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The Role of Atopic Disease in the Progression of Keratoconus

O Papel da Doença Atópica na Progressão de Queratocone

Março, 2020

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The Role of Atopic Disease in the Progression of Keratoconus

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Dedicatória

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The Role of Atopic Disease in the Progression of Keratoconus

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ABSTRACT

Purpose: To study the influence of atopic conditions in the progression of corneal ectasia in keratoconus patients.

Methods: Retrospective study of 56 eyes of 56 patients with Keratoconus, aged from 14 to 30 years old. Ectasia progression was evaluated between two scans separated by 12±3 months, using the tomographic variables Kmax, Km, K2, PachyMin, D-index, PCR and Corneal Astigmatism. Data regarding atopy and eye rubbing habits were collected from patients' clinical records, accessed through the SClinico System.

Results: The prevalence of atopy in this sample was 60.7% and the prevalence of eye rubbing habits was 76.8%. As for the prevalence of rhinitis, asthma and atopic dermatitis, it is 53.6%, 12.5% and 16.1%, respectively. A statistically significant association was found between atopy and eye rubbing (p=0.007), indicating that atopic patients have more tendency to rub their eyes. No significant difference was found in the variation of the tomographic indices Kmax, Km, K1, K2, PachyMin, D-index, PCR and Astig between the two scans, when comparing the atopic and non-atopic groups of patients (p=0.821, p=0.759, p=0.794, p=0.883, p=0.969, p=0.747, p=0.442 and p=0.720, respectively). There were no significant associations between ectasia progression and atopy, eye rubbing, rhinitis, asthma and atopic dermatitis (p=0.300, p=0.573, p=0.765, p=0.071 and p=1.000, respectively).

Conclusion: Despite the lack of difference in ectasia progression found between KC patients with and without atopy, an effective control of atopic conditions should be done in order to reduce eye rubbing, a well-stablished risk factor for Keratoconus.

INTRODUCTION

Keratoconus (KC) is a primary ectatic disease characterized by corneal thinning and cone-shaped protrusion, leading to irregular astigmatism, myopia and ultimately severe vision loss[1-15]. Its prevalence is currently estimated at 265 per 100,000 in the general population[15], with no significant difference between sexes, being considered one of the most common ectatic disorders affecting the cornea[10, 15]. It usually starts at the second or third decades of life and progresses until the fourth decade, when the progression normally slows down or might even arrest[4, 6, 10]. Although classically defined as a noninflammatory disease, recent evidence suggests that inflammatory mediators such as interleukin-1 (IL-1), interleukin-4 (IL-4), interleukin 6 (IL-6), interleukin-10 (IL-10), Interferon-gamma (IFN gamma) and Tumor necrosis factor alpha (TNF alpha) may play a role in the pathogenesis of KC, since their expression is altered in the tears of KC[1, 4, 7, 16]. Also, the levels of superoxide dismutase, aldehyde dehydrogenase class 3 (ALDH3) and catalase are reduced in KC, enzymes that remove reactive oxygen species which have a known role in inflammatory reactions[4]. Despite the uncertainty underlying the etiology and pathophysiology of the disease, there are some recognized/stablished genetic and environmental risk factors, such as atopy, eye rubbing, exposure to sunlight, family history of KC, ethnic differences and contact lens use[2, 4-6, 8, 10, 15, 17-19].

The exact mechanism linking atopy and KC is still unsettled. Atopy is defined as an increased predisposition to hypersensitivity reactions, comprehending asthma, eczema/atopic dermatitis and allergy, the latter including conditions such as rhinitis, vernal keratoconjunctivitis (VKC) and allergic conjunctivitis (AC)[4, 10]. In patients with allergic diseases, the exaggerated and vigorous eye rubbing due to increased ocular itch is one of the causal associations proposed, since eye rubbing is a long known and well-established risk factor[4, 8, 10, 20]. The microtrauma caused to the KC corneas epithelium by rubbing leads to increased levels of inflammatory mediators and matrix

metalloproteinases (MMPs) degradative enzymes, resulting in excessive degradation of extracellular matrix[1, 4, 7, 10, 19]. Higher levels of active forms of some MMPs were reported in the tears of a majority of VKC patients and, in both VKC and AC, T cells infiltrate the conjunctiva and are able to stimulate the expression of these enzymes, resulting in MMPs activation and, therefore, excessive epithelium turnover[10]. Moreover, the levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) seem to be reduced in the corneas of KC patients[1]. Such data points toward a possible relationship between atopy and KC that is independent from eye rubbing[10, 19]. Results of many studies show a positive association between atopy and KC, namely, an increased prevalence of atopic conditions in KC patients when compared to normal controls and more severe disease in KC patients with atopic conditions in comparison to KC patients without history of atopy[4, 10, 12, 14, 21]. Other studies, some that used a control group from the general population rather than an age- and sex- matched group, didn't find this positive association[4, 11, 13, 14]. Also, the parameters used to study atopy in this context vary widely between studies, since some authors used the parameter "atopy" as a whole, while others chose to analyze the individual atopic conditions (allergy, asthma and atopic dermatitis, or even specific allergic diseases)[4, 9].

