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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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OCULAR SURFACE AND TEAR FILM CHANGES IN GRAVES' DISEASE ACCORDING TO THYROID EYE DISEASE STATUS

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Abstract.

Background: Thyroid eye disease (TED) is one of the main extrathyroidal manifestations of Graves' disease, occurring in approximately 30% of cases. About 10% of affected patients develop severe forms associated with a risk of vision loss and disability.

Objective: To evaluate ocular symptoms and tear film parameters, including tear film break-up time and Schirmer test results, and to examine their associations with clinical characteristics in patients with Graves' disease and inactive thyroid eye disease.

Methods: This observational cross-sectional study included 53 patients: 21 with TED and 32 without ocular involvement. Clinical assessment was based on a standardized examination. All patients were evaluated for TED according to the EUGOGO criteria and underwent laboratory testing. TED activity at the time of examination was assessed using the Clinical Activity Score (CAS). Linear generalized estimating equation (GEE) models with a normal distribution and identity link function were applied to continuous outcomes, whereas logistic GEE models were used for binary outcomes.

Results: Patients with TED more frequently reported excessive tearing (61.9% vs. 12.4%) and a sensation of ocular pressure (38.1% vs. 3.1%). They also demonstrated more pronounced proptosis (β = 4.853, 95% CI 3.061-6.645; P < 0.0001) and a shorter tear film break-up time (β = -1.298, 95% CI -2.482 to -0.113; P = 0.032). No significant between-group differences were observed in Schirmer test values. Greater proptosis was associated with reduced tear film stability (β = -0.184, 95% CI -0.320 to -0.048; P = 0.008).

Conclusion: The associations of shorter TBUT with greater proptosis and higher TRAb levels in patients with TED suggest a combined influence of mechanical and autoimmune factors on the ocular surface condition.

Key words. Graves' disease, thyroid eye disease, Graves' orbitopathy, ocular surface abnormalities, tear film dysfunction.

Introduction.

Thyroid eye disease (TED) is a relatively uncommon but clinically significant autoimmune disorder, with an estimated prevalence of 90-300 cases per 100,000 individuals. It is characterized by upper eyelid retraction, and inflammatory changes affecting the orbital tissues [1]. In addition to these classical clinical manifestations, increasing attention has been directed toward ocular surface abnormalities, as they represent one of the leading causes of chronic ocular discomfort and impaired quality of life in patients with TED [2-4].

Ocular surface involvement in TED may present with both subjective symptoms, including dryness, excessive tearing, photophobia, and foreign body sensation, and objective signs, such as reduced tear film stability, abnormal Schirmer test result, corneal and conjunctival staining, and other indicators of ocular surface damage [5,6]. Notably, the severity of subjective symptoms does not always correlate with objective clinical findings, highlighting the importance of a comprehensive assessment that incorporates both patient-reported outcomes and objective ocular surface parameters [7].

Most contemporary studies investigating ocular surface changes in TED have focused on patients with active inflammatory disease, typically defined by a Clinical Activity Score (CAS) ≥3. These studies have consistently demonstrated more pronounced ocular surface impairment in patients with active TED, including reduced tear film stability, shorter tear break-up time, abnormal Schirmer test results, increased ocular surface staining, and greater severity of ocular discomfort symptoms [8,9]. In contrast, data regarding ocular surface status in patients with inactive or minimally active TED remain inconsistent. Although several studies have included patients with mild or inactive TED, the contribution of autoimmune and structural-mechanical mechanisms to the development of ocular surface abnormalities in the setting of low disease activity has not been fully elucidated [10,11].

Therefore, the objective of the present study was to evaluate ocular symptoms and tear film parameters, including tear film break-up time and Schirmer test results, and to examine their associations with clinical characteristics in patients with Graves' disease and inactive thyroid eye disease.

Methods.

