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Ocular surface alterations and changes of meibomian glands with meibography in type 1 diabetic children

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Abstract
Purpose To observe the changes of the ocular surface and meibomian glands by non-contact meibography in patients with type 1 diabetic children.
Methods A total of forty-three patients with type 1 diabetic children and 43 age-matched healthy subjects were included in the study. The ocular surface disease index (OSDI) questionnaire, invasive tear film break-up time (TF-BUT), fluorescein staining of the ocular surface and Schirmer II test were performed for all participants. Ocular surface and lid margins were evaluated by slit lamp. Non-contact meibography was performed with the Phoenix-Meibography module in Sirius corneal topographic device.
Results Both groups consisted of 25 (58.1%) female and 18 (41.9%) male children and the mean age was 14.4 ± 2.5 years. In the T1DM group, the mean disease duration was 6.8 ± 3.1 years. The mean TF-BUT ($p = 0.002$) and Schirmer II test ($p = 0.007$) measurements were lower in the diabetic group than those of in controls. Total eyelid score ($p = 0.027$) and meibomian gland (MG) secretion score ($p = 0.007$) were significantly high in diabetic children. MG area loss was also significantly high in both lower and upper eyelid ($p < 0.001$). In morphological analyses of meibomian glands thinning, shortening and presence of ghost areas ($p = 0.05$, $p = 0.027$ and $p = 0.000$, respectively) were more common in the diabetic group. There was no correlation between both lower and upper eyelid meiboscores and disease duration ($p = 0.51$ and $p = 0.61$), BMI ($p = 0.08$ and $p = 0.51$), serum HbA1c level ($p = 0.06$ and $p = 0.49$) and IGF-1 SDS ($p = 0.38$ and $p = 0.68$).
Conclusion The study revealed that the MG loss area increases and morphological alterations of meibomian glands occur in type 1 diabetic children. Disease duration and metabolic control of diabetes do not affect meibography measurements.
Clinical trials registration The study was organized in accordance with the ethical standards settled by the Ethics Committee of Faculty of Medicine, Afyonkarahisar Health Sciences University.
Trial registration number 2011-KAEK-2, 2021/106.
Trial registration date 02.05.2021.

Keywords Children · Dry eye · Meibography · Meibomian gland · Ocular surface · Type 1 diabetes

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia, has life-threatening and debilitating complications involving many organs such as the heart, kidney and eye. While it has been known for a long time that it has many complications such as cataract, diabetic retinopathy, neovascular glaucoma, its effect on the ocular surface has been emphasized in recent years. Several clinical and experimental studies have reported clinical and subclinical changes in cornea, conjunctiva, tear film and meibomian glands in diabetic patients [1]. The International Dry Eye Workshop (DEWS) II report classified diabetes as a risk factor for aqueous-deficient dry eye disease, although it may also have an evaporative component [2, 3].

Meibomian glands (MG) are modified sebaceous glands embedded in the upper and lower eyelids and secrete lipid-rich secretion called meibum to ocular surface. This lipid layer stabilizes the aqueous layer and reduces evaporation. Meibomian gland dysfunction (MGD) may cause lipid layer breakdown and result in evaporative dry eye. Non-contact meibography is a non-invasive technique that allows analyzing the morphologic characteristics of meibomian glands and the correlation between the clinical quantification of MGD grade and area loss in the upper and lower eyelids. Meibography is a useful tool with repeatable and objective measurements for the evaluation and follow-up of MGs. While the ocular surface and meibomian glands in type 2 diabetes have been studied widely, studies on type 1 diabetes are relatively less.

Therefore we aimed to evaluate ocular surface alterations and changes of meibomian glands with meibography in type 1 diabetes mellitus (T1DM). Additionally, their relationship with disease duration, serum hemoglobin A1c (HbA1c) level, body mass index (BMI) standard deviation score (SDS) and serum insulin-like growth factor-1 (IGF-1) SDS were aimed to be studied.

Materials and methods

Study population

This prospective comparative study was conducted in the Pediatric Endocrinology and Ophthalmology Clinic of Afyonkarahisar Health Sciences University. All of the study procedures were performed in accordance with the Declaration of Helsinki. Informed consent was obtained from patients and their parents. The study was organized in accordance with the ethical standards settled by the Ethics Committee of Faculty of Medicine, Afyonkarahisar Health Sciences University. Forty-three eyes of 43 patients with T1DM and 43 eyes of 43 age and age and sex-matched healthy children were included.

