



Keratoconus and the Impact of Treatment on Patients' Quality of Life: A Qualitative Study

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ABSTRACT

Introduction: Keratoconus has a significant impact on patients' quality of life (QoL), from diagnosis to the advanced stages of the disease. The aim of this research was to identify domains

of QoL affected by this disease and its treatment.

Methods: Phone interviews were conducted using a semi-structured interview guide, with patients with keratoconus stratified according to their current treatment. A board of

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keratoconus experts helped identify the guide's main themes.

Results: Thirty-five patients (rigid contact lenses, $n = 9$; cross-linking, $n = 9$; corneal ring implants, $n = 8$; and corneal transplantation, $n = 9$) were interviewed by qualitative researchers. Phone interviews revealed several QoL domains affected by the disease and its treatments: “psychological”, “social life”, “professional life”, “financial costs” and “student life”. All domains were impacted, independently of the treatment history. Few differences were found between treatment regimens and keratoconus stages. Qualitative analysis enabled the development of a conceptual framework based on Wilson and Cleary's model for patient outcomes common to all patients. This conceptual model describes the relationship between patients' characteristics, their symp-

toms, their environment, their functional visual impairment and the impact on their QoL.

Conclusions: These qualitative findings supported the generation of a questionnaire to evaluate the impact of keratoconus and its treatment on patients' QoL. Cognitive debriefings confirmed its content validity. The questionnaire is applicable for all stages of keratoconus and treatments and may help tracking change over time in regular clinical settings. Psychometric validation is yet to be performed before its use in research and clinical practices.

Keywords: Keratoconus; Quality of life; Questionnaire; Patient-reported outcomes; Contact lens; Cross-linking; Corneal ring implantation; Corneal transplantation

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Key Summary Points

Why carry out this study?

Keratoconus is a progressive disease that usually begins in late adolescence and gradually deforms and thins the cornea. Its treatment depends on the severity of the disease but also on the visual imperatives of the patient.

The disease and its treatments have a significant impact on the patients' quality of life.

The purpose of this qualitative study was to investigate and describe, with the help of patients, the impact of keratoconus and its treatments on the quality of life, disability and dependency in patients suffering from different stages of the disease, and to develop a detailed conceptual model of disease and treatment impact on the daily life of patients.

What was learned from the study?

A detailed and comprehensive conceptual model shows interactions between disease symptoms, patient characteristics and treatments, impact on visual function, interaction of environment, and impact on patients' quality of life.

Psychological, social, professional, educational, financial and daily life concepts were all impacted.

This study will allow us to develop a new questionnaire for the assessment of the impact of keratoconus and its treatment on the quality of life of patients.

deforms and thins the cornea, with generally both eyes being affected. While its exact origin is still uncertain, some associated risk factors have been identified: eye rubbing, Down's syndrome, family history of the disease, atopy, ethnic group, "floppy eyelid syndrome", connective tissue diseases, Ehlers–Danlos syndrome and Leber's congenital amaurosis [1]. The prevalence of the disease is estimated to be 1.38 per 1000 in the world's population [2]. Syndromic keratoconus forms, genetic (ORPHA: 522,564) or not (ORPHA: 98,623), are rare. Several classification systems for keratoconus have been proposed in the literature. The Amsler–Krumeich classification is still the most widely used where the severity of keratoconus is graded from stage 1 to 4 using spectacle refraction, central keratometry (K), presence or absence of scarring, and central corneal thickness [3, 4] (only one criterion is needed to determine the stage):

- **Stage 1:** eccentric steeping; myopia and astigmatism < 5.00D; mean central K readings < 48.00D
- **Stage 2:** myopia and astigmatism from 5.00 to 8.00D; mean central K readings < 53.00D; absence of scarring; minimum corneal thickness > 400 μm
- **Stage 3:** myopia and astigmatism from 8.00 to 10.00D; mean central K readings > 53.00D; absence of scarring; minimum corneal thickness from 300 to 400 μm
- **Stage 4:** refraction not measurable; mean central K readings > 55.00D; central corneal scarring; minimum corneal thickness 200 μm

The treatment depends on the severity of the disease but also on the visual imperatives of the patient: correction by glasses or rigid gas-permeable contact lenses (RGPCl) [5], corneal cross-linking (CXL) treatment to stop or delay the progression of the disease [6, 7], intrastromal corneal ring segments (ICRS)[8, 9] and/or corneal transplantation [10, 11]. These treatments can also be combined. However, despite improvement of visual acuity in most patients, this does not necessarily translate into an improvement in health-related quality of life (HRQoL). In fact, many patients still report

INTRODUCTION

Keratoconus is a progressive disease that usually begins in late adolescence and gradually

difficulties with driving at night, or complain of blurry vision, halos and discomfort [12].

The disease and its treatments have a significant impact on the patients' HRQoL, as soon as patients are informed of their diagnosis. Many studies have measured the QoL of patients with keratoconus using generic instruments for all types of ophthalmic diseases, such as the National Eye Institute Visual Function Questionnaire-25 (NEI-VQ25) [13–15]. To our knowledge, an instrument specific to keratoconus was developed in 2017, the Keratoconus Outcomes Research Questionnaire (KORQ), that assesses symptoms and the impact of the disease on patients ability to perform some activities [16]. Despite its having good psychometric properties, it measures only two QoL domains: activity limitation and symptoms. Other domains such as psychosocial wellbeing and inconveniences are still not included in the questionnaire. The development of a patient self-assessment questionnaire must be based on the patients' point of view in order to have solid content validity [17]. Qualitative research methods thus make it possible to collect the information necessary for the development of self-assessment questionnaires directly from patients [18]. To our knowledge, there is no published qualitative research supporting a model of impact of keratoconus and treatment across severity stages and therapeutic solutions.