We conducted a cross-sectional study at City Outpatient Clinic No. 5 and City Multidisciplinary Hospital No. 3 in Astana, Kazakhstan, between September and December 2025. Using a consecutive sampling approach, all patients registered with a diagnosis of Graves' disease at the participating institutions were invited to participate. Eligible participants were adults (≥18 years of age) with a confirmed diagnosis of Graves' disease. Exclusion criteria included ocular surgery or ocular trauma within the preceding 6 months; contact lens wear within the previous 3 months; acute ocular infections (including conjunctivitis, keratitis, and uveitis); active allergic conjunctivitis; cicatrizing ocular surface disorders (including ocular cicatricial pemphigoid, Stevens-Johnson syndrome, and sequelae of chemical burns); systemic diseases associated with secondary dry eye disease (including Sjögren's disease, rheumatoid arthritis, systemic lupus erythematosus, and other

connective tissue diseases); use of systemic medications known to affect tear production or ocular surface homeostasis (e.g., anticholinergics, antidepressants, antihistamines, isotretinoin); use of topical ophthalmic medications, with the exception of artificial tears; which were discontinued at least 24 hours before the examination; and receipt of specific treatments for ocular surface disease within the preceding 3 months, including topical immunomodulatory therapy, punctal occlusion, or device-based treatment for meibomian gland dysfunction. The presence of clinical manifestations of TED, including eyelid retraction, lagophthalmos, meibomian gland dysfunction, signs of dry eye disease (DED), and other ocular surface abnormalities, was not considered an exclusion criterion, as these features constituted the primary outcomes of the study. Graves' disease was diagnosed on the basis of clinical findings together with laboratory confirmation of thyroid hyperfunction and positivity for thyroid-stimulating hormone receptor antibodies (TRAb), as well as characteristic thyroid ultrasonographic findings.

All participants underwent a standardized assessment that included the collection of demographic and clinical data, including age, sex, age at the onset of Graves' disease, disease duration, and smoking status, given its established role as a risk factor for the development and progression of TED. Thyroid function was assessed by measuring serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and TRAb levels.

Patient-reported ocular symptoms, including dryness, excessive tearing, photophobia, and a sensation of ocular pressure, were analyzed at the patient level. In contrast, each eye was evaluated independently for objective ophthalmic parameters, as the severity of ocular surface involvement in Graves' disease may differ between the right and left eyes of the same individual. Objective ophthalmic assessment included exophthalmometry for the measurement of proptosis, the Schirmer test to evaluate aqueous tear production, and TBUT measurement to assess tear film stability.

All participants were evaluated for the presence of TED according to the European Group of Graves' Orbitopathy (EUGOGO) diagnostic criteria. Disease activity at the time of examination was assessed using the CAS score. Based on these assessments, participants were stratified into two groups. The TED group comprised patients with thyroid eye disease of any severity (n=21), whereas patients with Graves' disease who did not meet the EUGOGO diagnostic criteria for TED were assigned to the non-TED group (n=32).

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Data visualization and graphical presentation were generated using R version 4.5.2 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as the median and interquartile range (IQR), whereas categorical variables are expressed as frequencies and percentages. Comparisons between patients with and without TED were performed using the Mann-Whitney U test for continuous variables and the chi-square ($\chi 2$) test or Fisher's exact test, as appropriate, for categorical variables. For ophthalmic parameters, each eye was analyzed as a separate observational unit. Tear film break-up time, Schirmer test results, and exophthalmometry measurements were evaluated on an eye-specific basis. Analyses of patient-reported symptoms were performed at the patient level. Generalized estimating equations (GEE) were used to evaluate associations involving eye-level data (e.g., TBUT), accounting for the within-subject correlation between fellow eyes. For continuous outcomes, linear GEE models with a Gaussian distribution and an identity link function were fitted. For binary outcomes, logistic GEE models were applied. Interaction terms were included to assess whether the associations differed between patients with and without TED. A two-sided p value < 0.05 was considered statistically significant.

Ethics approval and consent to participate:

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethic Committee of the ART Science Innovation Center (Protocol No. 9-2024, dated October 10, 2024).

Data availability statement:

The dataset generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Results.

The demographic and clinical characteristics of the study participants are summarized in Table 1. Notably, patients in the TED group exhibited asymmetric orbital involvement. No significant differences were observed between TED and non-TED groups with respect to age, sex, age at disease onset, or smoking status.

