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Escuela de Doctorado Universidad de Valladolid

PROGRAMA DE DOCTORADO EN CIENCIAS DE LA VISIÓN

TESIS DOCTORAL:

EVALUACIÓN DE LA EFICACIA DE LOS DIFERENTES PROCEDIMIENTOS CLÍNICOS PARA EL MANEJO DE LA INCOMODIDAD CON LENTES DE CONTACTO

ANALYSIS OF THE EFFICACY OF COMMON INTERVENTIONS FOR THE MANAGEMENT OF CONTACT LENS DISCOMFORT

Presentada por Cristina Arroyo del Arroyo para optar al grado de Doctora por la Universidad de Valladolid

Dirigida por:
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SHORT BIOGRAPHY

Cristina Arroyo del Arroyo (12 of March of 1991) graduated in Optometry at the University of Valladolid in 2012. In 2011-2012, she got a University Scholarship to collaborate in research projects of the IOBA (University of Valladolid). Afterwards, she obtained a Master's degree in Clinical Optometry and Research in 2013 at the Camilo José Cela University (Madrid, Spain). The following year, she worked as an optometrist in Multiópticas in Salamanca. She finally joined the Ocular Surface Group in the IOBA in 2015, when she completed the Master in Research in Vision Sciences at the University of Valladolid. She also got a grant for research initiation from the CIBER-BBN (6 months). Then, she started her PhD and got a predoctoral grant from the University of Valladolid (2016-2020).

During the PhD, she has been attending to several seminars, courses and conferences. In addition, she has also collaborated in different research projects and eight peer-reviewed scientific articles. Besides, she was a teacher of contact lenses at the Optometry degree (including theory, practice, and final work tutoring). In 2018 she got one grant from Erasmus + and another grant from the University of Valladolid for a 3 months research stay at the Glasgow Caledonian University.

She has been working on her PhD studying the different managements of contact lens discomfort and developing a new questionnaire for detecting this condition. The questionnaire developed has been registered in the intellectual property registry, under the code 00/2019/2576.

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The following publications used data coming from the work carried out for this doctoral thesis:

Published scientific articles:

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- Arroyo-Del Arroyo C, Novo-Diez A, Blanco-Vázquez M, Fernández I, López-Miguel A, González-García MJ. Does placebo effect exist in contact lens discomfort management? Cont Lens Anterior Eye. 2020; doi: 10.1016/j.clae.2020.09.003. Epub ahead of print. PMID: 33071184.

Manuscripts submitted to scientific journals:

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- Oral communication: Arroyo-del Arroyo C, Fernández I, López-de la Rosa A, Pinto-Fraga J, López-Miguel A, González-García MJ. “Diseño de un cuestionario para la detección de la incomodidad con lentes de contacto”. XXV Congreso internacional OPTOM. 13-15/04/2018 (Madrid, Spain).
- Oral communication: Blanco-Vázquez M, Arroyo-Del Arroyo C, Novo-Diez A, López de la Rosa A, López-Miguel A, González-García MJ, Cañadas-Suárez P. “Análisis de la meibografía en función del uso de lentes de contacto y de la disfunción de las Glándulas de Meibomio”. XXV Congreso internacional OPTOM. 13-15/04/2018 (Madrid, Spain).
- Poster: Novo-Diez A, Blanco-Vázquez M, Arroyo-Del Arroyo C, Cañadas-Suárez P, López de la Rosa A, Pinto-Fraga J, López-Miguel A, González-García MJ. “Análisis de la variación a corto y a medio plazo de la incomodidad con lentes de contacto”. XXV Congreso internacional OPTOM. 13-15/04/2018 (Madrid, Spain).
- Oral communication: Arroyo-del Arroyo C, Fernández I, López-de la Rosa A, Pinto-Fraga J, López-Miguel A, González-García MJ. “Design and development of a new questionnaire: contact lens discomfort index”. 2019 BCLA Clinical Conference and Exhibition. 30/05-2019-01/06/2019 (Manchester, United Kingdom).
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Clinical Conference and Exhibition. 30/05-2019-01/06/2019 (Manchester, United Kingdom).

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- Poster: Arroyo-Del Arroyo C, Fernández I, Novo-Diez A, Blanco-Vázquez M, López-Miguel A, González-García MJ. “Creación de un score clínico ponderado para evaluar los signos clínicos en sujetos con incomodidad con lentes de contacto”. XXVI Congreso internacional OPTOM. 16-18/04/2021 (Madrid, Spain).

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THESIS OUTLINE

This Doctoral Thesis applies for the International-awarded Doctorate Degree. It has been performed at the Institute of Applied Ophthalmobiology (IOBA) of the University of Valladolid (Valladolid, Spain) and it has been supervised by Dr. María Jesús González García and Dr. Alberto López Miguel.

Additionally, part of this thesis has been performed during a three months stay at the Glasgow Caledonian University (Glasgow, Scotland) under the supervision of Dr. Suzanne Hagan.

The joint requirements are as follows: the whole manuscript has been written in English and a general summary in Spanish. This thesis contains eight main chapters, distributed as follows:

- *Chapter 1.* This section provides a review of the state of the art of the most important aspects related to contact lens wear, contact lens discomfort and its detection and clinical management.
- *Chapter 2.* This section presents the thesis justification.
- *Chapter 3.* This section provides the thesis hypothesis and objectives.
- *Chapter 4.* This section presents the development of the questionnaire "contact lens discomfort index" for detecting contact lens discomfort and the translation of the CLDI in English.
- *Chapter 5.* This section explains the outcomes of common interventions for managing contact lens discomfort.
- *Chapters 6.* This section presents the existence of a placebo effect in contact lens discomfort management.
- *Chapter 7*. Conclusions.
- *Capítulo 8*. Resumen de la tesis doctoral en español.

ABBREVIATIONS

AT: artificial tears

CCLRU: Cornea and Contact Lens Research Unit

CFA: confirmatory factor analysis

CI: confidence intervals

CL: contact lens

CLD: contact lens discomfort

CLDEQ: Contact Lens Dry Eye Questionnaire

CLIDE: contact lens induced dry eye

CLIQ: Contact Lens Impact on Quality of Life Questionnaire

DDCL: daily disposable contact lens

ETDRS: Early Treatment Diabetic Retinopathy Study

FBUT: fluorescein breakup time

FDA: Food and Drug Administration

GRCS: global rate changing scales

HEMA: 2-hydroxyethyl methacrylate

I: item

ICC: intraclass correlation coefficient

IRT: item response theory

LogMAR: logarithm of the minimum resolution angle

LTMA: lower tear meniscus area

LIPCOF: lid parallel conjunctival folds

LWE: lid wiper epitheliopathy

MG: Meibomian gland

MGD: Meibomian gland dysfunction

NITBUT: non-invasive tear breakup times

OCT: optical coherence tomography

OCI: Ocular Comfort Index

OSDI: Ocular Surface Disease Index

PAM: partitioning around medoids

PMC: partial credit model

RGP: rigid gas permeable

SESOD: Subjective Evaluation of Symptoms of Dryness

SiHy: silicone hydrogel

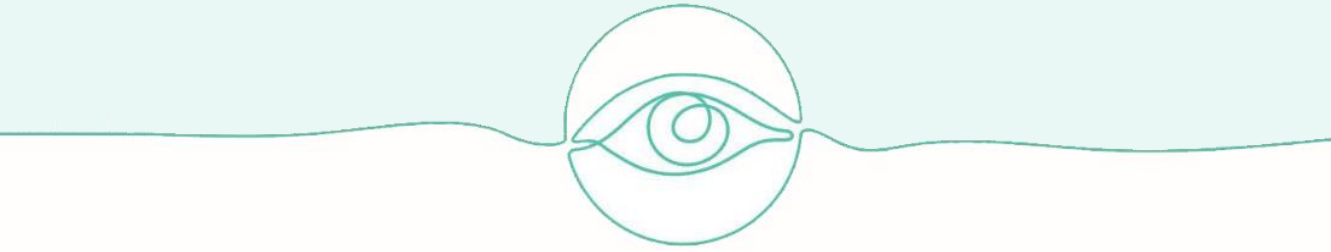
TBUT: tear breakup times

TFOS: Tear Film and Ocular Surface Society

V: visit

CHAPTER 1

INTRODUCTION



This chapter reviews the literature about contact lens (CL) wear and the principal problem related to its use, CL discomfort (CLD). It includes the definition, classification, associated factors and epidemiology as well as the symptomatology and signs of CLD. Besides, this chapter also contains a review about the different questionnaires used to detect and/or evaluate CLD. Finally, it provides the different approaches to manage CLD and its use in clinical practice.

1.1 CONTACT LENSES

Contact lenses (CL) are ocular prosthetic devices used by over 140 million people worldwide.[1,2] Primary applications of CL include vision correction, therapeutics, myopia control, and cosmetics.[2] According to the material, CL can be classified as rigid gas permeable (RGP) CL, composed of low modulus materials (minimally flexible) that has a water content lower than 10% and also hold a specific shape;[3] and hydrogel or soft CL, which are made of various plastic water-containing polymers (hydrophilic) that allow better comfort and higher flexibility than rigid lenses.[2] The polymer in all soft lenses was primarily 2-hydroxyethyl methacrylate (HEMA)-based (conventional hydrogel).[4] Silicone hydrogel (SiHy) materials, which are more highly oxygen permeable, are now the most common material in newer types of lenses.[4] Moreover, soft CL materials can differ in terms of oxygen permeability (expressed in Dk units, where D stands for diffusion and k for solubility), water content, surface characteristics (wettability), ultraviolet absorption, and structural consistency (stiffness or modulus). Indeed, the United States of America (USA) Food and Drug Administration (FDA) has developed a system for classifying soft CL based on different material properties (Table 1.1).[5]

Table 1.1. Food and Drug Administration (FDA) classification of hydrogel contact lens materials.

FDA classification	Material content	Water content	Surface charge
Group I	Conventional hydrogel	Low (<50% H_20)	Nonionic
Group II	Conventional hydrogel	High (>50% H_20)	Nonionic
Group III	Conventional hydrogel	Low (<50% H_20)	Ionic
Group IV	Conventional hydrogel	High (>50% H_20)	Ionic
Group V	Silicone hydrogel		

There is a wide variety of frequency of replacement for soft CL: daily disposable CL (DDCL), two-week replacement CL, monthly replacement, planned replacement lenses or traditional CL.[6] Soft CL are dominating the CL market, accounting for 87% of CL fits, of which, 72% are SiHy lenses.[7] In a significant way, DDCL represents the most widely prescribed soft CL with 45% of fits, followed by 39% of monthly replacement.[7] RGP CL account for 10% of CL fits, with an additional 3% of fits for orthokeratology.[7]

1.1.1 CL INTERACTIONS WITH THE OCULAR SURFACE

The ocular surface is part of an integrated functional unit protected from environmental stress by homeostatic processes that control tear flow and tear film formation.[8,9,10] The interactions between the CL, the tear film, and the ocular surface are very important for successful CL wear.

1.1.1.1 Tear film

The tear film is a thin fluid layer that covers and lubricates the ocular surface and plays an important role in the maintenance of the ocular health, comfort, and optical quality of the eye.[11] It is composed of three major components: water, mucins and lipids.

When a CL is placed on the eye, the tear film is divided into two layers, pre- and post-lens films (Figure 1.1), affecting both the biophysical and biochemical properties of the tear film.[12] In consequence, there are numerous clinical signs associated with CL wear, such as a decrease in tear film stability, pre-lens lipid layer thickness, and tear volume, as well as an increase in evaporation rate.[12]

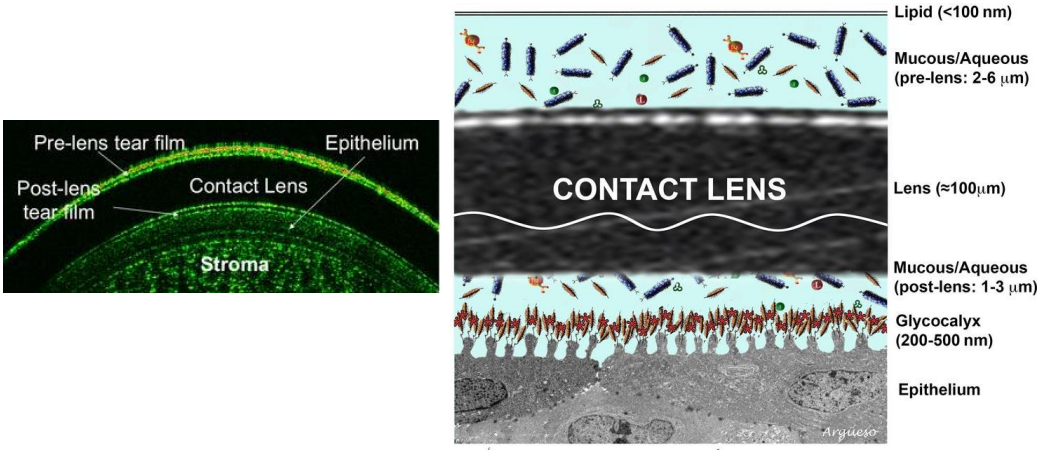


Figure 1.1. Tear film structure with a contact lens in situ. The tear film is divided into pre-lens and post-lens.

(Craig, JP, Willcox, MD, Argüeso, P, Maissa, C, Stahl, U, Tomlinson, A, et al. The TFOS International Workshop on Contact Lens Discomfort: report of the contact lens interactions with the tear film subcommittee. Invest Ophthalmol Vis Sci. 2013; 54:123-156. With permission of the Association for Research in Vision & Ophthalmology (ARVO). License number 1026834-1)

1.1.1.2 Cornea

The cornea is the transparent tissue situated on the ocular surface covering the iris and the pupil. Different effects of CL wear on the cornea have been reported, such as epithelial thinning and increased cell size.[13,14] CL wear also increases the chance of suffering epithelial damage detected by fluorescein staining.[15] Corneal nerve morphology has also been studied in CL wearers using *in vivo* confocal microscopy, and recent studies reported no alterations in the corneal sub-basal nerve plexus.[16,17] However, hydrogel CL wear might be involved in the recruitment of dendritic cells into the cornea, being a possible origin, its lower oxygen permeability compared to SiHy materials.[17]

1.1.1.3 Conjunctiva

The conjunctiva is a mucous, clear and thin membrane that covers part of the front surface of the eye and the inner surface of the eyelids. The portion of the conjunctiva that covers the anterior part of the sclera is known as bulbar conjunctiva, whereas the portion that covers the inner surface of both the upper and lower eyelids is the palpebral conjunctiva. CL movement or changes in tear film characteristics at the CL edge can provoke in soft CL wearers conjunctival staining at approximately 2 mm from the limbus, corresponding with the CL edge.[18] CL wear as well as the care solutions used for the CL maintenance have also been reported to increase tarsal,[19] bulbar[20] and limbal hyperaemia.[21] In addition, the friction produced during blinking in the marginal conjunctiva can cause some superficial damage detected with fluorescein or lissamine green and called lid wiper epitheliopathy (LWE) (Figure 1.2).

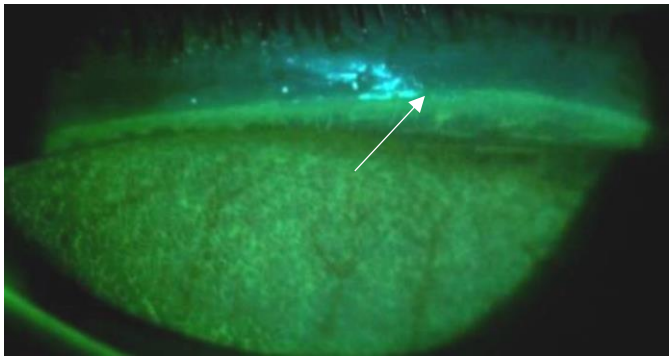


Figure 1.2. Lid wiper epitheliopathy with fluorescein staining in the upper eyelid (white arrow).

(From IOBA, Universidad de Valladolid)

1.1.1.4 Eyelids

The eyelids are the thin fold of skin that covers and protects the eye and contains three types of glands, the sebaceous glands of Zeiss, the sweat glands of Moll and the Meibomian glands (MG), which secrete meibum and generate the lipid layer of the tear film (Figure 1.3).[22] The meibum prevents the excessive evaporation of the aqueous layer,[23] helps spread of tear film, and prevent the collapse of tear film.[24] Thus, MG dysfunction (MGD) may rise symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease, being the major cause of evaporative dry eye.[25]

Arita et al.[26] found that CL wear likely affects the morphology of MG, with the effects being greater on the upper eyelid than on the lower eyelid. They also found that there was a higher partial or complete MG loss in CL wearers than in control individuals. Moreover, other study found that the duration of CL wear was correlated with acinar unit diameter, indicating signs of MG dropout, duct obstruction, and periglandular inflammation.[27] It has also been reported that early years of CL wear could be associated with increased expression of Matrix metallopeptidase 9 (MMP-9), parallel to the onset of changes in morphology and function in the MGs, indicating a low-level of inflammation during this phase of wear.[28] However, in the following years of CL wear, this finding was no longer observed, suggesting that some adaptation may have taken place.[28]

When the morphology of the epithelial-lamina propria junction of the tarsal conjunctiva was evaluated with confocal microscopy, it was found that although the majority of morphological parameters were insensitive, a more papillae circularity showed changes that could be related to CL wear.[29]

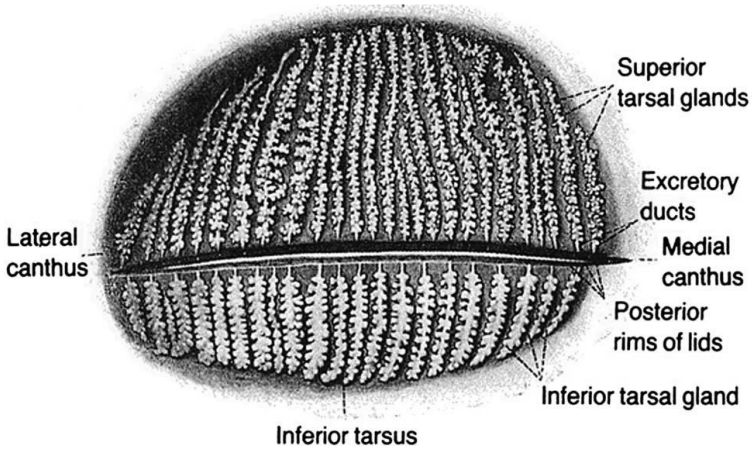


Figure 1.3. Diagram of Meibomian glands within the tarsal plates of the upper and lower eyelids.

