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Analysis of cardiovascular risk factors for the viability of cornea donors: a case–control study

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ABSTRACT

Objective The main objective of the study was to evaluate the influence of arterial hypertension, diabetes, dyslipidaemia, smoking, alcoholism and COPD (chronic obstructive pulmonary disease) on the viability of the extracted tissue as well as the donor.

Design Observational case–control study.

Setting Regional hospital in Northern Spain.

Participants 1517 corneas were registered.

Interventions Patients' medical history was reviewed after corneal donation and evaluation. Previous medical information (age, sex and cardiovascular risk factors (CVRFs)) and data related to the donor (type of donor), the corneal tissue and its evaluation, and the viability of the implant were collected.

Results A total of 1517 corneas were registered and 81.5% of the donors presented at least one CVRF. In relation to the viability of the donor, it was observed that having suffered from COPD reduced the viability of the donor (no COPD: 93.8% vs COPD: 88%; OR=0.49; 95% CI: 0.28 to 0.84) while alcohol consumption increased it (drinker or ex-drinker: 95.8% vs non-drinker: 92.5%; OR=1.84; 95% CI: 1.01 to 3.33). Regarding tissue viability, decreased viability was observed in the presence of COPD (no COPD: 72.5% vs COPD: 64; OR=0.67; 95% CI: 0.47 to 0.96) and diabetes mellitus (no diabetes: 72.9% vs diabetes: 67.2%; OR=0.76; 95% CI: 0.58 to 0.99). As regards the viability of the implant, a total of 1039 corneas (68.9%) were suitable, observing decreased viability when suffering from COPD (no COPD: 69.8% vs COPD: 60.7%; OR=0.67; 95% CI: 0.47 to 0.94) and increased when having an active smoking habit (no habit: 65.3% vs habit: 74.1%; OR=1.52; 95% CI: 1.21 to 1.91).

Conclusions Through this study, it can be concluded that in the absence of absolute exclusion criteria for donors, the assessment of how CVRF, alcoholism and COPD may affect the donor provides details about the quality of the tissue to be obtained.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Important confounders may be clarified and estimated: characteristics of donor age, death to preservation time or prior ocular history.
⇒ Discrepancies about smoking effects indicate the need to analyse this variable in depth.
⇒ 1517 corneas were examined on cell density, coefficient of variation and hexagonality.
⇒ The assessment of cardiovascular risk factor, alcoholism and chronic obstructive pulmonary disease provides details about the quality of the corneal tissue.

INTRODUCTION

Corneal transplantation is a surgical treatment in which a damaged or diseased cornea is replaced by another cornea that comes from a donation. This surgical technique is used to repair damaged tissue and restore or improve the patient's vision.

Corneal tissue can be obtained from brain-death donors, non-heart beating donors and/or tissue-only donors. From 2000 and 2014, the donation rate in Spain remained stable in a range of 33.9–36 donors per million population (pmp).[1] With the increased activity of the non-heart beating donation programme, the donation rate has increased to 49 donors pmp in 2019.[2] This increase in donation rates has translated into a greater availability of corneal tissue for transplantation.[3]

Due to the increase in the mean age of donors in recent years, from 34 to 59 years from 2005[4 5] to 2020,[1] respectively, a growing number of comorbidities can be observed among the population, which are related to lifestyle habits and which affect the condition of the corneal tissue in different ways and intensities, both in terms of corneal density and in the slit lamp (SL) evaluation. This can provide guidance for a more complete and reliable evaluation of the tissue viability and the potential donor.[4 6–13]

The selection of the potential donor, carried out by the transplant coordination staff, is governed by the criteria established by the Spanish Association of Tissue Banks and by the European Eye Bank Association.[4 5] In this regard, the assessment of corneal tissue is a complex process and, in order to qualify the

tissue as suitable for implantation, it must meet a series of requirements, the donor must not have absolute exclusion criteria, the viability of the tissue is given by the combination of viability using specular microscopy (SM) (quantitative) and SL (qualitative).[4] The viability of the tissue is obtained through the evaluation of corneal density evolution, the number of endothelial cells measured with SM and the SL evaluation. With this complete assessment, the value of the clear area is obtained and alterations such as corneal leucomas, corneal infiltrates, significant arcus, endothelial guttae can be ruled out.[4]

The main objective of this study was to evaluate the influence of arterial hypertension (AHT), diabetes, dyslipidaemia, smoking, alcoholism and chronic obstructive pulmonary disease (COPD) on the viability of the extracted tissue and of the donor.