Diagnostic criteria for DM in childhood and adolescence were based on blood glucose measurements and accompanying characteristic symptoms. While classic symptoms of diabetes (polyuria, polydipsia and weight loss) with high plasma glucose concentration were the most common admission form, in necessary cases if the diagnosis was in doubt, repeated glucose measurements with fasting and/or an oral glucose tolerance test (OGTT) were performed. In addition, depending on the etiology of diabetes, an OGTT was not needed, however, an overt hyperglycemia was detected. Criteria used for the diagnosis of DM;

- Classic symptoms of diabetes with high plasma glucose concentration ($\geq$ 200 mg/dL), or;
- Fasting plasma glucose $\geq$ 126 mg/dL (fasting was defined as no caloric intake for at least 8 h), or;
- Two-hour post-load glucose $\geq$ 200 mg/dL during OGTT [(During the test, 1.75 g/kg of body weight (max 75 g) oral glucose was taken orally (anhydrous glucose dissolved in water) and blood glucose was measured at the second hour], or;
- HbA1c $\geq$ %6,5 [4, 5]

Type 1 DM group was selected as cases with positive diabetes autoantibodies at admission, and insulin and/or c-peptide measurements suggesting insulinopenia during the hyperglycemia period. We included patients diagnosed with T1DM over 5 years in the prepubertal period and 2 years in the pubertal period for eye examination and anterior segment analysis of the eye.

The control group was selected randomly from children with no ocular and systemic disease applying to the ophthalmology clinic for mainly refractive errors. The exclusion criteria for both groups were as follows: a presence of any eyelid abnormalities, contact lens wear, active ocular infection or allergy, use of topical or systemic medications (except

insulin), history of ocular trauma or surgery and systemic diseases affecting ocular surface or eyelids.

Study protocol

The right eye of each participant was used for analyses. The examinations were conducted and recorded in the following order:

- The ocular surface disease index (OSDI): The OSDI (Allergan, Irvine, CA, USA) is a questionnaire of 12 items designed to assess the symptoms of ocular irritation in dry eye disease and how they affect functioning related to vision and association with environmental factors [6]. The patients marked the severity of symptoms on a scale of 0–4 (0: none of the time, 1: some of the time, 2: half of the time, 3: most of the time, 4: all of the time). The final score was calculated and ranged from 0 to 100 (score 0–12: normal, 13–22: mild dry eye disease, 23–32: moderate dry eye disease, greater than 33: severe dry eye disease).
- Invasive tear film break-up time (TF-BUT): The subjects were encouraged to blink 3–4 times after fluorescein instillation into the lower fornix. TF-BUT was measured by the time between the last blink and the first black spot. The results of three measurements were recorded.
- Fluorescein staining of the ocular surface: Oxford scale was used for ocular surface staining. Staining is represented by punctate dots on a series of panels (A–E). The dots are ordered on a log scale. Staining ranges from 0–5 for each panel and 0–15 for the total exposed inter-palpebral conjunctiva and cornea [7].
- Schirmer II Test: After instillation of topical 0.5% proparacaine hydrochloride into lower conjunctival sac standard Schirmer test paper was inserted in the outer one-third portion of the inferior fornix. The wetting length of the paper was measured and recorded.
- Evaluation of eyelid, lid margin, cornea and conjunctiva: Biomicroscopic anterior segment examination by slit-lamp was applied for ocular surface diseases such as pterygium, neoplasia, conjunctivitis or demodex infestation. Eyelid margin was evaluated in terms of telangiectasies, lid margin irregularity, obstructed MG orifices and anterior or posterior displacement of the mucocutaneous junction. Eyelid margin score was scored from 0 to 4 [8–10]. Then a stable pressure was applied to the middle part of the lower eyelid with finger and MG secretion was assessed. MG secretions were scored from 0 to 3 according to meibum quality: grade 0, clear; grade 1, cloudy; grade 2, cloudy with granular debris; and grade 3, thick and toothpaste-like [11].
- Non-contact Meibography: The Phoenix-Meibography module in Sirius (CSO, Florence, Italy) corneal topographic device was used for non-contact meibography. After patients were encouraged to rest their forehead and chin, upper and lower eyelid were everted with an applicator, respectively. At least three infrared tarsal conjunctival images for each eyelid were taken and good everted and clear images were used for meibography analyses. The experienced examiner signed the trapezoidal margins of the tarsus and encircled the meibomian glands. On images, meibomian glands appeared as hyperreflective areas that crossed the eyelid transversely. The Phoenix software submitted the measurements of the dropout by percentage, as well as grouped dropouts using a scale within the area, which was highlighted by the users' freehand tool: grade 0 = no loss at all, grade 1¼ = $\leq$ 25%, grade 2 = 26–50%, grade 3 = 51–75% and grade 4 = more than 75% [12]. Additionally, various meibomian gland features such as tortuosity, shortening, thinning and thicking, fluffy, ghost areas were recorded. Morphological characteristics of meibomian glands were defined as follows;
  - Tortuous: at least one prominent tortuous configuration in the gland
  - Shortened: the gland does not extend to its normal length
  - Thinned: thinned glands have a width that is less than half the width of a normal gland
  - Thickened: thickened glands have a width that is equal to or more than twice the width of a normal gland
  - Fluffy areas: amorphous white substance in areas where normal glands should have been present. Individual glands with sharp borders of normal architecture cannot be visualized.
  - Ghost areas: pale glands with the absence of the normal meibomian gland architecture [13].