(Arita, R., Fukuoka, S., & Morishige, N. Meibomian gland dysfunction and contact lens discomfort. Eye & Contact Lens: 2017;43:17-22. With permission of Wolters Kluwer Health, Inc. License number 4807100783848)

All these interactions of the CL with the ocular surface could be associated with complications related to its wear, such as hypoxia, inflammation, papillary conjunctivitis, allergic, or toxic reactions or microbial keratitis, among others.[30] However, nowadays, innovations in CL technology have allowed a better management of these complications.[31] Despite these new technological advancements in lens materials, design and fitting, end-of-day CL wear related discomfort remains an ongoing challenging issue, being the leading cause of CL discontinuation.[30] CLD is a substantial and persistent problem that CL wearers experience frequently. Moreover, many CL wearers alter their wearing habits due to the severity of the symptoms.[31] Therefore, CLD is an important problem that negatively affects CL wearers, practitioners and manufacturers, in fact, the cost to the industry is several hundred millions dollars each year.[1]

1.2 CONTACT LENS DISCOMFORT

1.2.1 DEFINITION AND CLASSIFICATION

The symptoms related to CL bothering have been named in different ways, such as CL dryness, CL dry eye, CL-related dry eye, or CL-induced dry eye (CLIDE).[32,33] However, the terms related to dry eye should be used for subjects who report dry eye conditions regardless of the use of CL.[1] The Tear Film and Ocular Surface Society (TFOS) published a review of this topic in 2013, “The International Workshop on Contact Lens Discomfort”. In this workshop, the CLD was defined as “a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear”.[32]

Discomfort is considered ‘‘a mental or bodily distress, or something that disturbs one’s comfort’’,[34] therefore, comfortable lens wear is the ability to wear the lens without sensation.[32] Various studies have established that successful CL wear should consider wearing time, handling, comfort, vision, ocular physiology, as well as CL factors.[35,36,37] In addition, the TFOS CLD workshop detailed the factors associated with CLD and proposed a classification scheme (Figure 1.4).

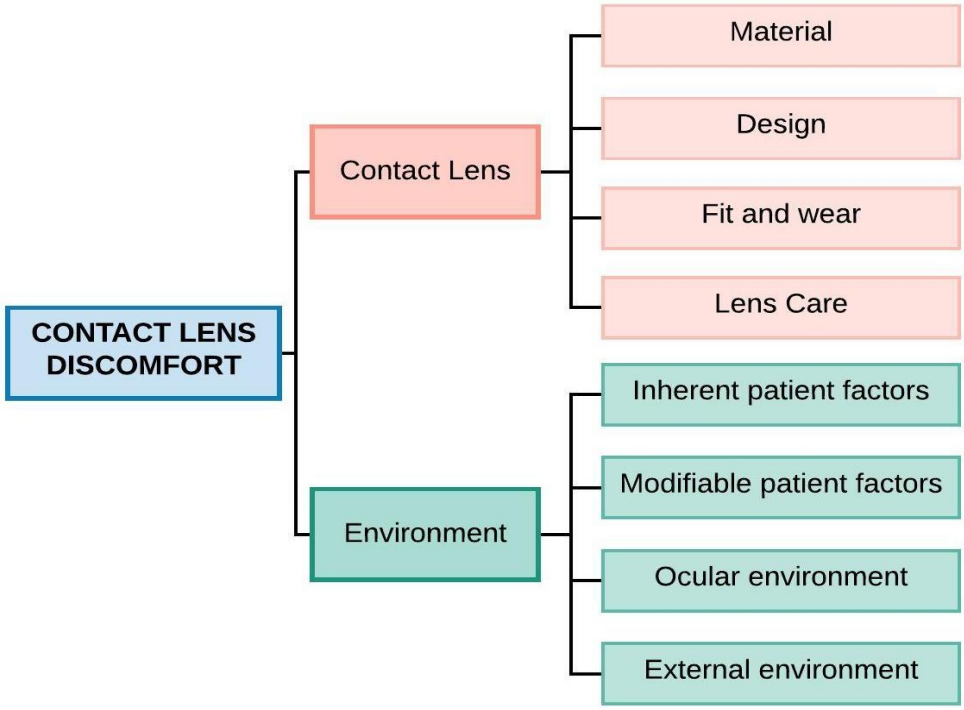


Figure 1.4. Classification scheme of contact lens discomfort according to the Tear Film and Ocular Surface Society.

(Nichols, K. K. *et al.* The TFOS International Workshop on Contact Lens Discomfort: report of the definition and classification subcommittee. *Invest. Ophthalmol. Vis. Sci.* 2013;54; 14-9. With permission of Association for Research in Vision & Ophthalmology (ARVO). License number 1036295-1)

1.2.2 CLD ASSOCIATED FACTORS

According to the TFOS classification, there are different factors related to CLD (Figure 1.4).

1.2.2.1 CL factors

Given the fact that around 90% of CL users wear soft CL,[7] the most described CL factors related to CLD are about this type of CL. In the past years, CL research has focused on comparing comfort between SiHy CL and hydrogel lenses. Ramamoorthy et al.[38] found, in a cross-sectional case-control study of 360 participants, that FDA material classification (Table 1.1) was a

strong predictor of CLD, being the FDA groups II and IV more related to dry symptoms. A more recent evidence-based review has evaluated the literature and has established that studies with robust experimental designs (masked, randomized or controlled) have shown no differences in subjective comfort between SiHy and hydrogel controls.[39] In line with these results, other studies found that switching wearers from hydrogels to SiHy may not necessarily help retain new wearers who are considering dropping out, suggesting that wettability of the ocular surface, individual patient and lens factors may also play a role.[35,40]

However, in both hydrogel and SiHy CL, it has been demonstrated that switching to a higher replacement frequency (daily disposable) improves CLD symptoms.[41–43] It could be related to the fact that DDCL reduces deposit accumulation, enhances comfort, visual quality, and decreases the risk of ocular infection.[44] However, Sapkota et al,[45] did not found significant changes in ocular surface physiology and comfort score between daily and monthly wear modalities, suggesting that CL signs and symptoms were associated with lens material characteristics. Therefore, they concluded that it would be better to recommend lenses according to the CL material, design and surface characteristics rather than wearing modality.

A clear advantage of wearing new lenses every day is avoiding the use of cleaning/storing chemicals of care solutions.[45] Soft CL care solutions are made of a wide range of components, and the combination and concentration of these agents could influence patient comfort.[46] Nevertheless, an individual component in a care solution might not have a direct impact on subjective symptoms. It has been shown that subjective satisfaction, particularly in symptomatic wearers, can be influenced by the combination of lens and solution prescribed.[47]

Regarding the CL fitting, some studies seem to suggest that centration or corneal coverage plays an insignificant role in CL comfort.[48,49] However, an

excessive CL movement can influence corneal staining and bulbar and limbal hyperemia,[50] and it could be associated with poorer comfort.[51] Although there is controversy, other studies have not found a relation between CL movement and comfort.[49,52] CL fitting is influenced by the CL design parameters (base curve, diameter, design, thickness and edge form), but changing solely one parameter and keeping the others constant is challenging in daily practice. In addition, the differences in base curves are too small to detect differences in CL comfort in the majority of the CLs.[46] However, both, base curve and diameter determine lens sag, and reducing sag increase movement and consequently decrease comfort, as it has been previously described.[51]

Regarding the design, it has been reported that multifocal CL has some vision-related problems, being this reason the main cause of discomfort.[35] It suggests that better designs are needed to optimise vision with current multifocals. In addition, toric designs have been generally expected to have a poorer success rate. Some studies have shown an association between thick stabilization zones in toric CL or certain shape edges and CLD symptoms as well as the presence of conjunctival indentation.[18,53] However, a recent study did not find a significant difference in retention rates between spheric versus toric designs,[35] reflecting a general improvement in toric designs over recent years.

1.2.2.2 Environmental factors

The influence of the environment on CLD is based on patient and environmental factors. Patient factors are divided into inherent (or permanent characteristic or attribute) existing factors, or modifiable factors.[54]

Non-modifiable factors include demographic factors (age, sex or race), as well as ocular and systemic disease. It seems that women report more CLD than men. However, it could be related to the fact that the percentage of women wearing CL is also higher than the percentage of men.[7] In fact, female sex does not appear to be a consistent factor relating to lens

dropout.[36,53,55,56] Age has been shown occasionally to be associated with CLD. Chalmers et al.[56] reported an inverse correlation between CLD and age, with more symptoms reported by younger wearers. Similarly to sex, it has not been identified a relationship between ethnicity and CLD.[15]

The application of a CL can alter the integrity of the tear film, affecting its characteristics and stability.[12] Thus, a poor tear film quality or quantity (reduced tear volume or production and/or a short tear breakup time) are predictors for symptomatic CL wearers.[54] It has been shown that asymptomatic CL wearers show a higher basal tear flow rate and greater tear stability than symptomatic wearers.[12,57] Other factors associated with CLD that have been reported are a higher rate of evaporation,[58] thinner lipid layer,[59] a decrease in the number of functional MG,[26] alterations of the meibum quality or plugged orifices,[60] reductions in globet cell density[61] or a decrease in the amount of secreted mucin.[12]

During CL wear, blinking assumes functions such as the maintenance of the optical quality of the anterior lens surface, hydration of soft lenses, and removal of debris and circulation of freshly oxygenated tears beneath the CL.[62] Although little is known about the association between changes in blink rate, incomplete blinking and comfort with lens wear, some studies have speculated that incomplete blinking and longer blink intervals may lead to dehydration of the inferior part of the soft lens, and therefore to epithelial desiccation, which can increase friction in this region.[62,63] In addition, the impact of blink rate on CLD is higher when the CL user is performing near vision tasks, because the concentration needed to focus on the visual task can reduce blink rate.[54,64]

Ocular and systemic diseases can affect the normal function of the tear film and ocular surface health, influencing the CL comfort.[54] This is caused by the fact that some diseases negatively impact the health and function of the tissues and glands of the ocular surface and its innervation.[54,65] In the case of allergies, some findings indicate that the ocular response to seasonal allergies

may be associated with reduced lens comfort.[66] Although it is possible to modulate a patient's disease through treatment, some medications can affect tear film production and preocular tissue health too.[67]

Modifiable factors of the patient related to CLD involve medication, diet or smoking among others. A repeated and/or chronic smoke exposure, use of specific soaps, lotions, and cosmetics may contribute to CLD.[54] The literature points toward benefits from long-chain omega-3 supplementation in alleviating dry eye symptoms and managing dry eye disease and CLD, although the evidence is uncertain and inconsistent.[68,69,70]

It is important also to consider the effect of patient compliance in the care and replacement of the CL. It has been found that CL wearers who reported poor compliance with replacement frequency had both reduced comfort and vision ratings at the end of the day (when lenses needed to be replaced) compared with compliant CL users.[71]

Environmental factors include climate, allergens/ pollutants, and visual demand. CL wearers are commonly exposed to artificially-controlled environments (i.e. air-conditioned or heated offices, vehicles, or airplane cabins), which can be associated with desiccating factors such as excessive heat, air flows, and low relative humidity. Adverse conditions produce a greater negative impact on the ocular surface than standard conditions in some clinical variables such as tear volume, tear stability, limbal and bulbar hyperaemia, and CL dehydration, as well as CL comfort.[72–74] Moreover, the majority of CL wearers spend a great number of hours using computers and/or video display terminals, which have been shown to increase symptoms. This could occur due to a reduced blink rate and an increased interblink interval, which reduces tear spreading and produces CL surface drying, resulting in an increase in symptoms.[75,76]

1.2.3 EPIDEMIOLOGY

It is estimated that 2.3 billion people worldwide have some refractive error (myopia, hyperopia and astigmatism), but only 1.8 billion people have access to eye examinations and affordable correction.[77,78] However, just 140 million are CL wearers.[1] The total number of CL wearers has not appreciably grown in recent years, indicating that the number of new wearers is similar to those who drop out of wearing lenses completely.[36,79] CLD affects up to 50% of CL wearers at a somewhat regular frequency.[1] Moreover, it has been estimated that between 12% and 51% of CL users drop out of CLs, being dryness and discomfort the main contributing factors.[36,55,80,81] The variability of these data could be caused due to the lack of gold standard tests to detect CLD.

1.2.4 SYMPTOMATOLOGY

It is well known that CL wearers report more ocular dryness symptoms than non-CL wearers.[56,82] In addition, symptoms such as soreness, grittiness, light sensitivity, pain, itching, burning, watering, blurred vision, or tiredness are also commonly reported,[80,83,84] being dryness and discomfort the symptoms more often reported in CL wearers.[36] CLD symptoms may be influenced by physical, visual experience and personal factors (Figure 1.5).[54,85]

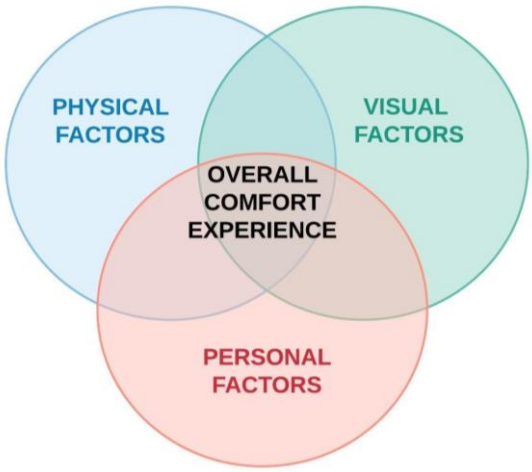


Figure 1.5. Contributors to the overall comfort experience of contact lens wear.

Regarding the physical experience of CL, the typical ocular discomfort and dryness sensations are low or absent immediately after insertion. However, the increase in severity over the course of a day of wear is more often evident in the end-of-day,[86] and finally decreases after lens removal.[56] Replacing the lens or performing a scleral swish part way through the wearing day does not improve end-of-day comfort.[87,88] It suggests that the decrease in comfort is not due to changes occurring to the CL during wear, but because of the physical presence of the lens and its interaction with the ocular surface and the changes in the ocular environment. Moreover, wearing the CL in short periods of wear undertaken at any time of day does not make significant changes in subjective comfort, suggesting that end-of-day discomfort is not caused by the fact that it is late in the day and the wearer is generally fatigued.[89] Indeed, a recent study concluded that CLs become uncomfortable during wear, indicating that discomfort is associated with the length of time of CL wear but not with the time of day when lenses are placed on-eye.[90]

Symptoms, as the ones mentioned above, could lead to the inability to wear lenses for as long as desired. However, comfort is complex and multifactorial,[85] and the CL experience is not only described by this sensation

of discomfort but also by the visual comfort. Visual discomfort involves from pain to ache or tiredness around the eyes, blurred or diplopic vision, headache and ocular fatigue.[85] Moreover, personal factors are also important, such as the motivation to wear CL and/or economics.[54] As it is represented in Figure 1.5, these factors may overlap. The overlapping between comfort and vision has been evaluated in a study that looked at the influence of vision on ocular comfort ratings.[91] Authors found that in some circumstances, comfort was reduced with induced visual blur.

1.2.5 SIGNS

A sign is defined as an indication of a particular disorder that is detected by a physician while examining a patient, but is not usually apparent to the patient.[92] CL wear is associated with several alterations of the ocular surface including a decrease of tear stability and volume, an increase in epithelial damage, dysfunction or loss of MG (Figure 1.6), or an increase of hyperaemia or corneal and conjunctival staining among others.[12,93,94] However, these alterations rarely have been related to CLD.[93] Some studies have compared differences between CL wearers and non-wearers to understand if there is a negative impact associated with CL wearing.[60,95,96] For example, it was found that there were minimal differences in MG atrophy between successful CL wearers and non-wearers. [60,96]

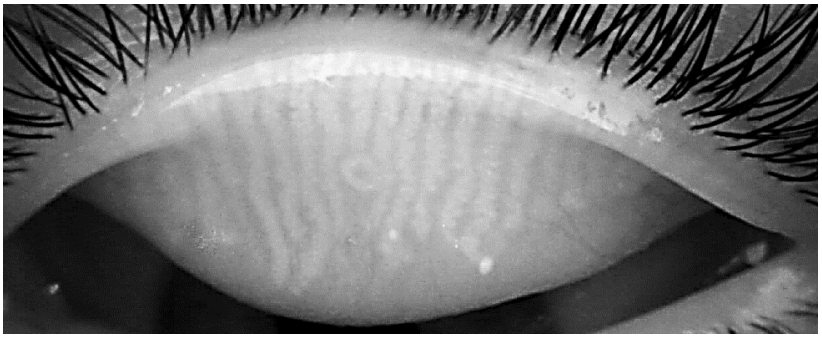


Figure 1.6. Upper lid meibography of a contact lens wearer with contact lens discomfort and loss of Meibomian glands.
(From IOBA, University of Valladolid)

Lid parallel conjunctival epithelial folds (LIPCOF) (Figure 1.7) and LWE (Figure 1.2) are thought to be clinical indicators of mechanical forces between the sliding partners of the CL surface and the lid wiper plus the CL back-surface and the ocular surface. It has been reported that these signs may have some association with CLD and are recognized as sensitive tests to predict and to evaluate CLD.[97–99,] LIPCOF are small bulbar conjunctival folds along the lower lid margin and are observed as extending perpendicularly from the temporal and nasal limbus, induced by the edge of hydrogel CL.[97] LWE is a clinically observable alteration in the epithelium of the advancing lid margin, the lid wiper. The prevalence of presenting this sign is higher in CL wearers than in non-wearers, likely due to the higher friction produced by wearing a CL.[100] Changes in the lid wiper have been linked to symptoms of dryness in both CL and non-CL wearers.[101,102] On the opposite, some authors did not observe any relationship between LWE and ocular symptoms in CL wearers.[103,104] Nonetheless, the variability of the results on the frequency and severity of the LWE is dependent on both, the type of lissamine green strip as well as the frequency of lid eversion, suggesting that LWE is not a strong predictor of CL comfort.[103] Moreover, neither LIPCOF nor LWE have a good correlation with corneal staining, bulbar hyperaemia or decreased tear break-up time (TBUT).[97]

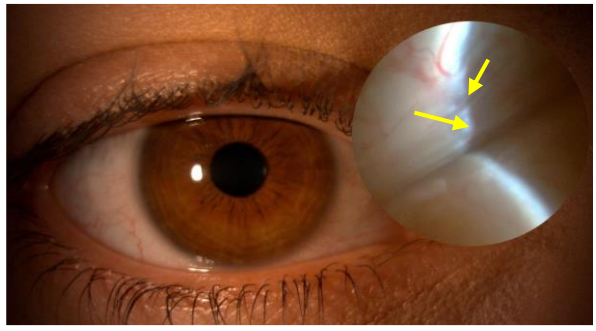


Figure 1.7. Lid parallel conjunctival folds (LIPCOF) (yellow arrows).

