ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 68 . 16
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 5, Issue –3, June - 2020, Page No. : 394 - 402

Tear film and corneal morphological changes in patients with Type II Diabetes Mellitus

[1]Apoorva Malhotra, Consultant, Ophthalmology, Dr KD's Eye Hospital, Pathankot, Punjab, India.
[2]S K Arya, Professor, Department of Ophthalmology, GMCH, Chandigarh, India.
[3]Amit Raj, Additional Professor, Department of Ophthalmology, AIIMS, Patna, Bihar, India
[4]Jyoti Deswal, Assistant Professor, Regional Institute of Ophthalmology, PGIMS, Rohtak, Haryana, India.
Corresponding Author: Jyoti Deswal, Assistant Professor, Regional Institute of Ophthalmology, PGIMS, Rohtak, Haryana, India.

Citation this Article: Apoorva Malhotra, S K Arya, Amit Raj, Jyoti Deswal, "Tear film and corneal morphological changes in patients with Type II Diabetes Mellitus ", IJMSIR- June - 2020, Vol – 5, Issue -3, P. No. 394 – 402.
Type of Publication: Original Research Article
Conflicts of Interest: Nil

Abstract

Purpose: To study tear film and corneal morphological changes on confocal microscopy in patients with type II diabetic mellitus.

Methods: A hospital-based prospective case control study in which 60 eyes of 30 persons having Type 2 Diabetes Mellitus and a similar number of age and gender matched controls were included. All patients underwent detailed ophthalmological examination that included Ocular Surface Disease Index (OSDI) questionnaire, Schirmer's I test (SIT), Tear film break-up time (TBUT), Ocular Protection Index (OPI), Tear Meniscus Height (TMH) and Oxford Ocular Surface Staining (OOSS). Confocal microscopy was done to assess stromal cells, corneal nerves, endothelial cell parameters.

Results: The presence of dry eye in diabetics was found to be higher than in non-diabetics, based on OSDI ($p<0.001$), SIT ($p=0.041$), TBUT ($p= 0.040$) and OPI ($p=0.013$). There was a positive correlation between OSDI, TBUT and OPI ($p<0.001$). Mean corneal nerve fiber length density and endothelial cell density in diabetics was found to be significantly less than in non-diabetics ($p < 0.001$); however no such difference was found in mean stromal cell density. Endothelial cell density showed a significant negative correlation with age ($p=0.05$). Also, the percentage of endothelial cells exhibiting polymegathism was higher in diabetics ($p<0.001$).

Conclusion: Due to the multifactorial etiology and high prevalence of dry eye in patients with diabetes, we recommend a comprehensive approach that incorporates routine dry eye screening and assessment of corneal morphological changes to cater to the dry eye symptoms in addition to the retinopathy screening.

Introduction

Diabetes mellitus is a major disease worldwide, and the incidence of diabetes has risen markedly in the past several decades. The complications associated with diabetes are the leading cause of blindness in the working age adults.Changes in the cornea can even be the earliest manifestation of diabetes. It has a significant effect on the morphological, metabolic, physiological and clinical aspects of the cornea which

can often be sight threatening. Diabetes can affect all five layers of the cornea. Keratopathy is a well-described ocular complication of diabetes, which has been linked to tear secretion abnormalities, decreased corneal sensitivity, poor adhesion between epithelial cells and their basement membrane and suppressed cell division.Even the corneal endothelium can exhibit abnormalities in cell morphology including decreased endothelial cell density and damaged endothelial cell structure that result in persistent postoperative corneal edema.[1]Diabetes mellitus (DM) has been identified as one of the leading systemic risk factors for dry eye syndrome (DES). The reported prevalence of DES in diabetics is 15–33% in those over 65 years of age and increases with age and is 50% more common in women than in men.[2] This study was planned so as to have a better understanding of the tear film changes in diabetics and the role of timely diagnosis of dry eye. The study also aims to appreciate the use of confocal microscopy as a newly emerging tool for the early assessment of the corneal changes in diabetes.