Comparative analysis of ocular manifestations between the study groups demonstrated statistically significant differences in the prevalence of excessive tearing (61.9% vs. 12.4%) and the sensation of ocular pressure (38.1% vs. 3.1%), both of which were more frequently reported by patients with TED (Figure 1A). In contrast, no statistically significant differences were observed between the groups in serum levels of pituitary-thyroid axis hormones, including TSH, FT3, FT4, or in TRAb levels (Figure 1B).

Using generalized estimating equation to account for inter-eye correlation, patients with TED were found to have significantly greater proptosis, as measured by exophthalmometry, than those without TED ($\beta = 4.853$, 95% CI 3.061-6.645, $P < 0.0001$). Median exophthalmometry values in the TED group were 23 mm (IQR, 20.0-25.5) in both the right (OD) and left (OS) eyes, compared with 17.5 mm (IQR, 16.0-19.0) in the right eye and 18.0 mm (IQR, 16.0-20.0) in the left eye in the non-TED group (Figure 2A). GEE analyses of TBUT demonstrated significantly reduced tear film stability in patients with TED compared with those without TED ($\beta = -1.298$, 95% CI -2.482 to -0.113, $P = 0.032$). The median TBUT in the TED group was 7 s (IQR, 5.5-10.0) in the right eye and 8 s (IQR, 5.5-10.0) in the left eye, whereas the corresponding values in the non-TED group were 8 s (IQR, 7.5-10.0) and 9 s (IQR, 8.0-10.0), respectively (Figure 2B). In contrast, GEE analysis accounting for inter-eye

Table 1. *Demographic and Clinical Characteristics of the Study Participants.*

Variable		TED group		Non-TED group (control)		P value
		Me	IQR	Me	IQR	
Age, years		45.5	37.5-56.2	48	39-57	0.884
Sex	Male	4	19%	7	21.9%	1.0
	Female	17	81%	25	78.1%	
Age at disease onset, years		34	31.7-42.5	41.5	29.5-50.2	0.266
Disease duration, years		5	2-15.7	4	2-15	0.199
Smoking		10	23.8%	11	17.5%	0.426
Severity of TED	Mild	12	57.1%			
	Moderate	9	42.9%			
Activity	Inactive	21	100%			
CAS, points		0	0-1			

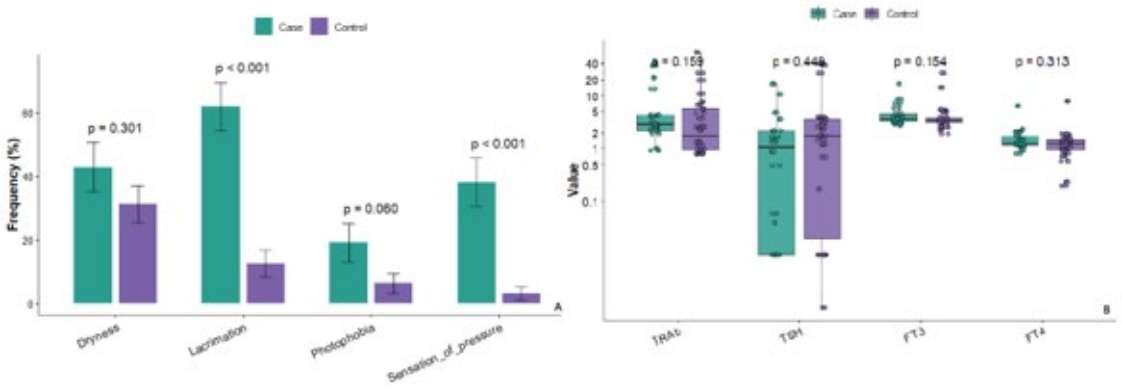


Figure 1. *Comparison of (A) Prevalence of Ocular Symptoms, and (B) Thyroid Function Test and TRAb Levels Between TED and non-TED groups.*

