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Statins, Caloric Restriction and Longevinex® in a One-eyed Patient with Macular Drusen

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Authors' contributions

This work was carried out as collaboration between all authors. Author AB compiled the data, created the figures and helped write and revise the manuscript. Author MK helped with revision. Author SR wrote and revised the text of the manuscript and compiled the literature. Author WS reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Aims: Evaluate the effects of Longevinex®, Statins, and caloric restriction in a one-eyed patient with Dominant Drusen.
Presentation of Case: A 44-year old male patient with OD congenital amblyopia (20/800 VA) and persistent OS confluent drusen (20/20 VA) (Dominant Drusen) was prescribed AREDS I supplementation for 13 years, with stabile vision and retinal exams. Subsequently, the patient developed worrisome OS Amsler grid distortion along with OS sub-retinal drusenoid deposits (SDD) and retinal architecture disruption.
Discussion: A significant increase in the drusen-free macular area (DFMA) of the patient occurred following 2 years of statin drugs and weight reduction and 4 years daily intake of a caloric restriction mimetic nutrient capsule. Only the Longevinex® red wine matrix nutrient complex

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resulted in complete Amsler grid resolution and sustainable normalisation of his retinal SD-OCT architecture.

Conclusion: This case provides a longitudinal perspective on a novel therapy for SDD amelioration with promising results. Within the context of previously published research on Longevinex®, this approach potentially provides an efficient, cost effective, and compassionate strategy for patients at risk for AMD as well.

Keywords: AMD; drusen; Longevinex®; resveratrol; statin.

1. INTRODUCTION

The gradual deterioration of retinal pigment epithelium (RPE) health in untreated and treated AMD patients is common, in spite of AREDS I or II supplement risk reduction or intra-vitreal anti-VEGF pharmaceuticals. This report in a younger patient, albeit with "Dominant Drusen" highlights the key role of multiple modalities (statins, weight reduction, caloric restriction and Longevinex®). We demonstrate drusen and retinal architecture improvement using objective Spectral Domain Optical Coherence Imaging (SDOCT). This technique provides an in vivo histological – type cross-section image of the retina and choroid. This case report is important because it details a potentially novel treatment for SDD amelioration, with even greater implications for the much larger older global population of AMD patients.

2. CASE PRESENTATION

BF is a 44-year-old Caucasian male with moderate myopia, congenital amblyopia and 20/800 Snellen visual acuity in the right eye (OD) and central, confluent sub retinal drusenoid deposits in the left eye (OS). Due to his young age at onset, his presumptive diagnosis was Dominant Drusen (mutation in EFEMP1). He is also at further risk for AMD by AREDS criteria. BF retained 20/20 vision (OS) since his original diagnosis at age 28. He was monitored yearly by a community ophthalmologist with 2 intervening retina specialist consultations and was prescribed the AREDS I AMD supplement in 2001. Nearly a decade later, BF added CoQ10 and low-dose fish oil supplements to his diet. Amsler grid central – 20 degrees x 20 degrees vision field distortion manifested in early 2009. BF's ophthalmologist described it as being "very frightening, as the distortion would move around "reposition itself at multiple central Amsler Grid locations), on a weekly, sometimes-daily basis". BF was then referred to a retina specialist / academic center (Bascom Palmer, Miami, FL USA) for consultation. This medical center provided all data and images, following HIPPA informed consent (BF).

A systemic medical review revealed progressive obesity (BMI 32.8), hyperlipidemia and long-term alopecia areata, which was diagnosed at age 33. BF's medications included short-term use of two statin drugs, 40 mg simvastatin (Zocor®) prescribed in May 2011 then replaced with atorvastatin (Lipitor®) in September 2012. Other medications included finasteride (Propecia®) and daily pabulum multivitamin. Statins were discontinued altogether in February 2014 when BF made dietary changes resulting in a 23 kg/50lb weight loss by early 2015. This regimen included a 14-day juice cleanse, followed by a calorie-counting weight-loss diet and exercise program, and subsequent addition of Longevinex® (Resveratrol Partners, Las Vegas, NV), a red wine matrix, caloric restriction mimic.

The nutrient components within 1 capsule of Longevinex ® include stabilised and micronized 100 mg trans resveratrol, 1200 IU vitamin D3, and 365 mg composed of extracts of French Red Wine and Giant Knotweed Leaf (polygonum cuspidatum), quercitin, rice bran phytate, ferulate and cyclodextrin.

