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Effect of diabetes mellitus on quantitative corneal anatomy – A systemic review

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Background: Corneal changes occur as a direct consequence of diabetes mellitus (DM). The central corneal thickness (CCT) is a useful parameter that provides information about the status of the metabolism of the cornea and can therefore help monitor the progression of DM.

Aim: The aim of this study was to determine the impact of DM on CCT and its correlation with diabetes duration and glycated haemoglobin (HbA1c) levels.

Methods: The systematic review was undertaken to answer: (1) What effect does DM have on CCT values? (2) What effect does DM duration have on CCT values? (3) What effect does HbA1c levels have on CCT values? The Web of Science was used to conduct a computerised search for articles of CCT values in DM.

Results: A total of 38 articles that met the criteria for inclusion were included in this systemic review. The researchers found 27 articles that observed increased CCT values in DM patients compared with control subjects. There were six studies in which increased CCT values were related to DM duration and 12 studies in which DM duration did not alter CCT values. Also, eight studies showed that CCT values increased with glycated haemoglobin levels, and 12 studies did not observe this finding.

Conclusion: Diabetes mellitus patients usually present with increased CCT values although there is no unanimity about the effect of DM duration and increased HbA1c levels (poor glycaemic control) in the CCT values of DM patients.

Keywords: diabetes mellitus; central corneal thickness; glycated haemoglobin levels; diabetes duration; systemic review; corneal endothelial pathology; pachymetry; ocular surface; corneal hydration.

Background

Diabetes mellitus (DM) is a clinical syndrome characterised by a disorder in the metabolism of carbohydrates, lipids and proteins because of a defect in insulin secretion, insulin action or both. Hyperglycaemia, a symptom that characterises this disease, causes long-term damage of different organs, such as kidneys, eyes, nerves, heart and blood vessels.[1] It is estimated that the prevalence rate of DM is around 6.4% worldwide, and there has been a drastic increase in people affected with DM over the last two decades.[2]

The development of DM complications is associated with disease duration and poor glycaemic control.[3] Within the eye, all structures are susceptible to changes because of DM. Thus, people with DM show several characteristic corneal signs, such as epithelial fragility, recurrent erosions, reduced sensibility, altered epi- and endothelial barrier functions, and stromal oedema.[4,5] All these signs are grouped under the term diabetic keratopathy that affects up to 70% of diabetic patients.[6]

Over the last few years, central corneal thickness (CCT) has played an important role in preoperative evaluation for refractive surgery,[7] detection of corneal dystrophies and ectasias,[8,9] dry eye management[10] and long-term contact lens wear assessment.[11,12] Central corneal thickness values depend on corneal endothelial function, and consequently, CCT is a useful parameter that provides information about the state or status of corneal metabolism, and it plays an important role in the assessment of intraocular pressure of certain ocular diseases, such as glaucoma, and of glycaemic control in DM.[13,14]

Several studies show a significant increase in CCT values in DM patients, [3,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] although the mechanism responsible for these changes in corneal structure and function remains to be fully understood. Some studies have found a correlation between DM duration and the increase of CCT values,[17,20,25] and others have observed an increase in CCT values when glycated haemoglobin (HbA1c) levels are elevated.[14,21,23] However, other studies did not find any relationship between CCT values, DM duration[3,15,16,18,19,22,24,26,27,28,29,30] and HbA1c levels.[3,15,16,18,19,22,24,26,27,28,29,30]

The main aims of this systematic review [31,32,33,34,35,36] were (1) to determine the impact of DM on CCT values, (2) to analyse the relationship between CCT values and DM duration and (3) to determine glycaemic control expressed through the HbA1c levels and its impact on the CCT of the DM patients.

Methods

This review aimed to determine the effect of DM on CCT values and its correlation with disease duration and glycaemic control. Consequently, the three study questions of this review included '(1) What effect does DM have on CCT values? (2) What effect does DM duration have on CCT values? (3) What effect does HbA1c levels have on CCT values?'.