Based on the apparent association mentioned above, it becomes pertinent to further explore the implications of atopy in KC patients, including the possible consequences in terms of disease progression. As far as literature is concerned, many of the previous studies focused mainly on studying the prevalence of atopy in keratoconus patients and its relation with disease severity. Nonetheless, only a few of them presented results specifically regarding the association between atopic conditions and ectasia progression. Such knowledge would be of extreme value for practitioners, since it may indicate or not the necessity of a closer follow-up or a more aggressive therapeutic approach for those patients. Despite the lack of a clear and consistent definition, the term "ectasia progression" is defined in the Global Consensus on Keratoconus and Ectatic Diseases (2015) by "a consistent change in at least 2 of the

following parameters (…): 1. Steepening of the anterior corneal surface; 2. Steepening of the posterior corneal surface; 3. Thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point"[17]. Nowadays, modern corneal tomography devices, such as Pentacam, allow to quantitatively evaluate changes in these parameters and so evaluate the ectatic progression over a certain period of time[3, 22].

Considering all the above, the scientific question that the present study intends to answer is: "Is there an association between the presence of atopic conditions in patients diagnosed with keratoconus and the progression of disease related corneal ectasia?".

MATERIALS AND METHODS

Retrospective study of 56 eyes of 56 patients diagnosed with Keratoconus (KC) in the Department of Ophthalmology of *Centro Hospitalar Universitário de São João*, Portugal. This study was approved by the local ethics committee and conducted in accordance to the requirements of Helsinki Declaration.

Patients included, aged from 14 to 30 years old, were patients followed in the Ophthalmology Corneal Department for 1 year minimum by a corneal specialist (JPC, LT or RM) and with a clinical and tomographic diagnose of clinical or subclinical KC, including at least 3 Scheimpflug tomography measurements (Pentacam HR, OCULUS Optikgeräte GmbH, Wetzlar, Germany). For the purpose of this study, the tomographic data selected to study ectactic progression was from two scans separated by 12±3 months of one eye of each patient (right eye chosen by default; left eye when absence of disease in the right eye). All measurements were performed by experienced Orthoptists and only patients whose measurements were labeled with “OK” by automated image quality check were included. All stages of KC were included, including subclinical Keratoconus only with early tomographic alterations if the other eye showed clear signs of clinical Keratoconus. For the assessment of atopic conditions, information was collected from clinical records of the patients using the SClínico informatic system.

Patients were eliminated if they met the following exclusion criteria: corneal cross-linking treatment before or during the interval between the 2 scans; intracorneal ring treatment before or during the interval between the 2 scans; patients with genetic syndromes, other ocular diseases besides Keratoconus or diseases with ocular injury; absence of clinical data regarding positive or negative history of atopic conditions. Excluding the latter, the adoption/selection of such exclusion criteria appears in the attempt to minimize factors that may influence the natural progression of KC and, thus, function as confounding factors in relation to atopy effects on ectactic progression.

For the evaluation of ectactic progression, tomographic variables analyzed were maximum keratometry (Kmax), minimum pachymetry (PachyMin), mean keratometry (Km), keratometry of flat meridian (K1), keratometry of steepest meridian (K2), corneal astigmatism (Astig = K2 – K1), posterior radius of curvature from 3.0 mm centered on the thinnest point (PCR) and Belin/Ambrósio D-Index (D). Except for K1, these variables are commonly accepted as progression markers with described cut-offs, although not validated. Values corresponding to progression in each parameter are presented in Table 1. Progression of KC was defined when at least two of the studied variables confirm progression.

Information collected from clinical records of selected patients focused on whether atopy was present or absent and, in the atopic patients, if they suffer from rhinitis, asthma, atopic dermatitis or different combinations of the three. Data regarding eye rubbing habits and use of corticosteroids or immunosuppressive drugs during the evaluation period was also collected.

Statistical Evaluation

For the description of the sample's characteristics, data are presented as counts and proportions for categorical variables, and as mean and standard deviation for continuous variables. To calculate the prospective variation in keratometric indices, values obtained from the first tomographic scan (readings at baseline) were subtracted from the second measurement readings. Therefore, a positive delta value corresponds in this case to an increase in the readings of the respective parameter.

Statistical analysis was conducted using SPSS statistical software package version 24 (SPSS inc., Chicago IL., USA), including descriptive statistical measures, inferential statistical measures, Chi-square tests to analyze differences in qualitative variables between groups and Student's T-Test to analyze differences in quantitative variables between groups. Levene's Test and Kolmogorov-Smirnov Test were used to

assess homogeneity of variances and normal distribution assumptions, respectively. To analyze progression, a multiple logistic regression model was applied to the variables of interest. Statistical significance level for p-value was set at 0,05 (i. e. p-values below 0,05 indicate statistically significant results).

RESULTS

A total of 56 eyes from 56 KC patients were included in this study, as they met the inclusion criteria, with data of 47 right eyes (83.9%) and 9 left eyes (16.1%) subjected to analysis. A sample characterization at baseline is presented in Table 2.

