

Drusen and Sub Retinal Drusenoid Deposits (SDD) in Age Related Macular Degeneration

Ahmed Darwish*

Department of Ophthalmology, Ain Shams University, Egypt

*Corresponding Author: Ahmed Darwish, Department of Ophthalmology, Ain Shams University, Egypt.

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Abstract

Purpose: To review drusen and sub retinal drusenoid deposits in age related macular degeneration as regards their pathogenesis, morphology, differentiation and their importance as regards the visual prognosis of age related macular degeneration (AMD).

Methods: Review of the above mentioned items based on published data.

Results: Each type of drusen or drusenoid deposits has a different visual prognosis, and the differentiation of them using multimodal imaging tests is important for the management of age-related maculopathies.

Conclusion: Multimodal imaging tests can differentiate different types of drusen and sub retinal drusenoid deposits, including their atypical forms, with consequent ability to foretell the prognosis in the various forms of presentation of AMD.

Keywords: *Drusen; sub retinal drusenoid deposits; Reticular pseudo-drusen; Age related macular degeneration*

Drusen are hallmark lesions of AMD, and the type, size, number, and total area of drusen are risk factors for the development of late AMD [1]. Although the stereoscopic color photography has been used for decades as the standard method of drusen evaluation, other imaging tests could provide additional information about drusen and enabled more accurate differentiation of drusen and drusenoid deposits, including soft drusen, cuticular drusen (basal lamina drusen), and reticular pseudo drusen (RPD) [2,3].

Variant SDD (Hyper auto fluorescent SSD)	RPD (Hypo auto fluorescent SSD)	Cuticular Drusen (basal lamina drusen)	Soft Drusen	Drusen Drusenoid Deposits
Yellowish white discrete lesions	Yellowish white discrete, interlacing or confluent lesions	Yellow small raised lesions	Whitish yellow mound - like elevations	Morphology
Usually near the fovea with reticular or isolated pattern	Along the archades particularly the superior & may reach midperiphery with reticular pattern	Random scattered from macula to periphery	Random, usually at macula	Distribution
63-250	125-250	50-75	63-1000	Size of deposits um
Variable	Variable	Early hyper fluoresce (stars in the sky appearance)	Late staining	FA
Hyper auto fluoresce	Hypo auto fluorescent	Hypo auto fluorescent	variable	FAF
Subretinal deposits	Subretinal deposits	Sub-RPE deposits saw tooth pattern	Sub-RPE deposits	SD OCT
Unknown , low association with late AMD	In late AMD	Pseudovitelliform macular detachment	In late AMD	Clinical significance

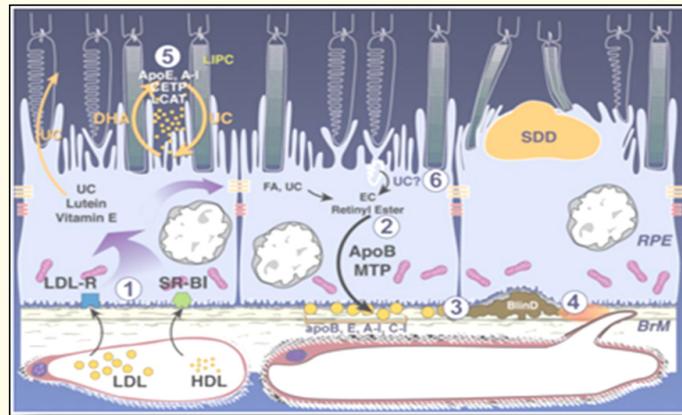


Figure 1: Pathogenesis of drusen and sub retinal deposits.

Soft drusen/Blin D, current

1. Plasma lipoproteins delivering lipophilic nutrients enter RPE.
2. Apo B, E lipoproteins secreted basolaterally by RPE (gold circles) are assembled from multiple lipid sources. Fatty acids are dominated by linoleate, implicating internalized plasma lipoproteins as a major source. Unesterified cholesterol (UC) from all sources is esterified to esterified cholesterol (EC).
3. Lipoproteins are retained by interacting with Br M extracellular matrix and accumulate throughout adulthood, creating a lipid wall on Br M’s inner surface.
4. Reactive oxygen species from neighboring mitochondria promote appearance of proinflammatory and toxic moieties. Lipoproteins fuse and form lipid pools and UC-rich liposomes within Blin D/soft drusen, rendering them biomechanically unstable.
5. Sub retinal drusenoid deposit, new disks in rod OS lose UC and gain docosahexaenoate in transit from OS base to tip (shown as loss of white). Outer segment–derived DHA stored as triglycerides in RPE after phagocytosis return to OS. High-density lipoprotein particles cycling between RPE and photoreceptors could handle both transfers as part of a vectorial lipid flow retainable within interphoto receptor matrix as UC-containing SDD, especially under rod rich perifovea.

