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ORIGINAL ARTICLE

Evaluation of the effects of serum iron levels on lacrimal gland secretion

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Abstract In our study we aimed to demonstrate the relationship between the serum iron levels, and tears quality and quantity in term newborns. This study was conducted at a single institution between March 2013 and May 2013. A total of 46 newborns were prospectively enrolled. Serum iron levels were measured via the umbilical cord blood. Infants were divided into two groups according to their serum iron levels. Group A, serum iron level $\leq$70 μg/dL ($n = 27$) and Group B, serum iron level $>$ 70 μg/dL ($n = 19$). The evaluation of the osmolarity was tested by using the TearLab Osmolarity System (TearLab Co, San Diego, CA, USA). The assessment of quantity was performed by using Schirmer I test. Osmolarity testing and Schirmer I test (with/without anesthesia) were performed bilaterally on the 1st day of life by an ophthalmologist. The outcomes of Schirmer I and tear osmolarity showed no statistically significant difference between right and left eyes of any infant in the groups. Moreover, there was no statistical difference between sexes in these two groups. Osmolarity was found to have a moderate negative correlation coefficient with serum iron level ($r = -0.4$, $p < 0.01$). Furthermore, there was a high positive correlation between Schirmer I with anesthesia and serum iron levels ($r = 0.7$, $p < 0.01$). We observed that the quality and quantity of the tears was lower in term newborns with lower serum iron levels than healthy newborns. These results indicate that low serum iron level could affect lacrimal gland functions.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Nutritional deficiencies may affect epithelial organs such as the exocrine and endocrine glands, the mucosa, and the immune system. Low iron store has been shown to correlate with many diseases, and is an important cause of morbidity. It may also contribute to mucosal atrophy, candidiasis, oral soreness, and dry eye. Low iron store may also further impair lymphocyte functions which is a source of several immunological diseases [1].

Tear film assessment has two main parts: tear volume or quantity and tear stability or quality. The tear film coating the eye, known as the precorneal film, has three distinct layers. Those are lipid, aqueous, and mucous layers. The lipid and mucus layers are responsible for the quality of the tear film, while the aqueous layer provides the quantity of tears needed. The lacrimal glands secrete lacrimal fluid, which is composed of water, electrolytes, and other substances such as proteins. However, to date no evidence has been demonstrated about the effect of low iron store on lacrimal gland functions. Lozoff et al. [2] showed that infants with low iron store had a lower eye blink rate than healthy infants. In that study, they hypothesized that reduced dopamine function in iron-deficient anemic infants could play a role in spontaneous eye blink rate [2]. Lower eye blink rate may affect tear volume by increasing tear evaporation, and there might be a relationship between serum iron level and tear function. In addition, lacrimal glands secretion activity is also thought to be affected by a low iron store. From this standpoint, investigation of the association between the lacrimal gland functions and the degree of low iron store may help us to understand the critical role of iron on exocrine glands secretion activity.

Therefore, in this study we aimed to analyze the relationship between lacrimal gland functions and cord iron levels in neonates immediately after birth.

Methods

Institutional review board (Istanbul Medipol University) approval was obtained for the study protocol. A prospective study was conducted on the eyes of 46 medically stable, full-term newborn infants (38—41 weeks after conception), who were born at a single institution between March 2013 and May 2013. The tenets of the Declaration of Helsinki were followed and informed consent was obtained from the mother for each case. Babies with lid abnormalities, epiphora, conjunctival congestion, discharge, corneal disease, or glaucoma were excluded.

