Original Article

Anterior-segment optical coherence tomography for tacrolimus therapy response monitoring of vernal keratoconjunctivitis

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ABSTRACT

Background: Vernal keratoconjunctivitis (VKC), a chronic bilateral eye disease, is a severe form of allergic conjunctivitis. Anterior-segment optical coherence tomography (AS-OCT) is a rapid, noninvasive, *in vivo* visualization modality for the anterior segment structures that has been used in diagnosing and staging diseases and assessing the treatment efficacy. We used anterior-segment optical coherence tomography (AS-OCT) to monitor the efficacy of the tacrolimus eye ointment in managing VKC.

Methods: In this prospective follow-up study, we included patients with active symptomatic VKC. All patients were treated with the 0.03% tacrolimus ophthalmic ointment twice daily for 2 months and then once daily for 1 month. All patients underwent AS-OCT before and 3 months after treatment as an objective method to assess the treatment efficacy.

Results: We included 20 eyes of ten patients (nine men and one woman) with active symptomatic VKC. The mean age was 17.3 (range: 11 – 36) years, with nine patients having a palpebral type and one patient having a mixed type of VKC. Substantial flattening and reduction in the papilla size were observed in all patients at the post-treatment follow-up. AS-OCT measurements revealed significant reductions in the vertical, horizontal, and total diameters of the palpebral papillae and limbal conjunctival thickness after 3 months of treatment compared to baseline measurements (all $P < 0.001$). No serious adverse effects attributable to tacrolimus administration were observed in the study period.

Conclusions: AS-OCT is a suitable objective method for evaluating the treatment efficacy of the 0.03% tacrolimus eye ointment in patients with VKC. Future large-scale studies including a wide range of age groups with longer follow-up periods and AS-OCT monitoring at multiple post-treatment visits are required to confirm our preliminary results. Moreover, the diagnostic accuracy of AS-OCT in monitoring patients with active VKC should be tested in comparison with objective scoring by an experienced corneal fellowship.

KEYWORDS

tacrolimus anhydrous, vernal keratoconjunctivitis, optical coherence tomography, papillae, side effects, palpebral conjunctiva, bulbar conjunctiva

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral severe allergic conjunctivitis [1]. Epidemiological studies do not consider VKC as a seasonal disease because it is usually persistent throughout the year, with increased severity in warmer weather [2]. It affects children aged 3 – 16 years but might appear earlier, persist into adulthood, and show a higher prevalence among men [3].

It can be classified as palpebral, limbal, or mixed. Ocular symptoms include eye discharge, photophobia, watering, redness, itching, and burning sensations. Ocular signs include papillae, punctate keratopathy, Horner – Trantas dots, and shield corneal ulcers [4]. The pathogenesis of VKC remains unclear. Recent findings have shown it to be complex, involving T-helper cell 2 (Th2) lymphocytes, mast cells, eosinophils, fibroblasts, and cytokines in the inflammatory process [5].

Topical medications for VKC management include corticosteroids, mast cell stabilizers, antihistamines, and immunomodulatory agents. Corticosteroids effectively treat this disease, but their extended use may lead to complications such as glaucoma and cataracts [6, 7]. The use of immunomodulatory drugs such as tacrolimus can avoid steroid-related complications [8, 9].

Tacrolimus is a calcineurin inhibitor, similar to cyclosporine, but with 100 times greater potency and is derived from *Streptomyces tsukubaensis* [3]. It inhibits Th2 lymphocyte activation, Th-cell-mediated B-cell proliferation, and cytokine production. It also suppresses the secretion of histamine from mast cells, thus relieving allergic symptoms [10]. Topical tacrolimus is effective in managing giant papillary conjunctivitis, atopic keratoconjunctivitis, and VKC [11-14].

Anterior-segment optical coherence tomography (AS-OCT) is a rapid, noninvasive, *in vivo* imaging modality that demonstrates ocular structures and is used for quantitative measurements. Recent advancements in its resolution and acquisition speed have resulted in improved image quality and reproducibility for more detailed anterior-segment imaging [15]. It is also used to assess seasonal allergic conjunctivitis [16] and ocular surface lesions [17, 18]. However, to the best of our knowledge, no study has used AS-OCT to monitor the treatment response to tacrolimus ointment in eyes with VKC.

