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Evaluation of meibomian glands in childhood malnutrition

Fuat Yavrum[1]✉, Begüm Yavrum[2], Elmas Yüksel-Şükün[3] & Nedime Sahinoglu-Keskek[4]

Childhood malnutrition is a condition that affects a large population and can have significant implications for eye health. Our study aims to assess the impact of childhood malnutrition to the ocular surface by evaluating meibomian gland morphology and function. This study included 92 patients aged 6–18 years, with 52 diagnosed with malnutrition and 40 serving as healthy controls. Patients' nutritional status was determined based on body mass index (BMI) according to WHO criteria. Meibomian gland morphology and function were assessed using non-invasive imaging techniques and clinical evaluations along with the bloodwork results, including serum ferritin, hemoglobin, serum 25-hydroxyvitamin D, and vitamin B12 levels. Children with malnutrition exhibited significantly lower mean BMI, hemoglobin, serum 25-hydroxyvitamin D, serum ferritin levels and significantly worse meibomian gland loss (MGL) compared to healthy controls ($p < 0.001$ for all). However, differences in mean non-invasive tear break-up time (NI-BUT) and vitamin B12 levels were not statistically significant. Subgroup analysis based on malnutrition severity revealed no significant differences in MGL or NI-BUT levels. Negative correlations were observed between BMI and MGL, as well as between MGL and serum ferritin and 25-hydroxyvitamin D levels ($p < 0.001$ for all). This study provides novel insights into the ocular consequences of malnutrition in children, highlighting significant alterations in meibomian gland morphology and function associated with nutritional deficiencies. These findings may inform targeted interventions to reduce ocular morbidity and improve the overall health outcomes of malnourished children.

Keywords Child malnutrition, Ophthalmology, Meibomian glands

Malnutrition remains a significant global health challenge, particularly among children. An estimated 45% of deaths among children aged under five years are attributed to undernutrition[1]. Despite concerted efforts, malnutrition persists as a leading cause of morbidity and mortality in many parts of the world, disproportionately affecting low- and middle-income countries[2]. The ramifications of malnutrition extend beyond its immediate health consequences, encompassing long-term developmental, cognitive, and ocular impairments[3].

Ocular manifestations of malnutrition have aroused interest in recent years due to their potential impact on visual health and overall quality of life. These manifestations include corneal thinning, conjunctival xerosis, Bitot's spots, and night blindness, all of which indicate underlying nutrient deficiencies[4,5]. Additionally, malnutrition may contribute to retinal dysfunction, optic neuropathy, and impaired visual development, further underscoring the breadth of its ocular effects[6,7].

Among the various ocular structures affected by malnutrition, the meibomian glands have emerged as a focus of interest. Located within the tarsal plates of the eyelids, the meibomian glands secrete lipids essential for the formation of the tear film, which lubricates and protects the ocular surface[8]. Any disruption in the structure or function of these glands can lead to evaporative dry eye, a common condition characterized by discomfort, visual disturbances, and potential damage to the ocular surface[9].

Although the effects of malnutrition on the ocular surface have been investigated, there are no studies in the literature directly examining its effects on the meibomian glands[4,5]. To address this gap in the literature, this study aimed to evaluate meibomian gland morphology and function in children with malnutrition, using non-invasive imaging techniques and clinical assessments. By elucidating the ocular consequences of malnutrition in this vulnerable population, our findings may inform targeted interventions to diminish the burden of ocular morbidity and improve the overall health outcomes of malnourished children.

[1]FEBO, Ophthalmology Department, Alanya Alaaddin Keykubat University Faculty of Medicine, Antalya, Turkey. [2]Pediatrics Department, Alanya Alaaddin Keykubat University Faculty of Medicine, Antalya, Turkey. [3]Ophthalmology Department, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Turkey. [4]Ophthalmology Department, Alanya Alaaddin Keykubat University Faculty of Medicine, Antalya, Turkey. ✉email: fuatyavrum@gmail.com

Methods

This cross-sectional study took place at Alanya Alaaddin Keykubat University Hospital from February 2023 to February 2024. Approval for the study was obtained from the local ethical review committee (registration no.: 10354421-2023/14–18), and all procedures were conducted following the Declaration of Helsinki. Informed consent was obtained from the parents or legal guardians of all participants.

