Subretinal drusenoid deposits: An update

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Abstract:
A wide spectrum of phenotypic manifestations characterizes age-related macular degeneration (AMD). Drusen is considered the hallmark of AMD and is located underneath the retinal pigment epithelium (RPE). In contrast, subretinal drusenoid deposits (SDDs), also known as reticular pseudodrusens, are located in the subretinal space, on top of the RPE. SDDs are poorly detected by clinical examination and color fundus photography. Multimodal imaging is required for their proper diagnosis. SDDs are topographically and functionally related to rods. SDDs cause a deep impairment in retinal sensitivity and dark adaptation. SDDs are dynamic structures that may grow, fuse with each other, or regress over time. An intermediate step in some eyes is the development of an acquired vitelliform lesion. The presence of SDD confers an eye a high risk for the development of late AMD. SDD leads to macular neovascularization, particularly type 3, geographic atrophy, and outer retinal atrophy.

Keywords:
Age-related macular degeneration, outer retinal atrophy, pseudodrusen, reticular drusen, reticular macular disease, reticular pseudodrusen, retinal angiomatic proliferation, subretinal drusenoid deposit, type 3 macular neovascularization

Introduction
Age-related macular degeneration (AMD) comprises a wide spectrum of phenotypic manifestations that vary from drusen to disciform scars. There has been a recent interest in defining the role and predictive value of subretinal drusenoid deposits (SDDs), also known as reticular pseudodrusen, reticular macular disease, and reticular drusen in the visual outcomes of AMD. SDD has been recognized as an important risk factor for the progression to late AMD. Several reviews have been published in the past few years, underscoring the research interest in this topic. In this narrative review, we aim to provide an updated description of this phenotypic characteristic of AMD.

Extracellular deposits in the fundus have been described for over a century and a half. However, it was not until the 1970s that Gass implicated drusen as part of the spectrum of AMD. Clinically, these lesions appear as oval or round yellowish deposits of varying sizes in the posterior pole. In 1990, Mimoun et al. used the term “les pseudo-drusen visibles en lumière bleue” (pseudodrusen best seen with blue light) to describe a yellowish interlacing reticular pattern of lesions of about 100 μ in size in patients with AMD. These were more easily seen under blue light. At the time, the authors were not sure what they were observing, thus the designation of pseudodrusen. They presumed that the lesions were located somewhere in the choroid. The fundoscopic appearance of SDD may resemble and may be confused with other phenotypic manifestations of AMD such as soft drusen or cuticular drusen. The differences in location with respect to the retinal pigment epithelium (RPE), differences in morphology, and the differences in optical filtering effects by the RPE and lesion composition determine their appearance.
under multimodal imaging. The Beer–Lambert law of light absorption explains these differences.\(^{[11]}\) It is important to make the distinctions between the different extracellular macular deposits to more accurately assess the risk of disease progression in each patient. In 1991, the Wisconsin Age-Related Maculopathy Grading System recognized reticular soft drusen as part of the spectrum of AMD. They characterized them as drusen that formed “ill-defined networks of broad interlacing ribbons” on color fundus photographs (CFPs).\(^{[12]}\) In 1995, Arnold et al.\(^{[13]}\) coined the term reticular pseudodrusen to describe a particular yellowish pattern under the retina that consisted of lesions of 125–250 μm wide. This pattern was best seen with the He-Ne beam, with the red-free light or the infrared wavelength of the scanning laser ophthalmoscope (SLO). They noted that unlike true drusen, these pseudodrusens did not fluoresce on fluorescein or indocyanine green angiography (ICGA). In addition, they correlated the presence of reticular pseudodrusen as an important risk factor in the development of macular neovascularization (MNV).\(^{[13]}\) During the next decade, histologic examination of donor eyes from an eye bank was shown to harbor deposits in the subretinal space in individuals with or without AMD. The protein components of these deposits were similar to drusen, hence their designation of SDD.\(^{[14]}\) A decade ago, Zweifel et al.\(^{[15]}\) and Schmitz-Valckenberg et al.\(^{[16]}\) used spectral-domain optical coherence tomography (SD-OCT) to co-localize the so-called reticular pseudodrusen to these SDDs. It is currently accepted that SDD and reticular pseudodrusen refer to the same findings.