Tests were conducted in moderate room lighting and both eyes were tested consecutively. During sample collection, the infants were resting in a cot or were held by a parent. If an infant was alert, their eyelids were not kept open manually. The eyelids were allowed to close for blinking every 5 seconds to minimize the stress on the infant and to minimize reflex tearing. Three consecutive measurements for all tests were obtained, and their mean was analyzed. The TearLab osmolarity test (TearLab Co., San Diego, CA, USA) utilizes a temperature corrected impedance measurement to provide an indirect assessment of osmolarity (range from 275 mOsm/L to 400 mOsm/L). The equipment consists of single use test cards containing microchannels to collect tear fluid, held by a pen designed to facilitate tear collection, and a portable reader unit which elaborates and displays the osmolarity results. After testing osmolarity by using the TearLab equipment, excess moisture on the eyelid margin was dried by a sterile cotton applicator. Then, a sterile Schirmer tear test strip (Alcon Laboratories Inc., Fort Worth, TX, USA) was placed over the lower eyelid margin in the inferotemporal area without any contact between the cornea and the test strip. After 5 minutes, reflex plus basal secretion (Schirmer I test without anesthesia) scores were recorded in millimeters by measuring the wetting of the strips. To measure basal tear secretion (Schirmer I test with anesthesia), a drop of topical anesthetic agent proparacaine hydrochloride 0.5% was instilled in each eye. After waiting 2 minutes, a sterile Schirmer test strip was placed in the same place and 5 minutes later, wetting was measured and recorded in millimeters as basal secretion. Schirmer I with anesthesia was found to be more objective and reliable in terms of diagnosing dry eyes than without anesthesia [3]. Therefore, Schirmer I with anesthesia was preferred when performing correlation analysis with serum iron level.

Serum iron levels of newborn babies were derived from the umbilical cord blood samples by using the colorimetric method with Ferrimat-Kit (Bio-Mérieux, Marcy l'Etoile, France) and Photometer 4010 (Boehringer, Mannheim, Germany). Neonates were divided into two groups according to their serum iron levels: Group 1, serum iron level $\leq$70 μg/dL ($n = 27$) as the study group and Group 2, serum iron level $>$ 70 μg/dL ($n = 19$) as the control group [4].

Statistical analysis

The right eye of each neonate was selected for analysis. The normality of the distribution of each of the parameters was checked using the Kolmogorov-Smirnov normality test. The scores of Schirmer I test and tear osmolarity were statistically measured using correlation analysis, paired samples *t* test, and independent *t* test. Correlation analysis of Schirmer I test with anesthesia and tear osmolarity with serum iron level was performed by the Pearson linear correlation test. Correlation was described as weak, moderate, strong, and very strong when the correlation coefficient (r) was 0.000—0.250, 0.250—0.500, 0.500—0.750, and 0.750—1.000, respectively.

Results

The study included 46 full-term infants who met the inclusion criteria. There were 24 (52.1%) males and 22 (47.8%) females. The gestational age ranged between 38 weeks and 41 weeks (average 39.3 $\pm$ 1.3 weeks). The majority of the babies (32/46; 69.5%) were between 39 weeks of gestational age and 40 weeks of gestational age. The birth weight ranged between 2.45 kg and 4.5 kg (average 2.88 $\pm$ 0.69 kg). The presence of clinical findings, serum iron level $\leq$70 μg/dL, were taken as evidence of low iron store [4]. Twenty-seven infants were included in Group A, as the low iron store group, and 19 infants were included in Group B, as the control group. Characteristics of the

infants' subgroups according to serum iron level are shown in Table 1.

There was no statistically significant difference in Schirmer I test with/without anesthesia and tear osmolarity scores between the right and left eyes of any infant in the groups (Table 2). The right eye was selected for analysis. The mean values of both total (Schirmer I test without anesthesia) and basal secretion (Schirmer I test with anesthesia), and tear osmolarity were significantly different in the low iron store infants than the healthy infants ($p = < 0.001$, $p = < 0.001$, $p = 0.001$, respectively; Table 3).

The evaluation of dry eye tests showed significantly lower Schirmer I test scores and higher tear osmolarity values in Group A patients compared to healthy infants. Serum iron level was strongly positive correlated with tear volume ($r = 0.7$, $p < 0.01$) and moderately negative correlated with tear osmolarity ($r = -0.5$, $p < 0.01$). Both the study and control groups' distribution curves of tear osmolarity versus serum iron level and Schirmer I test with anesthesia versus serum iron level were plotted in graphs (Figures 1 and 2, respectively).