Search strategy

The Web of Science (WoS) was used to conduct a computerised search of CCT values in DM. Peer-reviewed publications from 1980 to 2021 in indexed journals with a good impact factor as listed in Journal Citations Reports (JCR) were selected. The following terms were used in the search: 'diabetes and corneal thickness', 'diabetes and pachymetry', 'diabetes and ocular surface', 'corneal hydration and diabetes', and diabetes and corneal thickness disease'.

Inclusion and exclusion criteria

The inclusion criteria were the following: (1) studies published in English, (2) studies involving humans, (3) publications in indexed journals in JCR, (4) prospective studies related to DM effects on CCT values, (5) studies providing information about CCT in diabetic patients and (6) studies providing information on diabetes duration and HbA1c levels. The exclusion criteria were the following: (1) studies carried out on animals; (2) isolated clinical cases, reviews and retrospectives studies; and (3) studies on patients who underwent corneal surgery.

Data extraction and quality assessment

The following information was collected from the publications: first author, year of publication, study design, sample size, age and gender of study participants, type of DM, DM duration, HbA1c levels, CCT values, methods to determine CCT values and study quality.

The quality of selected studies was assessed according to journal article location on the JCR list of the year of publication, with the basis of higher quartile being the best quality for the article concerned. Thus, a maximum of four stars was assigned to those journal articles published on journals located in the first quartile (Q1), three stars to those published in the second quartile (Q2), two stars to those journal articles published in journals located in the third quartile (Q3) and one star to articles published in journals located in the fourth quartile (Q4) of their specialty according to the JCR list.

Ethical considerations

This study followed all ethical standards for research without direct contact with human or animal subjects.

Results

The characteristics of the studies that met the inclusion criteria in this review are shown in Table 1. From an initial number of 493 articles found in all databases of WoS, 38 articles were included in the systematic review after the application of the inclusion and exclusion criteria.

The devices used for obtaining the CCT values varied in the studies and included a Haag–Streit pachymeter, a digital pachymeter, specular microscopy, an ultrasonic pachymeter, a Scheimpflug camera, a biopachymeter, non-contact specular microscopy, non-contact corneal tomography, HR Pentacam tomography, an optical biometer, a pneumotonometer, a specular-type pachymeter and optical coherence tomography (OCT).

Based on studies included in this review, there are controversial results on increased CCT values in DM patients compared with control subjects. Twenty-eight studies observed that CCT values increased in DM patients as compared with control patients; however, 11 studies did not find this correlation (Figure 1).

As shown in Figure 2, studies that investigated whether there were positive correlations between CCT and DM duration were listed. There were six studies in which increased CCT values were related to DM duration and 12 studies in which DM duration did not alter CCT values. Another positive correlation was observed in DM patients, eight studies showed that CCT values increased in relation to HbA1c levels; while 12 studies did not observe this correlation (Figure 3).

Discussion

Several morphological, physiological and structural corneal changes have been described in people with DM.[6] DM duration and poor glycaemic control are considered important risk factors for developing DM complications.[3] An increase in CCT values is one of such complications; however, the results reported have been controversial.

TABLE 1: Studies included in this systematic review.

