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Effect of Multiple Intravitreal Injections of Ranibizumab on Corneal Endothelial Cells

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Abstract

Background: One of the leading causes of legal blindness in adults of working age globally is diabetic retinopathy (DR). One of the main causes of central vision impairment in people with DR is diabetic macular edema (DME). Longer duration of diabetes and higher levels of haemoglobin (HbAlc) that has been glycosylated are linked to a higher risk of developing DME.

Aim of Study: To examine corneal endothelial cells using specular microscopy to determine the impact of repeated intravitreal ranibizumab injections in diabetic patients.

Patients and Methods: This interventional prospective study was conducted on 20 eyes of 20 patients with diabetic macular edema from February 2021 to November 2022 on 20 eyes of 20 recruited from the Ophthalmology department, Ain Shams university hospital and Research institute of ophthalmology. All the study participants were investigated using specular microscopy before intravitreal ranibizumab injections and one month after three IV ranibizumab injections.

Results: According to the current study, there was no significant correlation between (sex, eye side, type of treatment and duration of diabetes) with endothelial cell density either before injection and after ranibizumab injection. Using logistic regression, after adjustment to other variables, it was shown that age was the significant independent factor affecting endothelial cell count (cell density). Cases with higher age have lower CD.

Conclusion: Intravitreal injection of ranibizumab on the corneal endothelium is a safe treatment during a short follow-up period.

Key Words: *Multiple intravitreal injections — Ranibizumab — Corneal endothelial cells.*

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Introduction

DIABETES mellitus (DM) affects almost 400 million people throughout the world; it is considered a global epidemic disease. By 2040, that number is predicted to rise reach to 640 million [1].

Diabetic retinopathy (DR) involves microaneurysms or worse lesions affecting at least a single eye. It is one of the most pervasive secondary microvascular complication intrinsic in diabetes mellitus **(DM),** induced by leakage from breakdown of the inner blood-retinal barrier and microvascular occlusion **[2].**

Diabetic macular edema (DME) is a sight threatening disease causes blindness for people in working age. The pathogenesis is multifactorial and complex. Diabetic macular edema (DME) pharmacotherapy addresses both the inhibition of vascular endothelial growth factor (VEGF) by the intravitreal injection of VEGF inhibitors and inflammatory processes by the intravitreal application of steroids [3].

DME can develop at any stage of DR as a result of chronic hyperglycemia; it is marked by vascular hyperpermeability and fluid buildup at the macular area as a result of the blood-retinal barrier being breached [4], and vascular endothelial growth factor (VEGF) plays a crucial role in the pathogenesis of DME ***[5].***

Anti-VEGF medications have been observed to block VEGF signal by binding to VEGF receptors, hence preventing the creation of aberrant blood vessels and reducing vascular permeability **[6].**

The corneal epithelium, stroma, and endothelium all contain VEGF and its receptors, so anti-VEGF therapies may have an impact on the cor-

nea **[7],** as it has been demonstrated that patients with DM have lower endothelial cell density (ECD) than non-diabetic controls **[8].** Therefore, intravitreal injections may further strain the already compromised endothelial cells of DME patients.

In light of the above, the purpose of this study was to evaluate the impact of the intravitreal antiVEGF injections, ranibizumab, on corneal endothelial cells using specular microscopy.

Aim of the work:

The aim of this work is to evaluate the effect of repeated intravitreal ranibizumab injections on corneal endothelial cells using specular microscopy in diabetic patients.

Patients and Methods

This study was carried out from February 2021 to November 2022 on 20 eyes of 20 patients attending outpatient clinic, Ophthalmology department, Ain Shams University Hospital and Research Institute of Ophthalmology. The ethical standards stated by the Ethical Committee of Ain Shams Hospital were followed. Informed written consent was obtained from all participating patients after explanation of the study purpose and procedures.

Inclusion criteria: Male and female patients aged 40-80 years old with type 2 DM. Clinically significant macular edema, diagnosed clinically and confirmed with OCT with a bestcorrected visual acuity (VA) of 20/30 or worse.