The purpose of this qualitative study was to investigate and describe, with the help of patients, the impact of keratoconus and its treatments on the HRQoL, disability and dependency in patients suffering from different stages of keratoconus; to develop a detailed conceptual model of disease and treatment impact on the daily life of patients; and ultimately to make recommendations on what needs to be assessed and how.

METHODS

Qualitative interviews were performed to collect the necessary information directly from patients. A scientific committee (SC) composed of 23 experts in ophthalmology in France was involved at each key milestone of the study to

discuss the research objectives, the qualitative study protocol, and the results.

Characteristics of Participants

The initial plan was to interview 48 patients suffering from keratoconus at different stages (1, 2, 3 and 4) according to the following treatment groups: RGPCL ($n = 12$), CXL ($n = 12$), ICRS ($n = 12$) and corneal transplantation ($n = 12$). Patients were recruited according to the following inclusion criteria:

- Patient aged 18 and over
- Patient with at least one eye with keratoconus
- Patient with at least one of the following treatments for keratoconus:
 - RGPCL without other treatment for at least 2 years
 - ICRS without other treatment for at least 2 years
 - CXL without corneal graft or contact lens for at least 1 year
 - Corneal transplantation without other treatment for at least 2 years
- Patient with cognitive and linguistic capacities allowing them to participate in an hour-long telephone interview
- Patient who has consented to participate in the interview

The following exclusion criteria were also considered for recruitment:

- Patient diagnosed with an ophthalmic disease other than keratoconus which would cause loss of vision and/or which would disturb the structural or functional evaluation of the cornea, from the moment when the first symptoms of keratoconus manifested themselves or from the time the clinical diagnosis was made.
- Patient with a major psychiatric disorder, a history of alcoholism or drug addiction, or another medical condition, which, in the opinion of the physician, would render the patient unfit to be questioned or unsuitable for the study, or would prevent the

patient from participating and meeting the study requirements.

Ophthalmologists working in Reference and Competence Centers for Keratoconus in France were in charge of patient recruitment. Patients were contacted by the investigators of each centre, who presented the study and offered the opportunity to participate if they met the selection criteria. If patients agreed to participate, the investigators hand-delivered or mailed to the patient an inclusion kit containing all the relevant information regarding the study, a consent form and a contact form to send to the interviewer so they may later contact the patient. The investigators also completed a case report form with the medical data of the patient for future analysis.

Qualitative Interviews

The exploratory interviews were conducted by an investigator trained in qualitative interview techniques. The interviews were carried out by telephone and lasted approximately 1 h. The interviews were semi-structured and followed a guide presenting the themes to be addressed [19].

The guide included themes identified in the literature but also themes subsequently added by the SC according to their clinical practice experience. The semi-directive technique involves open-ended questions in order to collect spontaneously reported information. If themes were not spontaneously addressed by the patient, the interviewer specifically probed these themes, as indicated in the interview guide. A sheet collecting socio-demographic data on the patient were completed by the interviewer at the end of the interview. Patients were then mailed a compensation worth 20 euros in the form of a gift voucher for the time spent in the interview.

Interviews were recorded in the form of audio recordings after patient agreement. The data were then transcribed verbatim to constitute the source-written documents. These source documents were made confidential as all

identifying characteristics such as names, places, etc. were deleted from the transcripts. Each audio-digital recording file was named with the internal project number, the number of the recruiting centre, a chronological number for the patient in the study, and the date of the interview. This file naming technique was used for each transcription.

Qualitative Analysis

A descriptive analysis of the population questioned was carried out on the basis of the medical and socio-demographic data collected.

A thematic qualitative analysis [20] was performed by coding the transcribed interviews. Two researchers coded transcripts and discussed their coding approach regularly to ensure standardization. This coding consisted in assigning a label – or code – (one or two words) to a word, a sentence or a paragraph of the interview transcripts, making it possible to categorize them according to the idea conveyed. This coding process is scalable and flexible. Thus, by comparison between transcripts as coding goes, the codes can be renamed or enriched with descriptors for more precision than in the first rounding of coding. In the second step, the codes were organized by themes. Those themes emerged from the data and the content they related to (e.g. social life impact versus financial impact). A conceptual model based on the model of Wilson and Cleary for patient outcomes was built on the themes that were found in the data. This conceptual model was discussed with the SC and refined after reaching consensus on each of its parts.

The analysis of the transcriptions was conducted using Atlas.ti software (version 8) [21].

Saturation

Saturation evaluation is a retrospective assessment of adequate sample size in qualitative research. Saturation is defined as the point at which no new, concept-relevant insights are likely to be obtained [22, 23]. Saturation is

considered to have been reached for a domain and sub-domain when a consistent pattern in participants' responses is achieved and – at the domain level – when no new domains emerge. The adequacy of the sample size and the complete elicitation of concepts were assessed through the development of a saturation graph that documented whether incremental interviews yielded additional information about the research question. The saturation graph was used to organize the data identified after each interview relevant to the impact of keratoconus and its treatment on patients' HRQoL, in chronological order. Each new concept is added to the list of concepts available starting with the first interview, i.e. new concepts arising in an interview are added cumulatively to the list of concepts identified in the interviews previously conducted. Saturation is considered obtained when a plateau is reached for consecutive interviews in a row, meaning that no new concepts are identified in new interviews.