The aim of the present study was to monitor the treatment response to tacrolimus ointment in eyes with VKC using AS-OCT as a novel *in vivo* diagnostic imaging modality.

METHODS

This was a prospective, interventional, follow-up case series study involving 20 eyes of 10 patients with active symptomatic VKC conducted at the Damietta Ophthalmology Hospital in Damietta, Egypt. The study protocol was approved by the Ethics Committee of the Faculty of Medicine of the Port Said University. The study procedures followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

VKC was diagnosed based on seven clinical symptoms and five signs described elsewhere [4, 10]. We included newly diagnosed treatment-naive patients with VKC of varying severities and those recalcitrant to conventional anti-allergic drugs, such as antihistaminic agents, mast cell stabilizers, and corticosteroids. Patients with known hypersensitivity to tacrolimus, a history of systemic immunosuppressive drug use, a history of herpes keratitis, coexisting eye infections, congenital ocular anomalies, a history of ocular surgery, a history of contact lens use, cataract, or glaucoma were excluded. Further, lactation, pregnancy, and unwillingness to participate were exclusion criteria.

All patients underwent detailed ophthalmic examinations at each visit, including assessment of best-corrected distance visual acuity using a Snellen chart (automatic chart projector ACP 1800 L; Chongqing Vision Star Optical Co., Ltd., Chongqing, China), slit-lamp examination (Photo-Slit Lamp 30 GL; Takagi Seiko Co., Ltd., Japan), detailed fundus examination with a + 90-D lens (Volk Optical Inc., Mentor, OH, USA) under a slit-lamp microscope, and measurement of intraocular pressure using a Goldmann applanation tonometer (KAT R-Type Keeler, USA) without fluorescein staining [19].

A questionnaire was administered to all patients to grade all symptoms on a four-point scale by a single examiner at the start of tacrolimus treatment and at each follow-up. Likewise, clinical signs were scored by a constant observer on a four-point scale of signs described elsewhere [4, 10]. The total score was then calculated. The symptom scores were determined using a questionnaire. Each symptom (seven in total) was graded on a scale of 0 – 3, with a total score of 21 for each individual. The score for signs was determined at each visit based on the observer's clinical judgment, in which each clinical sign (five in total) was graded by the observer on a scale of 0 – 3, with a total score of 15 for each individual.

All patients received 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India) twice daily for 2 months and then once daily for 1 month. Follow-up visits were scheduled at 1 week, 1 month, 2 months, and 3 months.

All patients underwent AS-OCT at baseline and 3 months post-treatment as an objective *in vivo* measure to monitor the treatment response using spectral-domain OCT (RTVue, Optovue, Fremont, CA, software version 6.1.1). AS-OCT has a corneal lens adapter (low-magnification cornea anterior module) fixed onto the main lens to scan the anterior segment. It captures a scan length of up to 10 mm and a scan depth of 3 mm. A CL-line scan (6 – 8 mm) was used to image all cases [20, 21]. Utilizing this standard line mode, the location of the line can be seen on the monitor, and a fixed conjunctival landmark (an area of palpebral conjunctiva 3 mm superior to the lid margin) was used in all eyes with palpebral VKC to ensure that OCT was performed in the same area of pre- and post-treatment scanning. One patient had a mixed-type VKC, and we used the CL-line scan perpendicular to the limbus in the same area as the pre- and post-treatment scanning. Using a distance-measuring tool (built into the software), conjunctival papillae were measured vertically and horizontally along with the limbal conjunctival thickness before and 3 months after treatment.

Data were analyzed using the IBM SPSS software package (version 20.0; IBM Corp., Armonk, N.Y., USA). Continuous data were tested for normality with the Kolmogorov – Smirnov test. The Wilcoxon signed-rank test was used to compare two periods for non-normally quantitative variables, while the Friedman test was used to compare over two periods, followed by the post-hoc test (Dunn's) for pairwise comparisons. The repeated-measures analysis of variance was used to compare over two periods, and post-hoc test (Bonferroni adjusted) was used for pairwise comparisons of normally distributed quantitative variables. *P*-values < 0.05 were considered to indicate statistical significance.