Descriptive analysis of the patients' sample shows a mean age of 24.34 years (s.d. 4.091), male sex predominance (73.2% men vs. 26.8% women) and a prevalence of atopy of 60.7%. As for the prevalence of each atopic conditions: 20 patients (35.7%) of all patients had only rhinitis; 1 patient (1.8%) had only asthma; 3 patients (5.4%) had only atopic dermatitis; 4 patients (7.1%) had rhinitis and asthma; 4 patients (7.1%) had rhinitis and atopic dermatitis; 2 patients (3.6%) had all of the three conditions (Table 3). This accounts for a total prevalence of 53.6% for rhinitis, 12.5% for asthma and 16.1% for atopic dermatitis.

A total of 13 patients (23.2%) reported no eye rubbing habits; 19 patients (33,9%) said they rarely rub their eyes, 18 patients (32.1%) said they sometimes rub their eyes and 6 patients (10.7%) said they often rub their eyes, making a total of 43 patients (76.8%) with eye rubbing habits.

As for the prevalence of eye rubbing in atopic patients, 31 patients (91.0%) of the 34 patients with atopy reported eye rubbing habits. Overall prevalence of eye rubbing habits was significantly higher in patients with atopy than in non-atopic patients ($p=0.007$).

Only 1 patient (1,8%) reported the use of corticosteroids or immunosuppressive drugs during the ectactic progression assessment period between the two tomographic scans.

At baseline, best corrected visual acuity was 0.80±0.21, with glasses or contact lenses, and the mean spherical equivalent of the studied eyes was -2.14±2.09 dioptres.

Concerning keratoconus severity classification, the majority of eyes were graded as stage 2 (n= 11; 19,6%) or stage 3 (n=14; 25,0%). Eyes in all stages of keratoconus were included except stage 4.

Variation in single tomographic parameters (Kmax, Km, K1, K2, PachyMin, D, PCR, Astig) in the group of atopic patients and in the group of non-atopic patients is presented in Table 4. A statistically significant association between the variations of keratometric readings and atopy was not found in any of the analyzed parameters.

Considering KC progression as a significant evolution in at least 2 tomographic variables, 38 eyes (67.9%) showed progression, with 23 of these eyes (41.1%) having progressed in 3 or more variables simultaneously. A total of 18 eyes were considered as non-progressive, including fourteen eyes (25.0%) with progression in only one variable and four eyes (7.1%) with no progression in any of the variables.

As for the progression in each one of the variables, 15 eyes (26.8%) progressed in Kmax; 16 eyes (28.6%) progressed in Km; 17 eyes (30.4%) progressed in K2; 15 eyes (26.8%) progressed in D-index; 25 eyes (44.6%) progressed in Astigmatism; 23 eyes (41.1%) progressed in PCR; 14 eyes (25.0%) progressed in minimum pachymetry (Table 5).

Comparison between the progressive group and the non-progressive group, did not show any statistically significant differences in the variables eye rubbing, atopy, rhinitis, asthma and atopic dermatitis (p=0.300, p=0.573, p=0.765, p=0.071 and p=1.000, respectively). A negative association was found between KC progression and asthma, with a majority of asthma patients not showing disease progression, but this association was not statistically different (p=0.071).

DISCUSSION

There is already some literature regarding the relation between atopy and keratoconus, specially the prevalence of certain atopic conditions and their possible role as risk factors for this primary ectactic disease. In this study, the main objective was to investigate the influence of atopy in keratoconus progression and, thus, the eventual necessity of a tighter follow-up in these patients, if faster or more severe ectasia evolution is present.

As far as the prevalence of atopy in Keratoconus patients is concerned, values vary widely among studies, although approximately concentrated in the 30% to 55% range[2, 4, 5, 8, 10, 14, 18]. Therefore, the 60.7% percentage of atopic patients in our cohort is slightly higher than expected. This discrepancy may stem from the different atopic conditions included in the definitions of "atopy" or "allergic diseases" variables in each study. Regarding prevalence of specific atopic conditions, there is also a wide variation of reported values in literature, being our patients' cohort percentages within the values described in previous studies[4, 5].

Most authors report that around 50% of keratoconus patients have the habit of rubbing their eyes[2, 4, 18, 20], a value lower than the 76.8% percentage calculated in our patients' sample. A significantly higher prevalence of eye rubbing habits was found in atopic patients comparing to non-atopic patients, a result that supports the hypothesis of eye rubbing being the link between allergic diseases and keratoconus, given its well-stablished role as risk factor for KC[4, 8, 10, 20].

Analysis of single tomographic parameter progression in the atopic patients' group and the non-atopic patients' group did not show statistically significant differences between the two in any of the variables. Also, unlike the results of previous studies in which a significant difference was found between progressive and non-progressive keratoconus patients regarding eye rubbing and atopy[13, 18], a significant positive association between progression of KC and eye rubbing, atopy, rhinitis, asthma and

atopic dermatitis could not be found in this study. The small sample size is one of the possible explanations for this lack of statistical significance. Other possible explanations are the absence of a clear definition for ectactic progression[17] and an excessively short progression evaluation period. It's also worth noticing that, in some clinical records, patients' data about their atopic conditions are self-reported instead of a diagnosis made by an immunoallergologist. This can lead to an information bias due to misdiagnosed allergic diseases reported by patients. In addition, some information might be missing, with some of the non-atopic patients having undiagnosed atopic conditions.