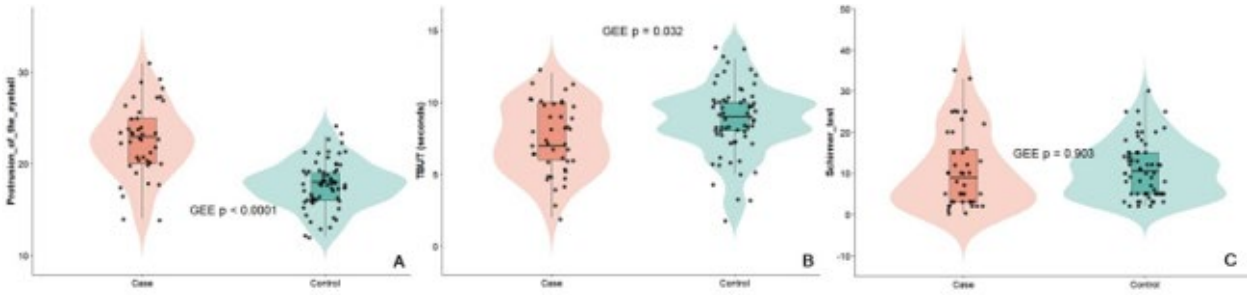


Figure 2. *Comparison of (A) Exophthalmometry, (B) TBUT, and (C) Schirmer Test Values Between Patients with TED and Controls.*

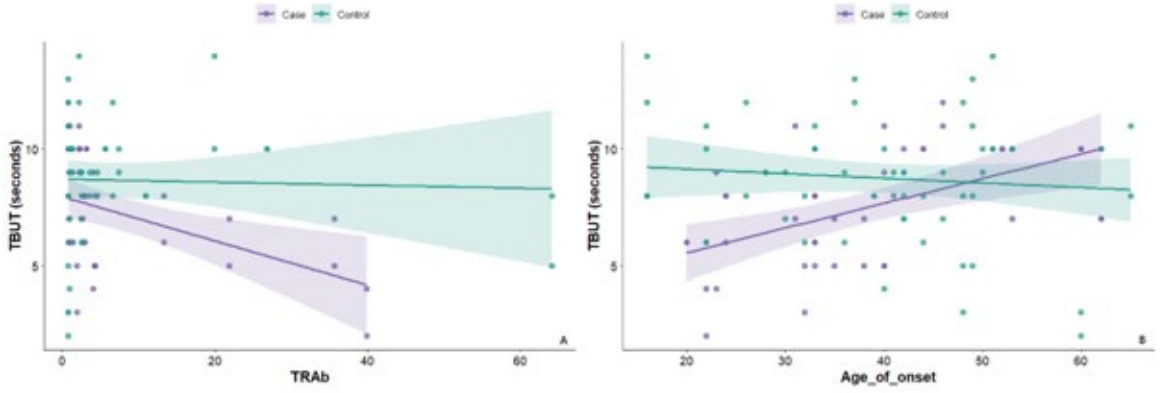


Figure 3. *Stratified Associations Between TBUT and Clinical Variables in TED and non-TED groups. (A) Relationship Between TRAb Levels and TBUT. (B) Relationship Between Age at Disease Onset and TBUT.*

correlation showed no significant association between TED status and Schirmer test values (β = -0.269, 95% CI -4.611 to 4.073, P = 0.903). Median Schirmer test values in the TED group were 10 mm (IQR, 3.0-20.0) in the right eye and 8 mm (IQR, 3.0-15.5) in the left eye, compared with 10 mm (IQR, 5.0-14.75) and 12 mm (IQR, 5.0-18.0), respectively, in the non-TED group (Figure 2C).

We next explored factors associated with tear film instability by performing additional generalized estimating equation analyses, with tear film break-up time specified as the dependent variable and selected demographic, clinical, and laboratory variables entered as independent predictors.

Significant interactions were identified between study group and TRAb levels (P = 0.030), as well as between study group and age at Graves' disease onset (P = 0.011), indicating that the associations of these variables with TBUT differed between patients with and without TED. Consequently, stratified GEE analyses were performed separately for the TED and non-TED groups. In the stratified GEE analyses, higher TRAb levels were significantly associated with shorter TBUT among patients with TED (β = -0.095, 95% CI -0.150 to -0.040, P = 0.001), whereas no such association was observed in the non-TED group (P = 0.828) (Figure 3A). Similarly, among patients with TED, age at Graves' disease onset was significantly associated with TBUT (β = -6.108, 95% CI -9.832 to -2.384, P = 0.001), no such association was observed in the non-TED group (P = 0.998) (Figure 3B).