RESULTS

We enrolled 20 eyes of 10 patients, including nine men and one woman. The mean age was 17.3 (range: 11 – 36) years, with nine (90%) patients showing the palpebral type and one (10%) patient showing the mixed type.

The primary symptoms were ocular itching and redness; however, the patients had varying degrees of other symptoms. All patients had papillary hypertrophy, and one patient had combined papillary hypertrophy, limbal inflammation, or a mixed type of VKC. The most common symptom was itching. It was present in all patients and the first symptom to respond to treatment within 2 weeks. The least frequent symptom was photophobia, observed in five patients. The most common signs were papillary hypertrophy and conjunctival hyperemia, present in all patients. The least frequent sign was the presence of Horner – Trantas dots, found in one patient.

Significant improvement in symptoms and decrease in the amount of eye discharge were observed within 2 weeks post-treatment ($P < 0.001$). The mean (SD) symptom score at baseline was 17.2 (2.3), which decreased significantly to 7.8 (2.2) and 3.2 (1.0) at 1- and 3-month post-treatment, respectively (both $P < 0.001$). The mean (SD) score for signs at baseline was 8.8 (1.6), which reduced significantly to 4.3 (0.5) and 2.5 (0.5) at 1- and 3-month post-treatment, respectively (both $P < 0.001$).

Figures 1-4 shows the clinical slit photographs and AS-OCT images before and at 3 months post-treatment. Substantial flattening and reduction in papillae size were observed in all treated eyes. AS-OCT images showed

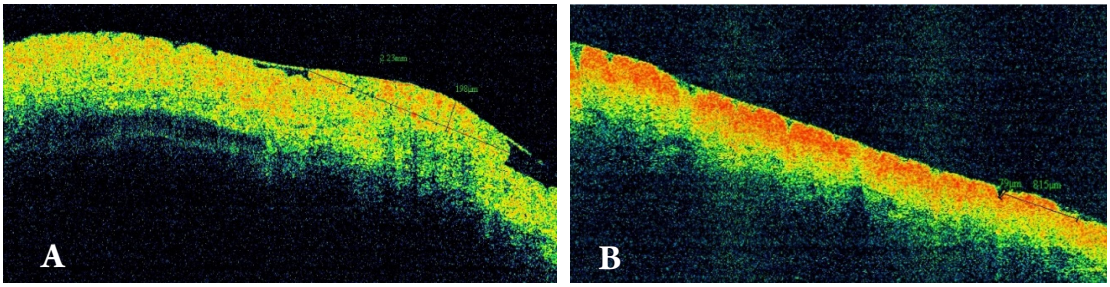

Figure 1. (A) Pretreatment spectral-domain anterior-segment optical coherence tomography (RTVue, Optovue, Fremont, CA, software version 6.1.1) image of the upper tarsal palpebral conjunctiva in the eye with palpebral vernal keratoconjunctivitis. (B) Post-treatment AS-OCT image of the same eye. Note (A) the large papilla in the AS-OCT image in the pretreatment assessment (B) with a marked decrease in papilla size in both horizontal and vertical dimensions as evident in the AS-OCT image at 3 months post-treatment with 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India).