Authors	Type of DM	Medication	Sample size	Study quality	Gender		Age (years)	Duration (years)	HbA1c levels (%)	Pachymetry	CCT values (µm)
					M	F					
Storr-Paulsen et al.[3]	2	OAM, PDM	107	4	51	56	72.1 ± 11.0	NA	7.3 ± 0.2	Non-contact specular microscopy	546.0 ± 7.0
Busted et al.[15]	1	NA	81	4	NA		34.0	15.0	NA	Haag–Streit pachymeter	544.0 ± 28.0
Olsen et al.[16]	1	NA	20	4	6	5	48.0 ± 64.0	22.0	NA	NA	561.0 ± 27.0
Larsson et al.[17]	1	Insulin	49	3	NA		36.0 ± 12.0	20.0 ± 11.0	10.4 ± 2.1	Specular microscopy	580.0 ± 50.0
	2	Insulin, OAA, diet	60				60.0 ± 10.0	13.0 ± 8.0	9.9 ± 2.1		570.0 ± 50.0
McNamara et al.[14]	1	Insulin	21	4	14	7	39.6 ± 8.8	22.1 ± 10.1	10.2 ± 1.52	Haag–Streit pachymeter	524.0 ± 6.8.0
Roszkowska et al.[18]	1	Insulin	30	2	NA		29.76 ± 3.43	15.3 ± 1.2	< 9.5	Specular microscopy	580.0 ± 20.0
	2	OHT	45				49.6 ± 6.16	17.2 ± 2.2			570.0 ± 20.0
Rosenberg et al.[19]	1	Insulin	44	4	16	7	45.2 ± 10.0	25.9 ± 8.1	NA	*In vivo* confocal microscopy	576.9 ± 48.0
Lee et al.[20]	1	NA	200	3	99	101	57.57 ± 8.5	10.87 ± 5.9	NA	Ultrasonic pachymetry	588.2 ± 72.7
Su et al.[21]	2	NA	748	4	NA		62.59 ± 9.36	NA	8.4 ± 2.0	Ultrasonic pachymetry	547.2
Oriowo et al.[22]	1	Insulin	51	1	NA		53.96 ± 11.9	13.5	NA	Ultrasonic pachymetry	610.0
Módis et al.[23]	1	NA	41	2	12	9	40.97 ± 15.46	10.88 ± 8.06	8.55 ± 1.83	Specular microscopy	570.0 ± 40.0
	2		59		10	20	64.36 ± 10.47	13.61 ± 6.50	8.79 ± 2.01		560.0 ± 30.0
Ozdamar et al.[24]	1	NA	100	3	51	49	58.4 ± 8.6	10.0 ± 7.7	NA	Ultrasonic pachymetry	564.0 ± 30.0
Calvo-Maroto et al.[25]	2	NA	37	3	16	21	45.5 ± 2.5	0.38 ± 0.12	7.66 ± 0.78	Ultrasonic pachymeter	546.0 ± 13.0
			40		17	23	52.2 ± 1.8	10.2 ± 0.8	7.78 ± 0.66		569.0 ± 11.0
Briggs et al.[26]	2	Insulin and OAM	125	1	76	49	57.1 ± 11.5	14.9 ± 8.3	NA	HR Pentacam tomography	539.7 ± 33.6
			57		34	23	52.8 ± 9.0	< 10.0			533.0 ± 29.2
			68		42	26	60.5 ± 12.9	> 10.0			545.4 ± 36.1
Sanchis-Gimeno et al.[27]	2	NA	35	3	17	18	33.8 ± 3.2	5.9 ± 1.2	6.7 ± 0.3	Non-contact corneal tomographer	567.4 ± 10.9
Altay et al.[30]	2	NA	127	3	NA		NA	0.0–4.0	NA	Scheimpflug camera	532.67 ± 39.35
