INTERLEUKIN-6 LEVELS IN THE SERA OF PATIENTS WITH DIABETIC RETINOPATHY

Diyabetik retinopatili hastalarda serum interlökin-6 düzeyleri

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Abstract

Purpose: *We aimed at determining the role of interleukin-6 (IL-6) in the pathogenesis and progression of diabetic retinopathy by measuring the serum levels of this cytokine.*

Patients and Methods: *We measured serum levels of IL-6 in 59 patients with diabetic retinopathy and 15 healthy controls using IL-6 EASIA kit (Medgenix Diagnostics). Twenty-six patients had non-proliferative and 33 proliferative diabetic retinopathy.*

Results: *Generally, serum samples from diabetic and control subjects contained comparable low levels of IL-6 which were below the detection limits of the essay (<2 pg/ml). IL-6 was observed in sera of 4 patients with early proliferative diabetic retinopathy (range: 24.90-266.31 pg/ml) and one with severe non proliferative diabetic retinopathy (196.49 pg/ml).*

Conclusion: *Detection of IL-6 in the sera of some of the patients with early proliferative diabetic retinopathy and severe non proliferative diabetic retinopathy may implicate a role of this cytokine in the pathogenesis of diabetic retinopathy. Determining the serum levels of IL-6 in larger series may provide further information on this cytokine as an indicator of progression of retinopathy.*

Key Words: *Cytokines, Diabetic retinopathy, Immunology, Interleukin-6, Retina,*

Özet

Amaç: *Bu çalışmada diyabetik retinopatili hasta serumlarında interlökin-6 (IL-6) düzeyleri ölçülerek retinopatinin patogenez ve ilerlemesinde bu sitokinin rolünün belirlenmesi amaçlandı.*

Hastalar ve Yöntem: *Diyabetik retinopatili 59 hastada ve 15 sağlıklı kontrolde IL-6 EASIA kiti kullanılarak (Medgenix Diagnostics) serum IL-6 düzeyleri ölçüldü. Hastaların yirmialtısında non-proliferatif ve otuzüçünde proliferatif diyabetik retinopati vardı.*

Sonuçlar: *Diyabetik ve kontrollerin serum IL-6 düzeyleri genellikle 2 pg/ml' nin altında ölçüldü. IL-6, erken proliferatif diyabetik retinopatili 4 hasta serumunda 24.90-266.31 pg/ml arasında ve şiddetli non-proliferatif diyabetik retinopatili bir hasta serumunda 196.49 pg/ml olarak tespit edildi.*

Sonuç: *IL-6'nın erken proliferatif diyabetik retinopatili bazı hasta serumlarında ve şiddetli nonproliferatif diyabetik retinopatili bir hasta serumunda tespit edilmesi, bu sitokinin diyabetik retinopatinin ilerlemesiyle ilişkisi olduğunun bir göstergesi olabilir ancak bu konuda daha geniş serilerde yapılacak çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler: *Diyabetik retinopati, Retina, Sitokinler, İmmünoloji, İnterlökin-6*

Interleukin-6 (IL-6) is a cytokine with a wide variety of immunologic effects including the stimulation of B cells; this inflammatory cytokine is characterized by pleiotropy and redundancy of action. Apart from its hematologic, immune, and hepatic effects, it has many endocrine and metabolic actions (1).

Interleukin levels in inflammatory eye diseases and proliferative vitreoretinopathies of several etiologies have been the subject of recent studies; many studies also focused on vitreous levels of this cytokine in vitrectomy samples obtained from eyes with proliferative diabetic retinopathy (PDR) however, obtaining vitreous samples is not possible and ethical in eyes with non proliferative diabetic

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retinopathy (NPDR). Knowledge of the early indicators of diabetic progression would be beneficial in determining those patients who are at risk of progression of their retinopathy. In an attempt to test this hypothesis, we investigated IL-6 levels in serum samples of patients with NPDR and PDR; the results were compared with the healthy controls.