(From IOBA, University of Valladolid)

Other clinical signs associated with CLD include subclinical conjunctival inflammation,[105] loss of functional visual acuity,[106] and an increased conjunctival staining.[95]

A multicentre study conducted by Young et al. in symptomatic CL wearers showed a wide range of clinical signs related to CLD, but there was not one single common sign that was present in all participants.[107]

1.3 CLD DIAGNOSIS

Measuring and detecting CLD is difficult due to the nature of the condition. It may be episodic, variable in degree and is usually resolved with lens removal. Several studies have measured CLD and clinical signs with CL wear, but they could not find a relationship between signs and symptoms.[42,108,109] Thus, it prevents a proper interpretation of outcomes related to CLD. Differences in the integrity of the tear film,[15,110] quantity of MG[26] and severity of ocular staining[15,95] between symptomatic and asymptomatic CL wearers have been found. Nevertheless, there is a poor correlation between these signs and dry eye symptoms.[111] According to the TFOS workshop, CLD is primarily reported by the symptoms as opposed to the observation of signs. Thus, symptomatology is an appropriate outcome for measuring CLD, because it relates directly to the patients' experience with CL, regardless of the presence of observable signs.[1] In addition, it is important to establish appropriate tests for measuring CLD, to quantify the condition and its impact, to determine if an intervention is needed, and/or to evaluate its effect.

Questionnaires are common instruments, which have demonstrated their ability to measure and diagnose dry eye symptoms in clinical practice as well as in research. Some authors have used questionnaires originally designed for diagnosing dry eye disease to evaluate CLD,[112] for example, the ocular surface disease index (OSDI),[113] the ocular comfort index (OCI)[114] or the McMonnies index.[115] However, when the OCI and the McMonnies were administered in a sample of CL wearers, it was concluded that although McMonnies performs better than the OCI in predicting dry eye in CL wear, both have a limited prediction.[116]

There are specific questionnaires designed for CL wearers, such as the contact lens impact on quality of life questionnaire (CLIQ),[117] or an adapted version of the subjective evaluation of symptoms of dryness (SESOD) questionnaire, initially designed for dry eye evaluation.[118] Nevertheless, as well as for dry eye disease, the diagnosis of CLD should be done using validated questionnaires that probe parameters of discomfort unique to CLD. There is one specific questionnaire designed for CL wearers that aims to identify soft CL wearers who are at risk of suffering CLD and need clinical management, the contact lens dry eye questionnaire (CLDEQ).[83] There is currently a short version, the CLDEQ-8,[119] with a recently established cut-off score.[120] According to the TFOS workshop no specific clinical outcome instrument can be recommended. However, the CLDEQ-8 most approaches the best validated device,[121] and at this time, it is the most used instrument for measuring the frequency and intensity of CLD. This questionnaire might be able to estimate CLD during the medium term (2 weeks), however, it cannot be used for short-term follow-up visits (i.e. assessing the change in CL comfort during the same day).[119]

For short term evaluations, visual analogue scales and numerical rating scales can be adequate tools for assessing the temporal characteristics of CLD such as onset, chronicity and duration, thus, they are commonly used for CLD evaluation.[87,118,122] Moreover, global rate of change scales (GRCS) are also very commonly used in clinical research to quantify a patient's improvement or deterioration over time, as they are simpler, shorter, easier to score, reproducible, validated and sensitive to change.[123]

The poor correlation between signs and symptoms could be the result of using diagnosing methods not accurate enough for properly classifying CL wearers as having CLD or not. It could also affect the decision of determining an intervention and/or to evaluate its effect.

1.4 CLD MANAGEMENT

It is important to understand all factors that contribute to the development of CLD in order to detect it in the early stages and prevent its progression to avoid CL discontinuation. As it has been previously reported, CLD can be associated with several factors (section 1.2.2. CLD associated factors).

1.4.1 TREATMENT OF COEXISTING SYSTEMIC AND OCULAR DISEASES

Before attributing the CLD symptoms to the CL itself, the presence of coexisting anomalies that are potentially responsible for the patient's symptoms should be first discounted, such as allergies, autoimmune diseases, anatomical and physiological abnormalities of the eyelids or conjunctiva, dry eye disease or MG dysfunction (MGD).[124]

The entities of dry eye disease and CLD can intertwine, suggesting that those patients who have traditional signs and symptoms of dry eye are more likely to have CLD when fitted with CL, however, its aetiology seems to be different from CLD.[83] The basic mechanism leading to dry eye disease is still not known exactly, indeed it has a multifactorial aetiology associated with many mechanisms.[125] Accordingly, a global consensus has not been established in the diagnosis and treatment of the disease, thus its management is highly complicated.[126] However, according to the TFOS report about dry eye disease there are some recommendations for the treatment of dry eye disease, such as education about the condition, avoid adverse environments, modification or elimination of offending systemic and topical medications, use of ocular lubricants, lid hygiene, prescription of drugs (topical antibiotic/steroid, cyclosporine, etc.), therapeutic CLs and/or consider other treatment options (including surgical procedures) if previous were inadequate.[127]

Regarding seasonal allergies, a study carried out by Chalmers and Begley[56] found that, although 42.6% of CL wearers reported a positive history of allergies, it was not a factor associated with dryness during lens wear. Other studies found that, in a subset of allergy sufferers, treating allergies with topical antiallergy agents enhanced CL comfort.[66,128] However, other management such as the use of DDCL, avoiding extended CL wear as well as the exposure to the allergen, or lubricate the ocular surface has also been recommended.[129]

According to a dry eye report based on a survey performed in 2018 by eye care practitioners in the USA,[130] the majority of clinicians (65%) classified most CLIDE patients as the evaporative type. As it has been previously reported, MGD may rise symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease, being the major cause of evaporative dry eye.[25] In CL wearers, MGD also reduces the stability and increases the evaporation of the pre-lens tear film, indicating that MGD is related to the complaints of CL wearers and contributing to CLD. In fact, the prevalence of MGD among CL wearers is between 14% and 37%.[131,132,133] Therefore, the treatment of this condition seems to be important for the management of the CLD.

1.4.1.1 Meibomian gland dysfunction treatment

There is no gold standard treatment for MGD, but rather a diversity of options.[134] Traditional and common recommendations include warm compresses and lid hygiene. Although this therapy can be effective,[135] patient compliance can be challenging, moreover, the precise technique varies greatly.[136] It usually consists of two components: application of heat (with or without moisture) and mechanical massage of the eyelids (Figure 1.8).[136] Therapies with warming of the eyelids can be expected to improve MG secretion by melting the altered lipids.

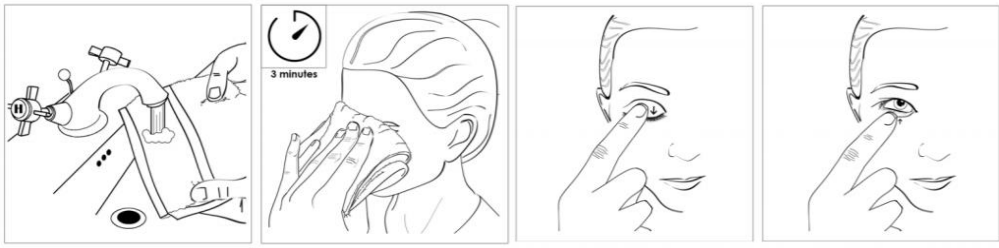


Figure 1.8. Steps recommended for lid hygiene treatment. First two images on the left represents the application of a warm compress, the other two images on the right represents the mechanical massage of the eyelid.

(From the patient information sheet of the Moorfields Eye Hospital. Available at: https://www.moorfields.nhs.uk/sites/default/files/Blepharitis.pdf)

Olson et al.[135] found that after 5 minutes of treatment with warm towel compresses applied to the skin of closed eyelids, the tear film lipid layer thickness increased by more than 80% in patients with MGD. They also observed that an additional 20% increase after 15 minutes of treatment. An improvement in the tear stability after 2 weeks of lid hygiene in symptomatic CL wearers was also found.[137] It has been reported that 3 weeks of intensive (twice a day) hygiene significantly improved the status of the eyelid margin tissues including the MG,[138] as well as decreased symptoms related to CL wear.[139] Paugh et al.[137] showed that symptoms reported by CL wearers were ameliorated by the improvement of lid hygiene and eyelid massage, and a review on evidence-based MGD treatment concluded that self-applied eyelid warming was effective against MGD.[136] However, according to the TFOS workshop on MGD, only patients with grade 1 (subclinical) or 2 (symptomatic minimal) of MGD could potentially benefit from lid hygiene.[136]

Recently, to be more effective than traditional lid hygiene, microwavable eye masks have been developed to increase moisture while simultaneously applying heat.[140,141] Similar results in tear film stability and tear evaporation improvement have been reported using these types of devices.[140] Another eyelid thermal pulsation treatment, known as LipiFlow (Tearscience®, Morrisville, NC, USA), applies heat to the palpebral surfaces

of the eyelids while simultaneously applying pressure on the eyelids to express the MG has been developed.[142] It was found to be more effective in treating MGD than conventional warm compresses and lid hygiene.[143,144]

Intense pulsed light therapy has been used for years in dermatology practices to improve the appearance of skin and now it is thought to improve signs and symptoms of MGD.[145] Several studies evaluating the effectiveness of intense pulsed light in the treatment of MGD have reported improvements in signs such as lid margin edema, redness and vascularity, meibum secretion quality, MG expressibility, tear film osmolarity, TBUT, corneal fluorescein staining and conjunctival injection, as well as improvement in symptoms.[146–149]

Other therapies such as topical lipid supplements, antibiotic agents, tetracyclines, steroids, sex hormones or essential fatty acids have been studied alone or in combination with lid hygiene.[134,136]

1.4.2 TREATING CONTACT LENS RELATED PROBLEMS

Having eliminated possible patient-related causes, the focus to manage any remaining symptoms of discomfort is on lens-related factors, such as material, design, replacement frequency, lens power, among others.

Dehydration of hydrogel CL plays a major role in the corneal epithelium integrity[150] and can have a negative impact on CL comfort.[150] Hydrogels with lower water content have been shown to have lower lens dehydration,[151] providing a better lens comfort than higher water content materials, with no direct impact of ionicity.[38,46,150] As it has been reported, although SiHy improves oxygen transmissibility, it may not necessarily help to reduce CLD.[39] Lens surface properties might play also an important role in CL comfort. Changing the physical properties (lubricity) of the surface of a soft CL does impact subjective comfort,[152] existing a significant association between the coefficient of friction and end-of-day comfort.[153] For this purpose, it has been

shown that the use of coatings and surface moisturising agents in the lens surface wettability improves CL comfort, reaching similar levels to those previously reported in a general population without lens wear.[152] New technology is being applied to improve the interfacial interactions of SiHy CLs with the ocular surface. A recent study showed that a biomimetic layer of hydrophilic glycosaminoglycan hyaluronic acid attached to the surface of a SiHy CL reduced contact angles, dehydration rate, and nonspecific deposition of lysozyme and albumin, while maintaining their optical transparency.[154]

The edge designs of the CL have been identified in the literature as ‘‘rounded,’’ ‘‘knife,’’ and ‘‘chisel’’. It was found that the lens with the thickest edge shape (rounded) gave poorer comfort than the chisel and the knife edge designs (Figure 1.9).[18,155] And thin, tapered edge designs can show a smoother transition between the conjunctiva and the lens surface and produce less disruption of conjunctival tissue at the lens edge.[156] Nevertheless, those sharper and pointed edge designs also show less movement than thicker, rounded edges and induce more pronounced conjunctival staining.[155] However, when dealing with CLD, it is difficult to isolate or change one single lens parameter, thus, it would be better to recommend lenses according to the combination of CL material, design and surface characteristics.

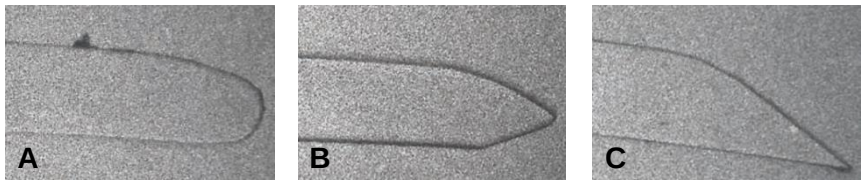


Figure 1.9. Cross-section of edge profile of a contact lens. A) Rounded edge contact lens; B) Chisel edge contact lens; C) Knife edge contact lens.
(Images from Hubner, T., Tamm, M., Sickenberger, W. Edge profiles of hydrogel contact lenses and their effect on fitting and wearing characteristics. Wöhlk contactlinsen. 2010;1–8. Available at: http://www.woehlk.com.hr/pdf/woehlk-wissen-02-en.pdf. Accessed June 21st, 2020).

Moreover, all soft CL show a gradual reduction in both comfort and wettability over time as part of its lifespan. These changes may be attributed to the accumulation of deposits in reusable CL, which will tend to increase over the period of lens use.[44] Thus, it suggests that replacing lenses before CL comfort is affected, would seem a reasonable approach. In fact, according to a dry eye report performed in 2018 among US optometrists, 52% of the practitioners would refit their CLD patients into a different CL with a more frequent replacement schedule, as the first-line recommendation in CLD management.[130]

1.4.2.1 Reducing replacement frequency

It is known that DDCL offers many advantages compared with conventional daily wear or frequent replacement (weekly/monthly) CL, such as reduced complication rate due to microbial contamination,[157] reduced depositions,[44] increased CL comfort, improved vision and relief symptoms from allergies; [44] and helps to address the issue of patient non-compliance with the CL replacement frequency.[158] Furthermore, it also improves the wearer´s convenience regarding CL cleaning, disinfecting, and storing.[45] In addition, soft CL may absorb different chemicals from the lens care solutions and toxic reactions can occur when they are released on the ocular surface during wear;[159] therefore, eliminating the care system may help to reduce CLD.[124] A survey conducted in United States, United Kingdom and Japan among 300 eye care professionals revealed that when prescribing DDCL, SiHy was preferred for being the healthiest lens material for the daily disposable patients.[160]

1.4.3 IMPROVING WEARER'S OCULAR SURFACE

The influence of hydration status on the tear film has been studied in a pilot study with a small group of subjects with dry eye disease. It was found that nearly 76% had decreased symptoms after being asked to increase their daily water intake for a 2-week period, although these results need to be validated in future studies.[161] Other study showed a strong association between poor sleep quality and an increased severity of dry eye symptoms, suggesting that preventing either one of the discomforts might alleviate the other.[162]

In addition, there are several published reports that support the use of tear supplements and wetting agents (also referred to as rewetting drops, lubricant drops, or artificial tears) in the management and treatment of CLD, being the second most recommended intervention (11%) among practitioners for the management and treatment of CLD.[130]

1.4.3.1 Use of tear supplements and wetting agents

Tear supplements are widely and easily available, and for many wearers, they are an effective solution for their symptoms. An investigation conducted in North America found that 47% of CL wearers reported moderate relief using rewetting drops.[83] Different types of artificial tears (AT), supplements or rewetting drops have been probed in CL wearers to manage CLD. They differ mainly in the composition of electrolytes, metabolites, viscosity, osmolarity and the presence or absence of compatible solutes and preservatives.[163] Although the use of AT with CLs is commonly prescribed by practitioners and self-prescribed by patients, it appears that there is no clear consensus among practitioners on the use of these drops in CL wearers for the treatment of CLD.[164]

A recent review of AT with CL suggested that AT and rewetting drops are safe and effective for the treatment of ocular surface disease in CL wearers, however, not all studies found drops effective at treating CLD.[164]

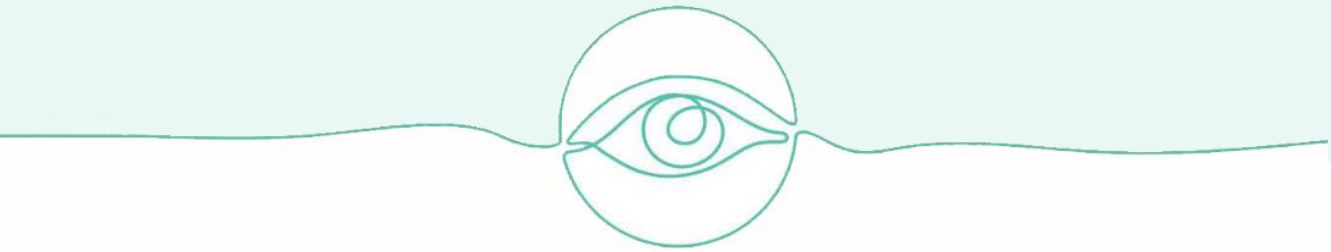
Differences between studies are likely to be related to drop formulations and differences in participant recruitment criteria. For example, preservative-free 0.9% sodium chloride ophthalmic solution has been evaluated in CL wearers experiencing CLD, and it was found a reduction in ocular surface discomfort and extended duration of CL wear without interfering with the tear film or CL materials.[165] Other study found that the use of a preservative-free hyaluronic acid-containing AT in soft CL wearers resulted in an improvement of symptoms, increased tear meniscus height, and improved corneal health at 2 months compared to baseline.[166]

Regarding hypo-osmotic saline drops, it has been studied that they have the potential to decrease CL osmolality, which may help to improve ocular comfort, thus, it might be preferred by a greater number of subjects.[167] Lubricants with aqueous solution composed of polyethylene glycol 400 (0.4%) have also been studied, and results showed that they are effective AT for alleviating symptoms of CLD when applying them before and after CL wear.[168] The use of a carboxymethylcellulose containing conditioning agent as a pre-treatment for new CL has been shown to provide a more physiologically suitable environment for a new lens, reducing the clinical signs associated with CLD.[169] Povidone 2% is a polymer that acts as a viscosity enhancer, and it can be used in AT by CL wearers and non-wearers to alleviate dry eye symptoms.[170] A non-lipid-based rewetting drops have shown worse results in terms of ocular signs and CL comfort when compared with eye drops with a microemulsion of two oils, a mineral oil and a polarphospholipid surfactant.[171]

Although AT use does help to reduce dryness symptoms, there appears to be a minimal longer-term benefit to comfort. Furthermore, increased lubricant viscosity did not lead to improved longer-term comfort.[124,172] The development of alternatives that can provide a sustained comfort and relief from CLD is a desirable target.