								4.0–9.0			524.54 ± 29.07
								> 10.0			537.20 ± 29.36
								0.0–4.0		Non-contact specular microscopy	553.13 ± 38.62
								4.0–9.0			544.59 ± 33.87
								> 10.0			558.00 ± 35.76
								0.0–4.0		Ultrasonic pachymeter	550.65 ± 38.68
								4.0–9.0			537.72 ± 36.36
								> 10.0			553.58 ± 40.08
Schultz et al.[37]	1	NA	31	3	NA		NA	21.0	NA	Digital pachymeter	540.0 ± 20.0
											530.0 ± 70.0
											540.0 ± 60.0
											540.0 ± 80.0
Keoleian et al.[38]	1	NA	28	3	NA		33.0 ± 12.0	22.0 ± 11.0	10.0 ± 1.4	Specular microscopy	560.0 ± 20.0
Inoue et al.[39]	2	NA	99	2	53	46	65.5 ± 7.5	9.1 ± 8.2	6.9 ± 1.3	Ultrasonic pachymetry	538.0 ± 36.0
Sudhir et al.[40]	2	NA	1191	3	637	554	54.8 ± 9.5	524.75 ± 34.52	NA	Ultrasonic pachymetry	524.75 ± 34.52
Ziadi et al.[41]	1	NA	6	3	4	2	36.0 ± 9.0	14.0 ± 9.0	8.2 ± 1.7	Ultrasonic pachymetry	560.0 ± 38.0
	2		9		2	7	55.0 ± 8.0	9.0 ± 6.0			547.0 ± 34.0
Sonmez et al.[42]	NA	Insulin and OHA	18	3	6	12	56.0 ± 16.0	8.67	10.58	Corneal pachymetry and ultrasonic biometry	542.89 ± 37.18
Wiemer et al.[43]	1	Insulin, OAM	102	3	58	44	39.96 ± 10.8	21.06 ± 11.7	8.16 ± 1.6	Scheimpflug camera	586.0 ± 30.0
	2		101		54	47	56.46 ± 7.0	8.86 ± 7.5	7.56 ± 1.4		544.0 ± 28.0
Kumar et al.[44]	NA	NA	16	4	10	6	52.0 ± 12.8	7.6 ± 3.8	7.9 ± 1.1	Ultrasonic pachymetry	583.4 ± 25.0
			9		8	1	55.4 ± 9.2	11.9 ± 5.5	8.09 ± 1.5		613.3 ± 28.8
Jeziorny et al.[45]	1	Insulin	50	4	27	23	9.5 (IQR 8.3–12.5)	Newly diagnosed	12.0 (IQR 10.8–13.2)	Digital pachymeter	Onset: 586 (IQR 563–616) After > 48 h: 572 (IQR 550–590)
	1		54		23	31	13.2 (IQR 10.6–16.2)	5.5 (IQR 2.4–8.2)	7.3 (IQR 6.9–7.7)		580.0 (IQR 556–602)
Luo et al.[46]	NA	NA	2599	4	1319	1280	60.6 ± 9.6	NA	7.8 ± 1.7	Ultrasonic pachymetry	545.3 ± 33.7
			6247		3080	3167	56.8 ± 9.8		5.7 ± 0.4		544.8 ± 33.9
Beato et al.[47]	2	Insulin and OAM	60	3	22	38	72.38 ± 5.66	10.98 ± 8.03	7.02 ± 1.13	Scheimpflug tomographer	557.7 ± 34.72
Ramm et al.[48]	1 & 2	Insulin and OAM	69	3	NA		69.0 ± 11.9	13.6 ± 9 years	> 7.0	Scheimpflug camera	561.8 ± 38