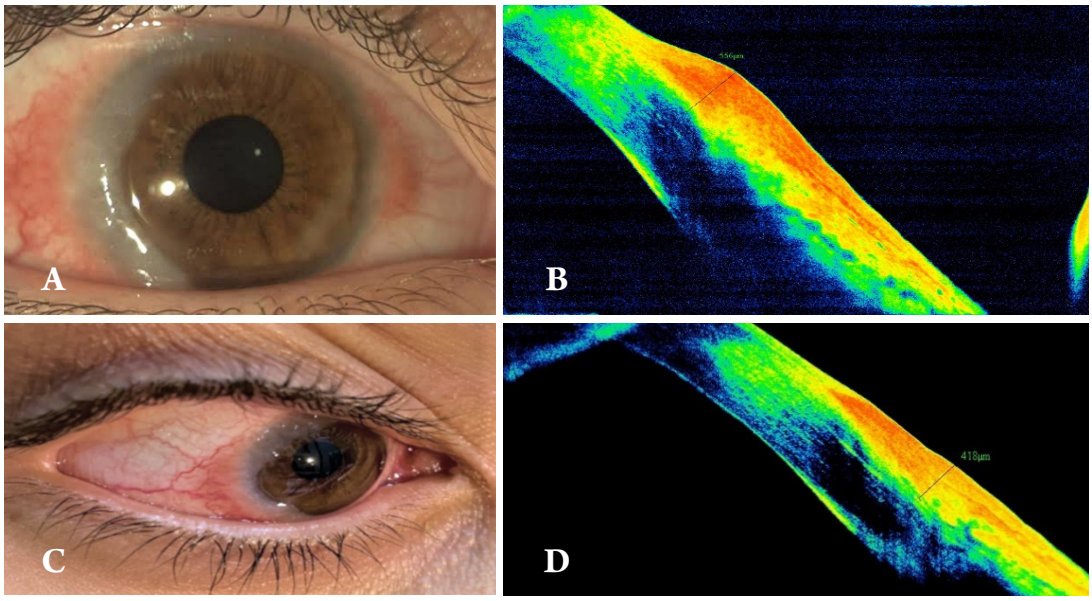

Figure 2. (A) Pretreatment slit photograph (Photo-Slit Lamp 30 GL; Takagi Seiko Co., Ltd, Japan) showing the eye with limbal vernal keratoconjunctivitis (VKC) and (B) spectral-domain anterior-segment optical coherence tomography (RTVue, Optovue, Fremont, CA, software version 6.1.1) image showing an increase in the thickness of the limbus. (C) Post-treatment slit photograph and (D) AS-OCT image of the same eye. Note (C) the improvement in limbal VKC in the clinical slit photograph and (D) the decrease in thickness of the limbus in the AS-OCT image at 3 months post-treatment with 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India).

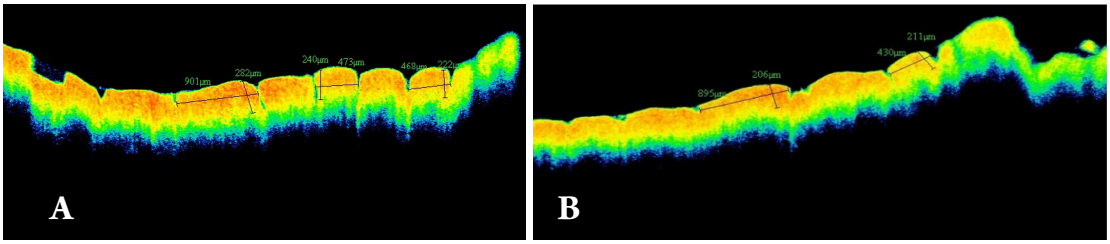

Figure 3. (A) Pre- and (B) post-treatment spectral-domain anterior-segment optical coherence tomography (RTVue, Optovue, Fremont, CA, software version 6.1.1) image in the eye with palpebral vernal keratoconjunctivitis. Note (B) the decrease in both vertical and horizontal dimensions of papillae in the AS-OCT image at 3 months post-treatment with 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India).

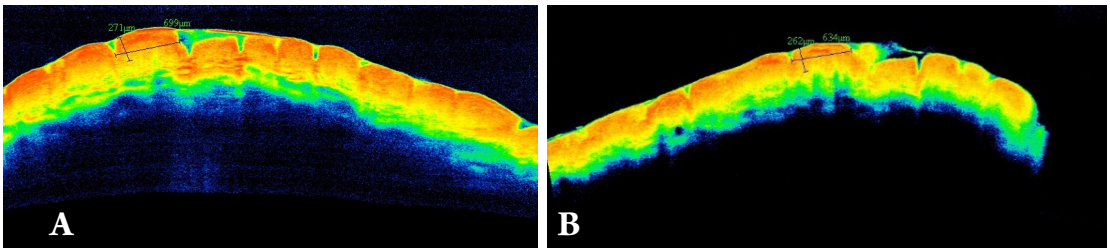

Figure 4. (A) Pre- and (B) post-treatment spectral-domain anterior-segment optical coherence tomography (RTVue, Optovue, Fremont, CA, software version 6.1.1) image in the eye with palpebral vernal keratoconjunctivitis. Note (B) the decrease in both vertical and horizontal dimensions of papillae in the AS-OCT image at 3 months post-treatment with 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India).

