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The influence of diabetes mellitus type 2 on the central corneal thickness

Uticaj dijabetesa melitusa tip 2 na centralnu debljinu rožnjače

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Abstract

Background/Aim. Complications of diabetes mellitus (DM) in the eye are the leading cause of blindness in the world. Although research on eye complications of DM is mainly focused on retinal damage, changes in the cornea are also associated with DM. Central corneal thickness (CCT) reflects the metabolic status of the cornea and is also affected by DM. Knowledge of CCT changes that occur within DM is important for accurate IOP measurement, diagnosis, and monitoring of patients with glaucoma. The aim of the study was to examine the effect of DM type 2 on the central corneal thickness. **Methods.** The study was designed as a clinical, cross-sectional, observational study. It consists of 96 patients, divided into two groups. The first group consisted of 49 patients diagnosed with DM type 2. The second group was the control group and consisted of 47 healthy subjects. The DM group was divided into subgroups depending on the status of diabetic retinopathy, the length of DM treatment, and the levels of glycosylated hemoglobin (HbA_1C). **Results.** A statistically significant difference in CCT was observed among DM patients and the control group. Analyzing only DM patients, the highest CCT values were observed in patients who had $HbA_{1C} > 7.0\%$, as well as those who have treated DM for more than 15 years, with a statistically significant difference in relation to the corresponding patient subgroups ($p = 0.002$ and $p = 0.037$, respctively). No statistically significant difference was observed depending on the status of retinopathy. Intraocular pressure (IOP) was statistically significantly higher in patients with DM compared to the control group. **Conclusion.** Our research demonstrated that the status of retinopathy had no statistically significant influence on CCT. Knowing that the increase in CCT also affects the measured IOP values, this research will be useful in better understanding and control of the patients who have glaucoma in addition to DM type 2.

Key words:
cornea; corneal pachymetry; diabetes mellitus, type 2; diabetic retinopathy; intraocular pressure; risk assessment.

Apstrakt

Uvod/Cilj. Komplikacije dijabetesa melitusa (DM) u oku su vodeći uzrok slepila u svetu. Iako su istraživanja o očnim komplikacijama DM uglavnom usmerena na oštećenje mrežnjače, promene na rožnjači su takođe povezane sa DM. Centralna debljina rožnjače (*central carneal thickness* – CCT) odražava njen metabolički status, a na njega utiče i DM. Poznavanje promena CCT koje se dešavaju u sklopu DM važno je za tačno merenje intraokularnog pritiska (IOP), dijagnozu i praćenje bolesnika sa glaukomom. Cilj studije bio je ispitivanje uticaja DM tipa 2 na CCT. **Metode.** Studija je dizajnirana kao klinička, opservaciona studija preseka, a obuhvatila je 96 ispitanika podeljenih u dve grupe. Prvu grupu činilo je 49 bolesnika sa dijagnozom DM tipa 2. Druga grupa bila je kontrolna grupa i sastojala se od 47 zdravih ispitanika. Grupa obolelih od DM bila je podeljena u podgrupe u zavisnosti od statusa dijabetesne retinopatije, dužine lečenja DM i nivoa glikoziliranog hemoglobina (HbA_{1C}). **Rezultati.** Statistički značajna razlika u CCT utvrđena je između bolesnika sa DM i kontrolne grupe. Analizirajući samo bolesnike sa DM, najveće vrednosti CCT uočene su kod bolesnika sa $HbA_{1C} > 7,0\%$, kao i kod onih koji su lečili DM duže od 15 godina, sa statistički značajnom razlikom u odnosu na odgovarajuće podgrupe bolesnika ($p = 0,002$ i $p = 0,037$, redom). Nije nađena statistički značajna razlika u zavisnosti od statusa retinopatije. Takođe, IOP je bio statistički značajno viši kod bolesnika sa DM u poređenju sa kontrolnom grupom. **Zaključak.** Naše istraživanje je pokazalo da status retinopatije nije imao statistički značajan uticaj

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na CCT. Znajući da povećanje CCT utiče i na izmerene vrednosti IOP, ovo istraživanje će biti od koristi boljem shvatanju i kontroli bolesnika koji, pored DM tipa 2, imaju i glaukom.

Ključne reči:
rožnjača; rožnjača, pahimetrija; dijabetes melitus, tip 2; dijabetesna retinopatija; intraokularni pritisak; rizik, procena.