Table 1 continues on the next page →

TABLE 1 (continues ...): Studies included in this systematic review.

Authors	Type of DM	Medication	Sample size	Study quality	Gender		Age (years)	Duration (years)	HbA1c levels (%)	Pachymetry	CCT values (µm)
					M	F					
Çolak et al.[49]	NA	NA	25	3	NA		52.9 ± 4.8	8.0 ± 3.0	7.4 ± 1.4	Non-contact specular microscopy	RE: 546.0 ± 31.6 LE: 533.0 ± 31.0
			20				54.0 ± 3.2	10.6 ± 3.6	9.2 ± 1.3		RE: 539.8 ± 27.1 LE: 536.6 ± 28.3
Hanyuda et al.[50]	2	NA	734	4	NA		66.9 ± 7.8	NA	6.7 ± 1.2	Specular-type pachymeter	554.3 ± 49.2
Taşlı et al.[51]	2	NA	68	3	28	40	61.50 ± 7.791	5.32 ± 2.06	7.02 ± 1.15	Non-contact specular microscopy	536.29 ± 51.68
			56		24	32	63.77 ± 8.17	9.07 ± 3.92	8.46 ± 1.41		538.84 ± 34.52
			71		35	35	62.37 ± 7.07	13.25 ± 4.33	9.13 ± 1.45		541.99 ± 33.21
Srećković et al.[52]	2	NA	49	1	24	25	57.7 ± 11.6	> 15.0	-	Ultrasound pachymetry	568.0 ± 18.0
								< 15.0			551.0 ± 12.0
								-	> 7.0		574.0 ± 15.0
									< 7.0		548.0 ± 13.0
Suraida et al.[53]	2	NA	50	4	29	21	58.24 ± 7.50	≥ 5.0	8.26 ± 1.77	Optical coherence tomography	524.60 ± 28.74
			50		13	37	57.38 ± 7.73		9.65 ± 2.57		529.26 ± 33.88
Wang et al.[54]	1 & 2	NA	50	3	23	27	10.04 ± 2.70	3.72 ± 0.27	7.58 ± 2.24	IOL Biometer	562.27 ± 28.48
Xiao et al.[55]	1	NA	54	3	25	29	10.59 ± 3.40 years	4.19 ± 2.69	7.71 ± 2.23	Pneumotonometer	560.29 ± 29.29
Deák et al.[56]	1	NA	12	4	4	8	14.0 ± 3.0	6.0 ± 3.0	7.82 ± 1.09	Heidelberg retina tomographer	562.067 ± 25.48
							16.0 ± 3.0	9.0 ± 3.0	8.14 ± 1.22		560.00 ± 34.89
			7		6	1	34.0 ± 6.0	22.0 ± 7.0	8.29 ± 0.93		560.46 ± 23.55
							36.0 ± 6.0	24.0 ± 7.0	8.43 ± 2.05		576.86 ± 33.28
Wang et al.[57]	2	NA	1455	4	591	864	64.6 ± 8.0	8.3 ± 6.7	6.8 ± 1.3	Optical biometer	546.4 ± 31.7
			383		193	190	64.1 ± 7.9	11.7 ± 7.5	7.7 ± 1.7		548.1 ± 31.7
Kim and Kim.[58]	2	Insulin and OAM	511	4	264	247	65.6 ± 11.1	10.8 ± 8.7	7.54 ± 1.78	Pentacam Scheimpfug camera	551.80 ± 34.10

NA, not available; HbA1c, glycosylated haemoglobin; CCT, central corneal thickness; M, male; F, female; OAM, oral antidiabetic medication; OHA, oral hypoglycaemic agents; OHT, oral hypoglycaemic therapy; OAA, oral antidiabetic agents; PDM, parenteral antidiabetic medication; RE, right eye; LE, left eye; IQR, interquartile range.

Increase in CCT values	No increase in CCT values
Storr-Paulsen et al.[3]	Schultz et al.[37]
Busted et al.[15]	Keoleian et al.[38]
Olsen et al.[16]	Inoue et al.[39]
Larsson et al.[17]	Sudhir et al.[40]
McNamara et al.[14]	Ziadi et al.[41]
Roszkowska et al.[18]	Sonmez et al.[42]
Rosenberg et al.[19]	Wiemer et al.[43]
Lee et al.[20]	Beato et al.[47]
Su et al.[21]	Wang et al.[54]
Oriowo et al.[22]	Xiao et al.[55]
Modis et al.[23]	Wang et al.[57]
Ozdamar et al.[24]	
Calvo-Maroto et al.[25]	
Briggs et al.[26]	
Sanchis-Gimeno et al.[27]	
Altay et al.[30]	
Kumar et al.[44]	
Jeziorny et al.[45]	
Luo et al. [46]	
Ramm et al.[48]	
Çolak et al.[49]	
Hanyuda et al.[50]	
Taşlı et al.[51]	
Srećković et al.[52]	
Suraida et al.[53]	
Deák et al.[56]	
Kim and Kim[58]	

CCT, central corneal thickness.

FIGURE 1: Comparative table showing studies that detected an increase in central corneal thickness values in diabetes mellitus versus those that did not.

Correlation between CCT values and diabetes duration	No correlation between CCT values and diabetes duration
Larsson et al.[17]	Storr-Paulsen et al.[3]
Lee et al.[20]	Busted et al.[15]
Calvo-Maroto et al.[25]	Olsen et al.[16]
Luo et al.[46]	Roszkowska et al.[18]
Srećković et al.[52]	Rosenberg et al.[19]
Kim and Kim.[58]	Oriowo et al.[22]
	Ozdamar et al.[24]
	Briggs et al.[26]
	Sanchis-Gimeno et al.[27]
	Altay et al.[30]
	Çolak et al.[49]
	Xiao et al.[55]

CCT, central corneal thickness.