In conclusion, our results do not demonstrate a difference in ectasia progression between keratoconus patients with and without atopy. Nevertheless, a significant association was found between the presence of atopy and eye rubbing habits. In light of these findings, we can conclude that effective control of atopic conditions can be beneficial for keratoconus patients by reducing the frequency of eye rubbing, a well-known risk factor for keratoconus and ectasia impairment.

The lack of association between atopy and disease progression found in this study could be a small glimpse of what will be the answer to the posed scientific question, and it would be of great interest to further analyze this relation, namely, in studies with larger patient cohorts.

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ABBREVIATIONS

Astig: Corneal astigmatism

D: Belin/Ambrósio D-index

K1: Keratometry of flat meridian

K2: Keratometry of steepest meridian

KC: Keratoconus

Kmax: Maximum keratometry

Km: Mean keratometry

PachyMin: Minimum pachymetry;

PCR: Posterior radius of curvature from the 3.0 mm centered on the thinnest point

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TABLES

Table 1. Keratoconus progression parameters and respective cut-off values used to document progression.

Variable	Cut-off value
Kmax(23)	1D increase
PachyMin[24]	2% decrease
Km[3]	0,75D increase
K2[25]	1D increase
Astig[26]	1D increase
PCR[3]	0.085mm decrease
D[27]	0.42 increase

Kmax, maximum keratometry; *PachyMin*, minimum pachymetry; *Km*, mean keratometry; *K2*, keratometry of steepest meridian; *Astig*, corneal astigmatism; *PCR*, posterior radius of curvature from the 3.0 mm centered on the thinnest point; *D*, Belin/Ambrósio D-index.

Table 2. Summary of the characteristics of the patients' sample and characterization of tomographic indices.

	Mean (SD)	Minimum	Maximum
Women, n	n=15 (26.8%)		
Right eye, n	n=47 (83.9%)		
Cort, n	n=1 (1.8%)		
Age, years	24.34 (4.09)	14	30
BCVA, decimal	0.80 (0.21)	0.10	1.00
Spherical equivalent, diopters	-2.14 (2.09)	-8.50	0.50
Kmax, diopters	55.29 (7.45)	42.40	78.00
∆Kmax, diopters	0.44 (1.48)	-2.20	5.90
Km, diopters	47.47 (5.00)	39.90	66.40
∆Km	0.32 (0.61)	-1.00	2.20
K1, diopters	45.91 (4.62)	39.20	63.60
∆K1	0.39 (1.10)	-0.90	7.30
K2, diopters	49.06 (5.68)	41	69
∆K2	0.37 (0.86)	-1.70	2.90
PachyMin, um	462.20 (47.23)	338	550
∆PachyMin	-0.6071 (11.25)	-32	23
D	8.44 (4.67)	1.90	24.22
∆D	0.34 (0.99)	-3.41	2.97
PCR, mm	5.05 (0.68)	3.39	6.52
∆PCR	-0.66 (0.15)	-0.57	0.52
Astig, diopters	3.14 (2.33)	-0.80	10.60
∆Astig	-0.02 (1.15)	-6.60	2.30

Results are expressed as mean ± *SD* (standard deviation) for continuous variables and female gender, right eyes and use of corticosteroids/immunosuppressive drugs are expressed as count and percentage. *BCVA*, Best corrected visual acuity; *Kmax*, maximum keratometry; *Km*, mean keratometry; *K1*, keratometry of flat meridian; *K2*, keratometry of steepest meridian; *PachyMin*, minimum pachymetry; *D*, Belin/Ambrósio D-Index*; PCR*, posterior radius of curvature from 3.0 mm centered on the thinnest point; *Astig*, corneal astigmatism. The ∆ before some of the variables represents the variation of readings between the first and the second measurement after 12±3 months in the respective variable.

Table 3. Number and percent of atopic conditions in the patients' sample.

	N (%)
Rhinitis	20 (35.7%)
Asthma	1 (1.8%)
Atopic dermatitis	3 (5.4%)
Rhinitis + Asthma	4 (7.1%)
Rhinitis + Atopic dermatitis	4 (7.1%)
Atopy (total)	34 (60.7%)

N, number of patients; *%*, percentage.

Table 4. Variations of tomographic indices in the atopic and the non-atopic groups of patients.

	No atopy (n=22)		**Atopy (n=34)**		**P value**
∆Kmax (mean, SD)	0.39	1.04	0.48	1.72	0.821
∆Km (mean, SD)	0.35	0.52	0.30	0.66	0.759
∆K1 (mean, SD)	0.34	0.58	0.42	1.35	0.794
∆K2 (mean, SD)	0.39	0.53	0.36	1.03	0.883
∆PachyMin (mean, SD)	-0.68	8.68	-0.56	12.76	0.969
∆D (mean, SD)	0.40	1.07	0.31	0.95	0.747
∆PCR (mean, SD)	-0.09	0.16	-0.05	0.13	0.442
∆Astig (mean, SD)	0.05	0.45	-0.06	1.44	0.720

Variations (represented by ∆) of tomographic indices in the group of patients with atopy ("Atopy") and in the group of patients without atopy ("No atopy") - measurements of the first tomographic scan subtracted from the measurements of the second tomographic scan. *Kmax*, maximum keratometry; *Km*, mean keratometry; *K1*, keratometry of flat meridian; *K2*, keratometry of steepest meridian; *PachyMin*, minimum pachymetry; *D*, Belin/Ambrósio D-Index; *PCR*, posterior radius of curvature from 3.0 mm centered on the thinnest point; *Astig*, corneal astigmatism.

