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Diagnostic Criteria for Terrien Marginal Degeneration: Nordic Terrien Degeneration Study

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Purpose: To refine the diagnostic criteria for Terrien marginal degeneration (TMD) based on experience in 3 Nordic countries.

Methods: This is a retrospective, multicenter, hospital-based cross-sectional study of 49 eyes of 29 white patients in tertiary referral centers in Finland, Sweden, and Denmark from 1998 to January 2018. The median follow-up was 3 years. Symptoms, best corrected visual acuity, astigmatism, corneal thickness, curvature and cavities, stage, and progression were analyzed.

Results: TMD was diagnosed equally likely between 15 and 86 years of age (median, 47 years). Twenty patients (69%) had bilateral disease, and 62% were men. Seventeen patients (59%) had symptoms including blurred vision and ocular surface disease symptoms without inflammatory signs. Eight patients (28%) had slightly reduced corneal sensitivity. Median best corrected visual acuity was 20/25 (range, 20/16–20/200) and astigmatism was 2.6 diopters (D) (range, 0–10) with a mean progression of 0.41 D per year (range, 0–5.4). Age and astigmatism were not correlated. All eyes had peripheral vascularization, lipid deposits, and hyperreflectivity throughout thinned peripheral stroma and its anterior edge. The thinning progressed in 15 patients (52%). Of 26 patients, 8 (31%) had single or confluent paralimbal intrastromal cavities, most commonly superiorly. By Süveges classification, the stage was 2 (92%) or 3 (8%). Minimum corneal thickness and corneal curvature were loosely associated, leading to different stages in Wang classification in 34 eyes (69%).

Conclusions: TMD is defined by peripheral corneal thinning, superficial neovascularization, lipid deposition at the leading edge, absence of ulceration and inflammation, and frequently cavitation. The most sensitive way to follow its progression is anterior segment optical coherence tomography.

Key Words: Terrien marginal degeneration, peripheral corneal thinning, lipid, neovascularization, cavities

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Terrien marginal degeneration (TMD) of the cornea is an infrequent, idiopathic, usually bilateral (56% to 86%), asymmetric, and often progressive disease;[1–3] it causes thinning, neovascularization, and lipid infiltration at the corneal periphery. The epithelium is, by definition, intact, and patients do not have systemic autoimmune diseases. TMD is usually diagnosed around the age of 40 years, but it can start at any age from 10 to 87 years, and male sex is often considered a predisposing factor.[1–3] Astigmatism, which can be as high as 30 diopters (D) and irregular, is the main reason for reduced vision. However, best spectacle corrected visual acuity (BCVA) can be surprisingly good.[4] Progression, although generally slow, can be rapid, inducing 1.5 D astigmatism or more in 3 years.[1] Perforations, mostly spontaneous but also traumatic, occur in 9% to 14% of patients.[1–3,5–16] Intracorneal cysts and cavities in the thinned peripheral stroma can appear, leading to filtering blebs and hypotony.[1,3,15,17–19]

TMD is commonly confused with infectious keratitis, Mooren ulcer, peripheral ulcerative keratitis, sclerokeratitis, pellucid marginal degeneration, Fuchs marginal superficial keratitis, and marginal furrow especially because no universally accepted diagnostic criteria are available.[20–22] Furthermore, any infectious, inflammatory, or traumatic cause can lead to secondary vascularization, lipid keratopathy, and peripheral thinning of the cornea. Excluding autoimmune disease is crucial.[11,20,22–25] In contrast to many of these differential diagnostic alternatives, the eye in TMD is painless in half of the patients and the other half has only mild ocular surface disease symptoms, hyperemia, or blepharitis.[1,3]

François[3] proposed a staging of TMD in 1936 based on the clinical findings. Stage 1 showed a lining of gray–white

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opacities at the superior peripheral cornea. In stage 2, a furrow with overlying vascularization appeared that increased in depth and circumferential width, and the opacities at the leading edge turned yellow. Peripheral corneal thinning could progress to up to 360 degrees. The peripheral cornea became locally ectatic in stage 3 and totally ectatic in stage 4. Alberth added stage 5 in which the central cornea became opaque.[26] Süveges merged their staging systems in 1972 (see Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B68).[27] Wang et al[2] introduced a new system in 2015, based on thinning and peripheral corneal curvatures as determined by anterior segment optical coherence tomography (AS-OCT; see Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B68). Corneal cross-linking has been suggested as a way to halt or prevent progressive thinning.[42]

Because of often small series and lack of uniform diagnostic criteria, no author has been able to generalize their data, especially in a white population. In our Nordic Terrien Degeneration Study (NOTED) that aims to refine clinical diagnostic criteria, we report, to the best of our knowledge, the largest data set of clinical findings with the longest average follow-up.