Soft drusen/BlinD, new 6 cone OS maintain high UC content along their length because their disks are comb-like projections of plasma membrane. Cone OS UC enters RPE via disk shedding, lysosomal uptake, and acid lipase activity. Unesterified cholesterol is released for intracellular transfer, esterification, and assembly into basolaterally secreted lipoproteins, especially under cone-rich fovea [4].

It was suggested that “typical” cuticular drusen may represent a continuous layer of early basal laminar deposit (BLamD) associated with membranous debris accumulation. As early BLamD thicken, the lesions become richer in solid lipid particles, and “atypical” cuticular drusen may develop.

Deposition of extracellular material between the basal lamina of the retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch’s membrane is generally referred to as drusen [5]. Drusen usually appear after the age of 50 years, and are considered as the main risk factors of age-related macular degeneration (AMD) [6]. Drusen may also uncommonly present an early (not age-related) onset, as in case of basal laminar drusen, also known as cuticular drusen, which usually appear in early adulthood (< 50 years old).

Cuticular drusen were first described in 1977 by Gass as small round yellow lesions randomly scattered in the macula and in the mid periphery of the retina [7]. Compared with typical AMD drusen, which fluoresce later during the angiogram, cuticular drusen fluoresce during the early arteriovenous fluorescein angiography (FA) phase, exhibiting a typical “stars-in-the-sky” appearance.

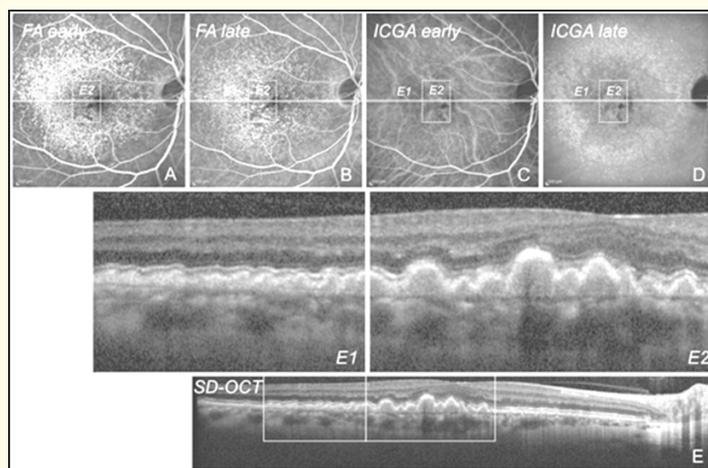


Figure 2: The early FA phase (a) reveals the peculiar “stars-in-the-sky” appearance, due to the early intense staining of innumerable, small cuticular drusen. This hyper-fluorescence slowly decreases only in the very late FA phase (b). Some “atypical” cuticular drusen appear, on early FA frame, as hyper-fluorescent lesions surrounded by faint hypo-fluorescent halos (a, dotted rectangle); these lesions became intensely hyper-fluorescent in the late FA phase (b, dotted rectangle). Similarly, on ICGA, most cuticular drusen show an early intense coloration, while some “atypical” cuticular drusen appear as hyper-fluorescent lesions surrounded by faint hypo-fluorescent halos (c, dotted rectangle); these “atypical” lesions become intensely hyper-fluorescent in the very late ICGA phase (d, dotted rectangle). SD-OCT clearly shows cuticular drusen either as “saw tooth” (E1, enlarged view) or confluent small “dome-shaped” retinal pigment epithelium (RPE) elevations (E2, enlarged view). By direct comparisons, “typical” cuticular drusen, presenting as early intense hyper-fluorescent on FA and ICGA, show the “saw tooth” RPE elevation aspect on SD-OCT (E1); “atypical” cuticular drusen, presenting as early hyper-fluorescent lesions surrounded by faint hypo-fluorescent halos on FA and ICGA, show the small “dome-shaped” RPE elevation aspect on SD-OCT (E2) [8].

