ORIGINAL ARTICLE

Associations of glycated hemoglobin (HbA1c) level with central corneal and macular thickness in diabetic patients without macular edema

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ABSTRACT

Objectives: To determine the correlation between central corneal thickness (CCT) and central macular thickness (CMT), and fasting plasma glucose levels and HbA1c levels before diabetic macular edema (DME) in type 2 diabetes mellitus (DM) patients without diabetic retinopathy.

Methods: Forty-four eyes of subjects diagnosed with type 2 DM, and 45 healthy control subjects participated in this study. Detailed ophthalmologic examination was performed with all participants. CMT was measured in both groups by Spectral-domain optical coherence tomography. CCT measurements were made with an Echoscan US-500 ultrasonic pachymeter. Blood biochemical tests for glycated hemoglobin (HbA1c) and fasting plasma glucose levels were run on all patients.

Results: The results of the study showed that the mean CCT was significantly thicker in type 2 DM patients 563.84 ± 33.25 μm than in the controls 550.13 ± 28.41 μm ($p = 0.039$). The mean of CMT was 231.27 ± 37.74 μm in the study group and 225.38 ± 38.33 μm in the control group ($p > 0.05$). No relationship was found between CCT and CMT and HbA1c level in the study and control groups.

Conclusions: The mean CCT was significantly thicker in type 2 DM patients without diabetic retinopathy than in the controls. The mean CMT is thicker in type 2 DM patients without diabetic retinopathy patients than in the controls, but this difference was not statistically significant. Optical coherence tomography can be a perfect detector for early detection of DME.

Keywords: Diabetic macular edema, HbA1c, fasting plasma glucose levels, central corneal thickness, central macular thickness

Diabetic retinopathy is defined as a particular microvascular complication of diabetes and is the major reason of vision loss within the preferred populace in many nations, together with the employed adult population and the old aged [1-4]. It was estimated that diabetic retinopathy would spread to more than 200 million people around the world by 2012 [5]. It was estimated that in 2000, the spread rate of diabetes for all age groups worldwide would be 2.8% and 4.4% in 2030. It is thought that the number of patients with diabetes all over the world will increase from 171 million in 2000 to 366 million in 2030 [6].

Diabetes is associated with alterations in multiple layers of the retina. For example, it is observed that vascular leak [7, 8] and therefore diabetic retinopathy

are caused by pericyte loss [9] and vascular endothelial damage [10].

Diabetic macular edema (DME) is the leading reason for visual acuity impairment in diabetic patients. DME is characterised by increased vascular permeability and accumulation of hard exudate in the central retina. DME can be seen at any phase of diabetic retinopathy [11]. DME has been noted to be seen in 10% of cases and is more common in type 2 diabetes mellitus (DM) than in type 1 [12]. DME affects the whole body adversely by prolonging the duration of diabetes, worsening glycemic control, increasing systolic blood pressure and serum lipids [13]. One way in which diabetic retinopathy can be prevented is through the systemic control of glycemia and tension in diabetic patients [2, 14]. The Diabetes Control and Complications Trial (DCCT) [15] and the United Kingdom Prospective Diabetes Study (UKPDS) [16] asserted that a tighter control of glycemia (intended glycated hemoglobin [HbA1c] level of < 7%) decrease the risk of growth and evolution of diabetic retinopathy and DME in type 1 DM and type 2 DM.

In diabetic cases, neovascular glaucoma, optical neuropathy, and front segment complications can also be observed besides retinopathy. 47-64% of diabetic patients show indications of corneal epitheliopathy even if it is not clinically a top priority [17]. Diabetes-related ocular surface and tear changes including corneal epitheliopathy are defined as "diabetic keratopathy" [17, 18]. There are corneal epithelial defects, recurrent corneal erosions, delayed epithelial recovery, corneal ulcer and dry eye disease in this range. Many studies point out that neurotrophic keratopathy is the main reason for corneal epithelial changes [19-21]. Despite the evidence of corneal epithelium and ocular surface changes in diabetic keratopathy, there are also wrinkles in the Descemet membrane and malformation and malfunction of the corneal endothelium [17, 18]. Increase in corneal stromal edema and central corneal thickness are observed more frequently in diabetic cases [22-24]. The increase in CCT has been claimed by some studies to be one of the earliest symptoms of the diabetic eye [25].

