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Proinflammatory biomarkers' level and functional genetic polymorphisms in periprosthetic joint infection

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ABSTRACT

Objective: The aims of this study were 1) to identify the level of inflammatory biomarkers interleukin (IL)-1α, IL-1β, IL-6, IL-8, IL-17, C-reactive protein (CRP), granulocyte colony-stimulating factor (GCSF), ferritin, and tumor necrosis factor (TNF)-α in serum and synovial fluid samples of patients who underwent revision arthroplasty surgery; 2) to establish the relationship between serum and synovial fluid levels; 3) to determine if any of the 11 genetic polymorphisms of TNFα, IL-1, IL-6, IL-8, IL-17, and GCSF on the encoding genes was associated with periprosthetic joint infection (PJI).
Methods: Synovial fluid and serum was collected from 88 patients who underwent revision arthroplasty surgery. The Musculoskeletal Infection Society definition was used to classify these patients into 2 groups: 36 PJIs and 52 aseptic failures. Synovial fluid and serum samples were tested for 9 biomarkers using a micro enzyme-linked immunosorbent assay. Genetic polymorphisms were evaluated with polymerase chain reaction and restriction endonuclease analysis.
Results: Synovial fluid-derived IL-1α, IL-1β, IL-8, IL-17, CRP, GCSF, TNFα, and serum-derived IL-6, IL-17, ferritin, CRP were found suitable to classify PJI and aseptic failure. In addition, IL-17 and CRP levels demonstrated a positive correlation between synovial fluid and serum. TNFα-238, IL6-174, GCSF3R, and IL1 RN-VNTR genetic polymorphisms occurred more frequently in individuals with septic failure.
Conclusion: Significant differences between the two groups were observed in the functional polymorphisms of the genes encoding the cytokines investigated. These differences could be interpreted as indicating that there is an association between PJI and genetic polymorphisms.
Level of evidence: Level III, diagnostic study.

Introduction

Total joint replacement, especially of the hip or knee, is one of the most successful surgical interventions worldwide.[1] Though the reported complication rate is 1%–3%, among all lower extremity (hip–knee) arthroplasties, periprosthetic joint infection (PJI) is the most common reason for revision of total knee surgeries and the third most common reason for total hip revision arthroplasties.[2] There have been studies in recent years that suggested that the real reason for aseptic arthroplasty failure was inflammation caused by bacteria and their synthesized products. These studies relied on evidence from implants previously revised due to aseptic arthroplasty failure.[3]

The use of synovial fluid and blood serum biomarkers, which include inflammatory proteins, such as cytokines, to diagnose PJI has been confirmed in several studies.[1,4,5] Jacovides et al[6] suggested that in the future, it may be possible for a dipstick test, the fast, easy, and successful method used in the diagnosis of pregnancy and

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urinary tract infections, to be performed to diagnose PJI based on their study of the levels of 46 inflammatory biomarkers in 74 samples of synovial fluid.

Functional polymorphisms defined in cytokine genes, such as interleukin (IL)-1, IL-6, IL-8, IL-17 and granulocyte colony-stimulating factor (GCSF), influence the onset, severity, and duration of inflammation by affecting both basal and stimulated cytokine levels.[7–14] The role of these polymorphisms in the onset and clinical outcome of various autoimmune, infectious, inflammatory, and malignant diseases has been extensively studied.[7–14] Results regarding the value of these inflammatory markers in the diagnosis of PJI have been contradictory. The hypothesis of the present study was that the polymorphisms affecting transcription levels may contribute to cytokine levels as well as to inflammation. To our knowledge, there is no other study in the literature investigating the relationship between functional polymorphisms defined in the genes encoding the investigated cytokines or their receptors, all of which have been identified as markers for PJI in various studies, and the occurrence of PJI.

