Diurnal Variation of Central Corneal Thickness and Intra-Ocular Pressure in Normal and Suspect Glaucomatous Eyes: A Review

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ABSTRACT

Normal physiological variations in central corneal thickness (CCT) are important as they provide a reference parameter for experimental and clinical research particularly in the field of glaucoma prediction and assessment. The literature has established that significant diurnal fluctuations in CCT occur in persons with no ocular pathology when CCT has been assessed over a 12-48 hour period. The consensus in the literature is that CCT is thickest in the morning upon awakening and gradually thins as the day progresses, with the greatest proportion of this variation occurring in the first three hours after awakening. Studies that have attempted to establish whether a diurnal variation in CCT exists in glaucomatous eyes have not been successful. To date, significant developments, although variable, have been made to better understand diurnal variation in CCT in individuals with no ocular pathology. This signifies the importance of monitoring CCT throughout the day in those individuals who may be at risk of developing glaucoma, as opposed to those individuals who already suffer from glaucoma, as it will ensure that the timing of glaucoma treatment will not be overlooked. This review discusses the current opinion on diurnal CCT in those individuals who have no ocular pathology and in those who are glaucoma suspects. It will also focus on the significance of diurnal variability with CCT and its relationship to intra-ocular pressure (IOP) diurnal variation.

Keywords: Central corneal thickness, intra-ocular pressure, diurnal variation, glaucoma

INTRODUCTION

Many of the body's physiological systems, such as blood pressure and glucose regulation[1,] have been found to vary over a 24 hour cycle.[2,3] Important parameters used for assessing the health of the eye, particularly intra-ocular pressure (IOP) and central corneal thickness (CCT) have also been shown to fluctuate over the period of a day. These rhythms may be either circadian (driven by an endogenous clock) or diurnal (driven by the cycle of light and dark).[4] Since the early 1980's a great deal of research[3,5,6,7] has been conducted on individuals with no ocular pathology to assess the diurnal variation of CCT. The mean CCT in the population varies between 535μm and 550μm depending on the race of an individual with African Americans having on average thinner corneas than Caucasians, Asians and Hispanics[8]. Normal physiological variations in CCT are important as they provide a reference parameter for experimental and clinical research particularly in the field of glaucoma prediction and assessment.[2,4,6]

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Glaucoma is an optic neuropathy characterised by cupping of the optic nerve head with corresponding nerve fibre loss and visual field defects.[9,10,11] The relevance of CCT to glaucoma assessment is in its influence on IOP testing. IOP, along with the optic disc and visual field assessment of an individual, are important parameters for glaucoma detection with the "gold" standard IOP evaluation (via a Goldmann tonometer) being set for a mean CCT of 545μm.[2,8,12,13] A deviation in CCT from the set 545μm would therefore produce inaccurate IOP measurements. This suggests that CCT variations are imperative when monitoring those individuals who are at risk of developing glaucoma as a variation in CCT throughout the day would cause a correspondingly different IOP measurement. Hence, the timing of treatment or current topical regimen for an individual may be overlooked if these factors are not considered.[7]

It has been well established throughout the literature that a significant diurnal fluctuation in CCT occurs in subjects with no ocular pathology when CCT has been assessed over a 12-48 hour period.[3,5,4] The consensus in the literature is that CCT is thickest in the morning upon awakening and gradually thins as the day progresses, with the greatest proportion of this variation occurring in the three hours after awakening.[3,4,5] More recent studies on individuals with no

ocular pathology,[5] and those who are glaucoma suspects,[7] which have explored daytime (circadian) variations in CCT and its relationship to the circadian variations in IOP have not been in agreement of the importance of regular CCT examination.[6,7] Furthermore, inconsistent findings in the literature have left many researchers with conflicting views on the status of the relationship between CCT and IOP with some believing that CCT varies independently to IOP[6,7] whilst others believe that there is a dependent relationship between the two.[13,14] It still remains unclear whether overnight changes in CCT are truly representative of the diurnal variation occurring throughout any 24 hour period. Or, whether CCT fluctuates significantly through the day and also if the pattern of corneal thickness is the same on successive days.[5]

This review compares those researchers who have[3,5,7] and have not[6,7] found a statistically significant diurnal variation in CCT in participants with no ocular pathology and those who are glaucoma suspects and reasons as to why the conflicting findings are proposed. This review will further highlight the importance of diurnal CCT testing in the early intervention of glaucoma.