MATERIALS AND METHODS

The aim of our study was to refine the clinical diagnostic criteria for TMD by examining and observing Nordic patients across 3 countries. The study was approved by the review board of the Head and Neck Center, Helsinki University Hospital, in Finland; Aarhus University Hospital in Denmark; and Linköping University Hospital in Sweden. Patients provided informed oral consent. The study protocol followed the tenets of the Declaration of Helsinki.

We defined TMD as a circumferential peripheral corneal thinning without ulcerations, neovascularization over the thinned cornea, and lipid deposition at the leading anterior edge (Fig. 1). Patients were allowed to have any symptoms, intrastromal cavities, pseudopterygium, filtering blebs, and perforations, but no chronic blepharitis, scleritis, or lid deformations (Table 1). We included patients who fulfilled these criteria and excluded those with systemic autoimmune disease by history, laboratory screening, and, as indicated, review by a rheumatologist (see Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/ICO/B69). Six patients (21%) had a family history of autoimmune diseases, such as rheumatoid arthritis, atopy, and type 2 diabetes among first-degree relatives. Systemic diseases and ocular comorbidities are listed in Table 2.

We diagnosed TMD retrospectively and prospectively during our study using the abovementioned criteria in consecutive patients from 1998 to 2018 and enrolled 17 Finns, 5 Swedes, and 7 Danes—none of whom was consanguineous. The 29 patients had 49 affected eyes (see Supplemental Fig. 1, Supplemental Digital Content 3, http://links.lww.com/ICO/B70). All patients underwent a comprehensive ophthalmic examination, including BCVA with spectacles, slit-lamp biomicroscopy, indirect ophthalmoscopy, color corneal photography, and AS-OCT (Casia SS 1000, Tomey, Nagoya, Japan, in Finland; Spectralis with AS-OCT attachment, Heidelberg Engineering, Heidelberg, Germany, in Denmark; and iVue, Optovue, Fremont, CA, in Sweden). Only horizontal scans were available from the Spectralis, whereas 21 patients had scans in various meridians by Casia and iVue. The scans from Casia in

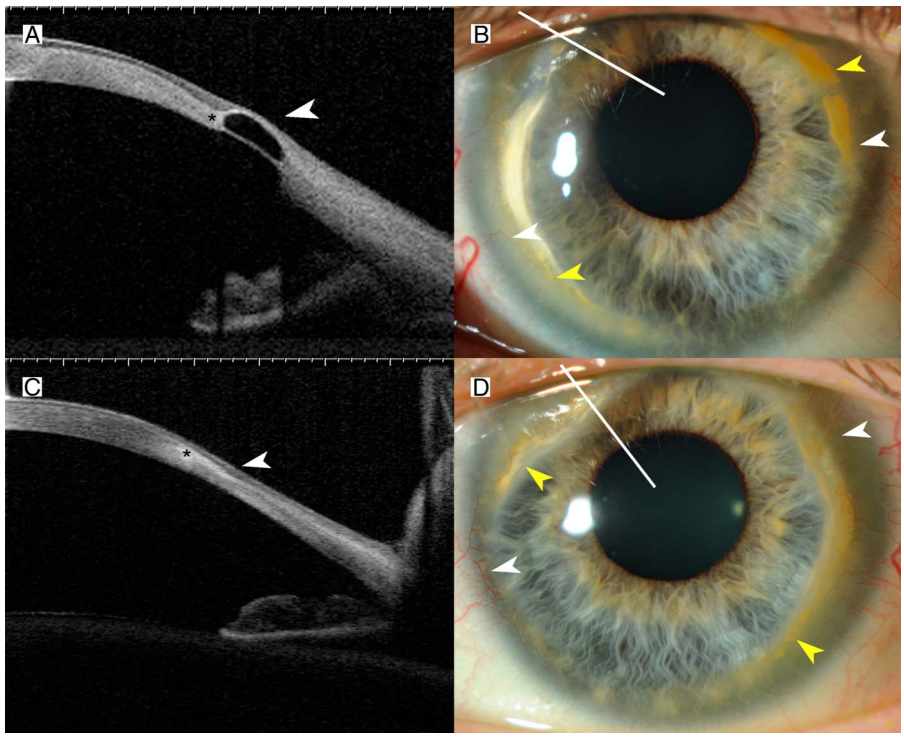

FIGURE 1. Clinical characteristics of Nordic patients with TMD. Clinical findings in the right (A and B) and left (C and D) eye. Cross-sectional AS-OCT images (A and C) that show hyperreflectivity throughout the thinned stroma (asterisk), stromal thinning (white arrows), an intrastromal cavity (A), and concave thinning (C) were obtained along the thin white lines shown on the color corneal photographs (B and D) that show neovascularization over the thinned corneal periphery (white arrows) and lipid accumulation (yellow arrows) without evident inflammation. (The full color version of this figure is available online at www.corneajrnl.com.)