We also found that greater exophthalmos was independently associated with reduced tear film stability. In the GEE model, each 1-mm increase in exophthalmos was associated with a 0.184-second decrease in TBUT (β = -0.184, 95% CI -0.320 to -0.048, P = 0.008).

Discussion.

Our findings demonstrated significantly reduced TBUT in patients with inactive TED compared with patients with Graves' disease without ocular involvement. These findings are generally consistent with previous studies demonstrating ocular surface dysfunction and impaired tear film stability in patients with TED. Importantly, most published evidence has been derived from cohort of patients with active TED, a disease stage characterized by more pronounced ocular surface inflammation. In these patients, previous studies have consistently demonstrated reduced TBUT, increased tear film osmolarity, a higher prevalence of dry eye symptoms, and elevated Ocular Surface Disease Index (OSDI) scores. Previous studies have suggested that these alterations are driven by the combined effects of local orbital inflammation and structural remodeling of the orbital tissues during the active phase of TED [11,12].

In contrast, studies focusing on inactive TED remain relatively limited and have yielded less consistent findings. Several investigations have demonstrated that, despite resolution of active inflammation, patients continue to experience ocular discomfort, while tear film stability remains impaired compared with healthy individuals. Consistent with our findings, Wang et al., Bui et al. and Allam et al. reported that patients with both active and inactive TED exhibited greater ocular surface impairment than healthy controls [8,10,13]. However, the severity of ocular surface abnormalities was consistently greater in patients with active disease, supporting the contribution of active orbital inflammation to ocular surface dysfunction.

In contrast, Rana et al. emphasized the substantial contribution of mechanical factors to ocular surface dysfunction in TED [14]. Increased proptosis, eyelid retraction, and lagophthalmos may promote excessive tear evaporation, impair tear film distribution across the corneal surface, and reduce TBUT, irrespective of inflammatory disease activity. These observations are consistent with our findings, which demonstrated significantly lower TBUT values and greater proptosis in patients with inactive TED compared with patients with Graves' disease without TED. Furthermore, the absence of significant differences in Schirmer test results, together with the independent association between exophthalmos and TBUT observed in our GEE analysis, supports the hypothesis that mechanical factors play a predominant role in tear film instability in patients with inactive TED.

Of particular interest, although TRAb levels did not differ significantly between the study groups, an inverse association between TRAb levels and TBUT was observed exclusively among patients with TED. This finding suggests that the clinical relevance of TRAb may depend less on their absolute circulating levels than on the presence of orbital involvement, where these autoantibodies may exert their pathogenic effects. The absence of a similar association in patients with Graves' disease without TED further supports the concept that orbital tissue susceptibility is required for TRAb-mediated ocular surface dysfunction. This finding is consistent with current understanding role of TRAb in the pathogenesis of TED. Expression of thyroid-stimulating hormone receptors on orbital fibroblasts and other periocular cells promotes activation of inflammatory and tissue-remodeling pathways that contribute to the development of TED. Accordingly, the observed inverse association between TRAb levels and TBUT may reflect the contribution of autoimmune mechanisms to ocular surface dysfunction in patients with TED.

An unexpected finding of our study was association between age at Graves' disease onset and TBUT, which was observed exclusively among patients with TED. To date, evidence regarding the influence of age at disease onset on ocular surface status in Graves' disease remains limited. It is possible that age at onset reflects differences in disease phenotype, cumulative exposure to autoimmune mechanisms, or age-related alterations in ocular surface tissues. However, this association should be interpreted with caution, as it was identified in an exploratory analysis and has not been consistently reported in previous studies. Accordingly, our findings should be considered preliminary and require confirmation in larger, independent cohorts.

