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Interleukin-6 single gene polymorphism in patients with inflammatory bowel diseases

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Abstract: Objective: Our study aimed to evaluate the association between single nucleotide polymorphism of IL-6-174G/C and the disease course in patients with ulcerative colitis (UC) and Crohn's disease (CD).
Methods: 105 patients (aged 18–75 years) with diagnosed inflammatory bowel disease (IBD), 50 with CD, and 55 with UC, were involved in the study. The controls consisted of 124 healthy individuals. In all patients, the following parameters were evaluated: disease duration, location, presence of complications, and past surgical procedures. Morphology, biochemical parameters, fibrinogen, interleukin 6 (IL-6) level, and IL-6 single nucleotide (174 G/C) polymorphism were assessed in all subjects. Associations of those markers with disease activity, location, complications, and inflammatory markers were evaluated.
Results: No statistically significant differences in IL-6 single nucleotide (174 G/C) polymorphism were observed between patients with UC, CD, and controls. In IBD patients with the GG genotype, a higher mean IL-6 level was noticed than in patients with other genotypes (4.685 ± 5.9 vs. 2.715 ± 5.1 in GC and 3.186 ± 3.6 in CC). A positive correlation was found between IL-6 and fibrinogen levels and CRP in UC and CD patients with GG and GC genotypes. In IBD patients with CC genotype, no correlation between IL-6 and fibrinogen was found ($p = 0.48$).
Conclusions: The risk of developing IBD appears not connected with IL-6 polymorphism. However, IL-6 variation might influence the course of the disease in UC patients.

Keywords: ulcerative colitis, Crohn's disease, Interleukin 6, genetic polymorphism.

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Introduction

The etiology of inflammatory bowel disease (IBD) is multifactorial and has not been fully understood until now. Genetic and environmental factors, microbiota changes, and cell-mediated and humoral immunity disturbances are involved in the development of the inflammatory process [1–5]. Modifications in cytokine synthesis, which have been associated, among others, with single nucleotide polymorphism (SNP) in gene promoter regions, signal sequences, and gene introns, play a significant role in IBD pathogenesis [6, 7].

Due to its dual role, interleukin-6 (IL-6) is one of the most interesting cytokines. It was discovered and cloned in 1986 [8]. It is produced by numerous cells, such as monocytes, macrophages, fibroblasts, endothelial cells, and T and B lymphocytes [9, 10]. Its production is upregulated in plasma and inflamed mucosa of IBD patients, and this process is more evident in Crohn's disease (CD) than in ulcerative colitis (UC) patients [11]. Il-6 is involved in acute and chronic inflammatory processes, affecting mucosal barrier integrity and function and modifying immune response against microbiota [11, 12]. It also induces fever, activates angiogenesis, contributes to the healing of intestinal injury, modulates bone remodeling, and regulates iron and lipid metabolism [11]. IL-6 plays a role in disrupting the integrity of the intestinal epithelial barrier during inflammation by enhancing intestinal permeability [11].

At the beginning of acute inflammation, it induces acute phase reactants such as C-reactive protein (CRP), fibrinogen, or serum amyloid A protein [8]. In chronic inflammation, IL-6 promotes mononuclear cell accumulation at injury sites through monocyte chemoattractant protein 1 production, vascular proliferation, anti-apoptotic function on CD4 T-cells, and promoting Th-17 cell differentiation [11, 13]. On the other hand, it takes part in the re-inhibition of TNF-α production. Its activity correlates with the severity of inflammatory processes. Therefore, Il-6 is considered a biomarker of IBD activity [9, 10, 14]. However, it also has several anti-inflammatory effects, including the ability to reduce the production of pro-inflammatory cytokines such as TNFα and IL-1 [11].