CHAPTER 2

JUSTIFICATION



CLs are ocular prosthetic devices, most commonly worn for vision correction, and used by over 140 million people worldwide. However, up to 50% of current CL wearers experience CL wear-related symptoms, such as discomfort, dryness, scratchy and/or watery sensation or blurry vision. This condition, previously known as CL related-dry eye or CLIDE, was named as CLD at the TFOS “International workshop on contact lens discomfort”. Furthermore, CLD is the first cause of CL discontinuation, thus it affects not only to CL wearers, but also to manufacturers and practitioners.

CLD is primarily diagnosed according to symptomatology as opposed to the observation of signs, thus, the use of symptoms as outcome measures is appropriate because it relates directly to the patients’ experience with CL. However, there is no specific instrument that could be recommended for CLD diagnosis.

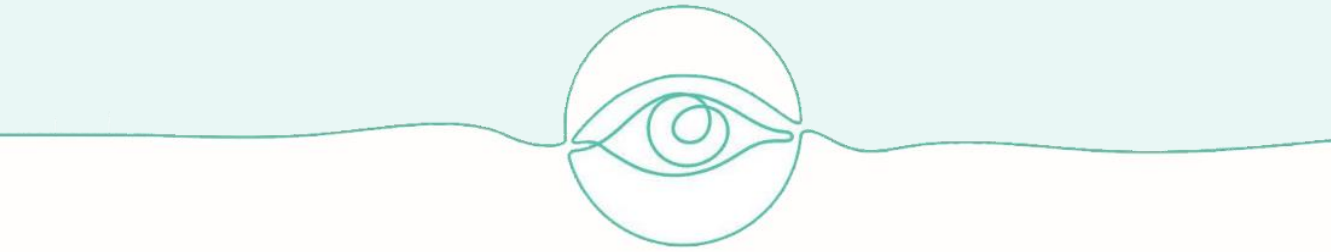
Management of this condition is challenging in the clinical practice. Common, although not permanent, treatments include CL refitting (changing materials or replacement schedules), the use of rewetting drops, changes in the CL care solutions, and lastly, CL removal. However, before attributing the CLD symptoms to the CL itself, the presence of coexisting anomalies such as MGD should be first treated. Lid hygiene is regarded as the mainstay of the clinical management of MGD, therefore, it should be considered when consulting with symptomatic CL wearers. Regarding the CL associated factors contributing to CLD, the first and most common step to solve CLD would be to refit the patient with a different CL, with better material, surface properties and reduced replacement frequency. In addition, DDCL reduces deposit accumulation, enhances comfort, visual quality, decreases the risk of ocular infection and avoids the use of cleaning/storing chemicals. Another way to ameliorate CLD problems would be to use topical lubricants, being this solution the second most recommended intervention among practitioners. Some authors have demonstrated that tear supplements and wetting agents

can be also helpful in CLD management. Nevertheless, in daily clinical settings, these interventions are not performed individually, but in consecutive order.

Considering these approaches, this thesis has been focused on developing a new subjective instrument for detecting CLD. This new instrument is a questionnaire specifically designed for CL wearers, which could help clinicians and researchers to classify better CL wearers according to their symptoms. In addition, it has been also carried out in parallel a clinical study to analyse the summative effect of the most common solutions on improving CLD. For this study, an objective instrument to assess changes in the ocular surface signs was created, resulting in a combined clinical score. Therefore, the outcomes of this study will provide evidence regarding the solutions that could be more effective when managing CLD.

CHAPTER 3

HYPOTHESIS AND OBJETIVES



3.1 HYPOTHESIS

The hypothesis of the present thesis is that contact lens discomfort diagnosis and management can improve by the design of new subjective and objective instruments based on the knowledge developed during the last few years.

3.2 OBJECTIVES

The main objective of this work was to study contact lens discomfort detection and management strategies using subjective and objective instruments. The following objectives are established as a way to design and develop one subjective (questionnaire) and one objective (combined clinical score) instrument to detect contact lens discomfort and to assess the possible improvement in clinical signs in subjects who suffer from contact lens discomfort.

Objective 1. To create a new questionnaire specifically designed for contact lens wearers capable of detect contact lens discomfort according to its current established definition.

Objective 2. To design a new combined clinical score capable of analyse better the clinical changes that can be observed after contact lens discomfort interventions to avoid using several scores to assess therapeutic efficacy.

Objective 3. To analyse the variation of symptoms and signs after performing different contact lens discomfort management strategies (lid hygiene, daily disposable contact lens refit and use of artificial tears).

Objective 4. To study the placebo effect in the management of contact lens discomfort.

CHAPTER 4

DETECTION OF CONTACT LENS DISCOMFORT: DEVELOPMENT OF THE QUESTIONNAIRE "CONTACT LENS DISCOMFORT INDEX"

This chapter presents the research work involving the development of a questionnaire designed to detect CLD. This chapter is divided in two parts. The first part of the work (Part I) that has been carried out at IOBA and consist on the designing of the questionnaire. The second part (Part II) explains the translation and analysis of the English version of the questionnaire and it has been carried out at Glasgow Caledonian University (Glasgow, Scotland) under the supervision of Dr. Suzanne Hagan and Dr. Eilidh Martin. The questionnaire was designed in collaboration with Dr. Itziar Fernández (biostatistician). The study performed at Glasgow Caledonian University was in compliance with the rules to be eligible to the "International mention" for this Doctoral Thesis. The resulting questionnaire, called the Contact Lens Discomfort Index (CLDI), has been registered in the intellectual property registry, under the code 00/2019/2576.

4.1 BACKGROUND

In the scientific literature, several methods have been used to detect CL wearers with CLD. Some authors have used questionnaires originally designed for diagnosing dry eye disease, to evaluate CLD,[112] whereas others have considered, for example, reporting discomfort during CL wear at least 3 times a week.[173] In addition, there are specific questionnaires designed for CL wearers, such as CLDEQ-8,[119,120] that aims to identify soft CL wearers who are at risk of suffering CLD and need clinical management.

CLDEQ-8 was recognized as the best validated instrument at the TFOS workshop,[31] however it does not include questions about quality of life, and its psychometric properties have not been evaluated.[174] TFOS workshop also concluded that there is no specific instrument that could be recommended for CLD diagnosis.[121] Therefore, since classifying CL wearers accurately is key for clinical and research practice, it would be necessary to design a new instrument according to the latest CLD criteria.

Consequently, the present study was divided in two parts. The main objective of the first part was to design a new questionnaire for detecting CLD, based on the currently-established CLD definition. Moreover, the availability of this questionnaire in English could be useful. Questionnaires can be influenced by sociocultural or language differences in the population, thus, it is important to maintain a correct process of translation to ensure the validity of the original instrument.[175] The translation process needs a cultural frame, a linguistic context [176,177] and a revalidation that guarantees the equivalence to the original.[178] Reports of validation and translation of instruments have used various techniques such as: forward and back translation, expert committee, or pilot study.[179,180] Therefore, the second part of this study was to translate the CLDI questionnaire into English, adapting it to the culture and validating it to facilitate a better understanding and a broader use of it.

PART I. DESIGN AND DEVELOPMENT OF THE CONTACT LENS DISCOMFORT INDEX (CLDI)

4.2 MATERIALS AND METHODS (PART I)

The study complied with the tenets of the Declaration of Helsinki, and was approved by the East Valladolid Health Area Ethics Committee and the Research Committee of the IOBA (Appendix 1, pages 224-225). The questionnaire design process explained in this first part of the chapter is summarized in Figure 4.1 (coloured part).

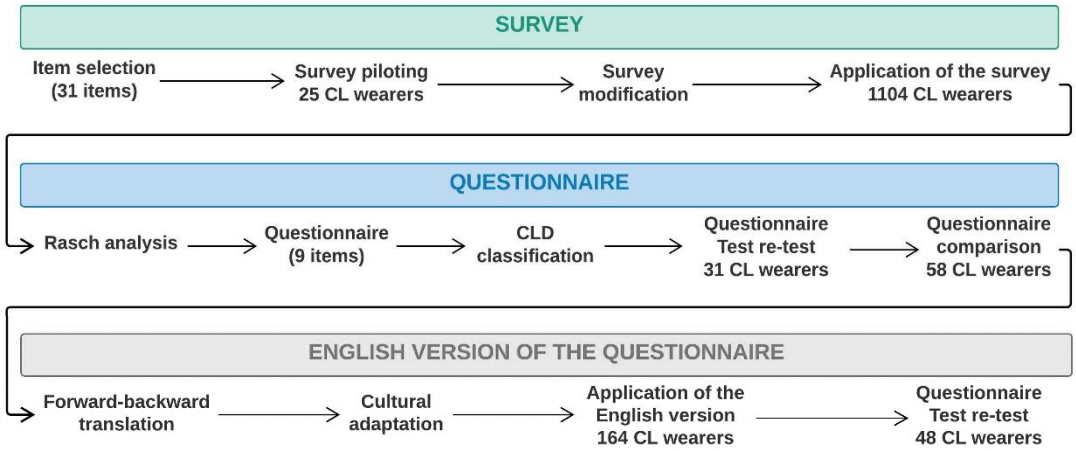


Figure 4.1. **Flow chart of questionnaire design and English translation**.
CL: contact lens; CLD: contact lens discomfort.

Statistical analyses were conducted using the statistical package for the social sciences software (SPSS 22.0 for Windows) and the R statistical software (version 3.1.1, Foundation for statistical computing, Vienna, Austria).[181]

4.2.1 PRELIMINARY SURVEY

In the first stage we designed and administered a survey to study and characterize the intended population (CL wearers), and to ascertain the main factors that could affect CLD.

4.2.1.1 Item identification and item selection

The available scientific literature (published in English) about CLD was reviewed by a MEDLINE database search. Terms included were: *contact lens discomfort, contact lens complications, contact lens related dry eye, contact lens induced dry eye, contact lens discomfort factors*, *contact lens drop out, contact lens discontinuation, contact lens abandonment, and lapsed contact lens wearers*. To ensure a good breadth of relevance, during the item selection, experiences and opinions were obtained directly from a focus group composed of optometrists with research and clinical expertise in the CL field, CL wearers, and also a biostatistician specialized in vision science. With this information, a first draft of the survey was designed to characterize CL wearers' habits and symptoms.

4.2.1.2 Survey piloting

This first draft of the survey was piloted to maximize item quality and its feasibility of use, assess its ease of understanding, and to evaluate test-retest reliability. Subjects included were CL wearers older than 18 years of age, participation in the study was voluntary, and volunteers provided informed consent prior to taking part in the pilot study (Appendix 2, pages 226-227). Participants had to fill out the survey twice, 15 days apart, via an online platform. When the survey was administered during the second time, participants did not have access to the answers that they provided when it was first administered. After completing the survey, participants were invited to comment on any aspect that involved difficulty when filling out the

questionnaire. A concordance analysis of the survey responses during the two administration sessions was performed using a chi-square and Wilcoxon test. Problems regarding comprehension and implementation were detected and the readiness and the understanding of the items of the original survey were improved, so that a definitive version of the survey was obtained.

4.2.1.3 Survey application

The definitive version of the survey was implemented on a web-based platform and an e-mail providing access to the survey was sent to students and staff of the University of Valladolid (Valladolid, Spain), inviting them to participate anonymously. Only current CL wearers aging 18 years and over, and without history of ocular surgery were allowed to fill out the entire survey. The online version of the survey included several preliminary questions (age, use of CL and history of ocular surgery) for checking the inclusion/exclusion criteria.

4.2.2 CONTACT LENS DISCOMFORT QUESTIONNAIRE

Survey outcomes were used to state the problem (i.e. CLD) and the intended population, and the relevant content was used to create a questionnaire to detect CLD. To do so, several steps were performed:

4.2.2.1 Rasch analysis

First, an item reduction phase was performed by determining what questions of the survey could detect and measure CLD more precisely. For that, the focus group selected the questions of the survey that corresponded better with the definition of CLD given by the 2013 TFOS Workshop on CLD, and with questionnaires published in the literature. The questions selected were those that asked about the factors involved in the presence of CLD.

To refine the candidate items for the questionnaire, the partial credit Rasch model (PCM) was fitted,[182] assessing the relation between the items and the latent variable of interest (CLD) on a scale. This approach allows the exclusion and modification of items determining the probabilistic relationship between a CL wearer´s response on any item and the CLD level that this CL user is suffering. The extended Rasch modeling (eRm) package of R was used.[183]

The different answers to survey items were coded into ordered categories, assigning higher values to responses more related to discomfort using CL, thus, severity of CLD was higher. The response category order for each item was verified, so that CL users with increasing amounts of CLD have increasing probabilities of selecting higher categories in each item. When this was not the case, it meant that the item exhibited category threshold disordering, thus, adjacent categories were collapsed receiving the same score.

In order to determine if individual items provided useful information for CLD score, item infit and outfit mean squares were used. Items with values outside of critical range from 0.7 to 1.3[184] were progressively eliminated.

The Andersen likelihood ratio test was used to assess whether the data fit properly to the PCM model. In addition, principal components analysis of the standardized model residuals was performed to check the unidimensionality of the CLD score (i.e. verifying that the data followed one dominant latent variable and there were no local dependencies). We considered as many dimensions as factors with eigenvalues greater than two. The targeting of the items to the sample was also assessed by comparing the mean item difficulty with the mean person score. Excellent targeting is achieved when the mean person score is close to 0 logits, and items less related to the target population (subjects with CLD) were removed.[185] Finally, the person separation reliability was calculated, which is an indicator of the precision of the instrument. For this indicator, higher values show better ability of the instrument to discriminate among subjects (ranging from -3 to 3), and values of at least 0.8 are considered acceptable.[184]

Once the set of items from the CLD questionnaire were selected and modified, the categorical item response system was converted into a continuous scale by overall sum score, resulting in a questionnaire called Contact Lens Discomfort Index (CLDI).

4.2.2.2 CLD classification

Then, the second aim of this first part of the study was to build plausible CLD classification (symptomatic vs asymptomatic) using an unsupervised cluster analysis. For that purpose, we calculated the Gower's general similarity coefficient to measure proximity for mixed data types.[186] The partitioning around medoids (PAM) algorithm was then used to find a sequence of medoids (in this case, CL wearers) centrally located in clusters, in which the CL users showed a high degree of similarity.[187] Silhouette width was used to

establish the number of groups.[188] The width displays a measure of how close each point in one cluster is to points in the neighboring clusters, and provides a way to visually assess parameters such as number of clusters. For this analysis, the package cluster of R was used.[189]

After identifying the clusters, intermediate CLDI score values (borderline subjects) had to be assigned to one of the clusters (symptomatic or asymptomatic). A decision tree was built to create a subscale that can help to assign more properly those CL wearers located between the two CLD clusters.

4.2.2.3 Test-retest agreement

To analyze the reliability of the CLDI, the questionnaire was administered twice in a 10-day period, recruiting a different sample of subjects that were included in the previous survey piloting study. Inclusion criteria were CL wear, age between 18 and 40 years, absence of anterior segment anomalies including dry eye disease, and/or ocular allergies that could affect CL wear. Informed consent was obtained from the subjects after explanation of the study.

Test-retest reliability of the CLDI scores was determined using the intraclass correlation coefficient (ICC), and the concordance between diagnoses (symptomatic vs asymptomatic) was evaluated using Cohen's kappa (k), with their corresponding 95% confidence intervals (CI). The literature recommends an ICC greater than 0.70 for discrimination between groups.[190] Concordance, according to the kappa values, was classified as follows: 0.00-0.20, slight, 0.21-0.40, fair, 0.41-0.60, moderate 0.61-0.80, substantial, and >0.80, almost perfect agreement.[191]

4.2.3 CONTACT LENS DISCOMFORT INDEX PERFORMANCE

Finally, a study to compare CLDI and CLDEQ-8 results was conducted in a sample of CL wearers (different from the survey piloting and the test-retest studies), where both questionnaires were administered by the same clinician during one session. Inclusion criteria were age between 18 and 40 years, visual acuity ≤0.0 logarithm of the minimum resolution angle (LogMAR), no diagnosis of dry eye disease, ocular allergies or other ocular surface alteration that could affect CL wear. Informed consent was obtained from the subjects after explanation of the study.

CLDI performance was assessed by comparing how CL wearers were classified using the CLDI and the CLDEQ-8 instruments. When subjects were differently classified by both questionnaires (symptomatic vs asymptomatic), responses of each item of the CLDI questionnaire were compared to those obtained by subjects equally classify by both questionnaires. The Chi-squared test and Bonferroni corrections were performed.

