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Cornea in Wilson Disease: Kayser Fleischer Ring & Beyond

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Abstract

The identification of Kayser-Fleischer (KF) ring remains the most important clinical sign for the diagnosis of Wilson disease (WD). Slit lamp biomicroscope (SL) examination by a skilled observer is still the preferred method of evaluating KF ring. Anterior segment optical coherence tomography (AS-OCT) is an alternative method of evaluating KF ring in WD. Hyper-reflective layer in the corneal periphery at the level of Descemet membrane (DM) is the characteristic appearance of KF ring on AS-OCT. In a suspected case of WD, features of KF ring on AS- OCT may alert the clinician to do a careful SL examination to look for early KF ring. AS-OCT has been found useful in measuring the length of KF ring with ease even in patients with severe rigidity and children. AS-OCT can measure the length of KF ring better compared to SL in patients with limbal pathology. Early detection of increased corneal copper even before KF rings appear is a potential area for future research.

Index terms— Kayser-Fleischer ring, Wilson disease, slit lamp biomicroscopy, optical coherence tomography, copper, cornea.

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I. Background r. Samuel Alexander Kinnier Wilson described Kayser-Fleischer (KF) ring as a corneal ring of pigment of a greenish golden colour, associated with a form of cirrhosis of the liver, and also with nervous symptoms which belong to the lenticular group. 1 Till date, the description holds good and the identification of KF ring remains the most important clinical sign for the diagnosis of Wilson disease (WD). WD is an autosomal recessive disorder of copper transport, characterized by impaired excretion of copper into bile as well as incorporation into transporter copper protein ceruloplasmin. 2 Copper is an essential trace element. It is an important cofactor for many enzymes required for cellular respiration, iron oxidation, pigment formation, neurotransmitter biosynthesis, antioxidant defense and connective tissue formation. 3 The source of copper for the human body is the food consumed and the absorption depends on the copper content of food. The human gastrointestinal system can absorb 30 to 40% of ingested copper from typical western diets. Copper absorption occurs primarily in the small intestine and a small fraction from stomach. 4 Liver maintains adequate concentrations of copper in plasma. Clinical manifestations are related to copper accumulation predominantly in the liver andbrain. 5 Though WD is thought to be an autosomal recessive disease, most affected individuals carry two different mutations (so-called compound heterozygotes) on each allele encoding the WD gene. 6,7 WD is due to mutations of the ATP7B gene onchromosome 13, which encodes a copper-transporting P-type ATPase (ATP7B) residing in the trans-Golgi network of the patocytes. ATP7B is responsible for transporting copper from intracellular chaperone proteins into the secretory pathway, both for excretion into bile and for incorporation into apo-ceruloplasmin for the synthesis of functional ceruloplasmin. The gene frequency in the healthy population is about one in 90. ATP7B is located on the long arm of chromosome 13 (13q14-q21). The most common mutation is the point mutation H1069Q in exon 14, accounting for 30-60% of all mutations in caucasian patients. 2,6 This mutation is associated with failure in catalytic phosphorylation and mislocalization of ATP7B. Mutational analysis has helped us to understand that the prevalence of WD being higher than traditionally perceived. 8

2 II. Diagnosis of wd

The worldwide prevalence of WD is estimated to be between 1 in 30,000 and 1 in 100,000 with a gene frequency of 0.56% and a carrier frequency of approximately 1 in 90. 2 It is even higher in certain populations with consanguinity. 2 WD should be considered in any person between the age of 3 and 55 years with typical symptoms and signs. 9 The most common presentations are with liver disease or neuropsychiatric disturbances. Asymptomatic patients are most often detected by family screening. 5 Late onset of symptomatic WD disease may occur occasionally. Neurologic signs are variable, most often tremor, ataxia, and dystonia. The most common form of tremor in WD is an irregular, and some what jerky, dystonic tremor. 10 Asymptomatic hepatomegaly, isolated splenomegaly, persistent elevations in serum aminotransaminases, jaundice, fatty liver, resembling autoimmune hepatitis, acute hepatitis, compensated or decompensated cirrhosis and acute liver failure are reported liver manifestations in WD. 9 Psychiatric manifestations include depression, neuroses, personality changes and psychosis. 11 Renal abnormalities which is rare include aminoaciduria and nephrolithiasis.