Data indicate that genes involved in regulating the level of the immune response in the inflammatory process might be risk factors in IBD development [15]. The IL-6-174G/C promoter in humans is localized on chromosome 7p15-7p21, affecting IL-6 transcription. The GG genotype seems to induce higher IL-6 levels, while the C allele (GC or CC) seems to be associated with decreased transcription and secretion of IL-6 [14, 16, 17]. Recently, Liu *et al.*, in their meta-analysis, demonstrated that IL-6 rs1800795 polymorphism was significantly associated with the risk of IBD in the overall population and Caucasians [18].

The study aimed to assess the relationship between SNP of IL-6-174G/C and IBD susceptibility and disease phenotype.

Material and Methods

Study population

The study included 105 patients with IBD: 50 consecutive subjects with CD (aged 18-69 years) and 55 straight subjects with UC (aged 19–69 years), in whom the disease was diagnosed based on classic histological, endoscopic, and radiological criteria [1, 19]. The patients included in the study were managed at the Department of Gastroenterology and Hepatology, University Hospital,

Krakow. The study followed the Helsinki Declaration's ethical principles, and all the participants signed the informed consent forms.

The exclusion criteria were pregnancy, other serious diseases, autoimmune diseases, and chronic inflammatory processes. The control group consisted of 124 healthy individuals aged 18 to 69.

Clinical assessment

All the subjects enrolled in the study were evaluated for the following elements: disease duration, location, complications, past surgical procedures related to IBD, and concomitant diseases. Complications were defined as the presence of abscesses, fistulas, obstructions, and extra-intestinal IBD-associated diseases.

All groups were divided according to their IL-6 polymorphism (CC, GC, and GG). Clinical data and all biochemical parameters were compared between the analyzed groups.

Laboratory tests

Testing of basic laboratory parameters and a complete blood count were routinely performed while the patients were hospitalized. Fasting blood samples were collected from the antecubital vein in the morning. On the same day, the following laboratory parameters were determined: blood cell count, hematocrit, blood platelets, albumin, fibrinogen, and CRP. CRP and albumin were assayed using a Modular P clinical chemistry analyzer (Roche Diagnostics, Mannheim, Germany). A complete blood count was performed with an automated Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Germany). Fibrinogen was measured with a Behring Coagulation System (BCS, Dade Behring, Marburg, Germany). Serum IL-6 (pg/ml) concentrations were determined using ELISA (R&D Systems, Minneapolis, Minnesota, USA). Genotyping for the IL-6- 174G/C polymorphism was performed by the polymerase chain reaction (forward primer TGACTTCAGCTTTACTCTTTGT; reverse primer CTGATTGGAAACCTTATTAAG), followed by digestion with *Hsp*92 II (Promega, Southhampton, UK) and agarose gel electrophoresis [20].

Statistical analysis

Statistical analyses were performed using Statistica software (ver. 12.0; StatSoft Inc., Tulsa, OK, USA). Data are expressed as percentages (categorical variables), means with standard deviations (normally distributed variables), and medians with interquartile ranges (non-normally distributed continuous variables). The Shapiro–Wilk test was used to explore the normality of the data distribution. The analysis of variance and Kruskal–Wallis tests were used to compare continuous variables. Categorical variables were analyzed using the χ^2 test. P values <0.05 were considered to indicate significance.

Results

The investigated groups are characterized in Table 1. The distribution of the IL-6-174 G/C polymorphism genotypes is presented in Table 2. The distribution of genotypes and the frequency of alleles and haplotypes of the IL-6 gene did not differ between patients with IBD and the control group. Both study groups' frequencies of single and complex genotypes were consistent with the distribution resulting from Hardy–Weinberg law.

Table 1. Characteristics of patients with ulcerative colitis, Crohn's disease, and the control group.