MATERIALS AND METHODS

Study design

An observational case–control study was carried out at the Coruña University Hospital Complex.

Patient and public involvement

None.

Settings

The last review of the database was carried out in January 2020. For data collection, the SIMON database from the registration system of the Tissue Bank of the Integrated Management Department of A Coruña was used.

Study size

In accordance with previous studies, the proportion of valid corneas evaluated with the SL should not be less than 60%. Thus, with these data, the confidence level should be 95% and precision should be at 5%. The required sample size was 405 corneas, assuming a 10% loss. A total of 1517 corneas were finally included.

Participants

All donors (1517) for multiorgan and tissue donation between 2017 and 2019 were selected in the study. Donors with characteristics incompatible with corneal donation were excluded (111; 7.4%): presence of ocular alterations prior to donation, positive serology (syphilis, HIV, hepatitis B and C), uncontrolled septic process, neurological diseases (neurodegenerative or demyelinating processes of unknown aetiology and prion diseases), as well as primary tumours (grades III and IV) of the central nervous system as stated by the WHO classification.

Variables

In order to build the database, a review of the patient's clinical history was carried out after donation and corneal evaluation. The collected data were as follows: previous medical information (age, sex, history and cardiovascular risk factors (CVRFs)) and data related to the donor (type of donor), corneal tissue, and evaluation and viability of the implant.

The following variables were analysed without an established and variable order. The viability of the donor, tissue viability, was based on two determinations: SM, which in turn, is subdivided into corneal density, the coefficient of variation (CV) and hexagonality (HEX) and SL and viability of the implant, which depended on the viability of the donor and tissue. If one of these two variables was not considered valid, or if the evaluation had not been performed, the tissue was discarded.

- Cell density (CD) is the number of cells per surface unit and constitutes a quantitative analysis of the corneal endothelium that reflects the structural integrity, but not the functional state that is obtained by cell size. Its normal value should be greater than 2000 cells/mm^2. There is an inversely proportional relationship between corneal density and average.
- CV assesses the existing variability with regard to cell size. It is calculated by dividing the mean cell area by the SD. Values indicating endothelial functional instability are normal average values of 33%–40%.[5]
- HEX reflects the percentage of existing hexagonal cells in the analysed area. Values greater than 50% are accepted as within the normal range of HEX. Therefore, the closer the value to 100%, the better the conservation of the cells.[6]

Statistical methods

A descriptive analysis of all the variables included in the study was carried out, expressing the qualitative variables as absolute value and percentage; quantitative variables were expressed as means and SD. In addition, the association between qualitative variables was studied using the χ^2 test.

A comparison of means was made, after verifying normality with the Kolmogorov-Smirnov test, Student's t-test or Mann-Whitney U test, as appropriate. In all analyses, ORs and 95% CIs were calculated for each covariate. For the multivariate analysis, the logistic regression model was used, between the variables that showed $p<0.05$ in the bivariate analysis.

For the analysis of the significance level in the case of contingency tables with two independent qualitative variables, we use the χ^2 test, except in the case that more than 20% of the cells have expected values more than 5, then Fisher's exact test is used. In the case of paired dichotomous data, the McNemar's test is used.

The data have been analysed by using the SPSS V.25.0 (IBM). A significance level of $p<0.05$ was used in all analyses.