Materials And Methods

This prospective case control study was conducted in a tertiary eye care centre in North India. 60 eyes of 30 persons of either gender having previously diagnosed Type 2 Diabetes Mellitus were taken up for study.60 eyes of 30 normal age and gender matched persons were taken as controls. Patients with history of current eye infection, corneal damage, allergy to proparacaine, contact lens wear, previous ocular surgery or trauma, systemic diseases known to impair tear function, regular usage of any known tear-interfering systemic or topical drug**,** glaucoma, trichiasis, entropion, pterygium, or severe movement disorders were excluded.A careful history of decrease in vision, use of glasses, redness, pain, photophobia, colored haloes, floaters, flashes, dry eye, itching, foreign body sensation, previous history of treatment with drugs or any previous ocular surgery or trauma, duration of diabetes, other systemic symptoms of diabetes was taken. Ocular Surface Disease Index (OSDI) questionnaire was answered by all the subjects and appropriate scoring was done. For tear film assessment, Schirmer's 1 test (S1T), Tear Break-up Time (TBUT), Ocular Protection Index (OPI), Tear Meniscus Height (TMH), fluorescein staining was done. SIT was performed under natural lighting conditions without topical anesthesia using a Whatman No. 41 filter-paper strips (5 x 35 mm). It was placed in the lower fornix, over the junction of the middle and lateral thirds of the lower eyelid and left in place for 5 minutes. The distance moistened was directly read off the scale on the paper itself. A reading less than 10 mm was considered abnormal and less than 5 mm was taken as dry eye. For TBUT, a fluorescein-impregnated strip was placed in the inferior fornix. The patient was asked to blink 3 times and then to look straight without any blink. The tear film was observed using a cobalt blue filter under wide beam illumination at the slit-lamp. The interval between the last blink and the appearance of the first randomly appeared corneal dry spot was measured and a reading less than 10 seconds was considered abnormal and less than 5 seconds was taken as dry eye. OPI was calculated by dividing TBUT (in seconds) by inter-blink interval. An OPI of more than or equal to 1 was considered normal. TMHwas evaluated by measuring the height of the tear film meniscus on slit lamp microscopy using cobalt blue filter, after staining the eye with fluorescein. On next day, lissamine green dye strip was used and upper

eyelid was lifted slightly to grade the whole corneal and conjunctivalsurface. Staining was represented by punctate dots on a series of panels. It was graded from 0-5 for each panel as per Oxford Ocular Surface Staining scheme. Nidek ConfoScan4 was used to study stromal cells, corneal nerves, endothelial cell density, endothelial cell size, endothelial cell hexagonality. A scan of the full thickness of the cornea was performed along the optical axis.

Results

The mean age in cases was 53.9 ± 8.8 years and in controls it was 51.03 ± 8.1 years. The case and control groups were comparable with respect to age (p=0.2). Of the 60 people enrolled, 32 (53.34%) were males and 28 (46.67%) were females. Male to female ratio was comparable in both the groups (p =0.3).Severe dry eye symptoms according to OSDI score, was found in 60% of cases versus 23.33% in controls; the difference being statistically significant (p<0.001) (Table 1).The presence of dry eye, taking into account Schirmer's I test reading less than 5mm, was 21.67% in cases versus 8.33 % in controls (p=0.041) (Table 2). The presence of dry eye, as per TBUT less than 5 seconds, was 16.67% in cases versus 5% in controls (p=0.04) (Table 3). OPI less than 1, was found in 20% in cases versus 5% in controls (p=0.013) (Table 4). The presence of dry eye, as shown by visible staining, was 36.67% in cases versus 6.67% in controls, the difference being statistically significant. There was a positive correlation between age and OOSS which is statistically significant (p=0.05). Also, we also found that there was a positive correlation between OSDI, TBUT and OPI which was highly statistically significant (p<0.001).The mean stromal cell density in cases was 39554.40 ± 5675.988 cells/mm^3 while that in controls was 37915.23 ± 7343.963 cells/mm^3.This difference was not statistically significant (p =0.174). *ImageJ*software calculated the sum length of all nerve fibers within each image (Figure 1,2). Corneal nerve fiber length density was derived by dividing this number by the area of the image. Mean corneal nerve fiber length density in cases was 18.86 ±10.403 nerve mm/$mm^2$and in controls was 37.15 ± 32.118 nerve mm/mm^2. This difference was highly statistically significant. (p< 0.001) . The mean endothelial cell density in cases was 2266 ± 352 while that in controls was 2564 ±384cells/mm^2(p<0.001) (Table7). The percentage of endothelial cells exhibiting polymegathism was significantly higher (p<0.001) in cases as compared to controls. Polymegathism was present in 65.38% of cases but only in 51.23% of controls. No such association was noted with respect to pleomorphism (Table 8, Figure3,4).