Parameters		Ulcerative colitis /mean ± SD/ /median (IQR)/	Crohn's disease /mean ± SD/ /median (IQR)/	Control group /mean ± SD/ /median (IQR)/
Age [years]		36 (21) *	29.5 (12) **	32.5 (22)
Gender	Female, n (%)	28 (50.9)	23 (46)	83 (66.93%)
	Male, n (%)	27 (49.1)	27 (54)	41 (33.07%)
Disease duration [years]		8.4 ± 4.2	7.8 ± 4.9	NA
Complications, n [%]		12 (21.8%)*	20 (40%)	NA
Past-surgery, n [%]		0	20 (40%)	NA
Localization				
E1/L1, n [%]		10 (18%)	12 (24%)	NA
E2/L2, n [%]		27 (49%)	6 (12%)	NA
E3/L3, n [%]		18 (33%)	32 (64%)	NA
–/L4, n [%]		NA	1 (2%)	NA
Laboratory tests				
BMI [kg/m^2]		22.75 ± 3.44 #	21.69 ± 4.21 **	26.21 ± 3.89
White blood cells [×10^3/ul]		7.24 (3.21) #	6.73 (3.16)	6.37 (2.54)
Hematocrit [%]		40.05 ± 4.46	39.64 ± 4.56	42.18 ± 3.65
Platelet count [×10^3/ul]		293 (128) #	317.5 (90) **	235.5 (91)
CRP [mg/l]		5.8 (14.9) * #	14.75 (26.71) **	1.81 (1.14)
Fibrinogen [g/l]		4.35 ± 1.97 *	5.21 ± 2.08 **	2.70 ± 0.58
Albumin [g/l]		41.45 ± 5.59	39.74 ± 5.67	46.01 ± 2.72
IL-6 [pg/ml]		2.39 (5.57)#	4.08 (4.17) **	1.69 (1.58)

Data are presented as mean ± SD and median (interquartile range) for the asymmetrical distribution. Abbreviations: BMI — body mass index; CRP — C-reactive protein; E1 — proctitis; E2 — left-sided UC; E3 — pancolitis; IRQ — interquartile range; L1 — CD with involvement of the small intestine; L2 — CD with involvement of the large intestine; L3 — CD with involvement of both the small and large intestine; L4 — CD with involvement of the upper gastrointestinal tract; NA — non-applicable; SD — standard deviation
*p <0.05 UC vs. CD; **p <0.05 CD vs. Control; #p <0.05 UC vs. Control

Table 2. Alleles, genotypes and carriers frequencies of the IL-6 promoter polymorphism at the position –174 (Chi^2 testing not significant).

Patients	Alleles frequency				Genotypes						Carriers			
	G		C		GG		GC		CC		G		C	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
CD	54	54	46	46	13	26	28	56	9	18	41	52	37	48
UC	56	51	54	49	14	25	28	51	13	24	42	29	41	71
Controls	125	50	123	50	30	24	65	52	29	24	95	50	94	50

In the control group, patients with GG genotype had significantly higher IL-6 levels ($p < 0.0001$) and lower fibrinogen levels ($p < 0.05$). None of such differences were noticed for CRP levels. Comparing patients with CC and G + (CG + GG) genotypes, a significant difference also was found between the distribution of IL-6 and fibrinogen.

Table 3 and Table 4 present baseline levels of laboratory variables studied in patients regarding the IL-6-174G/C polymorphism. No significant differences in CRP and fibrinogen distribution were found in IBD patients with different genotypes (CC, CG, GG). However, in IBD patients with the GG genotype, a higher mean IL-6 level was noticed than in patients with other genotypes (4.685 ± 5.9 vs 2.715 ± 5.1 in GC and 3.186 ± 3.6 in CC). In the UC group, the IL-6 level was slightly higher in patients with genotype GG ($p = 0.0499$). Comparing UC patients with GG and C+ (CC+CG) genotypes, a significant difference was demonstrated between the distribution of IL-6 and CRP concentrations ($p = 0.01889$, $p = 0.0396$, respectively). Patients with 174 different IL-6 genotypes in the CD group did not show statistically significant differences in IL-6, fibrinogen, or CRP levels.

Table 3. Baseline levels of laboratory variables studied in patients regarding the IL-6-174G/C polymorphism: C+ (CC and GC) and G+ (GC and GG) in the UC and CD groups.