PATIENTS AND METHODS

Fifty-nine patients with diabetic retinopathy who were referred to the retina clinic for flourescein angiography and 15 healthy controls were included in the study.
Twenty-six patients had NPDR and 33 PDR.
ETDRS classification was used for the grading of retinopathy according to fundus photography and fluorescein angiography findings (2-4). The control group consisted of 15 healthy volunteers who were referred to the eye clinic because of refractive errors in the range of ± 3 diopters; ophthalmological examination and the history did not disclose any evidence of diabetic eye disease or other ocular pathologies. The protocol was explained to the patients and the controls and informed consent was obtained. The study protocol was approved by the Erciyes University Hospital Ethical Committee. Chi-square test was used for statistical analysis; $p<0.05$ was considered as statistically significant.

The characteristics of the patients are summarized on Table 1. When the grading of retinopathy was different for each eye in the same patient, the eye with more severe retinopathy was included in tables for statistical analysis.

Measurement of IL-6 in serum:

A blood sample was drawn from the antecubital vein prior to the injection of fluorescein and used for interleukin-6 analysis.

The blood samples were collected into pyrogen-free test tubes and sera separated after centrifugation and kept at -20°C until analysed (maximum for 6 weeks).

IL-6 levels in serum samples were measured using an Immunoassay Kit (Medgenix EASIA™). The principle of the Kit procedures was based on a solid phase Enzyme Amplified Sensitivity Immunoassay performed on a microtiter plate where a blend of monoclonal antibodies directed against distinct epitopes of IL-6 are used. Following the analytical procedures of the Kit, the absorbances within the microtiter plate were colorimetrically read at the appropriate wavelength and the amount of IL-6 in samples were determined as pg/ml by interpolation from the plotted standard curve.

RESULTS

The characteristics of the patients are summarized on Table 1.
The patient group consisted of 38 females and 21 males. The mean (±SD) age of the patients was 61.15±7.76 (range: 42-75) years. The average (±SD) duration of diabetes was 12.37±5.38 (range: 2-20) years. Twenty-six patients had NPDR and 33 PDR.

In the NPDR group, the mean age of the patients was 59.15±8.36 (range: 42-71) years. The average duration of diabetes was 10.46±5.12 (range: 2-20) years.

The distribution of patients with NPDR was as follows: Thirteen had mild NPDR, 6 had moderate NPDR and 7 had severe NPDR. Ten patients had hypertension as the major accompanying systemic disorder. One had cardiac failure and chronic renal failure, one had bronchitis, one hemiplegia, and one rheumatic disease. Fifteen patients were on oral antidiabetics, 10 were receiving insulin treatment and in one patient, diabetes was controlled with diet alone.

In the PDR group, the mean age of the patients was 62.73±6.97 (range: 48-75) years. The average duration of diabetes was 13.88±5.15 (3-20) years.

The distribution of 33 patients with PDR was as follows: Twenty-six had early PDR and 7 had high-risk PDR. Four patients had hypertension as the

accompanying systemic disorder. Two had neuropathy, one had diabetic leg ulcer, one had chronic obstructive pulmonary disease and one, pulmonary tuberculosis. Eighteen patients were on oral antidiabetics whereas 5 were receiving insulin.

The difference between complications or accompanying systemic disorders of the NPDR or PDR groups was not statistically significant ($p>0.05$; chi-square test). In both groups, insulin treatment was initiated when oral antidiabetics proved unsatisfactory.

In the patients group, the IL-6 concentration were either below the detection limits of the essay (<2 pg/ml) or between 24.90 pg/ml and 266.31 pg/ml. Five patients exhibited detectable levels of IL-6; these were 4 patients with early PDR; patient no: 9 (87.52 pg/ml), patient no: 11 (266.31 pg/ml), patient no: 13 (92.94 pg/ml), patient no: 16 (24.90 pg/ml) and one patient with severe NPDR; patient no: 24 (196.49 pg/ml) .

Mean age of the control group was 61±2.25 years. None of the healthy volunteers in the control group had detectable levels of IL- 6 and all were below 2 pg/ml.