TABLE 1. Clinical Characteristics of TMD

Characteristic	Diagnostic Criteria for Typical TMD	Differential Diagnosis
Thinning	Circumferential peripheral corneal thinning, which may extend to midperiphery but rarely to the central cornea	Peripheral ulcerative keratitis
		Mooren ulcer
		Marginal corneal infiltrates
		Interstitial keratitis associated with infectious disease
		Neurotrophic ulcus
		Sclerokeratitis
		Pellucid marginal degeneration
		Keratoglobus
		Cogan syndrome
		Fuchs superficial marginal keratitis
		Marginal furrow degeneration
Epithelium	Intact epithelium	Ulceration
Neovascularization	Superficial corneal neovascularization extending to the leading edge of the peripheral corneal thinning, occasionally with engorged perilimbal vessels	Vernal keratoconjunctivitis
		Atopic keratoconjunctivitis
		Ocular graft versus host disease
		Reactive arthritis
Lipid	Circumferential yellow-brown lipid deposits central to the corneal thinning	Arcus senilis
		Lipid keratopathy
		Schnyder corneal dystrophy
		All corneal diseases causing necrosis of the cornea
Symptoms	None or mild ocular surface irritation from irregular surface of the cornea	Dry eye
	None or decreased visual acuity due to corneal astigmatism	Infectious corneal diseases
		Inflammatory corneal diseases
Comorbidities	No systemic autoimmune diseases	Rosacea, atopy, systemic lupus erythomatosus, granulomatosis with polyangiitis, polyarteritis nodosa, rheumatoid arthritis, Sjögren syndrome, sarcoidosis
Supportive criteria	Peripheral corneal cavities, astigmatism, spontaneous filtering bleb or perforation, pseudopterygium	

16 patients were of high resolution, which enabled measuring corneal thickness from the anterior stromal surface in addition to the air–cornea interface and detecting hyperreflectivity beneath the epithelium. We tested corneal sensitivity in 25 patients by gently touching the central cornea with a cotton swab and in 2 patients by a handheld Cochet–Bonnet esthesiometer (Luneau Technology, Pont-de-l'Arche, France). Sensitivity was graded as qualitatively normal (the patient blinked) or slightly reduced (the blink reflex was delayed, but the patient reported sensation). We recorded the history of eye surgeries and injuries, ocular comorbidities, ocular symptoms, use of topical eye medication and contact lenses, eye infection or inflammation, systemic disease, and family history of autoimmune diseases. We had a follow-up of more than 1 year for 27 patients.

We staged all patients according to the Süveges and Wang classifications (see Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/B68). We graded corneal curvatures by inspecting AS-OCT images because software used by Wang et al[2] was unavailable. We defined progression as increase in the thinned area, new thinning in AS-OCT, or increase in astigmatism >1 D.

The male-to-female ratio was compared against the ratio taken from the United Nations[28] world statistics, weighted according to the number of patients from Finland, Sweden, and Denmark, using binomial tests (StatXact-3; Cytel Software, MA). When analyzing BCVA, we excluded 3 eyes of 3 patients that had comorbidities (uveal melanoma, exudative age-related macular degeneration, and nonarteritic ischemic optic neuropathy). We excluded 2 more eyes at the time of diagnosis because of missing data. Median BCVA, astigmatism, and corneal thickness were analyzed using the mean of the 2 eyes if both were affected. The association of BCVA, astigmatism, and age at the time of examination was analyzed with linear regression (Stata 13; Stata Corp, College Station, TX). Cumulative frequency plot of age at the time of diagnosis was constructed. Spearman correlation was used for correlation analysis, and Fisher exact test to compare proportions. A 2-tailed P value <0.05 was considered significant. The progression rate was calculated by dividing the mean change in astigmatism with follow-up time.

