

What is the meaning of hs-CRP and HbA1c in patients with dry eye syndrome in diabetes?

Ji-Hun Kang*, Sang-Yol Shin**

*Professor, Dept. of Emergency Medicine at Inje University Busan Paik Hospital, Busan, Korea

**Professor, Dept. of Emergency Medical Service, Howon University, Gunsan, Korea

[Abstract]

The purpose of this study was to investigate the effects of systemic chronic inflammatory state on dry eye syndrome as a local chronic inflammatory condition. From June 16, 2016 to December 31, 2016, 726 patients who visited the general health examination center were screened using the Schirmer's test and the metabolic syndrome screening test. A total of 214 patients who were studied for hs-CRP and HbA1c were simultaneously selected for the study as well. Dry eye syndrome significantly increased in higher age groups ($p < 0.001$) and women ($p = 0.020$); there was no significant relationship with fasting plasma glucose, hs-CRP. In addition, as HbA1c increased the risk for dry eye syndrome also increased ($\beta = 1.960$, $p = 0.025$). Therefore, dry eye syndrome may not be caused by microvascular changes in the lacrimal gland due to chronic inflammatory conditions. In diabetic patients, long-term blood glucose control may be more important than short-term blood glucose control. The high prevalence of dry eye syndrome in diabetic patients is thought to be due to autonomic dysfunction rather than microvascular changes caused by chronic inflammation.

▶ **Key words:** Dry eye syndrome, Blood glucose, HbA1c, hs-CRP

[요 약]

본 연구는 2016년 6월 16일부터 2016년 12월 31일까지 건강검진센터를 방문한 726명을 대상으로 Schirmer's 검사와 대사증후군 검사를 통해 전신적 만성 염증성 상태가 국소적 만성 염증성 상태로서의 안구건조증에 미치는 영향을 알아보고자 시행하였다. 대상자중 hs-CRP, HbA1c를 동시 측정된 214명을 대상으로 연구를 진행하였다. 연구대상자 중 고 연령일수록 ($p < 0.001$), 성별로는 여성에서 유의하게 안구건조증이 증가하였으며($p = 0.020$), 공복혈당과 hs-CRP와는 연관이 없었다. 또한 HbA1c가 증가할수록 안구건조증에 대한 위험도가 증가하였다($\beta = 1.960$, $p = 0.025$). 따라서 안구건조증은 만성 염증성 상태로 인한 눈물샘의 미세혈관 변화에 의한 것이 아니며 당뇨병 환자의 경우 단기간의 혈당 조절보다 장기간의 혈당 조절상태가 더욱 중요하게 작용할 수 있음을 알 수 있으며 당뇨병 환자에서 안구 건조증의 높은 유병률은 만성 염증으로 인한 미세 혈관 변화보다는 자율 기능 장애로 인한 것으로 생각된다.

▶ **주제어:** 안구건조증, 혈당, HbA1c, hs-CRP

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- First Author: Ji-Hun Kang, Corresponding Author: Sang-Yol Shin
 - *Ji-Hun Kang (emmdkjh@naver.com), Dept. of Emergency Medicine at Inje University Busan Paik Hospital
 - **Sang-Yol Shin (since2000@howon.ac.kr), Dept. of Emergency Medical Service, Howon University
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I. Introduction

Dry eye syndrome has decreased tear production and the loss of tear film proceeds faster than normal, resulting in many symptoms such as dryness of the eyes and foreign body sensations. As age increases, the prevalence is high, especially those after menopause[1]. In the recently announced Tear Film & Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II), Dry eye syndrome is a multi-factor disease loss of homeostasis of the tear film and having many eye symptoms, which is a result of the instability of the tear film and hyperosmolarity, inflammation and damage of the eye surface and abnormal neurosensitivity[2]. According to this definition, treatment for dry eye syndrome is performed to maintain the amount of tears produced or through a conservative method of temporarily or permanently closing the tear pathway[3]. However, recently there have been various indications that this inflammatory disease is manifested, and it is suggested that the change of tear components, such as hyperosmolarity, promotes the production of inflammatory mediators on the surface of the eye due to disorders or disease of the lacrimal gland[4]. High sensitivity C-reactive protein (hs-CRP) is an indicator of atherosclerosis and endothelial dysfunction, a relatively simple and economic blood test widely used in the diagnosis of inflammation, including preclinical inflammation[5].