Meibomian gland features were considered positive when present in either the upper or lower meibography.

Statistical analysis

IBM SPSS statistics version 24.0 (IBM Corp. Armonk, NY) was used for statistical analysis. The data obtained by the measurements were shown as mean, standard deviation (SD) and percentage (%). Shapiro Wilk test was used to evaluate the normality assumption of numerical variables. Levene test was used to test the homogeneity of group variances. The student's *t*-test was used for the comparison of the measurement data of the two groups, for those that conform to the normal distribution, and the Mann–Whitney U test for those that did not conform to the normal distribution. Chi-square test was used for the comparison of categorical data. In the correlation of parameters; Pearson correlation analysis was used for normal distribution, Spearman correlation analysis was used for non-normal distribution. p-value < 0.05 was accepted as the significance level in the statistical evaluation.

Results

A total of forty-three eyes of 43 patients with T1DM and a total of 43 eyes of 43 sex and age-matched healthy controls were enrolled in this comparative prospective study. Both the study group and the control group consisted of 25 (58.1%) female and 18 (41.9%) male subjects, and the mean age was 14.4 ± 2.5 (range 9–18 years) years. In the T1DM group, the mean disease duration was 6.8 ± 3.1 (range 3–14) years. Comparison of OSDİ, TF-BUT and corneal staining score, Schirmer II test, MG secretion and eyelid score in terms of T1DM group and control group are given in Table 1. Although the mean OSDI and Oxford staining score were higher in the T1DM group, the difference was not statistically significant ($p = 0.09$ and $p = 0.16$, respectively). Invasive TF-BUT and Schirmer II test measurements were significantly lower in T1DM patients ($p = 0.002$ and $p = 0.007$, respectively). MG secretion and total eyelid score were also significantly higher in DM patients ($p = 0.007$ and $p = 0.027$, respectively).

Table 2 shows MG area loss percentage, meiboscore and morphological features of meibomian glands observed with non-contact meibography. The mean MG area loss percentage in the upper and lower eyelid was significantly high in T1DM patients ($p < 0.001$). While the meiboscore was higher in both the lower and upper eyelids in the DM group, only the upper meiboscore was statistically significant ($p < 0.001$ and $p = 0.06$). In the morphological evaluation of meibomian glands thinning and thicking, tortuosity, shortening, fluffy and ghost areas were observed more commonly in the T1DM group compared to the control group (Fig. 1). The difference was significant in thinning, shortening and ghost areas ($p = 0.05$, $p = 0.027$ and $p < 0.001$, respectively). In the T1DM group, there was a significant positive correlation between total eyelid score and upper meibography ($p = 0.002$ for MG area loss percentage and $p = 0.002$ for meiboscore). Lower meibography was not correlated with total eyelid score ($p = 0.27$ for MG area loss percentage and $p = 0.47$ for meiboscore).