Cognitive Debriefing

Cognitive debriefings were done to test the level of comprehension or understanding of each item of the questionnaire by the target audience, and if they deemed the formulation adequate, inappropriate or confusing. A cognitive debriefing is a qualitative method to assess respondents' interpretation of items within a self-completed questionnaire [24]. Cognitive debriefing targets the mental processes respondents use when completing such questionnaires, processes which are proposed to follow a question–answer model [25]. Participants complete the questionnaire and then answer questions to explain their understanding of each question or item on the questionnaire or instrument. In the interview the respondents restate in their own words what they think each item means.

Ethics

This study received the approval of the French regulatory and ethical institutions

(Consultative Committee on the Processing of Information in Research in the Health Field and National Commission for Information Technology and Liberties), as well as the National Council of the College of Physicians for the participation of experts in the SC.

Patient participation was voluntary and in accordance with the ethical principles of the Declaration of Helsinki. Each patient received full and adequate oral and written information about the study: nature, objectives, possible risks and potential benefits. Patients were informed that they had the option of stopping the study at any time. Patients had the opportunity to ask questions and had the time necessary to review the information received. No information from a patient or doctor was collected until the interviewer received the patient's consent and their contact request form.

Patients were able to stop the study at any time without loss of benefit and were informed of this by the investigator and the patient information letter. Apart from the contact request form, patient names did not appear on any document. Exploratory interviews did not influence the treatment or care that patients receive.

RESULTS

Participants

Thirty-five patients were recruited (RGPCl, $n = 9$; CXL, $n = 9$; ICRS, $n = 8$; corneal transplantation, $n = 9$). Their median age was 35.5 years (range 22–67 years). Most of the patients were married or in a relationship, were employed and had a relatively high level of education (Table 1). The stages of keratoconus were evenly represented, with 34.3% of patients being in stage 2. The most commonly present symptoms were discomfort in vision at night, blurry vision and photophobia. The most represented comorbidity was the presence of allergy in 17.1% of the patients (Table 2). Through their personal disease history, patients

Table 1 Socio-demographic characteristics

Socio-demographic characteristics	Total (<i>n</i> = 35)
Gender, <i>n</i> (%)	
Female	17 (48.6)
Male	18 (51.4)
Age, years	
Median (min–max)	35,5 (22–67)
Family status, <i>n</i> (%)	
In a relationship	27 (77.1)
Living alone	6 (17.1)
Living with parents	1 (2.9)
Other	1 (2.9)
Higher level of education, <i>n</i> (%)	
High school, did not graduate	3 (8.6)
High school and graduated	12 (34.3)
Higher education (+1 or 2 years)	10 (28.6)
Higher education (+3 years or more)	9 (25.7)
Other	1 (2.9)
Professional status, <i>n</i> (%)	
Full-time/part-time	24 (68.6)
Looking for a job	6 (17.1)
Sick leave (not keratoconus)	2 (5.7)
Retired	2 (5.7)
Student	1 (2.9)

went through a different number of treatments depending on the progression of their disease.

Conceptual Model

The conceptual model of keratoconus and its treatment impact on patients’ lives, developed from patient interviews (*n* = 35), is shown in Fig. 1 and was discussed with the SC. The following results were extracted from the 35 semi-directed interviews and were spontaneously reported by the patients.

Table 2 Medical data collected by site investigators

Baseline characteristics	Total (<i>n</i> = 35)
Time since diagnosis, years	
Median	11
Date of first diagnosis, month year	
Range	June 1979–August 2015
Keratoconus stage according to Amsler–Krumeich classification, <i>n</i> (%)	
Stage 1	7 (20.0)
Stage 2	12 (34.3)
Stage 3	8 (22.9)
Stage 4	8 (22.9)
Current keratoconus treatment*, <i>n</i> (%)	
RGPCl	9 (25.7)
CXL	9 (25.7)
ICRS	8 (22.9)
Corneal transplantation	9 (25.7)
Current symptoms, <i>n</i> (%)	
Discomfort in night vision	16 (45.7)
Blurred vision	15 (42.9)
Photophobia	10 (28.6)
Distorted vision	8 (22.9)
Eye irritation (watery eyes)	8 (22.9)
Monocular diplopia or polyopia	7 (20.0)
Other	5 (14.3)
Comorbidities, <i>n</i> (%)	
Allergy/allergy to drugs	6 (17.1)
Pulmonology/respiratory system	3 (8.6)
Dermatology	3 (8.6)
Neurology	2 (5.7)
Cardiology/cardiovascular	2 (5.7)
Upper limbs/lower limbs	1 (2.9)

Table 2 continued

Baseline characteristics	Total (n = 35)
Genitourinary system	1 (2.9)
Endocrinology/metabolism	1 (2.9)
Congenital genetic diseases	1 (2.9)
Other	2 (5.7)

[†]In case of multiple treatments, the last and most invasive was taken: (1) rigid gas permeable contact lenses (RGPCl), (2) corneal cross-linking (CXL), (3) intrastromal corneal ring segments (ICRS) and (4) corneal transplantation. In the case of cross-linking, no other treatments were associated with it

Impact on Patient’s HRQoL

Patient’s characteristics and functional visual deficiency can have an impact on several

aspects of the patient’s HRQoL. Quotes supporting HRQoL themes are available in Table 3.

a. Symptoms

Visual symptoms reported by patients during interviews included primarily sensitivity to light. Bright lights were particularly annoying as they prevented patients from driving at night or from performing routine daily tasks such as watching screens (“When it comes to light, that’s really annoying”). Patients also complained of blurry vision and decreased visual acuity as they had difficulties recognizing people unless they were close enough. Visual distortion was also recorded. Other symptoms included tiredness and migraines.

b. Functional visual deficiency

The symptoms that patients experienced had a lasting impact on their daily visual function, impeding a certain amount of their daily activities depending on the severity of their

