Original Article

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Association between Omega-6 and Omega-3 Polyunsaturated Fatty Acids Intake and *IL-6* G(-174)C Polymorphism with Hs-CRP Level in Healthy Subjects

Sağlıklı Bireylerde Omega-6 ve Omega-3 Çoklu Doymamış Yağ Asitleri Tüketimi ve *İL-6* Geni G(-174)C Polimorfizmlerinin Yd-CRP Düzeyi ile İlişkisi

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ABSTRACT

Objective: Studies have shown that omega-3 and omega-6 polyunsaturated fatty acids play a major role in the prevention of inflammation, and interleukin-6 (IL-6) levels can be associated with inflammation. The aim of this study was to investigate the relationship between G(-174)C polymorphism of *IL-6* gene with dietary omega-3 and omega-6 intake and high sensitive C-reactive protein (CRP) (hs-CRP] level.

Methods: This retrospective studywas carried out with a total of 302 healthy individuals, 152 women and 150 men, with a mean age of 50.1 years. Food consumption records, biochemical measurements, and genetic analyzes of individuals were recorded from patient files. Daily energy, fat, cholesterol, omega-6 and omega-3 intakes were evaluated from food consumption records.

Results: The CC variation was observed in 7%, GC variation in 31%, and GG variation in 62% of the subjects. Dietary cholesterol intake of individuals with CC variation and omega-6/omega-3 intake of individuals with GG variation were found to be positively and significantly correlated with hs-CRP (r=0.155; p=0.035).

Conclusion: Inflammation is the complete response of the organism to the stimuli. In order to prevent the formation of inflammation, it is recommended that individuals with GG variation increase their omega-6/omega-3 consumption rates in their diets towards omega-3.

Keywords: IL-6, G(-174)C, CRP, omega-3, omega-6

ÖZ

Amaç: Yapılan çalışmalar, enflamasyonun önlenmesinde omega-3 ve omega-6 çoklu doymamış yağ asitlerinin büyük rol oynadığını ve interlökin-6 (İL-6) seviyelerinin enflamasyonla ilişkilendirilebileceğini ortaya koymuştur. Bu araştırmanın amacı, *İL-6* geninin G(-174)C polimorfizminin diyetle omega-3 ve omega-6 alımı ve yüksek duyarlı C-reaktif protein (CRP) yd-CRP seviyesi ile ilişkisini araştırmaktır.

Yöntemler: Retrospektif olarak yürütülen bu araştırma, özel bir sağlık kurumuna başvurmuş olan yaş ortalaması 50,1±12,4 yıl olan 152 kadın, 150 erkek, toplam 302 sağlıklı birey ile gerçekleştirilmiştir. Bireylerin besin tüketim kayıtları, biyokimyasal ölçümleri ve genetik analizleri hasta dosyalarından kaydedilmiştir. Besin tüketim kayıtlarından günlük enerji, yağ, kolesterol, omega-6 ve omega-3 alım miktarları hesaplanmıştır.

Bulgular: Bireylerin %7'sinde CC varyasyonu, %31'inde GC varyasyonu ve %62'sinde GG varyasyonu bulunmuştur. CC varyasyonu görülen bireylerin diyet kolesterol alımları ve GG varyasyonu görülen bireylerin omega-6/omega-3 alımları ile yd-CRP arasında pozitif yönde ve anlamlı bir ilişki olduğu belirlenmiştir (r=0,155; p=0,035).

Sonuç: Enflamasyon, organizmanın uyaranlar karşısında başlatmış olduğu yanıtların tamamıdır. Enflamasyon oluşumunun engellenmesi için GG varyasyonuna sahip bireylerin diyetlerindeki omega-6/omega-3 tüketim oranlarını omega-3 yönünde artırmaları önerilmektedir.

Anahtar Sözcükler: İL-6, G(-174)C, CRP, omega-3, omega-6

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Introduction

According to the report published by the World Health Organization in 2016, 71% of the causes of death worldwide are cardiovascular diseases, cancer, respiratory system diseases and diabetes (1). It is stated that the basis of these diseases is the inflammatory response process (2).

