KERATOCONE - DIAGNOSIS AND CLINICAL MANIFESTATIONS: A LITERATURE REVIEW

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Abstract: Keratoconus is a non-inflammatory eye disease caused by corneal deformation. In the early stages of the disease, keratoconus is a disease that is difficult to identify due to the absence of symptoms. Objective: This study aimed to highlight the main diagnostic methods of keratoconus disease, as well as its definition and clinical manifestations. Method: The development of this research was based on a study characterized as descriptive, considering that it was sustained from a theoretical basis. Therefore, a qualitative approach was used, as authors of books, scientific articles and electronic publications were taken as a source of research. That said, the nature of the present study is considered as an integrative literature review. Results: it was observed that in terms of visual rehabilitation, procedures that interfere with the progression of keratoconus, such as special contact lenses, Cross linking and implantation of the intrastromal ring, changed the previous scenario, delaying the progression of the disease and, in some cases, postpone and even avoid corneal transplantation. Conclusion: through the study, it was possible to perceive that the availability of new treatments for keratoconus also contributed to the importance of early diagnosis.

Keywords: Keratoconus. Cornea. Diagnosis.

INTRODUCTION

According to Santos (2013), keratoconus is an ocular disorder, corneal ectasia or ectatic dystrophy, non-inflammatory and self-limited, described by a progressive thinning of the central portion of the cornea. Still according to the author, it influences the shape of the cornea, causing the perception of distorted images. As the cornea becomes thinner, the patient perceives a decrease in visual acuity, which can be mild or severe, depending on the amount of corneal tissue affected.

According to Gomes (2016), points out that the cornea, in a simple analogy, can be considered as the "lens" that covers the iris, projecting light onto the retina through the pupil. Through this "dysmorphia" in the cornea, keratoconus prevents the projection of images on the retina, promoting irregular astigmatism and myopia. The progression of this disease is marked by a series of symptoms, such as apical protrusion, stroma thinning, scar formation, irregular astigmatism, among others.

Still according to Gomes (2016), all these symptoms mentioned above impair the individual's visual acuity in a significant way. The treatment approach may vary according to the level of disease progression, and the therapeutic proposal can be used both curatively and preventively, controlling the progression of the disease.

With regard to the diagnosis, it can be difficult, as keratoconus can manifest in various clinical forms. For Lopes et al. (2015) there are cases of keratoconus that are subclinical, that is, that cannot be diagnosed. Furthermore, the symptoms of keratoconus can be varied, ranging from photophobia to double vision, polyopia or the formation of halos around light sources. It must be noted that there are cases in which, in the first stages, keratoconus does not have obvious symptoms that can be collected in an interview with the patient or in an anamnesis.

According to Vellara and Patel (2015), the analysis of local anatomy and biomechanics are performed using different methods. For the analysis of the anatomy, there are some computerized and manual procedures that can be performed, such as: the placid disc, computerized vidiokeratometry and computed tomography. The previously described methods are mainly applied in the analysis of the corneal anatomy.

According to Ambrósio et al. (2013), for the analysis of corneal biomechanics, highlight

the use of Corvis ST (abbreviation for Corneal Visualization Scheimpflug Technology), which in Portuguese is called Technology Scheimpflug of Corneal Visualization. From the Corvis, the professional uses a jet of air to cause a slight 'disturbance' in the cornea. During the air exit, the Corvis uses an Ultra High Speed (UHS) camera with lighting from a Blue LED source, capturing the image in super slow motion.

Therefore, this study sought to answer the following question: what are the main diagnostic methods and clinical manifestations of keratoconus?

This study is justified due to the fact that keratoconus is a disease that has a relatively significant incidence in the population with relevant sequelae. In addition, the study is even more justified, due to the need for improvement to diagnose this pathology accurately.

METHODS

This study is an integrative literature review, supported, therefore, by a bibliographical research. According to Prodanov and Freitas (2013), bibliographical research is:

> [...] elaborated from already published material, consisting mainly of: books, magazines, publications in periodicals and scientific articles, newspapers, bulletins, monographs, dissertations, theses, cartographic material, internet, with the objective of putting the researcher in direct contact with all already written material on the subject of the research. In bibliographic research, it is important for the researcher to verify the veracity of the data obtained, noting the possible inconsistencies or contradictions that the works may present (PRODANOV; FREITAS, 2013, p. 54).

According to Lakatos and Marconi (2001), bibliographical research, considered a secondary source of data collection, can be defined as cultural or scientific contributions made in the past on a particular subject, theme or problem that can be studied. It is also noteworthy that bibliographical research involves all bibliography already made public in relation to the subject studied, from separate publications, bulletins, newspapers, magazines, books, research, monographs, theses, cartographic materials, etc. Its purpose is to put the researcher in direct contact with everything that has been written, said or filmed about a given subject.