RESULTS

A total of 1517 corneas were registered and the mean age of the donors was 61.3 (SD: 12.7) years, with a higher proportion of males (55.6%). Of the donated corneas,

Table 1 Distribution of sociodemographic and clinical factors of donors (Spain, 2017–2022)

Age		61.32 (±12.7) years
Sex	Male	55.6%
Origin	Tissues	53.6%
	Brain death	36.7%
	Non-heart beating donation	9.8%
Cardiovascular risk factors	Arterial hypertension	48.6% (737)
	Smoking	41.6% (630)
	Dyslipidaemia	41.1% (624)
	Diabetes	20.9% (317)
	Alcoholism	20.6% (312)
	COPD	9.9% (150)

COPD, chronic obstructive pulmonary disease.

53.6% of the total came from tissue donation. Among the donors, 81.5% had at least one CVRF (table 1).

Donor viability

93% (1411/1517) of the donors were accepted as valid. Among the causes of non-viability of donors (7%; 103/1517), the following were the most commonly identified reasons: positive serology (29%; 27/1517), uncontrolled septic process (10.8%; 10/1517) and presence of neurodegenerative disease (4.3%; 4/1517).

In relation to the viability of the donor (online supplemental file 1), it was observed that having suffered from COPD reduced the viability of the donor (non-COPD: 93.8% vs COPD: 88%; p=0.08; OR: 0.49, 95% CI: 0.28 to 0.84), while alcohol consumption increased it (drinker or ex-drinker: 95.8% vs non-drinker: 92.5%; p=0.042; OR: 1.84, 95% CI: 1.01 to 3.33).

The logistic model created to predict the probability of a donor's viability was significant in general terms when including COPD and alcohol consumption as predictors. There was a significant negative relationship between a donor's logarithm of the odds for viability and having suffered from COPD. In the case of alcohol consumption, this relationship was also lower if the patient had had COPD. Specifically, the probability of a patient with COPD being viable was 0.49 lower than that of a patient without a diagnosis of COPD. The fact of having consumed alcohol showed a significant positive relationship, that is, the probability that a patient who had consumed alcohol could be viable was 1.84 times greater than that of a patient who had not consumed alcohol (table 2).

Tissue viability

A total of 1083 corneas (71.7%) were viable. Of the 428 non-viable ones, 241 (16.3%) were discarded by SM analysis and 257 (18.1%) by SL evaluation. 15.9% of the corneas evaluated by SM were discarded. The main reason for discarding them was a corneal density of less than 2000 cells/mm^2, the second cause being the detection of guttata (31.5%; 69/1517). At the same time, severe folds and high polymegethism both represented 3.2% of the causes for discarding corneas, respectively.

Regarding tissue viability (online supplemental file 1), a decrease was observed in the presence of COPD (no COPD: 72.5% vs COPD: 64%; p=0.028; OR: 0.67, 95% CI: 0.47 to 0.96) and diabetes mellitus (DM) (no diabetes: 72.9% vs diabetes: 67.2%; p=0.046; OR: 0.76, 95% CI: 0.58 to 0.99).

Table 2 Multiple logistic regression analysis of donor, tissue and implant viability and the influence of variables (Spain, 2017–2022)

	Donor viability	Donor tissues	Donor implant	Specular microscopy
P value OR 95% CI				
COPD	0.05; 0.461 (0.268 to 0.793)	0.005; 0.593 (0.411 to 0.856)	0.002 0.0573 (0.401 to 0.819)	–
Diabetes	–	0.089; 0.791 (0.603 to 1.036)	–	0.001 0.576 (0.422 to 0.787)
Tobacco	–	<0.001; 1.650 (1.298 to 2.097)	<0.001 1.625 (1.289 to 1.050)	0.067 1.308 (0.981 to 1.743)
Alcohol consumption (2 groups)	0.030 1.939 (1.065 to 3.259)	–	–	–
Constant	0.000 13.587	0.000 2.322	0.000 1.944	0.000 5.276

COPD, chronic obstructive pulmonary disease.