	Mean ± SD	Mean ± SD	p-value
	C+_UC	C+_CD	
IL-6 [pg/ml]	1.531 ± 3.8	4.317 ± 4.1	0.715
Fibrinogen [g/l]	3.53 ± 2.5	5.06 ± 2.9	0.068
CRP [mg/l]	3.42 ± 10.1	15.3 ± 33.1	0.007
Platelet count [$\times 10^3$/ul]	264.0 ± 101.0	319.0 ± 80.0	0.031
	G+_UC	G+_CD	
IL-6 [pg/ml]	2.807 ± 8.4	3.427 ± 4.5	0.836
Fibrinogen [g/l]	4.045 ± 3.7	4.93 ± 2.9	0.336
CRP [mg/l]	7.37 ± 16.3	14.2 ± 33.1	0.013
Platelet count [$\times 10^3$/ul]	267.0 ± 134.0	319.0 ± 81.0	0.458

Abbreviations: see Table 1.

Table 4. Baseline levels of laboratory variables studied in patients regarding the IL-6-174G/C polymorphism: (CC, GC, and GG) in the IBD and control groups.

	CC-controls	CC-IBD	p-value
	Mean ± SD	Mean ± SD	
Age [years]	37 ± 26.0	33.5 ± 14	0.002
BMI [kg/m^2]	25.9 ± 6.2	22.89 ± 8.7	0.000
IL-6 [pg/ml]	0.9 ± 0.48	3.186 ± 3.65	0.000
Fibrinogen [g/l]	2.65 ± 0.9	4.28 ± 1.9	0.004
CRP [mg/l]	1.922 ± 1.5	8.23 ± 15.5	0.028
Platelet count [$\times 10^3$/ul]	273.0 ± 108	306 ± 86	0.011
White blood cells [$\times 10^3$/ul]	6.35 ± 2.3	7.68 ± 4.2	0.085
Hemoglobin [g/dl]	14.2 ± 2.5	12.7 ± 2.2	0.002

	GC-controls	GC-IBD	p-value
	Mean ± SD	Mean ± SD	
Age [years]	33 ± 20	30.5 ± 16.5	0.072
BMI [kg/m^2]	25.2 ± 3.7	22 ± 4.5	0.000
IL-6 [pg/ml]	1.7 ± 1.1	2.7 ± 5.1	0.010
Fibrinogen [g/l]	2.59 ± 0.6	4.57 ± 3.5	0.000
CRP [mg/l]	1.8 ± 1.0	7.86 ± 32.2	0.000
Platelet count [×10^3/ul]	225 ± 85	291 ± 98	0.000
White blood cells [×10^3/ul]	6.27 ± 2.5	6.72 ± 2.9	0.055
Hemoglobin [g/dl]	13.9 ± 1.8	13.6 ± 2.4	0.020
	GG-controls	GG-IBD	p-value
	Mean ± SD	Mean ± SD	
Age [years]	29 ± 14	32 ± 25	0.362
BMI [kg/m^2]	26.8 ± 4.1	21.2 ± 5.0	0.000
IL-6 [pg/ml]	3.0 ± 2.3	4.68 ± 5.9	0.101
Fibrinogen [g/l]	2.3 ± 0.7	4.65 ± 3.6	0.000
CRP [mg/l]	1.63 ± 1.0	11 ± 18.8	0.000
Platelet count [×10^3/ul]	248 ± 63	338 ± 217	0.001
White blood cells [×10^3/ul]	6.9 ± 3.1	6.96 ± 3.1	0.592
Hemoglobin [g/dl]	13.9 ± 1.4	12.4 ± 2.5	0.002

Abbreviations: see Table 1.

In IBD patients, we observed a positive correlation between IL-6 level and fibrinogen ($r = 0.619$, $p < 0.0001$), IL-6, and CRP ($r = 0.664$, $p < 0.0001$). In the group of IBD patients with the CC genotype, IL-6 positively correlated with CRP ($r = 0.54$, $p = 0.009$), but no correlation was observed between IL-6 and fibrinogen values ($p = 0.48$).

No statistically significant differences were observed in IBD patients with IL-6 polymorphism and IL-6 values in dependence on age at diagnosis, disease location, and presented complications.