The aim of this study is to determine the correlation between CMT and CCT, and fasting plasma glucose levels and HbA1c levels before DME becomes clinically apparent in type 2 diabetic patients.

METHODS

Forty-four eyes of subjects diagnosed with type 2 DM, who were being followed by the endocrinology clinic, and 45 healthy control subjects participated in this study between January 2017 to June 2017. According to the principle of the declaration of Helsinki, the study was explained to the subjects and they were asked to sign a written informed consent. The research was approved by the local ethics committee. Information about the duration of diabetes was by self-report based on the date of detection by a medical practitioner. On each patient's first visit, a detailed systemic and ophthalmological medical history was taken, visual acuity was measured with the chart at 4 meters, a slit-lamp examination was performed, intraocular pressure was measured with Goldmann applanation tonometry, and a dilated fundus examination with a 90D lens was undertaken.

The central macular thickness (CMT) was measured in both groups by Spectral-domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany). The CMT was measured after providing pupil dilation with tropicamide drops 2 times, 10 minutes before measurements (Tropicamide 1%, Alcon Lab. Inc., USA). After receiving measurements with spectral-domain optical coherence tomography, 0.5% proparacaine hydrochloride (Alcaine, Alcon Laboratories Inc., Fort Worth, TX, ABD) was applied for topical anesthesia. Approximately 5 minutes later, CCT measurements were made with an Echoscan US-500 ultrasonic pachymeter (Nidek Co. Ltd, Aichi, Japan). Participants were asked to fix their gaze on a target during contact measurements, and the pachymetry probe was placed in the central cornea as steeply and gently as possible. During contact process, the probe tips and the double prism were disinfected with 3% hydrogen peroxide. Measurements were taken in the morning (between the hours of 9:00 am and 11:00 am). All procedures were performed by the same physician. Blood biochemical tests for HbA1c and fasting plasma glucose levels were run on all patients. All cases were subjected to HbA1c testing on the day of the ophthalmic examination.

Exclusion criteria included patients who received intraocular surgery (cataract surgery, pars plana vitrectomy, intravitreal injection of triamcinolone or Bevacizumab), keratoconus, contact lens use, glaucoma, dry eye, pseudoexfoliation syndrome, previous anterior segment surgery, rubeosis iridis, subtenon injection, photocoagulation therapy within 1 year of evaluation and severe vitreous hemorrhage or vitreous opacity that would interfere with the optical coherence tomography examination. Inclusion criteria for the study group included no visible findings of diabetic retinopathy (hard-soft exudate, microaneurysms) on retina at slit-lamp fundus examination with a +90D lens, type 2 DM, no other problems (such as hypertension, uveitis), and no history of ocular trauma, and high refractive errors (spherical equivalent between +1.00D and −1.00 D). Inclusion criteria for the control group patients included no ophthalmologic or systemic problems, no history of intraocular surgery or treatment of the retina, and no high refractive errors (spherical equivalent: between −1.0D and +1.0D).

Statistical Analysis

Statistical analyses were performed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Gender distribution between the groups was investigated by a chi-square test. The distribution of age and HbA1c values were evaluated by one-way ANOVA. Independent sample tests were used to compare the means between the diabetic and control groups. Pearson's correlationanalyses were conducted to evaluate the relationship between the parameters showing normal distribution, and Spearman's rho correlation analyses have been used to evaluate the correlation between the parameters not showing normal distribution. The level of significance was set at $p < 0.05$.

RESULTS

Of the 44 Type 2 DM patients included in the study, 24 were male (54.5%) and 20 (45.5%) were female and the mean age was 60.11 ± 8.17 (47-76). Twenty-one (46.7%) of the control group were male and 24 (53.3%) were female and the mean age was 59.40 ± 5.1 years (range, 50-70 years). There were no differences in sex, age and best corrected visual acuity (BCVA) between the groups ($p > 0.05$).

The results of the study showed that the mean CCT was significantly thicker in type 2 DM patients 563.84 ± 33.25 μm than in the controls 550.13 ± 28.41 μm ($p = 0.039$). The mean of CMT was 231.27 ± 37.74 μm in the study group and 225.38 ± 38.33 μm in the control group ($p > 0.05$).

The mean HbA1c level was $7.92 \pm 1.69\%$ in the study group and $5.18 \pm 0.51\%$ in the control group. The mean level of HbA1c was statistically higher in the study group than in the control group ($p = 0.001$). Fasting plasma glucose level was statistically higher in the study group than in the control group ($p = 0.001$). The duration of diabetes mellitus was 13.45 ± 5.5 years (range, 3-27 years) (Table 1).