Initially, 108 eyes of 108 patients aged 6–18 years were included in the study. However, 16 patients were excluded for various reasons (9 patients were unable to cooperate with the measurements, 3 patients were diagnosed with active conjunctivitis, and the parents of 4 patients did not want to participate to the study). Therefore total of 92 eyes of 92 patients were analysed. Patients with a low body mass index (BMI) according to the World Health Organization (WHO) classification[10] were diagnosed with malnutrition by a pediatrician and formed the case group ($n = 52$). The control group consisted of children with a normal body mass index (BMI), who matched the malnutrition group in terms of age and gender, visited the ophthalmology department for routine examinations, and had no history of ocular or systemic disease ($n = 40$). Patients were excluded in case of any ocular disease, previous ocular surgery, systemic disease other than malnutrition (e.g., heart failure, celiac disease), or non-cooperation with the ocular examination.

The case group was subdivided into mild, moderate, and severe subgroups based on the WHO malnutrition classification. Individuals with a BMI between − 1 standard deviation (SD) and − 2 SD were classed as having mild malnutrition, those with a BMI between − 2 SD and − 3 SD were classed as having moderate malnutrition, and those with a BMI below − 3 SD were classed as having severe malnutrition. BMI was calculated by dividing the patient's weight by the square of their height (kg/m2).

After a thorough systemic examination by the pediatrician (BY), patients' BMI and bloodwork results (serum ferritin, hemoglobin, serum 25-hydroxyvitamin D, and vitamin B12) were recorded. All participants then underwent a complete ophthalmic evaluation, including best corrected visual acuity, slit-lamp biomicroscopy, dilated posterior segment examination, non-invasive tear break-up time (NI-BUT), and meibography. Measurements from the right eye of all patients were included in the study. The NI-BUT and meibography evaluations were performed and calculated automatically using a Sirius Topographer (CSO, Firenze, Italy) by the same physician (FY) (Figs. 1 and 2). Meibography measurements were performed from the lower eyelid, and the meibomian gland loss (MGL, %) value was obtained after making the necessary markings on the topography device. Similarly, NI-BUT values (seconds) were recorded by leaving the eyelid open after two blinks, as described by the topography device.

Statistical analysis

Statistical analyses were performed using SPSS (Chicago, IL, USA) software version 23. The Kolmogorov–Smirnov test was used to confirm the normality of the data. The data were presented as mean with standard deviation for continuous data showing normal distribution, and as median (first quarter – third quarter) for continuous data with non-normal distribution. For categorical data, the data were presented as frequency and percentage. The chi-square test for categorical variables and independent-samples t-test for continuous variables with normal distribution were used to compare two groups. The Kruskal–Wallis test was used to determine malnutrition subgroup analysis, and the differences between the subgroups were analyzed using Mann-Whitney U test with Bonferroni adjustment. The correlation coefficient and significance were determined using the Spearman method. A p-value of less than 0.05 was considered statistically significant.

