Usefulness of corneal esthesiometry for screening diabetic retinopathy

Utilidade da estesiometria corneal na triagem da retinopatia diabética

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Keywords
Diabetic retinopathy, diagnosis. Sensitivity and specificity. Mass screening. Cornea. Corneal esthesiometry.

Abstract

Objective
To assess the usefulness of corneal esthesiometry for screening diabetic retinopathy.
Methods
A cross-sectional study was carried out comprising 575 patients attending a diabetic retinopathy-screening program in the city of São Paulo. Corneal esthesiometry was assessed with the Cochet-Bonnet esthesiometer. The presence of diabetic retinopathy was detected with indirect fundoscopy. The validity of corneal esthesiometry in identifying diabetic retinopathy was evaluated by the Receiver Operating Characteristic (ROC) curve.
Results
Sensitivity and specificity analyses of the corneal esthesiometry for detecting the stages of diabetic retinopathy using different cut-offs showed values less than 80%. The best indices (72.2% sensitivity and 57.4% specificity) were obtained for the identification of patients with proliferative diabetic retinopathy.
Conclusions
In the study series, corneal esthesiometry was not a good indicator of diabetic retinopathy.

Descritores
Retinopatia diabética, diagnóstico. Sensibilidade e especificidade. Triagem de massa. Córnea. Estesiometria corneal.

Resumo

Objetivo
Avaliar a utilidade da estesiometria corneal na triagem da retinopatia diabética.
Métodos
Foi realizado um estudo transversal (N=575) em um programa de triagem de retinopatia diabética da Cidade de São Paulo, SP. A sensibilidade corneal foi aferida utilizando-se o estesiômetro de Cochet-Bonnet. A avaliação da retinopatia diabética foi obtida por meio da fundoscopia indireta. A validade do uso da estesiometria corneal na identificação de pacientes com retinopatia diabética foi avaliada por meio de curvas de sensibilidade e especificidade (Receiver Operating Characteristics (ROC) curve).
Resultados
A análise da sensibilidade e da especificidade da estesiometria corneal na detecção dos diferentes graus de retinopatia, utilizando-se diferentes pontos de corte, mostrou resultados inferiores a 80%. O melhor resultado obtido ocorreu na identificação de

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pacientes com retinopatia diabética proliferativa, mostrando sensibilidade de 72,2% e especificidade de 57,4%.

Conclusões

Na série analisada, a estesiometria corneal não se mostrou um bom indicador da presença da retinopatia diabética.

INTRODUCTION

Diabetes, particularly diabetic retinopathy (DR), is the leading cause of new cases of blindness in adults in the United States and it is an increasing problem in Brazil due to the population aging. There is need to screen an enormous population of diabetic patients to identify those on risk of blindness and then be able to provide them treatment.[7,10]

The screening method considered to be the gold-standard in identifying DR and its different stages is the fundus photography.[1] This method not only requires expensive equipment but also implies recurrent cost. The current screening method in Brazil is the indirect ophthalmoscopy.[10]

The first description of corneal hypoesthesia in a diabetic patient credited the decreased sensitivity to the concomitant glaucoma.[3] In 1974 it was demonstrated that diabetic patients had a significant lower esthesiometry when compared to controls[17] but this study did not compare the relation to DR. In 1975 another study using the same data reported the usefulness of corneal esthesiometry to differentiate diabetic from non-diabetic patients.[5] The first citation of corneal esthesiometry being able to differentiate the stages of DR was published in 1980.[12] The use of corneal esthesiometry for screening DR with promising results was published in 1996.[15] The principle of this screening method is that corneal hypoesthesia and diabetic retinopathy are caused by a common factor (systemic disease) and tend to start and progress somewhat simultaneously.

The possibility of screening DR using a simpler method or even a device that could be handled by non-ophthalmologists has been explored. Methods assessing other features of diabetic cornea (autofluorescence[18] and epithelial fragility[14]) have been proposed. Using esthesiometry would be less cumbersome and it is also the most inexpensive of these methods. The Cochet-Bonnet esthesiometer is a portable non-electric device and its ability to identify DR was found to be similar to autofluorescence and epithelial fragility.[15]

Although the treatment of DR eventually demands an ophthalmoscopy, screening diabetic population with Cochet-Bonnet could maximize the capability of the public health system by helping non-ophthalmologists to identify those patients that should be referred to the ophthalmologist. Nevertheless, using esthesiometry for that purpose should only be advisable if the high sensitivity and specificity previously reported[15] were reproduced in a large diabetic population when compared to the current screening method.

