

## Epiretinal Membrane

Ayşe Gul Kocak Altıntaş<sup>1\*</sup> and Çağrı İlhan<sup>2</sup>

<sup>1</sup>Associated Professor, University of Health Sciences, Ankara Ulucanlar Eye Education and Research Hospital, Ankara, Turkey

<sup>2</sup>Hatay State Hospital, Hatay, Turkey

**\*Corresponding Author:** Ayşe Gul Kocak Altıntaş, Associated Professor, University of Health Sciences, Ankara Ulucanlar Eye Education and Research Hospital, Ankara, Turkey. **E mail:** aysegulkaltintas@hotmail.com

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### Abstract

Epiretinal membrane (ERM) is a relatively common macular disease characterized by wrinkling of the macular surface from cell proliferation in the vitreomacular interface. ERM can be classified as either secondary or idiopathic (primary) according to its etiology. Anomalous posterior vitreous detachment and vitreoretinal adhesion weakening results vitreoschisis and vitreoretinal traction, then abnormal glial proliferation and accumulation of collagen, fibronectin, and laminin cause formation of ERM. The prevalence of ERM is different in different populations according to race, ethnicity, sex, and age. Smoking, diabetes, arteriolar narrowing, and hypercholesterolemia; are known ERM associated risk factors. The most consistently identified risk factor is age and most ERMs occur in female gender. Spectral domain optical coherence tomography (SD-OCT) is the gold standard for diagnosis there are many OCT-based classification systems. Pars plana vitrectomy with or without internal limiting membrane (ILM) removal is the current treatment option and ILM removal prevents residual cellular component proliferation and decrease the risk of ERM recurrence.

**Keywords:** Epiretinal Membrane (ERM); Spectral Domain Optical Coherence Tomography (SD-OCT)

### Introduction

Epiretinal membrane (ERM) a disorder of the vitreomacular interface which involves both the macular or peri-macular regions can cause visual impairment, metamorphopsia, micropsia and occasionally monocular diplopia. Secondary ERM is associated with inflammatory and retinal vascular diseases or retinal detachments while idiopathic ERM is not associated other ocular conditions [1]. ERM occurs in a range from translucent wrinkling (cellophane maculopathy) usually asymptomatic whereas the more severe form, known as peri-retinal cellular proliferation (macular pucker) or pre-retinal macular fibrosis (PMF), may be associated with vision loss. ERM progression is generally slow but some patients need a treatment for visual complaints due to generated tangential traction on the macula causing fibrotic membranes [1]. Vitreoretinal surgery has been performed in ERM treatment for more than 30 years [2]. Since then, developments in surgery equipment and techniques provide safer surgery and better anatomical and functional results [3].

### Pathogenesis

Vitreous firmly attaches posterior lens capsule, peripheral retina, retinal vessels, peri-macular region, and optic disc. Vitreous liquefaction due to ageing causes weakening of these attachments and posterior vitreous detachment (PVD) is generally the first separation in these regions. PVD is occurred in nearly 95% of cases with idiopathic ERM [4]. According to widely accepted concept in pathophysiology of ERM, anomalous PVD occurs when vitreous liquefaction outpaces vitreoretinal adhesion weakening, resulting in vitreoschisis and vitreoretinal traction [5]. Then remnant cortical vitreous lefts in the macular region and vitreoretinal tractions induces the production of cytokines [6]. These cytokines such as basic fibroblast growth factor and nerve growth factor stimulate vitreous cell proliferation over the ILM [7,8]. Müller or astrocytes derive glial cells are the predominant cells of ERM formation and hyalocytes are another important identifiable cells [9,10]. Myofibroblasts can deposit collagen and induce intracellular contraction in late phases of idiopathic ERM [11]. Otherwise, the exact role of

macrophages in the pathogenesis of ERM is yet unclear [12]. Additionally, it is shown that retinal pigment epithelial (RPE) cells are found in only secondary ERM following retinal detachment [13].