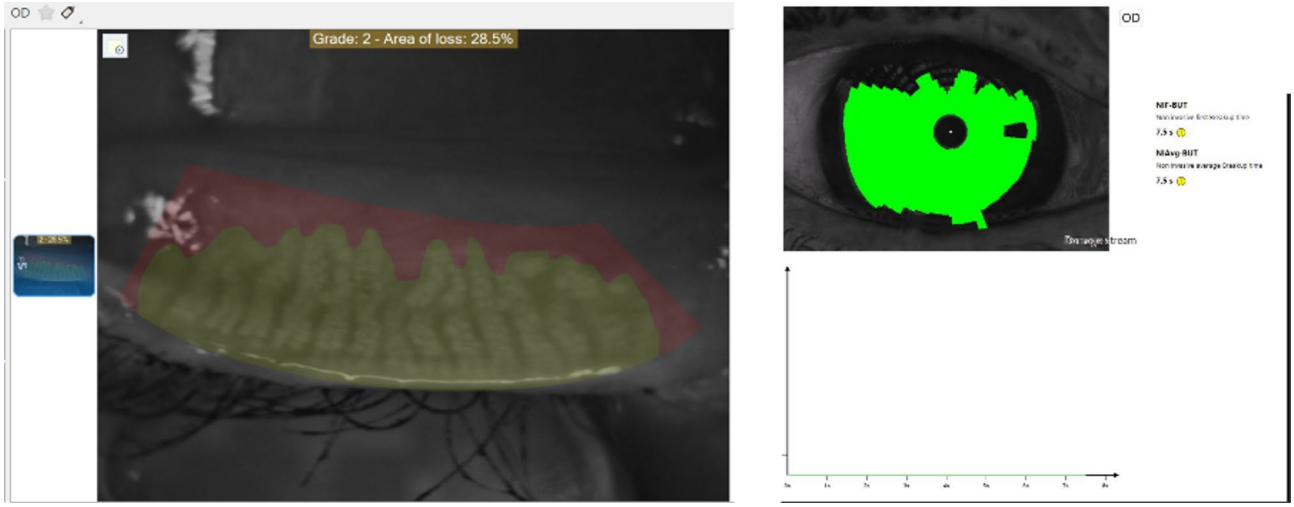

Fig. 1. Representative examples of meibography and NI-BUT images of malnutrition group gathered from topographer. NI-BUT: Non-invasive tear break-up time.

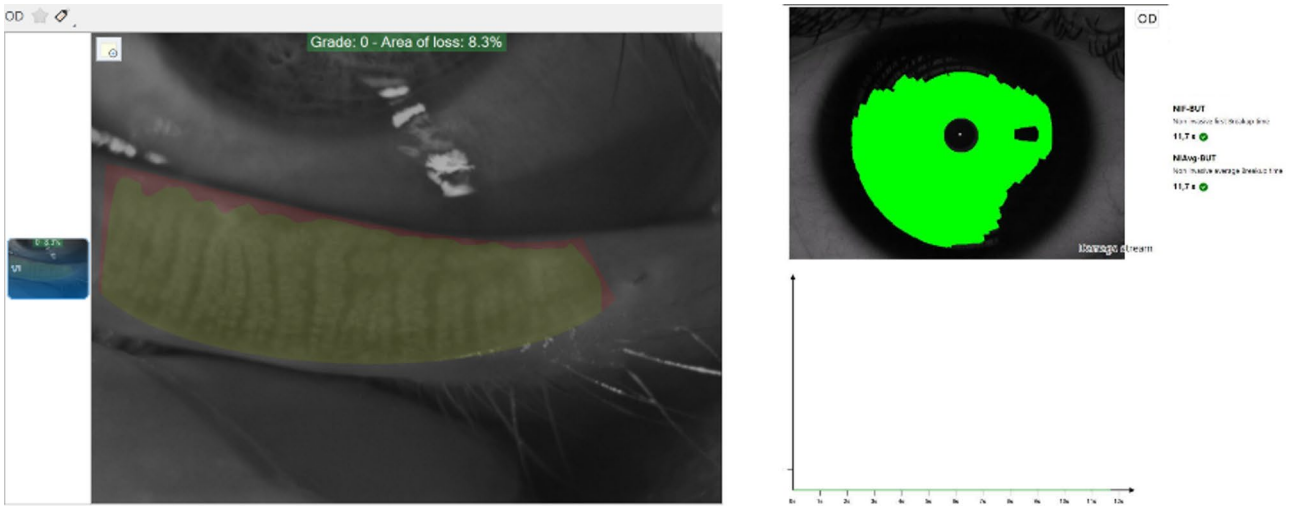

Fig. 2. Representative examples of meibography and NI-BUT images of control group gathered from topographer. NI-BUT: Non-invasive tear break-up time.