Introduction

Diabetes mellitus (DM) represents a systemic disorder that affects many different tissues and organs [1]. Ocular complications of DM are the leading cause of blindness worldwide. The most common complications are diabetic retinopathy, neovascular glaucoma, and diabetic cataract [1]. Morphological and functional changes in corneal tissue can also occur in DM patients [2]. These patients are at a higher risk of developing recurrent corneal erosions, neurotrophic corneal ulceration, stromal edema after intraocular surgical procedures, dry eye, slowed wound healing, and decreased corneal sensitivity [2–4].

Hyperglycaemia causes chronic metabolic stress which seems to be the reason for the disturbance of corneal endothelial cells. These cells are presented as a monolayer of hexagonal cells, and they do not possess the ability of regeneration [5]. They are responsible for maintaining the dryness of the cornea by pumping the ions and water into the anterior chamber. DM decreases the activity of Na^+–K^+ATPase pump in corneal endothelium [2]. By decreasing the number of corneal endothelial cells and interrupting their function, DM causes corneal edema followed by increased central corneal thickness (CCT) and eventually decreased visual acuity [6].

Changes in CCT can cause difficulties in the measurement of the intraocular pressure (IOP). It represents the most important and treatable risk factor for glaucoma. During the Goldmann applanation tonometry, due to stronger impedance, thicker cornea expresses falsely increased IOP values [7]. Some studies revealed that the raise of 25 μm of CCT increases the IOP value for 1 mmHg [8]. IOP, alongside visual field testing, gonioscopy, and fundus examination, is the most important criterion in diagnosing and monitoring the progression of glaucoma. That fact ensures the importance of precise measurement of IOP [9]. Some investigators claimed that the duration of DM and the level of glycated hemoglobin A_{1C} (HbA_{1C}), as well as the status of diabetic retinopathy, have a huge influence on the CCT in DM patients [3, 10, 11].

The aim of this study was to investigate the influence of DM type 2 on CCT.

Methods

The study was designed as a cross-sectional, observational study. It was approved by the local Ethics Committee and carried out at the Clinic for Ophthalmology, Clinical Center of Kragujevac, Serbia. The research was performed in February 2020. It included patients of both sexes with the confirmed diagnosis of DM type 2, as well as the health participants recruited in the control group.

The inclusion criterion was confirmed DM type 2 before the research. The study exclusion criteria were: the presence of other DM types, incomplete information of the DM status, corneal pathology (edema, degeneration, dystrophy), patients with previous intraocular surgeries or trauma, cataract, dry eye, pterygium, glaucoma, myopia, uveitis. Patients on long-term anti-inflammatory therapy, those with a history of photocoagulation in the last three months, contact lens wearers, and pregnant women were also excluded from the study. According to the tenets of the Declaration of Helsinki, all patients gave their written consent at the beginning of the study. Once the consent was obtained, demographic and clinical data were collected: gender, age, duration of DM, antidiabetic therapy, associated diseases, and HbA_{1C}.

A detailed ophthalmological examination was performed in every patient: the best-corrected visual acuity (BVCA), slit-lamp biomicroscopy, IOP measurement using Goldman applanation tonometer, detailed fundus examination in maximal mydriasis, ultrasound pachymetry (PalmScan P2000 FastPach, Micro Medical Devices, Inc., Calabasas, CA, 91302 USA), and in indicated cases fluorescein angiography and ocular ultrasound.

The investigation included 96 participants divided into two groups. The first group involved 49 patients with diagnosed DM type 2. The second group was the control group and consisted of 47 healthy participants. According to the clinical characteristics, based on the results from the Early Treatment Diabetic Retinopathy Study (ETDRS) [11], patients from the DM group were further divided into three groups: group without diabetic retinopathy (DR, n = 23 patients), group with nonproliferative DR (NPDR, n = 15 patients), and group with proliferative DR (PDR, n = 11 patients).

The DM group was also divided according to the duration of DM in the subgroup of patients who have treated DM for more than 15 years (19 patients) and the subgroup of patients who have treated DM less than 15 years (30 patients).

Finally, depending on the level of HbA_{1C} diabetic patients were divided into the subgroup of patients with HbA_{1C} < 7.0% (25 patients) and the subgroup of patients with HbA_{1C} with > 7.0% (24 patients).