Table 5. Number and percent of keratoconus eyes with progression according to each tomographic parameter.

Variable	Progressors
Kmax	15 (26.8%)
Km	16 (28.6%)
K2	17 (30.4%)
D	15 (26.8%)
Astig	25 (44.6%)
PCR	23 (41.1%)
PachyMin	14 (25.0%)

Kmax, maximum keratometry; *Km*, mean keratometry; *K2*, keratometry of steepest meridian; *D*, Belin/Ambrósio D-Index; *Astig*, corneal astigmatism; *PCR*, posterior radius of curvature from 3.0 mm centered on the thinnest point; *PachyMin*, minimum pachymetry; *%*, percentage. Cut-off values used to determine progression are presented in table 1.

Anexos

Cornea

Online Submission and Review System

Author Resources

Instructions for Authors (this page)
Reprint Ordering
Permissions Requests
Reprints

SCOPE

Cornea is a peer reviewed, scientific journal for the submission of original manuscripts describing clinical observations, clinical trials, basic investigation with clinical applicability, and unique and important case reports related to diseases of and medical and surgical treatment of the cornea and external eye.

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Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest and Source of Funding:" For example:

Conflicts of Interest and Source of Funding: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker's bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

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- 3-5 keywords
- Disclosure of any funding received for this work – Please clearly identify if your research was funded from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s)

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Organize the manuscript into four main headings: Introduction, Materials and Methods, Results, and Discussion. A conclusion section should not be included. Define abbreviations at first mention in text and in each table and figure. If a brand name is cited, supply the manufacturer's name and address (city and state/country). Acknowledge all forms of support, including pharmaceutical and industry support, in an Acknowledgments paragraph.

Abbreviations

For a list of standard abbreviations, consult the AMA Manual of Style or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

References

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Sample references are given below:

Journal article

1. Terry MA. The evolution of lamellar grafting techniques over twenty-five years. *Cornea* 2000;19:611-616.

Book chapter

2. Pels E, Beekhuis WH, Volker-Dieben HJ. Long-term tissue storage for keratoplasty. In: Brightbill FS, ed. Corneal surgery. Theory, technique, and tissue. St. Louis: Mosby, 1999:897.906.

Entire book

3. Brightbill FS, ed. Corneal surgery. Theory, technique, and tissue. St. Louis: Mostby, 1999.

Software

4. Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention; 1994.

Online journals

5. Friedman SA. Preeclampsia: a review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988; 71:22.37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 1996. Updated March 29, 1996.

Internet

7. Gostin LO. Drug use and HIV/AIDS [JAMA HIV/AIDS web site]. June 1, 1996. Available at: http://www.ama-assn.org/special/hiv/ethics. Accessed June 26, 1997.

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04 de Fevereiro de 2020

A Coordenadora da Unidade de Investigação

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n.º 08 / 2020

DIRECÇÃO CLÍNICA

6 / 2 / 2020

SÃO JOÃO

PEDIDO DE AUTORIZAÇÃO

Realização de Investigação

Exmo. Senhor Presidente do Conselho de Administração
do Centro Hospitalar de São João

CONSELHO DE ADMINISTRAÇÃO - REUNIÃO DE
Presidente do Conselho de Administração
(Prof. Doutor Fernando Araújo)
Diretora Clínica — Enfermeira Diretora — Vogal Executivo — Vogal Executivo
(Profª Doutora Maria João Seguins) — (Enfª Florentina Cardoso) — (Dr. Luís Porto Gomes) — (Drª Sofia Leal)

Nome do Investigador Principal:

Maria Leal Antão

Título da Investigação:

O Papel da Doença Atópica na Progressão de Queratocone

Pretendendo realizar no(s) Serviço(s) de:

Oftalmologia

a investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efetivação.

Para o efeito, anexo toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto respeitante à investigação, à qual enderecei pedido de apreciação e parecer.

Com os melhores cumprimentos.

O Investigador/ Promotor

Porto, 6 *de* Dezembro *de* 2019. Maria Leal Antão

assinatura

• Centro Hospitalar São João •
Centro de Epidemiologia Hospitalar
27 / 12 / 2020

CES-IM005-0

Parecer da Comissão de Ética do

Centro Hospitalar Universitário de São João / Faculdade de Medicina da Universidade do Porto

Título do Projecto: O papel da doença atópica na progressão de queratocone

Nome da Investigadora Principal: Maria Leal Antão, estudante do MIM da FMUP

Onde decorre o Estudo: No Serviço de Oftalmologia do CHUSJ. Dispõe de autorização do Prof. Doutor Fernando Falcão Reis.