	Malnutrition group ($n=52$)	Control group ($n=40$)	p
Age (years ±SD)	10.51±3.67	11.3±3.1	0.59
Sex (Male n, %/Female n,%)	24,46.1%/28, 53.9%	18, 45%/22, 55%	0.47
sdBMI (mean ±SD)	−2.32±1.21	0.57±0.44	**<0.001***
MGL (%,±SD)	28.9±9.1	18.6±4.5	**<0.001***
NI-BUT (sn, ±SD)	8.1±2.7	9±3.6	0.118
Hemoglobine (g/dL, ±SD)	12.42±1.19	12.89±0.59	**0.043***
Serum 25-hydroxyvitamin D (ng/mL, ±SD)	13.3±5.29	31.3±4.9	**<0.001***
Vitamin B12 (pg/mL, ±SD)	402.1±132.3	414.2±98.9	0.449
Serum Ferritin (ng/mL, ±SD)	19.9±15.4	42.4±11.3	**<0.001***

Table 1. The demographics and clinical findings of participants. sdBMI: Standard Deviation of body mass index NI-BUT: Non-invasive tear break-up time. *Independent Samples T test. Data are expressed as means ± standard deviations.

Results

The demographics and clinical findings of participants are shown in Table 1. The mean age and sex distribution were similar between the patient and control groups. In the malnutrition group, the mean BMI, serum 25-hydroxyvitamin D, hemoglobin and serum ferritin levels were significantly lower compared to the control group ($p<0.001$, $p<0.001$, $p=0.043$, and $p<0.001$, respectively), while the mean MGL levels were significantly higher ($p<0.001$). However, despite the lower mean NI-BUT and vitamin B12 levels observed in the malnutrition group, these differences were not statistically significant ($p=0.118$ and $p=0.449$, respectively).

The malnutrition group was divided into three subgroups (mild, moderate, and severe) according to BMI. As demonstrated in Table 2, no significant difference was found in mean MGL and NI-BUT levels between the subgroups ($p=0.335$, $p=0.383$, respectively). However, serum 25-hydroxyvitamin D and vitamin B12 levels were significantly different between the subgroups. ($p=0.003$ and $p<0.001$, respectively.) In the post-hoc analysis conducted within subgroups, serum 25-hydroxyvitamin D levels were found to be significantly higher in the mild malnutrition group compared to the moderate malnutrition group ($p=0.005$) and significantly higher in the mild malnutrition group compared to the severe malnutrition group ($p=0.001$). No statistically significant difference was found between the moderate and severe malnutrition groups ($p=0.143$). Similarly, vitamin B12 levels were found to be significantly higher in the mild malnutrition group compared to the moderate malnutrition group ($p<0.001$) and significantly higher in the mild malnutrition group compared to the severe malnutrition group ($p<0.001$). No statistically significant difference was found between the moderate and severe malnutrition groups ($p=0.086$).

A significant negative correlation was observed between BMI and MGL ($r = -0.435$, $p<0.001$), and a significant positive correlation was found between ferritin and serum 25-hydroxyvitamin D levels ($r=0.554$, $r=0.711$, respectively; $p<0.001$ for both; Fig. 3). Significant negative correlations were observed between MGL and ferritin and between MGL and serum 25-hydroxyvitamin D levels ($r = -0.443$, $r = -0.551$, respectively; $p<0.001$ for both; Fig. 4).

	Malnutrition scale			
	Mild ($n=24$)	Moderate ($n=14$)	Severe ($n=14$)	p
MGL (%)	28.8 (22.5–28.8)	29.3 (14.5–41.3)	29.2 (25.9–35.7)	0.335
NI-BUT (sn)	8.1 (7.2–10.5)	8.1 (7.8–8.1)	8.1 (8.1–8.1)	0.383
Hemoglobine (g/dL)	12.4 (11.8–12.8)	12.5 (11.4–13)	13.8 (10.6–14)	0.742
Serum 25-hydroxyvitamin D (ng/mL)	15.3 (13.53–20.8)	12.95 (8.85-15)	10.87 (7.9–13.3)	**0.003***
Vitamin B12 (pg/mL)	571 (426–599)	402 (320–596)	289 (249–402)	**<0.001***
Serum Ferritin (ng/mL)	17.1 (10.8–21)	20.4 (7.4–25.6)	20 (5.3–27.6)	0.570

Table 2. Distribution of clinical findings among malnutrition patients. MGL: Meibomian gland loss NI-BUT: Non-invasive tear break-up time. *Kruskal-Wallis H. Data are expressed as medians (Quarter 1 – Quarter 3).