Presence of KF rings and serum ceruloplasmin concentrations of less than 20 mg/dL are sufficient to establish the diagnosis. 12 The first step in screening for potential WD is often serum ceruloplasmin measurement. 13 When KF ring is not present (as is common in the hepatic manifestation of WD), ceruloplasminlevels are not always reliable. Serum ceruloplasmin may be decreased (autoimmune hepatitis, severe hepatic insufficiency in advanced liver disease, celiac disease, familial aceruloplasminemia, or in heterozygous carriers of ATP7B mutations) or increased (inflammation in the liver or elsewhere) in diseases other than WD. 5 The routine tests which are done in the diagnosis of WD include serum ceruloplasmin (decreased by 50% of lower normal value), 24-hour urinary copper >1.6 ?mol/24 h in adults and >0.64 ?mol/24 h in children, serum "free" copper >1.6 ?mol/L, hepatic copper >4 ?mol/g dry weight and identification of KF rings by SL examination. 5 Urine copper excretion measurement after a penicillamine challenge is considered a diagnostic tool for WD, and it has been commonly considered diagnostic when>1600 µg/24 h. This test is not recommended in children without symptomaticliver disease, because only patients with severe liver damage due to WD are likely to have a positive test. 14 In absence of KF ring, WD is difficult to diagnose and even centers with expertise regard diagnosis as a challenge in some cases. 15 III. kf Ring in wd KF ring is corneal copper deposition in the inner parts of Descemet membrane (DM) in the form of granules. 16 Histochemistry, electron microscopy and electron probe x-ray microanalysis have reported copper deposits within the periphery of DM causing KF ring. [17][18][19][20] Electron microscopy studies have identified copper bound to sulphur-containing moiety in electron dense granules seen throughout the cornea in patients with WD. It is 10 to 20 times higher in the corneal periphery. These granules are arranged in multiple, discrete layers with the smallest granules closest to the endothelium. 19 Almost all patients with neuropsychiatric symptoms will show KF rings, whereas about 50-60% of patients with hepatic WD will have this manifestation. 7 Cases of neurologic WD with no KF ring is regarded as less invasive form of WD. 21 It is seen in nearly 40% of pre-symptomatic WD patients. 22 The KF ring increases as the disease progresses. The morphological findings of copper deposits seem to differ from patient to patient depending on the stage of the disease. The ring is typically seen in the peripheral cornea, copper deposited on DM as greenish yellow or golden brown ring. (Figure1). The color of the KF ring and its localization seems to be related to the peculiar multilaminar arrangement of granules in the periphery. 19 It is almost always bilateral, starts superiorly first, then inferiorly and later becomes circumferential. 16 Though it is reported that in children presenting with liver disease, KF rings are usually absent, in our series of 10 patients, two were less than 12 years of age. Both had liver manifestations. There are case reports where KF ring was the first detectable manifestation of WD. 23 Significant correlations between KF at diagnosis and clinical neurological manifestations has been reported. 24 KF ring appears to be a predictive factor in the neurological and hepatic evolution of WD. 24

3 IV. Mechanism of Formation of KF Ring

The source of copper for incorporation into DM is not very clear. It is postulated that ionic copper loosely bound to albumin has its origin in the anterior chamber. Elevated levels of copper in the aqueous humor in patients with WD have been reported. 19 K-F ring is believed to be formed by the copper particles which infiltrate into DM through the endothelial cells from the aqueous humor. Finding of intracytoplasmic copper granules in endothelium, suggests a role for endothelium in absorption of copper from aqueous humor. 25 Tso et al proposed that cellular activity is required for deposition of copper material into the thick basement membrane. 26 The pattern of dense copper deposition in the periphery is attributed direction of aqueous flow and / or functional peculiarity of the peripheral corneal endothelium. The microenvironment of anterior chamber may be the key factor that affects the transfer of copper to basement membrane. 25 Other than aqueous humour, the other possible source of copper is limbal circulation. Innes et al reported a case of unilateral KF ring. 16 The eye without the ring was injured in childhood and had a low intraocular pressure. They postulated that the copper deposition is through aqueous (which was reduced in the eye with low intraocular pressure), rather than limbal circulation which was normal in the scared eye. The limbal circulation of the patient's right eye was not disturbed though it had a corneal scar and the intraocular pressure was low.

Cornea is also permeated by ionic copper. This accounts for high concentration of the copper in the cornea and lack of correlation between KF ring and corneal copper. Electron microscopy of KF ring showed the presence of electron dense deposits of varying size mainly in the DM. 27 They are arranged essentially in the middle third and in two linear zones. Posteriorly in relation to the endothelial surface, the deposits were fine and dust-like.