4.3 RESULTS (PART I)

SURVEY

4.3.1 PRELIMINARY SURVEY

4.3.1.1 Item identification and item selection

A 31-item survey was created according to the factors related to CLD defined by the literature search, CLD definition on TFOS report,[32] and the focus group indications. The survey included questions to assess patient related factors (age, gender, occupation, systemic and/or ocular disease, and allergies), factors associated with CLD (medication and CL compliance), CL use (type of CL, frequency replacement, days and hours of wear, CL care and CL wear habits), CL wear symptoms (appearance, duration, severity, activities that provoke those symptoms and environmental factors) and satisfaction with CL use. The English version of the survey is provided at the end of this chapter (pages 109-113).

4.3.1.2 Survey piloting

A sample of 25 CL wearers was recruited. Average participant age was 29.4±10.1 years (range: 20-52); 72% were female and 28% were male. The concordance evaluation of the responses of the pilot survey showed no significant difference ($p>0.05$) between the two rounds. According to feedback from the volunteers, 8 items were modified by adding some clarification or an additional response category where necessary; no questions were eliminated. No further issues were identified by the participants, with both comprehension of the questions and the time spent completing the survey reported to be acceptable.

4.3.1.3 Survey application

The community of the University of Valladolid was invited to participate in the survey. The survey was completed by 1104 CL wearers. Demographic data, CL characteristics, and CL wearing habits are summarized in Table 4.1.

Table 4.1. Demographic data and characteristics of contact lens (CL) wearers participating in the survey. N= 1104.

Factor	Survey sample
Age (years)	27.2±10.4 (range: 18-73)
Gender	67.6% female 32.4%male
Occupation	72.3% University students 27.7% University staff
CL wear (years)	8.2±7.2 (range: 2 months-43 years)
CL material	94.2% soft CL 5.8% gas permeable CL
CL replacement	18.5% daily; 4.9% biweekly; 62.0% monthly; 7.2% quarterly; 7.4% annual
Days per week using CL	4.6±2.0 (range: 1-7 days)
Hours per day using CL	7.8±3.4 (range: 1-24 hours)

4.3.2 CLD QUESTIONNAIRE

4.3.2.1 Rasch analysis

The selection of items from the survey was based on the TFOS definition of CLD and the CLD associated factors. Thus, the aspects that involve decreasing/discontinuation wearing time and ability to wear lenses as long as desired without problems corresponded with the items- (I-) 19 and I-21 of the survey. The items that asked about visual disturbance and symptoms resulted from a reduced compatibility between the CL and the environment were: I-23, I-23.1, I-23.2 and I-27. And those that asked about the adverse ocular sensations related to CL wear were: I-28, I-29 and I-30. Finally, I-31 corresponded with patients' own experiences (pages 109-113). The PCM results showed that I-28 (dirty lenses) and I-29 had poor fit with the model, thus, they were discarded. The item difficulty and the infit and outfit statistics of the items are shown in Table 4.2 and 4.3, respectively. For item characteristic curves, the steeper the curve, the better the item can discriminate. The flatter the curve, the less the item is able to discriminate since the probability of correct response at low ability levels is nearly the same as it is at high ability levels. In this study, category probability curves showed underutilization of the category 2 for the items 19 and 31, thus, categories 1 and 2 were collapsed. In addition, category 1 of the item 28 (all options) and category 2 of the item 28 (options: red eyes, watery eyes, itching and poor vision) were also underused, and categories 0 and 1 and 2 and 3 were collapsed, respectively. Item characteristic curves for all the items are provided at the end of this chapter (Rasch analysis part I, pages 114-116).

Table 4.2. Item difficulty of the items of the survey.

Item	Before the adjustment					After the adjustment				
	Category	$\hat{b}_i$	EE	IC 95% para $\hat{b}_i$		Category	$\hat{b}_i$	EE	IC 95% para $\hat{b}_i$	
				Inf.	Sup.				Inf.	Sup.
I-19. Do you wear your CL now as many hours per day or days per week as you have in the past?	Yes	1.18	0.08	1.02	1.34	Yes	1.51	0.07	1.36	1.67
	I wear them less because I prefer	1.22	0.09	1.04	1.40	-	-	-	-	-
	I wear them less because of discomfort	1.55	0.10	1.36	1.75	I wear them less because of discomfort	0.57	0.09	0.37	0.76
I-21. Do you wear your CL as much as you like to or need to?	No	-0.59	0.07	-0.73	-0.45	No	-0.91	0.07	-1.05	-0.76
I24. Do you usually have discomfort with the CL using electronic devices?	Yes	0.72	0.06	0.59	0.84	Yes	0.50	0.06	0.37	0.63
I-27. Do you usually have problems with your CL in adverse environments?	Yes	1.59	0.07	1.45	1.73	Yes	1.46	0.07	1.31	1.60
I-28. Have you ever suffered dryness while you were wearing CL?	Yes, without CL	-2.33	0.31	-2.95	-1.70	-	-	-	-	-
	Yes, with CL	2.54	0.08	2.38	2.70	Yes, with CL	1.64	0.07	1.49	1.78
	Yes, with and without CL	1.33	0.11	1.11	1.55	Yes, with and without CL	0.05	0.11	-0.16	0.26
I-28. Have you ever suffered discomfort while wearing CL?	Yes, without CL	-0.65	0.12	-0.90	-0.41	-	-	-	-	-
	Yes, with CL	1.91	0.07	1.76	2.06	Yes, with CL	0.84	0.06	0.71	0.98
	Yes, with and without CL	0.62	0.11	0.40	0.85	Yes, with and without CL	-0.85	0.11	-1.07	-0.63
I-28. Have you ever suffered red eyes while wearing CL?	Yes, without CL	-2.30	0.18	-2.67	-1.93	-				
	Yes, with CL	0.67	0.07	0.52	0.81	Yes	0.11	0.06	-0.01	0.24
	Yes, with and without CL	0.07	0.10	-0.13	0.27	-				
I-28. Have you ever suffered watery eyes while wearing CL?	Yes, without CL	-1.98	0.13	-2.25	-1.71	-				
	Yes, with CL	-0.24	0.08	-0.40	-0.07	Yes	-0.75	0.07	-0.89	-0.61
	Yes, with and without CL	-0.79	0.11	-1.02	-0.56	-				
I-28. Have you ever suffered itching while wearing CL?	Yes, without CL	-1.91	0.15	-2.21	-1.62	-				
	Yes, with CL	0.40	0.07	0.25	0.55	Yes	-0.14	0.06	-0.27	-0.01
	Yes, with and without CL	-0.13	0.10	-0.34	0.06	-				
I-28. Have you ever suffered poor vision while wearing CL?	Yes, without CL	-0.24	0.08	-0.41	-0.07	-				
	Yes, with CL	0.61	0.08	0.45	0.77	Yes	-0.11	0.06	-0.24	0.01
	Yes, with and without CL	0.50	0.09	0.31	0.70	-				
I-28. Have you ever suffered dirty lens while wearing CL?	Yes, without CL	-1.69	0.11	-1.92	-1.46	-	-	-	-	-
	Yes, with CL	-0.27	0.08	-0.43	-0.11	Yes, with CL	-1.14	0.07	-1.29	-0.99
	Yes, with and without CL	-2.60	0.24	-3.07	-2.13	Yes, with and without CL	-3.95	0.23	-4.41	-3.49
I-29. Have you ever felt the need to remove the CL due to those symptoms?	Yes	1.91	0.07	1.76	2.05	Yes	1.80	0.07	1.65	1.95
I-30. Describe your level of discomfort at the moment before removing your CL	Slightly uncomfortable	1.38	0.07	1.23	1.53	Slightly uncomfortable	1.34	0.07	1.19	1.49
	Uncomfortable	1.21	0.09	1.03	1.39	Uncomfortable	0.81	0.09	0.63	0.99
	Very uncomfortable	-0.00	0.14	-0.29	0.28	Very uncomfortable	-0.97	0.14	-1.26	-0.69
I-31. Describe your level of general satisfaction with your CL	Slightly satisfied	0.16	0.06	0.03	0.29	Slightly satisfied	-0.06	0.06	-0.20	0.06
	Slightly unsatisfied	-1.13	0.12	-1.38	-0.89	-	-	-	-	-
	Not satisfied	-2.71	0.28	-3.26	-2.15	Not satisfied	-1.73	0.12	-1.96	-1.49

-: collapsed categories.

Table 4.3. Infit and Outfit mean square fit statistics for the final items.

Survey question item	Outfit MSQ	Infit MSQ	Outfit t	Infit t	CLDI question number
I-19	1.13	1.09	3.37	2.37	Q-1
I-21	0.96	0.90	-0.60	-2.90	Q-2
I-23	0.94	0.95	-1.82	-1.99	Q-3 and Q-4
I-27	0.85	0.90	-3.01	-3.00	Q-5
I-28. Dryness	0.89	0.90	-2.93	-2.67	Q-6
I-28. Discomfort	0.93	0.93	-1.88	-1.78	
I-28. Red eyes	0.99	1.01	-0.34	0.48	Q-7
I-28. Watery eyes	1.21	1.10	3.19	2.86	
I-28. Scratchiness	0.97	0.96	-0.75	-1.44	
I-28. Blurry vision	1.03	1.03	0.79	1.28	
I-30	0.88	0.88	-3.16	-2.98	Q-8
I-31	0.71	0.76	-6.04	-6.40	Q-9

MSQ: mean square value. I-: Item.

Correspondence between the item in the survey and the CLDI question number is detailed in Table 4.3. Principal components analysis of the standardized model residuals revealed that all the factors had eigenvalues ≤1.3. Consequently, the instrument was considered unidimensional (all items fitted with the latent variable). The targeting of the items to persons was good as indicated by the mean item difficulty of 0.31 logits and mean person score of 0.23 logits (Figure 4.2. Person-item map, which displays the location of person abilities and item difficulties respectively along the same latent dimension). The person separation reliability was 0.89, thus, discrimination between high and low performers can be considered satisfactory. Finally, a 9-item questionnaire called the CLDI was created (See Figure 4.3 and 4.4 for the English and Spanish version of the CLDI respectively).

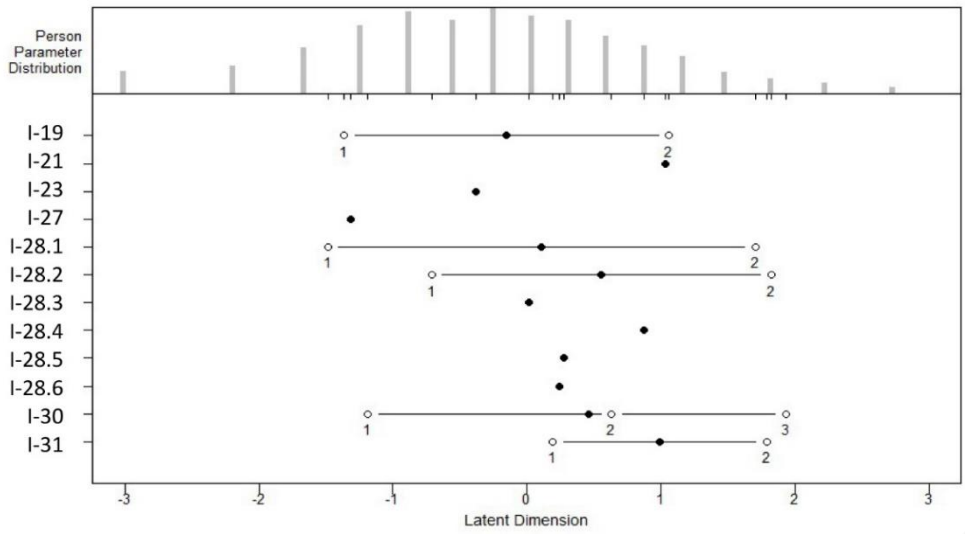


Figure 4.2 Person item map of the items of the questionnaire (Rasch analysis). I-: Item. The x-axis is the measure in logits, and the y-axis is the number of subjects or items located at that measurement location. Ideally, the average person measure would be closer to the average item measure, which is set to 0.

English version of the contact lens discomfort index (CLDI)

The *Contact Lens Discomfort Index* (CLDI) questionnaire is an easy instrument to measure the level of discomfort with the contact lenses.

Note: questions highlighted in grey correspond to the subscale score.

Please, answer the following questions.

1. Since you have been wearing this type of contact lens, have you always worn them the same number of hours per day?
- ☐ I currently use them more than previously (0)
- ☐ I use them the same amount as previously (1)
- ☐ I use them fewer hours per day than I previously did because I prefer to or because it was recommended to me (1)
- ☐ I use them fewer hours per day due to dryness and/or discomfort (2)

2. Do you wear these contacts as many hours as you wish/need to?
- ☐ Yes (0)
- ☐ No (1)

3. Do you USUALLY wear contact lenses while using electronic devices/video display terminals?
- ☐ No (respond to question 4.1) (0)
- ☐ Yes (respond to question 4.2) (0)

4.1 If you do NOT use your contact lenses when using electronic devices/video display terminals, what is the reason? (you can select multiple responses)
- ☐ Because I don't feel like it (0)
- ☐ Because I don't see well or my eyes become red (0)
- ☐ Because they bother me or I notice dryness (1)

4.2 If you DO use contact lenses while using electronic devices/video display terminals, do you USUALLY notice discomfort with them?
- ☐ No (0)
- ☐ Yes (1)

5. Do you USUALLY notice problems with these contact lenses when in dry environments (air conditioning or heat), with low humidity or in the wind?
- ☐ No (0)
- ☐ Yes (1)

6. Answer the following question by checking the box that best represents your response (only check one box per symptom). During a typical day in the past week, have you experienced any of the following symptoms?

	No, I have not experienced it (0)	Yes, I experienced it only while wearing contact lenses (1)	Yes, I experienced it both with and without contact lenses (2)
Dryness			
Discomfort			

7. During a typical day in the past week, have you experienced any of the following symptoms both with and without contact lenses on? (you can select multiple options)
- ☐ Red eyes (1)
- ☐ Itching (1)
- ☐ Poor vision (1)
- ☐ Watery eyes (1)
- ☐ None (0)

8. Describe the level of discomfort right before removing your contact lenses.
- ☐ No discomfort (0)
- ☐ Somewhat uncomfortable (1)
- ☐ Uncomfortable (2)
- ☐ Very uncomfortable (3)

9. Describe your overall satisfaction with the use of these contact lenses.
- ☐ Very satisfied (0)
- ☐ Satisfied (1)
- ☐ Not satisfied (2)

Figure 4.3 English version of the CLDI

Spanish version of the contact lens discomfort index (CLDI)

El cuestionario Contact Lens Discomfort Index (CLDI) es un instrumento sencillo creado para establecer la presencia y grado de incomodidad ocular con el uso de lentes de contacto según la sintomatología del usuario.

Nota: Las preguntas marcadas en gris son las que corresponden al cálculo de la subescala

Conteste a las siguientes preguntas marcando la casilla que mejor represente su respuesta.

1. Desde que usa estas lentillas ¿siempre las ha usado el mismo número de horas?
- ☐ Ahora las uso más (0)
- ☐ Sí, las uso igual (1)
- ☐ Las uso menos porque lo prefiero o me lo han recomendado (1)
- ☐ Ahora las uso menos porque me producen sequedad y/o incomodidad (2)

2. ¿Se pone estas lentillas tantas horas como desea o necesita?
- ☐ Si (0)
- ☐ No (1)

3. ¿Usa **HABITUALMENTE** el ordenador u otros dispositivos electrónicos (móvil, Tablet, TV…) con las lentillas puestas?
- ☐ No (responda solo a la pregunta 4.1 y continúe con la 5) (0)
- ☐ Si (responda solo a la pregunta 4.2 y continúe con la 5) (0)

4.1 Si no utiliza estas lentillas cuando usa el ordenador u otros dispositivos electrónicos (móvil, Tablet, TV…) ¿por qué motivo? (puede marcar varias opciones)
- ☐ Porque no me apetece o no lo necesito (0)
- ☐ Porque no veo bien o se me ponen los ojos rojos (1)
- ☐ Porque me molestan o noto sequedad (1)

4.2 Si las utiliza con el ordenador ¿nota HABITUALMENTE incomodidad con las lentillas cuando usa el ordenador u otros dispositivos electrónicos?
- ☐ No (0)
- ☐ Si (1)

5. ¿Nota **HABITUALMENTE** problemas con estas lentillas en entornos secos (aire acondicionado o calefacción), con baja humedad o con viento?
- ☐ No (0)
- ☐ Si (1)

6. Conteste a la siguiente pregunta marcando la casilla (solo una casilla por síntoma) que mejor represente su respuesta. Durante un típico día de la pasada semana, ¿ha notado alguno de los siguientes síntomas?

	No, nunca lo he notado (0)	Sí, lo noto solo con las lentillas (1)	Sí, lo noto tanto con las lentillas como sin ellas (2)
Sequedad			
Incomodidad			

7. Durante un típico día de la pasada semana, ¿ha notado alguno de los siguientes síntomas tanto con estas lentillas como sin ellas? (puede marcar varias opciones)
- ☐ Ojo rojo (1)
- ☐ Picor (1)
- ☐ Mala visión (1)
- ☐ Ojo lloroso (1)
- ☐ No, ninguno (0)

8. Describa la incomodidad justo en el momento antes de quitarse estas lentillas
- ☐ Nada incómodo (0)
- ☐ Algo Incómodo (1)
- ☐ Incómodo (2)
- ☐ Muy incómodo (3)

9. Describa la satisfacción general con el uso de estas lentillas
- ☐ Muy satisfecho (0)
- ☐ Satisfecho (1)
- ☐ Nada satisfecho (2)

Figure 4.4 Spanish version of the CLDI

4.3.2.2 CLD classification

As the result of the PCM analysis, a value was assigned to each response of each item of the CLDI (values for each response are shown in the English and Spanish CLDI versions, Figure 4.3 and 4.4, respectively). The scores for each answer of each item was assigned based on the presence and severity of CLD. The sum of all items corresponded to the total score, which ranged from 0 to 18.

Silhouette width showed that the appropriate number of clusters was two. By observing the information of the clusters defined, it was determined that the cluster with lower total score (≤5 points) was assigned to the asymptomatic group and symptomatic participants to the cluster with higher total score (≥11 points) (Table 4.4). When total scores were ≤5 or ≥11 points, they were considered to be the final CLDI score.