All of the responses initiated by the organism against exogenous and endogenous stimuli and necessary for vital continuity are considered as inflammatory responses (3). Numerous single point polymorphisms (single nucleotide polymorphism) have been defined in the interleukin (*IL*)-*6* gene in scientific studies (4-7). It is stated that IL-6 G(-174)C polymorphism is related to the formation of systemic inflammatory response. Specific inflammatory mediators such as IL-6 and C-reactive protein (CRP) are closely associated with inflammation (8). CRP is an acute phase protein, level of which increases immediately in case of inflammation and is synthesized in the liver under the control of IL-6. High sensitivity CRP (hs-CRP) is a value that is not different from normal CRP, only a more sensitive measurement system is used. Hs-CRP, which is more sensitive than standard CRP test, can detect inflammation that CRP cannot detect (9).

Inflammation, which is one of the basic components of the immune system, plays a critical role in the daily diet nutrients. Therefore, nutrition is defined as meeting the energy and nutritional needs of the individual, as well as strengthening the immune system and turning the inflammatory response in its favor (10).

It is known that fatty acids, which are an important component of nutrition, have an effect on immune functions both pathologically and physiologically (11). A diet rich in omega-3 polyunsaturated fatty acids suppresses inflammatory metabolism, while excessive consumption of omega-6 polyunsaturated fatty acids plays a role in increasing inflammation (12). Although there are various recommendations regarding the omega-6/omega-3 ratios that should be taken in the daily diet, it has been shown that inflammation markers decrease as the ratio approaches 1/1 (13). For this reason, it is extremely important to increase omega-6/omega-3 consumption in the daily diet in the direction of omega-3 (12).

According to the hypothesis of the research, high dietary omega-6/omega-3 consumption ratio increases yd-CRP levels with G(-174)C polymorphisms of *IL-6* gene. In this direction, the aim of the study was to investigate the relationship between G(-174)C polymorphisms of the *IL-6* gene and dietary omega-3 and omega-6 ratios and hs-CRP levels in individuals who were admitted to a health institution for genetic analysis.

Methods

The research was planned and conducted retrospectively. Inclusion criteria for the study were determined as being over the age of 18, not having a chronic disease, not using non-steroidal anti-inflammatory drugs (NSAIDs), having genetic tests done, and volunteering to use the registered information for research purposes. The research was conducted with a total of 302 healthy individuals, 152 women and 150 men, with an average age of 50.1±12.40 years, who were admitted to a private genetic testing center in Istanbul and had their genetic tests done between January 2015 and February 2018. Since the research was carried out retrospectively and with recorded data, the entire universe was included in the study without making a sample calculation.

This research was conducted after it was approved by the Ethics Committee with the decision number 9 at the meeting of the Ethics Committee of Okan University, dated 12.03.2018 and numbered 92. Institutional approval was obtained from the genetic testing center in order to conduct the research. It was conducted on a voluntary basis with individuals who agreed to participate in the research. When individuals were first admitted to the genetic testing center, approval was obtained that they would allow the use of their information for research purposes. After obtaining the consent of the individuals, the information form filled face to face by the dietician included the personal information of the individuals, anthropometric measurements, food consumption, exercise status, biochemical measurements and genetic analysis. Food consumption frequency, serum hs-CRP values and IL-6 G(-174)C analysis results were obtained from the information form of the individuals and used in the study.

While recording the frequency of food consumption, the foods consumed by the individuals on average for a year were questioned with the help of the food atlas and recorded in the patient information form. The frequency of food consumption from archived files was mathematically converted into one-day amounts. Daily energy, fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol, and omega-6 and omega-3 intakes were analyzed in the Nutrition Information System 7.2 (Pacific Company) program. These determined values were evaluated according to the recommended intake levels with reference to the Turkish Dietary Guidelines (TÜBER-2015). Presence of IL-6 G(-174)C polymorphism analyzed by using mass spectrometry (MassSpectrometer, MS) method and hs-CRP levels measured by using immunoturbidimetric method with Cobas 6000 (Roche Diagnostics International Ltd., Switzerland) device were taken from archived patient files.