**Subretinal Drusenoid Deposit and Conditions Other than Age-Related Macular Degeneration**

SDDs are commonly found in patients with all phenotypes of AMD but are not specific to AMD.\(^{[16-19]}\) The reported prevalence of SDD in AMD ranges from 9% to 70%.\(^{[13,17,20-22]}\) The prevalence of SDD is strongly associated to AMD severity. For instance, in the ALSTAR study, SDDs were present in 49% of early AMD and 79% of intermediate AMD (iAMD) patients.\(^{[23]}\) In patients with AMD and newly diagnosed MNV, 24% had SDD. The prevalence of type 3 MNV was significantly higher in eyes with SDD than in eyes without SDD.\(^{[17,23]}\) Geographic atrophy (GA) has also been associated with SDD.\(^{[23]}\) The prevalence of SDD was low in polypoidal choroidal vasculopathy (PCV) cases.\(^{[24]}\) SDDs have been reported in other conditions such as pseudoexanthema elasticum,\(^{[25,26]}\) Sorsby’s dystrophy,\(^{[27]}\) IgA nephropathy,\(^{[28]}\) Vitamin A deficiency,\(^{[29]}\) fundus albipunctatus,\(^{[30]}\) retinitis punctate albescens,\(^{[31]}\) adult-onset foveomacular dystrophy,\(^{[32]}\) and extensive macular atrophy with pseudodrusen-like appearance.\(^{[32]}\)

Some view SDD as an ocular manifestation of systemic disease and thus their designation of reticular macular disease.\(^{[33]}\) Patients with SDD have been associated with cardiovascular risk and decreased renal function.\(^{[34,35]}\) Patients with hypertensive choroidopathy and serous retinal detachment secondary to malignant hypertension and preeclampsia may develop lesions similar to SDD.\(^{[36]}\) The Beaver Dam Eye Study reported that patients who had reticular drusen at baseline had a 54% poorer survival.\(^{[37]}\) The Melbourne Collaborative Cohort Study did not find such an association.\(^{[38]}\) A recent study also reported an impaired retinal arterial dilation in response to flicker light stimulation.\(^{[39]}\)

SDD may even be present in healthy older individuals without any other ocular conditions. This finding raises the possibility that SDD may be a manifestation of aging or an earlier disease state of AMD.\(^{[40,41]}\) In the absence of any other phenotypic AMD, the presence of SDD does not affect rod-mediated dark adaptation.\(^{[42]}\)

**Diagnosis**

Over the past decade, it has been recognized that multimodal imaging is essential in the diagnosis of SDD. The imaging characteristics of SDD have been extensively reviewed by other authors.\(^{[3,6]}\) Improvement of the diagnostic accuracy of SDD requires confirmation with at least two different imaging modalities. SD-OCT and near infrared reflectance (NIR) have the highest sensitivities [Figures 1 and 2].\(^{[21,23,40,45]}\) Confocal blue reflectance, blue channel of CFP, and ICGA have a specificity of 100% but much lower sensitivities.\(^{[45]}\) Several groups have explored deep learning algorithms to diagnose the presence of SDD from different multimodal images of the posterior pole of the eye.\(^{[44,45]}\) van Grinsven et al.\(^{[44]}\) built a model that used NIR, CFP, and fundus autofluorescence (FAF) images from the Rotterdam Eye Study. Keenan et al.\(^{[45]}\) included CFP and FAF images from the AREDS2 dataset. Both of these studies have shown that deep learning models are not only capable but also exceed the diagnostic capabilities of ophthalmologists. Furthermore, the superior diagnostic properties of FAF over CFP were confirmed. Hu et al.\(^{[46]}\) have tried to develop an algorithm to automatically segment SDD from en face OCT images.