Exclusion criteria: Ocular disease that could alter the corneal endothelium morphology, such as Fuchs' corneal dystrophy or iridocorneal endothelial syndrome. Intraocular surgery within a 6-month period before and after ranibizumab injection. Laser treatment within a 2-month period before and 6-month period after the injection. Anti-VEGF antibody injection within a 6-month period before the injection. Endothelial cell count of $<1,500/mm^2$ before the initial ranibizumab injection. Patients experienced systemic or ocular complications after IVI including intraocular inflammation, endophthalmitis, or thromboembolic events. Patients with history of glaucoma or elevated intraocular pressure (TOP) during follow-up. If paracentesis was performed before or after anti-VEGF injection, the case was excluded. History of trauma or ophthalmic surgery. Coexisting retinal or neuro-ophthalmologic diseases. Patients with systemic diseases other than controlled hypertension or DM. Patients with history of contact lens use.

Methods:

Methodology: This was a prospective interventional study performed on patients presented to the clinic with DME indicated for intravitreal ranibizumab injections.

Intervention:

All included patients were subjected to the following:

Pre-operative assessment:

Detailed history taking including: Demographic data. Medical history and comorbidities (hypertension, hyperlipidaemia) of all participants were recorded. Detailed ocular history (Prior ocular surgeries, laser treatment, ocular surgery or other eye diseases or medications).

Clinical examination: Full systemic clinical examination. Standard ophthalmologic assessment including: Best corrected Snellen visual acuity. Intraocular pressure measurement using Goldman applanation tonometer. Slit-lamp examination. Binocular indirect ophthalmoscopy fundus examination. To confirm the diagnosis of DME, spectral domain optical coherence tomography (SDOCT; RTVue XR OCT Avanti; Optovue, Fremont, USA) was conducted. Before the initial injection, endothelial cell examination was done using specular microscopy measures.

A specular microscope CEM-530 (NIDEK, Gamagori, Japan) was used to quantify corneal endothelial cell density (ECD) in a small area (0.25 x 0.55 mm) while performing noncontact specular microscopy of the central cornea.

The specular microscope automatically calculated the ECD, average cell size (AVG), standard deviation of cell size (SD), coefficient of variation of cell size (CoV), maximum cell size (MAX), minimum cell size (MIN), and percentage of the hexagonal cells (Hex%). The central corneal thickness was assessed and optical pachymetry measures were also provided by specular microscopy. (Fig. 1).

Operative procedure:

Treatment with intravitreal ranibizumab 0.5mg (0.05m1 of 10mg/m1 solution). All patients plan to leading dose three injection.

Technique of injection:

Conjunctival anesthesia was 0.4% topically induced by instillation of Benoxinate eye drops. The eyelids and ocular surface were disinfected with iodine.

In an operating room, 0.5mg (0.5mg/0.05mL solution) of ranibizumab was given into the inferotemporal quadrant via the pars plana and into the vitreous cavity 3.5 to 4mm from the limbus using a 30-gauge needle.

The post-injection vision was assessed. A topical 0.5% levofloxacin eye drops was instilled four times daily for 3 days before and after each intravitreal injection.

Postoperative evaluation and follow-up: Endothelial cell analysis was repeated after one month of the last intravitreal ranibizumab injection.

10P measurement: The IOP in the cases before injection ranged from 13 to 22mmHg, with a mean of 17.85±2.13mmHg The IOP in the study cases after injection ranged from 12 to 22mmHg, with a mean of 17.40±2.33mmHg

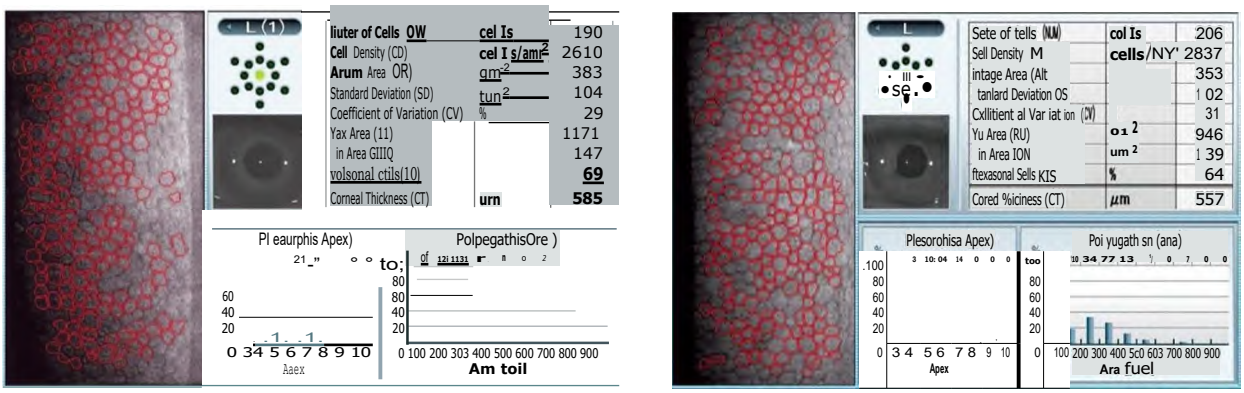
Statistical methods:

Analysis of the collected data was done using the Statistical Package for Social Science (IBM Corp., 2017 release), Paired t-test was used to assess the statistical significance of the difference between two means measured twice for the same study group. The type of data obtained for each parameter was given, and an appropriate analysis was carried out. p-value: Level of significance: p<0.05: Significance (S). p>0.05: Non significant (NS). p<0.001: Highly significant (HS).

Outcome:

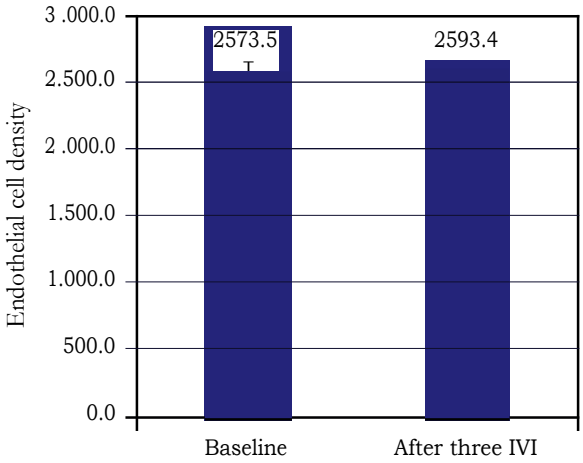
Primary outcome: To compare between corneal endothelial cells parameters before and after three intravitreal ranibizumab injections/monthly injection.

Secondary outcome: Complications of IVE on corneal endothelium: Change in BCVA and Change in CME.



(A): Pre operative WI. (B): Post operative one month after three IVI.

Fig. (1): This is specular microscopy imaging for the a female case 63 years old diabetes mellitus since 23 years ago. (A) Pre operative WI, (B) One month after three IVI.



Graph (1): Endothelial cell density at baseline and one month after three doses of IVI.

Results

A- Demographic data:

I- *Age:*

The mean age of the study group was 56.55± 9.62 years, ranging from 42.0 years to 76.0 years.

II- Sex:

The study included 14 females (70%) and 6 males (30%).

III- Duration of DM:

The mean duration of DM 17.60±5.56 years, ranging from 10.0 to 30.0 years.

IV- Treatment modalities of DM:

Twenty eyes participated in the study, of which thirteen were treated with insulin at a rate of sixty five percent, and seven cases were treated with OHG at a rate of thirty-five percent.

V- Eye injected:

Twenty eyes participated in the study, thirteen patients were injected in OS while seven of them were injected in OD, the rate of the OS was sixty five percent and the rate of the OD was thirty five percent.

B- Specular microscopy data:

I- *Mean endothelial cell density before and after injection:*

There was no statistically significant difference between males and females (p=0.630), insulin and

OHG treated patients (p=0.495), OD and OS eye (p=0.652), as regard endothelial cell density before injection and there was no statistically significant difference between males and females (p=0.669), insulin and OHG treated patients (p=0.275), OD and OS eye (p43.402), as regard endothelial cell density after injection (Table 1).

II- Correlation endothelial cell denisty between the results of specular microscopy wih the demographic data before and after injection:

There was no statistically significant Correlation between each of age, diseases duration and Cell count before and after injection (Table 2).

III- Regression to endothelial cell density before injection:

Using logistic regression, after adjustment to other variables, it was shown that Age was the significant independent factor affecting endothelial cell count (cell density). Cases with higher age have lower CD (regression coefficient=-18.19, CI=-34.9 to -1.47, p<0.05) (Table 3).

IV- Comparison between Specular microscopy data before and after injection:

There was no statistically significant difference between before and after injection endothelial cell count (ECD), AVG CV, MAX, MIN, HEX. However, There was a statistically significant difference between CT before and after injection (p=0.027) (Table 4).

V- Regression to endothelial cell density after injection:

Using logistic regression, after adjustment to other variables, it was shown that Endothelial cell count before injection was the significant independent factor affecting endothelial cell count (cell density) after injection (regression coefficient=0.704, CI=0.229 to 1.17, p<0.05) (Table 5).

Table (1): Relation between personal characteristics, endothelial cell density before and after injection.