Objectivos do Estudo:

Avaliar o papel da doença atópica na velocidade e grau de progressão de queratocone, num intervalo de tempo médio de 1 ano, numa visão retrospetiva.

Estudo realizado no âmbito do Mestrado Integrado em Medicina da FMUP, sob orientação do Dr. João Carlos Pinheiro Costa.

Concepção e Pertinência do estudo:

Estudo retrospetivo.

Ao analisar a influência de doença atópica na progressão desta patologia, poderão desenhar-se algumas conclusões no que diz respeito à necessidade ou não de um seguimento mais apertado ou tratamento mais agressivo em doentes com antecedentes de doença atópica.

Pretende-se, assim, recolher dados no SClínico relativos à avaliação de doentes com queratocone seguidos na consulta de Secção de Córnea do Serviço de Oftalmologia do CHUSJ, obtidos por Pentacam, durante um período de seguimento de cerca de 2 anos (2016 a 2018); recolher dados no SClínico relativos a antecedentes de patologia atópica (rinoconjuntivite alérgica; asma alérgica; dermatite atópica) nos doentes avaliados por Pentacam e selecionados anteriormente.

Benefício/risco: Não aplicável

Confidencialidade dos dados:

Os dados serão codificados, de modo a não permitir a identificação dos participantes.

Apresentou um pedido de reutilização de registos clínicos para Investigação e Desenvolvimento ao RAI.

Respeito pela liberdade e autonomia do sujeito de ensaio: Não aplicável

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: Março de 2020

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 23 de janeiro de 2020

O Relator da CE,

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

SÃO JOÃO

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

Questionário para submissão de Investigação

Exmo. Sr. Presidente da Comissão de Ética do Centro Hospitalar de São João/ Faculdade de Medicina da Universidade do Porto,

Pretendendo realizar a investigação infracitada, solicito a V. Exa., na qualidade de Investigador, a sua apreciação e a elaboração do respetivo parecer. Para o efeito, anexo toda a documentação requerida.

IDENTIFICAÇÃO DO ESTUDO

Título da investigação: O Papel da Doença Atópica na Progressão de Queratocone

Nome do investigador: Maria Leal Antão

Endereço eletrónico: marialealantao@gmail.com **Contacto telefónico:** 916562845

Caracterização da investigação:

☒ Estudo retrospetivo ☐ Estudo observacional ☐ Estudo prospetivo

☐ Inquérito ☐ Outro. Qual? _____

Tipo de investigação:

☐ Com intervenção ☒ Sem intervenção

Formação do investigador em boas práticas clínicas *(GCP)*: ☐ Sim ☒ Não

Promotor *(se aplicável)*: _____

Nome do orientador de dissertação/tese *(se aplicável)*: João Carlos Pinheiro Costa

Endereço eletrónico: joaopinh@hotmail.com

Local/locais onde se realiza a investigação: Serviço de Oftalmologia do Centro Hospitalar Universitário do São João

Data prevista para início: 15 / 09 / 2019 Data prevista para o término: 23 / 03 / 2020

PROTOCOLO DO ESTUDO

Síntese dos objetivos:
O objetivo da investigação é avaliar o papel da doença atópica na velocidade e grau de progressão de queratocone, num intervalo de tempo médio de um ano, numa visão retrospetiva.

Fundamentação ética (ganhos em conhecimento/inovação; ponderação benefícios/riscos):
A importância deste estudo reside nas implicações que os seus resultados poderão ter a nível de seguimento e tratamento de doentes com queratocone. Ao analisar a influência de doença atópica na progressão desta patologia, poderão desenhar-se algumas conclusões no que respeita à necessidade ou não de um seguimento mais apertado ou tratamento mais agressivo em doentes com antecedentes de doença atópica.
Dado tratar-se de um estudo retrospetivo, não de prevê que a realização do mesmo acarrete qualquer risco para os doentes.

CES-IM007-0

CONFIDENCIALIDADE

De que forma é garantida a anonimização dos dados recolhidos de toda a informação?

O investigador necessita ter acesso a dados do processo clínico? ☒ Sim ☐ Não

Está previsto o registo de imagem ou som dos participantes? ☐ Sim ☒ Não

Se sim, está prevista a destruição deste registo após o sua utilização? ☐ Sim ☐ Não

CONSENTI MENTO

O estudo implica recrutamento de:

Doentes: ☐ Sim ☒ Não Voluntários saudáveis: ☐ Sim ☒ Não

Menores de 18 anos: ☒ Sim ☐ Não

Outras pessoas sem capacidade do exercício de autonomia: ☐ Sim ☒ Não

A investigação prevê a obtenção de Consentimento Informado: ☐ Sim ☒ Não

Se não, referir qual o fundamento para a isenção:
Todos os doentes incluídos no estudo são já seguidos habitualmente no Serviço de Oftalmologia do Centro Hospitalar São João realizando os exames incluídos no estudo de forma rotineira e em ambiente normal de consulta, sem qualquer prejuízo para o doente ou encargo financeiro.