**Subretinal Drusenoid Deposit Subtypes**

Different morphological types of SDD have been described. Multimodal imaging allows characterization of SDD into three different categories: dots, ribbons, and
NIR and green FAF are recommended for detecting dots, whereas SLO pseudocolor is more useful for detecting ribbons. SDD subtypes may have different outcomes. Eyes with dot SDD subtype had a 2.5-fold increased risk of developing neovascular AMD (NV-AMD), whereas eyes with ribbon SDD subtype had a 4.3-fold increased risk of developing GA. Adaptive optic SLO has shed some light into the differences between the dot and ribbon subtypes. The characteristic cone mosaic pattern was present in unaffected areas of eyes with dot SDD, whereas this pattern was not present in the unaffected areas of eyes with ribbon SDD. This suggests that in the ribbon SDD subtype, the adjacent areas are not really unaffected and may have undergone some type of outer segment and interdigitation zone degeneration.

Epidemiology

SDDs have been identified in individuals of different ethnic and racial backgrounds, including Korean, Japanese, Caucasian, and African-American populations. There appear to be no ethnic differences in populations with SDD. SDD is more prevalent in women and increases with age. The reported incidence and prevalence of SDD will vary according to the imaging modality used to detect them.

The classification and risk stratification of AMD have conventionally been based on CFP. Although the Wisconsin Age-Related Maculopathy Grading System recognized reticular drusen, it did not discriminate between them from regular soft drusen. The AREDS simplified severity scale did not even acknowledge their presence. Older studies such as the Beaver Dam that used only CFPs are of historical interest since many eyes with SDD will be missed by CFP. Sole reliance on CFP for the detection of SDD will miss 30%–50% of cases. In addition, it is important to note that SDDs are often located outside the central macula, a location that has not been typically screened when assessing AMD severity. Thus, these traditional methods need to be replaced by others that account for the presence of SDD. More recent studies such as the Montrachet and Alienor studies incorporate multimodal imaging in their imaging protocol. In the Alienor study, the prevalence of SDD using multimodal imaging was 13.4% compared to only 4.5% when using CFP. In the AREDS 2 study, the prevalence of SDD, based on FAF images, was 24% of iAMD eyes or 29% of individuals with iAMD. The prevalence of SDD varied with the baseline AMD severity ranging from 6% in early AMD to 36% in eyes with GA.

Recently, Lei et al. devised a simple scoring system based solely on OCT criteria to assess the risk of progression of eyes with early AMD to late AMD. The OCT criteria included drusen volume within a central 3 mm circle ≥0.3 mm³, intraretinal hyperreflective foci, hyporeflective foci within a drusenoid lesion, and SDD. A point is assigned for the presence of each criterion (maximum risk score of 4 per eye). Then, the points are summed up to obtain a total score, and the risk is assessed by categorization of the total score. Given its novelty, this new risk assessment needs to be validated.

Genetics

Several polymorphisms in the CFH, ARMS2, and C3 genes that have been associated with AMD have also been associated with SDD. An AMD genetic risk score based on 52 variants was calculated for participants in the AREDS 2 study. Interestingly, as the genetic risk score increased, the prevalence of SDD increased. The association of CFH polymorphisms with SDD has not been consistent. Both the Beaver Dam Eye and Blue Mountain Eye studies, both of which relied on CFP to diagnose SDD, reported that the Y402H polymorphism in the CFH gene was associated with SDD. In contrast, other studies that used multimodal imaging have found no association between SDD and polymorphisms in the CFH gene. A meta-analysis confirmed the lack of association of CFH variants and SDD. ARM2 risk alleles for AMD, on the other hand, have been strongly associated with SDD.
Histopathology

Histopathological studies confirm that these SDDs are not benign.\textsuperscript{[14,64,65]} The pseudodrusen were found to be subretinal drusenoid deposits rich in vitronectin that extended into the photoreceptor outer segment and inner nuclear layers. These were associated with photoreceptor disruption, photoreceptor loss, localized Müller cell gliosis, and RPE alterations.\textsuperscript{[14,64,65]} In addition, the choroidal vasculature underlying the SDD areas appeared to be unaltered.\textsuperscript{[64]}

Pathophysiology

The exact mechanisms of development and progression of SDD have not been entirely elucidated, and their understanding has evolved over the years. There is a paucity of longitudinal studies using multimodal imaging. Based on these, the leading hypotheses that have been put forth to explain the pathogenesis of SDD includes choroidal vascular dysfunction,\textsuperscript{[35]} RPE dysfunction or that SDD are para-inflammatory phenomena.\textsuperscript{[66]} SDD and soft drusen are both extracellular deposits that contain similar components such as membranous debris, apoE, complement factor H, vitronectin, and to a lesser extent apoB and apoA-1. The main difference between SDD and soft drusen is the amount of cholesterol esterification. SDD is characterized by the large amount of unesterified cholesterol, whereas in soft drusen, the cholesterol is mostly esterified.\textsuperscript{[14]}