It was compared corneal esthesiometry of diabetic patients of a diabetic retinopathy screening program with of DR (and its stage) detection data using indirect ophthalmoscopy to assess the usefulness of corneal esthesiometry for screening diabetic retinopathy.

METHODS

This study was designed to test corneal esthesiometry as a diagnostic tool for diabetic retinopathy. Indirect ophthalmoscopy was the gold-standard exam.

A cross-sectional study was carried out in a DR screening program in the city of São Paulo. The study population was formed by individuals who spontaneously engaged in the aforementioned program.

The studied screening program provides treatment to all populations with no restriction of residence area and even accepts patients from other cities. Screenings are usually held on a monthly basis. The selection was made after an interview and a biomicroscopy evaluation. There was no refusals to participate in the study. None of the subjects refused to be interviewed or to undergo biomicroscopy and indirect ophthalmoscopy. Patients with previous bilateral ocular surgery (N=18), chronic use of topical medication (N=16), external eye disease (N=10), early (<35y) diagnosis of diabetes (N=30) or corneal, lens or vitreous opacity not allowing indirect fundoscopy (N=8) were excluded. Age ($F=0.42$, $p=0.52$), gender ($X=0.26$, $p=0.60$) and proportion of different stages of DR ($X=3.36$, $p=0.49$) did not differ between included (N=575) and excluded patients (N=82).

Included patients underwent corneal esthesiometry before indirect fundoscopy. Corneal esthesiometry was obtained using the Cochet-Bonnet esthesiometer under good illumination. Initially the nylon filament was fully extended to 60 mm. The tip of the fiber was steadily advanced towards the cornea. When the examiner detected that the end plate of the nylon filament was in contact with the cornea a mild pressure was exerted such that the fiber had the slightest bend just visible. The response was considered to be positive either by the patient's subjective response or objective blinking. If a positive answer was not detected the fiber length was shortened in steps of 5 mm each time and the procedure was repeated until there was a positive response. The readings were taken in the central cornea. The procedure was repeated three times. The values in millimeters were converted into pressure units (g/mm^2) according to the data provided by the manufacturer. All measurements were performed by the same examiner.

To allow the analysis of eyes that did not present a positive response with the shortest length (5 mm) of the esthesiometer fiber the reciprocal of the pressure unit was used. Eyes with no response were classified as having no sensitivity and their pressures were considered to be a maximum value (infinite). All data in g/mm^2 were transformed into mm^2/g and those eyes were labeled with the minimum value (zero).

Corneal esthesiometry of each patient was classified as both arithmetical mean (two eyes) and esthesiometry of the less sensitive eye.

After esthesiometry, patients underwent detailed indirect ophthalmoscopy. Each patient was assigned to one of the following groups according to the most severe stage of retinopathy detected. The following classification was based on the Early Treatment Diabetic Retinopathy Study definitions:[6] normal (NoDR) – no alteration considered to be due to DR; mild non-proliferative diabetic retinopathy (MNPDR) – microaneurisms, intraretinal hemorrhages in less than four quadrants and hard exudates; moderate non-proliferative diabetic retinopathy (MoNPDR) – cotton-wool spots, intraretinal hemorrhages in four quadrants, venous beading and intraretinal microvascular abnormalities (IRMA); severe non-proliferative diabetic retinopathy (SNPDR) – presence of intraretinal hemorrhages in four quadrants, venous beading in two quadrants or IRMA in one quadrant; proliferative diabetic retinopathy (PDR) – neovascularization of the disc and/or retina. The presence of typical retinal scar was considered to be an indicator of previous retinal photocoagulation.

Data was processed using the NCSS Statistical Software (NCSS, PASS), 2000 Edition. All tests were analyzed at a level of 0.05 significance. Anderson-Darling normality test was used to assess the normality of age and esthesiometry distribution. Numeric variables showed normal distribution in all the studied groups. The esthesiometry did not show an equal variance among the groups and data was log-transformed. One-way ANOVA and post-hoc Bonferroni test were used in numeric data comparisons. The correlation between the two values (mean/less sensitive eye) of corneal esthesiometry was analyzed using the Pearson correlation coefficient. Proportion of nominal variables was compared applying the Chi-square test. Yates correction for continuity was applied in comparisons with only one degree of freedom.