Inflammation can be caused by irritating stress, such as contact lenses and systemic inflammation, or an autoimmune disease, such as Sjogren's syndrome. The prevalence of dry eye syndrome in diabetic patients is higher than in normal controls; however, the exact cause is not known yet. It is presumed that autoimmune autonomic neuropathy is a microvascular change due to parasympathetic dysfunction and diabetic complication of the lacrimal gland[6]. Therefore, the aim of this study is to investigate the relationship between systemic inflammation of the body and dry eye syndrome of

a local inflammatory disease through hs-CRP, a chronic, inflammatory-inducing status marker. In addition, the relationship between HbA1c and hs-CRP along with the effect of chronic systemic inflammation in diabetic patients on microvascular changes, ocular dryness, and autonomic neuropathy is also investigated.

II. Study Method

2.1 Study subject

From June 16, 2016 to December 31, 2016, 726 patients who visited the general health examination center were screened using the Schirmer's test and the metabolic syndrome screening test. A total of 214 patients who were studied for hs-CRP and HbA1c were simultaneously selected for the study as well.

2.2 Measure of amount tear

The results of this study are as follows: Schirmer's test was performed to measure the amount of tears secreted into the conjunctival sac. Schirmer's test was performed by using a 5mm × 35mm Whatman NO.41 filter paper that was folded 5mm at one end and placed on the lower third of the eyelid touching the conjunctival sac. Eyelid movement remained free for 5 minutes while the eyes were open, and the amount of tear production was evaluated by measuring the portion of the filter paper that was wet with tears. If the amount of tears on the absorbent paper is less than 10 mm for either of the two eyes, the patient is diagnosed with dry eye syndrome; the patient's symptoms were not considered for objective indicators.

2.3 Blood test

To investigate the effects of diabetic and chronic inflammation on dry eye syndrome, we measured serologic tests for HbA1c, which reflected blood glucose changes for 2 to 3 months, as well as FBS, which also reflected short-term blood glucose changes. High sensitivity CRP (hs-CRP), a marker

of chronic inflammation, is classified into three groups: low risk 0~1mg/L, moderate risk 1~2mg/L, high risk 3mg/L and above[7].

2.4 Data analysis

The age of the subjects was divided into four groups: those less than 40 years old, those in their 40s, 50s, and 60s. The correlation between blood glucose, HbA1c, and hs-CRP was analyzed by simple correlation analysis. A Pearson's chi-square test and logistic regression model were used to examine the effects of age, sex, hs-CRP, and HbA1c on dry eye syndrome. Statistical analysis was performed by using SPSS version 12.0 (SPSS Inc., Chicago IL, USA), and the data was statistically significant when the p value was <0.05.

III. Results

3.1 General characteristics of study subjects

The mean age of the study subjects was 46.21±10.14 years; 23 subjects were over 60 years old, 55 subjects were between 50 and 59 years old, 76 subjects were between 40 and 49 years old, 60 subjects were less than 40 years old. There were 123 men and 91 women; only 4 subjects were diagnosed with diabetes and taking medications

3.2 Relationship between changes in gender, age, hs-CRP and dry eye syndrome

Among the subjects, 73 of the male subjects and 66 of the female subjects had dry eye syndrome, and statistically distribution was significantly higher in women (p=0.020). Dry eye syndrome increased with age and it was statistically significant (p<0.001). There was no statistical correlation between hs-CRP and dry eye syndrome <Table 1>.

