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Terrein's marginal degeneration: A new perspective on the periphery

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Abstract
Terrein's Marginal Degeneration (TMD) is a rare corneal disorder characterized by peripheral thinning of the cornea, primarily affecting the superior region. TMD is a progressive condition that can lead to significant visual impairment and ocular complications. Its etiology remains largely unknown, and it is often challenging to distinguish from other corneal disorders with similar features. Accurate diagnosis and effective management are crucial for optimizing patient outcomes and preserving visual function. Terrein's Marginal Degeneration is primarily identified through clinical assessment and advanced imaging, which reveal characteristic peripheral corneal thinning and irregular astigmatism. Complications may include progressive visual impairment, risk of corneal perforation, secondary infections, and psychological effects. Management strategies vary based on disease severity and progression, with options ranging from conservative approaches and corrective lenses to medical therapies and surgical interventions. Effective management of TMD requires a multifaceted approach tailored to individual patient needs. Early diagnosis and intervention are crucial in managing Terrein's Marginal Degeneration. Timely recognition of the condition can help prevent further visual decline and improve patient outcomes. Regular follow-up with an ophthalmologist is necessary to monitor the progression of the disease and adjust treatment strategies as needed.

Keywords: Terrein's marginal degeneration, corneal thinning, corneal ectasia, rigid contact lens, lamellar keratoplasty

1. Introduction
Terrein's Marginal Degeneration (TMD) is an enigmatic and relatively rare ophthalmic condition that primarily affects the peripheral cornea [1]. This degenerative disease is marked by characteristic thinning of the corneal tissue, leading to a variety of visual disturbances and, in some cases, significant visual impairment. Terrein's Marginal Degeneration (TMD), also called gutter dystrophy, peripheral furrow keratitis, and senile marginal atrophy, and is characterized by non-ulcerative thinning of the peripheral cornea [2]. The cornea, a transparent, dome-shaped surface that covers the front of the eye, plays a crucial role in focusing vision. Any disruption to its structure, particularly thinning and weakening, can lead to profound changes in vision quality. Terrein's Marginal Degeneration specifically involves the peripheral regions of the cornea, often sparing the central visual axis initially. This pattern of involvement distinguishes it from other more commonly encountered corneal degenerations and dystrophies, such as keratoconus and pellucid marginal degeneration. Predominantly affecting males more than females over the age of 40, TMD can occur at any age, with initial symptoms often being asymptomatic [3]. The progression of the disease is gradual and asymmetrical, with initial corneal opacification leading to characteristic symptoms such as against-the-rule astigmatism [4]. While typically painless and non-inflammatory, some cases of TMD present with inflammatory symptoms, necessitating differentiation from autoimmune or infectious peripheral ulcerative keratitis. Although infrequent, the disorder poses a considerable diagnostic and therapeutic challenge due to its subtle presentation and the overlap of its symptoms with other corneal pathologies.

2. Epidemiology
The prevalence of Terrein's marginal degeneration is still unknown mainly due to its potentially asymptomatic nature and rarity as some of the cases may go unnoticed [5]. It is generally accepted that TMD is more common in middle-aged adults, with no significant gender predilection. The condition has been reported globally, indicating that it is not confined to specific geographic or ethnic populations. Despite its rarity, awareness of TMD

is crucial for ophthalmologists, as early recognition and appropriate management can prevent significant visual impairment. It is crucial to remember that TMD can occur at any age even in females [2, 6]. The condition afflicted people of all ages, with a mean age of 44 (range 20-82) and a 54% male prevalence in one case series investigation [7]. In another study examining the age distribution of corneal diseases requiring a surgical procedure, 48.3% of 58 TMD specimens were obtained from patients aged 40 to 59; however, because the majority of TMD cases do not require surgery, this percentage cannot be interpreted as disease frequency [8].