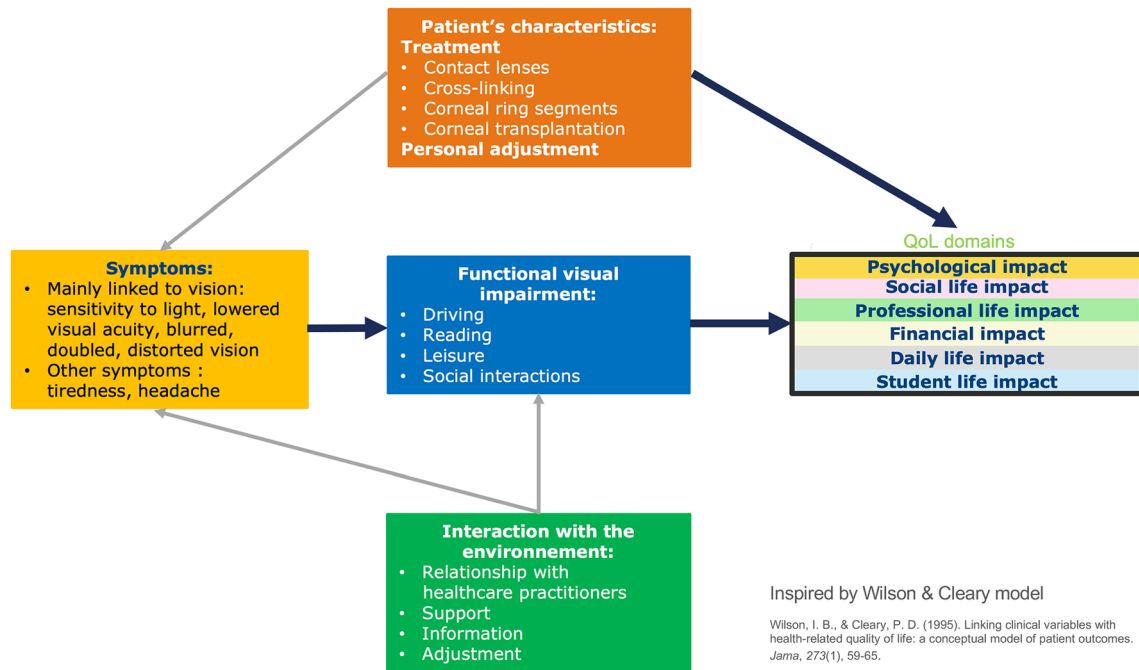


Fig. 1 Conceptual model of keratoconus and its treatment impact on patients’ lives. The conceptual model was developed and interpreted by the analyst using Wilson and Cleary’s model. The thickness of the arrows symbolizes the intensity of the relationship between the themes as

reported by the analyst. As our aim was to develop a quality-of-life questionnaire, we did not explore in depth the detailed evaluation and interpretation between the detailed concepts but only between the general concepts

Table 3 Themes identified in patient interviews regarding impact on quality of life and illustrative quotes

Concepts	Quotes (translated from French without linguistic validation)	Original quotes in French
Psychological Impact	<i>‘Well, to start, I avoid making long travels by car because it scares me that after a while, if I drive more than 20–30 min by car, my eyes will get tired, I’ll start to see really, really not well.’</i>	<i>‘Eh bien, déjà pour commencer, j’évite de faire de grands trajets en voiture parce que ça me fait peur qu’au bout d’un moment, si je fais plus de 20–30 min en voiture, j’ai les yeux qui vont se fatiguer, je vais commencer à voir vraiment, vraiment pas bien’</i>
	<i>‘I was afraid it wouldn’t work and lose an eye. Yeah, that was it. To become completely blind in one eye.’</i>	<i>‘J’avais peur que ça marche pas et de perdre un œil. Ouais, c’est que bon, c’était surtout ça. Donc devenir complètement aveugle d’un œil...’</i>
	<i>‘The transplantation was successful. Hopefully, my life would be more enjoyable than what I have lived in the last two or three years.’</i>	<i>‘Ben, la greffe a bien réussi. Si tout va bien, normalement, j’aurais une vie qui sera quand même plus agréable que ce que j’ai vécu ces deux ou trois dernières années.’</i>
	<i>‘It’s true that ... I was told when I was operated on my first eye: ‘It is hereditary, it can affect your children as much as your grandchildren or your nephews and nieces.’ Here. So I was told that. So it’s true that there is always a concern for my son in case he has it.’</i>	<i>‘Bon, le seul truc, c’est qu’on m’a dit que c’était héréditaire. Voilà. Et ça, c’est vrai que... On m’avait dit quand j’ai été opérée du premier œil: «C’est héréditaire, ça peut toucher autant vos enfants que vos petits-enfants ou vos neveux et nièces.» Voilà. Donc moi, on m’avait dit ça. Donc c’est vrai qu’il y a toujours une inquiétude pour mon fils au cas où il l’aurait quoi.’</i>
Social life Impact	<i>‘Yeah, well we’re going out. I alone, for example, will not take the wheel. Once, there were friends who had invited me a little far away, I said no, I do not ride alone, I will not ride alone. Here. If I don’t have my husband driving me, no, it’s not worth it – at night or in the evening, no.’</i>	<i>‘Ouais, ben on fait des sorties. Moi toute seule, par exemple, je prendrai pas le volant. Une fois, il y avait des amis qui m’avaient invitée un petit peu loin, j’ai dit non mais, je ne monte pas toute seule, je ne monterai pas toute seule. Voilà. Si je n’ai mon mari qui me conduit, non ce n’est pas la peine – de nuit ou en soirée, non’</i>
	<i>‘And people, on top of that, don’t know what it is. So ... Sometimes, we waste a lot of time perhaps explaining to people who ask questions, but that’s it. Even the family, well, by the way. They don’t necessarily realize what it is.’</i>	<i>‘Et les gens, en plus, ne savent pas ce que c’est. Donc... Des fois, on perd du temps peut-être beaucoup à expliquer aux gens qui posent des questions, mais voilà. Même la famille, hein d’ailleurs. Ils se rendent pas compte forcément de ce que c’est’</i>
	<i>‘Also, sometimes from afar, people who will say to me: ‘I saw you, I passed by you the other day, but you did not say hello to me. – No, I didn’t snub you, it’s just that I didn’t see you. That’s it. Recognizing people, they really have to be close for me to recognize them.’</i>	<i>‘Aussi, des fois de loin, des gens qui vont me dire: « Je t’ai vue, je suis passé à côté de toi l’autre jour, mais tu m’as pas dit bonjour. – Mais non, je t’ai pas snobé, c’est juste que je t’ai pas vu. Reconnaître les gens, il faut vraiment qu’ils soient proches pour que je les reconnaisse.’</i>