BF experienced partial clearing of foveal drusen without any changes in Amsler Grid or retinal SD-OCT while solely taking a statin Zocor ® for 9 months, without additional lifestyle changes (Fig. 1a-b). BF self-prescribed daily Longevinex® supplementation, while still on a second statin Lipitor® three months before his February 2013 ophthalmologic visit. This combination drug-supplement approach resulted in additional clearing of foveal drusen (Fig. 1c). By February 2014, BF had discontinued Lipitor® , taking only Longevinex® in addition to beginning a calorie-restricted diet and an exercise regimen. The Amsler Grid began to resolve and by late 2015, was "95% straight and crisp on the full plane". This improvement is reflected in the further increase in DFMA (Fig. 1d). As of BF's last retinal evaluation, December 2017, he has remained free of visual defects on the Amsler Grid test. BF received no anti-VEGF injections, including his mot recent photographs (Fig. 1e).

1a. Date: 12/22/2010
- AREDS I x 9yrs

Drusen-free macular area (DFMA):
15p x 16p = 240p

1b. Date: 2/6/2012
- AREDS I x 11yrs
- Simvastatin x 9mo

DFMA: 40p x 40p = 1600p

1c. Date: 5/20/2013
- AREDS I x 12yrs
- Simvastatin x 16mo
- Atorvastatin x 8mo then dc

DFMA: 86p x 59p = 5074p

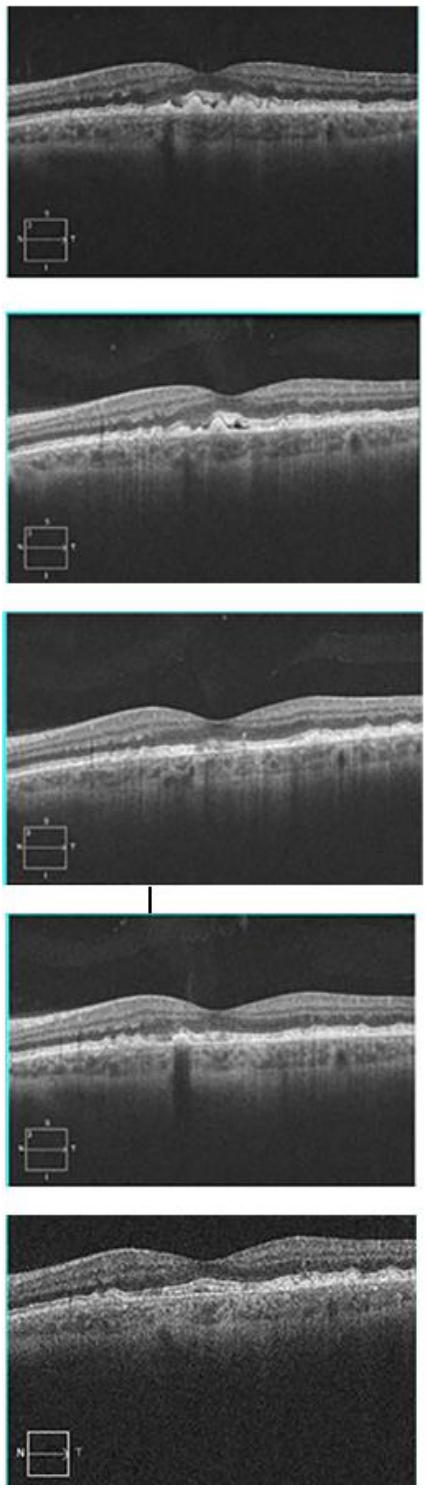
1d. Date: 6/23/2014
- AREDS I x 13yrs
- Longevinex x 16mo
- Weight reduction of 50 lbs by 2015
- Amsler grid stabilized at 95% by 2015

DFMA: 84p x 68p = 5712p

1e. Date: 1/27/2017
- AREDS I x 15yrs
- Longevinex x 46mo

DFMA: 103p x 88p = 9064p

Fig. 1a-e. The gradual improvement of BF's OS macular pathology. Five original digital jpeg colour images of 940 x 1060 pixels were scaled to an equalised optic nerve dimension of 68 x 68 pixels. The DFMA was then measured after 300% enlargement. Normalised colour fundus images (64 x 68 pixel equalised optic nerve size) at 5 time points with calculation of Drusen-Free Macula Area (DFMA). Funduscopy reveals the gradual increase in DFMA, centered at the fovea with successive therapeutic approaches in a young one-eyed patient taking the AREDS I supplement. The area grows 240 pixels in size (Dec 2010) to 9064 pixels (Dec 2016) following sequential prescription of statins, weight reduction and Longevinex®. An increase in DFMA occurred with statins, weight reduction and Longevinex®. However, near-total resolution of the patient's Amsler Grid wasn't achieved until statins were discontinued, leaving BF on his current regimen of caloric restriction, exercise, and Longevinex® supplementation