Discussion

Our study results revealed that Schirmer I test measurements were significantly lower and osmolarity was higher in low iron store cases when compared to healthy newborns.

Tear film examination can be divided into two areas: tear volume or quantity and tear stability or quality. Holly and Lemp [5] categorized the clinical spectrum of dry eye in five categories. The first category was mucin deficiency in which the wettability of the surface of the eye was disturbed. The second was lipid deficiency in which the stability of the tear film was disturbed by an inadequate or abnormal lipid layer. The third category was aqueous deficiency in which there was inadequate aqueous volume to the tear film. The fourth category was eyelid abnormality or inadequate blink function in which there was an inability to distribute the tear film. The final category was ocular surface abnormality in which the altered surface did not allow tear stability. The lipid and mucus layers have the most influence on the quality of the tear film, while the aqueous layer provides the quantity of tears needed.

Since low iron store is a disease with multisystem involvement, it might have impact on the lacrimation functions. Because iron is assigned in many biochemical reactions, its deficiency may negatively affect numbers of vital activities [1,6,7]. Gland function is one of the affected systems. A great number of studies on endocrine glands, in particular the thyroid gland, indicated that low iron store negatively affects the secretion activity of that organ [8–13]. Exocrine gland functions are also affected prominently from low iron store. Several studies have investigated the effects of low iron store on health problems such as glossitis, stomatitis, gastritis, but none of them could interpret the relationship objectively [13–15]. Previous studies reported that nearly 82–84% of the term infants secreted a normal amount of tears on the first day of the birth. Toker et al. [16] published their outcomes using conventional tests, Schirmer I–II, in 96 term medically stable infants and 22 preterm medically stable infants and reported a positive correlation between tear osmolarity and maturity. Beden et al. [17] supported this result with their study which was aimed to assess the quality and quantity of tears among 23 premature and 23 term newborns by using tear ferning and Schirmer's tests. Beden et al. [17] concluded that newborns secrete moderate quantity, good quality tears. The common conclusion was that by term, tear production is similar to that in adults [16–20]. Although those studies were conducted via using diagnostic tests already in use, especially Schirmer I–II, the value of investigating lacrimal gland functions with tears osmolarity was proposed as a gold standard technique a long time ago [21]. Normal tear osmolarity is essential for preserving the constitution of tear film components. Hyperosmolarity may be toxic to the corneal epithelium, compounding existing surface damage. TearLab (OcuSense, Inc., San Diego, CA, USA) is portable and lightweight diagnostic equipment, which is easy to use, noninvasive, and offers precise measurements [21–23].

Sullivan et al. [24] and Utine et al. [25] published their experiences in the comparison of TearLab and conventional dry eye tests in 2012 and 2011, respectively. Both studies showed that TearLab was a gold standard in assessment of tear osmolarity and its results were correlated with conventional dry eye tests. In another investigation, Versura et al. [23] strongly suggested combining TearLab and conventional tests to diagnose dry eye accurately.

We speculated that there might be a relationship between serum iron level and tear function. Lower Schirmer I test results in term newborns with lower serum iron levels compared with healthy newborns might point to a relative impairment in lacrimal glands secretion activity. In addition, we observed that tear osmolarity had a moderate negative correlation coefficient with serum iron level. This finding also leads us to hypothesize that not only quantity, but also quality of the tear film is affected by low iron store.

Table 1 Demographic data of the groups.

	Serum iron level ≤70 μg/dL $n = 27$	Serum iron level >70 μg/dL $n = 19$	p
Female/male	15/12	10/9	0.59[a]
Birth time (wk)	38.5 ± 1 (38–41)	38.2 ± 1.2 (38–40)	0.49[b]
Birth weight (g)	3208 ± 405 (2850–4620)	3312 ± 365 (2988–4560)	0.22[b]

[a] Chi-square test.
[b] Independent t test.

Table 2 Schirmer I test and tear osmolarity results within groups.