In the T1DM group, the correlation between ocular surface parameters and meiboscore with disease duration, BMI SDS, serum HbA1c and IGF-1 SDS was investigated (Table 3). Oxford ocular surface staining score was negatively correlated with disease duration ($r = -0.41$ and $p = 0.006$). Total eyelid score was correlated with HbA1c level positively and IGF-1 SDS negatively ($r = 0.31$ $p = 0.04$ and $r = -0.39$ $p = 0.009$, respectively). There was no association between BMI SDS and any parameters.

Discussion

In diabetes, expression of pro-inflammatory mediators such as IL-6, IL-1β, TNF-α and NF-KB increases, and MAPK and NF-KB is activated. This chronic inflammation results in goblet cell apoptosis, tear film instability and ocular surface damage [14, 15]. The mechanisms of morphologic and functional MG changes in diabetes are still unclear. A type 2 DM mouse model study revealed that expressions of apoptosis and inflammation-related genes increased and homeostasis of epithelial cells of MG disrupted with related pathways [16]. Ding et al. reported that insulin stimulated the proliferation of immortalized human MG epithelial cells, and high glucose level was

Table 1 Ocular surface and eyelid parameters

	T1DM group	Control group	*p*
OSDI score	17.05 ± 14.37 (0–52.3)	12.25 ± 10.91 (0–52.3)	0.09
Invasive TF-BUT (sec)	15.58 ± 2.77 (10–20)	17.42 ± 2.65 (10–23)	0.002
Oxford staining score	0.14 ± 0.46	0.02 ± 0.15	0.16
Schirmer II test (mm)	14.30 ± 1.08 (13–17)	15.09 ± 1.54 (11–21)	0.007
MG secretion score	0.60 ± 0.58 (0–2)	0.28 ± 0.50 (0–2)	0.007
Total eyelid score	0.44 ± 0.90	0.12 ± 0.39	0.027
Telangiectasie (n, %)	7 (16.3%)	2 (4.7%)	0.08
Lid margin irregularity (n, %)	3 (7%)	–	0.08
Obstructed meibomian gland (n, %)	6 (14%)	3 (7%)	0.29
Displacement of the muco-cutaneous junction (n, %)	3 (7%)	–	0.08

MG Meibomian gland, *OSDI* Ocular surface disease index, *T1DM* Type 1 diabetes mellitus, *TF-BUT* Tear film break-up time

Table 2 Comparison of the loss percentage of MG area, meiboscore and morphologic features of meibomian glands

	T1DM group	Control group	*p*
Upper meibography (%)	21.71 ± 11.95 (2.3–47.7)	9.10 ± 7.35 (1.4–31.9)	< 0.001
Upper meiboscore	1.5 ± 0.5	1.0 ± 0.2	< 0.001
Lower meibography (%)	18.63 ± 10.00 (2.1–45.4)	10.05 ± 9.18 (2.3–44.3)	< 0.001
Lower meiboscore	1.2 ± 0.4	1.1 ± 0.3	0.06
Morphologic features (n, %)			
Thickened	2 (4.7%)	–	0.15
Thinned	6 (14%)	1 (2.3%)	0.05
Tortuosity	24 (55.8%)	17 (39.5%)	0.13
Fluffy areas	14 (32.6%)	12 (27.9%)	0.63
Shortening	21 (48.8%)	11 (25.6%)	0.027
Ghost areas	14 (32.6%)	1 (2.3%)	< 0.001

T1DM Type 1 diabetes mellitus

toxic. The detrimental effect of insulin resistance/deficiency and hyperglycemia on meibomian glands may explain meibomian gland dysfunction in diabetic patients [17]. Previous studies reported that parasympathetic neurotransmitters and their agonists influence the function of human MG epithelial cells [18, 19]. The development of ocular surface inflammation in the deficiency of Neurturin, which is the neurotrophic factor for parasympathetic neurons, has shown that the neural system is important for providing ocular surface hemostasis [20].