Table 1. Correlation of between Gender, Age, hs-CRP and dry eye syndrome

Dry eye syndrome.		Negative (N=75)	Positive (N=139)	p
Gender	Female	25 (27.5%)	66 (72.5%)	0.020
	Male	50 (40.7%)	73 (59.3%)	
Age	< 40 years	33 (55.9%)	27 (45.0%)	<0.001
	40~49 years	26 (34.2%)	26 (65.8%)	
	50~59 years	13 (23.6%)	42 (76.4%)	
	> 60 years	3 (13%)	20 (87%)	
hs-CRP*	≤1mg/L	59 (36.2%)	104 (63.8%)	0.248
	1~3mg/L	10 (25.6%)	29 (74.4%)	
	≥3mg/L	6 (50.0%)	6 (50.0%)	

*hs-CRP: high sensitive C-reactive protein

3.3. The relationship between HbA1c and hs-CRP

HbA1c and hs-CRP showed a statistically significant positive correlation (r=0.159, p=0.020) <Table 2>.

Table 2. Pearson Correlation coefficient of HbA1c and hs-CRP

	HbA1c(r)
hs-CRP	0.159

3.4. Linear Logistic Regression Model for Dry eye syndrome with FBS and HbA1c

Linear logistic regression analysis was performed for HbA1c and FBS (fasting blood sugar). There was no statistically significant difference in the degrees of change of FBS <Table 3>, although the degree of change of HbA1c (β=1.960, CI 1.087-3.535) significantly increased.

3.5. Factors affecting Dry eye syndrome

The cause of dry eye syndrome was found to be statistically significantly higher: 3.085 times in women than men (CI 1.531-6.217, p=0.02). By age groups, there was significantly increased risk: 2.631 times for those in their 40s (CI 1.253-5.526, p=0.11),

3.831 times for those in their 50s (OR 3.831, CI 1.611-9.109), and 7.759 times for those in their 60s (CI 1.886-31.924, $p=0.05$) <Table 4>. FBS showed no statistically significant correlation. In addition, there was no statistically significant correlation between multivariate analysis and HbA1c, which was statistically significant with dry eye syndrome. There was no statistically significant difference in hs-CRP between the 1~3 mg/L group >3mg/L group compared with <1mg/L group.

IV. Discussion

Dry eye syndrome is accounted for in about 28% of the adult population. It is also associated with ocular surface irritation of the medial eyelid due to deficiency of tears or excessive tear evaporation[8]. The result of the study showed that 65% of the subjects had positive findings on the Schirmer's test. At 60 years old, the secretory function of the lacrimal gland declined, and the increase in age

was the cause of dry eye syndrome. Decrease of the androgens produced by the postmenopausal ovary, number of autoimmune diseases, such as Sjogren's syndrome, polymorphic erythema, antidepressants, antihypertensive, antipsychotics, antiparkinsonian agents, diuretics, and Vitamin A may cause dry eye syndrome[9]. Also, in the case of peripheral neuropathy, corneal nerve redistribution is delayed, tear secretion is reduced, and the corneal epithelium recovery is affected by the delay in corneal epithelium recovery by impeding the stability of the tear film[10]. Meanwhile, the prevalence of dry eye syndrome has been reported variously, but it increases with age[11]. In this study, the risk of dry eye syndrome increased with age 27 subjects (45%) younger than 40, 26 subjects (65.8%) in their 40s, 42 subjects (76.4%) in their 50s, and 20 subjects (87.0%) older than 60. Kang et al, reported that there was a significant correlation between HbA1c and tear film destruction time[12]. In this study, since the frequency and degree of diabetes complications

Table 3. Linear Logistic Regression Model for Dry eye syndrome with FBS and HbA1c

	B	S.E.	Wald	p	Exp	Confident Interval	
						Lower	Upper
FBS [†]	.023	.012	3.506	.061	1.023	.999	1.048
Hb A1c [‡]	.673	.301	5.003	.025	1.960	1.087	3.535

[†]FBS: Fasting Blood Sugar

[‡]HbA1c: hemoglobin A1C

Table 4. Factors affecting Dry eye syndrome

		B	S.E.	Wald	DOF	P-value	Exp(B)	Confident Interval	
								Lower	Upper
Gender	Female	1.126	.358	9.924	1	.002	3.085	1.531	6.217
	Male	1.967	.497	7.549	1	.053	4.4265	2.547	8.546
Age	40~49 years	.967	.379	6.529	1	.011	2.631	1.253	5.526
	50~59 years	1.343	.442	9.238	1	.002	3.831	1.611	9.109
	> 60 years	2.049	.722	8.061	1	.005	7.759	1.886	31.924
CRP	1~3mg/L	.663	.449	2.180	1	.140	1.941	.805	4.681
	3mg/L~	-.193	.643	.090	1	.764	.824	.234	2.907
	Constant	-4.372	2.158	4.107		.043	.013		
FBS		.007	.017	.175	1	.676	1.007	.975	1.041
HbA1c		.509	.377	1.827	1	.176	1.664	.795	3.480

vary depending on the regulation of blood sugar. The correlation between HbA1c and hs-CRP was measured and it was found that there was a statistically significant correlation.