	Serum iron level ≤70 μg/dL		p^a	Serum iron level >70 μg/dL		p^a
	Right eye	Left eye		Right eye	Left eye	
Schirmer I test without anesthesia (mm)	14.07 ± 2.9 (11–19)	15.01 ± 1.7 (12–21)	0.57	21.2 ± 2.7 (19–30)	22.6 ± 3.1 (17–31)	0.66
Schirmer I test with anesthesia (mm)	10.09 ± 3.10 (7–17)	10.72 ± 3.16 (7–20)	0.49	18.37 ± 4.94 (10–27)	18.03 ± 4.82 (9–26)	0.55
Tear osmolarity (mOsm/L)	321 ± 38.7 (314–328)	320 ± 46.7 (312–329)	0.59	294 ± 46 (280–298)	296 ± 45.2 (278–301)	0.74

[a] Paired samples *t* test.

Table 3 Schirmer I test and tear osmolarity results between groups.

	Serum iron level ≤70 μg/dL	Serum iron level >70 μg/dL	p^a
Schirmer I test without anesthesia (mm)	14.07 ± 2.9 (11–19)	21.2 ± 2.7 (19–30)	<0.001
Schirmer I test with anesthesia (mm)	10.09 ± 3.10 (7–17)	18.37 ± 4.94 (10–27)	<0.001
Tear osmolarity (mOsm/L)	321 ± 38.7 (314–328)	294 ± 46 (280–298)	0.001

[a] Independent *t* test.

However, ophthalmologic complications of low iron store have not yet been adequately investigated; low iron store disrupts various organ systems. To our knowledge, this is the first study to evaluate the integrity of lacrimation; evaluation of lacrimal gland functions with tear osmolarity and Schirmer I test could give us a chance of detecting the effect of iron on exocrine glands activity. Insufficient tear production and higher tear osmolarity shows that low iron store may not affect the lacrimal gland. Extra caution should be taken to preserve the functions of exocrine and endocrine glands of the newborns with insufficient iron levels in the umbilical cord. The results of this study need to be solidified by using larger test groups and different tests.

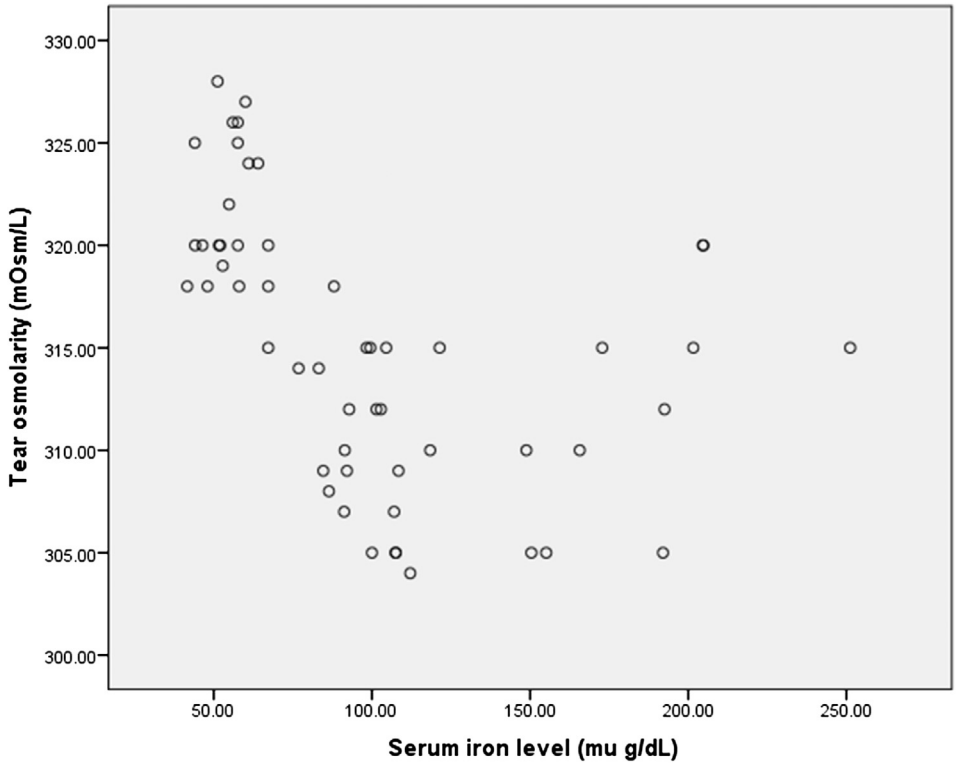

Figure 1. Correlation of tear osmolarity results with serum iron level.