The quality of corneal esthesiometry for screening DR was tested by the construction of Receiver Operating Characteristic (ROC) curves. For that the studied population was divided in three different ways: patients without DR/patients with any degree of DR; patients without DR or mild non-proliferative DR/ patients with any other stage of DR; patients without proliferative DR/patients with proliferative DR. For each division a curve was constructed to identify the power (sensitivity/specificity) of the esthesiometry in indicating the difference between the groups. The curves were analyzed by the area underneath it[8] and sensitivity/specificity at the best cut-off.

This study was approved by the Ethical Committee of the "*Universidade Federal de São Paulo*".

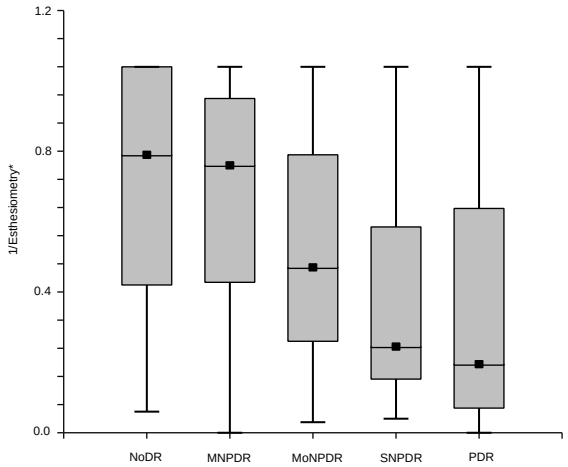
RESULTS

The mean age of included patients was 60.4 years (SD 9.6) and there was a slight predominance of fe-

Table 1 – Demographic features of included patients according to the presence and stage of diabetic retinopathy.

Feature		NoDR (N=282)	MNPDR (N=90)	MoNPDR (N=71)	SNPDR (N=24)	PDR (N=108)
Age (yrs) (Mean ± SD) F=0.36; p=0.78		60.6±9.7	61.6±9.1	63.6±10.7	63.7±8.9	59.9±9.3
Gender (%)	Male	48.9	43.3	51.4	29.2	48.2
X^2=4.72; p=0.32	Female	51.1	56.7	48.6	70.8	51.8

NoDR – Absence of diabetic retinopathy, MNPDR, MoNPDR, SNPDR – Mild, moderate, and severe non-proliferative diabetic retinopathy, respectively; PDR – Proliferative diabetic retinopathy.



NoDR – Absence of diabetic retinopathy, MNPDR, MoNPDR, SNPDR – Mild, moderate, and severe non-proliferative diabetic retinopathy, respectively; PDR – Proliferative diabetic retinopathy.
Median is the square in the center of the box. The top and bottom of the box are 25 and 75 percentiles. The end of the lines extends to the 90 and 10 percentiles.
*mm^2/g

Figure 1 - Distribution of corneal esthesiometry of the less sensitive eye according to the stage of diabetic retinopathy.

male patients (52.5%). These variables did not differ among the groups when patients were divided according to the stage of DR (Table 1).

It was detected a high correlation (r=0.933; p<0.001) between the two values (mean/less sensitive) of corneal esthesiometry. The distribution of the less sensitive eye esthesiometry according to the stage of DR is shown on Figure 1.

The comparison of these values showed that esthesiometry differed among the groups (F=24.32, p<0.001). Bonferroni post-testing indicated that corneal esthesiometry of patients with NoDR was less decreased than all the other groups (p<0.05). Among patients with any degree of DR the esthesiometry was similar only in groups adjacent in the DR severity spectrum (p>0.05 in the following comparisons: MNPDR x MoNPDR, MoNPDR x SNPDR, and SNPDR x PDR). All the others showed a significant difference (p<0.05) in esthesiometry when the groups were compared.

The distribution of corneal esthesiometry according to the presence of previous retinal photocoagulation in all different stages of DR is shown in Table 2. Forty-nine eyes were not included in the analysis due to previous ocular surgery (N=37) or chronic use of topical medication (N=12). The difference detected when eyes with previous photocoagulation were compared to those without a scar was not present in comparisons within each group of DR.