Table 3 Viability of tissues and values regarding cardiovascular risk factors (Spain, 2017–2022)

		Slit lamp		Specular microscopy	
		No	Yes	No	Yes
Arterial hypertension	No	124 (17.1%)	602 (82.9%)	116 (15.3%)	640 (84.7%)
	Yes	133 (19.2%)	560 (80.8%)	125 (17.2%)	600 (82.8%)
	P value OR, 95% CI	0.302 0.87 (0.66–1.14)		0.323 0.87 (0.66–1.15)	
Dyslipidaemia	No	145 (17.4%)	686 (82.6%)	128 (14.8%)	736 (85.2%)
	Yes	112 (19.0%)	476 (81.0%)	113 (18.3%)	504 (81.7%)
	P value OR, 95% CI	0.441 0.90 (0.68–1.18)		0.072 0.78 (0.59–1.02)	
Diabetes	No	203 (18.0%)	924 (82.0%)	170 (14.5%)	1000 (85.5%)
	Yes	54 (18.5%)	238 (81.5%)	71 (22.8%)	240 (77.2%)
	P value OR, 95% CI	0.849 0.97 (0.69–1.35)		<0.001 0.57 (0.42–0.78)	
COPD	No	235 (18.2%)	1053 (81.8%)	213 (15.8%)	1131 (84.2%)
	Yes	22 (16.8%)	109 (83.2%)	28 (20.4%)	109 (79.6%)
	P value OR, 95% CI	0.681 1.11 (0.68–1.79)		0.166 0.73 (0.47–1.14)	
Smoking	No	173 (13.6%)	639 (78.7%)	154 (14.1%)	709 (82.2%)
	Yes	82 (13.6%)	522 (86.4%)	87 (14.1%)	528 (85.9%)
	P value OR, 95% CI	<0.001 1.72 (1.29–2.30)		0.058 1.32 (0.99–1.75)	
Alcohol consumption	No	211 (18.8%)	912 (81.2%)	154 (14.1%)	709 (82.2%)
	Yes	46 (15.5%)	250 (84.5%)	87 (14.1%)	528 (85.9%)
	P value OR, 95% CI	0.197 1.26 (0.89–1.78)		0.465 0.88 (0.63–1.23)	

COPD, chronic obstructive pulmonary disease.

When analysing the tissue using the SM (table 3), tissues from donors who had suffered from DM were less viable (no diabetes: 85.5% vs diabetes: 77.2%; p<0.001. OR: −0.57, 95% CI: 0.42 to 0.78), while in the corneal analysis by means of SL it was observed that the viability increased in those patients with a smoking habit (no habit: 78.7% vs habit: 86.4%; p<0.001; OR: 1.72; 95% CI: 1.29 to 2.30).

The logistic model created to predict the probability of a donor's viability was significant in general terms when including COPD, smoking and history of DM as predictors. There was a significant negative relationship between a donor's logarithm of the odds for viability and having suffered from COPD and DM. In the case of tobacco use, the relationship was similar, but lower if the patient had had both diseases. Specifically, the probability of a patient with COPD and DM being viable was 0.67 and 0.76 lower than that of a patient without these diagnoses. The fact of having been a smoker presented a significant positive relationship in such a way that the probability that a patient who had smoked presented viability was 1.72 times greater than that of a patient who had not been a smoker (table 2).

From the values obtained by SM and their relationship with CVRFs, a decrease in corneal density was found in patients with AHT, dyslipidaemia, DM, COPD and an alcohol habit, while in those patients who were smokers, a greater corneal density was shown (online supplemental file 2).

Implant viability

Regarding implant viability (online supplemental file 1), a total of 1039 corneas (68.9%) were suitable, a decrease in implant viability was observed when suffering from COPD (no COPD: 69.8% vs COPD: 60.7%; p=0.022; OR: 0.67, 95% CI: 0.47 to 0.94), and an increase when having an active smoking habit (no habit: 65.3% vs habit: 74.1%; p<0.001; OR: 1.52; 95% CI: 1.21 to 1.91).

The logistic model created to predict the probability of a donor's viability was significant in general terms when including COPD and smoking as predictors. There was a significant negative relationship between a donor's logarithm of the odds for viability and having suffered from COPD, as well as a significant positive relationship with being a smoker. The probability of a patient with COPD being viable was 0.67 lower than that of a patient who did not have a COPD diagnosis. At the same time, being a smoker showed a viability of the implant 1.52 times greater than that of a non-smoker (table 2).