Discussion

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tears film instability with potential damage to the ocular surface.[3]Various studies have shown increased prevalence of dry eye in diabetes. Presence of autonomic dysfunction, reduced corneal sensitivity, abnormalities of tear film dynamics, damage to the microvasculature of the lacrimal gland and subclinical meibomian gland dysfunction can all attribute to increased prevalence and severity of dry eye disorders in patients with diabetes.[2,4,5]

In our study, the presence of dry eye symptoms in cases is 60% by OSDI questionnaire which is considerable higher which is due to the subjective profile of the test. Seifart*et al* showed that 52.8% of all diabetic subjects complained of dry eye symptoms, as against 9.3% of the controls.[2] Hom*et al* found that the most common

dry eye symptoms reported by patients with diabetes are burning and foreign body sensation.[5] Shah *et al*found a prevalence of 67% dry eye among the diabetic patients.[6]Schirmer's I test and TBUT values in our patients have been found to be significantly lower in diabetics as compared to controls, with a significant positive correlation between the two. We found that 51.76% and 71.67% of diabetics had an abnormal tear film as assessed by Schirmer's test and TBUT. This was consistent with Dogru*et al*who have reported that these values are even significantly lower in patients with diabetic retinopathy.[7]

In our study, the OPI<1, was found in 20% in cases versus 5% in controls, the difference being statistically significant. While the hallmark indication of dry eye has been tear-film instability, an interest in the role of blink patterns has recently been surfaced. Changes in blink pattern may cause longer inter-blink intervals potentially resulting in exaggerated amounts of corneal exposure and resultant inflammation. The values of Tear Meniscus Height were not found to be statistically different between diabetics and controls which areconsistent with the results of Goebbels *et al*.[8]In our study, as per the Oxford scheme, visible staining was found in 36.67% of cases which is significantly higher than in controls.

The difference between the mean stromal cell density in cases versus controls was not statistically significant which is consistent with the limited earlier studies done so far.[9,10]However, we found that there was a decrease in stromal cell density with the severity of dry eye as assessed by TMH and OOSS, which is highly statistically significant.

Mean corneal nerve fiber length density was found to be significantly lower in our cases as compared to controls. De Cilia *et al*found that the number of nerve fibers and reflectivity of fibers of the sub-basal plexus were significantly lower in diabetic patients than in control subjects, whereas tortuosity was significantly higher.[9] Most studies on the involvement of corneal sub-basal nerve plexus in diabetes have been performed with confocal microscopy, showing a marked reduction of sub-basal plexus nerve fibers with increasing severity of DR and neuropathy.[10,11,12]Bitirgen*et al* found that corneal nerve fiber damage precedes diabetic retinopathy in patients with type 2 diabetes mellitus.[13]

As far as the mean endothelial cell density is concerned, it was found to be significantly decreased in diabetics as compared to non-diabetics. Also, in diabetics, the percentage of endothelial cells exhibiting polymegathism was significantly higher. However, similar association was not found regarding pleomorphism. Also the degree of pleomorphism was found to increase with a decrease in TBUT.These results are consistent with Choo*et al*[14]and Shenoy*et al*[15]who found that the diabetic corneas have a significant increase in endothelial cell size and coefficient of variation.Bhojak*et al*found a negative correlation between duration of diabetes and endothelial cell density which is statistically significant, suggesting a cumulative effect of diabetes.[16]

The limitation of our study is that nerve fiber beading pattern, branching density, tortuosity, reflectivity could not be measured due to the non-availability of the software. Also, we incorporated patients with only Type II diabetes in our study; further studies can be done incorporating patients with Type I diabetes mellitus also.