No correlation was found between CCT and fasting plasma glucose level in the study ($p = 0.415$) and control ($p = 0.342$) groups. No relationship was found between CCT and HbA1c level in the study (p

Table 1. Demographic characteristics, values for CCT, CMT, and biochemical analysis in patients with type 2 diabetes without clinical retinopathy

Parameters	Study group (*n* = 44)	Control group (*n* = 45)	*p* value
BCVA (logMAR)	0	0	NS
IOP (mmHg)	15.0 ± 2.7	15.8 ± 2.1	NS
Age (years)	60.11 ± 8.17	59.40 ± 5.1	NS
Male/ Female	24/20	21/24	NS
CCT (*μ*m)	563.84 ± 33.25	550.13 ± 28.41	**0.039**
CMT (*μ*m)	231.27 ± 37.74	225.38 ± 38.33	NS
HbA1c (%)	7.92 ± 1.69	5.18 ± 0.51	**0.001**
Fasting blood glucose level (mg/100 ml)	213.09 ± 81.28	89.46 ± 13.92	**0.001**

Data are shown as mean±standard deviation or number. BCVA = best corrected visual acuity, CCT = central corneal thickness, CMT = central macular thickness, Control group = healthy subjects, HbA1c = glycated hemoglobin, IOP = Intraocular pressure, logMAR = logarithm of the minimum angle of resolution, NS = nonsignificant, Study group = patients with type 2 diabetes without clinical retinopathy

Table 2. Relationship between CCT, CMT, HbA1c, fasting blood glucose levels, and duration of DM in patients with type 2 diabetes without clinical retinopathy

Parameters	Study group		Control group	
	r	*p value*	r	*p value*
CCT-HbA1c	0.284	0.062	0.122	0.424
CCT-fasting plasma glucose level	0.126	0.415	0.145	0.342
CCT-duration of DM	0.077	0.617	-	-
CMT-HbA1c	-0.031	0.841	0.025	0.870
CMT-fasting plasma glucose level	-0,07	0.649	0.111	0.469
CMT-duration of DM	0.074	0.634	-	-

CCT = central corneal thickness, CMT = central macular thickness, Control group = healthy subjects, DM = diabetes mellitus, HbA1c = glycated hemoglobin, *r* = relation between two variables, Study group = patients with type 2 diabetes without clinical retinopathy,

= 0.062) and control groups (*p* = 0.424). No relationship was found between CMT and fasting plasma glucose level in the study (*p* = 0.649) and control (*p* = 0.469) groups. No relationship was found between CMT and HbA1c level in the study (*p* = 0.841) and control groups (*p* = 0.870; Table 2).

DISCUSSION

DM can affect almost all ocular structure. DM does not only lead to an ocular complication, diabetic retinopathy, but it is also believed to lead to some changes in the anterior segment of the eye [26, 27]. Examples of these abnormalities are a decrease in endothelial cell density and hexagonality, and an increase in polymegathism, pleomorphism and CCT [23, 28]. In this study, ultrasonic pachymeter examinations were performed in type 2 diabetic patients without DME. The mean CCT was significantly thicker in type 2 DM patients than in the controls. Additionally, no statistically significant relationship was found between CCT, HbA1c, and fasting plasma glucose level in either group.

Many studies have used specular microscopy and shown that DM-diagnosed patients have many structural changes in the corneal endothelium compared to healthy individuals [29, 30]. It is stated that hyperglycemia affects the corneal thickness in diabetic patients by impairing corneal hydration, thereby destroying the corneal structure by McNamara *et al*. [32]. Schultz *et al*. [29] examined the barrier and pump function of corneal endothelium using a fluorometric method and found that there were some deficiencies as a result. Consequently, it has been claimed that change in corneal thickness is common in patients with DM. As reported by the results of Herse's experimental study [32], the evaluated fall in Na+/K+ ATPase activity of diabetic rabbits proves that abnormal corneal hydration system of the diabetic rabbits which are not controlled is managed by a functional disorder of endothelial fluid pump. The biological basis of corneal changes in the eyes of diabetic patients is not yet found and the underlying mechanisms are still unknown. Su *et al*. [33] studied the association of diabetes and hyperglycemia with CCT in 3239 eyes where 748 diabetic patients participated and showed a 6.5 μm thicker CCT than the healthy group in non-diabetic patients. Lee *et al*. [23] found that CCT was higher in patients with DM than in the control group, as a result of studying the CCT of diabetic patients with normal fundus and DR history. Inoue *et al*. [24] and Choo *et al*. [11] reported that diabetic group CCT data did not show any significant difference from control groups. According to the results of the study conducted by Ozdamar *et al*. [34], CCT values in diabetic group were significantly higher than the control group. The same study shows no correlation between HbA1c and CCT. Although HbA1c is a marker of long-term DM control, we assume that high glucose levels may lead to corneal thickening than at any other time in the life of a diabetic patient.