In one series, some “atypical” cuticular drusen appeared, on early FA frames, as hyperfluorescent lesions surrounded by faint hypo-fluorescent halos. These “atypical” cuticular drusen showed the same angiographic aspects also on early ICGA. These lesions, which became intensely hyper-fluorescent in the late FA and ICGA phases, appeared, on SD-OCT, as small, confluent “dome-shaped” RPE elevations [8]. Conversely, “typical” cuticular drusen, intensely staining in the early FA phase, appeared as “saw tooth” RPE elevation on SDOCT [9].

Interestingly, in some regions, cuticular drusen appeared as less intensely staining on both FA and ICGA from the early until the late phase, yet still distinguishable when compared with a cuticular drusen-free region; in these regions, SD-OCT showed an irregular slight thickening of RPE/Bruch’s membrane complex, without clear evidence of “saw tooth” or “dome-shaped” RPE elevations.

Recently, Sarkis, *et al.* [10] Correlated basal laminar deposit (BLamD) and membranous debris, including basal linear deposit (BLinD), with the evolution of early AMD. The authors found that the first appearance of basal linear deposit (BLinD) coincided with a continuous layer of early BLamD [10]. BLamD could be thought of as excess basement membrane secreted by the RPE (a common strategy used by cells attempting to recover from injury, allowing them to remain attached to a tissue’s “scaffolding”), and, in terms of the disease process, appears inert [10].

Because the appearance of BLinD coincides with a continuous layer of early BLamD, a threshold level of RPE injury may trigger the production of membranous debris. As BLamD thickens, accompanied by an increasing number of basal mounds/BLinD, it progressively separates the basal RPE surface from its original basement membrane and choroidal blood supply, exacerbating the metabolic insufficiency caused by decreasing the permeability of Bruch’s membrane [11].

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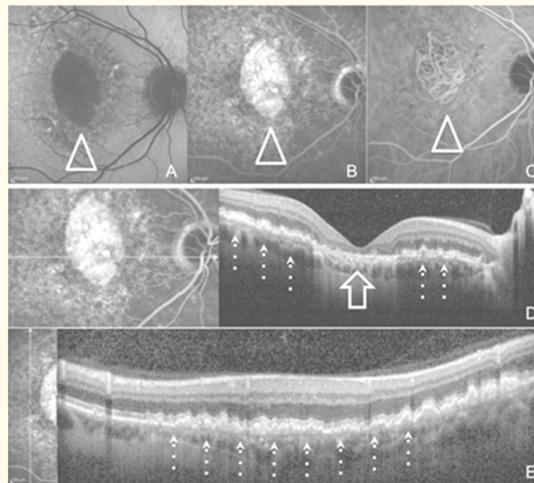


Figure 3: FAF (a) shows cuticular drusen as areas of ill-defined auto fluorescence centered by punctate hypo auto fluorescent lesions, as well as a large hypo-auto fluorescent macular lesion (arrowhead). FA reveals the peculiar “stars-in-the sky” appearance (b), due to the intense staining of innumerable, small cuticular drusen, as well as hyper-fluorescence from the large central lesion due to window effect (arrowhead). On ICGA (c), cuticular drusen show intense staining; large choroidal vessels are clearly visible within the macula due to atrophic changes (arrowhead). SD-OCT B-scan referenced on late FA frames shows the geographic atrophy within the macula (open arrow) as well as cuticular drusen as “saw tooth” retinal pigment epithelium elevations (d and e, dotted arrows) [8].

Based on the findings from integrated imaging, of Querques, *et al.* [8] it could be hypothesized that regions of less intensely staining cuticular drusen (FA and ICGA), which appear on SD-OCT as an irregular slight thickening of RPE/Bruch’s membrane complex, may represent patchy early BLamD reported by Sarkis, *et al.* [10]. Typical cuticular drusen appearing as small, hyper-fluorescent lesions on early FA phase (“stars-in-the sky” appearance in the fundus), and appearing as “saw tooth” RPE elevations on SD-OCT scans, may represent the continuous layer of early BLamD associated with membranous debris accumulation (including basal mounds/BLinD).

