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ORIGINAL ARTICLE

Influence of Orthostasis and Daytime on Retinal Thickness in Uveitis-Associated Cystoid Macular Edema

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ABSTRACT

Aim: To identify influence of orthostasis and daytime on retinal-thickness in cystoid-macular-edema (CME) using SD-OCT.

Methods: In this cross-sectional study 18 eyes with uveitis-associated CME (uvCME) were included. Orthostatic-changes of retinal-thickness were analyzed using a Cirrus™ SD-OCT. Retinal-thickness was measured with patients lying horizontally on their side, followed by a fast sitting-up and OCT-measurement in sitting-position. Diurnal-change in thicknesses were assessed by Spectralis™ OCT between 8 AM and 8 PM.

Results: Approximately 20 s elapsed between position-change and the following OCT-measurement. In horizontal-position, the mean central retinal thickness (CRT) was $496 \pm 37\,\mu m$, in upright position, the mean CRT was reduced to $412 \pm 43\,\mu m$ ($p = 0.032$), thus position-change led to a 17% decrease in CRT. None of the other ETDRS-subfields showed a statistically significant decrease in thicknesses ($p > 0.05$). In the second experiment, diurnal-CRT decreased over time, whereas the main decrease happened in the morning (8 a.m. $559 \pm 35\,\mu m$, 12 p.m. $533 \pm 36\,\mu m$, 4 p.m. $538 \pm 32\,\mu m$, 8 p.m.$551 \pm 38\,\mu m$, $p = 0.01$). Thicknesses in all other ETDRS-subgrids did not decrease statistically significantly.

Conclusions: Intraretinal-fluid in uvCME may show a high mobility: CRT decreases within seconds after a patient changes position, indicating that position effects retinal-thickness. Main diurnal-decrease in CRT occurs before noon, which is likely due to a position-change in the morning. Patient-population (walk-in patients versus hospitalized, lying patients) and previous waiting-position should be considered when interpreting retinal-thickness in clinical-practice.

Keywords: Circadian rhythm, CME, cystoid macular edema, diurnal changes, intraretinal fluid distribution, orthostasis

INTRODUCTION

Cystoid macular edema (CME), which results in impaired vision, is associated with many ophthalmic diseases.[1] Although the exact mechanisms by which it develops are not clear, CME in uveitis is known to be caused by an increase in retinal vascular permeability mediated by a variety of inflammatory agents.[2] In 1982, a circadian change in visual acuity (VA) was reported in patients suffering from CME,[3] which was proposed to be caused by a diurnal variation in retinal thickness. More than 20 years later, a diurnal variation in central retinal thickness (CRT) was demonstrated in diabetic macular edema (DME).[4] A subsequent study in which Stratus™ optical coherence tomography (OCT) was used showed a similar change but only in patients with

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DME whose CRT was more than 300 μm in the morning.[5] Today's high resolution spectral-domain (SD) OCTs like those from Spectralis and Cirrus allow a more precise retinal evaluation. In particular, the eye tracking system of the Spectralis OCT allows the exact same position of the retina to be scanned at every follow-up visit, making highly accurate evaluations of thickness changes over time possible.

Previous studies suggested that clinically relevant diurnal changes in DME and central retinal vein occlusions are most likely due to orthostatic mechanisms.[5,6] The present study was the first to analyze retinal fluid mobility during the daytime and the influence of rapid orthostatic changes on fluid distribution and retinal thickness in uveitis patients, using a new high definition SD-OCT.

Possible factors confounding retinal thickness are of great importance because CRT is still commonly used for evaluating treatment efficacy and the need for further treatment.