In a recent review, Spaide et al.\textsuperscript{[5]} reported that several investigators used SD-OCT and swept-source (SS)-OCT to demonstrate that SDD are associated with age-related choroidal atrophy, choroidal thinning, and a reduced macular choroidal volume. It appears that these changes in the choroid are driven by changes in the choroidal vasculature. The advent of OCT-angiography (OCTA) allowed several groups to study the choriocapillaris in eyes with SDD. Eyes with SDD manifest a significantly decreased choriocapillaris vessel density and larger areas of choriocapillaris nonperfusion.\textsuperscript{[67,68]} Despite these findings, they emphasized that the mere presence of choroidal thinning was not sufficient to give rise to SDD. They noted that elderly myopic patients despite their extremely thin chorioids do not develop SDD.\textsuperscript{[5]} Choriocapillaris ischemia leads to RPE hypoxia.

An increasing body of evidence of histopathological\textsuperscript{[69]} SS-OCT\textsuperscript{[70]} and SD-OCT\textsuperscript{[71,72]} studies implicates choroidal vascular dysfunction in the pathogenesis of both AMD and SDD. SDD may be a manifestation of choroidal vascular disease. Some believed that SDD was an ocular marker of cardiovascular disease that led to an impaired choroidal filling.\textsuperscript{[34]} They have noted the association between SDD and multilobular GA,\textsuperscript{[73]} the location of SDD along the choroidal watershed zones,\textsuperscript{[72]} and the association of SDD with choroidal thinning. In the Alienor study, patients with choroidal thickness at baseline were more prone to develop SDD.\textsuperscript{[98]} A cross-sectional study that corrected for confounding variables through a multivariate analysis showed that in eyes with intermediate AMD with SDD, the choroid was attenuated when compared to eyes without SDD.\textsuperscript{[74]} Eyes with SDD have a decreased mean macular choroidal thickness, choroidal vascular thickness, and choroidal vascularity index.\textsuperscript{[74]}

The spatial association between SDD and the choroidal vasculature has been fraught with controversy. On the one hand, several authors claimed that SDDs result from fibrous replacement of the choroidal stroma to outer retina lipid cycling.

Patients with iAMD exhibit a systemic dysregulation of the complement system. However, the complement factor levels were not related to the presence or absence of SDD.\textsuperscript{[75]}

Natural History

SDDs are dynamic structures and undergo changes. A three-stage SD-OCT-based grading system was proposed in 2010.\textsuperscript{[14,64]} In Stage 1, granular hyperreflective material was deposited in the interdigititation zone between the RPE and the inner segment/out segment layer. When mounds of material alter the contour of the ellipsoid line, Stage 2 is reached. In Stage 3, thicker material adopts a conical appearance and breaks through the ellipsoid. Stage 4 was added a few years later to characterize fading of material due to migration and reabsorption within the inner retinal layers.\textsuperscript{[3,4,6]} Spaide\textsuperscript{[80]} recognized that on SDD regression, outer retinal atrophy (ORA), a previously unrecognized form of late AMD, developed. This ORA was characterized by the collapse of the outer nuclear layer, an attenuated ellipsoid zone, thin choroid, and an intact RPE. He differentiated ORA from GA. A histopathological survey and clinicopathological correlation of eyes with SDD confirmed the progression of SDD to ORA on SDD regression.\textsuperscript{[66]} This observation led to recognition of ORA led to Classification of Atrophy Meetings group.