Neuropathy is one of the most common complications of DM and many studies revealed that corneal nerve density is reduced in T1DM [21–23]. This neuropathy may alter meibum production and delivery to the ocular surface. Misra et al. reported that the lipid layer grade and tear film stability were reduced in type 1 diabetes cases [24]. Meibomian gland secretions deliver and disperse over the ocular surface with each blink. The blink rate decreases in diabetic patients as a result of decreased corneal sensitivity [25]. Decreased blink rate may lead to stasis of meibomian gland

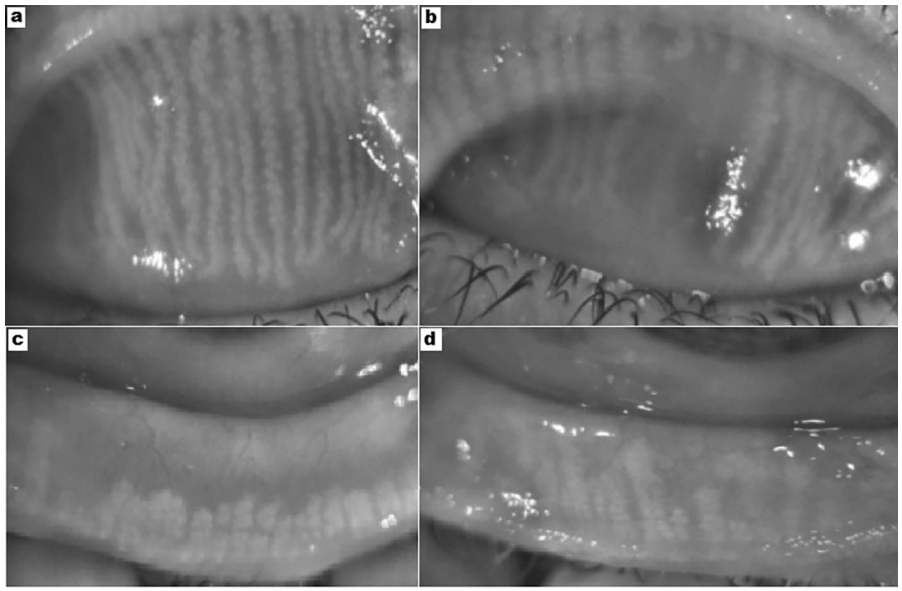

Fig. 1 Non-contact meibography images of upper (**a**, **b**) and lower (**c**, **d**) eyelids in type 1 diabetes mellitus cases: shortening of meibomian glands and ghost areas (**a**), shortening of meibomian glands and drop-out area (**b**), severely shortened meibomian glands and drop-out area (**c**), presence of ghost areas surrounded by black circle (D), marked meibomian gland loss, ghost and fluffy areas (**d**)

Table 3 The correlation between ocular surface and meibography measurements with disease duration, BMI SDS, serum HbA1c level and IGF-1 SDS

	Disease duration		BMI sds		HbA1c level		IGF-1 sds	
	r	*p*	*r*	*p*	*R*	*P*	*r*	*p*
OSDI	− 0.28	0.08	− 0.10	0.50	− 0.14	0.37	− 0.26	0.10
TF-BUT	0.23	0.12	0.18	0.22	0.20	0.18	0.17	0.25
Oxford staining score	− 0.41	0.006	− 0.04	0.79	− 0.08	0.60	0.09	0.53
Schirmer II test	− 0.06	0.66	0.11	0.45	0.04	0.77	0.09	0.56
MG secretion score	− 0.18	0.23	0.01	0.97	− 0.11	0.48	− 0.25	0.09
Total eyelid score	− 0.11	0.47	− 0.06	0.67	0.31	0.04	− 0.39	0.009
Upper meiboscore	0.10	0.51	− 0.26	0.08	− 0.29	0.06	0.13	0.38
Lower meiboscore	− 0.08	0.61	− 0.10	0.51	− 0.10	0.49	0.06	0.68

BMI Body mass index, *MG* Meibomian gland, *OSDI* Ocular surface disease index, *sds* Standart deviation score, *TF-BUT* Tear film break-up time

secretions and gland occlusion [26]. While MGD was widely investigated in type 2 DM in the literature, studies on T1DM were very limited [26–28].