Anteriorly towards the stromal surface they were fewer number but larger in size. The larger deposits with a central nidus probably result from coalescence of the smaller particles over a period of time. It is not clear why the deposits are at the periphery. It may be related to the direction of aqueous flow or to V. Methods of Evaluating kf Ring 1. Naked eye examination of KF ring is less sensitive method compared to SL. On naked eye examination, thick KF rings are visible as yellow or brown rings in the peripheral cornea. 2. Direct ophthalmoscope can be used as a bed side evaluation method of thick KF rings. Early KF rings can be missed.

In long standing cases, the deposits become thick and granular. The larger KF ring size correlates to WD severity. 30 The deposits rarely are seen more than 5mm centrally and gradually fade towards the centre of the cornea. The description of a clear ring of peripheral cornea to the K-F ring seems to because of variable position of Schwalbe's line. The intensity of KF ring seems to be correlated to the severity of WD. KF ring does appear to be a predictive factor in the neurological and hepatic evolution of WD. 24 Telinius N et al suggested Schiempflug imaging as an important tool to diagnose KF ring. 32 On Scheimpflug images, the KFR could be seen as a bright subendothelial band peripherals. Patients with a KF ring, had a significantly higher subendothelial signal compared to both WD patients with a KF ring and the control group. 6. In vivo confocal microscopy -Ceresara G et al reported the confocal microscopy of corneal copper in a series of 20 WD patients. 33 Laser scanning confocal microscopy showed peripheral hyper reflective granular micro deposits at the level of Descemet's membrane in 75% of patients whereas peripheral corneal deposits were found in 25% patients by means of traditional slitlamp and goldman three mirror lens. Confocal grading of the superior cornea was significantly higher than in other quadrants. 7. Anterior segment optical coherence tomography (AS-OCT)

4 a) AS-OCT findings of KF ring

In the last two years, I have evaluated 10 patients with KF ring seen on SL, by AS-OCT. First introduced by Izatt et al. in 1994, AS-OCT is a noncontact and non-invasive imaging technique that captures high resolution cross-sectional images of the anterior segment. 34 AS-OCT has been found to be useful in exploring the anterior segment of the eye, mainly the cornea, anterior chamber and chamber angle. 35 OCT imaging is based on measuring the delay of light (typically infrared) reflected from tissue structures. The technology utilizes a Michelson interferometer, which creates a reference beam usually of infra-red light against which it measures multiple other beams of light as they return from the variably reflective tissue layers of the eye. The device collects reflected light from the sample at reference beams, thereby creating an interference pattern. My experience of AS-OCT of KF ring in a retrospective case series of 7 WD patients was presented. **??**6 The KF ring on grey scale of AS-OCT was visualized as hyper-reflective deep corneal layer at the level of DM in all eyes. The OCT color scale revealed KF ring as a greenish/greenish yellow/yellow/ yellow orange band. The grey scale of AS-OCT was found to measure with relative ease the length of KF ring in two patients. I suggested that AS-OCT is an alternative method of evaluating KF ring in WD which can be used in combination with SL examination and KF ring can be easily measured using the grey scale of AS-OCT.

5 b) Advantages of evaluating KF ring by AS-OCT

AS-OCT as an alternative method of looking at KF ring. Detection of KF ring on SL requires experience of a clinician. An ophthalmologist, who has not seen KF ring on SL before, may miss an early KF ring. On the other hand in a suspected case, hyper-reflectivity of deep corneal layer in the periphery on AS-OCT may alert the clinician to do a careful SL examination to look for early KF ring. Non -Ophthalmologists like neurophysicians and gastroenterologists may be able to

6 Slit lamp biomicroscope (SL) using a gonioscope-

This method used to assess the angle of the eye.