RESULTS

All 29 patients were white, and 18 (62%) were men (Table 2), a percentage that did not differ from the weighted population mean of 50.5% (P = 0.24, binomial test). The median age at diagnosis was 47 years (range, 15–86), and 10 patients (34%) were younger than 40 years. At the time of our

TABLE 2. Characteristics of 29 Patients With TMD Ordered by Age at the Time of Examination

Patient No./ Sex/Age, yrs	Laterality	Thinning, Clock Hours, Right/Left	Ocular Comorbidity	Symptoms	Family History of Autoimmune Disease	Systemic Diseases
1/M/23	Unilateral	3/0	No	No	No	No
2/M/29	Unilateral	0/4	No	Blurred vision	Arthritis unknown type	No
3/F/30	Bilateral	4/4	No	Blurred vision	No	Pituitary dwarfism, hypothyroidism
4/F/31	Bilateral	12/12	No	Hyperemia	No	
5/M/36	Unilateral	0/5	Bilateral LASIK, viral kerato-conjunctivitis	Astigmatism	No	No
6/M/37	Bilateral	6/6	No	No	No	No
7/M/41	Unilateral	0/3	No	No	No	No
8/M/45	Bilateral	5/6	No	Blurred vision	Arthritis unknown type	Asthma, factor V Leiden
9/M/46	Unilateral	0/2	No	Blurred vision, foreign body sensation	No	No
10/F/47	Unilateral	12/0	No	lurred vision, hyperemia, irritation	No	No
11/M/50	Bilateral	5/5	No	No	No	No
12/M/53	Bilateral	11/11	No	Blurred vision, glare	No	No
13/M/54	Bilateral	12/12	No	No	No	No
15/M/58	Unilateral	0/8	Iritis and episcleritis in left eye	No	Atopy	No
16/F/59	Unilateral	0/6	No	Blurred vision, diplopia, tenderness	No	No
17/M/60	Bilateral	12/12	Iritis in left eye	Mild occasional irritation	Rheumatic disease	No
18/M/64	Bilateral	12/12	No	No	No	DM type II
19/F/67	Bilateral	8/11	No	Blurred vision	No	DM type II
20/F/67	Unilateral	12/0	No	Blurred vision, intermittent pain and hyperemia	Rheumatoid arthritis	Hyper-cholesterolemia, hypertension
21/F/68	Bilateral	12/5	Glaucoma	No	No	Hypertension
22/F/69	Bilateral	10/11	No	Hyperemia, irritation, epiphora, mild pain	No	No
23/F/71	Bilateral	12/12	No	No	No	No
24/F/73	Bilateral	12/12	Glaucoma	Mild ocular surface disease	No	No
25/M/73	Bilateral	12/12	veal melanoma in right eye	No	No	No
26/M/76	Bilateral	12/12	HZV keratitis in left eye	No	No	No
27/M/76	Bilateral	12/12	NAION in left eye, pseudophakia	No	Rheumatoid arthritis	Hypertension, coronary artery disease, DM type II
28/M/83	Bilateral	12/12	Glaucoma, pseudophakia	No	Rheumatoid arthritis	No
29/M/89	Bilateral	12/12	Exudative AMD, macular pucker and pseudophakia in left eye	No	No	Coronary artery disease

AMD, age-related macular degeneration; DM, diabetes mellitus; HZV, herpes zoster virus; LASIK, laser assisted in situ keratomileusis; NAION, nonarteritic ischemic optic neuropathy.

examination, their median age was 58 years (range, 23–89). The cumulative frequency plot shows that TMD was diagnosed equally likely every decade after the age of 15 years (Fig. 2A).

Clinical Findings

By definition, all patients exhibited peripheral corneal thinning, superficial neovascularization over the thinned cornea, lipid deposition at the leading edge, no corneal ulceration, and no chronic periocular or ocular inflammation (see Supplemental Fig. 1, Supplemental Digital Content 3, http://links.lww.com/ICO/B70). Twenty patients [69%; 95% confidence interval (CI), 51–83] had bilateral disease. Twelve patients were asymptomatic, and 17 patients (59%; 95% CI, 41–75) had symptoms; 11 patients (38%) had blurred vision, and 12 patients (41%) reported mild ocular surface irritation.