A notable strength of the present study is that the majority of patients with TED had inactive disease and low CAS values. Despite the absence of clinically active inflammation, these patients exhibited significantly reduced TBUT, a higher prevalence of ocular symptoms, and greater proptosis than patients with Graves' disease without TED. These findings suggest that ocular surface dysfunction may persist beyond the active inflammatory phase of TED and support the concept that mechanisms other than active inflammation, including structural

and mechanical changes, contribute to tear film instability in inactive disease. Taken together, our findings support the concept that ocular surface dysfunction in TED is multifactorial, resulting from the combined effects of immune-mediated inflammation and structural alterations of the orbit and eyelid. These results also highlight the importance of disease activity, as clinically meaningful tear film dysfunction may persist even during the inactive phase of the disease.

Limitations.

This study has several limitations. First, it was conducted at a single center and included a relatively small sample size, which may limit the generalizability of the findings to the broader population of patients with Graves' disease. Second, the cross-sectional design precludes causal inference regarding the relationships between clinical characteristics of Graves' disease and ocular surface parameters. In addition, the exploratory associations identified in this study, particularly those involving age at disease onset and TRAb levels, should be interpreted with caution and require validation in larger, prospective, multicenter studies.

It should also be considered that ocular surface assessment was based primarily on patient-reported symptoms, TBUT, and the Schirmer test. Other established diagnostic modalities, including corneal and conjunctival staining with fluorescein or lissamine green, tear film osmolarity measurement, quantitative assessment of meibomian gland function, and validated dry eye symptom questionnaires, were not incorporated into the study protocol. Consequently, the present findings should be interpreted as reflecting selected features of ocular surface dysfunction and tear film instability rather than a comprehensive of dry eye disease according to contemporary diagnostic criteria.

Conclusion.

Patients with Graves' disease and inactive TED demonstrated shorter tear film break-up time, more pronounced exophthalmos, and a higher frequency of ocular symptoms than patients without ocular involvement. The absence of a significant between-group difference in Schirmer test results suggests that these changes may be related primarily to increased tear evaporation and impaired tear film distribution associated with structural and anatomical changes in the orbit and eyelids, rather than reduced tear production.

The independent negative association between the degree of exophthalmos and TBUT, together with the association between higher TRAb levels and shorter TBUT observed exclusively in patients with TED, suggests that both mechanical and autoimmune factors may contribute to reduced selected tear film parameters, particularly TBUT, in these patients. The association between TBUT and age at Graves' disease onset should be considered a preliminary finding requiring confirmation in larger prospective studies. These findings support the need for comprehensive ocular surface assessment in patients with TED, irrespective of disease activity.

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Изменения поверхности глаза и слезной пленки при болезни Грейвса в зависимости от статуса эндокринной орбитопатии

Актуальность: Эндокринная орбитопатия (ЭОП) является одним из основных внещитовидных проявлений болезни Грейвса, встречаясь примерно в 30% случаев, при этом 10% пациентов имеют тяжелые формы, сопряженные с риском потери зрения и инвалидизации.

Цель: Оценить глазные симптомы и параметры слезной пленки, включая время распада слезной пленки и результаты теста Ширмера, а также изучить их связь с клиническими характеристиками у пациентов с болезнью Грейвса с неактивной тиреоидной офтальмопатией.

Методы: В это обсервационное одномоментное поперечное исследование были включены 53 пациента: 21 с тиреоидной офтальмопатией и 32 без поражения глаз. Клиническая оценка была основана на стандартизированном обследовании, всем пациентам оценивалось наличие тиреоидной офтальмопатии согласно критериям

EUGOGO и лабораторные показатели, активность TED на момент осмотра оценивалась по шкале CAS. Для непрерывных результатов применялись линейные модели GEE с нормальным распределением и функцией связи идентичности. Для бинарных результатов использовались логистические модели GEE.

Результаты: У пациентов с офтальмопатией чаще отмечались слезотечение (61,9% против 12,4%) и ощущение давления в глазах (38,1% против 3,1%), наблюдались более выраженная протрузия глазного яблока (β = 4,853, 95% ДИ 3,061-6,645, p<0,001) и снижение времени разрыва слезной пленки (TBUT) (β = -1,298, 95% ДИ от -2,482 до 0,113, p=0,032). Значимых различий по тесту Шримера не выявлено. Выраженность экзофтальма была ассоциирована со снижением стабильности слезной пленки (β = -0,184, 95% ДИ от -0,320 до -0,048, p = 0,008).