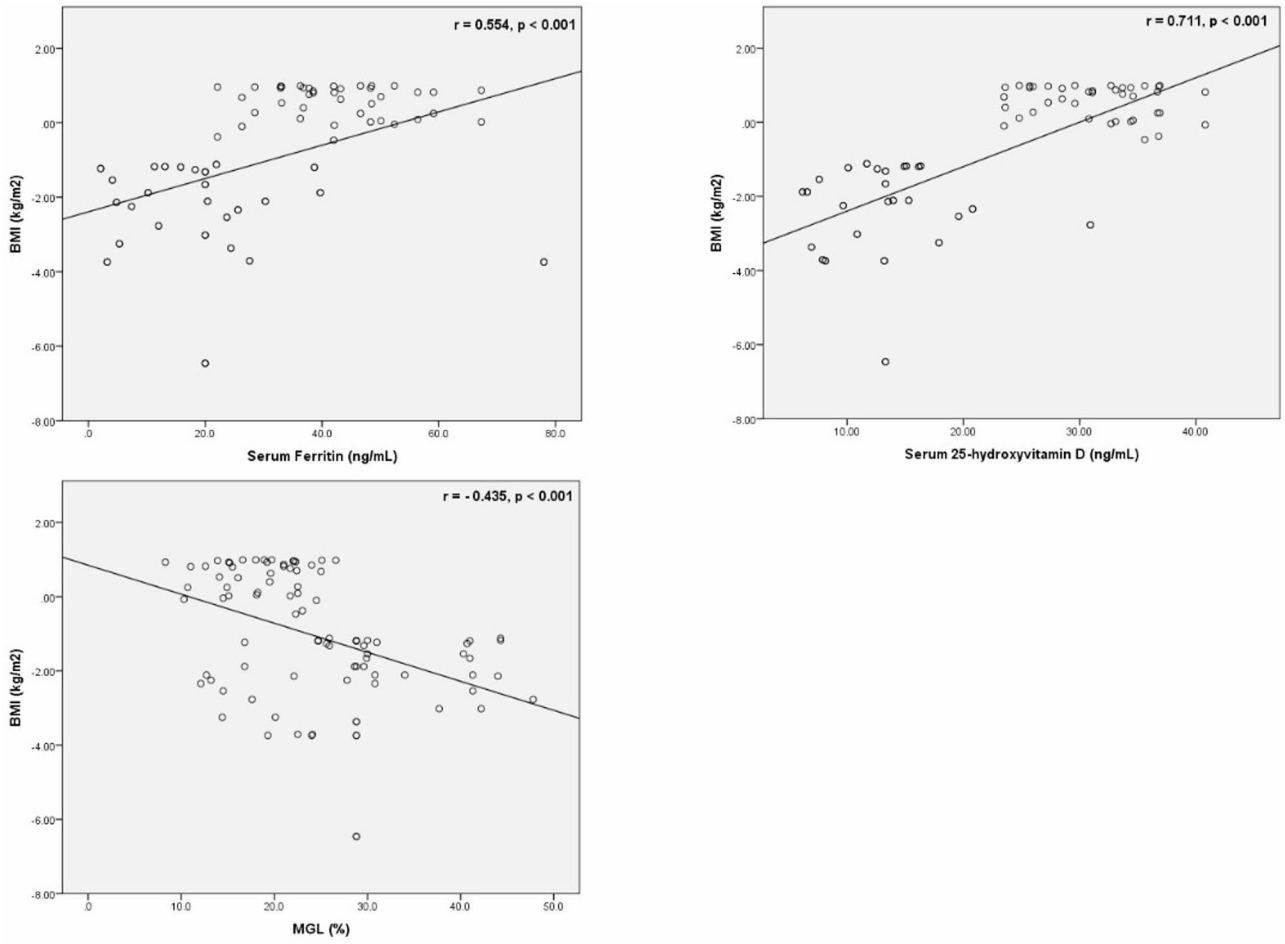

Fig. 3. Correlation graphics between BMI and serum ferritin, serum 25-hydroxyvitamin D, MGL. BMI: Body mass index MGL: Meibomian gland loss.