Table 3 continued

Concepts	Quotes (translated from French without linguistic validation)	Original quotes in French
Professional life Impact	<i>“Last year, I did not go. It’s been two years since I’ve not been there because of the problem with my professional activity, I have to try to find a day where I can go to [center] without disturbing my employer.”</i>	<i>“L’année dernière, je n’y ai pas été. Ça fait deux ans que j’y ai pas été parce que le problème par rapport à mon activité professionnelle, moi il faut que j’essaie de trouver une journée où je peux aller à [ville] sans que ça gêne mon employeur.”</i>
	<i>“Well for example, when I am brooming, sometimes I can forget about dust like that on the floor for example. So for that. Well, little things like that, but after all, in general, I’m not going to choose a job that is too meticulous. I, for example, do not feel able to work on a computer all day.”</i>	<i>“Ben par exemple, quand je passe le balai, dès fois, je peux oublier des poussières comme ça sur le sol par exemple. Donc pour ça. Bon, des petits trucs comme ça, mais enfin après, en général, je vais pas choisir un métier qui soit trop minutieux. Moi, par exemple, je ne me sens pas capable de travailler sur un ordinateur toute la journée.”</i>
	<i>“I had the intervention of [organism] at my workplace, so I have adapted equipment. Uh, I work perfectly well. I am better at work than at home.”</i>	<i>“J’ai eu l’intervention de [organisme] sur mon lieu de travail, donc j’ai du matériel adapté. Euh, moi je travaille parfaitement bien. Je suis mieux, je vais dire à la limite, au travail que chez moi.”</i>
Financial life Impact	<i>“A rigid lens is roughly 250 euros. And then, I have flexible ones below and it’s roughly 80 euros per month. So that’s it. When I have to add products that I buy, so products for the rigid and products for the flexible one. So it’s a big monthly investment indeed. So it definitely has an impact since I have less money to put on other things.”</i>	<i>“Dans le sens où une lentille rigide, c’est en gros 250 euros. Et après, j’ai des souples en-dessous et c’est en gros 80 euros par mois. Donc c’est ça + après, quand il faut que je rajoute des produits que j’achète, donc des produits pour la rigide et des produits pour la flexible. Donc c’est un gros investissement mensuel effectivement. Donc ça a forcément un impact puisque j’ai moins d’argent pour mettre sur d’autres choses.”</i>
	<i>“I had a lot of expenses that were not covered, in any case, as much for the pick-up of the hotel, as the tolls, as the petrol, the wear of the car.”</i>	<i>“J’ai eu plein de frais qui ont été pris en charge par moi-même, en tous cas, autant pour la prise en charge de l’hôtel, que les péages, que l’essence, l’usure de la voiture”</i>

Table 3 continued

Concepts	Quotes (translated from French without linguistic validation)	Original quotes in French
Daily life Impact	<p><i>'I took a high-definition screen. Every screen I have at home were changed, now it's really high definition, plasmas, all that. In terms of sight, there is only that. As I told you, while driving, I have GPS for long journeys or when I don't know the road too well, I have my GPS with voice on.'</i></p> <p><i>'She was the one who helped me put my makeup, put on my eyeliner, because in fact, that's what I'm telling you, you do everything by automatism and by habit. You know that, you have to do it like that to get it right, because you can't verify the result, actually. She was verifying how I was dressed.'</i></p>	<p><i>'J'ai pris un écran haute définition. Tout ce qui est télévision et écran, c'est pareil, ça a été changé, maintenant c'est vraiment des hautes définitions, des plasmas, tout ça. Au niveau de la vue, il y a que ça. Comme je vous l'ai dit, pendant la conduite, j'ai le GPS pendant les longs trajets ou quand je ne connais pas trop bien la route, j'ai mon GPS.'</i></p> <p><i>'C'est elle qui m'aidait à me maquiller, à mettre mon eye liner, parce qu'en fait, c'est ce que je vous dis en fait, vous faites tout par automatisme et par habitude. Vous savez que ça, faut le faire comme ça pour que ce soit bien fait, parce que vous ne pouvez pas vérifier le résultat, en fait. Euh, ben c'était déjà vérifier comment j'étais habillée'</i></p>
Student life Impact	<p><i>'I was always in front. If I was in the middle or at the back I could not see. I had to copy the notes of my friend sitting next to me.'</i></p> <p><i>'My eyesight has gone down, so I had to leave engineering school to get into, so to speak, training that doesn't require a lot of eye work. So I had to reorient myself towards work on, training on, let's say, on exercise science, all that is physical activity, physical education.'</i></p>	<p><i>'J'étais toujours devant. Si j'étais vers le milieu ou vers le fond, quand la copine d'à côté, elle écrivait, je copiais sur elle.'</i></p> <p><i>'Ben après, la vue, elle a baissé, donc j'ai dû quitter l'école d'ingénieur pour intégrer, on va dire, une formation qui nécessite pas beaucoup un travail des yeux. Donc j'ai dû me réorienter vers un travail sur, une formation sur, on va dire, sur science de l'exercice, tout ce qui est activité physique, éducation physique là.'</i></p>