As early BLamD thicken, and basal mounds/BLinD increase in number, the lesions become richer in solid lipid particles. At this stage, atypical cuticular drusen, appearing as hyper-fluorescent lesions surrounded by faint hypo fluorescent halos on early angiographic frames, and as small, confluent “dome-shaped” RPE elevations on SDOCT (resembling age-related soft drusen), may develop.

The continuous accumulation of BLamD and membranous debris (including basal mounds/BLinD) affects RPE cells, and may eventually lead to geographic atrophy (GA). Figure 3 this would explain why, in the series of Querques, *et al.* [8], in the case of GA, they did not find the presence of small, confluent “dome-shaped” RPE elevations on SD-OCT: it may be that “atypical” cuticular drusen were no longer visible once GA developed, because these lesions were involved in the atrophic process [12]. Alternatively, affected RPE cells may eventually lose their anchoring to both the basement membrane and to adjacent cells, and be shed into the Subretinal space [12]. This would be responsible for the development of vitelliform macular detachments in some patients [8].

Reticular pseudodrusen (RPD) have been associated with late-stage age-related macular degeneration (AMD) since their initial identification using blue light photography [13] and their inclusion in the Wisconsin Grading System using color fundus (CF) photographs to grade AMD.[14]The first comprehensive study of RPD found a higher incidence of choroidal neovascularization (CNV) within this subset of patients [2]. Several subsequent studies found further associations between RPD and CNV, [15-18] although a comprehensive epidemiologic study of RPD found an overall increased incidence of late-stage AMD in patients with RPD without preference for CNV over atrophic AMD [19].

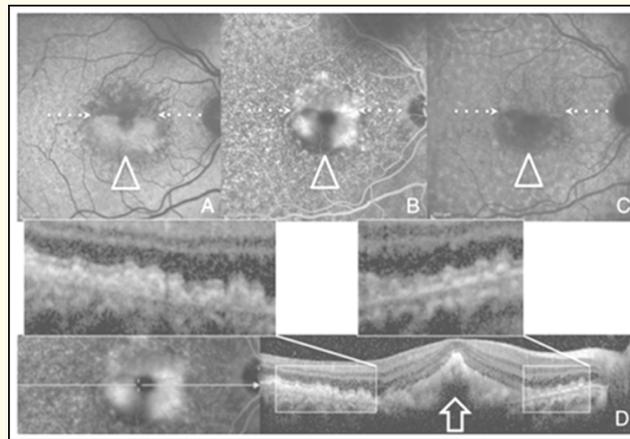


Figure 4: FAF (a) shows cuticular drusen as areas of ill-defined auto fluorescence centered by punctate hypo auto fluorescent lesions, as well as a large hyper-auto fluorescent macular lesion (arrowhead). FA reveals the peculiar “stars-in-the sky” appearance (b), due to the intense staining of innumerable, small cuticular drusen, as well as the large central lesion, which shows inhomogeneous late hyper-fluorescence (arrowhead). On ICGA (c), cuticular drusen show discrete late staining, while the large central lesion appears as hypo-fluorescent (arrowhead). Of note, the large central lesion shows an upper level (due to sedimentation) on FAF, FA, and ICGA (dotted arrows). SD-OCT B-scan (d) referenced on late FA frame clearly shows cuticular drusen as “saw tooth” retinal pigment epithelium elevations (enlarged views). SD-OCT B-scan (d) also shows a large vitelliform macular detachment (open arrow) [8].

With advances in imaging technology since RPD were first reported, characteristic reticular patterns were also noted in indocyanine green angiography [20] and Autofluorescence [21] images, leading to the broader definition of reticular macular disease (RMD) [22].

The varying clinical appearances, ranging from dots to ribbons, raise the possibility of multiple subretinal drusenoid deposit (SDD) subtypes or stages of progression or both, with distinctive ultrastructural correlates and compositions. The name reticular pseudodrusen appears inaccurate for this lesion, which is neither universally reticular (network), pseudo (false), nor drusen (sub-RPE) [4].

Subretinal drusenoid deposit and Blin D are common in non-Neovascular AMD, and the fact that they may occur together in the same eye with AMD means that it is important to distinguish them. SDD is robust and as prevalent as Blin D and located preferentially in the perifovea, in contrast to Blin D’s predilection for the fovea. These distinct lesion topographies plausibly reflect differential aspects of rod and cone photoreceptor physiology [4].