Table 4.4. Distribution of survey participants according to the Contact Lens Discomfort Index (CLDI) total score.

Score	Cluster 1 (Asymptomatic) (n)	Cluster 2 (Symptomatic) (n)
0	8	0
1	27	0
2	36	0
3	65	1
4	102	1
5	119	7
6	97	15
7	91	41
8	58	62
9	28	85
10	16	71
11	3	67
12	6	46
13	2	24
14	0	16
15	0	9
16	0	1
17	0	0
18	0	0

Because 564 total scores (Table 4.4) did not associate well with the clusters (asymptomatic or symptomatic), scores ranging from 6 to 10 were further evaluated following a decision tree (Figure 4.5).

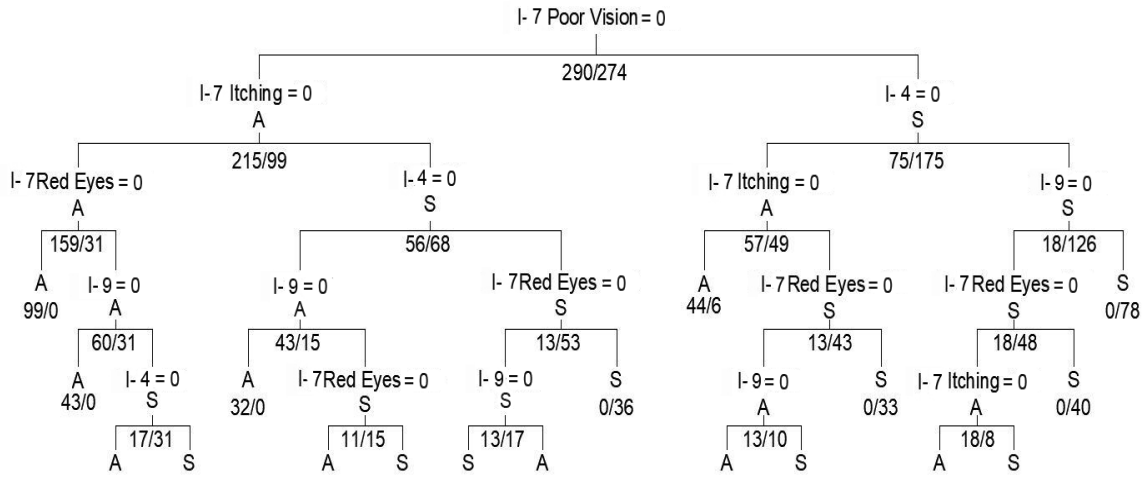


Figure 4.5. **Decision tree created using the items of the survey.**
I-: item; A: asymptomatic; S: symptomatic

A subscale score was then created with the scores obtained for I-4, I-7 (itching), I-7 (poor vision), I-7 (red eyes), and I-9 included in the final version of the CLDI.

- If the sum of this subscale score was ≤2 points, the number of items of this subscale having a value of 0, was subtracted from the total score to obtain the final CLDI score.
- If the sum of this subscale score was >2 points, the subscale score was added to the total score to obtain the final CLDI score.

As a result, a final CLDI score was obtained and values >8 points were assigned to the symptomatic cluster, while values ≤8 points were classified into the asymptomatic cluster (Figure 4.6).

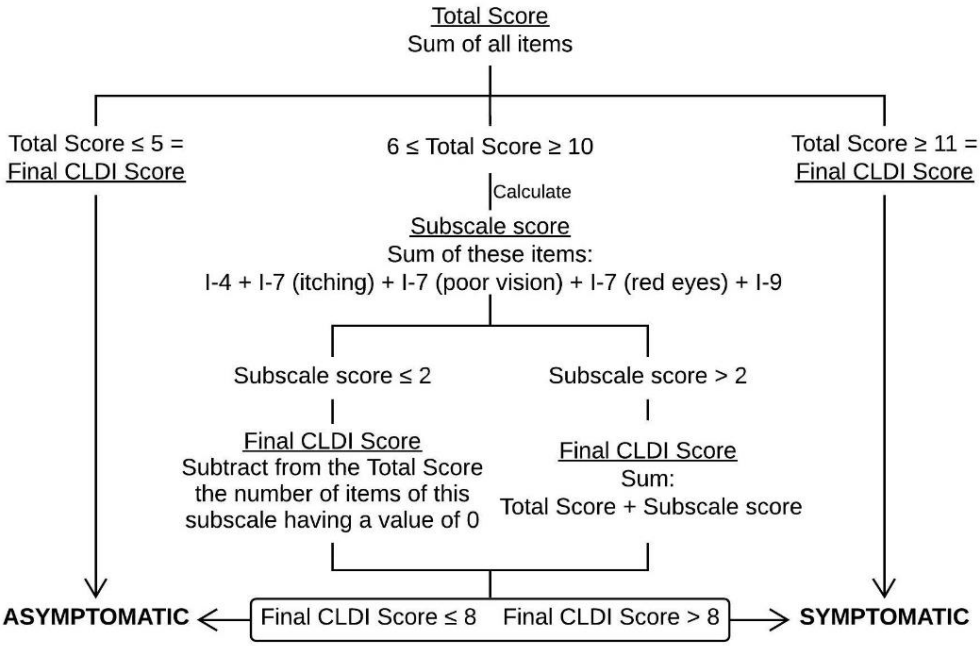


Figure 4.6. **Flow chart of the score system calculation.**

I-: item; CLDI: Contact Lens Discomfort Index.

No significant differences in age (p= 0.49) and gender (p= 0.39) were found between the clusters (symptomatic and asymptomatic). Significant differences between clusters were found for all the CLDI items, except for the response “Slightly uncomfortable” (p=0.76) corresponding to the I-8 (Table 4.5).

Table 4.5 Responses to Contact Lens Discomfort Index (CLDI) items of the two clusters (asymptomatic and symptomatic).

Item		Cluster 1 (asymptomatic) (%)	Cluster 2 (symptomatic) (%)	P-value
1. Use of CL	Same use than before	27.05	19.51	*0.001*
	Less use than before because of dryness/discomfort	12.77	30.72	*<0.0001*
	Less use than before for other reason than dryness/discomfort	60.18	49.78	*0.002*
2. Wishing to wear the CL more time (No/Yes)		85.56/14.44	61.43/38.57	*<0.0001*
3. CLD with electronic devices (No/Yes)		66.72/33.28	19.06/80.94	*<0.0001*
5. CLD in desiccating environments (No/Yes)		35.87/64.13	17.71/82.29	*<0.0001*
6. Dryness	No	31.61	11.66	*<0.0001*
	Yes (without CL)	58.36	72.2	*<0.0001*
	Yes (with and without CL)	10.03	16.14	*0.01*
6. Discomfort	No	48.18	22.2	*<0.0001*
	Yes (with CL)	43.77	65.25	*<0.0001*
	Yes (with and without CL)	8.05	12.56	*0.05*
7. Redness (No/Yes)		73.21/26.29	29.6/70.4	*<0.0001*
7. Watery eye (No/Yes)		79.64/20.36	63.45/36.55	*<0.0001*
7. Scratchiness (No/Yes)		81.31/18.69	32.06/67.94	*<0.0001*
7. Blurry vision (No/Yes)		79.18/20.82	33.63/66.37	*<0.0001*
8. CLD before removing CL	No discomfort	34.95	9.87	*<0.0001*
	Slightly uncomfortable	44.68	48.88	0.76
	Uncomfortable	17.02	33.63	*<0.0001*
	Very uncomfortable	3.34	7.62	*0.009*
9. Satisfaction with CL	Satisfied	78.57	23.54	*<0.0001*
	Slightly satisfied	18.24	62.11	*<0.0001*
	Unsatisfied	3.19	14.35	*<0.0001*

CL: contact lens; CLD: contact lens discomfort

4.3.2.3 Test-retest agreement

Thirty-one CL wearers (25 female and 6 male) aging 23.3±4.9 years (range: 18-40) participated in the reliability study. ICC value obtained for test–retest reliability was 0.88 (95% CI, 0.75–0.94), while k value was 0.67 (95% CI, 0.41-0.93).

4.3.3 CONTACT LENS DISCOMFORT INDEX PERFORMANCE

The study sample recruited to compare the CLDI and the CLDEQ-8 (see the CLDEQ-8 in Appendix 3, page 228) outcomes was composed by 58 CL wearers (40 females and 18 males) with a mean age of 25.9±5.6 years (range 18-40). It was observed that 41 subjects (70.7%, 95% CI: 57.1%-81.5%) of the sample were classified in the same group (either symptomatic or asymptomatic) by both CLDI and CLDEQ-8 questionnaires. Nonetheless, there was a discrepancy in the classification of 17 subjects (29.3%, 95% CI: 18.46%-42.91%). All of them were classified as asymptomatic by the CLDI and symptomatic by the CLDEQ-8 (Table 4.6).

Table 4.6. Distribution of the sample according to CLDI and CLDEQ-8 questionnaires outcomes.

	CLDEQ-8: Asymptomatic	CLDEQ-8: Symptomatic	Total
CLDI: Asymptomatic	16	17	33
CLDI: Symptomatic	0	25	25
Total	16	42	58

CLDEQ-8: Contact lens dry eye questionnaire 8. CLDI: Contact lens discomfort index.

After comparing the CLDI responses of the 17 CL wearers classified as asymptomatic by the CLDI and symptomatic by CLDEQ-8, and the 25 CL wearers classified as symptomatic by both questionnaires, significant different

outcomes were observed for items I-2, I-4.2, I-7 (third option) and I-9 (Table 4.7).

Table 4.7. Comparison of responses to CLDI items that significantly differed between CL wearers that were differently classified by CLDI and CLDEQ-8.

CLDI item	Group A/S (Yes, %)	Group S/S (Yes, %)	P-value
2. I wear the CL as many hours as I wish/need	82.3	48.0	**0.05**
4.2 I have problems with the CL while using the computer	47.1	88.0	**0.01**
7.3. My eyes itches with or without my CL on	23.5	60.0	**0.04**
9. I am satisfied with my CL	35.3	0.0	**0.01**

Group A/S: CL wearers classified as asymptomatic by the CLDI and symptomatic by CLDEQ-8. Group S/S: CL wearers equally classified as symptomatic by both questionnaires.

PART II. ENGLISH TRANSLATION OF THE CONTACT LENS DISCOMFORT INDEX (CLDI)

4.4 MATERIALS AND METHODS (PART II)

The English translation and analysis process explained in this second part of the chapter is summarized in Figure. 4.1 (coloured part).

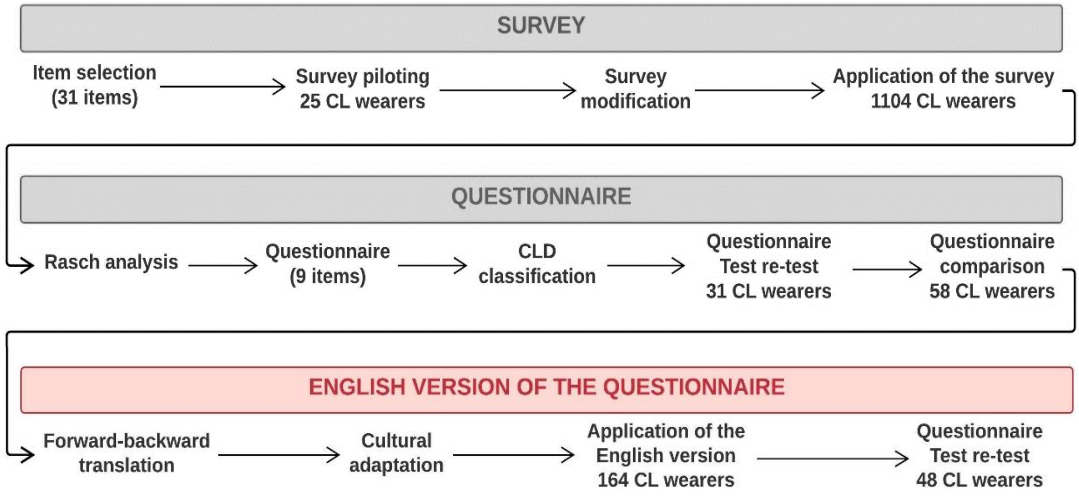


Figure 4.1. **Flow chart of questionnaire design and English translation**.
CL: contact lens; CLD: contact lens discomfort

Statistical analyses were conducted using the statistical package for the social sciences software (SPSS 22.0 for Windows) and the R statistical software (version 3.1.1, Foundation for statistical computing, Vienna, Austria).[181]

ENGLISH VERSION OF THE QUESTIONNAIRE

4.4.1 TRANSLATION PROCESS

The translation of the 9 item CLDI questionnaire have followed the generally accepted and used forward and back translation technique.[176,192] This process involves different steps (Figure. 4.7).

- Forward translation: 2 different native English speakers and bilingual optometrists and familiar to vision science, translated the CLDI from Spanish to English. They were asked to translate the questionnaire not in a literal way but adapted to their clinical experience.
- The result of this process was reviewed by the team that created the questionnaire. The semantic equivalence of the two CLDI versions was evaluated and counselled for an improved version.
- Backward translation: the result of the forward translation was given to 2 different native Spanish and bilingual optometrists who translated the English version back into Spanish. They were blinded to the original version of the CLDI. The result of this process was again reviewed by the same team ensuring that the backward translation was equivalent to the original one.

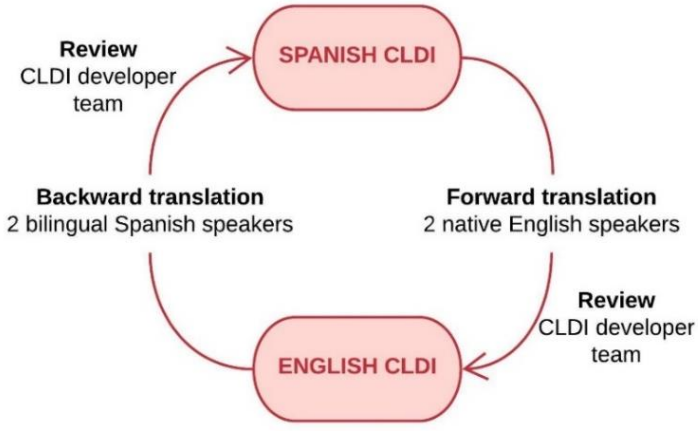


Figure 4.7 Flow chart of the translation process.

CLDI: Contact Lens Discomfort Index

4.4.2 CULTURAL ADAPTATION

A couple of researchers in vision science of the United Kingdom reviewed the final version of the English CLDI and suggested some changes to a better understanding.

4.4.3 APPLICATION OF THE CLDI ENGLISH VERSION

The analysis of CLDI English version was performed at the Glasgow Caledonian University (Glasgow, Scotland). The study complied with the tenets of the Declaration of Helsinki, and was approved by the Ethics Committee of the University (study code HLS/LS/A17/056).

The English version of the CLDI questionnaire was sent via an online platform. Participants were students or staff of the Glasgow Caledonian University or patients attended in the Vision Centre of the University. The inclusion criteria were cognitively able to respond to a questionnaire, age ≥ 18 years old and native English speaker who wear soft CL currently. The exclusion criteria were history of refractive or other type of corneal surgery, rigid CL wearer or previous CL wearer.

4.4.3.1 Item correlation

The correlation between the items of the CLDI was calculated to identify the items that could result confusing. To measure the association of two dichotomous or binary variables, Phi coefficient or Matthews correlation coefficient were used; for one binary variable and one continuous variable, the point biserial correlation coefficient was used (is a special case of Pearson's correlation coefficient); for two continuous variables, it was used the Spearman's Rho correlation coefficient. According to Hinkin recommendations[193] the correlation should be at least 0.4. In addition, the correlation between each variable and the total score of the CLDI was calculated using a polyserial correlation, in which a correlation lower than 0.3 indicated a problem with that variable. A polycor package of R was used.[194]

4.4.3.2 Reliability

Internal consistency of the English version of the CLDI was determined using the Cronbach α coefficient. Values of Cronbach´s α between 0.7–0.8 were considered acceptable to guaranty the reliability of the instrument; 0.8–0,9 good; and>0,9 excellent.[184] The variation of this coefficient when a variable was deleted was also observed, thus, a significant improvement of the coefficient leaded in the elimination of that specific variable. The package ltm of R was used.[195]

4.4.3.3 Confirmatory factor analysis

Confirmatory Factor Analysis (CFA) is a statistical technique used to verify the factor structure of a set of observed variables. It allowed us to test the hypothesis that a relationship between observed variables and their underlying latent constructs exists. The Confirmatory Data Analysis, of the package lavaan of R, was used to accept or reject this theoretical model.[196] Due to the data observed was ordinal, in CFA models, the Diagonally Weighted Least Squares was applied to adjust this one-factor model. In CFA, several statistical tests were used to determine how well the model fits to the data. For the evaluation of the goodness of fit of the model, the chi-square contrast, the root mean square error of approximation, the comparative fix index and the non-normed fit index were calculated.

4.4.3.4 Rasch analysis

The psychometric properties of the CLDI were assessed using item response theory (IRT) models for polytomous responses, they were used to investigate item functioning and to suggest action that could improve the instrument.[197] For this, PCM and Rasch model were used. The response category order for each item was verified, so that CL users with increasing amounts of CLD have increasing probabilities of selecting higher categories in each item. When this was not the case, adjacent categories were collapsed receiving the same score.

In order to determine if individual items provided useful information for CLD score, item infit and outfit mean squares were used. Items with values outside of critical range from 0.7 to 1.3[184] were progressively eliminated.

The Andersen likelihood ratio test was used to assess whether the data fit properly to the PCM model. Principal components analysis of the standardized model residuals was performed to check the unidimensionality of the CLD score. We considered as many dimensions as factors with eigenvalues greater than two.