The ultrastructure of early idiopathic ERM is characterized by a dense, irregular network of extracellular fibrils that are oriented at random [14]. The stage of ERM determines the diameters of these extracellular fibrils which are ranging from 6 nm to 15 nm in diameter for cellophane maculopathy, while ranging from 18 nm to 56 nm in diameter for macular pucker [14]. Types I, II, III, IV, and VI collagens, fibronectin and laminin are found in extracellular matrix components of ERMs. Especially, type II collagen is the main component of early phase idiopathic ERM [14]. Type VI collagen provides the attachments between ERM and ILM and it is largely present in cellophane maculopathy [14]. On the other hand, macular pucker, contains large amounts of collagen types I and II [14].

Secondary ERM is occurred in younger patients and associated with other ocular conditions such as posterior uveitis, cytomegalovirus retinitis, diabetic retinopathy, retinal vein occlusion, blunt trauma, retinal detachment and repair, argon laser photocoagulation, and cataract surgery [15,16]. So, secondary ERM can be considered as an abnormal wound healing in terms of cellular proliferation, migration, and adhesion triggered by inflammation [17]. Interleukin (IL)-6, IL-8, and monocyte chemoattractant protein-1 mediate collecting inflammatory cells including macrophages, T-cells, and B-cells that have been identified in secondary ERM [18]. In some etiological conditions, vascular endothelial growth factor causes angiogenesis with secondary ERM formation [19].

### Prevalence and risk factors

Epidemiologic studies addressed the prevalence of ERM varies from 2.2% to 28.9% depending on the population being studied. According to different studies results it has been estimated that 30 million people of advanced age in the US have an ERM in at least one eye [20]. In Multi-Ethnic Study of Atherosclerosis reported ERM prevalence as 39% in Chinese, 29.3% in Hispanics, 27.5% in Caucasian, and 26.2% in Africans [21]. However the rates were given less in other studies in the literature and there are irrelevant results about the prevalence of ERM. For example, the rates had been given in the Handan Eye Study as 3.4% in North China, the Blue Mountains Eye Study as 7% in Australia, and in the Los Angeles Latino Eye Study as 19.9% in the USA [1,22,23]. Its reported that the prevalence of ERM is 4.0% in Japan, in Shanghai Study of China and the Beijing Eye Study the prevalence of ERM as observed 1.02% and 2.2%, respectively [21,24-26]. The prevalence of ERM

was 2.9% in the Korean population 40 years of age or older. Several studies showed, the prevalence of ERM in East Asia was significantly lower than that in western countries [27]. McCarty, *et al.* reported that the age-standardized ERM prevalence was lower in a Japanese (2.8%) than in western population (5.1 - 9.1%). However, a higher prevalence of ERM in Asian ethnicities has been reported in some multi-ethnic studies [28]. Reasons for such variability of prevalence between the different racial/ethnic groups are not yet well understood, but could be related to different sampling methodology, study designs, different rates of detection and definition of ERM, especially when the earliest stages are present. Therefore, the prevalence of ERM was affected by the ethnicity or environment remains unclear.

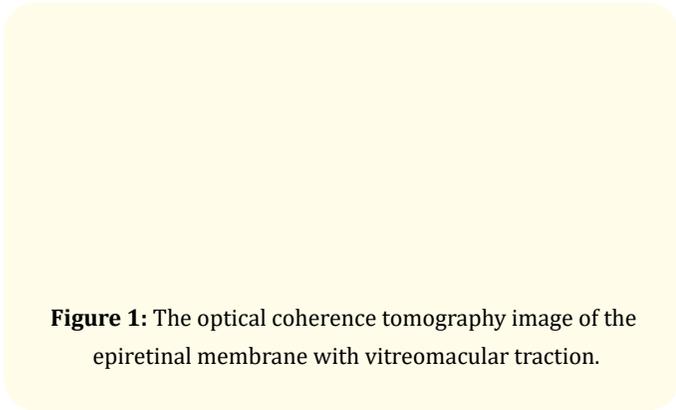
The prevalence of ERM in subjects less than 20 years of age is around 1 in 20,000. Xiao, *et al.* had reported the risk factors of ERM in a meta-analysis and they had found only female gender and ageing as ERM associated risk factors [24]. Diabetes, hypertension, hyperlipidemia, body mass index, myopia, and early age-related macular degeneration are not ERM associated risk factors according to this study [24].