The assessment of the natural history of an individual SDD is challenging.\textsuperscript{[77]} Even the Heidelberg Spectralis has alignment inaccuracies of the confocal scanning laser ophthalmoscope (cSLO) + SD-OCT with an alignment error of up to 35 μm.\textsuperscript{[78]} According to Steinberg et al.,\textsuperscript{[77]} analysis of a single corresponding follow-up scan does not suffice. To minimize these problems, they recommend a very dense OCT volume scan of at least <11 μm between scans coupled to analysis of the neighboring scans.\textsuperscript{[77]} Using this strategy, they reported that in 18 eyes with a median observational time of 5 months, none of the individual SDD disappeared. In
contrast, if only the corresponding follow-up scan was used, 21% of the SDD lesions had vanished.

The lifecycle of an individual SDD is more dynamic and does not necessarily progress through the different stages. Reiter et al. reported that after 12 months of follow-up, in 6 eyes of 4 patients, 69% of the SDD grew, 15% shrank, 6% remained unchanged, 11% disappeared, and 0.6% re-appeared following regression.

Some studies have suggested that microglia may be involved in the regression of SDD. Others have challenged this idea and have stated that there is currently no evidence to suggest that invading phagocytes are involved at all. They instead ascribe it to fluctuations in the activity of surrounding outer retinal cells.

SDD has been recognized as an important risk factor for the progression to the late stages of AMD. Sattler’s layer vessel density, choriocapillaris vessel density, and Haller’s layer vessel density were all reduced in eyes with SDD. Furthermore, the luminal to total choroidal area ratio was lower, and the stromal to total choroidal area ratio was thinner choroids when compared to the eyes with drusen.

EDI SD-OCT images have shown that eyes with SDD and eyes with drusen experienced progressive thinning of the choroid. In contrast, normal control eyes did not experience any choroidal thinning over the same time period. The rate of thinning was similar between luminal and stromal areas; however, overall, the SDD eyes had thinner choroids when compared to the eyes with drusen.

EDI SD-OCT and SS-OCT have shown that most eyes with SDD have a thinner choroid than iAMD eyes without SDD and age-controlled healthy individuals. Sattler’s layer has been implicated in one report. In contrast, most recent investigations point to the choriocapillaris. Spaide et al. have emphasized that the choroid is not uniformly thin in eyes with SDD and some patients with SDD have a thick choroid.

Several iAMD phenotypes that predispose to the development of GA, including SDD, large drusen, refractile deposits, pigment epithelial detachments, and vitelliform lesions, were identified. The rates of GA progression were compared among these precursor lesions. Eyes with SDD were associated with the fastest GA enlargement.

Reiter et al. reported that the presence of SDD accelerated the progression of GA, particularly in the superior-temporal and temporal sectors.

Several precursor lesions of GA, including large subretinal pigment epithelial drusen, SDD, refractile deposits, pigment epithelial detachment, and vitelliform lesions, have been identified. Of these, the presence of SDD is associated with the fastest GA enlargement.

Eyes with iAMD and SDD develop progressive outer retinal degeneration, which manifests itself as decreases in scotopic and mesopic retinal sensitivities.

In eyes with exudative NV-AMD, the presence of SDD is an important risk factor for the development of macular atrophy. SDD hastens the GA enlargement rate.

Structural Changes

Enhanced depth imaging (EDI) SD-OCT and SS-OCT have shown that most eyes with SDD have a thinner choroid than iAMD eyes without SDD and age-controlled healthy individuals. Sattler’s layer has been implicated in one report. In contrast, most recent investigations point to the choriocapillaris. Spaide et al. have emphasized that the choroid is not uniformly thin in eyes with SDD and some patients with SDD have a thick choroid.

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In addition, the luminal to total choroidal area ratio was lower, and the stromal to total choroidal area ratio was higher in eyes with SDD than the eyes with drusen and the control eyes. An OCTA comparative analysis of eyes with SDD, eyes with drusen, and eyes with both SDD and drusen and normal controls revealed total choroidal vessel density, choriocapillaris vessel density, Sattler’s layer vessel density, and Haller’s layer vessel density were all reduced in eyes with SDD. Furthermore, the vessel to stroma ratio at all the choroidal vascular layers was reduced significantly. These findings support the notion that choroidal vascular depletion and fibrotic replacement occurs in eyes with SDD.