DISCUSSION

The evaluation of the potential donor of the cornea is a thorough process in which the data provided by a patient's medical history and by the family must be assessed. In the absence of exclusion criteria, such as active infections, haematological processes, hepatitis, etc, the patient must be analysed as a whole and taking into account the different chronic processes they have suffered and which affect the tissue.

Health changes affect tissues in different ways, as shown in the study by Sati *et al*.[7] According to this study, patients with renal replacement therapy presented an alteration in corneal density and central corneal thickness when compared with patients who were not subjected to this type of therapy. In the same way, the study published by Cankaya *et al*[14] verified that patients with vitamin D deficiency presented changes in corneal density, CV and HEX.

In the present study, the relationship between CVRFs and donor viability, SM, and SL evaluation was assessed; subsequently, tissue viability (convergence between viability evaluated through SM and with SL) and viability of the implantation (convergence between donor and tissue viability) were also determined.

In our study, 18% (257/1419) of the corneas evaluated by SL were discarded due to keratopathies present in the tissue, mainly guttata (20.4%) and severe folds (8.8%). In our sample, the discard rate by SL is lower than that found in the studies by Cruz *et al*,[15 16] but slightly higher than the study published by Patil *et al*[17] (18% vs 14.9%). However, it should be noted that when comparing the causes of tissue discard secondary to endothelial folds, our study presents a lower percentage of discard (8.8% vs 21.8%). This difference may be due to the extraction technique used, tissue evaluation temperature or even the time elapsed from extraction to SL evaluation.

Regarding the presence of AHT, no studies were found that related to the presence of AHT and how it affected corneal tissue donation. However, the results obtained indicate that AHT had a negative effect on the data provided by SM evaluation, in such a way that the CD and percentages of hexagonal shape in the corneal endothelium decreased when compared with patients who did not suffer from AHT.

According to the results from the study by Tenorio-Guajardo *et al*,[8] there was a correlation between patients with elevated intraocular pressure and uncontrolled diastolic hypertension. Suffering from high intraocular pressure values and/or glaucoma is related to the loss of endothelial cellularity[9 18]; therefore, those patients with AHT tend to present decreased corneal density.

In those patients who suffered from dyslipidaemia, a significant relationship was found, with a decrease in CD and an increase in the average (since both parameters present an indirect relationship). In the literature described, studies that relate the presence of the corneal arch with cardiovascular diseases and coronary disease were found, especially in patients under 50 years of age,[10 19] but no study assessed the effect of patients who suffered from dyslipidaemia in the values measured through SM.

The effect of DM on the cornea is one of the most studied variables in the literature. In the present study, it was found that patients with DM had lower CD. These results agree with the publications by Anbar *et al*[6] and Chen *et al*,[11] while this decrease was not present in the study by Beato *et al*.[20] Another piece of indirect data regarding the decrease in CD is an increase in average (AVE). Although no studies have been found that focus on this variable, after analysing the data, an increase in AVE was shown in those patients who suffered from DM, with the consequent negative impact on CD; therefore, when the AVE increases, CD tends to decrease.

Regarding the HEX and CV variables, the present study does not agree with results of corneal endothelial morphology in children with DM1, where such values show variation and, therefore, suffering from DM and its duration are determined as favourable factors for suffering from polymorphism and polymegethism. However, these results were not found in the present study despite not considering the duration of DM in the cohort studied.

As COPD is a complex disease with pulmonary and extra pulmonary manifestations, it affects the corneal tissue. This, along with the effects of the associated treatment, results in a tissue of worse quality than that of patients who do not suffer from COPD.

In this study, patients with COPD had lower donor viability, which is due to the fact that they are fragile multipathological patients, especially in the final stages of the disease. When evaluating these potential donors, they did not present absolute exclusion criteria despite having died from infectious processes under adequate antibiotic treatment. Thus, accepting these types of patients as donors is motivated by their inclusion in the corneal culture process. In this way, the tissue is extracted and blood cultures are taken to rule out bacteraemia. Despite receiving antibiotic treatment adjusted by antibiogram, patients and their tissues are discarded when some germ grows in the blood cultures that leads to rejected donation.