### Diagnosis and classification

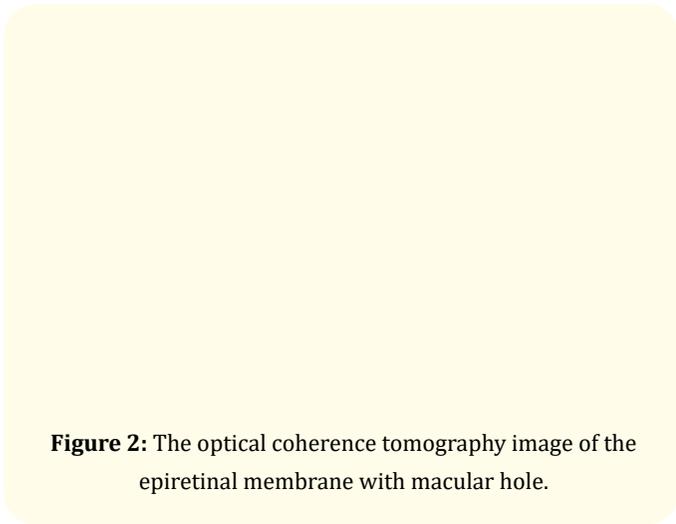
ERM diagnosis had based on clinical evaluation before optical coherence tomography (OCT) and then, cellophane maculopathy and macular pucker (pre-retinal macular fibrosis) terms has been commonly used [25]. In early stages this membrane does not distort the retina, and does not cause visual impairment; therefore, cellophane macular reflex can be an incidental finding on routine clinical examination. Fundus evaluation of cellophane maculopathy reveals a glinting, water-silk, shifting light reflex from the inner surface of the retina. In later stages, pre-retinal macular fibrosis develops as the membrane thickens, becoming opaque and gray which may obscures the underlying retinal features then it contracts, with the appearance of superficial retinal folds or traction lines resulting in visual impairment in most of the cases. In severe cases vascular dilation or tortuosity retinal hemorrhages, exudates, vascular abnormalities, edema, macular pseudoholes, and macular holes can be observed [14,15,29]. In addition to slit lamp examination, a variety of tests can be used in the diagnosis and classification of ERM; such as fluorescein angiography and OCT.

OCT provides noninvasive high-resolution cross-sectional images retina and it more sensitive than clinical examination and FFA, it is considered as gold-standard in ERM diagnosis and their associated complications, such as vitreomacular traction and mac-

ular hole (Figure 1 and 2). Nowadays, three-dimensional reconstruction images obtained from spectral domain OCT (SD-OCT) is extensively used as a standard diagnostic technique. Nevertheless, the etiological classification as idiopathic or primary and secondary ERM terms are currently used. The International Vitreomacular Traction Study Group classified vitreomacular interface disorders based on OCT findings. This group defined and classified some terms including vitreomacular adhesion, vitreomacular traction, full-thickness macular hole. They noted the relationship between anomalous PVD and ERM but they did not classified ERM [30-35].



**Figure 1:** The optical coherence tomography image of the epiretinal membrane with vitreomacular traction.



**Figure 2:** The optical coherence tomography image of the epiretinal membrane with macular hole.

There are different OCT-based ERM classification systems in the literature. One of them, classifies ERM according to foveal involvement and it was summarized in table 1 [36]. In another OCT-based ERM classification system is classified ERM according to presence or absence of PVD and [37]. In another OCT-based system use central foveal thickness and inner segment ellipsoid band integrity [38]. This is more meaningful because increased central foveal thickness and outer retina are directly associated with decreased visual acuity so it can thinkable that this classification is based on either OCT and clinic [38].