Interestingly, it was reported that each type of drusen or drusenoid deposits might have different visual prognosis, and the differentiation of them using multimodal imaging tests may be important for the management of age-related maculopathies.

Reticular pseudodrusen was defined by multiple yellowish white lesions with reticular pattern in color photography with or without blue channel examination, hyporeflectant lesions with reticular pattern in NIR imaging, light lesions with interlacing network in RF imaging, multiple reticular hypofluorescent lesions in FAF, and Subretinal deposits in SD OCT. According to the extent of involvement of retinal areas, eyes were divided into three distribution types: localized, intermediate, and diffuse [3].

Previously, it was reported that late AMD was accompanied in 26.7% to 71.4% of RPD eyes [23-29]. Considering this high association between late AMD and RPD, [23-28], Lee & Ham [3] however, suggested that the presence of a variant SDD (table 1) might be associated with low accompanying rate of late AMD in eyes with RPD. In addition, variant SDD were more frequently found in eyes with the localized and intermediate distribution types of RPD than in eyes with the diffuse distribution type.

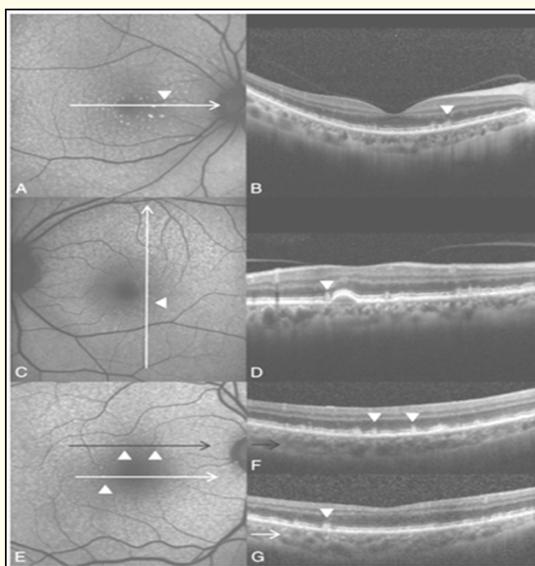


Figure 5: Fundus auto fluorescence images and SD OCT scans of 3 Cases (A and B), (C and D), and (E, F, and G). The SD OCT scan (B, D, F, and G) is located at the corresponding white or black arrow on the FAF images (A, C, and E). Spectral domain optical coherence tomography scans show sub retinal variant SDD (sub retinal drusenoid deposits extending through the inner/outer segment junction of the photoreceptor cell layer (B, D, and G, white arrow heads) at the corresponding points of hyper auto fluorescent deposits in the FAF images (A, C, and E, white arrow heads along the white arrow). Reticular pseudodrusen, which extend the inner/outer segment junction of the photoreceptor cell layer in the SD OCT scan (F, white arrowheads), show hypo auto fluorescence in the FAF image (E, white arrow heads along the black arrow). [3].

Although it has been still unknown whether the localized distribution is a mild or early form and the diffuse distribution is a severe or old form, a recent study reported that the prevalence of late AMD is significantly higher in the diffuse type (56.7%) than in the localized or intermediate type (13.9% and 13.8%, respectively) [30].

The presence of variant SDD may be a sign of favorable visual prognosis all variant SDD are usually intermixed with RPD and show common imaging features. They are yellowish white lesions on color photographs, multiple light lesions in RF photographs, hyporeflectant lesions in NIR photographs, and hypofluorescent in indocyanine green angiography photographs, which were similar to RPD. However, variant SDD are usually present as discrete lesions in a smaller number than RPD; the number of lesions ranges from 5 to 40, and 5 to 10 lesion is most common. Interconnecting lesions are infrequently found with no confluent lesions. They are more commonly located inside the major vascular arcade. The size of lesion varies from smaller to larger lesions than adjacent RPD, which range from 63 mm to 250 mm. Hypoauto fluorescence with variable intensity in FAF photographs is the most distinct feature to differentiate variant SDD from RPD, which typically show hypoauto fluorescence. Hyper auto fluorescent drusenoid deposits were distributed in the reticular or isolated pattern in the FAF photographs [3].

Eyes with regression of reticular pseudodrusen (hypo auto fluorescent SSD) may develop outer retinal atrophy and loss of the underlying choroidal thickness. This represents a late form of age-related macular degeneration that is not in current classification systems [31].