METHODS

Patient Selection and Setting

This observational study included 18 eyes from 16 individuals with uveitis-associated CME (uvCME), recruited at the Department of Ophthalmology, Vienna General Hospital, Medical University of Vienna. Untreated eyes with new-onset uvCME and eyes with chronic recurrent uvCME for $\geq$3 months were included. To assure good image quality and accurate grading, patients with lens opacities greater than 2 in the Lens Opacities Classification System (LOCS) and active uveitis (more than +0.5 anterior chamber cells and more than +1 anterior chamber haze or vitreous haze according to the SUN working group classification) were excluded.[7] Patients with vitreomacular traction or an epiretinal membrane on SD-OCT were also excluded. Patients presenting comorbidities which can cause CME like diabetes mellitus, vascular occlusion and age-related macular degeneration were excluded to avoid confounding factors of fluid behavior, e.g. new vessels or abnormal intravascular pressure levels. To eliminate further confounding factors an initial SD-OCT scan was graded to ensure retinal or choroidal scars/fibrosis and fibrin exudation or maculopathies were absent and that the external limiting membrane, photoreceptor layer and retinal pigment epithelium were intact. Scans were taken at a room luminescence of 12 cd/m^2. Each patient agreed to participate in the clinical study, accepted the study protocol and gave informed consent before entry. The study design adhered to the tenets of the Declaration of Helsinki, was approved by the local ethics committee and registered at clinicaltrials.gov (NCT 01299129).

Patients with a confirmed diagnosis of CME yet not receiving any treatment attended the Department of Ophthalmology at 7.15 a.m., when starting with the right eye, each eye was tested for best-corrected visual acuity (BCVA) using the ''Early Treatment Diabetic Retinopathy Study'' (ETDRS) charts at 4 m.[8] Pupils were then dilated and eyes examined with SD-OCT (OCT Spectralis^{TM}, Heidelberg Engineering GmbH, Heidelberg, Germany, Software Version 1.6.5.4) at 8 am, 12 pm, 4 pm and 8 pm The orthostatic test, which measured the retinal thickness with patients in a lying followed by a sitting position was performed at 4 pm using a Cirrus^{TM} SD-OCT (Software version 4.0, Carl Zeiss, Meditec Inc., Dublin, CA). The two different imaging-devices were chosen because Spectralis^{TM} SD-OCT offers the follow-up function, ideal for the exact observation of retinal thickness changes, and Cirrus^{TM} SD-OCT allows fast scanning in lying and sitting position, which is required to observe changes in thickness within seconds.

Study Variables

Diurnal Thickness Change

SD-OCT was performed by one OCT-certified ophthalmologist using a Spectralis^{TM} OCT. Spectralis^{TM} OCT section scans with 37 B- scans, 20 × 15 and 6 mm scan-length each were performed. If necessary, a center point for accurate retinal thickness evaluation was adapted according to the foveal depression, foveal intraretinal-layer convergence, central photoreceptor detachment and optic nerve head location at the baseline visit. Scans at 12 p.m., 4 p.m. and 8 p.m. were performed with the follow-up function. Any line errors were corrected with the Heidelberg software. Retinal thickness was measured from the inner limiting membrane (ILM) to the Bruch's membrane according to the Spectralis^{TM} OCT software. Afterwards, CRT was evaluated at the central millimeter. The remaining ETDRS subgrids were divided into inner inferior (IF), inner superior (IS), inner nasal (IN), inner temporal (IT), outer inferior (OI), outer superior (OS), outer nasal (ON) and outer temporal (OT) subfields. ETDRS volume was calculated by summing all nine ETDRS grid subfield volumes.

Orthostatic Thickness Change

The rapid orthostatic retinal thickness measurements were performed with a Cirrus^{TM} SD-OCT using the macular cube 512 × 128 scans. The nine ETDRS subfield grid-regions listed above and the ETDRS volume were evaluated with patients in a lying and in an upright sitting position. The patients were first positioned lying horizontally with horizontal head position on their side on a tiltable examination table. The study eye was always the upper eye. Their blood pressure and pulse were measured until stable for