Discussion

Numerous pro-inflammatory cytokines may alter the inflammatory process in the intestine of IBD patients [10]. This study shows evidence that SNP in the IL-6-174G/C gene does not play a role in influencing IBD susceptibility but has some significance in the disease phenotype, though not to a highly significant extent.

Our study did not demonstrate statistically significant differences in IL-6-174G/C SNP frequency between the patient and the control groups and the UC and CD groups. Similarly, numerous researchers did not observe a relationship between IL-6-174G/C polymorphism and the occurrence of IBD [6, 15, 21, 22]. However, Balding *et al.* noticed that IL-6-174G/C heterozygotes are more frequent in the CD than in the UC group [15]. Similarly, Guerreiro *et al.* stated that patients

homozygous for the IL6-174G/C polymorphism had a six-fold higher risk for CD [23]. On the contrary, Stankovic *et al.*, analyzing 72 CD patients, found that the carriers of GC and CC genotypes were more likely than those of the GG genotype to develop CD [24]. The differences in the results between the studies discussed might be related to relatively small groups of investigated patients.

Regarding IBD phenotypes, we found no differences between IL-6 polymorphism and clinical features such as age at disease onset, disease location, and presence of complications. Data regarding this problem are heterogeneous. Whereas some researchers do not observe any relationship with the age of diagnosis [15], others found male patients with GG phenotype are characterized by early disease onset [17]. Schulte *et al.*, assessing 193 IBD patients, noticed that patients with ileocolonic CD locations in more significant numbers possess the IL-6-174 GG genotype, and patients with isolated colonic disease more frequently possess the IL-6-174 CC genotype [21]. The authors also evaluated the association between IL-6 polymorphism and mineral bone disease. Still, they did not find such a relationship [21], which is in contradiction with the results of Todhunter *et al.*, who found that total hip bone mineral density in CD patients was significantly lower in patients with the GG genotype (48%) than the CC genotype (15%) [25]. Analyzing clinical features, we have to underline that the investigated groups were divided into smaller subgroups; discrepancies between studies probably resulted from the small groups' samples.

Focusing on inflammatory markers concentration levels, our study observed higher IL-6 levels in the UC patients with IL-6-174GG genotype. Also, in this subgroup, correlations of IL-6 with fibrinogen and CRP levels were more substantial than in the subgroup with IL-6-174CC genotype. On the contrary, Takać *et al.* noticed statistically significantly higher IL-6 and CRP levels in the UC patients with IL-6-174CC genotype [22]. Finally, some authors evaluated the therapy response in dependence on IL-6 variants. Gonçalves *et al.* stated that IL6 variants did not predict IBD patients' TNF-α inhibitor therapy response [26]. In turn, other researchers found that the genetically proxied blockade of the IL-6 receptor may reduce the risk of CD development [27]. In a recent study conducted in China among patients with rheumatoid arthritis, genetic polymorphisms in IL-6 and IL-6 receptors showed the potential as predictive biomarkers for clinical response to tocilizumab [28].

In conclusion, the risk of developing IBD appears not to be connected with IL-6 polymorphism. However, IL-6 variation might influence the course of the disease in UC patients. This study has some limitations. First, the number of studied patients was small, so the statistical power might be limited in detecting genetic polymorphisms with weaker effect sizes. Second, we did not examine other pro-inflammatory cytokine polymorphisms. Studies with a larger sample size are required in the future to confirm or reject the observed associations.

Contributions

D.O. conceived the study's concept. All authors contributed to the research design. D.O., D.C., and K.J. were involved in data collection. D.O., D.C., and K.J. analyzed the data. D.C. wrote the manuscript. D.O., K.J., and M.Z.W. critically revised the article. All authors edited and approved the final version of the manuscript.

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Conflict of interest

None declared.

Abbreviations

CD — Crohn's disease
IBD — inflammatory bowel disease
SNP — single nucleotide polymorphism
UC — ulcerative colitis

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