Statistical Analysis

The data were evaluated with SPSS (v22.0) statistical program. Categorical variables were expressed as numbers (n) and percentage (%), continuous variables were expressed as mean ($\bar{X}$), standard deviation (SD). Shapiro-Wilks, one of the normal distribution tests, was used in the analysis of the data, and parametric tests were used because the data showed normal distribution. The means of more than two independent groups were compared with the "one-way ANOVA test". Pearson correlation coefficient was calculated for the relationship between numerical measurements. A p value <0.05 was considered statistically significant.

Results

A total of 302 individuals were included in the study to examine the effects of omega-6/omega-3 intake and *IL-6* gene G(-174)

C polymorphism on hs-CRP levels in healthy individuals. The mean age of the individuals was 50.1±12.40 years, and the mean body mass index was 27.3 kg/m^2 (lower-upper: 16.4-46.1 kg/m^2). The mean hs-CRP value was found to be 2.9±4.2 mg/L. Of the individuals 7.0% had the CC, 31.0% CG and 62% GG genotypes (not shown in the Table).

The comparison of hs-CRP levels according to *IL-6* gene variations in individuals included in the study is given in Table 1. There was no statistically significant difference between the mean hs-CRP values of the individuals and the polymorphism groups (p>0.05).

Comparison of energy and fat intake values according to *IL-6* gene variations is shown in Table 2. When the differences between the polymorphism groups in terms of the energy and fat intakes from the daily foods were evaluated, there was no significant difference between the mean daily dietary fat intake of individuals (p>0.05), only the saturated fat (%) intake differed significantly between polymorphism groups (p<0.05). The mean values of saturated fat (%) of individuals with CC polymorphism were significantly higher than the mean values of individuals with GC and GG polymorphisms (Table 2).

The correlation between daily energy and fat intake and blood hs-CRP levels of individuals with *IL-6* gene CC variation is shown in Table 3. There was a positive and significant relationship between individuals' cholesterol intake and hs-CRP level (p<0.05). As individuals' cholesterol intake increased, hs-CRP levels increased at the same rate (Table 3).

As shown in Table 4, there was no statistically significant correlation between daily energy and fat intake and blood hs-CRP levels of individuals with *IL-6* gene GC variation (p<0.05).

The correlation between daily energy and dietary fat intakes and blood hs-CRP levels of individuals with *IL-6* gene GG variation is shown in Table 5. There was a positive and significant relationship between individuals' omega-6/omega-3 intake ratio and hs-CRP level (p<0.05). As the omega-6/omega-3 intake ratio increased, the hs-CRP level also increased (Table 5).

Discussion

Within the scope of this study, the relationship between *IL-6* gene G(-174)C polymorphisms and dietary omega-3/omega-6 ratios and hs-CRP levels were investigated in individuals who did not use NSAIDs.

When hs-CRP levels of individuals were compared with daily energy and fat intake values, cholesterol intake (p<0.05) in CC

Table 1. Comparison of *IL-6* gene variations and hs-CRP levels

	SNP	S	χ^2	SS	F	p
hs-CRP (mg/L)	CC	21	3.4	5.1	1.002	0.368
	GC	94	3.3	5.3		
	GG	187	2.6	3.4		

One-Way ANOVA test. p>0.05
hs-CRP: High-sensitive C-reactive protein, F: Frequency