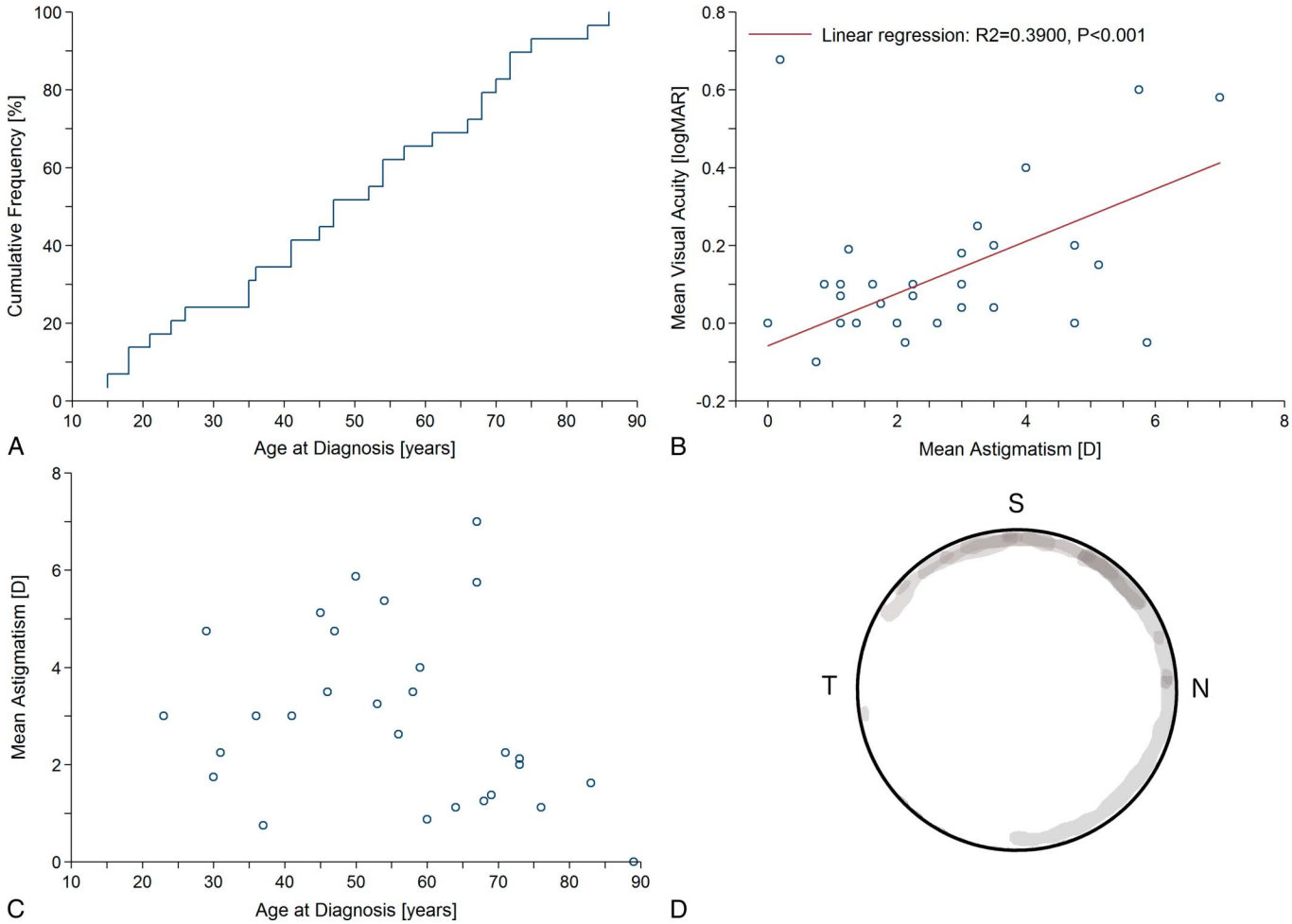

FIGURE 2. Analysis of clinical characteristics of Nordic patients with TMD. Cumulative frequency plot shows that the diagnosis is made equally over many decades of age (A). Linear association exists between worsening BCVA and increasing astigmatism (B), but not with age and astigmatism (C). Grayscale heat plot of cavity location; darker gray shade indicates more frequent involvement (D). N, nasal; S, superior; T, temporal. (The full color version of this figure is available online at www.corneajrnl.com.)

Three patients had undergone cataract surgery before diagnosis, and one patient underwent cataract surgery before our examination. At the time of diagnosis, the median BCVA was 20/22 (range, 20/200–20/20) and median astigmatism was 1.5 D (range, 0–5.75). The median BCVA at the time of our examination was 20/25 (range, 20/16–20/200): 20/22 for the better eyes and 20/25 for the worse affected eyes. The median astigmatism for all patients by subjective refraction was 2.6 D (range, 0–10; Table 3). We found a linear association between worsening BCVA and increasing astigmatism ($R^2 = 0.39$, $P < 0.001$; Fig. 2B). No association between age and astigmatism was noted (Fig. 2C). The median progression rate of astigmatism was 0.4 D per year (range, 0–5.4); we excluded 1 patient because of cataract surgery during follow-up and another one because of missing data. Central corneal sensitivity was graded normal in 19 (70%) of 27 patients and was slightly reduced unilaterally or bilaterally in the remaining ones.