In addition, dry eye syndrome may be caused by an inflammatory disease or wounds of the lacrimal gland that secrete components of the tear film. And the incidence of dry eye syndrome increases in diabetic patients as a systemic disease[13]. According to the previous studies on diabetic patients, Schirmer's test has been found to be associated with autonomic neuropathy syndrome increases in diabetic patients as a systemic disease[13]. According to the previous studies on diabetic patients, Schirmer's test has been found to be associated with autonomic neuropathy and decreased production of tears reduced the function of the autonomic nervous system, suggesting a correlation between changes in the microvascular blood vessels of the lacrimal gland and dry eye syndrome[14]. Seifart et al[15], compared diabetic patients aged 7 to 69 years with normal controls; 52.8% of diabetic patients had dry eye syndrome, whereas only 9.3% of control subjects were diagnosed with dry eye syndrome. We conclude that the management of blood glucose in diabetic patients is important for the control of dry eye syndrome. In the meantime, hs-CRP is a higher risk factor for diabetic patients, and it contributes directly to atherosclerosis and is a risk factor and predictor of cardiovascular disease. It is also known to be an independent factor causing microvascular complications[16,17,18]. Therefore, if there is a significant correlation between hs-CRP and dry eye syndrome, dry eye syndrome may be caused by microvascular changes in the lacrimal gland. Indirectly, dry eye syndrome in diabetic patients is affected by microvascular changes in addition to autonomic neuropathy. Furthermore, since oxidative stress causes corneal epithelial damage and active oxygen is involved in the inflammatory response, attempts to treat dry eye syndrome by suppressing oxidative stress have been actively made[19].

There was a statistically significant correlation between HbA1c and hs-CRP ($r=0.159$, $p=0.020$) the increase in HbA1c affects the increase in hs-CRP. There was no statistical significance in the relationship between fasting blood glucose and dry eye syndrome. There was a statistically significant positive correlation between the amount of change and the risk in HbA1c ($\beta=1.960$, $p=0.025$). Oh et al, reported that HbA1c increases with increasing hs-CRP, which is similar to our experimental results[20]. These results suggest that long-term blood glucose control is more important than short-term blood glucose control for dry eye syndrome.

Indirectly, dry eye syndrome in diabetic patients may affect microvascular changes in addition to autonomic neuropathy; antioxidants may be added to the current treatment for dry eye syndrome.

V. conclusion

In dry eye syndrome in diabetics, there was no significant relationship with fasting plasma glucose and hs-CRP. However, HbA1c increased the risk of dry eye syndrome.

In conclusion, the high prevalence of dry eye syndrome in diabetics is thought to be due to autonomic dysfunction rather than microvascular changes caused by chronic inflammation.

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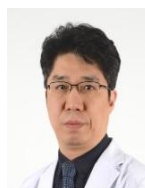
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Authors



Ji-Hun Kang received the B.S., M.S. and Ph.D. degrees in Medicine from Jeonbuk National University, Korea, in 1995, 1999 and 2014, respectively. Dr. Kang joined the faculty of the Department of Emergency

Medicine at Inje University Busan Paik Hospital, Busan, Korea, in 2017. He is interested resuscitation, toxicology, intensive care and biomedicine.



Sang-Yol Shin received the M.S. degrees in Public Health from Jeonbuk National University, Korea, in 2008, respectively He is a doctor course completion in Medicine from Wonkwang University, Korea, in 2012.

Shin joined the faculty in the Department of Emergency Medical Service at Howon University, Gunsan, Korea, in 2008. He is currently a Professor in the Department of Emergency Medical Service, Howon University.