As for the approach, the present study was carried out based on a qualitative research, as it sought to understand the phenomena from their explanation and reasons. For Minayo (2014), this type of research is concerned with the level of reality that cannot be quantified, that is, it is based on the universe of meanings, motivations, aspirations, beliefs, values and attitudes. Regarding the objective, the present research presented an exploratory-descriptive character, considering that it sought to achieve greater familiarity in understanding the object of study and the relationship between its variables.

To search for publications on the theme discussed to compose this research, the databases SciELO (Scientific Electronic Library Online), Pubmed and Google Scholar were used. The time frame used comprised the period from 2013 to 2022. The descriptors used were, based on the DECS/MESH (descriptors in health sciences), keratoconus, corneal dystrophies and corneal diseases. For this, the AND logical operator was used, thus allowing an objective direction for the search for articles.

The inclusion criteria taken into consideration for the preparation of this research included studies published as articles, dissertations, monographs, case studies (of all types), in addition to studies published in national and international journals available in full in Portuguese, English and Portuguese.

Spanish, whose access has been free. In addition, publications that covered the period from 2013 to 2022 and that approached the theme discussed in this study were considered.

For the selection of publications, the articles were analyzed through a direct and analytical reading about the studies that addressed the theme presented here. From the reading, the conceptions among the authors were analyzed and compared. To highlight the position of scholars, a table was developed containing the author and year of publication, the objective of the study, the methodology used and the main results obtained.

It is worth emphasizing that the present study did not have ethical implications, considering that it used secondary information, as it was based on previous studies. Therefore, as there was no identification of the patients, it was not necessary to apply the Free and Pre-Established Consent Form, in accordance with Resolution 466/12. It must be noted that this study was carried out in accordance with the required ethical standards.

RESULTS

In order to develop this review, 25 articles were selected from the virtual databases SciELO, Pubmed and Google Scholar. After reading and analyzing the articles, 12 were excluded because they had little connection with the theme addressed. After applying the time cutoff of 10 years, 07 articles were excluded because they did not fit this requirement. Therefore, 06 articles remained, which were used for data collection.

After selecting those that corresponded to the topic addressed in this study and that were published in Portuguese, English and Spanish and that were part of the time frame corresponding to the period from 2013 to 2022, these articles were organized as shown in Table 1.

DISCUSSION

The study carried out by Santos (2013) aimed to address keratoconus. For this, a literature review was carried out in order to highlight the types of the disease, its etiology, the main symptoms and signs, as well as its treatment. This study showed that, due to the evolution of medicine, it was possible to develop solutions for cases of keratoconus, considering that new lenses were created, as well as the use of gene therapy techniques, in order to prevent the appearance and disease progression.

The study by Lopes, Pinto and Sousa (2015) sought to reveal relevant aspects regarding the epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment and complications of keratoconus. To support the study, a literature review was carried out. With the study, it became clear that keratoconus generally begins in adolescence and may even affect young adult patients. With the onset of the disease, the patient may present physical, biochemical and molecular changes in the corneal tissue, however, the literature does not clearly show the clinical findings, nor the ocular and non-ocular associations associated with the disease.

Based on the study by Vellara et al. (2015), carried out with a sample of 152 eyes, sought to evaluate ocular biomechanical metrics, as well as corneal and orbital components additionally derived with the use of a tonometer. It was revealed that AD was significantly correlated with patient age. However, it did not correlate with gender or ethnicity. Regarding the multiple linear regression analysis, there were significant correlations between AD and age, and AD and IOP. Age was correlated with DMC, DOM and DEC. Male patients had lower DOM than females. There were no differences in DMC or DEC between genders. Furthermore, there were no representative differences between ethnicities for CMD,