In our study, we found that invasive TF-BUT and Schirmer II test was significantly lower in T1DM patients. Previous studies also reported that Schirmer test and tear film break-up time were lower in the DM group ($p = 0.001$) similar to our study [29, 30]. Oxford corneal staining score and OSDI score were not different between the groups. The present study demonstrated significant differences in terms of MG secretion score and total eyelid score in diabetic children as compared to healthy children. In addition, the diabetic group showed higher MG area loss percentage and meiboscore in upper meibography. While the percentage of MG area loss in the lower

eyelid was significantly higher, the lower meiboscore was not significant. In a study by Gunay et al., MG area loss both in upper and lower eyelid was found to be higher in diabetic patients than controls, but the difference was not statistically significant ($p = 0.10$) [28].

Although some studies reported that MG loss was more in the lower eyelid than upper eyelid in dry eye disease, in our study, upper meibomian gland loss was higher in both diabetic and control groups [28, 31, 32]. Additionally, we evaluated the morphologic features of meibomian glands and concluded that thinning and shortening of meibomian glands and presence of ghost areas in non-contact meibography were more common in diabetic children ($p = 0.05$, $p = 0.027$ and $p < 0.000$, respectively). Although thickening and tortuosity of meibomian glands and fluffy areas were also common in the T1DM group, this finding was not statistically significant ($p = 0.15$, $p = 0.13$ and $p = 0.63$, respectively). There is no study in the literature evaluating the morphological features of meibomian glands in T1DM patients. Thinning and shortening of meibomian glands and the presence of ghost areas may be an early sign of MGD. The results also showed a significant correlation between upper eyelid meibography and total eyelid score. Therefore, evaluation of upper eyelid meibography may provide more useful information in the presence of findings such as telangiectasies, lid margin irregularity, obstructed meibomian gland orifices and anterior or posterior displacement of the mucocutaneous junction in the eyelid margin examination of patients with T1DM.

Akinci et al. [30] concluded that the duration of T1DM has an effect on TF-BUT and Schirmer test results ($t = 3.29$, $p < 0.001$, $t = 3.67$, $p < 0.001$, respectively). In another study, HbA1c level correlated only with tear film osmolarity measurements, not with TF-BUT and Schirmer [28]. We investigated the correlation between ocular surface parameters and meiboscore with disease duration, BMI SDS, serum HbA1c level and IGF-1 SDS in T1DM patients. Disease duration was negatively correlated with Oxford ocular surface staining score ($r = -0.41$ and $p = 0.006$). While there was no association between BMI SDS and any parameters, total eyelid score was correlated positively with HbA1c level and negatively with IGF-1SDS ($r = 0.31$ $p = 0.04$ and $r = -0.39$ $p = 0.009$, respectively). Ding et al. reported that IGF-1 has a significant role on the function of human meibomian gland epithelial cells via activating PI3K/Akt and FoxO1 pathways, stimulating proliferation and promoting lipid accumulation in the cells [33]. In our study, the total eyelid score was lower in those with high IGF-1 level. There was no correlation between both lower and upper eyelid meiboscores and disease duration, BMI, serum HbA1c level and IGF-1 sds.

The main limitations of the aforementioned (our) study were the relatively small sample size, the examination of the lower and upper eyelids together when calculating the total eyelid score, evaluation of the MG secretion score only in the lower eyelids. The strengths of the study were the recording of morphological alterations of meibomian glands in addition to the meiboscore in non-contact meibography, and the evaluation of the aqueous component of tear with the Schirmer test.

Conclusion

In conclusion, we found lower invasive TF-BUT and Schirmer II test measurements and higher MG secretion and total eyelid score in children with T1DM than in the control group. MG area loss was also significantly high in diabetic children. Morphological evaluation of the meibomian glands in addition to the meiboscore with the findings such as thinning, shortening and ghost areas can be beneficial to detect early meibomian gland dysfunction. We could not observe a correlation between the disease duration or metabolic control and meibography measurements. All these findings showed us that ocular surface parameters are impaired and morphologic MG changes accompany the MG loss in type 1 diabetic children. Upper eyelid meibography may be more valuable in T1DM since meiboscore is higher in the upper eyelid and is correlated with the total eyelid score. Larger scale studies are needed to understand the importance of meibography measurements and morphologic alterations of meibomian glands in diabetic children.

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Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study was organized in accordance with the ethical standards settled by the Ethics Committee of Faculty of Medicine, Afyonkarahisar Health Sciences University.

Consent to participate Informed consent was obtained from patients and their legal guardians.

Consent to publish All the authors mentioned in the manuscript have given consent for submission and subsequent publication of the manuscript.

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