FIGURE 2: A comparative table showing studies that observed positive correlations between central corneal thickness values and diabetes duration versus those that did not.

One study whose aim was to study CCT values and corneal endothelium in DM patients was carried out by Busted et al.[15] In this study, 81 Type-1 DM patients were included. The authors concluded that the increase in CCT values could be considered one of the first detectable changes in the diabetic eye caused by an increase in corneal hydration and dysfunction of endothelial activity. Significant correlations between DM duration, fasting blood glucose and CCT values were observed.

McNamara et al.[14] evaluated the corneal response to oxidative stress under hyperglycaemia and euglycemia

Correlation between CCT values and HbA1c levels	No correlation between CCT values and HbA1c levels
McNamara et al.[14]	Storr-Paulsen et al.[3]
Su et al.[21]	Olsen et al.[16]
Modis et al.[23]	Roszkowska et al.[18]
Luo et al.[46]	Rosenberg et al.[19]
Ramm et al.[48]	Oriowo et al.[22]
Srećković et al.[52]	Ozdamar et al.[24]
Wang et al.[57]	Briggs et al.[26]
Kim and Kim[58]	Sanchis-Gimeno et al.[27]
	Altay et al.[30]
	Çolak et al.[49]
	Suraida et al.[53]
	Xiao et al.[55]

CCT, central corneal thickness.

FIGURE 3: A comparative table showing studies that observed a positive correlation between central corneal thickness values and HbA1c levels versus those that did not.

conditions in Type-1 DM patients. Blood glucose levels were pharmacologically controlled in these patients. They observed that corneal oedema in DM patients was higher than that observed in control subjects. When both conditions were analysed, they showed that corneal oedema was significantly less in the DM group during hyperglycaemia compared with that during euglycemic conditions. This finding was the first direct evidence that hyperglycaemia and glucose levels have an influence on the aqueous humour that may affect corneal hydration, because endothelial permeability is lower in diabetic patients under hyperglycaemic conditions.[35]

Based on the studies included in this review, three studies compared DM Type-1 and -2 [17,18,23] and found an increase in CCT in both patient groups. Larsson et al.[17] found significant differences in CCT values in Type-1 DM patients compared with their control subjects. In Type-2 DM patients, an increase in CCT values was observed with respect to their controls but was not statistically different. Significant correlation was observed between DM duration and CCT values in Type-2 DM patients but not between HbA1c levels and CCT values in either group. However, Roszkowska et al.[18] found higher CCT values in Type-1 and Type-2 DM patients than their respective age-matched control subjects although CCT values were higher in Type-1 DM patients than in those in Type-2 DM patients. They hypothesised that this increase is caused by a decrease in endothelial function that implies an increase in corneal hydration and, consequently, an increase in CCT values. It is essential to underline that glycaemic control was less severe.

The third comparative study was conducted by Modis et al.[23] They observed that corneas of DM patients were thicker than those from age-matched control groups. Moreover, they found a statistically significant correlation between blood glucose levels and CCT values in Type-1 DM patients but not in subjects with Type-2 DM. Morphology alterations of corneal endothelium observed in Type-1 DM patients could explain the increase in CCT values.[23] This hypothesis corresponds with results obtained from previous studies.[14,15,17,18,20,21,35]