Imaging Findings and Staging

By high-resolution AS-OCT, all 29 imaged corneas had hyperreflective perilimbal stroma, limited to the thinned region, most prominent beneath the epithelium, and adjacent to its central edge (Figs. 1A, C). Of the 16 corresponding patients, 6 patients (38%) had ocular irritation and occasional redness, and 4 patients (67%; 95% CI, 30–91) of the latter had the subepithelial band-like hyperreflectivity at least in 1 eye (Fig. 1C) as the 6 (60%; 95% CI, 31–83) of 10 asymptomatic patients.

In addition to corneal thinning, omega-shaped peripheral intrastromal cavities were evident in 10 of 43 eyes (23%; 95% CI, 13–38) in 8 of 26 patients (31%; 95% CI, 16–50). The cavities, single or confluent with another one, localized to superior quadrants in 9 eyes (90%) and were always found adjacent to the limbus (Fig. 2D). They all connected to the anterior chamber, at least through another cavity. Seven patients with peripheral cavities also showed concave peripheral thinning of the anterior stroma.

TABLE 3. Findings in 49 Eyes of 29 Patients With TMD Ordered by Age at the Time of Examination

	BCVA, LogMAR		Astigmatism, D				
Patient No.	Diagnosis	Examination	Diagnosis	Examination	Progression	Treatment	Follow-up Time, yrs
1	20/22	20/30	1.25	3.00	Yes	Sclerocorneal graft	7.6
2	20/22	20/20	3.25	4.75	Yes	Steroid	6
3	20/20	20/32	No	3.25	No	Soft contact lenses	12
	20/20	20/16	No	0.25			
4	20/22	20/25	0.50	3.50	Yes	Methotrexate, topical steroid	7
	20/25	20/22	0.75	1.00			
5	20/22	20/25	0.75	3.00	No	Lubricants	0.4
6	20/16	20/16	0.25	0.50	No	Lubricants	2
	20/20	20/16	0.50	1.00			
7	N/A	20/22	N/A	3.00	Yes	No	4
8	20/20	20/40	No	9.00	Yes	Topical steroid, scleral contact lenses	18
	20/22	20/20	No	1.25			
9	20/50	20/32	3.00	3.50	Yes	No	8
10	20/20	20/32	2.50	4.75	Yes	Topical steroid	11
11	20/30	20/20	9.50	9.50	No	Topical cyclosporine, lubricants	6
	20/20	20/16	2.25	2.25			
12	20/30	20/40	2.00	3.00	No	Methotrexate, lubricants	5
	20/25	20/32	1.50	3.50			
13	20/100	20/200	1.50	10.00	Yes	Topical steroid, corneal patch graft	17
	20/30	20/40	3.50	0.75			
14	20/20	20/20	5.00	0.75	Yes	No	2.25
	20/20	20/20	0.00	4.50			
15	20/20	20/22	3.50	3.50	Yes	Topical and systemic steroid, methotrexate	3.8
16	20/30	20/50	4.00	4.00	Yes	No	10
17	20/20	20/25	1.00	1.00	No	Lubricants	2.3
	20/20	20/25	0.75	0.75			
18	20/22	20/25	0.75	0.50	Yes	Topical steroid, methotrexate, corneoscleral rim transplant	2.1
	20/25	20/25	1.75	1.75			
19	20/25	20/30	7.00	7.00	Yes	Topical steroid, cyclosporine, patch graft	15
	N/A	20/200	2.00	7.00			
20	20/200	20/80	5.25	5.75	Yes	Topical steroid	1
21	20/20	20/30	0.50	0.75	No	No	1.8
	20/20	20/32	1.00	1.75			
22	20/20	20/20	0.75	0.75	No	Topical steroid with oxytetracycline	3
	20/20	20/20	2.00	2.00			
23	20/20	20/25	1.75	2.00	Yes	Topical steroid	2.8
	20/22	20/25	1.50	2.50			
24	20/22	20/16	1.75	2.00	No	No	1
	20/22	20/20	1.50	2.25			
25	20/200*	Enucleated*	1.00*	Enucleated*	No	No	1
	20/20	20/20	2.00	2.00			
26	20/20	20/20	0.75	0.75	No	No	3
	20/20	20/30	0.50	1.50			
27	20/20	20/20	1.75	1.75	No	No	1.1
	20/22	20/40†	0.75	0.50			
28	20/70	20/20‡	3.25‡	2.75	No	No	0.3
	20/50	20/32‡	0.75‡	0.50			
29	§	§	N/A	N/A	No	No	1
	20/20	20/20	No	No			

N/A, not available.
*Enucleated, uveal melanoma.
†Nonarteritic ischemic optic neuropathy.
‡Pseudophakia.
§Exudative age-related macular degeneration.

