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Application of over-sampling nano-sensitive optical coherence tomography for monitoring corneal internal structural changes in corneal cross-linking

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ABSTRACT

Corneal cross-linking (CXL) has grown from an interesting concept to a practical clinical treatment for corneal ectatic disease globally in the past three decades. In both understanding the principle of how CXL proceeds and monitoring the clinical procedure, detection of structural changes during cornea CXL plays a significant role. This paper demonstrates a novel over-sampling nano-sensitive optical coherence tomography (osnsOCT) method, which is potential to detect nanoscale structural changes in various tissues, to simultaneously measure the structural variations during the corneal CXL treatment.

Keywords: Optical coherence tomography, nanoscale structure, cornea, Fourier transform

1. INTRODUCTION

Combining ultraviolet-A light and a photosensitizer (riboflavin), the cornea can be stiffened and progressive keratoconus can be effectively arrested. During the last three decades, corneal cross-linking (CXL) has already become a clinical treatment for cornea ectatic disease worldwide from the initial concept. To understand the principle of CXL and monitor the clinical procedure during the surgery, it is worthy to detect the structural changes during the CXL treatment. In this paper, we propose a novel non-invasive over-sampling nano-sensitive optical coherence tomography (osnsOCT) method, which is based on the spectral-domain OCT system but can differentiate nanoscale structure alterations, to monitor the internal changes during the CXL procedures. As a proof of concept, two periodic Bragg gratings samples are first used to verify the nanoscale sensitivity of the proposed osnsOCT method. The experimental results on *ex vivo* bovine eyes show that the spatial periods significantly decrease after subsequent UVA irradiation.

Corneal ectasia causes impaired quality of life [1] and is a key clue for corneal transplantation [2]. Keratoconus is an ocular disorder characterized by corneal degeneration due to corneal thinning that results in a focally deceased radius of corneal curvature, abnormal wavefront aberrations and other reduced biomedical

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properties [3-5]. Corneal cross-linking (CXL) using a photosensitizer riboflavin and ultraviolet-A light (UVA) with a 365 nm wavelength has already become a clinical treatment for progressive keratoconus and currently is the only therapeutic approach that is able to halt disease progression [6]. In order to better understand the principle how CXL proceeds and assess the clinical treatment, it is worthwhile to monitor the corneal internal structural changes during the CXL process. The structural changes inside the cornea is potential to provide more details which would improve our knowledge of disease progression and our ability to assess treatments.

Optical coherence tomography, which is an interference-based modality, has been widely applied especially in ophthalmology. Nonetheless, the axial resolution of OCT is always limited in micrometer level due to the narrow bandwidth of light source, which is not suitable to detect sub-micron structures [7-10]. Recently, a novel technique called nano-sensitive optical coherence tomography, which was proposed to retain the high spatial frequency information in OCT image, has the ability of detecting nanoscale structure alterations in tissues [11-14]. The previous publications has illustrated the theories and the data processes to achieve nano-sensitive OCT approach. Based on the principle of nano-sensitive OCT, here we propose a further sensitivity-improved version by over-sampling the spatial frequency windows. For every single pixel on the image, the dominant spatial period is evaluated through locating the maximum amplitude in the spatial frequency profile and the corresponding median spatial period in each divided window, therefore the narrower window would bring out a higher spatial sensitivity. In this paper, we propose an over-sampling nano-sensitive OCT method to monitor the internal structural alterations during the CXL treatment on *ex vivo* bovine eyes.

2. EXPERIMENTAL RESULTS

Initially, as a proof of concept demonstration, two periodic Bragg gratings with different periodicities from Corp. OptiGrate (Florida, United States) are used as the samples. We place an infrared card (random structural sizes) and two Bragg gratings (with 441.7 nm and 431.6 nm periodicities, respectively) together in one imaging area as shown in Fig.1. Each periodic layer was fabricated with sinusoidal refractive index varies 1.483 ± 0.001. No variation in periodicity vs time if temperature of usage is <400°C (period will be stable better than 1 pm). A commercial spectral domain OCT (SDCOT) system Telesto III (Thorlabs, Inc.), whose axial resolution is 5.5 μm and imaging depth is 3.5 mm in air, is used for the OCT imaging and spectra raw data acquisition. The conventional OCT B-frame image is reconstructed as shown in Fig.1(a), which includes infrared card, 441.7 nm and 431.6 nm Bragg gratings (from left to right). It is impossible to measure their internal structural differences using conventional OCT method. However, the osnsOCT image would present more information related to internal structural variations. As shown in Fig.1(b), we could clearly see the differences between the three samples: 1) the result of infrared card presents various colors, which illustrate the random structures inside; 2) the middle sample (441.7 nm) shows a larger dominant structure size compared with the right sample (431.6 nm). Even the structural difference between two Bragg grating is around 10 nm, we would still be able to clearly detect.