2a.
Date:
1/31/2011
Signal Strength:
7/10

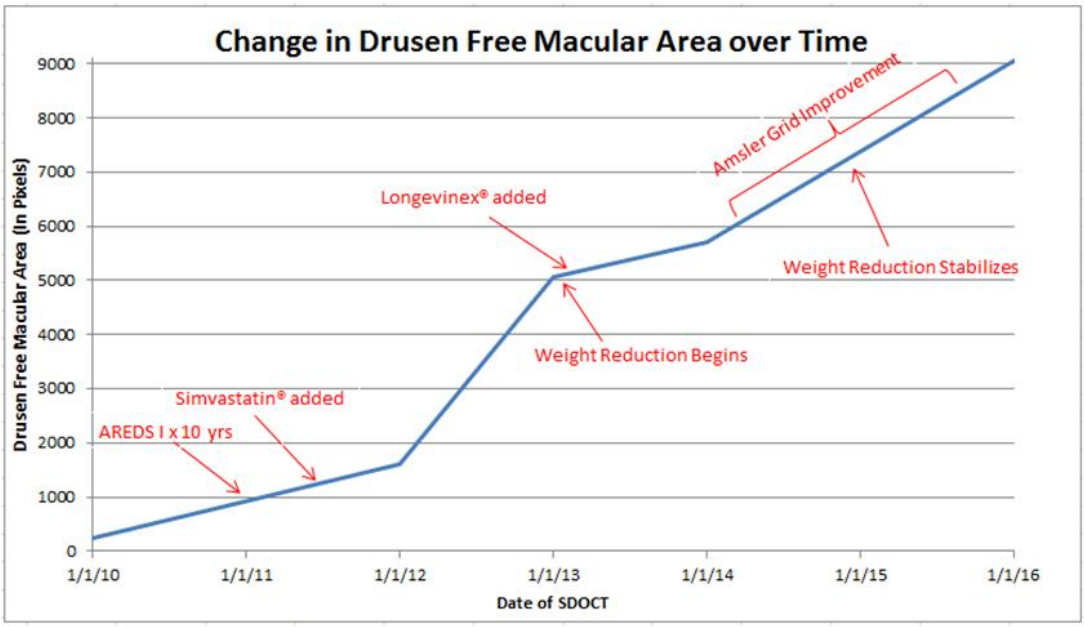
2b.
Date: 2/6/2012
Signal Strength:
10/10

2c.
Date:
5/20/2013
Signal Strength:
9/10

2d.
Date:
11/24/2014
Signal Strength:
10/10

2e.
Date:
12/12/2016
Signal Strength:
9/10

Fig. 2a-e. SDOCT macula images showing gradual retinal structure normalisation. Note improved global structural integrity involving the foveal photoreceptor/RPE layer, preserved IS/OS junction without atrophy, and preserved choroidal thickness without atrophy. Visual acuity remains stable at 20/20 four years after beginning Longevinex® and weight reduction



Macular Area (In pixels)	Date
240	12/12/2010
1600	02/6/2012
5074	5/20/2013
5712	6/23/2014
9064	12/16/2016

Fig. 3. Drusen free macula area (in pixels) over time with sequential treatment with AREDS I, statins, weight reduction and Longevinex® over a 6 year time period. Raw data is below graph

3. DISCUSSION

Statins are among the most researched drugs in medicine. They provide cardiovascular benefits for millions of patients around the world, reducing hospital admissions and overall mortality in patients with the known cardiovascular disease [1,2]. Yet studies have shown that statins have little to no effect on cardiovascular disease when utilised as primary prevention [3-5]. Additionally, several significant side effects can result from statins, including memory loss, myopathies, cataracts, and increased risk of diabetes. The biochemical process for statin's therapeutic benefits also explain the adverse clinical effects [6]. Statins act as a HMG-CoA reductase inhibitor, which reduces blood cholesterol levels by impairing hepatic cholesterol synthesis. This presents with two clinical dilemmas, the first being increased risk for systemic underproduction of the various hormones and cellular structures that are derived from cholesterol. Furthermore, while statins appear to prevent formation of new cholesterol deposits, they have not been shown to stop or slow drusen formation, nor the progression of AMD [7].