Forty-five eyes (92%; 95% CI, 80–97) represented stage 2 and 4 eyes (8%) represented stage 3 according to Süveges classification (see Supplemental Table 3, Supplemental Digital Content 4, http://links.lww.com/ICO/B71). The Wang classification requires AS-OCT; we could evaluate 45 eyes of 28 patients. We had to exclude 1 eye from 2 patients because of poor alignment. Based on the peripheral corneal curvature criterion, 18 (40%; 95% CI, 27–55) eyes represented stage 2, 15 (33%) stage 3, 8 (18%; 95% CI, 9–32) stage 4, 3 (7%) stage 5, and 1 stage 6. We obtained from 29 eyes of 16 patients the thinnest peripheral corneal thickness as measured from both the air–corneal interface and the anterior stromal surface. The median measured minimum thickness was 533 μm (range, 112–701) and 403 μm (range, 112–474), respectively. Based on the thinnest peripheral corneal thickness, 14 eyes (48%; 95% CI, 31–66) represented stage 1, 8 (28%) stage 2, 3 (10%) stage 3, 1 stage 4, 2 (7%) stage 5, and 1 stage 6. In 9 eyes (31%; 95% CI, 17–49), Wang stage was the same based both on thickness and curvature. Of 20 patients with bilateral TMD, 11 (55%) had the same stage in both eyes by the curvature criterion of Wang classification, and 17 patients showed the same stage in both eyes based on Süveges classification.

Longitudinal Analysis

The median follow-up time was 3 years (range, 0–18). Progression was detected in 15 patients (52%; 95% CI, 34–69). Ten (67%; 95% CI, 42–85) of 17 symptomatic patients progressed as compared to 5 (42%; 95% CI, 19–68) of 11 asymptomatic patients (P = 0.70, Fisher exact test). Interestingly, 1 patient with a previous spontaneous perforation was asymptomatic. The median time from the first visit to first progression among the Finnish patients was 11 months (range, 6–32). Three Finnish patients showed progressive peripheral corneal thinning by AS-OCT, and one also had increased astigmatism. One patient with a previous spontaneous perforation developed a new cavity and a spontaneous perforation. In Denmark, progression mainly was evident not only as increasing astigmatism but also as increased width of the thinned zone. In Sweden, progression increased astigmatism as measured with AS-OCT. We found no difference in either sex distribution or frequency of progression between patients older or younger than 40 years of age (see Supplemental Table 4, Supplemental Digital Content 5, http://links.lww.com/ICO/B72).

Sixteen patients (55%; 95% CI, 38–72) received treatment. Thirteen patients (45%; 95% CI, 28–62) received or had received immunomodulatory medication such as topical or peroral steroid, topical cyclosporine, or peroral methotrexate. Four patients (14%) had contact lenses, and 4 (14%; 95% CI, 5–31) underwent patch grafting surgery for imminent perforation. Two and 4 of the 5 Finnish patients who showed progression, progressed despite peroral methotrexate and topical corticosteroids, respectively.

DISCUSSION

To the best of our knowledge, our study is the largest series with the longest follow-up reported in the literature of TMD and the first in the Nordic population. It is the first multicenter study, which should reduce selection bias. We defined TMD as peripheral corneal thinning, lipid deposits at the leading edge, vascularization over the thinned corneal periphery, and mild bulbar paralimbal conjunctival hyperemia without other inflammatory findings. Epithelium had to be intact and the patient free of autoimmune diseases. We found no evidence that TMD would be significantly more frequent in men than in women. As a new finding, all patients fulfilling the above criteria had hyperreflectivity throughout the peripheral thinned stroma and, especially, at its central edge by AS-OCT. Perilimbal cavities connecting to the anterior chamber were another conspicuous feature.

Based on the clinical findings, 2 types of TMD have been suggested—an inflammatory and a quiescent one.[12,29–31] Most patients with the suggested inflammatory type characterized by pain and redness were younger than 40 years. In our series, none of the patients had clear enough symptoms to make such a distinction, in part, by definition, and we found no difference in the frequency of progression between patients older or younger than 40 years. Although younger patients might have been treated more actively, immunomodulatory medication in general did not seem to be effective in prevention or slowing of progression.

Of our patients, 59% reported mild ocular surface disease symptoms. We believe that in part these symptoms are caused by irregular tear film distribution because of the thin peripheral cornea. Blurred vision and irritation were equally frequent. The frequency of progression was comparable in patients with and without symptoms; thus, all patients must be regularly reviewed.