Based on previous investigations, the aims of this study were 1) to identify the level of inflammatory biomarkers IL-1α, IL-1β, IL-6, IL-8, IL-17, C-reactive protein (CRP), GCSF, ferritin, and tumor necrosis factor (TNF)-α in serum and synovial fluid samples of patients who underwent revision arthroplasty surgery (as a result of either septic or aseptic reasons), 2) to establish the relationship between serum and synovial fluid levels of these markers and PJI in order to identify them as biomarkers of PJI, and 3) to determine if any of the 11 functional polymorphisms of TNFα, IL-1, IL-6, IL-8, IL-17, and GCSF on the encoding genes was associated with PJI among patients undergoing surgery for infection or aseptic loosening.

Patients and methods

The study was approved by our Institutional Ethics Review Board. All of the participating patients provided signed informed consent prior to being enrolled in the study, and the study was conducted in accordance with the Declaration of Helsinki.

This prospective, single-center, controlled study was conducted with a total of 88 patients who underwent revision arthroplasty surgery for either septic or aseptic reasons. Patients with malignancy or antibiotic treatment within 2 months before revision surgery were excluded. The study group included 27 men and 61 women with a mean age of 68 years (range: 44–83 years). Fifty-nine of the samples were knee samples, while 29 were hip samples. Patients undergoing revision arthroplastic surgery had preoperative laboratory tests, which included measurement of sedimentation (ESR), CRP, and synovial fluid white blood cell (WBC) count with a differential cell count. Patients who met the study criteria were classified as septic or aseptic on the basis of the Musculoskeletal Infection Society (MSIS) definition of PJI.[15] Thirty-six of the 88 patients had surgery for presumed infection, including irrigation and debridement or first stage of a two-stage exchange; 52 patients had surgery for presumed aseptic loosening or a mechanical complication of a hip or knee arthroplasty. Intraoperative deep tissue samples were collected for conventional microbiological culture.

All 88 patients with total joint arthroplasty requiring a reoperation due to failure underwent surgery and were followed prospectively between November 2010 and May 2014. Synovial fluid and peripheral blood samples were collected from the patients. Peripheral whole blood samples were collected 30 min before the revision total joint arthroplasty, prior to the administration of preoperative antibiotic prophylaxis in the operating room. Synovial fluid samples were collected intraoperatively before joint capsulotomy. All samples were centrifuged in the hospital clinical laboratory; the separated serum from the peripheral blood sample and supernatant of the synovial fluid were transferred to 2 mL sterile cryotubes and stored at −80 °C until studied. Blood samples from all the patients enrolled in the study were also drawn in tubes containing ethylenediaminetetraacetic acid in order to extract total DNA for analysis of the functional polymorphisms.

Levels of biomarkers in the serum and joint aspirates were determined using an enzyme-linked immunosorbent assay (R&D Systems, Inc., Minneapolis, MN, USA). All assays were carried out according to the manufacturer's instructions. Total DNA was extracted from the blood samples using a total DNA extraction kit (Qiagen, N.V., Hilden, Germany) per the manufacturer's instructions. Polymerase chain reaction-restriction endonuclease analyses were performed to determine the functional polymorphisms defined in the genes encoding the analyzed cytokines according to previously published methods.[7–14,16–19]

Biomarker expression levels in the serum and synovial fluid were compared in patients with and without PJI. The Kruskal–Wallis test was used to assess biomarkers of serum and synovial fluid expression. Pairwise comparisons were performed using the Mann–Whitney U test.

Within-patient comparisons of serum and synovial fluid biomarkers levels were performed using the Wilcoxon test for paired data. Spearman's test was used to evaluate correlations. Receiver operating characteristic curve analysis was used to determine serum and synovial fluid-derived biomarker levels for the diagnosis of PJI. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each assay were calculated.

The allele and genotype frequencies of genes in the patients were compared to controls using a chi-square test. The linkage disequilibrium between 2 single nucleotide polymorphisms (SNPs) was examined using the SNPAnalyzer 2.0 (Istech Corp., Goyang, South Korea). The Hardy–Weinberg equilibrium was tested using a goodness-of-fit chi-square test with 1 degree of freedom to compare the observed genotype frequencies between the patients with the expected genotype frequencies. Comparisons between groups were made with two test (nominal data) or Student's t-test (interval data). Values of $p < 0.05$ were considered significant.