The link between statins and "Dominant Drusen' is unknown. However, the connection between coronary artery disease, and specifically hypercholesterolemia, has been long established with studies showing coronary artery disease is associated with a thinner macular choroid [8] and a thinner choroid is associated with increased drusen [9]. The Alabama Study on Early AMD (ALSTAR) recently found that SDD is strongly associated with AMD, with SDD patients 2.24 times more likely to have AMD at 3 years of follow up (95% CI 1.36-3.70) [10]. AMD is a progressive disease and is the leading cause of irreversible vision loss among people over 65 years old in developed countries. In recent years evidence has shown that atherosclerosis shares many risk factors with AMD, including age, smoking, and elevated BMI. This led many to hypothesise that statins could provide protective benefits against AMD. Recent meta-analysis concluded that "evidence from currently available

RCT's is insufficient to conclude that statins have a role in preventing or delaying the onset of AMD" [11]. On the contrary, the balance of evidence continues to suggest that statin usage increases cataract risk. [12,13] though this remains a mildly controversial topic. While statins have undoubtedly proven to be a life-saving drug for patients with cardiovascular disease, the side effects must be carefully factored into the risk-benefit analysis for all patients.

This case report is important because it details a potentially novel treatment for SDD amelioration. Perhaps the most significant finding of this case is that BF showed sustained fovea-macular drusen resolution with intact sub-retinal structure. This contrasts with the typical course of drusen resolution, which involves destruction of the photoreceptor/RPE layer, a significant problem with traditional anti-VEGF treatment(s).

Caloric restriction along with daily Longevinex® supplementation accomplished what 13 years of AREDS I supplementation and 2 years of statins failed to do: alter the natural time course of Dominant Drusen. This dual lifestyle/epigenetic approach resulted in clearing of BF's Amsler Grid and regression/stabilisation of his retina. The unique timeline of this case suggests that Longevinex® has a much greater capacity for clearing existing SDD than statins. This case report mirrors published findings of stem cell regeneration using the low molecular weight matrix of labile copper binding resveratrol, red wine solids, vitamin D3 and divalent metal binding inositol hexaphosphate (bran factor) as well as the cyclodextrin found in Longevinex® [14].

The existing studies on Longevinex®, have involved relatively few patients, but have nonetheless demonstrated numerous systemic health benefits. These benefits include decreased inflammation, decreased plasma cholesterol levels, and decreased calcification of arteries [15]. This nutrient complex has also been shown to greatly improve endothelial function in patients with metabolic syndrome [16]. Longevinex® has been shown to confer particular benefits upon ocular health, including decreased HIF-1 and VEGF gene expression [15] and increased vasodilation and corresponding thickening of the choroidal layer of the retina. In regards to ocular health, the presence of cyclodextrin within Longevinex® is particularly notable because it has been shown to bind and remove drusen from the RPE [17]. Due to FDA restrictions, Longevinex® has not been studied in human randomised, controlled trials. However animal trials have shown that Longevinex® restores myocardial dysfunction in hypercholesterolemic animals, prevents cardiac reperfusion injury in canine experimental cardiac vessel ligation [18] and reduces SDD in rhesus monkeys [14]. To date Longevinex® consumption has shown no side effects or cytotoxicity at high doses, though validation of this would require a large-scale clinical trial.

The correlation between atherosclerosis and AMD, the ubiquity of statin therapy, and the potential negative impact of statins on eye health demand further scientific investigation when considered in totality. This case provides a longitudinal perspective on a novel therapy for SDD amelioration with promising results. Within the context of previously published research on Longevinex®, this approach is potentially an efficient, cost effective, and compassionate strategy for patients at risk for AMD as well. As an adjunctive epigenetic approach, it appears to be the logical next step to accompany anti-VEGF AMD treatments and secure long term vision benefits for the growing patient populations diagnosed with AMD.

Learning points from the discussion are as follows:

- The US NIH, National Eye Institute, Age Related Eye Disease Studies (AREDS) have identified a subset of nutrients important to patients afflicted with AMD. While beneficial to retinal health, these nutrients do not typically result in resolution of oxysterol based cholesterol deposits known as retinal drusen. Nor do they result in improvements in visual function.
- Epigenetics and the control of aging are at the center of basic science and should be applied to patients with few if any clinical options – such as Dominant Drusen. This includes caloric intake / exercise recommendations and prescribing caloric restriction molecular mimics such as Longevinex®.

4. CONCLUSION

- Longevinex® and statins (as well as traditional standard of care AREDS II supplements) are all tools to be considered by the *individual eye practitioner* treating the *individual patient.*

5. FULL DISCLOSURE

Resveratrol Partners LCC (Las Vegas, NV, USA) makers of Longevinex® and Longevinex Advantage® capsules provided clinical research laboratory development funding to SR in the past. AB, MK, SR and WS have no patent, commercial or financial interest in Longevinex®, US patent # 9,226,937 B2 and AMD patent application including salutary effect on retinal health, US Patent # PCT/US2011/042130.

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CONSENT

This medical center acquired all images and digital data from Bascom Palmer (Miami, FL, USA), following HIPPA informed consent from patient (BF), at his request.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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