DIURNAL VARIATION OF CCT AND IOP

Harper et al[5] conducted a cross sectional study on eight subjects to elucidate the diurnal variation in human CCT with no ocular pathology over a 48 hour period. They found a mean increase in CCT during sleep of 5.5% with a total mean deviation in CCT of 7.3%. This suggested that overnight changes in CCT were not truly representative of the diurnal variation in CCT as this study revealed a considerable variation during waking hours, and a much greater variation compared to that previously reported of 4%.[11] A study by Kiely et al[3] also found a relatively smaller percentage of CCT thinning throughout the day as compared to Harper et al[5]. However, there were notable differences between the Harper et al[5] and the Kiely et al[3] inclusion and exclusion criteria. Harper et al[5] utilised rigorous criteria such that only subjects free from ocular disease, had adequate tear production and were not contact lens wearers were included. Where applicable, no female participant was included whilst menstruating or ovulating at the time of the study, as increases in oestrogen are associated with an increase in CCT[15]. Furthermore, participants abstained from alcohol consumption and maintained a normal diet throughout the study, as acute alcohol intake has been shown to bring about temporary corneal oedema and a consequence cause an artificial thickening of CCT.[16]In comparison, Kiely et al[3] did not state any inclusion criteria that were adhered to and participants were only excluded on the basis of corneal pathology and contact lens wear. Other factors which could potentially influence CCT, as noted in Harper et al's[5] study, were not considered. In addition, Harper et al[5] utilised an ultrasonic pachymeter, which is a popular clinical method which offers good accuracy and reproducibility.[2,17] Kiely et al[3] on the other hand utilised a less recognised optical pachymeter, the Haag Striet pachymeter, which is not as accurate as ultrasound pachymetry as it has been shown to have a larger range of error.[18,19] Perhaps the most striking factor between the two studies that may help explain the differing results obtained is the sizeable age range of the participants included in the Harper et al[5] study. Harper et al[5] included subjects between the ages of 10 and 63 with a mean age of 38 years compared to that of a mean age of 20 years in the study conducted by Kiely et al[3]. The relevance of this in relation to CCT measurements is that as the human eye ages the corneal dynamics change in such a way that our endothelial cells tend to decrease in number and corneal epithelial cells take longer to regenerate, therefore making the corneas of an older population significantly thinner than those of their younger counterparts.[20,21] Harper et al[5] studied a more representative sample of individuals.

A study by Toit et al[4] on the diurnal variation of corneal sensitivity and thickness found similar results to that of Harper et al[5]. This study was performed on 20 non-contact lens wearers to assess the diurnal variation of corneal sensitivity and thickness over a 24 hour period. A 4% variation in CCT was found over the period of a day which is amid that found by Harper et al[5] (7.3%) and Kiely et al[6] (2.1%). However, a considerable variation of 1.3% to 7.2% suggested that the way in which CCT varies throughout the period of a day is not constant between individuals. Similarly to Harper et al[5], Toit et al[4] showed methodological strengths with a large population sample and a strict inclusion and exclusion criteria. Furthermore, both of these studies withdrew the use of local anaesthetic prior to CCT testing. This is important as local anaesthetic has been shown to have an artificial affect on CCT measurements through inducing lacrimation and resulting in a disruption to corneal epithelial cells.[22]

Limited studies[6,7] have been conducted that have specifically focused on the circadian variations of CCT and their relationship to diurnal IOP measures during daylight hours. As mentioned earlier, the relevance of this relationship is such that a relatively minor change in CCT may produce a clinically significant change in IOP measurements, as a thick cornea will lead to an overestimation of IOP and a thin cornea will lead to an underestimation.[7,8,13] Laiquzzaman et al[6] performed a study on 42 normal eyes and found the difference between the CCT values for any time period was not significant suggesting that IOP varies independently of the variation in CCT.

Like Laiquzzaman et al[6], Shah et al[7] also assessed the daily circadian fluctuations in CCT and IOP, however they studied 28 glaucoma suspects. Similar results were found showing no significant correlation between IOP and CCT in any patient, nor were there any significant correlations between

the mean diurnal variations of CCT and IOP. The reported average of CCT variation was less than 1%. Shah et al[7] should be acknowledged for their choice of equipment to measure CCT (ultrasonic pachymeter) and IOP (Goldmann tonometer), however a major failing of this study is that IOP was measured prior to CCT. CCT measurements can be affected following applanation tonometry due to the probe of the Goldmann tonometer damaging and possibly removing corneal epithelial cells as it takes an IOP measurement.[2] This may cause an artificial thinning of the CCT.

The times at which CCT is measured has varied considerably between researchers and may be a potential reason for the minimal diurnal variations found in CCT by Laiquzzaman et al[6] and Shah et al[7]. Harper et al[5] and Toit et al[4] performed CCT measurements over a 24 and 48 hour period. Even though the study by Harper et al[5] was conducted over a 48 hour period there was little difference in the total diurnal variation of CCT after the 24 hour mark. The mean CCT diurnal variation on day one was 7.1% compared to that of 7.4% on day two. A confounding feature of the study by Harper et al[5] that may explain the much higher percentage of fluctuation in CCT was the fact that corneal thickness was measured immediately before sleep when the cornea is theoretically at its thinnest then immediately upon awakening when the cornea is theoretically at its thickest. Consecutive measurements were then made at 15 minute intervals for the first hour followed by 30 minute intervals for the next 2 hours, followed by 2 hour intervals for the remainder of the day. It appears that Harper et al[5] administered this intense testing schedule to highlight the times in which CCT is assumed to vary the most, which is during the three hours after awakening.[3,4,5] Testing schedules for Toit et al[4] and Kiely et al[3] were not as involved as Harper et al[5]. They measured CCT at 1 hour intervals throughout the day with the only difference being that Toit et al[4] like Harper et al[5] measured CCT immediately prior to sleep. The pre-sleep CCT measurement was the lowest value obtained and was used as a baseline which could also explain the difference in the magnitude of the CCT diurnal variations seen in these studies.[28] Laiquzzaman et al[6] who performed CCT measurements during normal clinical consulting hours (8am, 11am, 2pm and 5pm) and Shah et al[7] who performed CCT measurements during extended clinical consulting hours (8am, 12pm, 4pm and 8pm) found no significant circadian fluctuations in CCT. These findings may be explained by the fact that CCT was only measured at 4 different times during this time frame and missed those times when CCT is at its thinnest and thickest. This is compared to a total of 16 CCT readings performed by Harper et al[5] and 13 conducted by Toit et al[4]. However, Laiquzzaman et al[6] and Shah et al[7] methodological design cannot be criticised as ophthalmological measurements such as CCT and IOP are generally carried out on patients during normal hospital or clinical consulting hours, this being between 8am and 5pm.[6]