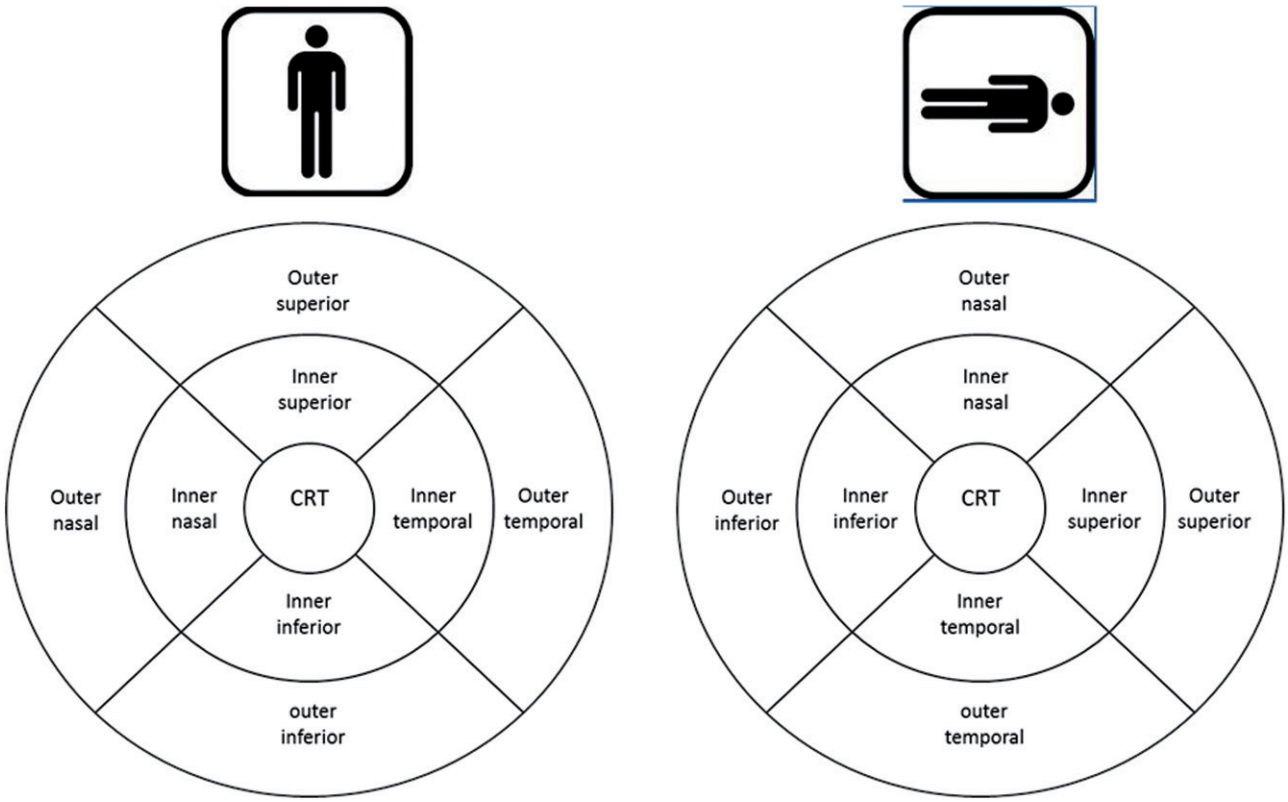

FIGURE 1. Orthostatic measurement procedure: When the left eye was scanned patients were lying on their right side. Thus, the ETDRS grid was turned 90° clockwise. When the right eye was scanned patients were lying on their left side, hence ETDRS was turned anticlockwise. Here the potential scan of a left eye is shown with the patient in a lying position.

2–3 min as usually performed in tilt table tests. Then OCT was performed while the patient was in this lying position. Afterwards, a chair was prepared and the height of the Cirrus^{TM} OCT was adapted to the scan in normal sitting position. Patients were instructed to sit on the chair as fast as possible and SD-OCT examinations were generated as fast as possible.

The center point position and line errors were adjusted before thickness evaluation. Retinal thickness was measured from the ILM to the retinal pigment epithelium according to the Cirrus^{TM}OCT software. The ETDRS subgrid was turned 90° clockwise or anti-clockwise for the thickness evaluation, according to whether the left or right eye was being scanned in lying position (Figure 1). Based on the lying position, the temporal subgrids were always the bottommost subgrids.