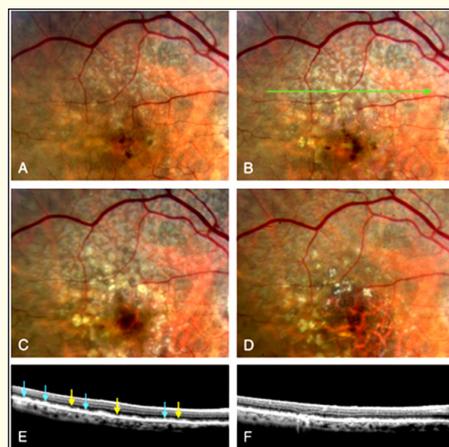


Figure 6: A. Two years before entry into the original study, this 88.3-year-old woman had scattered pseudodrusen visible in the superior macula.
 B. On entry into the study, more numerous pseudodrusen is seen.
 C. The pseudodrusen were somewhat more confluent 1.5 years later.
 D. When examined 4.6 years after entry, the regression of the pseudodrusen appearance was noted.
 E. On entry to the study, the spectral-domain OCT examination shows numerous subretinal deposits (cyan arrows) and preservation of the ellipsoid zone (yellow arrows). This spectral-domain OCT is from the area shown by the green arrow in (B).
 F. The same location was scanned at the time the color photograph in (D) was taken. Note the correlative loss of the subretinal drusenoid deposits. Also the patient shows loss of the ellipsoid zone band [31].

Summary and conclusion

Although the stereoscopic color photography has been used for decades as the standard method of drusen evaluation, other imaging tests could provide additional information about drusen and enabled more accurate differentiation of drusen and drusenoid deposits

Drusen usually appear after the age of 50 years, and are considered as the main risk factors of age-related macular degeneration (AMD) [6]. Drusen may also uncommonly present an early (not age-related) onset, as in case of basal laminar drusen, also known as cuticular drusen, which usually appear in early adulthood (< 50 years old) [6].

The continuous accumulation of BLamD and membranous debris (including basal mounds/BLinD) affects RPE cells, and may eventually lead to geographic atrophy (GA) [8].

Alternatively, affected RPE cells may eventually lose their anchoring to both the basement membrane and to adjacent cells, and be shed into the Subretinal space [12]. This would be responsible for the development of vitelliform macular detachments in some patients [8].

Reticular pseudodrusen (RPD) have been associated with late-stage age-related macular degeneration (AMD) and a higher incidence of choroidal neovascularization (CNV). According to the extent of involvement of retinal areas, eyes were divided into three distribution types: localized, intermediate, and diffuse [3]. Prevalence of late AMD is significantly higher in the diffuse type (56.7%) than in the localized or intermediate type (13.9% and 13.8%, respectively) [30].

Eyes with regression of reticular pseudodrusen (hypoautofluorescentSSD) may develop outer retinal atrophy and loss of the underlying choroidal thickness. This represents a late form of age-related macular degeneration that is not in current classification systems [31].

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Variant SDD table 1 might be associated with low accompanying rate of late AMD. The presence of variant SDD may be a sign of favorable visual prognosis [3].