3. Etiology

The exact etiology of TMD remains unclear [5], but several theories have been proposed. One prevailing theory suggests that TMD is a degenerative condition, possibly linked to age-related changes in the corneal stroma. Another hypothesis considers the possibility of an autoimmune component, given the peripheral location of the lesions and the presence of inflammatory cells in some cases. Genetic factors may play a role, as familial clustering has been observed in a small number of cases. Pathologically, TMD is characterized by the presence of peripheral corneal thinning, typically located superiorly. Histological examination reveals a loss of stromal tissue, particularly in the anterior layers, with relative sparing of the posterior stroma and Descemet's membrane. This thinning is accompanied by a reduction in the number of keratocytes and an increase in extracellular matrix degradation products.

- Degenerative changes - TMD demonstrates traits of degenerative illnesses, including lipid accumulation, an extended course, mild progression, and no apparent symptoms. According to Iwamoto *et al*., fatty degeneration occurs in typical individuals with TMD as a manifestation of idiopathic tissue hypoxia in the stromal lamella [9].
- Inflammatory origin- Iwamoto and Austin & Brown put forth the inflammatory origin theory for TMD [4, 9], which postulates that the disease is initially brought on by immune-mediated responses. According to Iwamoto's theory, the basement membrane's immunogenic component is secreted by degenerating basal epithelial cells, triggering hypersensitivity. This sort of inflammation may culminate in conjunctival injection, photophobia, positive fluorescein staining, and recurrent eye discomfort.
- Collagen Phagocytosis by Histocyte-Suveges hypothesized that [10] phagocytosing stromal collagen in an affected region is a manifestation of histiocyte-like cells migrating from capillaries. Hayasaka and colleagues observed elevated activity of the lysosomal enzyme N-acetyl-β-D-glucosaminidase in the tears of individuals with TMD, indicating an infiltration of cells resembling histiocytes [11].

4. Clinical Presentation

Patients with Terrein's Marginal Degeneration typically present with gradually progressive visual disturbances. The most common symptom is blurred vision, often associated with astigmatism due to the irregular corneal surface. Some patients may also report mild ocular discomfort or a sensation of dryness, though pain is generally absent. On slit-lamp examination, TMD is characterized by a peripheral band of thinning, most commonly in the superior cornea [12]. This thinning is typically non-inflammatory and does not involve vascularization or lipid deposition, distinguishing it from other peripheral corneal disorders such as Terrien's Marginal Degeneration and Mooren's ulcer.

4.1 Opacification of the Peripheral Cornea (Stage 1): Similar to arcus senilis, Terrien's Marginal Degeneration begins with a thin, white, punctate peripheral opacity in a circular band. Although this opacity can occur across the cornea, it often manifests more prominently in the superior and potentially inferior regions. Lipid deposition is usually considered to be the root cause of the opacification [13]. Between the limbus and the opacity, like in arcus senilis, there is a zone of transparent cornea; but, in TMD, vascularization will penetrate this clear zone and enter the band opacity. While there are usually no symptoms at this stage, in around one-third of instances, there may be a little, non-intrusive irritation that might be indicative of mild conjunctivitis or dry eye.

4.2 Thinning of the Peripheral Cornea (Stage 2): A section of the cornea affected by vascularization and lipid opacity has stromal thinning at this stage, resulting in the formation of a gutter. The gutter's inner slope advances significantly while the outside slope slowly decreases. This thinning does not cause fluorescein staining since the epithelium covering the gutter floor is still intact. The gutter eventually expands circumferentially as the disease progresses to stage three, even though the disease process is incredibly sluggish.

4.3 Corneal ectasia (Stage 3): In case corneal thinning extends extensively either around the perimeter or at the center, leading to the compromised structural integrity of the cornea, it is termed as corneal ectasia. Localized ectasias occur at the point of greatest thinning [14]. If stage one and two alterations predominantly affect the superior cornea, corneal ectasia typically commences superiorly, but it can also develop in the inferior cornea if those regions are affected. The flattening over peripheral thinning regions is the initial step in the alterations in corneal topography that result in astigmatism. Astigmatism causes a slow, progressive reduction in vision. Relative steepening of the corneal surface is reported at 90° from the center of the thinned region [15] when thinning predominates in one corneal meridian, leading to against-the-rule astigmatism. Extensive thinning and ectasia might result in uneven astigmatism that cannot be corrected with glasses. The central cornea does not experience any changes in corneal sensitivity, but sensitivity is diminished in the ectatic cornea and may be affected on the gutter floor. Pseudopseudopterygia develops in 20% of cases, progressing obliquely into the cornea in stages one, two, or three. 15% of cases lead to corneal perforation, which could require surgical correction if self-sealing is not accomplished [2].