Discussion

We investigated the morphology and function of the meibomian glands in children with malnutrition. Our findings revealed significant alterations in meibomian gland structure and secretion dynamics compared to healthy controls.

MGL refers to a reduction in the number of functional meibomian glands. This can compromise the quality and quantity of meibum secretion, leading to evaporative dry eye[11]. Our study observed a higher prevalence of meibomian gland disease (MGD) in children with malnutrition compared to healthy controls. This finding is consistent with previous research indicating an association between nutritional deficiencies and MGD[12,13]. Nutrients such as omega-3 fatty acids, vitamin A, and zinc play crucial roles in maintaining meibomian gland function and lipid composition[7,14].

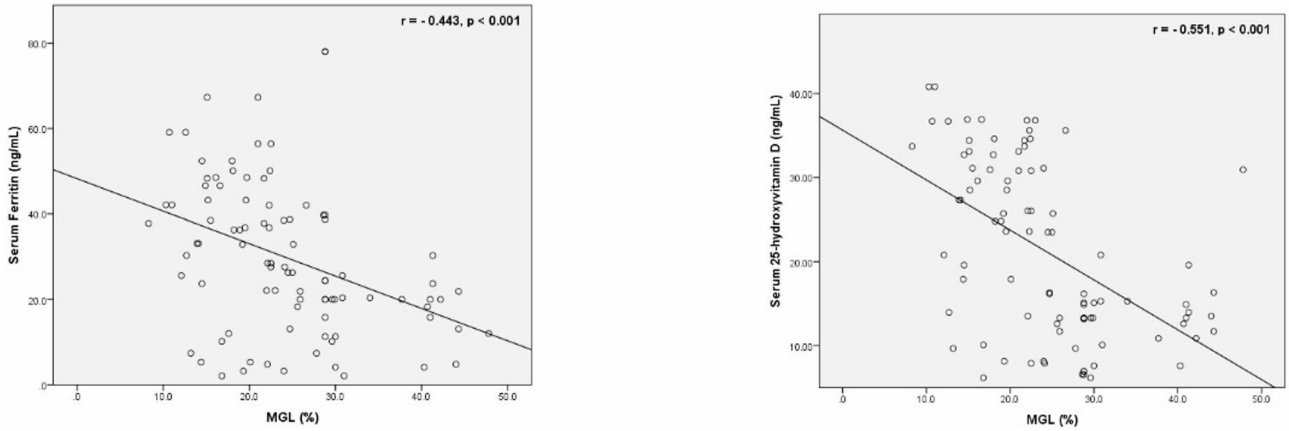

Fig. 4. Correlation graphics between MGL and serum ferritin, serum 25-hydroxyvitamin D. MGL: Meibomian gland loss.

Interestingly, we found a significant negative correlation between MGL and BMI, with lower BMI associated with higher degrees of MGL. This correlation may be attributed to micronutrient deficiencies commonly observed in malnourished individuals, such as choline, folate, and vitamin D. Inadequate intake of folate has been linked to retinal vascular diseases, potentially affecting ocular health[15]. Choline, another essential nutrient, plays a role in maintaining ocular function and has been implicated in the pathogenesis of ocular surface diseases[16]. We also observed significantly lower vitamin D levels in the patient group, which correlated with BMI. Previous studies have shown that vitamin D deficiency is associated with various ocular diseases, including dry eye syndrome[17]. Vitamin D receptors exist in many ocular structures, including corneal epithelial cells[18]. Considering that vitamin D is an important immunomodulator and has anti-inflammatory effects, its deficiency is likely to emerge as a significant factor in dry eye disease[19]. This suggests that micronutrient deficiencies, particularly vitamin D, may contribute to meibomian gland dysfunction in malnourished children[20].