A complete ophthalmological examination was conducted. We calculated CCT as the mean value of the three consecutive measurements.

IBM SPSS version 22.0 was used for the statistical analysis. According to the normality of distribution, the paired *t*-test, χ^2, Person's test, Mann-Whitney test were performed in analyzing the association between the values of continuous variables (CCT, patients' demographic characteristics). In analyzing statistical differences of CCT between the more than two subgroups, we used ANOVA. The Pear-

son's correlation test was used to calculate the relationship between continuous variables. The results were shown as mean ± standard deviation (SD). Values $p < 0.05$ and $p < 0.001$ were considered statistically significant.

Results

The DM group consisted of 25 female and 24 male patients. The control group included 47 healthy participants, 26 females and 21 males. No statistically significant difference was recorded between groups in sex distribution ($p = 0.668$). The mean age in the control group was 58.5 ± 11.6 years (range 47–70 years), while it was 57.7 ± 11.6 years (range 38–72 years) in the DM group. No statistically significant difference was noticed between these two main groups ($p = 0.701$).

However, a quite different age distribution was presented between DM subgroups (Table 1). According to the status of DM, a statistically significant difference in age distribution was recorded between patients without DR compared to those in the NPDR subgroup ($p = 0.041$) and to patients who had PDR ($p = 0.038$). No statistical significance was seen between those with NPDR and PDR ($p = 0.067$). High statistical significance was noticed among participants who were treating DM for more than 15 years, compared to those who treated it for less than 15 years ($p = 0.027$). Depending on the level of HbA_{1c} statistical significance was not found in patients' age ($p = 0.058$).

Table 1

Age distribution in diabetic subgroups

Patients	Mean age ± SD (years)
Without DR	46.9 ± 3.1
NPDR	54.4 ± 6.4
PDR	56.5 ± 4.2
DM > 15 years	56.4 ± 9.1
DM < 15 years	48.1 ± 4.6
HbA_{1c} < 7.0%	47.8 ± 4.4
HbA_{1c} > 7.0%	50.2 ± 5.1

SD – standard deviation; DR – diabetic retinopathy; DM – diabetes mellitus; HbA_{1c} – glycated hemoglobin A_{1C}; DR – diabetic retinopathy; NPDR – non-proliferative DR; PDR – proliferative DR.

CCT was carefully measured in every participant. The DM group had CCT of 558 ± 27 μm, while it was 523 ± 14 μm in the control group. High statistically significant difference was noticed between groups ($p = 0.013$). Examining CCT in DM patients and comparing them to each other, the differences between the DM subgroups were revealed. Depending on the status of DR, the highest CCT value was measured in patients with PDR (553 ± 13 μm). Patients with NPDR had CCT 550 ± 12 μm, while those without DR had CCT 544 ± 12 μm. However, the difference among these subgroups was insignificant. Patients treating DM for more than 15 years had obviously thicker cornea (568 ± 18 μm) compared to those who have treated DM less than 15 years (551 ± 12 μm). This difference was statistically significant ($p = 0.037$). In patients with $HbA_{1c} > 7.0\%$, the highest CCT values was found (574 ± 15 μm), while the patients with $HbA_{1c} < 7.0\%$ had CCT 548 ± 13 μm. The difference between these subgroups was highly statistically significant ($p = 0.002$).

Analyzing all participants, the highest CCT value was measured in 5 patients who had $HbA_{1c} > 7.0\%$ and had treated DM for more the 15 years. Their mean CTT was 578 ± 17 μm.

IOP was significantly higher in the DM group (16.2 ± 2.1 mmHg) in comparison with the control group (12.4 ± 2.3 mmHg) ($p = 0.034$). Analyzing only DM patients, subgroups with DM duration > 15 years and $HbA_{1c} > 7.0\%$ had the highest IOP values (Figure 1). Results in these patients were significantly higher compared to the adequate subgroups ($p < 0.001$). We calculated a moderately positive correlation between IOP and CCT values in patients treating DM for more than 15 years ($r = 0.34$), and strongly positive correlation in patients with $HbA_{1c} > 7.0\%$ ($r = 0.57$).