Several studies found an increase in CCT values in Type-1 DM patients as compared with control subjects.[14,15,16,19,20,22,24,45,48,56] Oriowo et al.[22] analysed CCT values in Type-1 DM patients with and without dry eye disease. They observed that DM patients without dry eye showed an average increase of 27 µm in CCT values with respect to their control subjects. Statistically significant correlations between CCT values, DM duration and HbA1c levels were not found.[22] Lee et al.[20] found that CCT values were correlated significantly with DM duration after monitoring for age. These results were based on the theory of corneal endothelial pump dysfunction.[14] Contrastingly, some studies [52,58] evaluated the effects of Type-2 DM on CCT values. [21,30,50,51,52,53,58] Srećković et al.[52] found that CCT was increased in the DM group compared with healthy subjects. They also observed that greater CCT values were found in DM patients with HbA1c levels > 7% and those with diabetes duration for more than 15 years. Kim and Kim[58] supported these findings in their retrospective cross-sectional study. Regarding HbA1c levels and DM duration, CCT values were thicker in patients with diabetes duration beyond 10 years (particularly after 50 years) and HbA1c levels > 7% (at the age of 40 years). In studies in which DM patients were divided according to blood glucose levels, CCT values were also higher in DM patients than control subjects.[21,24] Although a significant correlation between CCT and hyperglycaemia was observed in Type-2 DM patients,[21] the authors speculated that the reason was because of corneal endothelial dysfunction with resulting stromal hydration and corneal swelling.[14]

Storr-Paulsen et al.[3] divided Type-2 DM patients according to glycaemic status. And they found that CCT values were significantly higher in DM patients than control subjects, and a poor glycaemic control was associated with lower endothelial cell density (ECD). A cross-sectional analysis of the Singapore Epidemiology of Eye Diseases was conducted from 2004 to 2011 [46] to evaluate the association between DM, random glucose and HbA1c with CCT values. Results from this study demonstrated that corneas from diabetic patients were thicker than those without DM, and increased CCT values were associated with higher random glucose and higher HbA1c levels. Ramm et al[48] also found similar results in their study of 69 diabetic and 68 healthy subjects, whereby CCT was significantly increased in DM patients with poor control of their HbA1c levels (n = 23; HbA1c: > 7%; CCT: 571.1 ± 43.5 µm) than in well-controlled DM patients (n = 37; HbA1c: ≤ 7%; CCT: 551.9 ± 29.7 µm). They also found CCT to be 9.3 ± 2.6 µm higher in the DM group than in healthy subjects. Other studies, such as Calvo-Maroto et al.[25] and Briggs et al.,[26] divided Type-2 DM patients according to DM duration to evaluate the impact of this factor on CCT values. The first study classified patients into short-term (less than one year from the time of diagnosis) and long-term diabetic subjects (those diagnosed and treated for 10 years or more). They found that CCT values were significantly higher in long-term DM patients than short-term DM patients. Moreover, ECD was significantly lower in long-term DM patients than short-term DM patients. Thus, these results

support the theory that DM duration predisposes factors in CCT and ECD alterations.[25]

Briggs et al.[26] observed that Type-2 DM patients who had been diagnosed for > 10 years showed an increase of 15 µm in CCT values with respect to the other group, diagnosed less than 10 years before. Significant correlations between CCT values and DM duration were not found, and glycaemic control had no additional effect on CCT values.

Another study conducted by Sanchis-Gimeno et al.[27] showed regions of corneal thickening in Type-2 DM patients compared with control subjects. DM patients showed the highest corneal thickening in the upper cornea (62.9%), followed by the nasal cornea (25.7%) and the temporal cornea (11.4%). They concluded that DM patients showed higher corneal thickness values in central and paracentral regions than control subjects. These results confirmed the findings obtained in previous studies.[3,15,18,20,21,24,25] However, significant correlations between CCT values, HbA1c levels, and DM duration were not found.[27]

As mentioned previously, all ocular structures are susceptible to damage because of DM.[4,5] Diabetic retinopathy (DR) is a microvascular complication that remains one of the leading causes of blindness worldwide (29). There are some studies that have studied the CCT values on different degrees of retinopathy.[53,56] Thus, Wang et al.[57] investigated the association between ocular parameters and DR in Chinese people with Type-2 DM. The authors showed that CCT was positively correlated with HbA1c levels; however, no significant correlation was found between CCT and DR.