Table 1. Measurements of pre- and 3-month post-treatment papillae sizes in vertical, horizontal, and total diameters along with the percentage change in study participants*

Variables	Pre-treatment	3-month Post-treatment	*P*-value **
Vertical (μm), Mean ± SD	251.2 ± 58.8	175.7 ± 76.7	**< 0.001**
Decrease (%), Mean ± SD	30.3 ± 17.9		
Horizontal (μm), Mean ± SD	884.2 ± 352.5	601 ± 148.1	**< 0.001**
Decrease (%), Mean ± SD	32.2 ± 18.7		
Total (μm), Mean ± SD	567.7 ± 396.2	388.8 ± 238.8	**< 0.001**
Decrease (%), Mean ± SD	28.4 ± 18.3		

Abbreviations: μm, micrometer; SD, standard deviation; %, percentage of change. Note: *P*-values < 0.05 are shown in bold (Wilcoxon signed-rank test); *Patients had bilateral vernal keratoconjunctivitis and were treated with 0.03% tacrolimus ophthalmic ointment (Entrak Soothe; Entod Pharmaceuticals Ltd., Mumbai, India). All underwent pre- and 3-month post-treatment imaging with spectral-domain anterior-segment optical coherence tomography (RTVue, Optovue, Fremont, CA, software version 6.1.1).**

an evident decrease in the size of papillae and limbal conjunctival thickness 3 months post-treatment (Figures 1-4). AS-OCT measurements of mean pre- and 3-month post-treatment papillae sizes in vertical, horizontal, and total diameters along with the percentage change, indicated a statistically significant decrease in papillae size at 3 months post-treatment (all $P < 0.001$; Table 1). No serious adverse effects attributable to tacrolimus were observed or subjectively self-reports during the study period.

DISCUSSION

AS-OCT was a suitable *in vivo* imaging modality to monitor the treatment response to 0.03% tacrolimus eye ointment in patients with VKC. We observed a significant decrease in the conjunctival papillary size in parallel with significant improvement in the severity of clinical symptoms and signs.

VKC is a severe form of ocular allergy characterized by tarsal papillae at the upper palpebral conjunctiva (palpebral type) or a gelatinous mass at the limbus (bulbar type) [22]. Antiallergic drugs are often insufficient in severe ocular allergies that require long-term treatment, and the use of corticosteroids is associated with an increased risk of complications, such as glaucoma and cataract [12]. Cyclosporine is an effective alternative treatment. However, the results have been inconclusive [23-25], and patients have reported a burning sensation [24, 26]. Tacrolimus is a powerful immunosuppressive agent that significantly reduces cytokine synthesis by stimulated T-cells involved in VKC pathogenesis [27, 28]. Topical tacrolimus is highly effective in decreasing the number of inflammatory cells and inhibits calcineurin 100 folds more than cyclosporine [10, 29]. Similarly, we observed a significant improvement in clinical and imaging findings 3 months after the administration of 0.03% tacrolimus ophthalmic ointment in eyes with VKC.

Treatment of VKC using topical tacrolimus has significantly changed its management, which was previously challenging to control without corticosteroids and considered to be a sight-threatening condition due to the severity of its manifestations or steroid-related complications [2, 4, 30, 31]. Similar to the present study, several studies have demonstrated the efficacy and safety of topical tacrolimus in managing this disease [2, 4].

In the present study, the mean baseline scores for both clinical symptoms and signs had significantly reduced after 12 weeks of treatment with topical tacrolimus. These results are consistent with those of other recent studies [8, 12, 22]. However, to the best of our knowledge, this is the first study to document the efficacy of 0.03% tacrolimus eye ointment using AS-OCT as a novel imaging modality for assessing improvement and monitoring treatment response, along with the resolution of symptoms and signs scored on a four-point scale.