Statistical Analyses

Statistical analyses were done using R (www.r-project.org) and SPSS 11.5 (SPSS Inc., Chicago, IL). Diurnal data were analyzed by repeated measures ANOVA. Both eyes were included in further statistical analyses in cases of bilateral uvCME. Data were mean-scaled because there was more than a twofold variance in CRT between individual patients at 8 a.m. (range from 411 μm to 879 μm) and therefore the mean CRT of all patients at each time point would not reflect the mean diurnal course within daytime. The mean CRT for every individual patient was then calculated by summing up CRT data for all four time points and dividing this sum by the mean. Afterwards, each single CRT value from every patient was divided by its individual mean. Subsequently, not the mean of the absolute values, but the mean of percent changes was evaluated, showing the course of diurnal variation. The significance level was set to ≤ 0.05. A p-value correction with Bonferroni-Holmes was done for a multiple t-test evaluation of ETDRS subgrids, CRT and retinal volume in the orthostasis examination. Data were indicated as the mean and standard error. The median, 25% and 75% percentiles were shown in box plot graphics.

RESULTS

All 18 eyes of 16 patients could be included in the analysis (10 women, six men). Seven patients had new onset uvCME and nine patients had chronic recurrent uvCME with a mean duration of 14.9 ± 9.8 months (mean $\pm$ SD). Thirteen patients (72%) presented subretinal fluid and cystoid macular edema and five

patients (28%) presented with cystoid macular edema only. The mean age was 48.2 ± 13.5 (mean $\pm$ SD) and the mean ETDRS BCVA was logMAR 0.53 ± 0.3. Six patients had previously suffered from anterior and ten from intermediate uveitis. Two patients had ankylosing spondylitis and one rheumatoid arthritis. The three patients with systemic involvement were on stable systemic immunosuppressive therapy (two patients with anti-TNFα and methotrexate [MTX] and 1 with MTX and 7.5 mg prednisolone). The remaining 12 patients did not have a known systemic inflammatory disease. None of the patients received previous treatment for current uvCME. Mean rising time was 6 a.m. (range 5.20 a.m.–6.30 a.m.)

Rapid Orthostatic Thickness Change

The total time elapse between the position change and OCT measurement was approximately 20 s. In the horizontal position, the mean CRT was 496 ± 37 μm in the 512×128 macular cube scans (median 484.5 μm, Figure 2A). In the upright position, the mean CRT was 412 ± 43 μm (median 372 μm, Figure 2A), (uncorrected p value = 0.004, corrected $p = 0.032$). None of the eight other subfields showed a statistically significant decrease in thicknesses after Bonferroni-Holmes correction for multiple testing (Table 1). The ETDRS volume also did not change statistically significantly. The mean ETDRS volume was $12.42 \pm 0.9\,mm^3$ (median $12.1\,mm^3$, Figure 2B) in the lying position and $12.36 \pm 0.9\,mm^3$ (median $11.9\,mm^3$, Figure 2B, $p = 0.88$) in the upright position (Table 1).

Absolute CRT reduction due to position change did not differ between the new onset uvCME patients and the chronic recurrent uvCME patients (51 ± 25.2 μm versus 62.1 ± 35.6 μm, $p = 0.83$). CRT decrease is also impressively demonstrated in the Cirrus ILM-RPE map, generating a fully-fledged dent (Figure 3).

TABLE 1. Orthostatic ETDRS subfield region and retinal volume thicknesses.

	Lying (μm)	Sitting (μm)	p Value (Bonferroni-Holmes corrected)
Inner ETDRS field			
CRT	496 ± 37	412 ± 43	0.032*
Inner inferior	449.9 ± 26.6	407.3 ± 34.9	0.1
Inner superior	433.3 ± 27.8	426.1 ± 33.8	0.5
Inner nasal	444.8 ± 25.5	419.8 ± 29.8	0.1
Inner temporal	431.8 ± 31.4	419.7 ± 35.9	0.3
Outer ETDRS field			
Outer inferior	351.5 ± 24.2	336.1 ± 22.4	0.2
Outer superior	362.3 ± 23.8	355.6 ± 26.8	0.5
Outer nasal	364.8 ± 22.6	371.5 ± 27.2	0.4
Outer temporal	324.1 ± 27.1	321.6 ± 34.4	0.9
ETDRS volume (mm^3)	12.42 ± 0.9	12.36 ± 0.9	0.8

*$p \leq 0.05$.
Orthostatic change in individual subfield thicknesses and in ETDRS volume in a lying compared with a sitting position. 20 s passed between these two measurements. CRT= central retinal thickness.