Early KF ring is visible as deposit in Schwalbe's line of angle, which is where the DM of cornea terminates. Performing and interpreting gonioscopy required expertise. 4. Slit lamp biomicroscope (SL) using diffuse and direct focal illumination-A SL by an experienced/ skilled observer is required to identify KF rings. 5 SL was invented by Gullstrand in 1911. 28 On SL, using diffuse illumination and direct focal examination, KF ring is seen as seen as golden-brown, brown-green, green-yellow, golden-yellow, bronze or reddishbrown coloring of the DM in the peripheral limbal area of the cornea. (Figure Rarely the color of the deposit may be ruby red, bright green or ultramarine blue in color. 19,29 5. Scheimpflug photography & Imaging The usefulness of Scheimpflug photography in the follow-up of WD disease patients has been presented in one case by Obara H1 et al. 31 In the case presented by them, during 15 year follow-up the yellowish-brown granular opacification on the anterior lens capsule had mostly disappeared, but the same type of opacification had emerged on the posterior lens capsule, showing disease progression. The changes in the lens were difficult to detect by SL examination alone, but were clearly picked up by Scheimpflug slit images. The authors suggested this modality is valuable in follow-up studies of eye involvement in WD. look at KF ring on AS-OCT. 37 AS-OCT was found useful in measuring the length of KF ring. Method of measuring KF ring and calculating KF ring score has been suggested by Esmaeli et al. 38 Standard narrow-beam direct illumination slit-lamp photographs (20 x magnification) were taken at 6 o'clock and 12'o clock vertical corneal meridians in each eye. After masking and randomizing the photographic slides, a single observer measured the length of KF ring at 6 o' clock and 12'o clock vertical corneal meridians using

a Castroviejo caliper under 4 x magnification. The average KF ring score was obtained by summation of all vertical length measurements in both eyes as per the number of meridians examined by SL photomicrographs. The nasal and temporal rings were not measured due to technical difficulty using slit-lamp photographs in these meridians. With eye aligned properly and cursor positioned, KF ring can be easily measured using the grey scale of AS-OCT. Even nasal and temporal measurements could be obtained and when the measurement is less than 1 mm, the KF ring measurement in microns is given on grey scale. Using AS-OCT, KF ring can be easily measured in patients what are not co-operative for SL examination. With a combination of KF ring & signal density, KF ring can be quantified using AS-OCT. 39,40 WD patients with severe rigidity who cannot be examined by SL can have AS-OCT evaluation and length of KF ring measured. AS-OCT can be performed in children and even in neonates. AS-OCT evaluation of congenital corneal opacities between 2 days and 2.5 years of age has been reported. 41 Recently, I saw a 12 year old male with liver failure and cirrhosis who was diagnosed as WD based on presence of KF ring and low serum ceruloplasmin. In this case, the hyper reflective pattern in the peripheral DM membrane was seen despite increased limbal pigmentation. The length of KF ring measured using SL was less compared to AS-OCT because of increased limbal pigmentation as limits of KF ring could not be clearly delineated as pigmentation was extending into cornea (Figure2). Hyper reflectivity on grey scale and its measurement is shown in Figure **??**.This case suggests that AS-OCT can measure the length of KF ring better in patients with limbal pathology.

7 c) Possible other advantages of using AS-OCT in

evaluating KF ring which needs to be studied further AS-OCT can possibly determine the density of KF ring and hence help us to assess the severity of disease. Anti-copper therapy leads to KF regression. No significant correlations were observed between KF regression and clinical neurological or neuro-imaging improvement nor between KF modifications and clinical hepatic improvement. 24 The reappearance of KF ring in a medically treated patient suggests non-compliance with therapy. AS-OCT can be a good tool to assess response and compliance to treatment in WD. Further studies are required to confirm the advantages stated above.

Case reports of pigmented corneal rings similar to KF ring have been reported in patients with chronic aggressive hepatitis, cryptogenic cirrhosis and alcoholic patient with cirrhosis with normal serum and liver copper levels. [42][43][44][45][46][47] We need to study all patients with liver cirrhosis for corneal deposits with SL, AS-OCT and also perform genetic analysis. These patients may be heterozygous carriers of ATP-7B mutations with associated liver disease who do not show copper overload disease and inflammation of liver or elsewhere could have caused the ceruloplasmin concentration to rise to normal level or be high, as it is an acute phase protein.

AS-OCT can differentiate KF ring of WD from hypercupremia of other causes and further studies are required in this direction. In WD, the hyper-reflectivity is in the peripheral cornea at the level of DM, whereas in hypercupremia of other causes, the hyper-reflectivity can be expected to be seen in the para-central or peripheral cornea at the level of DM.