The targeting of the items to the sample was also assessed by comparing the mean item difficulty with the mean person score. Excellent targeting is achieved when the mean person score is close to 0 logits. Finally, another indicator of instrument performance was calculated: the person separation reliability. For this indicator, higher values show better ability of the instrument to discriminate among subjects. Values of at least 0.8 are considered acceptable.[184] The eRm package of the version 3.6.0 of R was used.[183]

4.4.4 TEST-RETEST AGREEMENT

For the test-retest reliability, the English version of the CLDI was sent to another sample of volunteers twice in a 15-day period. In case some subjects failed to return the second questionnaire, they were e-mailed again. During the second round, participants did not have access to the answers that they provided when the survey was first administered. All volunteers were provided with a written explanation of the nature of the study. Test-retest reliability of the English version of the CLDI was determined using the ICC, and the concordance between diagnoses (symptomatic vs asymptomatic) was evaluated using Cohen's kappa (k). It was followed the same criteria as for the analysis of the CLDI Spanish version.[190,191]

4.5 RESULTS (PART II)

4.5.1 APPLICATION OF THE ENGLISH VERSION OF THE CLDI

The English version of the CLDI was created (see Figure 4.3). Data were obtained from 164 CL wearers English native speakers. Demographic data, CL characteristics, and CL wearing habits are summarized in Table 4.8.

Table 4.8. Demographic data and characteristics of contact lens wearers participating in the survey. N=164.

Factor	Survey sample
Age (years)	34.21±12.92 (range: 18-69)
Gender	79.3% female 20.7%male
Occupation	31.7% University students 68.3% University staff or patients of the clinic
CL wear (years)	13.6±10.9 (range: 2 months-51 years)
CL material	92.7% soft CL 7.3% gas permeable CL
CL replacement	50.6% daily; 11.6% biweekly; 26.8% monthly; 1.8% quarterly; 9.2% annual
Days per week using CL	4.5±2.3 (range: 0-7 days)
Hours per day using CL	10.79±3.6 (range: 2-24 hours)

CL: contact lens

When comparing the results of this English sample to the characteristics of the original sample (Spanish CLDI design: 1104 volunteers), we observed that this sample was significantly older ($p<0.0001$); was composed by a greater proportion of women ($p=0.002$) and a lower proportion of students ($p<0.0001$); were more experienced CL wearers ($p<0.0001$); used CLs with a more replacement frequency ($p<0.0001$) and wore their CL more hours per day ($p<0.0001$). Moreover, the final score of the CLDI obtained by

the English sample was significantly (p<0.0001) lower than the final score of the original sample (5.52±3.95 vs 7.17±4.31 points). Consequently, the proportion of symptomatic CL wearers according to this questionnaire in the English sample was also significantly (p<0.0001) lower than in the original sample (23.8% vs 41.4%).

4.5.1.1 Item correlation

The correlation matrix of the different items of the CLDI is represented in Figure 4.8. The items with a poorer correlation with the other items are I-5, I-6. Dryness, I-7 Red eyes, I-7 Watery eyes and I-7 Poor vision, whose threshold is lower than 0.4. Specially, I-7 Red eyes and I-7 Poor vision, whose correlation is lower than 0.3.

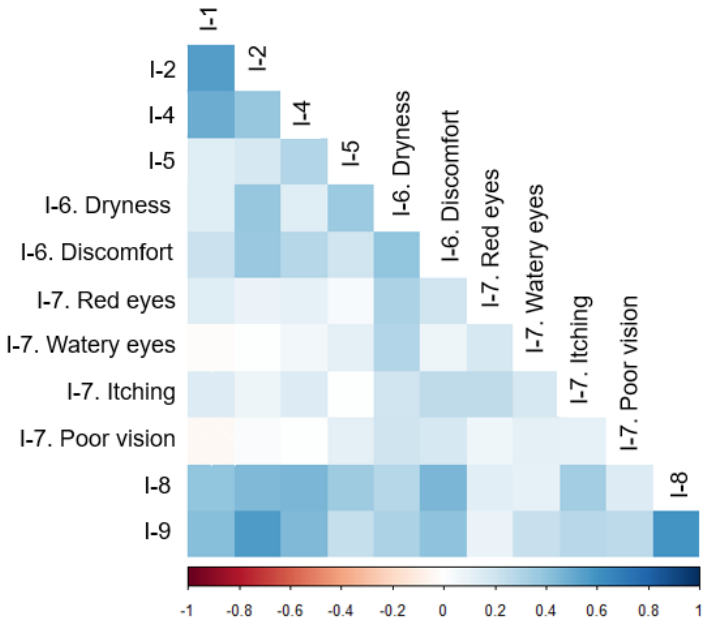


Figure 4.8. Correlation matrix of the items of the Contact Lens Discomfort Index (CLDI) questionnaire English version. I: item.

Regarding the correlation between each variable and the total score of the CLDI using a polyserial correlation, all the items, with the exception of I-7 Red eyes, I-7 Watery eyes and I-7 Poor vision, show a good polyserial

correlation (higher than 0.3). However, the correlation value for these three items did not present significant differences.

4.5.1.2 Reliability

Internal consistency determined using the Cronbach α coefficient was 0.763 (95% CI: 0.71-0.80). Values of α when items were eliminated one by one is presented in Table 4.9. When eliminating I-7: Red eyes, I-7: Watery eyes and I-7: Poor vision, the Cronbach α increased to 0.768, however, the increase was not significantly different (p>0.05).

Table 4.9 Internal consistency of the English version of the Contact Lens Discomfort Index (CLDI).

Items	Modified α	CI 95% bootstrap for α Inf.	Sup.
I-1: Nº hours using the CL	0.745	0.696	0.788
I-2: Use of CL as wished/needed	0.740	0.683	0.783
I-3/I-4: Use of CL with computer	0.741	0.681	0.784
I-5: CL problems in adverse environments	0.753	0.701	0.792
I-6: Dryness	0.742	0.682	0.786
I-6: Discomfort	0.738	0.675	0.780
I-7: Red eyes	0.766	0.713	0.807
I-7: Watery eyes	0.766	0.719	0.803
I-7: Itching	0.756	0.704	0.794
I-7: Poor vision	0.768	0.717	0.810
I-8: Discomfort before removing the CL	0.721	0.659	0.768
I-9: Satisfaction with the CL	0.716	0.650	0.760

α: Cronbach coefficient; CI: confidence interval; I: item; CL: contact lens

4.5.1.3 Confirmatory factor analysis

This is a model of one factor in which all the item loadings were high, unless the loadings related to the I-7 (Red eyes, watery eyes and poor vision). However, all of these factors' loadings are significantly different from 0.

The evaluation of the goodness of fit of the model using different test is presented in Table 4.10. The root mean square error of approximation, the comparative fix index and the non-normed fit index indicated a good adjustment, however, the Chi-square test indicated that the model did not adjust well (p=0.0007).

Table 4.10. Outcomes of the test evaluating the goodness of fit of the model.

Goodness of fit	Value
Chi-square	93.613
df	54
p-value	0.0007
Chi-square/df	1.73
RMSEA	0.067
IC 90%	0.043, 0.089
H_0: RMSEA≤0.05	0.1089
CFI	0.966
NNFI	0.958

Df: degrees of freedom; RMSEA: Root Mean Square Error of Approximation; CI: confidence interval; H_0: hypothesis; CFI: Comparative Fix Index; NNFI: Non-Normed Fit Index.

4.5.1.4 Rasch analysis (English version of the CLDI)

No category threshold disordering was observed. The infit and outfit statistics for the items are shown in Table 4.11. The I-2 presented a mean square value lower than 0.7, suggesting that it could result repetitive; and I-7: Poor vision presented a mean square value higher than 1.3, which indicates a bad adjustment to the model. Item characteristic curves for all items are provided at the end of this chapter (Rasch analysis part II, pages 117-119).

Table 4.11. Infit and Outfit mean square fit statistics for the final items.

Survey question item	Outfit MSQ	Infit MSQ
I-1: Nº hours using the CL	1.018	1.029
I-2: Use of CL as wished/needed	0.557	0.783
I-3/I-4: Use of CL with computer	0.724	0.862
I-5: CL problems in adverse environments	1.075	1.057
I-6: Dryness	0.951	0.953
I-6: Discomfort	0.896	0.920
I-7: Red eyes	1.297	1.067
I-7: Watery eyes	1.250	1.111
I-7: Itching	0.928	1.035
I-7: Poor vision	1.686	1.159
I-8: Discomfort before removing the CL	0.663	0.670
I-9: Satisfaction with the CL	0.633	0.672

MSQ: mean square value. I-: Item.

Principal components analysis of the standardized model residuals revealed that all the factors had eigenvalues <2. Consequently, the English version of the CLDI was considered unidimensional. The mean item difficulty was 0.47 logits and mean person score was -0.57 logits. Finally, the person separation reliability was 0.88. Andersen likelihood ratio test showed a good adjustment to the model (Likelihood Ratio value=11.087; degrees of freedom. = 15; p=0.746).

4.5.2 TEST-RETEST AGREEMENT (ENGLISH VERSION OF THE CLDI)

Forty-eight CL wearers (35 female and 13 male) aging 26.9±9.9 years (range: 18-60) participated in the reliability study. ICC value obtained for test–retest reliability was 0.84 (95% CI, 0.73–0.91), while k value was 0.62 (95% CI, 0.41-0.93).

4.6 DISCUSSION

Measuring CLD can be difficult because the condition itself may be episodic and variable in degree, and the discomfort can be addressed by removing the CLs.[112] However, it is still important to establish appropriate tests for measuring CLD, to quantify the condition and its impact, to determine if an intervention is needed, and/or to evaluate its effect. In this study, we have developed the CLDI questionnaire (Figure 4.3 and 4.4), which is a new instrument designed to help clinicians and researchers to diagnose CLD. It is simple to understand, quickly administered, and provides a score that assesses CLD.

The TFOS defines CLD as a condition related to lens wear that can lead to decrease wear time and discontinuation of lens wear.[32] Typically, these patients present ocular discomfort symptoms while wearing CLs that usually increase over the day, and can be triggered by the external environment.[1] CLD is reported mainly by its symptoms, thus, it is directly related to the patients' own experiences or satisfaction with CLs.[1] Considering these characteristics and based on published data estimating the number of CL wearers in Spain,[198] we created a survey that was completed by approximately 60% of the CL wearers at the University of Valladolid. The composition of the sample in terms of gender, age, type of CL or habits of CL wear is similar to the reported data describing CL fittings in Spain in 2018.[199]

This study followed the methodological steps recommended in the scientific literature for the design of health science questionnaires.[184] The CLDI was developed based on a wide consensus among experts and researchers in the field and was well accepted by the target group (CL wearers). Our 9-item CLDI questionnaire was designed to obtain information about different symptoms, activities, wearing habits, environmental triggers and discomfort with CL. Furthermore, the CLDI includes an item regarding the subjects' satisfaction with their CLs, making it a potentially useful tool for easily

capturing subjective outcomes of new CLD solutions. The item identification and reduction methods used in its development were systematic and rigorous in order to ensure content validity.[184] The number of items selected from the survey was small so the questionnaire was short, and reduce the potential misdiagnosis due to incorrectly completed questionnaires. The Rasch analysis revealed that all items fit the model and, together with the residual principal component analysis, confirmed its unidimensionality.

CLDI demonstrated its ability to classify CL wearers according to the symptomatology in two clusters: asymptomatic or symptomatic. In addition, in the CLDI score system, it was included a reanalysis of those subjects with borderline scores (from 6 to 10) to better classify them in the most appropriate cluster. This approach is adequate to avoid misclassifying borderline subjects, because the accuracy of questionnaires based on one single cut-off score might be limited in those cases.

With regard to consistency of the CLDI, the questionnaire achieved good test-retest reliability both for the final CLDI scores obtained (ICC=0.872) and for the classification (asymptomatic vs symptomatic) of CLD (k=0.668). Therefore, the results showed that the CLDI questionnaire had acceptable psychometric properties.

During the assessment of CLDI performance, we selected the CLDEQ-8 questionnaire as a comparison, because it has been recognized as a validated instrument during the 2013 TFOS workshop.[121] The percentage of CL wearers in our sample that was identified as symptomatic using the CLDI was 43.1 % and 72.4% for CLDEQ-8 (Table 4.6). The common percentage of CL users suffering from CLD has been reported to be around 50%,[1] consequently it seems that in our sample the percentage of subjects with CLD as measured with CLDEQ-8 is higher, while the estimation with the CLDI seems closer to the one published. Nearly two-thirds (70.7%) of the CL wearers were classified equally by both questionnaires, however, almost one-

third (29.3%) of the sample was classified as symptomatic by the CLDEQ-8 in contrast to the CLDI, which classified the same CL users as asymptomatic (Table 4.6). As there is no gold standard test to diagnose CLD, the differences between both questionnaires could be caused by the different factors addressed in each one.

In order to analyse deeper the response of these subjects, we compared their CLDI responses (Group A/S, Table 4.7) with those reported by the CL users who were classified as symptomatic by both questionnaires (Group S/S, Table 4.7). It was observed that the majority of CL wearers of the controversial group (Group A/S) used their CL as much as they wished to (at least 82.3% of them), suggesting that most of those wearers may have not started decreasing their wearing time, and thus, not having CLD yet. Contrastingly, this percentage in the Group S/S (symptomatic based on both questionnaires) was significantly lower (48%), indicating a possible appearance of CLD in half of them at least. Also, the percentage of subjects that referred problems while using the computer was significantly lower in the Group A/S than in the Group S/S. The same fact is found when subjects are asked for eye itching, where the percentage of subjects with this symptom is lower in the Group A/S. Itching is a symptom that can be also related to other entities such as ocular allergy or dry eye, however, 60% of the subjects in Group S/S referred to having this symptom, while a significant lower percentage of subjects (23.5%) referred itchy eyes in the Group A/S, indicating again that, in general, this group had less symptoms. Finally, the I-9, which can be a useful discrimination item, showed that Group A/S was more satisfied (35.3%) with their current CL than Group S/S, where no one was satisfied with their CL. Although 35.3% of the sample could seem a low percentage of CL wearers satisfied with their current CL in case of being asymptomatic, it is important to note that CL use satisfaction can be affected by more aspects than just discomfort, such as CL handling difficulties, vision or CL cost.[200] Therefore, according to the current CLD definition,[1] it could be

concluded that the CL wearers included in this controversial group (differently classified by CLDEQ-8 and CLDI), were much less likely to suffer from CLD, thus, it seems that they were more properly classified by the CLDI as asymptomatic.

Moreover, the English translation and application of the CLDI was performed to allow clinicians and researchers to obtain patient reported outcomes from English spoken CL wearers. This English version of the CLDI has presented, in general, a good level of consistency and reliability, close to the Spanish version of the CLDI.

For the analysis of the English CLDI questionnaire, a study with a sample of 164 participants was performed. However, the characteristics of this sample were significantly different than the sample that was used for the CLDI design. The final scores and the symptomatic classification were also different, probably due to the differences in the sample characteristics. Similar to the outcomes of Chalmers et al,[56] we have found a significantly lower rate of CLD in an older sample of CL wearers.

Regarding the item correlation to detect confusing items, it was found that two items (I-7: Red eyes and I-7: Poor vision) were poor correlated and could need a review. Moreover, the CFA used to determine the loadings of each item showed that those items had lower loadings than the rest of the items, indicating a poor relationship between those variables and the latent variable. In addition, the Rasch analysis used revealed that those items did not adjust well to the model and when they were eliminated, the reliability of the questionnaire increased slightly. However, those changes in the questionnaire were not significant, and the reliability and adjustment of the model were considered appropriate.[184] And together with the PCM analysis its unidimensionality was confirmed.

The item difficulty was higher than the mean person score indicating that the item difficulty is higher than the ability of people to mark responses related to CLD. These outcomes are related to the fact that this sample achieved lower results of CLD according to the CLDI score. Finally, the person separation reliability was 0.88, thus, it can be considered satisfactory to distinguish between high and low performers.

For the test-retest analysis, the sample was composed of 48 volunteers. The literature recommended a sample size of 30 to 40 measurements for new translations.[201] Two weeks was considered a long enough period to avoid remembering the previous answer selected, but short enough for any significant fluctuations in the CLD symptoms. The consistency of the English version of the CLDI achieved good test-retest reliability, very similar to the original CLDI version. Repeatability outcomes were considered appropriate for both, the final CLDI scores obtained (ICC=0.84), and for the classification (asymptomatic vs symptomatic) of CLD (k=0.62).

The present study has some limitations. One is that the diagnosis of CLD is based on subjective outcomes, however, there is no current gold standard for objectively measuring the presence or absence of this condition.[121] Another limitation is the nature of the study sample, because all the volunteers are from a university population. Nevertheless, age and gender distribution of the sample is similar to the CL wearers in Spain.[199] Regarding the CLDI English version, the results showed that this version had acceptable psychometric properties, however, the main limitation is the nature of the English sample, which differs significantly from the original sample (Spanish population). According to the demographic characteristics of CL wearers worldwide,[7] this sample is closer to these characteristics than the original sample. Thus, the poorer results in some statistical tests could be caused by this limitation. A review of some categories of the I-7 will be needed to ensure a better design of the questionnaire. Further research is needed to obtain

more evidence on CLDI questionnaire validity in different populations (e.g., different socioeconomic status) and determination of the cut-off value for the minimal clinically important difference. Thus, it will allow clinicians and researchers to differentiate statistically significant changes from real clinical ones.

In conclusion, this study provides a well-structured instrument that is able to detect CLD. The CLDI questionnaire is a reliable tool, designed to be easily and quickly completed by CL wearers.