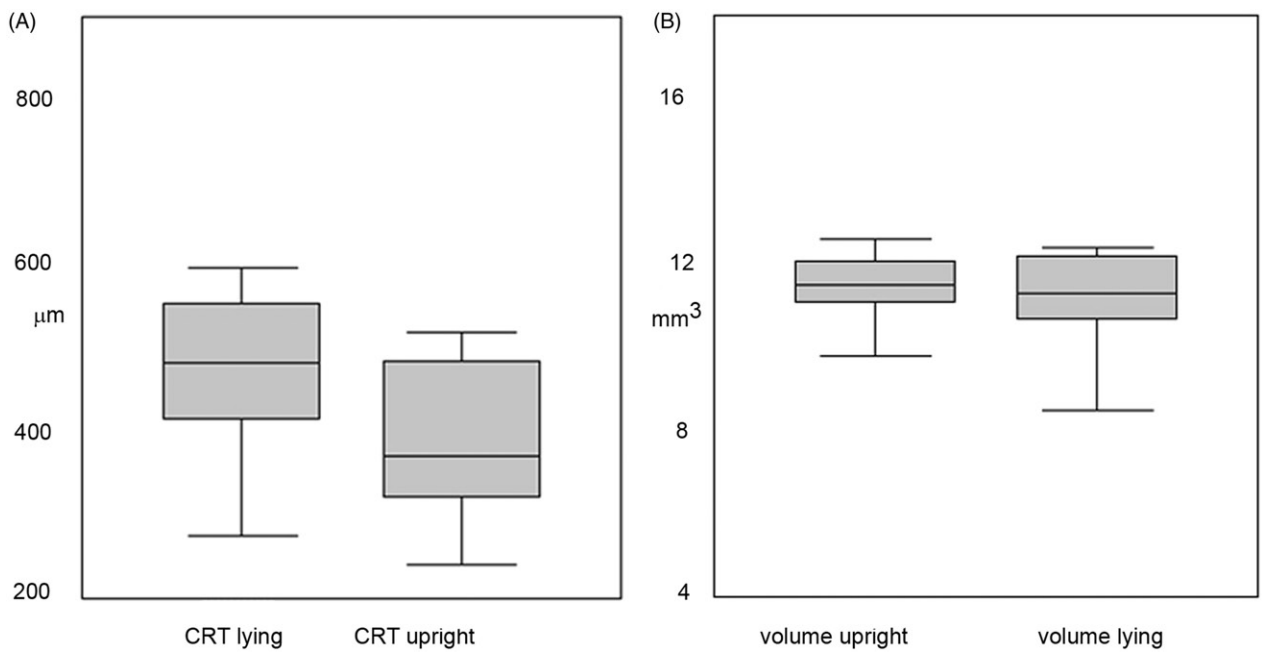

FIGURE 2. (A) Median of central retinal thickness (CRT in μm) in patients in horizontal position, and median of CRT in an upright position, measured immediately after changing to the upright position. (B) Median of retinal volume (mm^3) in the patients in a horizontal position and median of retinal volume in an upright position, measured immediately after changing to the upright position.