It should also be noted that the number of pachymetry measurements taken at each time interval and the standard deviation of these measurements differed between studies. For example, in the study conducted by Harper et al[5] a total of 10 measurements were taken with a maximum standard deviation of 2μm. By doing this the reliability of recordings was strengthened given that if the standard deviation rose above 5μm, reliability would have decreased considerably.[5,23] However, this variable was at no point discussed by Laiquzzaman et al[6] making it difficult to assess whether this could have influenced the reported diurnal CCT variation.

Overall, results from the Laiquzzaman et al[6] and Shah et al[7] studies suggest that a single measurement of CCT is sufficient when assessing both individuals with no ocular pathology and those with suspected glaucoma. That is, a change in CCT would not predict a rise or fall in IOP. These results support the notion that IOP varies independently of CCT. However, the findings from these studies should be considered with caution as subjects were not age and sex-matched and local anaesthetic was instilled prior to the CCT measurements. Furthermore, the validity of their conclusions are uncertain as these studies both have methodological limitations and oversights. As the participants in the Shah et al[7] study exhibited either disc cupping or visual field loss the use of a control group that consisted of individuals with no ocular pathology for comparison would have been useful. Moreover, due to the fact that early glaucoma can show variable peaks in IOP, the finding by Shah et al[7] is unexpected as their population sample was one that had suspect glaucoma and one would therefore anticipate variable CCT measures through the day.[7,24] Therefore any generalizations drawn from this study could be considered unreliable. Unlike those studies conducted on individuals with no ocular pathology that have established a definite diurnal variation in CCT exists,[3,4,5] those that have attempted to investigate this trend in glaucomatous subjects have not been successful.[2,7] This can be seen in a study by Fogagnolo et al[2] who performed a cross-sectional study on 30 individuals with primary open angle glaucoma (POAG) and found minimal circadian variations in CCT (1.2%) that did not seem to interfere with circadian IOP assessment. This highlights that future research should focus on individuals with no ocular pathology rather than those with glaucoma. There is strong support that a diurnal variation in CCT does exist in individuals with no ocular pathology, however due to insufficient research6 the relationship between diurnal CCT and IOP in these individuals remains uncertain.

CONCLUSION

To date significant developments, although variable, have been made to better understand diurnal variation in CCT.[3,4,5,6] Harper et al[5] discovered a new revelation which opened the way for a better insight into diurnal CCT. They found that in addition to a significant increase in CCT during sleep a significant variation occurred during waking hours. Toit et al[4] and Kiely et al[3] further highlighted that

significant fluctuations in CCT do occur in subjects with no ocular pathology. The studies that have focussed on subjects with no ocular pathology[3,4,5] have been important in establishing that significant fluctuations in CCT do exist, with the consensus in the literature supporting that on average diurnal variation in CCT is 4% over a 24 hour period.[3] However, a major limitation of these studies is that they neglected to test the relationship between diurnal CCT and IOP. Furthermore, any generalisations drawn from the only study that did assess this relationship in subjects with no ocular abnormalities[6] are questionable due to methodological flaws. Future research would need to address these limitations in the methodological design in order to establish a better understanding of diurnal CCT and IOP in individuals without ocular pathology. A way of overcoming these short fallings are to ensure that future studies perform pachymetry prior to tonometry and a slit lamp examination should also be conducted before each CCT measurement to confirm the absence of corneal epithelial defects. This practice should be applied for reasons related to the effect of applanation tonometry on CCT measurements.[2] Furthermore, a sufficient sample size and the use of a single examiner with adequate expertise to minimise operator bias when taking measurements should also be adopted.[6]

Despite the differences reported by various researchers there is support in the literature that a diurnal variation in CCT does exist in the normal population. This signifies the importance of monitoring CCT throughout the day in those individuals who may be at risk of developing glaucoma as it will ensure that the timing of glaucoma treatment will not be overlooked through errors in the evaluation of IOP measurements. The relationship between the diurnal variation of CCT and its effect on IOP measurements is still an area that requires future research as there is disagreement in the literature as to whether the relationship between the two is dependant or not.

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