	Sex		Teatment		Eye side	
	Female	Male	Insulin	OHG	OD	OS
Before Endothelial cell density (ECD):						
Mean	2552.50	2622.50	2540.23	2635.29	2532.57	2595.54
±SD	311.00	240.17	338.55	158.04	413.70	208.46
P	0.630		0.495		0.652	
Sig.	NS		NS		NS	
After Endothelial cell density (ECD):						
Mean	2611.64	2550.83	2542.00	2688.86	2519.57	354.28
±SD	195.92	441.93	306.97	209.01	2633.15	237.91
P	0.669		0.275		0.402	
Sig.	NS		NS		NS	

*Student t-test.

Table (2): Correlations between each of age, diseases duration and endothelial cell density before and after injection.

	Age			Duration of diabetic		
	r	p-value	Sig.	*r*	p-value	Sig.
ECD before injection	-.359	.120	NS	.139	.560	NS
ECD after injection	-.183	.441	NS	.128	.590	NS

*Pearson Correlation.

Table (3): Multivariate logistic regression to study independent factors affecting endothelial cell density before injection.

	Regression Coefficients (B)	*P*	Sig.	%95.0 Confidence Interval for B	
				Lower Bound	Upper Bound
Age	-18.191	0.035	S	-34.903	-1.478
Sex	-118.317	0.381	NS	-397.71	161.07
Duration of diabetic	26.55	0.063	NS	-1.663	54.77
Medication	-51.037	0.711	NS	-339.401	237.32

Table (4): Comparison between before and after injection specular microscopy parameters.

	Mean	±SD	*p*	Sig.
Endothelial cell count before injection	2573.50	287.13	0.706	NS
Endothelial cell count after injection	2593.40	280.14		
AVG before injection	393.80	49.80	0.761	NS
AVG after injection	390.45	47.98		
SD before injection	133.10	107.54	0.582	NS
SD after injection	119.25	36.46		
CV before injection	34.10	17.42	0.592	NS
CV after injection	31.90	6.29		
MAX before injection	1285.20	732.29	0.158	NS
MAX after injection	1035.55	222.12		
MIN before injection	137.00	15.59	0.748	NS
MIN after injection	138.6	13.6		
HEX before injection	68.00	6.42	0.102	NS
HEX after injection	64.40	7.04		
CT before injection	538.40	43.50	0.027*	S
CT after injection	528.85	37.08		

*Paired t-test.

Table (5): Multivariate logistic regression to study independent factors affecting endothelial cell density after injection .

	Regression Coefficients (B)	*P*	Sig.	%95.0 Confidence Interval for B	
				Lower Bound	Upper Bound
Age	4.96	0.536	NS	-11.849	21.788
Sex	112.59	0.346	NS	-135.066	360.260
Duration of diabetic	-1.438	0.912	NS	-28.872	25.996
Medication	-109.62	0.363	NS	-359.744	140.500
Endothelial cell density before injection	0.704	0.007	HS	0.229	1.179

Discussion

Therapeutic intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents represent a novel therapy in ophthalmology. Ranibizumab is a (Fab) fragment of a humanized monoclonal anti VEGF-A antibody, also against all VEGF-A isoforms [91.

The aim of this work was to evaluate the effect of repeated intravitreal ranibizumab injections on corneal endothelial cells using specular microscopy.

This interventional prospective study included 20 eyes of 20 DME patients. The mean age of this study patients was 56.5 years, 70% of them were females.

All the study participants were investigated using specular microscopy before IV ranibizumab injections and one month after three IV ranibizumab injections.

Among the present study patients endothelial cell count (ECD) before injection was 2573.5± 287.13 cells/mm^2 and after injection was 2593.4± 280.14 cells/mm^2, the difference was statistically insignificant.

Joshi et al. [io] found no difference in endothelial cell density, central corneal thickness, coefficient of variation, or intraocular pressure before and after a single intravitreal injection over a month of follow-up.

In agreement with the current study, Guzel et al. [in reported that in patients with DME there was no significant difference between endothelial cell count before and after 3rd intravitreal ranibizumab injection; 2198.9±253.4 cells/mm^2 and 2231.6± 259.8 cells/mm^2, respectively.

Perez-Rico et al. **[12]** investigated the effect of intravitreal injection of ranibizumab on the corneal endothelium in patients with choroidal neovascu-

larization in age-related macular degeneration. The results were supporting to this study, where there non-significant difference between Endothelial cell count before and after **3rd** intravitreal ranibizumab injection.