Table I. Characteristics of the patients

NPDR Patient No:	Eye	Sex	Age	V.A.	Duration of Diabetes (years)	Accompanying systemic disorders/ complications	Treatment	IL-6 level (pg/ml)	Diabetic retinopathy Stage
1	R	F	58	10/10	9		oad	*	NPDR mild
2	R	F	58	8/10	14	HT	ins	*	NPDR mild
3	R	M	47	10/10	4		ins	*	NPDR mild
4	R	F	65	9/10	15	HT,CF,CRF	oad	*	NPDR mild
5	R	F	45	10/10	10		oad	*	NPDR mild
6	R	F	65	10/10	5		oad	*	NPDR mild
7	R	F	48	7/10	14	bronchitis	ins	*	NPDR mild
8	R	F	55	8/10	4	HT, hemiplegia	ins	*	NPDR mild
9	L	M	65	9/10	12	HT	oad	*	NPDR mild
10	L	F	67	8/10	10	HT	oad	*	NPDR mild
11	R	M	61	10/10	17		oad	*	NPDR mild
12	R	M	57	6/10	15		oad	*	NPDR mild
13	R	F	71	3/10	2	Rheumatic disease	diet	*	NPDR mild
14	R	F	66	10/10	10	HT	oad	*	NPDR moderate
15	L	M	55	5/10	2		oad	*	NPDR moderate
16	L	F	71	5/10	10		ins	*	NPDR moderate
17	R	F	69	7/10	12	HT	ins	*	NPDR moderate
18	L	F	55	9/10	8		oad	*	NPDR moderate
19	L	F	42	6/10	8		ins	*	NPDR moderate
20	R	F	64	5/10	7		ins	*	NPDR severe
21	R	M	52	10/10	18	HT	oad	*	NPDR severe
22	R	F	61	p+p+	18		ins	196.49	NPDR severe
23	L	F	65	50cm fc	4		oad	*	NPDR severe
24	L	F	62	3/10	20		ins	*	NPDR severe
25	R	F	67	8/10	14		oad	*	NPDR severe
26	R	M	47	8/10	10		oad	*	NPDR severe

Table I. Characteristics of the patients (continued)

PDR Patient No:	Eye	Sex	Age	V.A.	Duration of Diabetes (years)	Accompanying systemic disorders/ complications	Treatment	IL-6 level (pg/ml)	Diabetic retinopathy Stage
1	R	F	58	4/10	15		oad	*	PDR early
2	L	M	68	10/10	20		oad	*	PDR early
3	L	M	73	4m fc	4		ins	*	PDR early
4	R	F	55	7/10	5	HT	oad	*	PDR early
5	L	M	68	4m fc	17	HT	ins	*	PDR early
6	R	F	60	1/10	20		ins	*	PDR early
7	R	M	67	1/10	5		oad	*	PDR early
8	L	F	50	6/10	3		oad	*	PDR early
9	R	M	52	2/10	15		ins	87.52	PDR early
10	L	F	70	4m fc	15		ins	*	PDR early
11	R	F	68	1/10	15		ins	266.31	PDR early
12	R	M	61	2m fc	17		ins	*	PDR early
13	R	M	60	5/10	20	neuropathy	oad	192.94	PDR early
14	R	F	50	10/10	13		ins	*	PDR early
15	R	F	60	7/10	12	HT	oad	*	PDR early
16	R	M	67	1/10	15	COPD	ins	24.90	PDR early
17	R	M	65	4/10	15	leg ulcer	ins	*	PDR early
18	L	F	74	9/10	15		oad	*	PDR early
19	L	F	59	7/10	20		oad	*	PDR early
20	L	M	75	20cm fc	14		oad	*	PDR early
21	L	F	63	3/10	15		oad	*	PDR early
22	R	F	60	10/10	20		oad	*	PDR early
23	L	F	63	4/10	20		oad	*	PDR early
24	L	F	58	7/10	10		oad	*	PDR early
25	L	M	68	4/10	20		ins		PDR early
26	R	M	67	1/10	5	HT	oad	*	PDR early
27	R	M	60	p+	13	neuropathy	ins		PDR high risk
28	L	M	64	3/10	15	TB	ins	*	PDR high risk
29	L	F	58	7/10	20		ins	*	PDR high risk
30	R	F	48	9/10	10		ins	*	PDR high risk
31	L	F	73	3m fc	10		oad	*	PDR high risk
32	L	F	65	2/10	10		oad	*	PDR high risk
33	L	F	63	50cm hm	15		oad	*	PDR high risk