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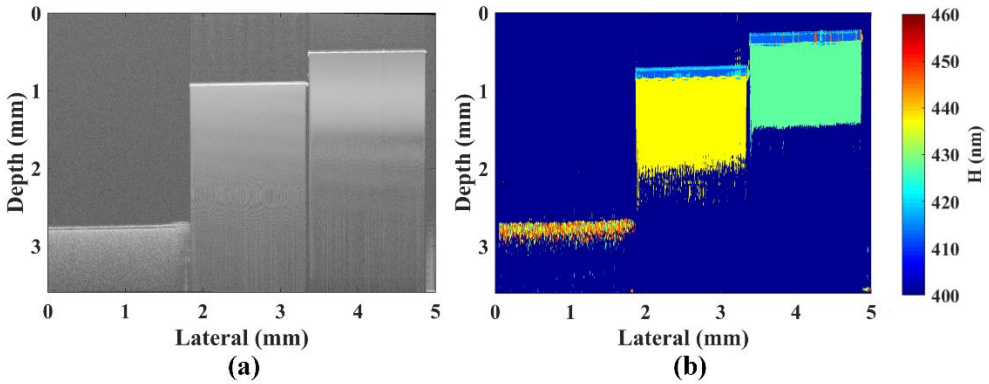

Figure 1. (a) The conventional OCT image of infrared card, 441.7 nm Bragg grating and 431.6 nm Bragg grating (from left to right); (b) the corresponding osnsOCT image showing different structure differences between threes samples. The color bar presents the spatial periods with unit nanometer.

From the experimental demonstration, one see that osnsOCT is an effective way to distinguish nanoscale alterations. Furthermore, the depth information that can be captured in conventional OCT is also reconstructed in the proposed method. We apply osnsOCT as a potential way to investigate the corneal internal structural changes, which would provide finer structural details to better understand how CXL influence corneal stiffness and monitor the treatment during the CXL treatment.

In the experiments, bovine eyes were harvested in the evening of slaughter from a local abattoir (Athenry Quality Meats Ltd, County Galway, Ireland) within 2 hours post mortem and stored at 4°C. The abattoir granted permission for the eyes to be used in research. Eye globes with intact epithelium and clear cornea were selected for the *ex vivo* studies. Following the so-called "Dresden" protocol, which is the current standard approach for corneal CXL, we use a photosensitizer riboflavin and ultraviolet-A light (UVA) with a 365 nm wavelength for the CXL treatment. First the epithelium is removed before dropping riboflavin known as a epi-off cross-linking process. Then we keep dropping riboflavin every second minute and 30 minutes in total, after that the UVA light with 3.0 mW/cm^2 irradiance is cumulated on the cornea for another 30 minutes until the end of the CXL treatment.

As shown in Fig.2, both of the conventional OCT B-frame images and osnsOCT images were recorded before and after the CXL treatment. Fig.1(a) and (b) present the OCT images of virgin cornea (without any treatment) and treated cornea, respectively. We could not see any obvious structural variations from conventional OCT images. However, the spatial period alterations can be easily detected by osnsOCT method, as illustrated in Fig.2(c) and (d). One can see that the dominant structural size turns to be smaller after CXL treatment since the dominant color has a significant blue shift.

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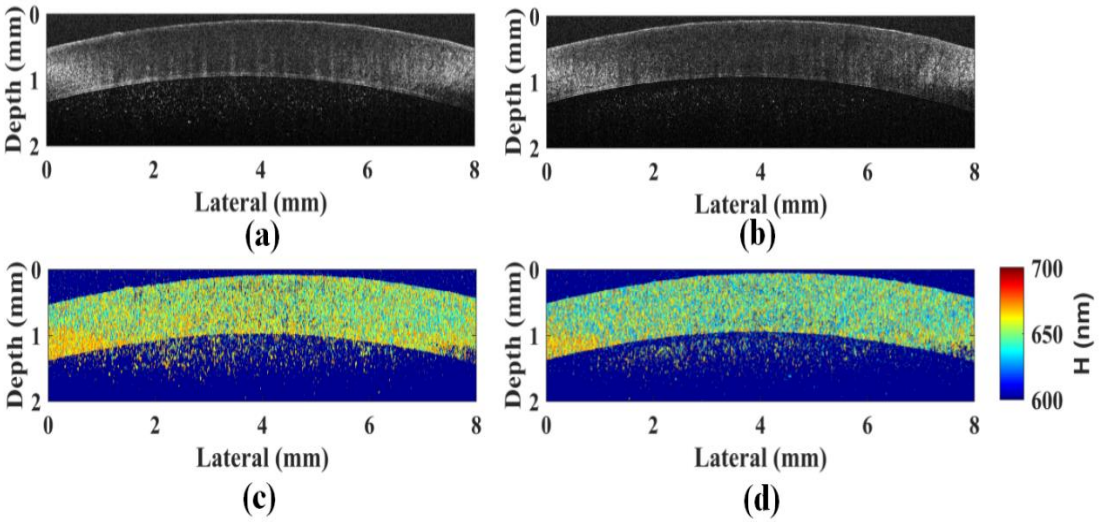

Figure 2. (a) The conventional OCT image of bovine cornea before treatment; (b) the conventional OCT image after corneal cross-linking treatment; (c) the corresponding osnsOCT image of bovine cornea before treatment; (d) the corresponding osnsOCT image after the cross-linking treatment. The color bar presents the spatial periods in the range from 600 nm to 700 nm.

3. CONCLUSION

In conclusion, this paper proposes a novel osnsOCT method, which can exact extra high-frequency information from raw interference spectral data, to detect the nanoscale alterations inside cornea during the CXL treatment. Results on *ex vivo* bovine eyes have shown that the corneal internal spatial periods change to be smaller after the CXL treatment. The proposed method can be implemented using existing OCT system, without any additional components, therefore it can be relatively straightforward to be applied in *in vivo* tissues and translated to clinical use as a novel imaging system. Furthermore, this non-invasive and fast method can be applied for assessing the corneal CXL treatment procedure and is potential to a real-time monitoring tool in clinics.

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