The ROC curves provided by the mean esthesiometry (between eyes) and the one corresponding to the less sensitive eye were similar in all the three sample subgroups. The area underneath the curves showed values from 0.655 to 0.736. The best area and the best sensitivity and specificity values were detected in patients with proliferative DR (Figure 2). Using a cut-off of 0.58 mm^2/g patients with proliferative DR were detected with 72.2% sensitivity and 57.4% specificity.

DISCUSSION

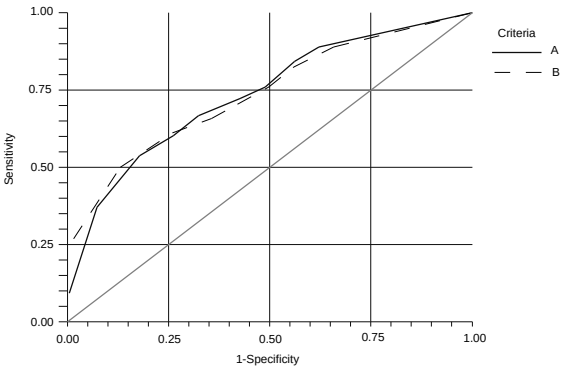
Blindness related to DR can only be prevented by providing diabetic patients an early diagnosis and treatment.[7] Not all diabetic patients have access to ophthalmology centers and a simple but effective screening would be beneficial, especially in developing countries. An ideal method of screening diabetic patients should be not expensive, be widely available, and feasible in the public health system. Corneal esthesiometry suits that but despite previous encouraging results,[15] its validity in screening diabetic patients has not been proved.

As the studied population spontaneously sought medical assistance, there may be a population bias with a higher number of severe cases (decrease in visual acuity) than the actual incidence of severe cases in the population. For that reason the predictive val-

Table 2 – Corneal esthesiometry according to the presence of retinal photocoagulation scar and the stage of diabetic retinopathy (per eye analysis). (N=1,101)

Diabetic Retinopathy	Photocoagulation scar				
	Absent		Present		
	%	Esthesiometry (mm^2/g) (Mean ± S.D.)	%	Esthesiometry (mm^2/g) (Mean ± S.D.)	p*
NoDR (N=555)	100.0	0.86±0.13	0	-	
MNPDR (N=180)	92.8	0.85±0.12	7.2	0.82±0.07	0.56
MoNPDR (N=138)	81.9	0.46±0.16	18.1	0.46±0.20	0.87
SNPDR (N=50)	80.0	0.26±0.13	20.0	0.26±0.12	0.95
PDR (N=178)	81.5	0.27±0.11	18.5	0.26±0.15	0.81
Total (N=1,101)	92.6	0.71±0.27	7.4	0.41±0.25	<0.001

NoDR – Absence of diabetic retinopathy, MNPDR, MoNPDR, SNPDR – Mild, moderate, and severe non-proliferative diabetic retinopathy, respectively; PDR – Proliferative diabetic retinopathy.
*One-way ANOVA.



A – Mean (area =0.736)
B – Less sensitive eye (area =0.736)

Figure 2 - Receiver Operating Characteristic (ROC) curve for corneal esthesiometry. Identification of patients with proliferative diabetic retinopathy.

ues (positive and negative) of corneal esthesiometry found in this series would not be useful when dealing with screening program with different ways of access, particularly in programs based on active search of patients in the community.

The methods of measuring corneal esthesiometry and staging DR were chosen based on the availability in the Brazilian public health system.[10] For corneal esthesiometry the Cochet-Bonnet esthesiometer is considered the standard method[9] and aside from being the most used instrument for that purpose is also an easy to handle device.

The use of fundus photographs analyzed in reference centers could have provided more accurate data regarding staging DR. Using that information instead of indirect ophthalmoscopy would not have elucidated whether corneal esthesiometry could provide similar results when compared with the current methods available in the Brazilian public health system.

The distribution of esthesiometry in groups with different stages of DR showed that hypoesthesia is progressive and parallels DR. This finding is important because this is an assumption when trying to use corneal esthesiometry for screening DR. Nevertheless, the analysis of Figure 1 also reveals that despite the progressive decrease in the median and 25-75 percentiles there is an important overlapping among the distributions. The distributions stretch through all the esthesiometry spectrum. This feature indicates that esthesiometry has limitations in identifying different groups and therefore for screening.