Existe informação escrita aos participantes: ☐ Sim ☒ Não

PROPRIEDADE DOS DADOS

A investigação e os seus resultados são propriedade intelectual de:

☐ Investigador ☐ Promotor ☐ Ambos ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

BENEFÍCIOS, RISCOS E CONTRAPARTIDAS PARA OS PARTICIPANTES

Benefícios previsíveis:
Nenhuns

Riscos/incómodos previsíveis:
Nenhuns

São dadas contrapartidas aos participantes:

- ***pela participação*** ☐ Sim ☐ Não ☒ Não aplicável
- ***pelas deslocações*** ☐ Sim ☐ Não ☒ Não aplicável
- ***pelas faltas ao emprego*** ☐ Sim ☐ Não ☒ Não aplicável
- ***por outras perdas e danos*** ☐ Sim ☐ Não ☒ Não aplicável

CUSTOS / PLANO FINANCEIRO

Os custos da investigação são suportados por:

☐ Investigador ☐ Promotor ☐ Serviço onde é realizado

☒ Não aplicável Outro: _____

Existe protocolo financeiro? ☐ Sim ☒ Não

LISTA DE DOCUMENTOS ANEXOS

- [x] Pedido de autorização ao Presidente do Conselho de Administração do Centro Hospitalar de São João *(se aplicável)*
- [ ] Pedido de autorização à Diretora da Faculdade de Medicina da Universidade do Porto *(se aplicável)*
- [x] Protocolo do estudo
- [x] Declaração do Diretor de Serviço onde decorre o estudo
  (sendo um estudo na área de enfermagem deve anexar também a concordância da chefia de enfermagem)
- [x] Profissional de ligação
- [x] Informação dos orientadores
- [ ] Informação ao participante
- [ ] Modelo de consentimento
- [ ] Instrumentos a utilizar *(inquéritos, questionários,escalas, p.ex.)*: _____
- [x] Curriculum Vitae abreviado *(máx. 3 páginas)*
- [ ] Protocolo financeiro
- [x] Outros:

Pedido de reutilização de Registos Clínicos para Investigação e Desenvolvimento

COMPROMISSO DE HONRA E DECLARAÇÃO DE INTERESSES

Declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (1960 e respetivas emendas), e da Organização Mundial da Saúde, Convenção de Oviedo e das "Boas Práticas Clínicas" (GCP/ICH) no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo, nos últimos três meses. Comprometo-me a entregar à CES o relatório final da investigação, assim que concluído.

Porto, 06 *de* Dezembro *de* 2019

Nome legível: Maria Leal Antão _____ Maria Leal Antão
assinatura

Parecer da Comissão de Ética do Centro Hospitalar de São João/ FMUP Emitido na reunião plenária da CE de 23 / 01 / 2020

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética

08.20

RESPONSÁVEL PELO ACESSO À INFORMAÇÃO

SÃO JOÃO

Pedido de Reutilização de Registos Clínicos para Investigação e Desenvolvimento (I&D)

Número do Pedido

[2|0|0|0|1|4|8|4]

(A preencher pelo Gabinete de Apoio ao RAI)

Exmo. Senhor
Responsável pelo Acesso à Informação
(Artigo 9.º da Lei n.º 26/2016, de 22 de agosto)
Dr. Rui de Vasconcellos Guimarães

SÃO JOÃO

28/01/2020

1. Identificação do(s) Investigador(es) *Preenchimento Obrigatório*

1.1. Investigador Principal

Nome Maria Leal Antão

Contacto telefónico [9|1|6|5|6|2|8|4|5| | |]

Endereço eletrónico marialealantao @ gmail.com

1.2. Investigador(es) Associado(s)

Número Total: [1]

Nome João Carlos Pinheiro Costa

Contacto telefónico [9|6|8|1|0|4|5|2|7| | |]

Endereço eletrónico joaopinh @ hotmail.com

Nome _____

Contacto telefónico [| | | | | | | | | | | |]

Endereço eletrónico _____ @ _____

Nome _____

Contacto telefónico [| | | | | | | | | | | |]

Endereço eletrónico _____ @ _____

1.3. Afiliação Institucional do Investigador Principal

1.3.1. Grupo Profissional

☐ Médico(a) ☐ Enfermeiro(a) ☐ Docente ☒ Estudante

☐ Outro. Qual? _____

1.3.2. Documento de identificação pessoal ou profissional

☒ Cartão de Cidadão ☐ Bilhete de Identidade ☐ Célula Profissional

☐ Cartão de Docente ☐ Cartão de Estudante ☐ Outro. Qual? _____

Número de Documento [1|4|9|0|1|2|8|4| | | | |]

2. Enquadramento e Identificação do Trabalho de Investigação e Desenvolvimento *Preenchimento Obrigatório*

2.1. Enquadramento da investigação

☒ Trabalho académico de investigação e desenvolvimento:

- ☐ Não conferidor de grau
- ☒ Conferidor de grau: ☐ Licenciatura ☒ Mestrado ☐ Doutoramento

☐ Projeto de investigação e desenvolvimento

RAI-IM002-0

2.2. Entidade(s) que tutela(m) a investigação

☒ Centro Hospitalar de São João
Serviço: Oftalmologia

☒ Universidade do Porto
Faculdade / Instituto: Faculdade de Medicina da Universidade do Porto

☐ Outra Instituição. *Qual?* _____

Há alguma parceria entre instituições?