In the malnutrition group, we observed significantly lower serum ferritin and hemoglobin levels compared to the healthy controls. This may be attributed to several factors commonly associated with malnutrition, including inadequate intake of iron-rich foods, impaired absorption due to gastrointestinal dysfunction, and increased iron losses through mechanisms such as bleeding or hemolysis[21,22]. Iron deficiency is a well-documented consequence of malnutrition and can lead to decreased hemoglobin synthesis and subsequent anemia[23]. It has been shown that iron deficiency anemia causes damage to ocular structures through oxidative stress, and its role in meibomian gland dysfunction warrants further investigation[24].

The observed changes in meibomian gland morphologies may reflect underlying inflammatory processes and oxidative stress associated with malnutrition[25,26]. Chronic inflammation can disrupt the normal architecture of the meibomian glands, impairing their function and contributing to ocular surface dysfunction. Our findings suggest that malnutrition may compromise the lipid composition of the meibum, leading to tear film instability and evaporative dry eye. Previous studies have highlighted the role of dietary omega-3 fatty acids in modulating the meibum composition and improving tear film stability[27]. Although we could not measure these levels, supplementation with omega-3 fatty acids has been shown to alleviate symptoms of dry eye and improve meibomian gland function in both adults and children[12].

No statistically significant difference was observed in vitamin B12 levels between the patient and control groups. However, in the analysis between the malnutrition subgroups, significantly lower vitamin B12 values were observed in the severe malnutrition group. Low levels of vitamin B12, commonly associated with malnutrition, have been linked to various ocular manifestations, including chalazion, in the pediatric population[28]. This finding could indicate that low vitamin B12 levels may affect meibomian gland health, potentially exacerbating meibomian gland dysfunction in malnourished children.

Although our study provides valuable insights into the ocular consequences of malnutrition, several limitations should be acknowledged. Firstly, the cross-sectional design limits our ability to establish causality between malnutrition and meibomian gland changes. Secondly, in our study, we were unable to include other parameters indicating meibomian gland function, such as gland expressibility, lipid turbidity, and eyelid margin abnormalities. A different issue is that the meibography test itself has certain limitations. These primarily include factors such as the potential impact of image resolution, contrast, and lighting conditions on the measurements, inconsistencies between the software and the examiner, and the difficulty of standardizing eyelid margin positioning. Despite all these limitations, meibography remains an important tool in the evaluation of meibomian glands in the literature. To minimize these limitations, it is recommended that measurements be performed by the same examiner, in the same room, and using the same device[29]. In our study, all measurements were performed using the same device, in the same room, and by the same examiner, which minimized these limitations to the lowest possible level. Another point is that the study does not clarify whether malnutrition-induced gland atrophy is reversible or permanent. Therefore, a future study examining changes after treatment would be necessary to determine whether gland atrophy induced by malnutrition is reversible. Additionally, the small sample size and homogeneity of the study population may limit the generalizability of our findings. Future

research should include larger, more diverse cohorts to validate our results and explore potential confounding factors.

Our study highlights the significant impact of malnutrition on meibomian gland morphology and function in children. To our knowledge, this is the first study in the literature to investigate the effects of malnutrition on the meibomian glands in a pediatric population. The observed alterations in meibomian gland structure and secretion dynamics underscore the importance of early nutritional intervention in preserving ocular health and preventing long-term complications. By elucidating the ocular consequences of malnutrition, our findings may inform targeted interventions to mitigate the burden of ocular morbidity and improve the overall health outcomes of malnourished children.

Data availability

The participants of this study did not give written consent for their data to be shared publicly, so due to the sensitive nature of the research supporting data is not available. Data can be requested by contacting the corresponding author (FY).

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Author contributions

Involved in design and conduct of this study (FY, BY, EYS, NSK); involved in collection, management, analysis, and interpretation of the data (BY, EYS); involved in preparation, review, or approval of the manuscript (FY, BY,

EYS, NSK).

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to F.Y.

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