Results

The final cohort contained synovial fluid and serum samples from 88 patients with a minimum of 2 years (mean: 43 months, range: 28–71 months) of clinical and laboratory follow-up. The patients were classified as infected ($n = 36$; 40.9%) or uninfected ($n = 52$; 59.1%). Mean age was 68.7 years, and did not differ significantly between the 2 groups. There were more female patients in the overall cohort (female: 69.3%, male: 30.7%) and more knees than hips were revised (knees: 67%, hips: 33%) but these variables did not differ significantly between the 2 groups ($p > 0.05$). Of the 88 patients, 8 had systemic inflammatory disease (2 patients with PJI and 6 patients with aseptic loosening), and there was no significant difference between the study groups ($p > 0.05$).

No bacterial pathogen was cultured in 9 patients in the septic group, while an organism was isolated preoperatively or intraoperatively in 27 patients of that group (Table 1). No purulence was observed intraoperatively in any patient with aseptic loosening, and no organisms were isolated in cultures.

Significant local increases in the biomarkers IL-1α ($p < 0.002$), IL-1β ($p < 0.001$), IL-8 ($p = 0.002$), IL-17 ($p < 0.001$), CRP ($p < 0.001$), GCSF ($p < 0.001$), and TNF-α ($p < 0.001$) were observed in the synovial fluid of patients with PJI compared with those with aseptic loosening. Only IL-6 ($p < 0.001$), IL-17 ($p < 0.001$), ferritin ($p < 0.001$), and CRP ($p = 0.001$) serum levels were significantly

Table 1
Distribution of the microorganisms.

Microorganisms	Number of Patients (n = 36)
Staphylococcus	9 (%25)
Coagulase Negative Staphylococcus	5 (%14)
Streptococcus spp.	4 (%11)
Corynebacterium striatum	2 (%6)
Escherichia coli	2 (%6)
Enterobacter spp.	3 (%8)
Pseudomonas aeruginosa	1 (%3)

higher in the septic group (Table 2). IL-17 in synovial fluid had the highest diagnostic accuracy with an area under the curve (AUC) of 0.85, 78% sensitivity, and 87% specificity ($p < 0.001$). The most accurate serum biomarker was IL-6, with an AUC of 0.82, 75% sensitivity, and 79% specificity ($p < 0.001$) (Table 3).

The level of 2 biomarkers (IL-17, CRP) demonstrated a significant positive correlation between synovial fluid and serum ($r > 0$; $p < 0.05$) (Table 4). There were no significant correlations found between functional polymorphisms and cytokine levels ($p > 0.05$).

Four of the genetic polymorphisms, TNFα-238, IL6-174, GCSF3R, and IL1 RN-VNTR, occurred more frequently in the individuals with septic failure. TNFα-238 polymorphism carrying at least 1 G allele ($p = 0.006$) and IL6-174 polymorphism with at least 1 C allele ($p = 0.03$; OR: 9.71) were associated with septic arthroplasty failure. For the GCSF3R C > T polymorphism, a T allele was statistically more frequently found in the septic group ($p = 0.002$; OR: 9.31). Finally, for IL1 RN-VNTR, the haplotypes of which are shown in Table 5, 1/2 and 2/2 alleles were regarded as risk for developing septic failure ($p = 0.002$) (Table 6).

Discussion

The diagnosis of PJI depends on several clinical and laboratory entities that may be difficult to interpret, especially in the setting of

Table 4
Correlation of local and systemic biomarkers level, which are showed statistically significant change, in study participants requiring revision total joint replacement for septic and aseptic causes.

	IL-17	CRP
p value	<0.05	<0.05
r value	+0.228	+0.222

(r value: correlation coefficient).

Table 2
Summary statistics for local and systemic biomarkers level, which are showed statistically significant change, in study participants requiring revision total joint replacement for septic and aseptic causes.