symptoms and the disease progression. This included driving (*"Well, to start, I avoid making long travels by car"*), reading (*"Before developing my keratoconus, I read a lot of books. Afterwards, I couldn't anymore, so I really had books in very, very large print."*), social interactions (*"Once, there were friend who had invited me a little far away, I said no"*) and performing leisure activities.

c. Patients' characteristics

Patients were adapting from these different symptoms by either changing their behaviours and daily habits (*"I pay attention, I drive more slowly, and I concentrate"*; *"I have my glasses to watch TV, to work on the computer, to drive"*) or by

consulting their healthcare professionals to find medical solutions for their visual symptoms. Medical solutions include glasses, RGPCL, CXL, ICRS and corneal transplantation (*"So I saw a professor [...] because I had a letter from my ophthalmologist that said that I needed a corneal transplantation"*; *"we had tried a new model of contact lenses [...] and then the following year I went back to rigid ones"*).

d. Psychological impact

The idea of fear, worry and anxiety during patients' lifetimes was the most reported sub-concept, and mostly involved fear of losing an eye, fear of getting into a car accident because of

inability to see (e.g. being blinded, not being able to read signs) or fear of going into surgery (e.g. for the first time for surgery naïve patients, or a second time for those who already had a bad experience). However, patients also reported being confident in their current treatment, regardless of its present nature. They reported accepting and adapting to their condition, whether they had no to medium visual impairment, as long as they were benefitting from a treatment. Patients reported being worried for their children, as most patients reported that they were informed their disease had a genetic factor and that their offspring could be affected by the same visual impairments. Some patients also reported that they were disappointed in their current treatment as they were still struggling in their daily life (mostly related to RGPCL) and were looking forward to benefitting from another solution.

e. *Social life impact*

The most impactful sub-concept reported by patients was their inability to drive at night/in the evening on their own to go to a social gathering. They often had to drive at night to come back from their event, which was very challenging due to sensitivity to light and difficulty reading signs. In some cases with ICRS, patients were able to see “circles in their eyes at night with street lights”, which could be a burden. The fact that the people in their social circle had difficulties understanding their daily struggle was another impact reported by patients, as they felt they were misunderstood. Indeed, that their visual handicap was not visible at first to other people could lead to socially challenging situations, especially if they were treated with a surgery and not RGPCL. The inability to recognize people on the street was reported by some patients as being sometimes awkward and difficult socially.

f. *Professional life impact*

The most reported sub-concept impacting patients' professional lives was the obligation to save paid leave to go to the nearest Reference and Competence Centre for Keratoconus in France, which could sometimes be far away. Patients reported that they had to comply with

their employer's schedule and sometimes provide written proof to be able to go to their hospital appointment. They also reported that in some cases they felt less efficient in their work, due to high fatigability with computer screens, sensitivity to light, dusty environment or difficulty driving frequently. Some patients reported that their employers were not aware of the exact nature of their impairment, leading to misunderstandings and sometimes career challenges. Some patients were able to benefit from adjustment in their work conditions after discussions with their employers (e.g. new lights, new screens, protective goggles, etc.). In some other cases, patients had to interrupt their career and change jobs, often after a prolonged sick leave. The only difference found between treatments was the duration of the sick leave after going through medical intervention, with CXL being the shortest and corneal transplantation the longest.

g. *Financial impact*

The greatest impact related to costs reported by patients was the cost of RGPCL, especially when they did not perfectly fit the patient's eye and were prone to falling out. Patients going through surgery did not mention additional costs, as most of these were covered by the French national health insurance system. Some patients mentioned the cost of travelling to the Reference and Competence Centers for Keratoconus, and that the cost was not always covered by health insurance. Patients also reported costs of home adjustments to help them with their keratoconus (e.g. buying specific tools or software). Finally, patients reported the additional cost in time they spend due to their condition, to put in or remove lenses, or to plan their way to an unfamiliar location.

h. *Daily life impact*

The most reported impact to daily life was all the adjustments made by patients in their own house to help them cope with their condition. The adjustments could range from special electronic devices (e.g. special fonts on their computer, bigger screens, voice-activated GPS, etc.), to specific tools (e.g. magnifying glass, sunglasses, protective glasses, etc.) and adjustment

to lights (e.g. switching to “warm” lights, lowering shutters half-way during the day, etc.). Patients also reported they were less efficient in performing regular tasks at home, such as cleaning, cooking or gardening. They reported that they were also struggling with daily tasks performed outside of their household such as grocery shopping, using public transportation or orienting themselves in a place they had seldom been. The only difference pertaining to treatment was regarding RGPCL and the fact that some patients were losing them due to adjustment difficulties. This could sometime lead to inability to see properly until they could find a replacement for their lost lens. In some specific cases, the cost of lenses would be a limiting factor for replacement, as discussed above.

i. *Student life impact*

Patients reported that they had trouble when they were studying due to keratoconus, either currently or during their past student life. The most reported impact was that they often had trouble seeing what was written on the blackboard. In some cases where the activity involved a lot of reading or manual working within a dusty environment, patients had to choose another career or field of study. For the others, when they were aware of their condition, they could ask for a special status for handicapped students to grant them more time during their final exams.