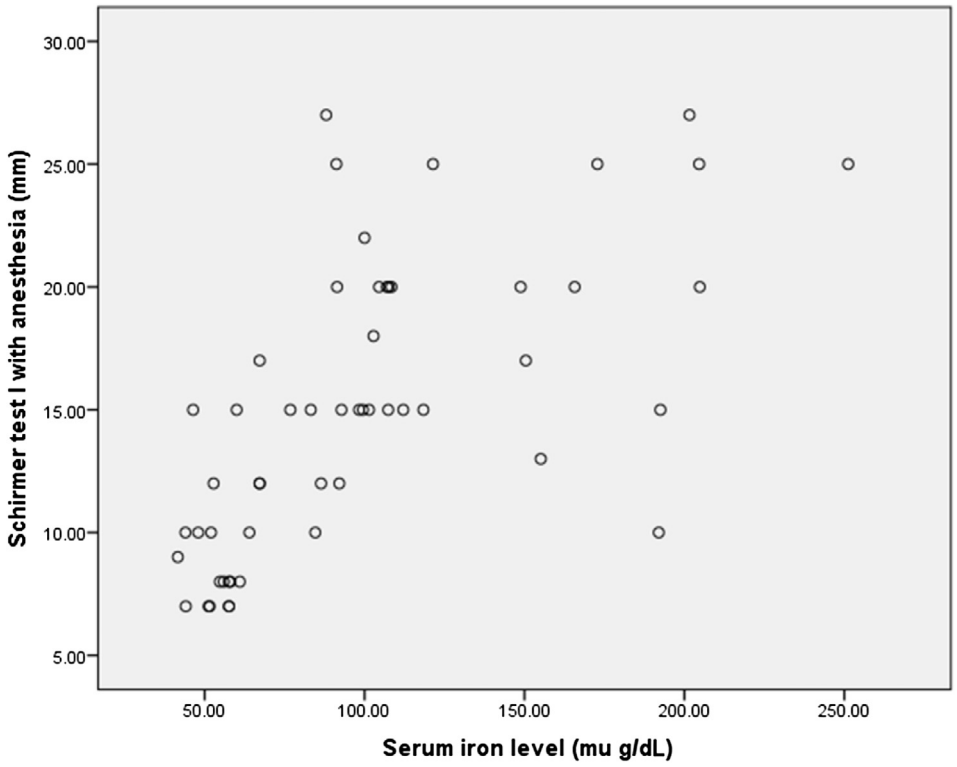

Figure 2. Correlation of Schirmer I test with anesthesia results with serum iron level.