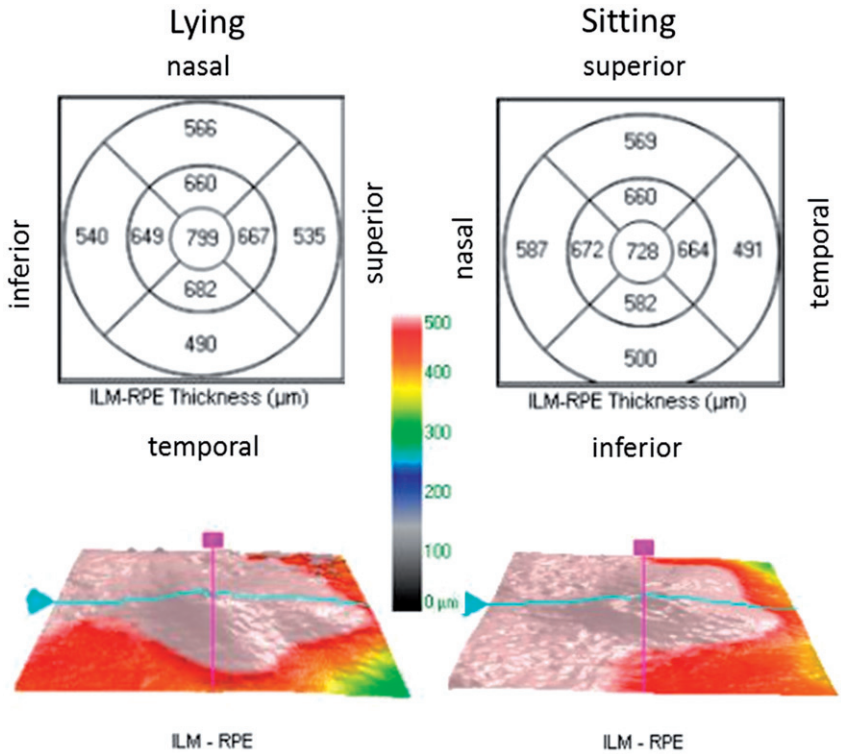

FIGURE 3. An example of the fast orthostatic thickness decrease within 20 s. The affected left eye was initially scanned with the patient in a side lying position with the nerve head turned 90° clockwise. Afterwards, a scan was performed as fast as possible in sitting position. In the ETDRS subfields the fast thickness change within the subfields, especially the statistically significant decrease in the central subfield, is visible. Accordingly, this decrease is visible in the ILM-RPE map, generating an impressive fully-fledged dent.

TABLE 2. ETDRS subfield region and volume thicknesses within 12 h.

	8 a.m.	12 p.m.	4 p.m.	8 p.m.	*p* Value (ANOVA)
Inner ETDRS field					
CRT	559 ± 35	533 ± 36	538 ± 32	551 ± 38	0.01**
Inner inferior	497.8 ± 33.2	487.0 ± 31.4	468.5 ± 26.3	465.2 ± 23.6	0.1
Inner superior	459.3 ± .40.3	455.7 ± 38.1	451.3 ± 25.8	450.6 ± 26.9	0.3
Inner nasal	475.7 ± 31.4	464.9 ± 31.4	461.2 ± 24.4	474.4 ± 26.2	0.5
Inner temporal	480.5 ± 27.2	462.5 ± 33.7	463.0 ± 26.3	464.0 ± 30.3	0.2
Outer ETDRS field					
Outer inferior	402.0 ± 36.3	396.3 ± 34.9	386.1 ± 27.7	364.8 ± 22.6	0.1
Outer superior	375.4 ± 33.1	379.8 ± 30.5	367.5 ± 25.4	388.4 ± 29.6	0.5
Outer nasal	397.9 ± 26.5	392.6 ± 28.7	381.2 ± 23.3	395.6 ± 24.7	0.4
Outer temporal	378.5 ± 2.9	372.6 ± 24.9	356.4 ± 18.4	355.6 ± 19.5	0.1
ETDRS volume (mm^3)	10.64 ± 1.1	10.56 ± 1.4	10.2 ± 1.1	10.17 ± 1.1	0.2

Diurnal change in individual subfield and ETDRS volume thicknesses within 12 h measured at 8 a.m., 12 p.m., 4 p.m. and 8 p.m. CRT= central retinal thickness. **$p \leq 0.01$.

Diurnal Thickness Change

In addition to the fast orthostatic regulation, we analyzed the changes of retinal thickness during the day, from 8 a.m. to 8 p.m. When evaluated by repeated-measures ANOVA, CRT showed a statistically significant decrease compared with 559 ± 35 µm at 8 a.m. (12 p.m. 533 ± 36, 4 p.m. 538 ± 32, 8 p.m.551 ± 38, $p = 0.01$), whereas changes of the ETDRS volume ($p = 0.2$) and other ETDRS subfields were not statistically significant (Table 2). The diurnal course of CRT is shown in Figure 4. As pictured, most of the thickness change occurred between 8 a.m. and 12 p.m.

Mean diurnal CRT-decrease from 8 a.m. to 8 p.m. of new onset uvCME and chronic-recurrent uvCME did not differ (14.3 ± 6.6 versus 19.7 ± 4.7, $p = 0.57$).