The influence of photocoagulation on the esthesiometry detected when all eyes with presumed photocoagulation were compared to eyes without scars (Table 2) was not present when the sample was divided according to DR stage. The total analysis was probably influenced by the significant predominance of patients with NoDR in the group without scar.

Alterations on corneal esthesiometry caused by retinal photocoagulation have been cited in the literature[11,12] but this factor was not related to a decrease in corneal esthesiometry in the present series. Recent studies with modern lasers have also failed to detect this relation.[13,16] In the study group it might be due to the fact that scars were not quantitatively analyzed. Patients with non-proliferative DR probably had focal laser for macula edema that requires fewer pulses/ low energy and the amount of energy is related to the induced hypoesthesia.

ROC curves are useful to compare a diagnostic tool to a gold-standard diagnosis. These curves can only be used for graded variables. Initially, the studied population is divided according to the gold-standard (positive/negative) and the potential diagnostic variable is measured in each patient. To plot the curve, the sensitivity and specificity of different cut-offs (all possible grades of the variable) are determined. If the distribution of the variable in the positive and negative groups (determined by the gold standard) does not overlap the variable is a perfect diagnostic tool and will show at least one cut-off with 100% sensitivity and 100% specificity. In such case, the specificity will only decrease in cut-offs with 100% sensitivity. Therefore, the area underneath the curve will be 1.0. When the distribution shows overlapping between groups, increasing the sensitivity will decrease the specificity.

ROC curves are useful to show how the potential diagnostic variable is capable of reaching high sensitivity without significant decrease in the specificity. Cut-offs with high sensitivity and specificity values will cause a left shift in the curve increasing the area below it. The total absence of diagnostic value for one variable will be detected if an increase in the sensitivity is paralleled by an equal decrease in sensitivity. In that case the area underneath the curve will be 0.5. If the calculated area underneath a ROC curve is smaller than 0.5 it only indicates that the relation of the potential diagnostic variable to the gold-standard (e.g. higher values indicates positive patient) should be considered the opposite way. There is no standardization to analyze the areas of ROC curves. Usually, a suitable diagnostic variable should present an area larger than the midpoint (0.75) of the possible range (0.5 to 1.0).

The area under the ROC curves showed small val-

ues (0.655–0.736) and indicated that esthesiometry was not a valid method to screen diabetic retinopathy in the studied population. The sensitivity and specificity of the method were more useful in the identification of patients with proliferative DR, but even in that differentiation the best cut-off (0.58 mm^2/g) showed sensitivity of 72.2% and specificity of 57.4%. These indices are very low and would not facilitate screening.

Corneal esthesiometry is changed in several conditions and that may also contribute to the lack of specificity of esthesiometry in identifying diabetic retinopathy. It has been shown that corneal esthesiometry is decreased in brown-eyed and elderly patients (especially if arcus senilis is present). Other ocular (e.g. herpetic infection, trauma, contact lens wearer) and systemic (e.g. neuropathies, congenital abnormalities) conditions may also cause corneal hypoesthesia.[9]

The 1980 report[12] showing good correlation of esthesiometry and DR stage described only 37 patients. Despite showing good differentiation between groups at the ends of the DR severity spectrum (NoDR and PDR), the author did not make considerations on patients in intermediate positions. In the study group if only NoDR and PDR were considered there would probably be better results, but only comparisons considering all patients are helpful in testing a diagnostic tool.

The study that detected the best results of esthesiometry for screening DR[15] also found it better in identifying proliferative disease. The differences in sensitivity and specificity between that study and the series herein presented are significant. Their report did not specify whether or not controls were used for the construction of ROC curves. The inclusion of controls would have a striking effect on ROC curves. Controls do not present DR and tend to have normal esthesiometry. These characteristics would cause a left shift of the curve. Per eye analysis could also have caused a reverberation effect. The fact that both eyes are under the same systemic conditions (glycemia, disease duration, use of hypoglycemic drugs, insulin dose, and so on) and the fact that those uncontrolled conditions are very related to corneal hypoesthesia[2,4,9,17] indicates that both eyes could not be considered independent statistical units.

As a conclusion the study data showed that corneal esthesiometry was decreased in patients with DR and was related to the stage of DR. Nevertheless, a significant number of patients showed different progress in hypoesthesia and DR leading to low indices of sensitivity/specificity when esthesiometry was compared to indirect ophthalmoscopy. Therefore, esthesiometry might not be considered a valid screening method.

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