Marker	Median level (min–max)		SEM		p value
	Septic	Aseptic	Septic	Aseptic	
Joint aspirate					
IL-1α (pg/ml)	0.01 (0.00–250.00)	0.00 (0.00–21.35)	69.31	4.48	<0.001
IL-1β (pg/ml)	11.84 (0.00–250.00)	0.00 (0.00–222.68)	76.07	32.96	<0.001
IL-6 (pg/ml)	500.00 (0.00–500.00)	500.00 (0.00–500.00)	155.73	195.81	0.066
IL-8 (pg/ml)	1000.00 (129.03–1000.00)	434.22 (29.55–1000.00)	301.70	434.22	0.002
IL-17 (pg/ml)	12.800 (0.000–369.50)	0.000 (0.000–12.50)	79.38	2.09	<0.001
CRP (pg/ml)	25.00 (25.00–25.00)	25.00 (1.37–25.00)	0.00	7.96	<0.001
G-CSF (pg/ml)	82.15 (0.65–2500.00)	14.25 (0.00–2014.50)	798.46	315.54	<0.001
Ferritin (ng/ml)	432.40 (0.00–802.56)	544.74 (0.00–994.32)	238.123	544.74	0.063
TNF-α (pg/ml)	48.01 (13.10–756.50)	26.850 (0.00–1000.00)	127.923	136.67	<0.001
Serum					
IL-1α (pg/ml)	0.00 (0.00–112.02)	0.00 (0.00–0.94)	19.716	0.13	0.063
IL-1β (pg/ml)	0.00 (0.00–2.25)	0.00 (0.00–250.00)	0.460	35.00	0.053
IL-6 (pg/ml)	33.23 (0.00–500.00)	1.95 (0.00–500.00)	86.38	69.70	<0.001
IL-8 (pg/ml)	16.85 (0.00–482.70)	17.42 (0.00–1000.00)	79.52	184.83	0.152
IL-17 (pg/ml)	0.09 (0.08–0.10)	0.08 (0.07–0.09)	0.0042	0.0037	<0.001
CRP (pg/ml)	25.00 (0.82–25.00)	3.72 (0.00–25.00)	10.08	10.86	0.001
G-CSF (pg/ml)	0.13 (0.09–0.90)	0.13 (0.09–3.96)	0.133	0.532	0.561
Ferritin (ng/ml)	87.06 (9.15–554.43)	31.14 (0.00–341.67)	167.70	51.47	<0.001
TNF-α (pg/ml)	0.08 (0.05–0.31)	0.07 (0.05–1.44)	0.4343	0.2170	0.983

(SEM = standard error of the mean, IL = interleukin, TNF = tumor necrosis factor, G-CSF = granulocyte colony stimulating factor).

Table 3
Discriminatory strength of local and systemic biomarkers levels.

Marker	AUC (95% CI)	p value	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Joint aspirate							
IL-1α (pg/ml)	0.681 (0.572–0.777)	0.002	0.7	47.22 (30.4–64.5)	88.24 (76.1–95.5)	73.9	70.3
IL-1β (pg/ml)	0.758 (0.655–0.843)	0.001	4	63.89 (46.2–79.2)	82.69 (69.7–91.7)	71.9	76.8
IL-8 (pg/ml)	0.689 (0.581–0.784)	0.001	673.7	75.00 (57.8–87.9)	64.71 (50.1–77.6)	60.0	78.6
IL-17 (pg/ml)	0.851 (0.759–0.918)	0.001	0.1	77.78 (60.8–89.9)	86.54 (74.2–94.4)	80.0	84.9
CRP (pg/ml)	0.644 (0.535–0.743)	0.017	19.99	100.00 (90.2–100.00)	28.85 (17.1–43.1)	49.3	100.0
G-CSF (pg/ml)	0.766 (0.664–0.850)	0.001	21.58	75.00 (57.8–87.9)	73.08 (59.0–84.4)	65.9	80.9
TNF-α (pg/ml)	0.725 (0.620–0.815)	0.001	29.7	75.00 (57.8–87.9)	65.38 (50.9–78.0)	60.0	79.1
Serum							
IL-6 (pg/ml)	0.824 (0.728–0.897)	0.001	16.2	75.00 (57.8–87.9)	78.85 (65.3–88.9)	71.1	82.0
IL-17 (pg/ml)	0.734 (0.629–0.823)	0.001	0.085	61.11 (43.5–76.8)	73.08 (59.0–84.4)	61.1	73.1
CRP (pg/ml)	0.701 (0.594–0.794)	0.005	4.073	72.22 (54.8–85.8)	65.38 (50.9–78.0)	59.1	77.3
Ferritin (ng/ml)	0.740 (0.636–0.828)	0.001	82.67	55.56 (38.1–72.1)	92.31 (81.4–97.8)	83.3	75.0