Table 2. Comparison of *IL-6* gene variations and energy and fat intake values

Energy and fat intake	*IL-6* gene	S	χ^2	SS	F	p
Energy (kcal)	CC	21	2.127	567.6	0.273	0.761
	GC	94	2.070	644.4		
	GG	187	2.032	637.3		
Fat (g)	CC	21	97.5	31.9	0.523	0.593
	GC	94	103.9	35.8		
	GG	187	99.7	36.7		
Fat %	CC	21	41.4	8.2	1.856	0.158
	GC	94	44.8	8.2		
	GG	187	43.9	7.0		
SFA (g)	CC	21	28.9	8.6	1.375	0.254
	GC	94	33.2	13.0		
	GG	187	31.1	13.2		
SFA (%)	CC	21	12.4	2.9	4.493	0.012
	GC	94	14.7	4.1		
	GG	187	13.7	3.3		
MUFA (g)	CC	21	40.3	16.5	0.606	0.546
	GC	94	41.7	16.5		
	GG	187	39.5	15.8		
MUFA (%)	CC	21	17.1	4.8	1.100	0.334
	GC	94	18.1	4.1		
	GG	187	17.4	3.8		
PUFA (g)	CC	21	22.1	9.7	0.325	0.723
	GC	94	23.2	10.1		
	GG	187	22.3	10.1		
PUFA (%)	CC	21	9.3	2.9	0.841	0.432
	GC	94	10.2	3.5		
	GG	187	9.9	3.2		
Cholesterol (mg)	CC	21	335.3	142.7	0.310	0.734
	GC	94	366.8	158.4		
	GG	187	362.0	172.0		
Omega-3 (mg)	CC	21	2.5	0.9	1.403	0.247
	GC	94	2.8	1.4		
	GG	187	2.6	1.2		
Omega-6 (mg)	CC	21	19.6	9.2	0.182	0.834
	GC	94	20.4	9.0		
	GG	187	19.8	9.3		
Omega-6/ omega-3	CC	21	8.0	3.2	0.592	0.554
	GC	94	7.7	2.7		
	GG	187	8.1	3.1		
ALA (mg)	CC	21	1.5	0.6	2.806	0.062
	GC	94	2.0	0.9		
	GG	187	2.1	1.0		
EPA+DHA (mg)	CC	21	0.4	0.3	2.570	0.078
	GC	94	0.6	0.6		
	GG	187	0.5	0.4		

ALA: Alpha linolenic acid, DHA: Docosahexanoic acid, EPA: Eicosapentaenoic acid, F: Frequency, g: Grams, kcal: Kilocalorie, mg: milligrams, MUFA: Monounsaturated fatty acid, PUFA: Polyunsaturated fatty acid, SFA: Saturated fatty acid

genotype and omega-6/omega-3 intake ratio ($p<0.05$) in GG genotype were found be significantly different. It was found that hs-CRP levels increased as individuals' cholesterol and omega-6/omega-3 intake ratios increased.

Karaman (14) investigated the relationship between *IL-6* gene variants and hypertension in the population of Adıyaman. It was stated that 63.9% of the population had GG, 31.5% GC and 4.6% CC variations of IL-6 G(-174)C polymorphism in the healthy group. Ferrari et al. (15) investigated the relationship between IL-6 promoter polymorphisms, diet and lifestyle factors, bone mass and osteoporosis, and it was reported that 13.7% of the participants had CC variation, 50% CG variation, and 36.3% GG variation. Lacopetta et al. (16), on the other hand, stated that they detected the CC allele in 21%, CG in 44%, and GG in 35%, according to the results of their study only on women. Examining the relationship between IL-6 and CRP gene polymorphisms in obese children with metabolic syndrome, Todendi et al. (17) showed that 45.3% of them had GG, 43.8% GC, and 10.9% CC variation in their study with 470 students in Brazil. Although genetic polymorphisms of IL-6 have different effects on diseases, they may have different allele structures in each population and may not be a determining factor for the population.

Table 3. Correlation between diet, daily energy and fat intake and blood hs-CRP levels of individuals with CC variation (n=21)

Energy and fat intake	χ^2 ± SD		hs-CRP
Energy (kcal)	2127.5 (567.6)	r	0.336
		p	0.136
Fat (g)	97.5 (31.9)	r	0.144
		p	0.533
Fat %	41.4 (8.2)	r	-0.256
		p	0.262
SFA (g)	28.9 (8.6)	r	0.153
		p	0.508
SFA(%)	12.4 (2.9)	r	-0.190
		p	0.409
MUFA(g)	40.3 (16.5)	r	0.133
		p	0.566
MUFA (%)	17.1 (4.8)	r	-0.178
		p	0.440
PUFA (g)	22.1 (9.7)	r	0.051
		p	0.827
PUFA (%)	9.3 (2.9)	r	-0.219
		p	0.341
Cholesterol (mg)	335.3 (142.7)	r	0.502*
		p	0.020
Omega-3 (mg)	2.5 (0.9)	r	0.106
		p	0.648
Omega-6 (mg)	19.6 (9.2)	r	0.043
		p	0.852
Omega-6/omega-3	8 (3.2)	r	-0.086
		p	0.709
ALA (mg)	1.5 (0.6)	r	0.073
		p	0.752
EPA+DHA (mg)	0.4 (0.3)	r	0.143
		p	0.537