j. *Interaction with the environment*

Patients reported that their interaction with their environment could improve or worsen the way they could cope with the symptoms, functional visual impairment and treatment, leading to lower or greater impact on their HRQoL. Family was reported as one of the greatest daily supports they could have, for regular tasks such as driving, taking care of the household chores or providing emotional and physical support for difficult events, such as a surgery. Friends and associations were also mentioned for such tasks. Patients would sometimes feel dependent of their surroundings when performing regular or specific tasks. Healthcare practitioners were seldom

mentioned for support, except for experts in keratoconus; patients often reported that general practitioners or regular ophthalmologists lacked knowledge regarding the disease, which led to diagnostic errors and a feeling of abandonment.

Saturation

Saturation was calculated for each treatment group separately to ensure that all topics were covered, even those specific to each treatment solution. Results are shown in Fig. 2.

DISCUSSION

This study explored the impact of keratoconus and its different treatment on patients' HRQoL. For this, we have interviewed patients with different keratoconus stages and various experiences with keratoconus treatment, including RGPCL, CXL, ICRS and corneal transplantation. Interestingly, patients with keratoconus generally encountered similar struggles and challenges in their lives, independent of their current treatment. Some specificities were found regarding each treatment, especially between non-invasive solutions (i.e. RGPCL or CXL) and invasive solutions requiring surgery (i.e. ICRS or corneal transplantation). These specificities were related to costs of RGPCL, or fear of going through medical intervention. Most of the patients interviewed experienced allergies as the most common comorbidity, which is consistent with the literature [26].

A conceptual model was developed on the basis of the model of Wilson and Cleary of patient outcomes [27], summarizing the patients' experiences of keratoconus and its treatment on their HRQoL. This conceptual model was presented to the SC, and the relevance of each module was discussed with experts caring for patients with keratoconus. Few differences between treatments and stages of the disease were found during the interviews, which enabled us to develop a conceptual model common to all patients. This model helped us summarize efficiently and clearly the

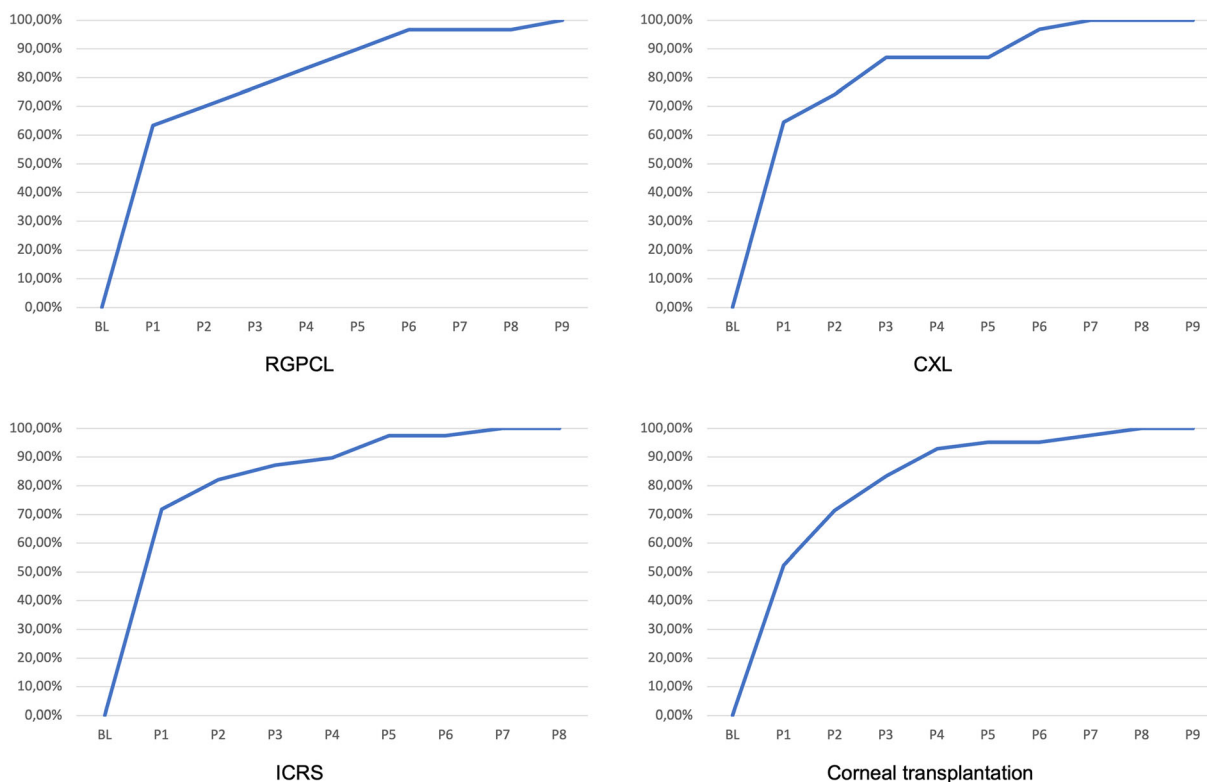


Fig. 2 Cumulative percentage of new concepts during interviews with RGPCL, CXL, ICRS and corneal transplantation patients. RGPCL patients: 61% of the concepts were found in the first interview ($n = 9$), and 96% of the concepts were obtained in the sixth interview. Total number of concepts, 29. CXL patients: 65% of the concepts were found in the first interview ($n = 9$), and 87% of the concepts were obtained in the third interview. Total number of concepts, 30. ICRS patients: 71% of the concepts were found in the first interview ($n = 8$), and

90% of the concepts were obtained in the fourth interview. Total number of concepts, 38. Corneal transplantation patients: 52% of the concepts were found in the first interview with corneal transplantation patients ($n = 9$), and 92% of the concepts were obtained in the fourth interview. Total number of concepts, 41. RGPCL stands for rigid gas permeable contact lens; CXL for corneal cross-linking; ICSR for intracorneal stromal rings; P for patient; and BL for baseline

impact of keratoconus and its treatments on patients' HRQoL in general.