Discussion

The average CCT in the healthy population is about 540 ± 30 μm [8]. CCT represents the metabolic status of the cornea as well. Due to that fact, CCT is prone to change in various metabolic disorders, such as DM. Many previous studies indicated that CCT is higher in patients with DM [12, 13]. These results are in a correlation with the results collected from our

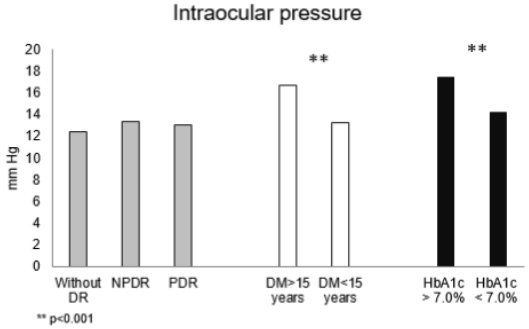

Fig. 1 – Mean intraocular pressure (IOP) in diabetes mellitus (DM) subgroups – group without diabetic retinopathy (DR), group with non-proliferative DR (NPDR), and group with proliferative DR (PDR).
HbA_{1c} – glycated hemoglobin A1c.

study. We noticed a statistically significant difference in CCT between the control and the DM group. It could be concluded that the changes in corneal tissue were directly associated with DM.

Some authors believe that increased values of CCT are among the first changes that occur in people with DM [5, 6]. A possible pathophysiological mechanism is that hyperglycemia leads to endothelial pump dysfunction, which leads to stromal hydration and increased CCT values [14]. Experimental studies have shown that DM reduces Na^+–K^+ATPase activity in the corneal endothelium. One of the proofs of interrupted endothelial pump function is the decreased ATP production [15]. That is caused due to the slowed Krebs cycle, which is present in diabetic cornea [11]. Another postulated mechanism is that hyperglycemia increases the level of aldose reductase, an enzyme involved in sorbitol synthesis. That activates the sorbitol pathway and increases its level in the cornea. Sorbitol acts as an osmotic agent and causes stromal hydration [16]. By increasing the corneal permeability, these mechanisms lead to morphological changes, such as decreased endothelial cell density, decreased percentage of the hexagonal cell below 50%, and increased coefficient of variation of cell area [17, 18]. That is subsequently followed by increased CCT.

Earlier studies showed quite different CCT values among DM patients depending on glycemic control, presence of retinopathy, or duration of disease [3, 10]. We found no statistically significant difference among patients with PDR, NPDR, and patients without DR. That finding was in accordance with the results of Canan et al. [16]. However, we examined statistically significantly thicker cornea in patients treating DM for more than 15 years. It could be concluded that mechanisms mentioned to be responsible for swelling the cornea in DM patients had an accumulative effect during the years. Regarding the HbA_{1C} level, our research found a correlation with elevated CCT. These results were quite similar to the investigation of Yazgan et al. [19]. Opposite of these findings, Scheler et al. [20] have not reported a significant difference comparing the healthy population and DM patients with good metabolic control, with DM patients who had $HbA_{1C} > 7\%$.

IOP stands as the most important risk factor in glaucoma development. Unlike age, gender, race, refractive error, IOP is a risk factor that can be corrected. Prescribing adequate antiglaucoma therapy, the progression of glaucoma can be stopped or at least delayed [9]. Therefore, accurate IOP measurement is extremely important in diagnosing and treating glaucoma. Changes in CCT in DM patients can affect IOP values. Many earlier studies advocated that IOP values were higher in DM patients compared to the healthy population [3, 7, 14]. Our results were similar to these findings. Highly statistically significant difference between the healthy participants and the DM patients was noticed. The highest IOP values we recorded were in patients with PDR and DM > 15 years and patients who had $HbA_{1C} > 7\%$.

Conclusion

Previous research mostly investigated the influence of DM on the posterior eye segment. Our research throws light on the complication that DM can produce in the cornea. Regarding that the increase of CCT also affects the measured values of IOP, this study could be useful in better understanding and better control of patients with DM type 2 who also have glaucoma. Our results indicated that the strongest effect on CCT and subsequently IOP had patients with poor glycemic control, as well as those who have treated DM for more than 15 years. We can assume that the presence of a positive correlation between IOP and CCT values in these two DM subgroups points out that some other, still unknown mechanisms, might have an influence on IOP and CCT in these patients. That hypothesis will be better understood when some future investigations are done. In addition, our research demonstrated that the status of retinopathy had no statistically significant influence on the central corneal thickness.

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