Bibliography

1. Davis MD., *et al.* "The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17". *Archives of Ophthalmology* 123.11 (2005): 1484-1498.
2. Spaide RF and Curcio CA. "Drusen characterization with multimodal imaging". *Retina* 30.9 (2010):1441-1454.
3. Lee MY and Ham D. "Subretinal drusenoid deposits with increased autofluorescence in eyes with reticular pseudodrusen". *Retina* 34.1 (2014): 69-76.
4. Curcio CA., *et al.* "Subretinal drusenoid deposits in non neovascular age related macular degeneration: Morphology, prevalence, topography and biogenesis model". *Retina* 33.2 (2013): 265-276.
5. Zarbin MA "Current concepts in the pathogenesis of age related macular degeneration". *Archives of Ophthalmology* 122.4 (2004): 598-614.
6. Pauleikhoff D., *et al.* "Drusen as risk factors in age-related macular disease". *American Journal of Ophthalmology* 109.1 (1990): 38-43.
7. Gass JD "Stereoscopic atlas of macular diseases". (1977).
8. Querques G., *et al.* "Insights into pathology of cuticular drusen from integrated confocal scanning laser ophthalmoscopy imaging and corresponding spectral domain optical coherence tomography". *Graefe's Archive for Clinical and Experimental Ophthalmology* 249.11 (2011): 1617-1625.
9. Leng T., *et al.* "Punjabi OS Spectral domain optical coherence tomography characteristics of cuticular drusen". *Retina* 29.7 (2009): 988-993.
10. Sarks S., *et al.* "Relationship of Basal laminar deposit and membranous debris to the clinical presentation of early age-related macular degeneration". *Investigative Ophthalmology Visual Science* 48.3 (2007): 968-977.
11. Starita C., *et al.* "Hydrodynamics of ageing Bruch's membrane: implications for macular disease". *Experimental Eye Research* 62.5 (1996): 565-572.
12. Sarks SH and Sarks JP. "Age-related maculopathy: nonneovascular age-related macular degeneration and the evolution of geographic atrophy". In: *Ryan S (ed) Medical Retina, 3rd edn. Mosby, St. Louis, (2001) 1064-1099.*
13. Mimoun G., *et al.* "[Macular drusen]". *Journal Francais d'Ophthalmology* 13 (1990): 511-530.
14. Klein R., *et al.* "The Wisconsin AgeRelatedMaculopathy Grading System". *Ophthalmology* 98.7 (1991): 1128-1134.
15. Prenner JL., *et al.* "Risk factors for choroidal neovascularization and vision loss in the fellow eye study of CNVPT". *Retina* 23.3 (2003): 307-314.
16. Cohen SY., *et al.* "Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularization". *British Journal of Ophthalmology* 91.3 (2007): 354-359.
17. Smith RT., *et al.* "Autofluorescence characteristics of early, atrophic, and high-risk fellow eyes in age-related macular degeneration". *Investigative Ophthalmology Visual Science* 47.12 (2006): 5495-5504.
18. Hwang JC., *et al.* "Predictive value of fundus Autofluorescence for development of geographic atrophy in age-related macular degeneration". *Investigative Ophthalmology Visual Science* 47.6 (2006): 2655-2661.
19. Klein R., *et al.* "The epidemiology of retinal reticular drusen". *American Journal of Ophthalmology* 145.2 (2008): 317-326.
20. Arnold JJ., *et al.* "Indocyanine green angiography of drusen". *American Journal of Ophthalmology* 124.3 (1997): 344-356.
21. Lois N., *et al.* "Fundus Autofluorescence in patients with age-related macular degeneration and high risk of visual loss". *American Journal of Ophthalmology* 133.3 (2002): 341-349.
22. Luna XU., *et al.* "Reticular macular disease is associated with multilobular geographic atrophy in age related macular degeneration". *Retina* 33.9 (2013): 1850-1862.
23. Arnold JJ., *et al.* "Reticular pseudodrusen. A risk factor in age-related maculopathy". *Retina* 15.3 (1995): 183-191.

24. Cohen SY, *et al.* "Prevalence of reticular pseudodrusen in age-related macular degeneration with newly diagnosed choroidal neovascularization". *British Journal of Ophthalmology* 91.3 (2007): 354-359.
25. Smith RT, *et al.* "Reticular macular disease". *American Journal of Ophthalmology* 148.5 (2009): 733-743.
26. Zweifel SA, *et al.* "Prevalence and significance of subretinal drusenoid deposits (reticular pseudodrusen) in age-related macular degeneration". *Ophthalmology* 117.9 (2010): 1775-1781.
27. Sarks J, *et al.* "Evolution of reticular pseudodrusen". *British Journal of Ophthalmology* 95.7 (2011): 979-985.
28. Pumariega NM, *et al.* "A prospective study of reticular macular disease". *Ophthalmology* 118.8 (2011): 1619-1625.
29. Lee MY, *et al.* "Clinical characteristics of reticular pseudodrusen in Korean patients". *American Journal of Ophthalmology* 153.3 (2012): 530-535.
30. Lee MY, *et al.* "Clinical features of reticular pseudodrusen according to the fundus distribution". *British Journal of Ophthalmology* 96.9 (2012): 1222-1226.
31. Spaide RF "Outer retinal atrophy after regression of subretinal drusenoid deposits as a newly recognized form of late age related macular degeneration". *Retina* 33.9 (2013): 1800-1808.

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