Conclusion

Evaluation of diabetic patients for dry eye symptoms using a questionnaire is a good method of identifying dry eye in its early stages. In-vivo confocal microscopy can prove to be an efficient tool for picking up subtle changes in corneal nerve fibers and endothelium in patients with diabetes. It has emerged as a promising tool for the early assessment and management of corneal changes in diabetes. Due to the multifactorial etiology and high prevalence of dry eye in patients with diabetes, we recommend that Diabetic clinics must include routine dry eye screening by evaluation of tear film parameters and confocal microscopy; if available. Patients diagnosed with dry eye need suitable management according to the stage. Management of dry eye needs to be incorporated in the wholesome approach of treating a diabetic patient.

References

1. Skarbez K, PriestlyY, Hoepf M, Koevary SB. The effects of Diabetes on Ocular Health: A Comprehensive Review. *Expert Rev Ophthalmol*2010;5(4): 557-577.
2. Seifart U., Strempel I. The dry eye and diabetes mellitus. *Ophthalmology* 1994; 91(2): 235-239.
3. Research in dry eye: report of the Research Subcommittee of the International Dry Eye Work Shop (2007). *Ocul Surf*2007; 5(2):179-193.
4. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 2000; 118(9):1264-1268.
5. Hom M, De Land P. Self-reported dry eyes and diabetic history. *Optometry* 2006;77(11):554-558.
6. Shah S, Jani H. Prevalence and associated factors of dry eye: Our experience in patients above 40 years of age at a Tertiary Care Center.*Oman J Ophthalmol*2015; 8(3): 151–156.
7. Dogru M, Katakami C, Inoue M. Tear function and ocular surface changes in noninsulin-dependent diabetes mellitus. Ophthalmology 2001; 108: 586–592.
8. Goebbels M. Tear secretion and tear film function in insulin dependent diabetes. *British Journal of Ophthalmology*2000; 84(1):19
9. De Cilla S,Ranno S,Carini E, Fogagnolo P, Ceresara G, Orzatest N,*et al.*Corneal Sub-basal Nerves Changes in Patients with Diabetic Retinopathy: An In Vivo Confocal Study. *Investigative Ophthalmology & Visual Science* 2009; 50 (11): 5155-5158.
10. Rosenberg ME, Tervo TMT, Immonen IJ, Muller LJ, Gronhagen-riska C, Vesaluoma MH. Corneal structure and sensitivity in type I diabetes mellitus. *Investigative Ophthalmology and Visual Science* 2000c; 41: 2915–2921.
11. Leppin K, Behrendt AK, Reichard M, Stachs O, Guthoff RF, Baltrusch S, *et al.* Diabetes mellitus leads to accumulation of dendritic cells and nerve fiber damage of the sub-basal nerve plexus in the cornea.*InvestOphthalmol Vis Sci*2014 (29);55(6):3603-3615.
12. Kallinikos P, Berhanu M, O'Donell C, Boulton AJ, Efron N, Malik R,*et al*. Corneal nerve tortuosity in diabetic patients with neuropathy. *Investigative Ophtahlmology& Visual Science* 2004; 45: 418-422.

13. Bitirgen G, Ozkagnici A, Malik RA, Kerimoglu H. Corneal nerve fibre damage precedes diabetic retinopathy in patients with type 2 diabetes mellitus.*Diabet Med* 2014;31(4): 431-438.

14. Choo M, Prakash K, Samsudin A. Corneal changes in type II diabetes mellitus in Malaysia. *Int J Ophthalmol*2010; 3(3): 234-236.

15. ShenoyR , Khandekar R , Bialasiewicz A, Al Muniri A. Corneal endothelium in patients with diabetes mellitus: a historical cohort study.*European Journal of Ophthalmology*2009, 19(3): 369-375.

16. Bhojak A, Sanghavi K, Satani D. Corneal endothelial evaluation in relation with diabetes. *Int J Int Med Res* 2016; 3(4): 41-44.