Legend for Table 1: NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative retinopathy; IL-6: interleukin-6; * IL-6 level < 2pg/ml; V.A. : visual acuity; p+p+ :perception and projection of light present; fc: finger counting; hm: hand motions; oad: oral antidiabetics; ins: insulin; HT: hypertension; CF: cardiac failure; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; TB: tuberculosis

DISCUSSION

IL-6 is an immunoregulator and multifunctional cytokine which is believed to play an important role in a broad spectrum of diseases. IL-6 shares several activities with IL-1 and TNF. It is synthesized by many cells including fibroblasts, T cells, macrophages, endothelial cells, keratinocytes and mast cells. Purified from natural sources, it behaves as a single chain of molecular mass 21-28kDa (5) . The gene for human IL-6 is on the short arm of chromosome 7 p15-p21. IL-6 stimulates T cells and thymocytes, induces B cell differentiation and promotes growth of hybridomas and also induces IL-2 production. On the other hand, a variety of stimuli including TNF, IL-1, platelet-derived growth factor, antigens, mitogens, and bacterial endotoxin induce the production of IL-6 (6). IL-6 has been shown to increase with age and significantly higher median levels of IL-6 were found in subjects with cancer, heart attack, and high blood pressure (7).

Cytokines are known to play an important role in autoimmunity and have been suggested as involved in the pathogenesis of diabetes mellitus. In one study, Cavallo et al. have measured IL-6 and other cytokines in sera from 50 diabetic patients; detectable levels of IL-6 was found in the serum of only a small percentage of subjects and were not significantly different between patients and controls (8).

The manner in which the dysfunctional immune system damages beta cells is yet to be revealed. In our study we investigated this by determining serum levels of interleukin-6 in an attempt to detect any circulating levels of this cytokine and found detectable levels compared to controls.

Electron microscopic studies performed by Buschard and coleagues showed that rIL- 6 caused beta-cell specific degenerative changes and concluded that human IL-6 stimulates insulin production and secretion in vitro and induces similar ultrastructural changes in beta-cells (9). Huang et al also found significantly high expression levels of IL-6 mRNA in patients with IDDM (10).

Interleukin levels have been the subject of interest in many ocular pathologies. It has been found to increase in tears and tarsal conjunctival homogenates in vernal keratoconjunctivitis (11). Uveitis is another ocular pathology where IL-6 has been extensively studied, in humans (12-16) as well as in experimental animal models (17). IL-6 levels in aqueous humor was found to be increased in uveitis (18) and in Fuchs' heterochromic cyclitis (19). Raised IL-6 levels were detected in the vitreous of patients with uveitis (20). It was suggested that IL-6 may play a crucial role in the occurrence of inflammation after cataract surgery (21, 22). In glaucoma filtration surgery, a possible role of this cytokine in the reduced success rate was also investigated; TNF and IL-1, but not IL-6, were found as capable of inducing the proliferation of Tenon's capsule fibroblasts (23). In an oncologic study, Likhvantseva et al. investigated the presence of IL-6 in the serum and tears of patients with uveal melanoma and concluded that the rate of IL-6 detection in the serum and the iridociliary localization of the tumor correlated with tumor development (24).

In our study, detectable amounts of IL-6 were observed in sera of 4 patients with early PDR (range: 24.90-266.31 pg/ml) and one with severe NPDR (196.49 pg/ml). In many studies, vitreous levels of IL-6 have been studied extensively. Kauffmann et al. searched for the presence of IL-6 in vitreous samples obtained from patients with proliferative vitreoretinopathy (PVR) and from those with miscellaneous lesions such as vitreous hemorrhage from trauma, and non-PVR patients with retinal detachment (25). IL-6 levels ranged from < 30 to 5487 pg/ml, with the highest values observed in the PVR patients. They also compared IL-6 content of vitreous from miscellaneous causes with PVR patients. A significantly elevated levels of IL-6 were observed in the PVR patients (91.5 +/- 18 pg/ml) compared to the miscellaneous group (10.3 +/- 3.7 pg/ml) .There was also a positive correlation of IL-6 values with the severity of the PVR cases.