4.4 Total ectasia of the cornea (Stage 4): Significant thinning that results in the gutter around the cornea and complete ectasia are the characteristics of this stage. This stage is not particularly common. The corneal protrusion is similar to that observed in keratoconus; however, because the thinning is peripheral, the central cornea is less steep. At this time, significant astigmatism is common; however the center of the cornea may still have remarkable symmetry [16].

4.5 Opacification of the central cornea (Stage 5): Small opacities that indicate a breakdown of corneal transparency owing to excessive straining emerge in the ectatic central

cornea, likely analogous to cone scarring in keratoconus during this last stage [2]. Since perforation, drastic therapy, or patient death usually intervene before this level is reached, this stage is rarely observed.

5. Diagnostic tool

Advanced diagnostic imaging plays a crucial role in the diagnosis and assessment of Terrein's Marginal Degeneration. Several imaging modalities can provide detailed information about the corneal structure and help confirm the diagnosis:

- **Corneal Topography:** This non-invasive imaging technique maps the surface curvature of the cornea. In TMD, corneal topography typically reveals irregular astigmatism corresponding to the area of peripheral thinning [17]. The topographic map may show steepening or irregularity in the superior cornea, reflecting the changes in corneal shape [15].
- **Anterior Segment Optical Coherence Tomography (AS-OCT):** AS-OCT provides high-resolution cross-sectional images of the cornea, allowing precise measurement of corneal thickness and detailed visualization of the corneal layers. In TMD, AS-OCT can show localized thinning of the superficial stroma with relative sparing of the posterior stroma and Descemet's membrane [18]. This imaging modality is particularly useful for distinguishing TMD from other conditions that cause diffuse thinning or involve deeper layers of the cornea [19].
- **Pachymetry:** This diagnostic test measures the thickness of the cornea at various points. In TMD, pachymetry will reveal a reduction in corneal thickness in the affected peripheral areas. Pachymetry maps can help quantify the extent of thinning and monitor changes over time.
- **Confocal Microscopy:** This imaging technique provides microscopic views of the corneal layers *in vivo*. Confocal microscopy can reveal a reduction in the number of keratocytes in the thinned areas of the cornea, as well as changes in the extracellular matrix. While not routinely used in all cases, confocal microscopy can provide valuable insights into the cellular changes associated with TMD [10, 20, 21].

6. Histopathology

In some cases, a histopathological examination of corneal tissue may be necessary to confirm the diagnosis of Terrein's Marginal Degeneration [9, 21]. This is particularly useful in atypical cases or when the diagnosis remains uncertain despite clinical and imaging findings. Histopathology typically shows localized loss of stromal tissue, particularly in the anterior layers. This thinning is associated with a reduction in the number of keratocytes and changes in the extracellular matrix [10]. Consistent with the non-inflammatory nature of TMD, histopathological examination should show an absence of significant inflammatory cells or infiltrates. This helps differentiate TMD from inflammatory corneal conditions like Mooren's ulcer [22]. Histopathology should confirm the absence of new blood vessel formation in the thinned areas, distinguishing TMD from conditions like Terrien's Marginal Degeneration, which often show vascularization.

7. Treatment

The management of TMD poses significant challenges due to the condition's variable progression and impact on visual function. Treatment strategies must be tailored to the individual patient, taking into account the severity of the disease, the extent of corneal thinning, and the patient's visual needs. This section provides a comprehensive overview of the treatment options for TMD, including conservative management, medical therapies, contact lenses, and surgical interventions.