Functional Changes

SDD by virtue of their anatomic location overlying the RPE may alter photoreceptor structure and in turn influence retinal function even in early stages. Histopathological examination of an eye with SDD...
and non-NV-AMD showed photoreceptors with loss of the inner segment deflection and outer segment shortening. SDDs are most commonly located in the superior macula and surrounding the optic nerve. The most severely affected areas were the superior areas and the least affected were the central areas. In eyes with SDD, the functional changes correlated with the physical and topographical distribution of the SDD, which happen to coincide with the topographical distribution of rods.

Several investigators have compared functional parameters such as best-corrected visual acuity, low luminance visual acuity, dark adaptation times, retinal sensitivity between healthy age-controlled eyes, iAMD eyes with SDD, and iAMD eyes without SDD. A recent pilot study suggests that the magnitude of functional losses in eyes with iAMD and SDD are greater than eyes with iAMD without SDD. These losses are similar to those from parafoveal atrophy.

In contrast, Neely et al. reported that SDD in the eyes of older individuals without any other signs of macular pathology do not exhibit any functional deficits.

This preference of SDD toward rods partly explains the results of multifocal electroretinogram (mERG) on eyes with SDD. Since the main mERG signals are cone driven, it is not surprising that the presence of SDD did not appear to alter the electrophysiological activity of areas affected by SDD when compared to eyes without SDD. Loss of chromatic sensitivity has been observed in eyes with SDD. Recent studies have shown that cones are affected as well.

**Treatment**

Despite the success of anti-VEGF drugs in the management of NV-AMD, many eyes do not gain or maintain useful vision. Eyes with GA have no treatment currently available. Some researchers have reasoned that intervention at the iAMD stage may modify the natural history of the disease.

Subthreshold nanopulsed laser treatment of a mouse model of AMD, characterized by a thickened Bruch’s membrane, caused an upregulation of genes involved with turnover of Bruch’s membrane extracellular matrix. Some investigators have explored subthreshold nanopulsed laser as a means of slowing the progression of iAMD to late AMD and preventing visual loss. At 3 years of follow-up, subthreshold nanosecond laser delivered every 6 months caused a twofold increase in progression in eyes with iAMD and SDD, whereas eyes with iAMD without SDD had a fourfold reduction in progression. A 24-month observational extension of the study confirmed these observations. The mechanism underlying subthreshold nanopulsed laser treatment is not entirely understood but is presumably based on selective photo-thermalization where the laser pulse leads to RPE loss which triggers a wound healing response. Eyes with SDD may be so damaged that they are unable to heal and instead the laser pulse hastens their demise.

The PASCAL-GA trial is an ongoing single-center, nonrandomized, phase I-II pilot study that aims to assess if subthreshold laser can restore the RPE function in eyes with SDD and incipient GA. Power titration was performed to obtain a barely visible threshold burn. Eyes were treated with end point management consisting of 30% of the power required to obtain the barely visible threshold burn with a pattern of 5 × 3 spots (1.27 mm² area). The treatment area was selected within the vascular arcades but outside the fovea. Results at 3 months of follow-up demonstrated SDD stage regression and outer nuclear layer thickening in the areas of treatment.

Patients with iAMD and SDD exhibit significantly reduced macular pigment optical density when compared to control subjects and patients with iAMD featuring intermediate and large drusen. Following a 3-month supplementation of lutein and zeaxanthin, the macular pigment optical density (MPOD) in the SDD eyes improved, but the best corrected visual acuity (BCVA) and the retinal sensitivity, as measured by microperimetry, remained unchanged.

Future treatment trials of iAMD need to phenotypically stratify eyes according to the presence or absence of SDD. As illustrated by the LEAD study, treatment outcomes may differ depending on the presence or absence of SDD. Eyes with SDD may be irreversibly committed to undergo disease progression.

**Summary**

SDDs are extracellular deposits located in the subretinal space. They differ in content from drusen by having more esterified cholesterol. SDDs have a predilection for perifoveal rod-rich areas in contrast to soft drusen that preferentially appears in the cone-rich fovea. IR reflectance and SD-OCT are the preferred methods of diagnosis. The presence of SDD may be a poor prognostic sign for eyes with iAMD and may signify irreversible disease progression to the development of late forms of AMD such as GA, type 3 MNV, and ORA.

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**Conflicts of interest**

The authors declare that there are no conflicts of interests of this paper.
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