Elevated levels of IL-6 in the vitreous in PVR may implicate a role for this cytokine in the pathogenesis of this ocular disorder.

In another study the presence of IL-6 and other cytokines were investigated in vitreous and aqueous aspirates from eyes undergoing vitrectomy for the treatment of several inflammatory conditions (26). IL-6 was observed in 6 samples from eyes with diabetic retinopathy (range : 5-480 pg/ml). None of the cytokines measured were detected in any of the control vitreous. The authors suggested that cytokines, particularly IL-6 and IL-1, may act as local amplification signals in pathological processes associated with chronic eye inflammation.

Limb et al. determined the presence of several cytokines in the vitreous from eyes with PVR or RD (27). The results showed that IL-1 and IL-6 predominated in vitreous and that concentrations of IL-6 greater than 20 pg/ml were more frequently found in PVR than in RD or control specimens . Their observations provide further evidence that cytokine-mediated pathways of inflammation are involved in the pathogenesis of PVR . Kenarova and associates investigated the levels of some cytokines in subretinal fluid in proliferative vitreoretinopathy and found significantly increased levels (28).

Abu el Asrar et al. investigated cytokines in the vitreous of patients with proliferative diabetic retinopathy (29). Vitreous interleukin-6 levels positively correlated with ocular disease activity. Serum samples from diabetic patients and control subjects contained comparable low levels of interleukin-6. Because interleukin-6 can function as B-cell differentiation factor, this cytokine may have a role in immunoglobulin deposition in the ocular tissues and in the immunopathologic characteristics of proliferative retinopathy.

It was shown that human RPE could produce IL-6 and may be the source of this cytokine in ocular inflammatory states (30, 31). Limb et al. reported on the immunohistochemical staining for cytokine proteins of 26 epiretinal membranes obtained from eyes undergoing surgery for the treatment of PVR (32). Staining for cytokines IL-6 was observed in 9 membranes. The present findings support growing evidence that cytokine-mediated pathways of inflammation are involved in the pathogenesis of proliferative vitreoretinopathy. The presence of IL-1 beta, IL-6 and TNF alpha mRNA-positive cells within retinal membranes provides further evidence of a pathogenic role of these cytokines in proliferative vitreoretinopathy(33) .

Although vitreous levels of IL-6 have extensively been studied, serum levels of this cytokine in proliferative or non-proliferative diabetic retinopathy has not been studied in detail. Obtaining vitrectomy samples, particularly in those with mild or moderate NPDR is not practical and ethical. On the other hand, patients with NPDR would also get benefit from early knowledge as to whether their retinopathy is likely to get worsened and show progression during their follow-up. Knowledge of the early indicators of diabetic progression by performing a non-invasive test at serum level would be beneficial in determining those patients who are at risk of progression of their retinopathy.

In our study, we found that serum samples from diabetic and control subjects contained comparable low levels of interleukin-6 which were below the detection limits of the essay (<2 pg/ml) and that IL-6 was observed in sera of 4 patients with early PDR (range: 24.90-266.31 pg/ml) and one with severe NPDR (196.49 pg/ml). It is interesting to note that all detectable IL-6 levels were seen in PDR (4 patients) and severe NPDR patients. Although the serum concentrations of IL-6 did not correlate with the degree of diabetic retinopathy and the relatively small numbers did not make statistical comparison possible, increased IL-6 levels in sera of some of the patients with progressive forms of diabetic retinopathy may indicate that this cytokine may have an important role in the pathogenesis of diabetic retinopathy, however, further studies are necessary in larger series to improve our knowledge about the prognostic importance of serum levels of this cytokine.

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