asthmatic patients. A large population-based study by Laerum et al. showed that low current fish intake was associated with greater odds of asthma and wheeze.[20] A cross-sectional study by Miyamoto et al. also indicated a significant inverse association between fish intake and the prevalence of

asthma in young female Japanese adult.[21]

It has been suggested that higher intake of ω-6 fatty acids, particularly linoleic acid, and lower intake of ω-3 fatty acids may be involved in the inflammatory process of asthma.[22] This effect may be mediated by effects of PUFAs on eicosanoid production and inflammatory cell membrane fluidity.[23] It has been implied that ω-3 fatty acids inhibit the conversation of linoleic acid to arachidonic acid, the precursor of prostaglandin E2 (PGE2).[24] Decreased production of PGE2 consequently leads to the diminished production of IL- 4, IL- 5 and IL- 10 from T-cells (Th_2-cytokines) and increased production of Interferon-gamma and IL-2 (Th_1-cytokines).[25]

In the present study, the serum levels of inflammatory factors (TNF-α, hs-CRP and leptin) were significantly higher in asthmatic group than those in healthy group. Similarly, Olafsdottir et al. indicated asthmatic patients had higher levels of hs-CRP than healthy individuals and hs-CRP level was significantly associated with respiratory symptoms and non-allergic asthma.[26] A population-based study by Jousilahti et al. also indicated more concentration of CRP among asthmatics comparing to healthy individuals.[27] It has been proposed that ω-3 fatty acids can modulate inflammatory process by inhibiting the production of pro-inflammatory cytokines.[22,25] Epidemiologic studies also indicated a relationship between the little amount of EPA and DHA intake and the higher levels of hs-CRP.[28] Therefore, the low intake of EPA and DHA in asthmatic group could reinforce the elevated levels of inflammatory factors in these patients. However, the correlation between inflammatory factors and dietary intakes of ω-6, ω-3 and ω-6: ω-3 ratio was not statistically significant in our study. Since the main objective of this study was focused on the comparison between asthmatic and healthy groups, the present study was designed as a case-control study. Therefore, the relatively small sample size could explaine the lack of statistical significance for correlation results.

Our results also showed that the ratio of ω-6: ω-3 intake was considerably higher than the ideal ratio (1:1) in both groups. This could be partially explained by the nutritional transition, which occurred in developing countries.[29]

Fatty acids have been recognized as the important modulator of visceral fat adipokine expression like leptin or adiponectin directly by interaction with transcription factors, or indirectly via unknown mechanisms, possibly linked to fatty acid oxidation, synthesis or storage.[30,31] Leptin has systemic pro-inflammatory effects that could be related to asthma pathogenesis.[32,33] The human data regarding the correlation between serum adipokine levels and the risk of asthma are inconclusive.[32] In a large Finnish cohort study, Jartti and coworkers did not show any independent association between serum leptin concentrations and asthma prevalence.[34] However, a large cross-sectional population-based study in the United State showed a positive association between the highest quartile of serum leptin concentration and the risk for asthma in women.[33] The present study also showed that asthmatics significantly had higher leptin levels comparing to healthy individuals. A significant positive correlation between leptin levels and weight, WC, WHR and total fat intake was also found in the healthy control group. As previously mentioned, leptin is a new hormone of adipose tissue and a relationship between leptin level and BMI, WC, and WHR has been demonstrated in several studies.[33] However, the results of the present study did not show any significant correlation between leptin and anthropometric indices in the asthmatic groups. It seems that the higher levels of leptin in asthmatic patients was affected by disease-induced inflammation rather than adiposity or related anthropometric indices.[35] Furthermore, being in the normal weight range of study population and relatively small sample size of the survey may disrupt some of statistical correlations.

Several studies have shown that leptin concentration is associated with nutrient intake. Fatty acids are as the potential modifiers for leptin concentration.[30,31,36] In the present study, higher intake of dietary fat was associated with higher serum leptin levels. Similar results were also reported by Penumetcha et al.[37] According to the previous studies, fatty acids are strong ligands for peroxisome proliferative-activated receptor gamma (PPARγ) that, by acting via PPARγ, could influence on adipose tissue metabolism and increase leptin secretion.[37]

In contrast, adiponectin inhibits pro-inflammatory signaling via suppression of nuclear factor κappa B (NF κB) and induces the anti-inflammatory cytokines including IL-10.[32,33] In most studies, low adiponectin levels are associated with the elevated levels of pro-inflammatory cytokines including TNF-α, IL-6 and CRP.[31,38] So the higher levels of pro-inflammatory cytokines might justify the lower levels of adiponectin in

asthmatic patients compared to healthy group in this study. Similarly, in a study carried by Guzik, a protective association between serum adiponectin concentration and the risk for asthma was reported.[32] Sood A et al. also showed that the mean of serum adiponectin concentration was lower in asthmatic women than those in healthy womens.[39] In the present study, a significant negative correlation between serum adiponectin levels and saturated fatty acid intakes was identified in both groups. There is too little information regarding the relation between adiponectin levels and dietary intakes in asthma. Fernandez-Real et al. also showed a negative association between circulating levels of adiponectin and palmitate (a major dietary SFA) in human serum.[40] According to the previous studies SFAs (such as palmitate) inhibit the transcription of adiponectin gene and the release of adiponectin from fat cells. Palmitate may also increase lysosomal degradation of newly synthesized adiponectin.[41] The important strengths of our study were the case- control design, considering essential fatty acids separately in the form of ω-3 and ω-6 regarding asthma, and also using appropriate statistical analysis to adjust the effect of other confounding variables related to asthma. Because of some limitations, sophisticated laboratory tests and spirometric data were not collected in this study.

As a summary, higher intake of ω-3 fatty acids and lower levels of inflammatory factors in the healthy control group compared to asthmatic group may explain the protective role of essential fatty acids in asthma. However, no significant correlation between ω-3 and ω-6 intakes and serum levels of inflammatory factors was found in this study. Therefore, subsequent studies with larger sample size are needed in this regard.

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