The state of the tissue assessed by SM indicated a decrease in CD and an increase in AVE, which were related and inversely proportional data. The decrease in CD was due to the damage suffered by the tissue and was secondary to hypoxia, which leads to neuronal death. Thus, due to corticosteroid treatment, which motivates an increase in intraocular pressure as a side effect, a decrease in CD and an increase in AVE[21 22] were observed. These results indicate that corneas from patients suffering from COPD consist of a suboptimal tissue whose recovery capacity is limited.

Therefore, it must be taken into account that after manipulation during the extraction, implantation or even previous surgeries of the donor,[23] the tissue may suffer damage that motivates discarding it.

Despite the extensive negative effects that smoking has on health, the data obtained in our study indicate that smoking has a protective effect on the cornea. Thus, patients with a smoking habit had a greater viability by SL and by SM evaluation. Through this study, it was observed that patients who were smokers presented a higher CD than non-smokers. These data go against what was described by Frifelt *et al*,[23] as the studies they included mentioned a decrease in CD. None of the studies included in this meta-analysis had a larger study population than the one selected for this work, so the population factor may be key in determining the discrepancy with their study. In addition, other studies indicate that smoking does not affect CD.[13 24]

The influence of alcoholism on the viability of the donor is based on the pathological processes that lead to death, the main cause being an end-stage cirrhotic process or associated complications, such as oesophageal varices. However, this does not determine causes for discarding the patient. In the present study population, patients who were donors and were classified as alcoholics presented greater donor viability, a fact that may suggest that alcohol is a protective factor. Another case is the effect of alcohol on ocular tissue, where a decrease in CD and an increase in AVE can be observed, as well as a higher CV. The cause of this deteriorated corneal tissue is the toxicity of ethanol on endothelial cells, as well as alcohol-induced hypoglycaemia that causes corneal oedema. The data from the present study correlate with what Sati *et al*[25] published in relation to decreased CD, but not with another study by Karmakar *et al*,[26] where CD did not present changes when compared with that of the control group. However, an increase in CV was indeed identified, and this may be due to the fact that they had selected a smaller study population. Despite the statistical difference found in the present study, the differences in DC values have no clinical relevance.

CONCLUSIONS

As a result of this study, it can be concluded that in the absence of absolute exclusion criteria for donors, the assessment of how CVRF, alcoholism and COPD affect the donor provides guidance on the quality of the tissue to be obtained. For this reason, the sum of the different comorbidities that the possible donor presented can help to rule out the donor for suboptimal quality tissue.

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Supplementary File 1. Viability values regarding cardiovascular risk factors (Spain, 2017-2022).

		Viability								
		Donor			Tissues			Implant		
		No	Yes	P-value Odds Ratio IC 95%	No	Yes	P-value Odds Ratio IC 95%	No	Yes	P-value Odds Ratio IC 95%
Arterial Hypertension	No	56 (7.2%)	721 (92.8%)	0.521 1.14 (0.76-1.70)	214 (27.5%)	565 (72.5%)	0.447 0.92 (0.73-1.15)	238 (30.7%)	538 (69.3%)	0.710 0.96 (0.77-1.19)
	Yes	47 (6.4%)	690 (93.6%)		214 (29.2%)	518 (70.8%)		231 (31.6%)	501 (68.4%)	
Dyslipidaemia	No	53 (6.0%)	837 (94.0%)	0.118 0.73 (0.49-1.09)	241 (27.1%)	647 (72.9%)	0.222 0.87 (0.69-1.09)	259 (29.3%)	626 (70.7%)	0.067 0.81 (0.65-1.01)
	Yes	50 (8.0%)	574 (92.0%)		187 (30.0%)	436 (70.0%)		210 (33.7%)	413 (66.3%)	
Diabetes	No	86 (7.2%)	1113 (92.8%)	0.265 1.35 (0.79-2.31)	324 (27.1%)	870 (72.9%)	0.046 0.76 (0.58-1.00)	360 (30.2%)	833 (69.8%)	0.131 0.82 (0.63-1.06)
	Yes	17 (5.4%)	298 (94.6%)		104 (32.8%)	213 (67.2%)		109 (34.6%)	206 (65.4%)	
Overweight	No	91 (6.8%)	1245 (93.2%)	0.987 1.01 (0.54-1.87)	373 (28.0%)	960 (72.0%)	0.391 0.86 (0.61-1.21)	410 (30.8%)	920 (69.2%)	0.499 0.89 (0.64-1.24)
	Yes	12 (6.8%)	165 (93.2%)		55 (31.1%)	122 (72.0%)		59 (33.3%)	118 (69.2%)	