Wang et al[2] published a new classification to evaluate the course of TMD based on change in focal corneal curvatures and corneal thickness by AS-OCT. In our series, their classification differentiated eyes better than the Süveges classification because according to the latter, all eyes represented stage 2 or 3. The thinnest corneal thickness and highest corneal curvature in our series did not correspond to each other as well as in Wang's study,[2] leading to a different stage in 69% of eyes depending on whether thickness or curvature criterion was used. However, our staging by visual evaluation of corneal curvature differed from their software-based analysis.

We found a 130 μm median difference in thickness of the thinnest peripheral cornea depending on whether thickness was measured from air interface or anterior stroma, measuring the corneal thickness from the air interface exaggerates the corneal thickness because the epithelium and tear film tend to fill in any groove. We propose that the smallest corneal thickness and, preferably, only stromal thickness without epithelium should be used when diagnosing and staging TMD. Measuring corneal thickness without epithelium is especially important when planning surgery, including corneal cross-linking.[32]

To the best of our knowledge, the largest series hitherto reported reviewed 43 eyes of 25 Canadian patients with TMD.[1] Our series was comparable in mean age (P = 0.87, Fisher exact test), sex (P = 0.78), number of eyes with cavities (P = 0.18), laterality (P > 0.99), and frequency of

perforations (P = 0.12). Median follow-up was 6 months longer in our series, and progression of astigmatism was a little slower (0.41 vs. 0.56 D per year). However, the range of 0 to 5.4 D per year signifies wide variation among patients in our study. Progression also was commonly intermittent. The largest differences between the 2 series are in clinically evident ocular surface inflammation and blepharitis, and lack of systematic autoimmune disease screening in the Canadian study. We did not observe evident surface inflammation and excluded patients with chronic blepharitis because marginal corneal infiltrates can mimic TMD. Meibomian gland dysfunction was reported as the most common comorbidity in Canada, present in 40% of patients, and 20% of patients had rosacea that is linked with an increased risk for a wide variety of autoimmune disorders.[33]

Rodriguez et al[34] proposed that high-resolution AS-OCT could differentiate inflammatory and noninflammatory peripheral corneal thinning by their reflectivity changes in the anterior stroma. We found no association between ocular surface disease symptoms or progression and anterior stromal reflectivity in high-resolution AS-OCT. All patients had hyperreflectivity throughout the thinned periphery and its anterior edge. We suspect that increased reflectivity results from scar formation, accumulation of metabolites, or both, previously seen by light and electron microscopy and in vivo confocal imaging in non-inflamed areas.[4,6,27,30,35,36,36–41]

Single and confluent cavities of the peripheral corneal stroma support the diagnosis of TMD, and they are commonly located asymmetrically. Cavities most commonly emerge in superior quadrants adjacent to the limbus and are best seen in vertical and diagonal scans. Wang et al[2] proposed that cavities form when thinned cornea bulges anteriorly. One patient had an incipient peripheral cavity without adjacent anterior stromal thinning. Without further studies, it is unclear whether the cavities indicate a specific stage or a subtype of TMD.

Our study has limitations because of its retrospective nature and differences in imaging devices between participating centers. For example, Casia and iVue provided vertical and diagonal scans in addition to horizontal ones by Spectralis, which made the classification less dependent on localization. The patients had several ocular comorbidities that were often the reason for referral. Three patients had undergone cataract surgery in 5 eyes before diagnosis, which improved BCVA and possibly altered astigmatism. Bilateral LASIK was performed to 1 patient 11 years before unilateral TMD occurred which may alter the biomechanics of the cornea, but no flap displacement was detected. TMD was commonly diagnosed coincidentally because many patients were asymptomatic. Thus, we believe that TMD is more prevalent than we know. Larger population-based studies are needed to ascertain male predominance, if any.

In conclusion, our NOTED study is the largest series of TMD reported and aims to set more uniform clinical diagnostic criteria. Clinical diagnostic criteria of TMD we applied are peripheral corneal thinning, lipid accumulation at the anterior edge, and superficial neovascularization extending from limbus over the thinned periphery. Peripheral intrastromal cavities, found adjacent to the limbus in superior quadrants, and hyperreflectivity throughout the thinned stromal periphery and its anterior edge support the diagnosis. Autoimmune diseases and other causes for corneal changes must be excluded. Patients may have mild ocular surface disease symptoms and, occasionally, engorged perilimbal vessels, but no evident bulbar inflammation. TMD can begin at any age. Patients retain a surprisingly good BCVA despite increasing astigmatism. Age is not a predictor of progression. The most sensitive way of detecting progression is the reduction in peripheral corneal thickness, preferably measured from anterior stromal surface, by AS-OCT. Follow-up is essential for all patients because progression is common and variable in speed.

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