Suraida et al.[53] aimed to compare anterior ocular segment biometry amongst Type-2 DM patients with no DR and non-proliferative DR against control subjects. They found that the CCT mean value was significantly higher in DM patients than in their control group; however, the presence of non-proliferative DR did not affect CCT. They also found no significant correlations between HbA1c and anterior segment biometry in people with diabetes regardless of their retinopathy status.

Another complication of DM is the diabetic peripheral neuropathy that is a leading cause of lower-limb amputation and disabling neuropathic pain.[59] Kumar et al.,[44] in their study to evaluate the relationship between CCT and diabetic peripheral neuropathy severity, found that CCT is increased in patients with diabetic peripheral neuropathy compared with their control group (11% and 5.6% increase in CCT amongst severe and mild diabetic peripheral neuropathy, respectively), increases progressively with the severity of the disease (4.9%, increase in CCT amongst severe cases compared with mild cases). In accordance with diabetes complications, Olsen et al.[16] evaluated the importance of neovascularisation in diabetic eyes, and they observed an increase in CCT values. They concluded that this characteristic effect in DM patients was not a secondary process caused by neovascularisation, which is a consequence of several factors including ischemia, which, in turn, can occur in both DM patients and control subjects. However, the type of DM and HbA1c levels were not considered in the study by Olsen et al.[16] In clinical practice, accurate measurements of CCT can be useful to determine endothelial cell function; therefore these measurements must be rapid, precise and reproducible.[28] Thus, a comparative study[30] evaluated the agreement in CCT measures carried out by different devices (Scheimpflug Pentacam camera, non-contact specular microscopy and ultrasonic pachymetry) in Type-2 DM patients. All CCT measures were classified according to HbA1c levels and DM duration. They found higher CCT measurements in DM patients than control subjects by three devices, but the measurements were not statistically significant. Based on this analysis, the authors concluded that HbA1c levels could determine CCT measurement better than duration.[30]

All the studies mentioned found significant differences in CCT values in Type-1 and Type-2 DM patients compared with their respective controls. However, this systematic review also found studies in which CCT values were not statistically different between DM subjects and control subjects (Figure 1). Keoleian et al.[38] studied CCT values in 14 Type-1 DM patients and controls and in 14 age-matched controls. They observed that there was no difference in CCT values between either group of subjects.

Inoue et al.[39] evaluated CCT measurements in Type-2 DM patients divided according to the degree of retinopathy and control subjects. They observed that CCT values were similar in all diabetic groups, and the differences between DM patients and controls were not statistically significant. These results were supported by Sudhir et al.[40]

Ziadi et al.[41] evaluated the control of corneal hydration in DM patients (Type-1 and Type-2) during contact lens-induced hypoxia. They observed that CCT measures were not statistically different in either the DM groups or the control subjects. Other studies did not find significant differences between people with DM and control subjects.[42,43]

In children, Xiao et al.[55] investigated the influence of Type-1 DM on ocular biometry, and they showed that the CCT values of the healthy children were slightly higher (571.02 µm) than that of the DM children (560.29 µm); however, neither HbA1c nor DM duration was correlated with ocular biometry and CCT in the DM group. These results coincide with those of other studies such as Beato et al.[47] and Wang et al.[54] where control groups were found to have higher CCT values than the DM groups. In another study carried out by Jeziorny et al.[45] on children with newly diagnosed Type-1 DM, higher CCT values were found at the onset of diagnosis compared with values observed after 48 h of metabolic compensation. Negative correlations were also found between CCT and CO_2 ($r = –0.33$; $p = 0.032$) and CCT and pH ($r = –0.26$; $p = 0.088$) values, respectively.

Although this review included studies that measured CCT values with different devices, some of them failed to classify DM patients for common variables, such as type of DM, DM duration or HbA1c levels.

Conclusion

The results from this review reveal the disparity between the published studies in the scientific literature. In addition, the findings indicate the impact of poor glycaemic control and long-term diabetes on CCT values. Thus, this parameter could be included in regular examinations in diabetic patients because its progressive increase may indicate endothelial pathological changes.

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Authors' contributions

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