Saturation was calculated for each treatment population separately to ensure that all concepts and sub-concepts were explored before stopping the qualitative data collection. We attained saturation of themes in most of our treatment groups, except for the RGPCL group where a sub-concept related to headache while wearing lenses was found in the last interview. However, this specific sub-concept was raised in another treatment group while talking about past treatments. Even though the actual number of patients interviewed was less than

originally planned, the overall saturation was attained, showing that heterogeneity within and across treatment options and disease stages was less than initially expected.

Previous studies have measured HRQoL of patients with keratoconus using generic instruments (e.g. NEI-VQ25). While NEI-VF25 covers the main areas of HRQoL related to vision, it does not cover the impact of treatments on HRQoL [28, 29]. A specific tool for keratoconus was developed recently by Khadka et al. [16]. The development of the KORQ led to a 29-item questionnaire focusing on symptoms and activity limitation. The authors discussed the

fact that one of the limitations of the KORQ was that their patients did not raise social or psychological issues. They suggested that this may be due to the use of an open-ended questionnaire instead of direct interviews with patients (e.g. face to face interview, focus group) [16]. Using an alternative way of collecting qualitative data (i.e. phone interview), the patients we have interviewed referenced the same activity limitations and symptoms as Khadka et al., but also referenced additional social and psychological impacts of keratoconus and its treatment on their HRQoL. These added data helped us to improve our conceptual model to have a fuller picture of its impact on patients' HRQoL, and are in line with Khadka et al.'s study limitation.

According to the 2009 patient-reported outcome (PRO) guidance from the US Food and Drug Administration, the development of a patient self-assessment questionnaire must be based on the patients' point of view to have solid content validity [17]. On the basis of this study's qualitative work, we developed a new questionnaire to assess keratoconus and its treatment impacts on patients' HRQoL. After discussion with the SC regarding the conceptual model, the structure of this new questionnaire was as follows: psychological impact, social life impact, professional and/or student life impact, financial impact, daily life impact, activities/hobbies impact and a last module regarding dependencies and vulnerabilities. Twenty-five items were generated on the basis of patients' own words to foster understanding by the general keratoconus population. While performing the interviews, we found that most patients were benefitting from an adequate solution for their keratoconus that day. Over the course of their lives, most of them had used RGPCL and some patients who suffered from an advanced form of keratoconus actually went through multiple medical interventions leading to drastic change in visual acuity over the course of a year. As such, we decided that the new questionnaire should assess impact of keratoconus and its treatment "over the course of the last year", as well as assessing its impact "today". This may help ophthalmologists understand how a patient reacts to a new treatment, or how the disease is progressing according to the

patient. In more common diseases, there are numerous options of generic/specific tools for HRQoL assessment (primary or follow-up), whereas the availability of such tools is often scarcer for rare diseases due to multiple development challenges [30]. As such, the questionnaire was designed as a multipurpose tool for healthcare practitioners; it may be used as a retrospective primary assessment, a routine/follow-up assessment and a change assessment questionnaire. Such a tool could help healthcare practitioners assess current and past patient status and encourage a discussion with their patients to find or confirm appropriate treatment.

Cognitive debriefings were performed with a new set of patients suffering from different stages of the disease and benefitting from different treatments ($n = 9$). These debriefings were performed to ensure that the items were covering all aspects of the concept being measured, to check sufficient comprehension, the relevance and the clarity of the questionnaire, and to allow collection of patients' reformulation proposals [31]. Overall, the questionnaire was well understood and quick to complete, and patients' input resulted in minor item revisions (e.g. reformulation, moving questions to a different place and adding a new question). The revisions were presented to the SC, and a pilot version with a total of 26 items was designed for use in regular clinical settings. Once psychometric validation study results are available, this tool could also be used in clinical trial settings.

Our study specifically explored four types of treatment (RGPCL, CXL, ICRS and corneal transplantation). Most of the patients we interviewed had used or were still using glasses, especially patients with RGPCL who had a hard time adapting to this medical solution. A patient group who wore glasses only was not one of our target groups, which could be a limitation.

CONCLUSION

This study aimed at investigating the impact of keratoconus and its treatment on the HRQoL, disability and dependency of patients suffering

from different stages of keratoconus. Phone interviews conducted with patients treated with RGPCl, CXL, ICRS or corneal transplantation revealed concepts and sub-concepts that allowed for the development of a detailed and comprehensive conceptual model. This model summarizes and shows interactions between disease symptoms, patient characteristics and treatments, impact on visual function, interaction with environment and impact on patients' HRQoL. The HRQoL concepts impacted by keratoconus and its treatment are psychological, social, professional, educational, financial and daily life. This qualitative work was the starting point of a new questionnaire developed for the assessment of the impact of keratoconus and its treatment on the HRQoL of patients. This new multipurpose tool could be used as a retrospective primary assessment, a routine/follow-up assessment and a change assessment questionnaire in regular clinical setting. The questionnaire showed good content validity when tested with patients. Further studies should be performed to define scores and assess the questionnaire's psychometric validity for clinical study use.

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Data Availability. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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