Tacrolimus ointment alone was administered to all patients. The stinging sensation was the only side effect; however, it was well tolerated by most patients and lasted for a few days. Except for stinging sensations, all patients experienced significant improvements in signs and symptoms, with no significant side effects. The most common symptom in the present study was itching, present in all patients and first responded to treatment within 2 weeks. Similarly, Samyukta et al. [4] found that itching, the first symptom, responded to treatment. Wan et al. [10], after 1 week of 0.1% tacrolimus eye drop administration twice daily, most symptoms improved in all patients. In the present study, the improvement in tarsal papillae and limbal VKC occurred as early as 2 weeks. However, in Samyukta et al.'s study [4], improvement in tarsal papillae was delayed by over 2 weeks. We used AS-OCT to measure the size of the tarsal papillae and thickness of the conjunctiva at the limbus for the first time in eyes with VKC. AS-OCT demonstrated 32.2% and 30.3% decrease in mean horizontal and vertical papillae sizes, respectively.

A patient with mixed VKC and AS-OCT demonstrated a 30% decrease in the thickness of the conjunctiva at the limbus (Figure 2). Raj et al. [32] used AS-OCT to evaluate and measure primary pterygium. Thus, AS-OCT was used to measure the pterygium and conjunctival thicknesses at the limbus. Similar to the present study, AS-OCT was used to monitor the treatment of seasonal allergic conjunctivitis with loteprednol etabonate. The total central corneal epithelial and non-epithelial thicknesses and the lower and upper tear meniscus areas were measured using AS-OCT [16]. A statistically significant difference was observed between pre- and post-treatment values of total central corneal and central corneal non-epithelial thicknesses and lower tear meniscus area [16]. Similarly, the suitability of this imaging modality has been tested in diagnosing benign or malignant ocular surface lesions [17, 18] or evaluating their treatment response [17, 33].

In a prospective study, Kutluturk et al. [34] monitored conjunctival thickness in eyes with primary open-angle glaucoma on topical anti-glaucomatous medications using AS-OCT up to 6 months post-treatment. They found a decrease in the conjunctival thickness after administration of topical anti-glaucomatous medications. This thinning effect was significant in eyes treated with prostaglandin analogs. Their results prove the suitability of AS-OCT in monitoring treatment-related complications [34], as this observed thinning effect in the conjunctiva may be crucial for future filtration surgery. Similarly, we found AS-OCT to be a suitable and safe *in vivo* imaging modality for monitoring treatment responses in the present study.

We also included patients with VKC from the pediatric age group and found that they cooperated during AS-OCT image acquisition. Similar to our experience, Cauduro et al. found AS-OCT to be a feasible imaging technique for evaluation of anatomical details of the anterior segment and diagnosis of anterior-segment abnormalities in the pediatric population [35].

To the best of our knowledge, this is the first study monitoring the treatment response to tacrolimus ointment in eyes with VKC using AS-OCT. However, this study has some limitations. First, we included a limited number of eyes with VKC. Second, the eyes were inhomogeneous in terms of previous treatment history and treatment-naive or recalcitrant to previous conventional treatments. Third, this study was a case series with a short follow-up period without randomization. Future double-blind randomized clinical trials with more patients and longer follow-up periods should be conducted to confirm these preliminary findings.

CONCLUSIONS

AS-OCT was a suitable objective method for monitoring the treatment response to 0.03% tacrolimus eye ointment in patients with VKC. Treatment with 0.03% tacrolimus eye ointment relieved the signs and symptoms of VKC, along with significant reduction in the conjunctival papillary size, as documented by AS-OCT. This noninvasive *in vivo* imaging modality could be used to document improvements in patients with VKC. Future large-scale studies, including a wide range of age groups with longer follow-up periods and AS-OCT monitoring at multiple post-treatment visits, are required to confirm these preliminary results. Moreover, the diagnostic accuracy of AS-OCT in monitoring patients with active VKC should be tested in comparison with objective scoring by an experienced corneal fellowship under slit-lamp examination.

ETHICAL DECLARATIONS

Ethical approval: The study protocol was approved by the Ethics Committee of the Faculty of Medicine of the Port Said University. The study procedures followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.
Conflict of interest: None.

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