COPD	No	85 (6.2%)	1279 (93.8%)	0.008 0.49 (0.28-0.84)	374 (27.5%)	987 (72.5%)	0.028 0.67 (0.47-0.96)	410 (30.2%)	948 (69.8%)	0.022 0.67 (0.47-0.94)
	Yes	18 (12.0%)	132 (88.0%)		54 (36.0%)	96 (64.0%)		59 (39.3%)	91 (60.7%)	
Smoking	No	64 (6.2%)	818 (92.7%)	0.422 1.18 (0.78-1.79)	280 (23.2%)	598 (68.1%)	< 0.001 1.55 (1.23-1.96)	304 (25.9%)	572 (65.3%)	< 0.001 1.52 (1.21-1.91)
	Yes	39 (6.2%)	590 (93.8%)		146 (23.2%)	484 (76.8%)		163 (25.9%)	466 (74.1%)	
Alcohol consumption	No	90 (7.5%)	1115 (92.5%)	0.042 1.84 (1.01-3.33)	343 (28.6%)	856 (71.4%)	0.634 1.07 (0.81-1.41)	379 (31.6%)	820 (68.4%)	0.400 1.12 (0.86-1.48)
	Yes	13 (4.2%)	296 (95.8%)		85 (27.2%)	227 (72.8%)		90 (29.1%)	219 (70.9%)	

Supplementary File 2. Specular microscopy values regarding cardiovascular risk factors (Spain, 2017-2022).

	Arterial Hypertension			**Dyslipidaemia**			**DM**			**COPD**			**Smoking**			**Alcohol consumption**		
	No	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**	**No**	**Yes**	**p-value**
Corneal Density	2627.25 (436.27)	2510.95 (426.83)	p<0.01	2604.93 (437.26)	2520.60 (42828)	p<0.01	2587.29 (424.47)	2504.46 (470.60)	p=0.004	2580.25 (435.98)	2476.74 (420.34)	p=0.009	2546.97 (436.58)	2603.13 (432.54)	p=0.018	2588.7 (422.27)	2501.46 (476.02)	p=0.002
Coefficient of variation	37.28 (6.72)	37.81 (5.18)	p= 0.107	37.73 (6.58)	37.27 (5.10)	p=0.159	37.51 (6.24)	37.65 (5.12)	p=0.741	37.45 (6.13)	38.36 (4.84)	p=0.098	37.42 (5.12)	37.69 (7.07)	p=0.411	37.35 (5.30)	38.25 (8.16)	p=0.025
Hexagonality	58.85 (12.77)	57.49 (5.88)	p=0.011	58.27 (12.23)	58.07 (5.51)	p=0.716	58.31 (10.93)	57.69 (5.20)	p=0.354	58.29 (10.44)	57.21 (4.58)	p=0.241	58.43 (12.33)	57.84 (5.60)	p=0.283	58.31 (10.96)	57.71 (5.23)	p=0.361
Average	392.20 (95.38)	414 (124.20)	p<0.01	395.98 (97)	412.80 (127.75)	p=0.006	397.82 (94.24)	422.52 (158.70)	p=0.013	98.45 (2.79)	190.09 (16.54)	p=0.044	405.84 (99.80)	398.71 (124.52)	p=0.239	399.10 (108.24)	417.02 (119.60)	p=0.014