Also, Bentez-Herreros et al. **[13]** used corneal specular microscopy to undertake a morphometric examination of corneal endothelium following 0.5 mg intravitreal ranibizumab injection in AMD patients. There was no significant difference in corneal endothelial cell density at 6 months in their investigation.

Conversely, Urban et al. **[14]** found that among age-related macular degeneration (AMD) patients the mean ECD before intravitreal ranibizumab injection was 2397.14±459.33 cells/mm^2, and it was significantly lower after each intravitreal ranibizumab injection. The difference from the current study may be attributed to the mean age difference (72.36 years versus 56.5 years in their study and current study, respectively).

The average corneal cell size (AVG), maximum of cell size (MAX) and also, minimum of cell size (MIN) before and after injection were 393.8pm ±49.80 SD and 390.4pm±47.98 SD, respectively, With standard deviation of cell size (SD) before injection 133.1p m±107.54 SD and after injection 119.25pm±36.46 SD. The differences were statistically non-significant. The percentage of hexagonal cell (HEX) before injection was 68.00pm±6.42 SD and after it became 64.40pm±7.04 SD, with insignificant difference.

Perez-Rico et al. **[15]** conducted a prospective observational case series research on the influence of intravitreal ranibizumab on corneal endothelium in individuals with age-related macular degeneration to support the current study. The study found no significant differences in endothelial cell count, coefficient of variation, % of hexagonal cells, or central corneal thickness after a 6-month follow-up.

On the other hand, Urban et al. **[14]** looked into changes in the proportion of hexagonal cells (% Hex) in AMD patients receiving injections of ranibizumab. After each intravitreal ranibizumab injection and six months after the initial injection, the percentage of hexagonal cells started to fall. These variations were statistically significant.

The results were different from this study, this can be explained by the different baseline hexagonal cells, where in Urban et al. **[14]** it was lower (53.7±8.6%) than the present study.

Corneal thickness (CT) before injection in this study was 538.40p m±43.50 SD, and after injection was 528.85pm±37.08 SD. The Corneal thickness (CT) difference after injection was significantly thinner. Although this is a statistically significant result, however, such minor changes (10pm) this difference could be related to the machine reproducibility rather than actual thinning

In contrast to this result, some studies show no significant difference in the central corneal thickness (CCT) before and after the injection, Urban et al. **[14],** Perez-Rico et al. **[15],** Bentez-Herreros et al. [in Joshi et al. [10] and Chiang et al. [16] reported no statistically significant difference in the CCT before injection at one-, three-, and six-months after the injection.

According to the current study, there was no significant correlation between (sex, eye side, type of treatment and duration of diabetes) with endothelial cell density either before injection and after ranibizumab injection. Using logistic regression, after adjustment to other variables, it was shown that age was the significant independent factor affecting endothelial cell count (cell density). Cases with higher age have lower CD. The same was reported in Vila Gonzalez et al. **[17]** study.

This can be supported by the fact that ECD, CCT and the average size of corneal endothelial cells directly correlated with age **[18].** Furthermore, other Egyptian study detected that mean endothelial cell density (MCD) significantly decreased with an increase in age, while mean cell area (MCA) increased with age **[19].**

In a population-based study age and sex were significantly correlated with ECD **[20].**

Conclusion:

Intravitreal injection of ranibizumab is a safe treatment during a short follow-up period.

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تأثير الحقن المتعدد لمادة الرانيبيزوماب بالجسم الزجاجى للعين على الخلايا المبطنت للقرنيت

أعتلال الشبكية السكرى هو أحد الأسباب الرئيسية للعمى لدى البالغين فى السن المبكر فى جميع أنحاء العالم.

مرض ارتشاح الماقولة السكرى سبب رئيسى لضعف مركز الإبصار بين مرضى اعتلال الشبكية السكرى ويرتبط خطر الإصابة بالارتشاح السكرى بمدة أطول لمرض السكر وارتفاع مستويات السكر التراكمى.

يقدر معدل الانتشار العالمى للارتشاح فى مركز الإبصار بنحو ٧,٥٪، ويؤثر على ما يقرل من ٢١ مليون فرد.

نظراً لأن معدل انتشار مرض السكرى يتزايد بكثرة ومن المتوقع أن يرتفع بأكثر من ٥٠٪ على مستوى العالم من عام ٢٠٠٠ إلى عام ٢٠٣٠، حيث يُقدر أن يصل عدد حالات الإصابة بمرض السكرى إلى ٣٦٦ مليوناً فى جميع أنحاء العالم بحلول عام ٢٠٣٠، وبالتالى فإن مرض ارتشاح الماقولة السكرى سيسبب عبئاً طبياً هائلاً على مستوى العالم.