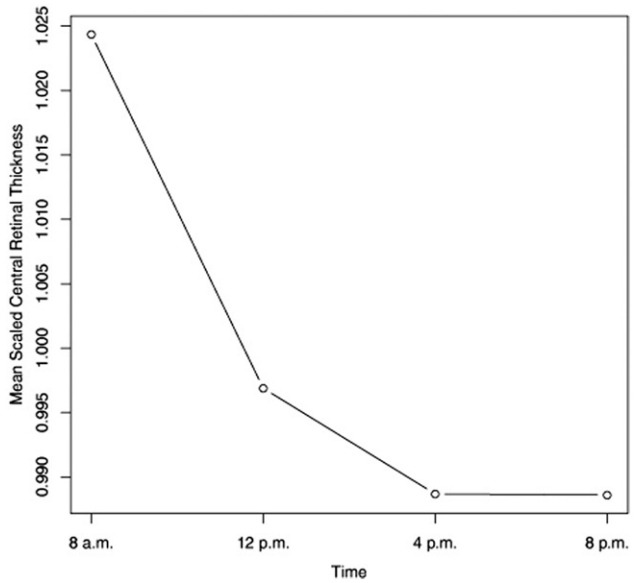

FIGURE 4. Mean scaled diurnal changes of central retinal thickness (CRT) over 12 h between 8 a.m. and 8 p.m. Data from each timepoint for each subject were summed and divided by the mean value. Consequently, not the mean of the different time-points, but the diurnal course was evaluated and the decrease in CRT is visible.

DISCUSSION

In the present study, we demonstrated a fast decrease up to 20% in CRT without a significant decrease in total retinal thickness within seconds after a change from a lying to an upright position. We also found a diurnal decrease of about 4% from 8 a.m. to 8 p.m. with a peak before midday.

Diurnal Fluid Mobility and Thickness Decrease

A diurnal decrease in retinal thickness, especially in CRT, has been shown in previous studies of DME.[5,9,10] The present study used SD-OCT to evaluate diurnal changes, ETDRS subfield thickness and ETDRS volume in uvCME patients. Our data confirm the previous assumptions that orthostatic and hydrostatic pressures may play a major role in the diurnal CRT decrease and fluid (re-) distribution.[4,5,9] As has been noted before we also observed a remarkable CRT decrease in the morning between 8 a.m. and 12 p.m., supporting the important role of the orthostatic pressure on retinal thickness. Also the failure of retinal artery contraction, previously described in DME, leading to an increase in the ocular perfusion pressure in recumbent position, might be responsible for the increased CRT value in the morning.[11,12] Other factors which might be associated with this diurnal change have already been evaluated in previous studies: Cortisone levels and serum osmolality seem to influence CRT in CME, whereas light intensity, aldosterone concentrations, HbA1c and blood pressure showed no apparent influence. Arterial blood pressure as a confounding factor is a controversial discussion.[10,13–15]

Most previous studies investigated central thickness, but the evaluation and the use of OCT-devices were heterogeneous. Nevertheless, each study reported some kind of diurnal central thickness decrease.[6,9,13–16] Only a few studies evaluated parafoveal diurnal thickness changes beside CRT,[10,13,15,16] and only Polito et al. evaluated diurnal changes in ETDRS subfields in CME.[5] Thus, Polito et al.'s results seem most comparable to our findings. They found a statistically significant diurnal thickness decrease in 7 of the 9 ETDRS subfields of nine patients with DME greater than 300 µm.[5] Macula thicknesses with a CRT < 300 µm did not decrease significantly.[5] In our study all nine ETDRS subfields showed increased thickness values compared with the ETDRS subgrid thicknesses of healthy eyes evaluated in a previous study and each patient had an initial CRT > 300 µm.[17] However, while CRT changed statistically significantly, the other subfields and retinal volume did not significantly change. The differences between our results and those of that study might be due to the different imaging devices used and their different segmentation algorithm.[18] Polito et al. used Stratus OCT and in our study Spectralis™ OCT was used. The time-domain OCT (TD-OCT) uses six radial scans and thus examines only 5% of the macula. The retinal volume is then extrapolated between the six radial scans. A difference in retinal thickness outcome between these two devices seems therefore reasonable and was already reported in previous studies.[19,20]