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References

[1] Corapci F, Radan AE, Lozoff B. Iron deficiency in infancy and mother-child interaction at 5 years. J Dev Behav Pediatr 2006; 27:371—8.
[2] Lozoff B, Armony-Sivan R, Kaciroti N, Jing Y, Golub M, Jacobson SW. Eye-blinking rates are slower in infants with iron-deficiency anemia than in nonanemic iron-deficient or iron-sufficient infants. J Nutr 2010;140:1057—61.
[3] Li N, Deng XG, He MF. Comparison of the Schirmer I test with and without topical anesthesia for diagnosing dry eye. Int J Ophthalmol 2012;5:478—81.
[4] Georgieff MK, Wewerka SW, Nelson CA, Deregnier RA. Iron status at 9 months of infants with low iron stores at birth. J Pediatr 2002;141:405—9.
[5] Holly FJ, Lemp MA. Tear physiology and dry eyes. Surv Ophthalmol 1977;22:69—87.
[6] Hijaz NM, Septer SS, Degaetano J, Attard TM. Clinical outcome of pediatric collagenous gastritis: case series and review of literature. World J Gastroenterol 2013;19:1478—84.
[7] Felt BT, Peirano P, Algarin C, Chamorro R, Sir T, Kaciroti N, et al. Long-term neuroendocrine effects of iron-deficiency anemia in infancy. Pediatr Res 2012;71:707—12.
[8] Hu X, Teng X, Zheng H, Shan Z, Li J, Jin T, et al. Iron deficiency without anemia causes maternal hypothyroxinemia in pregnant rats. Nutr Res 2014;34:604—12.
[9] Bastian TW, Prohaska JR, Georgieff MK, Anderson GW. Fetal and neonatal iron deficiency exacerbates mild thyroid hormone insufficiency effects on male thyroid hormone levels and brain thyroid hormone-responsive gene expression. Endocrinology 2014;155:1157—67.
[10] Bastian TW, Anderson JA, Fretham SJ, Prohaska JR, Georgieff MK, Anderson GW. Fetal and neonatal iron deficiency reduces thyroid hormone-responsive gene mRNA levels in the neonatal rat hippocampus and cerebral cortex. Endocrinology 2012;153:5668—80.
[11] Mansourian AR. Metabolic pathways of tetraidothyronine and triidothyronine production by thyroid gland: a review of articles. Pak J Biol Sci 2011;14:1—12.
[12] Bastian TW, Prohaska JR, Georgieff MK, Anderson GW. Perinatal iron and copper deficiencies alter neonatal rat circulating and brain thyroid hormone concentrations. Endocrinology 2010;151:4055—65.
[13] Yun GW, Yang YJ, Song IC, Park KU, Baek SW, Yun HJ, et al. A prospective evaluation of adult men with iron-deficiency anemia in Korea. Intern Med 2011;50:1371—5.
[14] Colacci E, Pasquali A, Severi C. Exocrine gastric secretion and gastritis: pathophysiological and clinical relationships. Clin Ter 2011;162:e19—25.
[15] Adeyemo TA, Adeyemo WL, Adediran A, Akinbami AJ, Akanmu AS. Orofacial manifestations of hematological disorders: anemia and hemostatic disorders. Indian J Dent Res 2011;22:454—61.
[16] Toker E, Yenice O, Ogut MS, Akman I, Ozek E. Tear production during the neonatal period. Am J Ophthalmol 2002;133:746—9.
[17] Beden U, Turgut-Coban D, Aygun C, Ulu-Gungor I, Sullu Y, Erkan D, et al. Tear secretion and ferning patterns among premature and full-term newborns. Turk J Pediatr 2008;50:155—9.
[18] Yazici B. Tear function in babies: author reply. Ophthalmology 2005;112:526—7.
[19] Dogru M, Karakaya H, Baykara M, Ozmen A, Koksal N, Goto E, et al. Tear function and ocular surface findings in premature and term babies. Ophthalmology 2004;111:901—5.
[20] Akar Y, Cira A, Apaydin C, Erman MA, Yilmaz A. The effect of prematurity on tear production. Curr Eye Res 2004;28:145—51.

[21] Hassan Z, Szalai E, Berta A, Modis Jr L, Nemeth G. Assessment of tear osmolarity and other dry eye parameters in post-LASIK eyes. Cornea 2013;32:e142—5.
[22] Versura P, Campos EC. TearLab Osmolarity System for diagnosing dry eye. Expert Rev Mol Diagn 2013;13:119—29.
[23] Versura P, Profazio V, Campos EC. Performance of tear osmolarity compared to previous diagnostic tests for dry eye diseases. Curr Eye Res 2010;35:553—64.
[24] Sullivan BD, Crews LA, Sonmez B, de la Paz MF, Comert E, Charoenrook V, et al. Clinical utility of objective tests for dry eye disease: variability over time and implications for clinical trials and disease management. Cornea 2012;31:1000—8.
[25] Utine CA, Bicakcigil M, Yavuz S, Ciftci F. Tear osmolarity measurements in dry eye related to primary Sjogren's syndrome. Cur Eye Res 2011;36:683—90.