Author /Year	Goal	Methodology	Main Results
Santos (2013)	Discuss keratoconus, highlighting its types, etiology, main symptoms and signs, and treatment.	Literature review	It became evident that with the evolution of medicine, definitive solutions emerged for several diseases and in the case of keratoconus it was no different, considering the development of new lenses or the use of gene therapy techniques, in order to prevent the appearance and progression of the disease.
Lopes, Pinto And Sousa (2015)	Highlight aspects about the epidemiology, pathophysiology, clinical manifestations, diagnosis, treatment and complications of keratoconus.	Systematic literature review.	Keratoconus is characterized by bilateral involvement, usually asymmetrically. Normally, the condition begins in adolescence and may also affect young adults. The etiology for keratoconus involves physical, biochemical and molecular changes in the corneal tissue. However, no theory fully explains the clinical findings and the ocular and non-ocular associations related to keratoconus. It is noteworthy that it is known to association with hereditary diseases, atopic diseases, some systemic diseases, prolonged use of contact lenses and collagen diseases.
Vellara et al. (2015)	Analyze ocular biomechanical metrics and additionally derived corneal and orbital components using a non-contact Scheimpflug-based tonometer (CorVis ST) in a population of healthy eyes.	152 eyes of 152 participants were examined by slit lamp biomicroscopy, corneal tomography and CorVis ST (CST) to determine the distribution of CST outputs such as strain amplitude (AD) and additional derived parameters.	The mean age of the participants was 35.88 ± 13.8 years. AD correlated significantly with age ($r = 0.24$, $P = 0.002$), but not with sex or ethnicity ($P > 0.05$). Multiple linear regression analysis revealed significant correlations between AD and age ($r = 0.19$, $P = 0.006$) and AD and IOP (intraocular pressure) ($r = -0.59$, $P < 0.001$). Age correlated with CMD (maximum corneal deformation) ($r = 0.20$, $P = 0.01$), DOM (maximum orbital strain) ($r = 0.18$, $P = 0.03$) and DEC (energy dissipation of the cornea) ($r=0.39$, $P<0.001$). Males had lower DOM than females (0.24 vs. 0.26 mm, respectively, $P = 0.01$). However, there were no differences in DMC or DEC between genders ($P > 0.05$). There were no significant differences between ethnicities for CMD, DOM and DEC ($P > 0.05$). A multiple linear regression analysis revealed significant correlations between CMD and IOP ($r = -0.65$, $P < 0.001$), DEC and age ($r = 0.41$, $P < 0.001$), DEC and IOP ($r = 0.28$, $P = 0.001$), and between DEC and central corneal thickness (CCE) ($r = -0.36$, $P < 0.001$).
Jacinto (2018)	Identify and model representations of features of orneal biomechanics from exam images generated by Corvis ST to apply them to machine learning techniques for the early diagnosis of keratoconus.	Examinations of 686 normal eyes and 406 eyes with keratoconus in grades I to IV, considering the bases of exams in Europe and Brazil, for treatment and validation of the applied data.	The best models identified occurred with apparent batch image pachymetry, with application of wavelet level 4 and processed with fast large margin (European database), with a score of 0.8247, sensitivity of 89.5% and specificity of 92. 14%, 2D histogram of apparent pachymetry, with LeNET5. At the base in Brazil, the score was 0.8361, sensitivity of 88.58% and specificity of 94.39%.
Gomes e Lobo (2020)	To analyze corneal endothelial counts in patients with keratoconus by specular microscopy how to correlate with keratoconus stage.	Cross-sectional study carried out in ninety-three eyes of 61 patients with keratoconus. For this, the eyes were classified in keratoconus stages 1 to 4 according to the Amsler-Krumeich classification using keratometry obtained through corneal topography and pachymetry readings obtained by specular microscopy.	It was observed that the age ranged from 12 to 43 years, mean ± (standard deviation) 22.1 ± 6.7 years. Mean keratometry ranged from 42.25 to 71.4 D (53.0 ± 6.1 D). Pachymetry ranged from 350 to 606 μm, (461.7 ± 47.1 μm). As for the classification, 23 patients (24.7%) had stage 1, 24 (25.8%) stage 2, 5 (6.5%) stage 3 and 41 patients (44.1%) stage 4. No linear correlation was identified between mean keratometry and endothelial cell count (Pearson's correlation coefficient = -0.05). In the early to moderate stages of keratoconus, the mean endothelial cell count was 2738.3 ± 285.4 cells/mm2, whereas in the advanced keratoconus group (stages 3 and 4) it was 2670.6 ± 262.7 cel/mm2, p= 0.24.
Hilgert et al. (2020)	Conduct a review on keratoconus diagnosis, focusing on available propaedeutic methods.	Literature review. In addition, the manual Preferred Practice Pattern (PPP) of the American Academy of Ophthalmology, as well as the website "eyewiki.aao. org" for the use of figures.	The diagnosis of keratoconus has evolved since its first description. In this sense, it is suggested that the diagnosis be made in the early stages due to the high morbidity potential of the disease. Thus, a possible integration between the multiple diagnostic indices, genetic investigation, molecular biology and artificial intelligence is sought in view of the search for greater diagnostic accuracy.

Table1 –Characterization of articles

The own author

DOM and DEC. Multiple linear regression analysis revealed significant correlations between CMD and IOP, DEC and age, DEC and IOP, and between DEC and ECC.