The relationship between CMT, HbA1c and fasting plasma glucose levels was also observed in patients with type 2 diabetes who did not have clinical diabetic retinopathy in our study. Although the mean CMT was thicker in type 2 DM patients without diabetic retinopathy compared to healthy subjects, this difference was not statistically significant. There was no positive correlation between fasting plasma glucose level and CMT in patients with diabetes mellitus and

without retinopathy. CMT was not increased by mild or high levels of HbA1c (7.92 ± 1.69%). CCT and CMT were not affected by the duration of diabetes mellitus in patients with diabetes type 2 without retinopathy.

Browning *et al*. [35] reported in their study that in patients without clinically macular edema in spite of being diagnosed with diabetic retinopathy, especially the variations in central subfield macular thickness and total macular volume (TMV) in optical coherence tomography were not greater than the measurement variation in eyes with or without DME. It was stated that the changes, which are more than 10% compared to the initial macular thickness, should be considered as a real change, whereas the remaining values could be due to measurement variations, diurnal variations, or variations of the long-lasting scale. Sugimoto *et al*. [36] found that the retinal thickness increased and the retinal nerve fiber layer thickness decreased in the superior quadrant in the eyes of patients with non-diabetic retinopathy in the study they tried to confirm early diabetic injury and evaluate optical coherence tomography as a clinical test. They also reported that it is possible to detect early signs and structural changes with optical coherence tomography at a much earlier stage and that optical coherence tomography can be used in early treatment planning. Bressler *et al*. [37] determined in their studies evaluating macular thickness with optical coherence tomography in type 1 and type 2 diabetic patients without retinopathy or with very mild retinopathy and no macular thickening on clinical examination that the macular thickness values of these diabetic patients without retinopathy or with very mild retinopathy were similar to those of normal individuals but found that the average central subfield thickness in males was statistically significantly higher than that of females (209 ± 18 μm vs. 194 ± 23 μm).

Glycemic control is critical for DM treatment and can be assessed periodically by HbA1c measurement. Chou *et al*. [11] demonstrated that 8% or more of HbA1c in diabetic retinopathy-diagnosed diabetic patients is associated with an increase in macular thickness. Moreira *et al*. [38] demonstrated that no other variables other than HbA1c were associated significantly with macular edema. According to the findings of the Los Angeles Latino Eye Study (LALES), there is a 22% increase in the spread of

diabetic retinopathy and a 1% increase in HbA1c level [39]. The Wisconsin Epidemiology Study of Diabetic Retinopathy (WESDR) reported that the presence of high levels of HbA1c increased the risk of developing DME within a 10-year period [40]. The most widely accepted pathophysiological model for diabetic retinopathy development involves microvascular dysfunction. Abnormalities in glucose metabolism lead to changes in the capillary vessels of the retina and deterioration of the blood/retinal barrier, resulting in microaneurysms, hemorrhages, and retinal exudate. These retinal changes cause retinal thickening that can be detected with 0ptical coherence tomography. Since HbA1c levels were recorded for only 3 months, it is difficult for this study to determine whether the positive correlation between chronic HbA1c level and macular thickness is more harmful to microvasculature caused by high chronic hyperglycemia.

The Limitations of the Study

There are limitations to the study. One of these is the small sample size in both groups and another is that none of the patients had diabetes mellitus for longer than 20 years.

CONCLUSION

In this study, the mean CCT was significantly thicker in type 2 DM patients without diabetic retinopathy than in the controls. The mean CMT is thicker in type 2 DM patients without diabetic retinopathy than in the controls, but this difference was not statistically significant. No correlation between HbA1c, fasting plasma glucose levels and duration of DM was found with both CCT and CMT. Optical coherence tomography can be a perfect detector for early detection of DME.

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