Вывод: Связи между выраженностью экзофтальма, более коротким TBUT и уровнями антител к рецепторам ТТГ у пациентов с ЭОП свидетельствуют о сочетанном влиянии механических и аутоиммунных факторов на состояние глазной поверхности.

Ключевые слова: болезнь Грейвса, эндокринная орбитопатия, тиреоидная офтальмопатия, нарушение глазной поверхности, дисфункция слезной пленки.

გრეივის დაავადების დროს თვალის ზედაპირისა და ცრემლსადენი ფილმის ცვლილებები ენდოკრინული ორბიტოპათიის სტატუსის მიხედვით

რეზიუმე: ენდოკრინული ორბიტოპათია გრეივის დაავადების ერთ-ერთი მთავარი ფარისებრი ჯირკვლის გარეთ გამოვლინებაა, რომელიც გვხვდება შემთხვევათა დაახლოებით 30% - ში, ხოლო პაციენტების 10% - ს აქვს მძიმე ფორმები, რომლებიც დაკავშირებულია მხედველობის დაკარგვისა და ინვალიდობის რისკთან.

მიზანი: შეაფასეთ თვალის სიმპტომები და ცრემლსადენი ფილმის პარამეტრები, მათ შორის ცრემლსადენი ფილმის დაშლის დრო და შირმერის ტესტის შედეგები და შეისწავლეთ მათი კავშირი კლინიკურ მახასიათებლებთან პაციენტებში გრეივის დაავადებით ფარისებრი ჯირკვლის არააქტიური ოფთალმოპათიით.

მეთოდები: ეს სადამკვირვებლო ჯვარედინი კვლევა მოიცავდა 53 პაციენტს: 21 TED-ით და 32 თვალის ჩართულობისგარეშე.კლინიკურიშეფასებაეფუძნებოდა სტანდარტიზებულ გამოკვლევას. ყველა პაციენტი შეფასდა TED-ისთვის EUGOGO კრიტერიუმების მიხედვით და გაიარა ლაბორატორიული ტესტირება. TED აქტივობა გამოკვლევის დროს შეფასდა კლინიკური აქტივობის ქულის (CAS) გამოყენებით. ლინერული განზოგადებული შეფასების განტოლების (GEE) მოდელები ნორმალური განაწილებისა და იდენტობის კავშირის ფუნქციით გამოიყენებოდა უწყვეტ შედეგებზე, ხოლო ლოგისტიკური GEE მოდელები გამოიყენებოდა ბინარული შედეგებისთვის.

შედეგები: ოფთალმოპათიის მქონე პაციენტებს უფრო ხშირად აღენიშნებოდათ ცრემლდენა (61.9% 12.4%- ის წინააღმდეგ) და თვალებში წნევის შეგრძნება (38.1% 3.1%-ის წინააღმდეგ), თვალის კაკლის უფრო გამოხატული პროტრუზია (β = -4.853, 95% CI -3.061-დან -6.645-მდე, p<0.001) და ცრემლსადენი ფილმის რღვევის დროის შემცირება (TBUT) (β = -1.298, 95% CI-95% 2.482-0.113, p=0.032). შრიმერის ტესტში მნიშვნელოვანი განსხვავებები არ ყოფილა. ეგზოფთალმოსის სიმძიმე ასოცირდება ცრემლსადენი ფილმის სტაბილურობის შემცირებასთან (β = -0.184, 95% CI: -0.320 - დან -0.048, p = 0.008).

დასკვნა: TED-ით დაავადებულ პაციენტებში უფრო მოკლე TBUT-ის ასოციაციები უფრო დიდი პროპტოზით და TRAb-ის უფრო მაღალი დონით მიუთითებს მექანიკური და აუტოიმუნური ფაქტორების კომბინირებულ გავლენაზე თვალის ზედაპირის მდგომარეობაზე.

საკვანძო სიტყვები: გრეივის დაავადება, ენდოკრინული ორბიტოპათია, ფარისებრი ჯირკვლის ოფთალმოპათია, თვალის ზედაპირის, ცრემლსადენი ფილმის დისფუნქცია.