Group 1: fovea-involving ERM	
1A	Outer retinal thickening and minimal inner retinal change
1B	Outer retinal inward projection and inner retinal thickening
1C	Prominent thickening of the inner retinal layer
Group 2: fovea-sparing ERM	
2A	Formation of a macular pseudohole
2B	Schisis-like intraretinal splitting

**Table 1:** According to foveal involvement, OCT-based ERM classification\*.

\*: From Hwang, *et al.* study.

OCT: Optical Coherence Tomography; ERM: Epiretinal Membrane.

### Treatment

The treatment options for ERM are still limited and consist of either observation or surgical intervention. Conservative management such as observation is supported by some authors, the fact that most ERMs are completely asymptomatic, diagnosed on routine examination, do not progress, and some ERMs even regress. In addition, the reduction in visual acuity is variable. Therefore, the optimal surgical time has not yet been well standardized [34-38].

In clinical practice, surgery is considered for patients whom daily life is influenced due to visual symptoms with metamorphopsia, micropsia or macropsia, photopsia or decreased visual acuity (VA) below 20/40. On the other hand, some authors have reported that visual recovery is better with earlier removal of the epiretinal membrane, in addition early surgery was recommended to prevent irreversible retinal damage. Surgical ERM removal may be more beneficial for patients with aggressive and progressive, secondary ERM than patients with stable idiopathic ERM [39,40].

Pars plana vitrectomy (PPV) with or without ILM removal is the unique treatment option in both idiopathic and secondary ERMs. ILM removal prevents residual cellular component proliferation and decrease the risk of ERM recurrence [34,41]. However, there is no consensus in the literature on which technique offers the best anatomic and functional results. Some surgeons observed that the peeling of the ILM does not influence vision acuity improvement. On the other hand, some studies demonstrate that without internal limiting membrane peeling, the recurrence rate of epiretinal membrane increases, which might be due to remaining fragments of the ERM. Since the internal limiting membrane serve as a platform and bridge for cellular growth, it may enable residual glial cells, hyalocytes and myofibroblasts to proliferate and re-form another ERM. In addition, peeling of the internal limiting membrane after ERM removal may ensure full ERM removal, therefore lower-

ing the recurrence rate of epiretinal membrane. Some studies suggest a recurrence rate was changing between 7.5 - 50% when the ILM is left in place, whereas the recurrence rate of ERM is 9% when the ILM is removed [40,41]. It also depends on the nature of the membrane, secondary ERMs are more likely to recur, potentially because of more extensive damage or ongoing inflammation at the vitreoretinal interface. On the other hand some studies have shown that eyes that underwent ILM peeling developed atrophy spots in the paramacular neurosensory layer, the secondary macular hole and changes in the microperimetry.

In ERM peeling surgery to enhance the visualization of these transparent or semitransparent membrane and to prevent ERM recurrence, various staining methods have been used, including triamcinolone acetonide (TA), indocyanine green (ICG), trypan blue (TB), and brilliant blue G (BBG) [42]. Of these stains, BBG was superior than those others which shows no retinal toxicity or adverse effects related to the dye were observed in animal and human studies [35,41,43,44].

25-gauge PPV provides earlier postoperative visual recovery, in patients with both idiopathic and secondary ERM [36]. Gas tamponade and face-down positioning should be performed in case of macular hole or retinal break associated with ERM.

Surgical results are commonly satisfied but surgery association complications including endophthalmitis, and retinal detachment, may cause a serious ocular condition [36,38]. In general, surgical treatment may be more beneficial for patients with secondary ERM than patients with idiopathic ERM. Preoperative visual acuity, symptom duration, cystoid macular edema, and appearance of the photoreceptor layer on SD-OCT are important prognostic factors for postoperative best-corrected visual acuity [39,41].

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