Legends Tables and Figures

Table 1: Grades of OSDI Scores in Cases and Controls

OSDI Score	Grade of Dry eye	Cases (N=60)	Controls (N=60)	p value
0-12	Normal	4 (6.67%)	18 (30%)	0.001
13-22	Mild	8 (13.33%)	16 (26.67%)	0.068
23-32	Moderate	12 (20%)	12 (20%)	1.000
33-100	Severe	36 (60%)	14 (23.33%)	<0.001

Table 2: Grades of Schirmer's I test in Cases and Controls

SIT value	Cases	Controls	p value
>10 mm	29(48.34%)	51 (85%)	<0.001
5-9 mm	18 (30%)	4 (6.67%)	0.001
<5 mm	13 (21.67%)	5 (8.33%)	0.041

Table 3: Grades of TBUT in Cases and Controls

TBUT	Cases	Controls	p value
>10 seconds	17 (28.33%)	47 (78.33%)	<0.001
5-9 seconds	33 (55%)	10 (16.67%)	<0.001
<5 seconds	10 (16.67%)	3 (5%)	0.040

Table 4: Grades of OPI in Cases and Controls

OPI	Cases	Controls	p value
>1	39 (65%)	57 (95%)	<0.001
=1	9 (15%)	0 (0%)	0.002
< 1	12 (20%)	3 (5%)	0.013

Table 5: Grades of TMH in Cases and Controls

TMH	Cases	Controls	p value
> 1 mm	14 (23.33%)	30 (50%)	0.002
< 1 mm	40 (66.67%)	30 (50%)	0.064
Barely visible	6 (10%)	0	0.012

Table 6: Grades of Oxford Ocular Surface Staining in Cases and Controls

Grade	Staining	Cases	Controls	p value
0	Absent	38 (63.33%)	56 (93.33%)	<0.001
1	Minimal	13 (21.67%)	4 (6.67%)	0.018
II	Mild	5 (8.33%)	0	0.022
III	Moderate	4 (6.67%)	0	0.042
IV	Marked	0	0	-
V	Severe	0	0	-

Table 7: Endothelial cell density in Cases and Controls

Cells/mm^2	Cases (n=60)	Controls (n=60)	p value
<1500	1 (1.67%)	0 (0%)	0.315
1500-2500	41 (68.33%)	22 (36.67%)	0.001
2500-3500	18 (30%)	38 (63.33%)	<0.001

Table 8: Comparison of the parameters measured on confocal microscopy in diabetics versus controls

Parameter	Cases	Controls	p value
Mean stromal cell density(cells/mm^2)	39554.40	37915.23	0.174
Mean corneal nerve fiber length density(mm/mm^2)	18.86	37.15	<0.001
Mean endothelial cell density (cells/mm^2)	2266	2564	<0.001
Mean polymegathism (%)	65.4	51.23	<0.001
Mean pleomorphism (%)	32.9	39.6	0.233

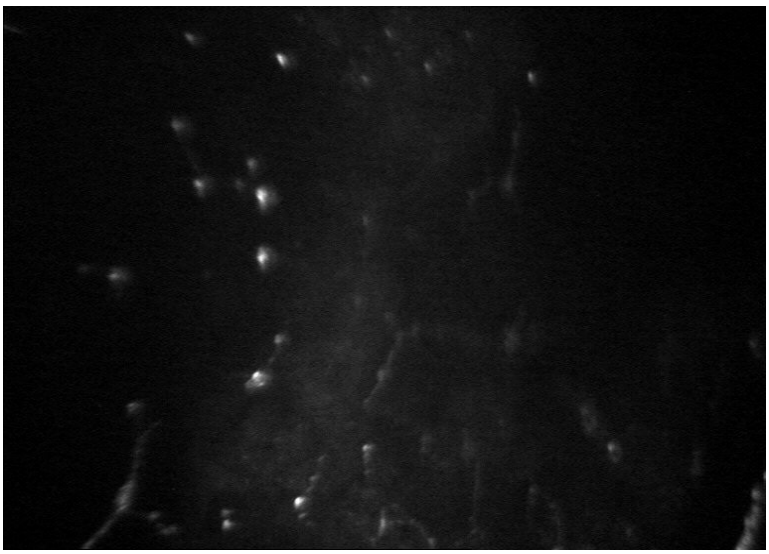

Figure 1: Confocal microscopy image showing beading pattern in a nerve fiber in a diabetic