(AUC = area under the curve, CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value).

Table 5
Genotype and allele frequencies of studied polymorphisms.

Gene	Polymorphism	Genotype	No. with Septic/Control	Significant Genotype	p value	OR
TNFα	TNF-α − 238G/A	G/G G/A A/A	23/36 5/0 1/0	A allele increases risk	0.006	[a]
IL6	IL6 − 174G/C	G/G G/C C/C	21/34 6/1 2/1	C allele increases risk	0.035	9.71
GCSF	GCSF3R C/T	C/C C/T T/T	3/17 23/14 3/5	CT genotype increases risk	0.02	9.31
IL-1	RN-VNTR	2/2 2/1 1/1 1/3 3/3	2/0 5/0 19/35 0/1 3/0	2 Haplotype increases risk	0.002	[a]

OR: Odds Ratio.
[a] Not calculated.SNP: Single Nucleotide Polymorphism.

Table 6
IL−1 RN VNTR haplotypes.

511 C/T	31 T/C	IL−1 RN VNTR	Septic	Aseptic	p
C	T	1	3	2	0.645
T	T	1	7	13	0.985
T	C	2	2	0	0.186
T	C	1	20	35	0.293
Other (T/C/3)			4	2	[a]
Total			36	52	

[a] Not calculated.

systemic inflammatory disease. Synovial fluid aspiration, diagnostic imaging, traditional culture, peripheral serum inflammatory markers, and intraoperative frozen sections each have their limitations, but continue to be the mainstay for diagnosis of PJI.[20] The MSIS recently assembled to set the terms of a guideline for clinicians to use in the diagnosis of PJI.[15] As with any criteria-based tool, there are some practical, clinical difficulties in using the MSIS definition for PJI.[15] Synovial fluid and serum biomarkers have demonstrated great promise to provide a highly accurate diagnosis of PJI.[1,22,23]

Functional polymorphisms can be a risk factor for several diseases, influencing the onset, severity, and duration of inflammation by affecting basal and stimulated cytokine levels.[7–14] Although thus far, to our knowledge, there is no other study in the literature that investigated the relationship between functional polymorphisms and PJI, potential risk factors for the development of PJI were defined at the International Consensus Meeting of Periprosthetic Joint Infection.[15]

This study has several weaknesses. First, the limited sample size lowered the statistical power of the data acquired from the study. Second, patients with recent antibiotics use were excluded, creating a condition unlike daily clinical practice. Furthermore, in order to investigate the role of genetic polymorphisms in the development of arthroplasty failure (either septic or aseptic), arthroplasty patients who did not develop failure should also be investigated. Our study did not include such a patient group.

There are several strengths to the present study. Patients with systemic inflammatory diseases are generally excluded from this kind of study[1]; however, they were included in this study in order to make it similar to daily clinical practice. The difference in the distribution of these patients in the PJI and aseptic groups was not statistically significant. Second, contrary to other studies in which the PJI group only consists of staphylococcal infections,[1,24] our study resembled the large cohort study of Aggarval et al.[25] Finally, knee samples have been most often used in similar studies because of the greater quantity of synovial fluid that can be obtained.[23] This study included 33% hip-derived synovial fluid samples.