☒ Não ☐ Sim. Qual(is)? _____

2.3. Orientador *Se Aplicável*

Contacto telefónico 968104527

Endereço eletrónico joaopinh@hotmail.com

2.4. Título provisório

O Papel da Doença Atópica na Progressão de Queratocone

Deverá posteriormente indicar o título definitivo para emissão do Certificado de Reutilização pelo RAI – DAta REuse Certificate for Research – DARE através dos contactos disponíveis no fim deste formulário.

2.5. Acesso requerido

☐ Ficheiro

Descrição do património informacional a que pretende ter acesso, identificando a informação a obter, i.e. nome, morada, diagnóstico, idade, códigos dos distritos, entre outros.

☐ Consulta de processos clínicos em ambiente papel:

☐ Bloco ☐ Consulta Externa ☐ Hospital de Dia ☐ Internamento ☐ MCDT ☐ Urgência

Deverá anexar ficheiro(s) contendo a identificação do pretendido, i.e. números de processos, episódios, números de utente, entre outros.

Anexar ficheiro no ato de envio

☒ Consulta de registos clínicos eletrónicos

Especificar os Sistemas de Informação:
SClínico. Pentacam.

Data previsível de fim de utilização das credenciais de acesso 2020 - 03 - 23

☐ Outro Acesso. Qual?

2.3. Pareceres e Autorizações

☐ Autorização da Hierarquia
☐ Protocolo Científico Aprovado [1]
☒ Parecer da Comissão de Ética para a Saúde (CES) [1]
☐ Parecer do Centro de Epidemiologia Hospitalar [1]

Deverá anexar ficheiro(s) contendo cópia dos documentos referentes às opções selecionadas.

Anexar ficheiro no ato de envio

[1] *Obrigatório quando aplicável.*

3. Observações *Preenchimento Facultativo*

_____

_____

_____

_____

_____

4. Aceitação dos Termos e Condições da Reutilização

Cumulativamente com as obrigações decorrentes da lei já citada *(n.º 2 e 3 do artigo 21 e o n.º 1 e 2 do artigo 12, ambos da Lei n.º 26/2016, de 22 de agosto)* ao submeter o presente pedido concordo e fico ainda vinculado aos seguintes termos e condições:

- Comprometo-me a manter confidencial toda a informação à qual vou ter acesso;
- Não vou elaborar registos, susceptíveis de identificar ou tornar identificável a identidade das pessoas a quem os mesmos dizem respeito;
- Não vou elaborar, nem ficar na posse, de cópias de bases de dados utilizadas na recolha de informação;
- Comprometo-me a obter junto da Comissão Nacional de Proteção de Dados (CNPD) as necessárias autorizações, para eventuais bases de dados que venha a conceber e utilizar no âmbito da presente investigação;
- Comprometo-me a devolver ao Centro Hospitalar de São João, na pessoa do seu Diretor Clínico, as bases de dados e o resultado da investigação;
- Comprometo-me a ocultar os elementos de identificação da(s) pessoa(s) a quem os registos digam respeito, em futuras e eventuais publicações de resultados;
- Comprometo-me a consultar os processos clínicos nas instalações que me forem indicadas para o efeito;
- Comprometo-me a obter os necessários pareceres, quer da Comissão de Ética do Hospital, quer do Centro de Epidemiologia Hospitalar, sempre que necessário;
- Comprometo-me a citar as fontes sempre que publicitar o trabalho de investigação independentemente de requerer a Certidão de Reutilização (DAta REuse Certificate for Research – DARE);
- Tomei conhecimento, que a violação de qualquer dos compromissos aqui assumidos, resultará no apuramento de responsabilidades disciplinares, civis e penais e ainda, à impossibilidade futura de aceder a informação de saúde para fins de investigação.

5. Decisão do investigador sobre requerer a DAta REuse Certificate for Research – DARE *Preenchimento Obrigatório*

☒ Pretendo desde já requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710*.

☐ Não pretendo requerer a Certidão de Reutilização (DARE) cujo sentido, valor e significado consultei em *http://portal-chsj.min-saude.pt/pages/710*.

6. Assinatura

Nota 1: Se o presente pedido for submetido eletronicamente ou faz assinatura digital qualificada; ou posteriormente vem ao Centro Hospitalar de São João exibir o seu documento de identificação pessoal; ou no âmbito do seu espaço de liberdade e como manifestação expressa do seu consentimento envia cópia do referido documento, neste caso, concluído o processo ser-lhe-á devolvida ou eliminada a cópia do documento de identificação pessoal, conforme as indicações que dê.
Nota 2: Se o presente pedido for entregue presencialmente, assina e exibe o documento de identificação a quem recebe o pedido.

Data 2019 - 12 - 06

Maria Paula Antão

Investigador Principal

Em caso de dúvida no preenchimento contacte através dos endereços eletrónicos
rai.reutilizacao.id@chsj.min-saude.pt **ou** ruiguimaraes@chsj.min-saude.pt
ou pelos números de telemóvel 962 204 194 **ou** 918 880 299

SUBMETER