The study carried out by Jacinto (2018) aimed to observe and model representations about the characteristics of corneal biomechanics based on exam images generated by the Corvis ST in order to apply machine learning techniques for the early diagnosis of keratoconus. To carry out the study, exams of 686 normal eyes and 406 eyes with keratoconus in grades I to IV were used. It turned out that the best identified models were those in which they were performed with apparent batch image pachymetry, having used wavelet application level 4 and processed with fast large margin where a score of 0.8247 was indicated, sensitivity of 89.5 % and specificity of 92.14%, 2D histogram of apparent pachymetry, with LeNET5, taking into consideration, baseline data from Europe. In the case of Brazil, the score was 0.8361, sensitivity of 88.58% and specificity of 94.39%.

The study carried out by Gomes and Lobo (2020), through a cross-sectional study, aimed to evaluate the endothelial count of the cornea in patients with keratoconus through specular microscopy. In addition, it sought to correlate the referred count with the stage of the disease. Ninety-three eyes of 61 patients diagnosed with keratoconus were analyzed. The study revealed that mean keratometry ranged from 42.25 to 71.4 D. Pachymetry ranged from 350 to 606 μm. Regarding the classification, 24.7% of the patients presented stage 1, 25.8% stage 2, 6.5% stage 3 and 44.1% stage 4. In the present study, no linear correlation was identified between mean keratometry and cell count endothelial. It was highlighted that, in the early to moderate stages of the disease, the mean endothelial cell count was 2738.3 ± 285.4 cells/mm2. In the advanced keratoconus group, that is, in stages 3 and 4, the count was 2670.6 ± 262.7 cells/mm2.

The study by Hilgert et al. (2020), through a literature review, aimed to develop a review on the diagnosis of keratoconus, highlighting the propaedeutic methods. The study highlighted that the diagnosis of the disease has been evolving. Thus, it was suggested that the diagnosis of keratoconus be made in the early stages due to the high morbidity potential of the disease. It was highlighted that a possible integration between the multiple diagnostic indices, as well as genetic research, molecular biology and artificial intelligence are factors that are sought in order to obtain greater accuracy in the diagnosis of keratoconus.

Taking into consideration, the studies selected for this review, it is observed that with the advancement of medicine, solutions for the diagnosis and treatment of keratoconus have been developed due to the creation of new lenses and use of gene therapy techniques, according to a study by Santos (2013). In the study by Hilgert et al. (2020), it was also highlighted that the diagnosis of keratoconus has been evolving and it was suggested that this process be carried out in the early stages because of the great morbidity potential of the disease. In addition, it became evident that in order to obtain a better accuracy of the disease, an integration between the multiple diagnostic indices must be made, in addition to genetic investigation, molecular biology and artificial intelligence.

The study carried out by Lopes, Pinto and Sousa (2015) highlighted that the clinical manifestations of keratoconus are physical, biochemical and molecular changes in the corneal tissue. The study by Vellara et al. (2015), highlighted that AD had a representative relationship with the patient's age, but had no relationship with gender or ethnicity. Significant correlations were also revealed between AD and age, and AD and IOP. Furthermore, age was correlated with

CMD, DOM and DEC. No differences were found regarding CMD or DEC between genders and no significant differences were found between ethnic groups for CMD, DOM and DEC. Through multiple linear regression, representative correlations were revealed between CMD and IOP, DEC and age, DEC and IOP, as well as between DEC and ECC.

In the study carried out by Jacinto (2018) on the early diagnosis of keratoconus, it was highlighted that the best models identified were those in which they were performed with apparent batch image pachymetry, in view of the tests carried out from the databases of Europe and from Brazil, as representative scores, sensitivity and specificity were revealed.

As for the study developed by Gomes and Lobo (2020), it was clear that patients with keratoconus presented stages from 1 to 4, in view of the variation in relation to pachymetry. The study also highlighted that no linear correlation was observed between mean keratometry and endothelial cell count.

CONCLUSION

The purpose of this study was to discuss keratoconus, highlighting its diagnosis and clinical manifestations. To substantiate the theme, an integrative literature review was carried out, since it was based on research already carried out regarding the discussed topic.

With the development of this research, it was clarified that keratoconus has gained prominence, in view of the wide dissemination about the disease with regard to the diagnosis. This fact was enhanced due to the advancement of medicine, which has provided the creation of methods for diagnosing the disease at an early stage. Diagnosis in the initial stage of the disease is essential, as its morbidity rate is high when keratoconus is not treated.

This study also showed that the integration between diagnostic indices, artificial intelligence, genetic research and molecular biology can be a relevant aspect in the identification of keratoconus. Furthermore, the availability of new treatments for the disease helps in early diagnosis. It was also highlighted that ocular biomechanics models can be used in the diagnosis of the disease.

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