Rapid Orthostatic Fluid Mobility

Starling's law has been discussed as a possible factor for diurnal thickness decrease.[14] Capillary tonicity, blood hydrostatic pressure, blood colloid osmotic pressure, interstitial fluid hydrostatic pressure, interstitial fluid colloid pressure and vascular permeability generate an equilibrium. Additionally due to possible failure of arterial blood flow control (so far described in DME), supplementary extracellular fluid accumulate in recumbent position due to increased ocular perfusion pressure.[11,12] According to these factors, the retinal capillary intravasal hydrostatic pressure would decrease and reduce fluid leakage in standing position.[14] Our findings demonstrate CRT decrease without statistically significant changes in ETDRS volume. Hence, additional mechanisms causing local thickness changes in CME seem possible. Eventually, a continuous reallocation of intraretinal and subretinal fluid occurs due to changed orthostatic conditions and gravity, while a stable oncotic pressure and osmotic

gradient, built up by continuously leaking albumin, stabilizes and maintains retinal volume.[21] It has been proposed that a single cystic space rather than multiple cysts delineated by tissue structures exists in CME.[22] Since intraretinal fluid interconnects, intraretinal fluid may simply redistribute with rapid changes of position. Also, subretinal fluid may simply shift according to gravity and orthostatic conditions. Unfortunately only macular thickness and volume can be examined, precluding detection of possible thickness changes in the retinal periphery. The shift/re-shift of fluid from outside the ETDRS-subgrid may also hide possible significant thickness changes due to position change, especially in the bottommost subgrids.

Orthostatic regulatory mechanisms such as activation of the sympathetic nerves by stimulation of baroreceptors in the carotid sinus and aortic arch, due to reduced venous return and decreased cardiac output and inhibition of parasympathetic nerves prevent hypotension during positional changes. This positive sympathomimetic activation leads to temporal inotropic and chronotropic heart activation and vasoconstriction. Stroke volume can decline up to 40% during positional changes. Retinal circulation is lacking autonomic nervous innervation,[23] thus immediate reduction of retinal blood flow due to the change of position may be insufficiently compensated by vasoconstriction. Beside the lack of autonomic nervous innervation, impaired autoregulation may also contribute to a fast change in CRT in uvCME. Hence, insufficient orthostatic reaction lacking adequate retinal arterial diameter increase and vein diameter decrease,[11,12] which was described in DME may also occur in uvCME. This may lead then to reduced intravasal hydrostatic pressure and therefore, reduced retinal thickness. In summary, the lack of autonomic innervation, reallocation of fluid, gravity and Starling's law may be involved in this fast central thickness decrease. But what happens after this fast 20% thickness decrease? We have already begun to examine the distribution of fluid after this fast decrease in more detail. Redistribution of fluid (and therefore CRT increase) seems to be as fast as the orthostatic phenomenon, but more observations are needed and the orthostatic and hydrostatic factors involved are under investigation. Longer follow-up of retinal-thickness in the recumbent position, in addition to the upright position, is also warranted to determine further retinal thickness changes in the ETDRS-subgrid in horizontal position.

Based on previous studies, and on the mechanisms discussed above, we assume that DME as well as CME due to retinal vein occlusion behave similarly. However, further evaluation is warranted to determine whether retinal thickness in neovascular age-related macular degeneration is also subject to fluctuation according to daytime, orthostasis and gravitation. Limitation of our study may be the limited sample size, making it difficult to explain possible changes in the ETDRS subfield. Examination of blood pressure while patients changed their position from lying to sitting was not possible, due to the nature of the study, i.e. investigating OCT-changes in the shortest possible interval between lying and upright position. Patients with autonomic dysfunctions may therefore not have been detected and such patients could react differently after orthostatic position changes; however, none of our patients indicated orthostatic symptoms.

So far, the dynamics of extracellular fluid in CME is poorly understood and needs further evaluation. In the meantime, patient population (walk-in patients versus hospitalized predominantly lying patients) and previous waiting position should be considered when interpreting retinal thickness in clinical practice.

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DECLARATION OF INTEREST

The authors indicate no financial support or financial or proprietary conflict of interest.

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