The first purpose of this study was to investigate locally increased levels of synovial biomarkers in PJI patients. It was not surprising to detect biomarkers synthesized from WBC in the joint when WBC levels are locally elevated in synovial fluid during PJI.[1] Seven biomarkers (IL-1α, IL-1β, IL-8, IL-17, CRP, GCSF, TNFα) that we determined to demonstrate a local increase in synovial fluid were previously similarly described in the literature.[1,21,22] Although IL-17 had the highest diagnostic value among these biomarkers, with 77% sensitivity and 86% specificity in our study, a synovial biomarker with the diagnostic value of 100% sensitivity and specificity in PJI has been referenced in the current literature.[1,23]

Our second objective was to detect the diagnostic value of serum-derived biomarkers and to evaluate the correlation of locally increased synovial biomarkers in PJI. Among the 4 systemically elevated biomarkers (IL-6, IL-17, CRP, Ferritin) in PJI that we detected in our study, IL-6 and ferritin have been said to be useful in early diagnosis of PJI by several authors.[26] IL-6, as demonstrated in other studies in the literature, was found to have the highest diagnostic value among systemic biomarkers in our study.[22] Chen et al reported that, at this point, there is no serum biomarker test that can accurately diagnose PJI.[22] The data obtained in our study, yielding a diagnostic value for IL-6 with 75% sensitivity and 78.8% specificity supports this statement. There are only few studies in the literature that have explored local and systemic levels of the same biomarker.[1,27,28] In our research, significantly increased levels of 2 biomarkers (IL-17, CRP) in both serum and synovial fluid were detected in the PJI group. Additionally, a significant correlation was found between local and systemic levels of these biomarkers. Parvizi et al reported that there was a positive correlation between local and systemic levels of CRP in PJI and associated this with the increased synovial permeability due to local inflammation that results in the diffusion of serum CRP into the joint.[27] However, as yet there is no such study for IL-17.

In conclusion, our data suggested that at least 1 G allele in the TNFα gene, and at least 1 C allele for IL-6 polymorphism were associated with septic arthroplasty failure. For GCSF polymorphism, the T allele was statistically more frequently found in the septic group. For IL-1 1/2 and 2/2 alleles were regarded as a risk factor for septic failure. No statistically significant association was found between the serum and synovial fluid levels of biomarkers and gene polymorphisms in septic and aseptic groups. Although there is currently no study regarding the relationship between PJI and genetic polymorphisms, several studies[18,19] have described a relationship between genetic polymorphisms and bone atrophic nonunion in the orthopedic literature. Sathyendra et al observed genetic risk factors for atrophic nonunion in their study, and they reported that identification of a patient as having a genetic risk of delayed or impaired fracture healing at the time of a fracture may justify more aggressive initial treatment of the fracture.[18] Our hypothesis is similar: if a genetic risk factor can be identified for PJI, more aggressive initial treatment, such as use of antibiotic-laden bone cement for primary joint arthroplasty surgery, may be justified.

The process leading to PJI may be associated both with polymorphisms of genes involved in the immune response, as well as environmental factors, which were not explored in the present study. Although significant differences regarding the functional polymorphisms of the genes encoding the investigated cytokines were observed between the septic and aseptic groups, these differences can only be considered risk factors for developing septic

failure. In order to investigate their role in developing arthroplasty failure (either septic or aseptic), arthroplasty patients who did not develop failure should also be investigated with respect to the above-mentioned polymorphisms. The positive correlations found in our study between the serum and synovial fluid levels of biomarkers could be interpreted as indicating that serum derived biomarkers appear to have promise as for the diagnosis of PJI in the future. However, large, well-designed studies may be required to validate our results.

Disclosure

Each author certifies that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

The study was approved by Ethics Review Board of Ankara University.

Our study was performed in Department of Orthopedics and Traumatology, Ankara University.

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