8 VI. Differential Diagnosis of kf Ring

Though KF ring is said to be diagnostic of WD, corneal pigment rings have been reported in various other liver diseases and hypercupremia of various causes. Corneal pigment rings should not be regarded as pathognomonic of WD in the absence of neurological symptoms. 16 It is recognized that KF like rings occur in other conditions, particularly when severe cholestasis is a feature. Pigmented corneal rings similar to KF ring have been reported in patients with primary biliary cirrhosis and progressive intrahepatic cholestasis of infancy and childhood. 19,39,44,45 In patients with primary biliary cirrhosis, these rings were described as yellowish-green or golden-brown in color and extended around the periphery of each cornea in the region of DM. The rings were seen only by SL and not with unaided eye or an ophthalmoscope. These rings resembled KF rings seen in early or minimal manifestations of WD. They are not reported to be thick and granular. All these patients were associated with high levels of hepatic copper, serum copper, urinary copper and serum ceruloplasmin. Pigmented corneal rings in this situation is believed to because of long standing cholestasis in which an excessive copper deposition occurs in the liver and in other organs due to failure of biliary copper excretion.

Case reports of pigmented corneal rings similar to KF ring have been reported in patients with chronic aggressive hepatitis, cryptogenic cirrhosis, and alcoholic patients with cirrhosis with normal serum and liver copper levels. [42][43][44][45][46][47][48][49] In chronic active hepatitis, it was seen as crescents superiorly and inferiorly of a yellowgreen colour. 42 They have also been described as brownish pigmentation around the entire periphery of each cornea or as bilateral circumferential KF rings. The deposits in this situation have been called as pseudo-KF rings or KF-like rings. These patients had normal or high serum ceruloplasmin levels. The nature of these deposits is not clear as in one patient, the intensity of his rings was noted to fluctuate with his serum bilirubin concentration. It was speculated that bilirubin could produce at least some of the pigment in patients with KF-like rings. Phinney RB et al four patients with corneal staining who had total bilirubin levels more than 26 mg/dl. Bilirubin pigmentation was more prominent in the peripheral than central cornea. In one patient of this series evaluated by SL, the epithelium was intact and entire stroma was stained yellow, more densely in the peripheral 2 to 3 mm. 50 The deposition of copper on DM has also been reported in cases of hypercupremia associated with multiple myeloma, pulmonary carcinoma, benign monoclonal gammopathies,

chronic lymphocytic leukemia and secondary to oral contraceptives. [51][52][53][54][55][56] They have also been reported with schistosoma infection, galactosialidosis, and intraocular copper foreign body. 57 These patients were found to have abnormally elevated serum copper and elevated or normal ceruloplasmin levels. Copper deposition in malignancies and secondary to oral contraceptive use was seen as bluishgreen or greenish brown in color and it involved the paracentral or central cornea.

VII. kf Ring Following Treatment of wd K-F rings are reversible with medical therapy or after liver transplantation. [58][59][60] The reappearance of either of these eye changes in a medically treated patient suggests non-compliance with therapy. Esmaeli et al found the average rate of reduction in KF ring size was 14% per year. **??**6 The KF rings disappear on treatment first in the nasal and temporal aspects, before the inferior and superior cornea. 29,38 There appears to be a correlation between KF ring regression and improvement in brain MRI. 24 There is lack of correlation between KF rings and neurologic findings and despite complete disappearance of KF ring, patient may be neurologically disabled. 59 VIII.

9 Assessing Copper Content of Cornea

KF ring does not represent the total copper content of cornea. Belkin M et al measured corneal content by X-ray excitation spectrometry in two controls and in seven patients of WD. 61 Two patients were on D-Penicillamine for three to four years, had no detectable KF ring, were in excellent clinical condition and their copper signals were normal. One patient had an indistinct KF ring and a much higher copper signal. One patient had a prominent ring, but a low copper signal.

Patient 5, was allergic to D-penicillame, was examined before and after a course of dimercaprol. The copper signal fell to 45% after dimercaprol, although the appearance of her KF ring did not change. Patient 6 was in poor clinical condition, had a very indistinct KF ring, but had a high copper signal. Patient 7 was diagnosed 13 years ago. She had received D-penicillame for the first 2 years only and was on no treatment since then. Her KF ring was seen with naked eye, and the corneal copper concentration was at least 10 times higher than those other patients. Based on the results it was inferred that KF ring is a crude indicator of corneal copper content, and appearances were not correlated with the measured corneal signal. The authors highlighted that they could detect changes in corneal copper content which SL examination missed.