على الرغم من أن السبب فى ارتشاح مركز الإبصار لم يتم توضيحه بالكامل بعد، فمن المعروف أن المستويات المرتفعة لعامل نمو بطانة الأوعية الدموية فى الجسم الزجاجى مع زيادة نفاذية الأوعية الدموية تلعب دوراً فى تطور الارتشاح الماقولة السكرى.

أظهر العلاج داخل الجسم الزجاجى المضاد لعامل نمو بطانة الأوعية الدموية نتائج واعدة لعلاج الارتشاح فى مركز الابصار فى العديد من التجارب السريرية العشوائية الكبيرة مؤخراً. أصبح الحقن داخل الجسم الزجاجى للعوامل المضادة لعامل نمو بطانة الأوعية الدموية هو خط العلاج الأول لمرضى ارتشاح مركز الابصار الناتج عن السكر.

وبالتالى، فإن الغرض من هذه الدراسة هو تقييم تأثير حقن رانيبيزوماب داخل الجسم الزجاجى المتكرر على الخلايا البطانية للقرنية بإستخدام الفحص المجهرى المرآوى.

تضمنت هذه الدراسة ٢٠ مريضاً من المرضى الذين يعانون من ارتشاح فى مركز الابصار الناتج عن مرض السكرى. كان متوسط عمر المرضى فى هذه الدراسة ٥٦,٥ سنة ٧٠٪ منهم إناث.

تم فحص جميع المشاركين فى هذه الدراسة باستخدام الفحص المجهرى المرآوى قبل حقن رانيبيروماب وبعد شهر واحد من ثالث جرعة حقن رانيبيزوماب.

وجد أن عدد الخلايا البطانية قبل الحقن ٢٥٧٣,٥ خلية ±٢٨٧,١٣مم٢ وبعد الحقن كان ٢٥٩٣,٤ خلية ±٢٨٠,١٤ مم٢، والفارق ليس له دلالة إحصائية.

وجد أن متوسط حجم خلية القرنية، والحد الأقصى لحجم الخلية وأيضاً، الحد الأدنى لحجم الخلية قبل الحقن وبعده ٣٩٣,٨ ميكرون ±٤٩,٨٠ و ٤٥,٣٩٠ ميكرون ±٤٧,٩٨، على التوالى، مع المقياس المعيارى لحجم الخلية قبل الحقن ١٣٣,١٠ ± ١٠٧,٥٤ وبعد الحقن ١١٩,٢٥ ± ٣٦,٤٦. لم تكن الفروق ذات دلالة إحصائية. كانت النسبة المئوية للخلية السداسية قبل الحقن ٦٨,٠٠٪ ± ٦,٤٢ وبعدها أصبحت ٦٤,٤٠٪ ± ٧,٠٤، مع فارق ليس له دلالة إحصائية.

وجد أن سمك القرنية قبل الحقن فى هذه الدراسة ٥٣٨,٤٠ ميكرومتر ±٤٣,٥٠ وبعد الحقن ٥٢٨,٨٥ ميكرومتر ±٣٧,٠٨. كان الفرق فى سمك القرنية بعد الحقن آرق بشكل ملحوظ وكان الفارق ذو دلالة إحصائية، وعلى الرغم من أن هذه النتيجة ذات دلالة إحصائية مختلفة إلا أن هذا التغيير ضئيل بنسبة (١٠ ميكرومتر) ويعود ذلك إلى إحتمالية تكرار القراءة فى جهاز المجهر المرآوى مما قد يجعل سمك القرنية أرق.

وفقاً للدراسة الحالية، لم نجد ارتباطاً بين (الجنس وجانب العين ونوع العلاج ومدة مرض السكرى) مع كثافة الخلايا البطانية سواء قبل الحقن أو بعد حقن رانيبيزوماب. بإستخدام الإنحدار اللوجيستى فى الإحصاء، وبعد التعديل مع المتغيرات الأخرى، تبين أن العمر هو العامل المستقل المهم الذى يؤثر على عدد الخلايا البطانية (كثافة الخلية). فبالتالى كثافة الخلية فى الحالات ذات العمر الأكبر تكون أقل.

فى الختام، يعتبر الحقن داخل الجسم الزجاجى من رانيبيزوماب علاجاً أمناً خلال فترة متابعة قصيرة.