The aim of non-surgical treatment for Terrien's Marginal Degeneration (TMD) is to improve visual acuity, reduce symptoms, and prevent disease progression. In early stages, TMD is characterized by the presence of mild astigmatism which can be corrected with spectacles [23] without the need for intrusive surgeries. However, regular follow-ups and prescription updates are required. Rigid gas permeable (RGP) lenses may be required as the disease progresses and the astigmatism becomes more pronounced, or as irregular astigmatism emerges [24]. Compared to soft contact lenses, these lenses offer a more stable and transparent refractive surface, which enhances visual acuity. RGP lenses should have a small diameter and high oxygen permeability to ensure proper corneal physiology and reduce additional damage, hence preventing irritation of the degenerated peripheral cornea. Scleral lenses are advised for people who are intolerant to RGP lenses [25]. These larger lenses lie on the sclera after vaulting above the corneal surface [26]. They provide a tear-filled reservoir over the cornea, which, by producing a smooth refractive surface, can significantly reduce discomfort and enhance vision [27, 28]. As the progression of terrain Marginal degeneration can result in significant corneal thinning it is essential to keep the eyes protected from any injuries and damages that may result in corneal perforation. Usually, patients are recommended to use polycarbonate protective glasses [1, 29]. To track the progression of the disease regular check-ups are essential especially in the early stages, before surgical intervention. Patient should be advised to avoid rubbing their eyes as it can worsen the corneal thinning thereby increasing the probability of perforation. Imaging techniques like OCT (Optical coherence Tomography) can be employed to assess the thickness and cross-sectional changes of the cornea [18].

Surgery is the last resort for managing Terrein's marginal degeneration when nonsurgical approaches fail. It is indicated for imminent corneal perforation owing to progressive thinning or when severe astigmatism considerably affects visual acuity [30]. Corneal cross-linking is a procedure that strengthens the corneal tissue by inducing collagen cross-links through the application of riboflavin (Vitamin B2) and ultraviolet (UV) light. This technique has been successful in stabilizing corneal ectatic conditions like keratoconus [31]. While CXL has shown promise in treating other corneal disorders with similar thinning patterns, its use in TMD is still under investigation. Preliminary studies suggest that CXL may help stabilize the cornea and prevent further thinning in TMD, but more research is needed to establish its efficacy and safety.

Lamellar keratoplasty involves the transplantation of donor corneal tissue to the affected area while preserving the patient's own endothelium. This technique can be used to replace the thinned peripheral cornea with healthier tissue. Lamellar keratoplasty has the advantage of reducing the risk of graft rejection and postoperative complications compared to penetrating keratoplasty [32]. It also allows for targeted treatment of the thinned areas without affecting the central cornea. Lamellar keratoplasty is typically considered for patients with significant corneal thinning [33] and visual impairment that cannot be managed with other means. It may also be used in cases where there is a risk of corneal perforation [34].

Penetrating keratoplasty involves the full-thickness transplantation of donor corneal tissue. This procedure is more invasive than lamellar keratoplasty and requires the replacement of the entire corneal thickness. Penetrating keratoplasty [35, 36] is reserved for cases where lamellar keratoplasty is not feasible or has failed. It is also considered in cases of severe corneal thinning or perforation. The procedure carries risks such as graft rejection, infection, and prolonged recovery. Patients require close postoperative monitoring and may need immunosuppressive medications to prevent rejection.

8. Conclusion

Terrein's Marginal Degeneration, while rare, can lead to a range of significant complications that impact both vision and overall ocular health. These complications, including progressive visual impairment, corneal perforation, secondary infections, secondary ectasia, psychological impact, and complications related to surgical interventions, highlight the importance of early detection, comprehensive management, and regular follow-up. The treatment of Terrein's Marginal Degeneration requires a multifaceted approach tailored to the individual patient. Conservative management, refractive correction, medical therapies, and surgical interventions each play a role in addressing the various aspects of the condition. Early detection and regular monitoring are crucial for managing symptoms and preventing complications. As research continues, new therapies and advancements may further improve the management and outcomes for patients with TMD.

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