Though identification of KF rings by ophthalmologists helps in diagnosis of WD, it is important to realize that by the time KF ring appears, significant other potential life threatening tissue damage involving the liver and central nervous system would have already appeared. Challenge in WD would be to detect increased corneal copper before KF ring appears. In vivo detected of increased copper in cornea would be useful for early diagnosis, assess treatment response and also to find the compliance to medical treatment in WD. Research in this direction needs to be re-initiated. X-ray fluorescence (XRF) spectroscopy which is found suitable for investigating the elemental composition of biological tissues, has been recently used to find copper in liver specimens. 62

10 IX. Conclusions

SL examination by a skilled observer is still the standard method of evaluating KF ring In WD, AS-OCT is an alternative method of evaluating KF ring in WD. Further studies are required to study the potential advantages of AS-OCT including assessing the density of KF ring, as a tool to assess response to treatment in WD, in differentiating KF ring of WD disease from copper deposits in hypercupremia and pigmented corneal rings in non-Wilsonian liver disease. In-vivo methods need to be developed to determine corneal copper content

Figure Captions

1 2 3

[2]Cornea in Wilson Disease: Kayser Fleischer Ring & Beyond

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Figure 1:

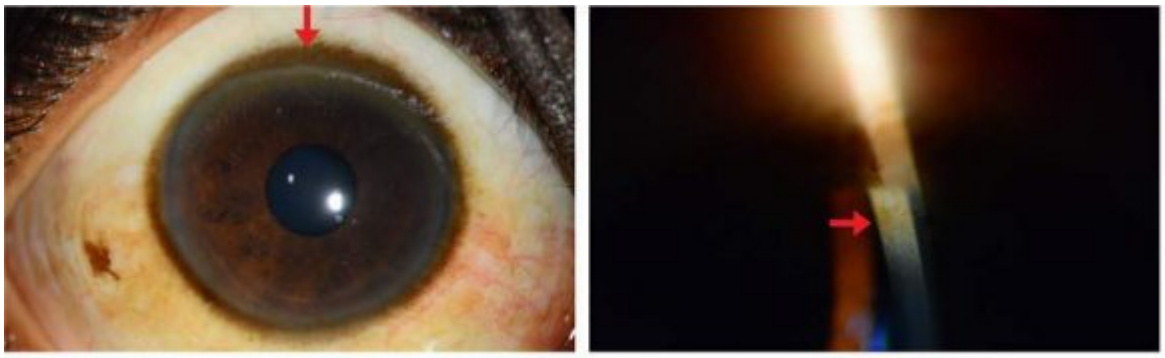


Figure 2: F

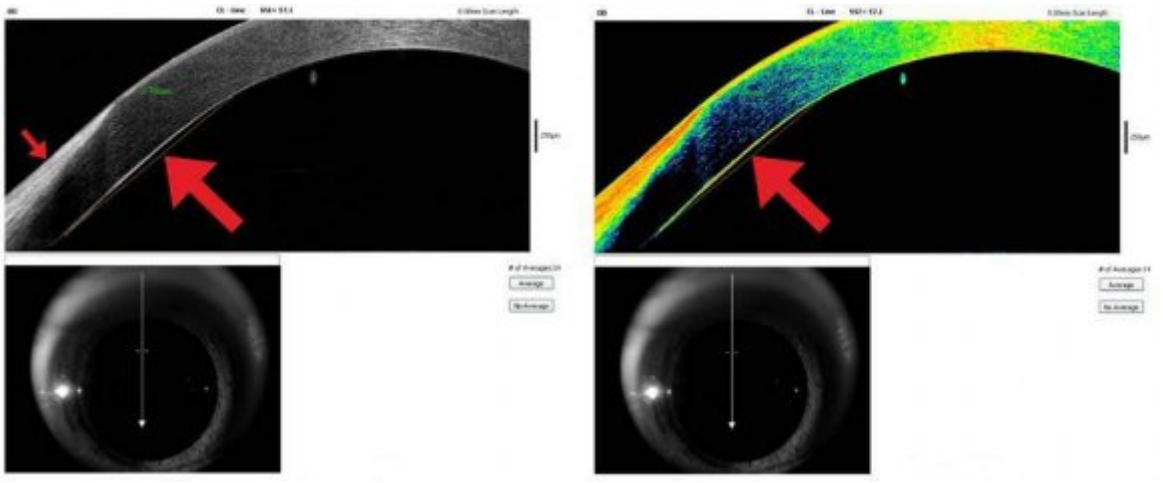
disclosure 

Figure 3: Financial disclosure :F

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