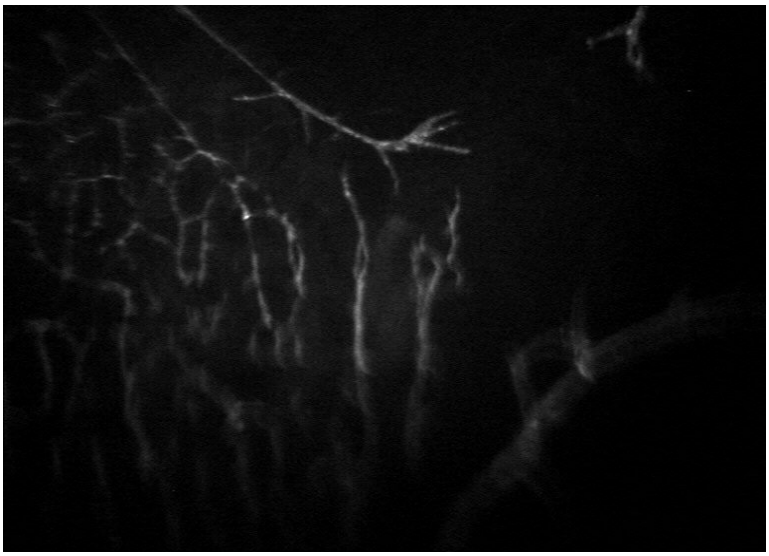

Figure 2: Confocal microscopy image showing branching pattern in a nerve fibre in a normal control

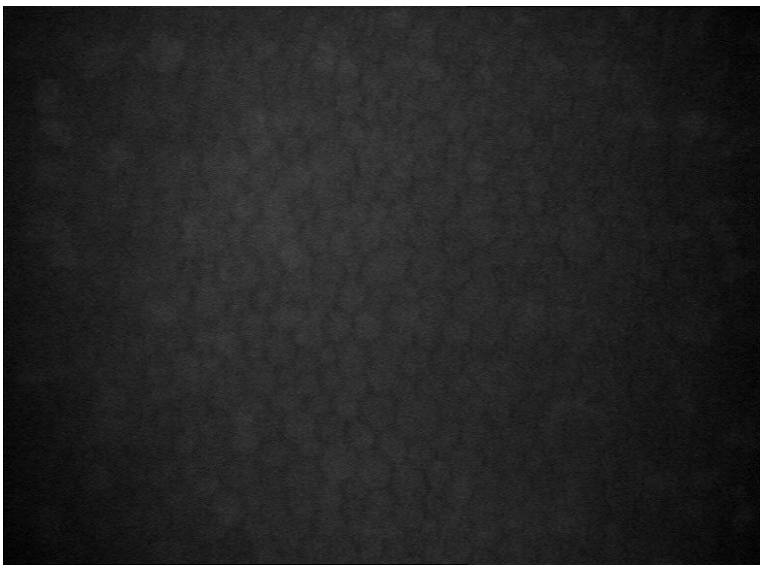

Figure 3: Confocal microscopy image showing polymegathism and pleomorphism in a diabetic

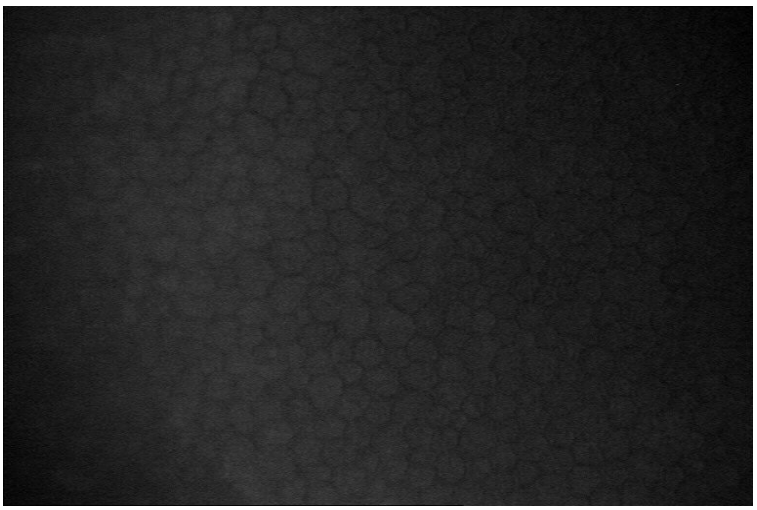

Figure 4: Confocal microscopy image showing endothelial cells in a normal control