ALA: Alpha linolenic acid, DHA: Docosahexanoic acid, EPA: Eicosapentaenoic acid, g: Grams, kcal: Kilocalorie, mg: milligrams, MUFA: Monounsaturated fatty acid, PUFA: Polyunsaturated fatty acid, SFA: Saturated fatty acid, SD: Standard deviation, hs-CRP: High sensitivity C-reactive protein

Table 4. Correlation between dietary, daily energy and fat intake and blood hs-CRP levels of individuals with GC variation (n=94)

Energy and fat intake	χ^2 ± SD		hs-CRP
Energy (kcal)	2070.2 (644.4)	r	0.057
		p	0.583
Fat (g)	103.9 (35.8)	r	-0.056
		p	0.594
Fat %	44.8 (8.2)	r	-0.167
		p	0.108
SFA (g)	33.2 (13)	r	-0.091
		p	0.382
SFA (%)	14.7 (4.1)	r	-0.151
		p	0.146
MUFA (g)	41.7 (16.5)	r	-0.009
		p	0.929
MUFA (%)	18.1 (4.1)	r	-0.116
		p	0.267
PUFA (g)	23.2 (10.1)	r	-0.082
		p	0.430
PUFA (%)	10.2 (3.5)	r	-0.168
		p	0.105
Cholesterol (mg)	366.8 (158.4)	r	-0.007
		p	0.945
Omega-3 (mg)	2.8 (1.4)	r	-0.193
		p	0.063
Omega-6 (mg)	20.4 (9)	r	-0.065
		p	0.536
Omega-6/omega-3	7.7 (2.7)	r	0.162
		p	0.120
ALA (mg)	2 (0.9)	r	0.026
		p	0.802
EPA + DHA (mg)	0.6 (0.6)	r	0.056
		p	0.590

ALA: Alpha linolenic acid, DHA: Docosahexanoic acid, EPA: Eicosapentaenoic acid, g: Grams, kcal: Kilocalorie, mg: milligrams, MUFA: Monounsaturated fatty acid, PUFA: Polyunsaturated fatty acid, SFA: Saturated fatty acid, SD: Standard deviation, hs-CRP: High sensitivity C-reactive protein

In the study of Aslan (18) in which they compared serum hepcidin levels with CRP and IL-6 levels in neonatal sepsis, they found statistically strong and significant relationships between IL-6 and CRP values. Tonet et al. (19) investigated the relationship between the G(-174G)C polymorphism of the *IL-6* gene and cardiovascular disease risk factors in elderly women in Brazil and stated that GG homozygotes had higher serum IL-6 and yd-CRP levels compared to carriers of the C allele. It has also been emphasized that GG homozygotes are more prone to inflammatory diseases than other alleles. According to another study investigating the relationship between the alleles of CRP and IL-6, it was stated that the IL-6 -174CC genotype was associated with significantly worse overall survival compared to the GG or GC genotypes. It has been shown that people with the CC allele are more prone to inflammation than those with the CG and GG alleles (16). However, in this study, mean hs-CRP values of individuals did not differ significantly between polymorphism groups (p>0.05) (Table 2).

Table 5. Correlation between diet, daily energy and fat intake and blood hs-CRP levels of individuals with GG variation (n=187)

Energy and fat intake	χ^2 ± SD		hs-CRP
Energy (kcal)	2032.7 (637.3)	r	0.019
		p	0.800
Fat (g)	99.7 (36.7)	r	-0.016
		p	0.831
Fat %	43.9 (7)	r	-0.103
		p	0.162
SFA (g)	31.1 (13.2)	r	-0.044
		p	0.548
SFA (%)	13.7 (3.3)	r	-0.092
		p	0.211
MUFA (g)	39.5 (15.8)	r	-0.022
		p	0.760
MUFA (%)	17.4 (3.8)	r	-0.064
		p	0.384
PUFA (g)	22.3 (10.1)	r	0.047
		p	0.520
PUFA (%)	9.9 (3.2)	r	0.025
		p	0.732
Cholesterol (mg)	362 (172)	r	0.062
		p	0.403
Omega-3 (mg)	2.6 (1.2)	r	-0.062
		p	0.399
Omega-6 (mg)	19.8 (9.3)	r	0.053
		p	0.475
Omega-6/omega-3	8.1 (3.1)	r	0.155*
		p	0.035
ALA (mg)	2.1 (1)	r	-0.034
		p	0.644
EPA+DHA (mg)	0.5 (0.4)	r	0.045
		p	0.540

ALA: Alpha linolenic acid, DHA: Docosahexanoic acid, EPA: Eicosapentaenoic acid, g: Grams, kcal: Kilocalorie, mg: milligrams, MUFA: Monounsaturated fatty acid, PUFA: Polyunsaturated fatty acid, SFA: Saturated fatty acid, SD: Standard deviation, hs-CRP: High sensitivity C-reactive protein

As researches on the benefits of omega-6 and omega-3 fatty acids to human health increase, the importance of them has increased in the society (20). Moertl et al. (21) investigated the effect of omega-3 intake on systolic left ventricular function, endothelial function and inflammation markers, and found that omega-3 supplementation dose-dependently increased the left ventricular ejection fraction, but when a dose of 4 g was reached, there was a significant decrease in IL-6 level. Reinders et al. (22) showed in a study on men that the blood value of omega-3 fats was inversely related to hs-CRP levels. Saravanan et al. (23) defined omega-3 fatty acids as pleiotropic agents with beneficial effects on the cardiovascular system and stated that the most important effect was to reduce mortality after myocardial infarction. Kalogeropoulos et al. (24) found in a study conducted in healthy individuals that the ratio of omega-6/omega-3 fatty acids had a strong positive correlation with inflammatory markers. Reinders et al. (22) found in a study on men that the value of omega-3 fatty acids in the blood was inversely proportional to the CRP levels. It is recommended to increase the intake of omega-3 fatty acids and decrease the intake of omega-6 in the treatment of diseases and reducing the effect of inflammation (12). In this study, it was observed that there was a positive and significant relationship between the dietary omega-6/omega-3 ratio and hs-CRP in individuals with GG variation (p<0.05). As the omega-6/omega-3 ratio of people with this genotype increased, the hs-CRP value also increased. However, there was no significant relationship between omega-6/omega-3 ratio and hs-CRP values of individuals with GC and CC variations (p>0.05). When the relationship between omega-3 alone and hs-CRP was evaluated between polymorphism groups, no significant relationship was found (p>0.05).

Study Limitations

The research had some limitations. The findings obtained as a result of the research should be evaluated with these limitations. The first limitation was that the sample of the study consisted of individuals who were admitted to a single center and had their genetic analysis done. Therefore, the results of the study could not be generalized to the general population. Other important limitations of the study were that the data were obtained retrospectively from the records and the daily amount of food consumption was calculated mathematically based on the frequency of food consumption.

Conclusion

As a result of this study, it was found that as omega-6/omega-3 intake ratios of individuals with IL-6 G(-174)C GG variation increased, hs-CRP levels increased and inflammation increased. For this reason, it is recommended that people with this variation

increase their omega-3 consumption and reduce their omega-6 consumption. In this direction, increasing the consumption of foods such as mackerel, salmon, trout, herring and sardines in order to increase omega-3 consumption. In order to reduce omega-6 intake, it is recommended to limit the consumption of vegetable oils rich in omega-6, such as sunflower oil and corn oil.

Ethics

Ethics Committee Approval: This research was conducted after it was approved by the Ethics Committee with the decision number 9 at the meeting of the Ethics Committee of Okan University, dated 12.03.2018 and numbered 92.

Informed Consent: Institutional approval was obtained from the genetic testing center in order to conduct the research.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: E.G., Concept: E.G., H.Ö.Y., Design: E.G., H.Ö.Y., Data Collection or Processing: E.G., Analysis or Interpretation: E.G., H.Ö.Y., Literature Search: E.G., H.Ö.Y., Writing: E.G., H.Ö.Y.

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