ENGLISH VERSION OF THE CONTACT LENS WEAR SURVEY

1. Gender

- ☐ Male
- ☐ Female

2. Age

3. What kind of environment do you work in?

- ☐ I am a student
- ☐ I am a driver
- ☐ I work indoors (office, lab, school, hospital)
- ☐ I work outdoors
- ☐ I work both indoors and outdoors

4. What kind of activities do you like to do in your free time? (you can choose more than one option)

- ☐ Sports
- ☐ Outdoor activities
- ☐ Reading, writing or handicrafts
- ☐ Indoor activities
- ☐ Others (specify)
- ☐ PC/TV/Tablet/cinema

5. Do you have allergies, asthma or eczema?

- ☐ No
- ☐ Yes (specify)

6. Do you take any medications regularly?

- ☐ No
- ☐ Yes

6.1 Specify the reasons for the medications: (you can choose more than one option)

- ☐ Allergies
- ☐ Heart problems
- ☐ acne
- ☐ Arthritis
- ☐ Oral contraceptive
- ☐ Others (specify)
- ☐ Depression or anxiety

7. Have you ever had eye surgery?

- ☐ No
- ☐ Yes (specify)

8. Do you currently use contact lenses?

- ☐ Yes, I do
- ☐ No, I do not
- ☐ No, but I did in the past

9. How many years have you been using contact lenses?

10. Do you have regular check-ups or eye exams for your contact lenses?

- ☐ Yes, I go to see my doctor/optometrist when I have a problem
- ☐ Yes, I usually go once a year
- ☐ No, I do not

11. Specify when the last time you changed the type of contact lenses you wear was.

- ☐ I have never changed the type of contact lenses I wear
- ☐ Less than 1 year ago
- ☐ 1-2 years ago
- ☐ 2-5 years ago
- ☐ More than 5 years ago

11.1 What was the reason why you changed the type of contact lens worn? (you can choose more than one option)

- ☐ To improve comfort
- ☐ Intolerance to old material
- ☐ Professional recommendation
- ☐ To better adapt my contact lenses to my daily activity
- ☐ To save money
- ☐ Other (specify)

12. Select the type of contact lens that you are currently wearing

- ☐ Rigid or gas permeable lenses
- ☐ Soft lenses (hydrogel)
- ☐ Silicone hydrogel lenses

13. Select the replacement frequency of your current contact lenses.

- ☐ Annually
- ☐ Quarterly
- ☐ Monthly
- ☐ Biweekly
- ☐ Daily

14. Do you usually fail to dispose of them at the end of the recommended replacement interval?

- ☐ No
- ☐ Yes

14.1 If yes, select the reason why you do not dispose of lenses at the recommended replacement interval (You can choose more than one option).

- ☐ Because I do not wear my contact lenses every day
- ☐ I replace my contact lenses when the lenses feel uncomfortable
- ☐ To save money
- ☐ Because I do not remember when I opened the last pair of contact lenses
- ☐ Others (specify)

15. Select the cleaning method that you use to clean the contact lenses. (you can choose more than one option)

- ☐ Multipurpose solution
- ☐ Hydrogen peroxide solution
- ☐ I do not clean them because they are daily disposable contacts
- ☐ Others (specify)

16. When you clean your contact lenses, do you rub them?

- ☐ No
- ☐ Yes, when I put my contact lenses
- ☐ Yes, when I remove my contact lenses

17. How many hours, on average, do you use your contact lenses per day?

18. How many days, on average, do you use your contact lenses per week?

19. Since you have been wearing contact lenses, do you wear your contact lenses now as many hours per day or days per week as you have in the past?

- ☐ Nowadays I wear my contact lenses more than before
- ☐ Nowadays I wear my contact lenses less than before
- ☐ Yes, I use my contact lenses with the same frequency as I previously did

19.1 Select the reasons why you wear your contact lenses less frequently at present: (you can choose more than one option)

- ☐ Discomfort
- ☐ I do not mind wearing my glasses
- ☐ Dryness
- ☐ Professional recommendation
- ☐ Not necessary
- ☐ Others (specify)
- ☐ To save money

20. How would you describe your desire for wearing contact lenses?

- ☐ High
- ☐ Low
- ☐ Moderate

21. Do you wear your contact lenses as much as you like to or need to?

- ☐ Yes, I do
- ☐ No, I do not

22. Do you sleep with your contact lenses?

- ☐ No
- ☐ Yes (specify how many days per month)

23. Do you usually wear your contact lenses while using electronic devices/video display terminals?

- ☐ No
- ☐ 3-5 hours/day
- ☐ Less than 1 hour /day
- ☐ 5-8 hours/day
- ☐ 1-3 hours/day
- ☐ More than 8 hours/day

23.1 If you wear your contact lenses while using electronic devices/video display terminals, do you usually have problems of discomfort?

- ☐ No, I do not
- ☐ Yes, I do

23.2 If you do not wear your contact lenses while using electronic devices/video display terminals, what are the reasons? (you can choose more than one option)

- ☐ Because I do not want to wear them
- ☐ Because I do not see well
- ☐ Because my eyes get red
- ☐ Because the contact lenses are dry
- ☐ Because the contact lenses are uncomfortable

24. Select, regardless the hours of contact lens use, which of the following activities that you do while wearing your contact lenses cause you problems of discomfort: (you can choose more than one option)

- ☐ I never have problems of discomfort
- ☐ At work
- ☐ When I read, study or work in near distance
- ☐ Sports
- ☐ Outdoor activities
- ☐ Driving
- ☐ When I watch the TV or go to the movies
- ☐ Others (specify)

25. Do you use artificial tears when you wear your contact lenses?

- ☐ No
- ☐ Yes, I occasionally use artificial tears
- ☐ Yes, I usually use artificial tears once or more times per day

26. Have you ever had complications or diseases associated with your contact lens use?

- ☐ No
- ☐ Yes (specify)

27. Do you usually have problems with your contact lenses in dry environments (air conditioning or heated air), with low humidity or wind?

- ☐ No, I do not
- ☐ Yes, I do

28. Have you ever suffered any of these symptoms while you were wearing contact lenses? (you can choose more than one option)

- ☐ Dryness
- ☐ Redness
- ☐ Watery eyes
- ☐ Discomfort
- ☐ Scratchiness
- ☐ Blurry distance vision
- ☐ Blurry near vision
- ☐ Dirty lenses
- ☐ No, none of them

28.1 Indicate whether you have suffered any of those symptoms while you were NOT wearing your contact lenses: (you can choose more than one option)

- ☐ Dryness
- ☐ Redness
- ☐ Watery eyes
- ☐ Discomfort
- ☐ Scratchiness
- ☐ Blurry distance vision
- ☐ Blurry near vision
- ☐ Dirty lenses
- ☐ No, none of them

29. Have you ever felt the need to remove the contact lens because of those symptoms?

- ☐ No
- ☐ Yes

29.1 How long, after inserting your contact lenses, do you experience the above symptoms?

- ☐ Less than 1 hour
- ☐ 1-3 hours
- ☐ 3-5 hours
- ☐ 5-7 hours
- ☐ 7-9 hours
- ☐ More than 9 hours

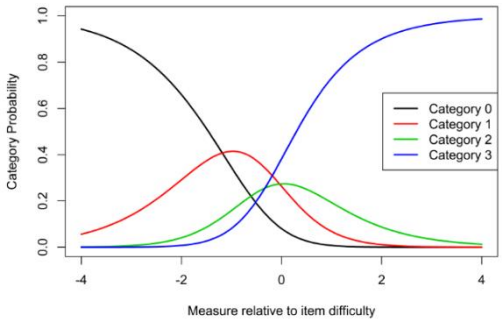
30. Describe your level of discomfort at the moment just before removing your contact lenses:

- ☐ No discomfort
- ☐ Slightly uncomfortable
- ☐ Uncomfortable
- ☐ Very uncomfortable

31. Describe your level of general satisfaction with your contact lenses:

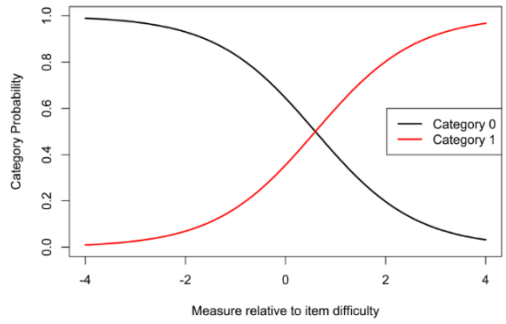
- ☐ Very satisfied
- ☐ Satisfied
- ☐ Slightly satisfied
- ☐ Unsatisfied

RASCH ANALYSIS: ITEM CHARACTERISTICS CURVES (PART I)



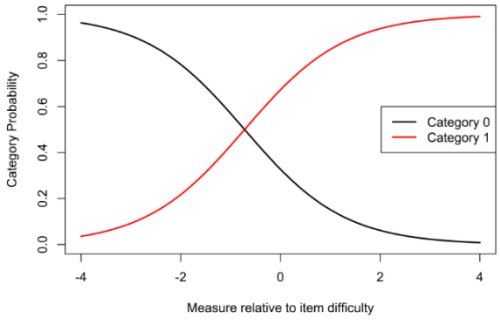
Item 19. Do you wear your CL now as many hours per day or days per week as you have in the past? Categories:

I currently use them more than previously (0)
I use them the same amount as previously (1)
I use them fewer hours per day than I previously did because I prefer to or because it was recommended to me (2)
I use them fewer hours per day due to dryness and/or discomfort (3)



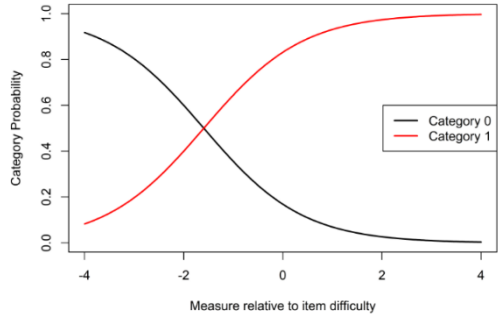
Item 21. Do you wear your CL as much as you like to or need to? Categories:

Yes (0)
No (1)



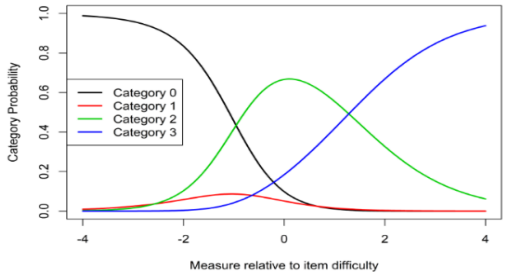
Item 23. Do you usually have discomfort with the CL using electronic devices? Categories:

No (0)
Yes (1)



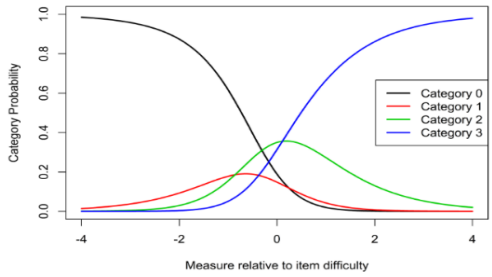
Item 27. Do you usually have problems with your CL in adverse environments? Categories:

No (0)
Yes (1)



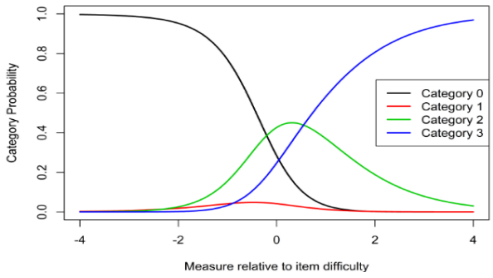
Item 28. Have you ever suffered discomfort while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



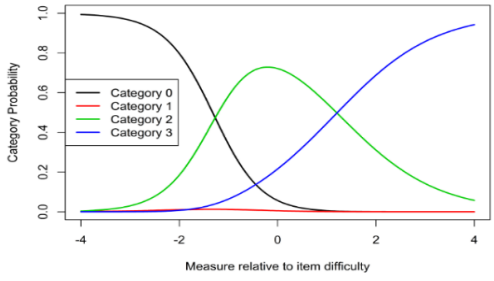
Item 28. Have you ever suffered poor vision while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



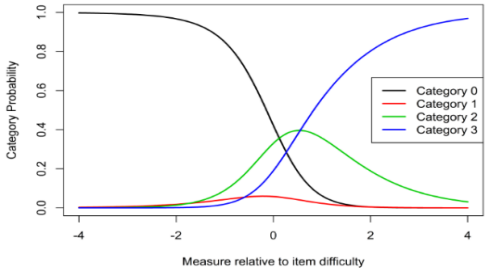
Item 28. Have you ever suffered itching while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



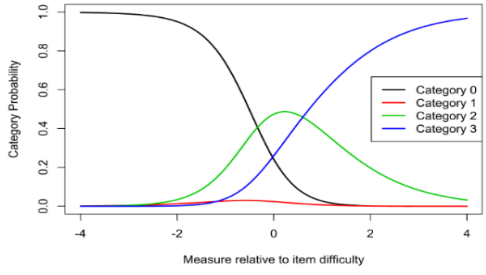
Item 28. Have you ever suffered dryness while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



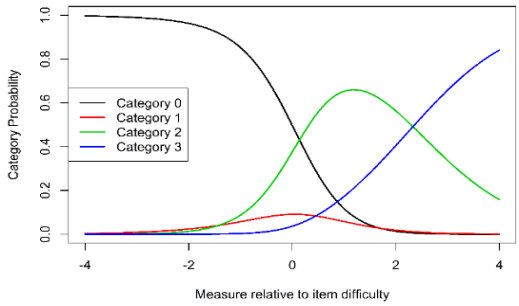
Item 28. Have you ever suffered watery eyes while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



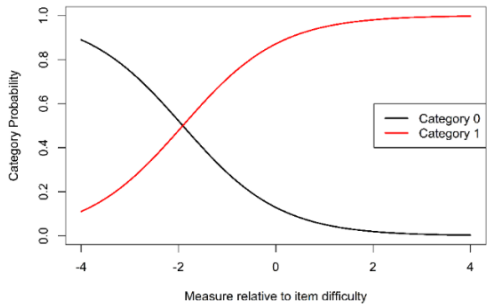
Item 28. Have you ever suffered red eyes while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



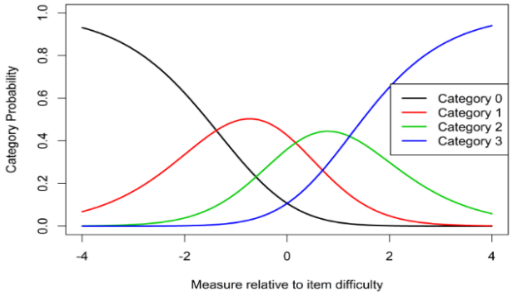
Item 28. Have you ever suffered dirty lenses while you were wearing CL? Categories:

No (0)
Yes, without the CL (1)
Yes, with the contact lenses (2)
Yes, with and without the CL (3)



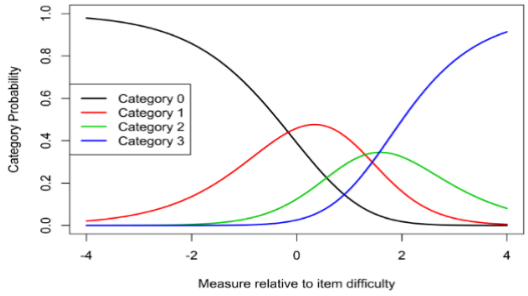
Item 29. Have you ever felt the need to remove the CL because of those symptoms? Categories:

No (0)
Yes (1)



Item 30. Describe your level of discomfort at the moment just before removing your CL. Categories:

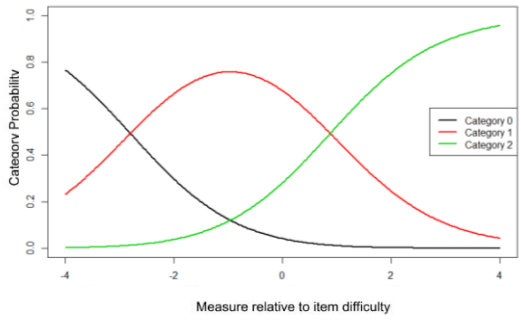
No discomfort (0)
Somewhat uncomfortable (1)
Uncomfortable (2)
Very uncomfortable (3)



Item 31. Describe your level of general satisfaction with your CL. Categories:

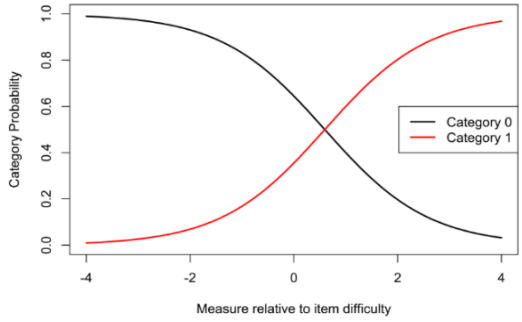
Very satisfied (0)
Satisfied (1)
Slightly satisfied (2)
Unsatisfied (3)

RASCH ANALYSIS: ITEM CHARACTERISTICS CURVES (PART II)



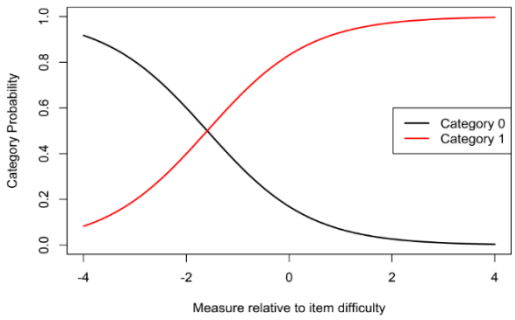
Item 1. Do you wear your CL now as many hours per day or days per week as you have in the past? Categories:

I currently use them more than previously (0)
I use them the same amount as previously (1)
I use them fewer hours per day than I previously did because I prefer to or because it was recommended to me (1)
I use them fewer hours per day due to dryness and/or discomfort (2)



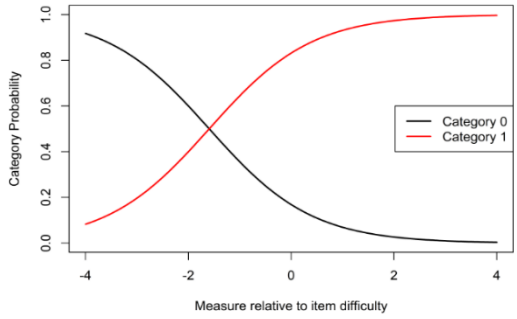
Item 2. Do you wear your CL as much as you like to or need to? Categories:

Yes (0)
No (1)



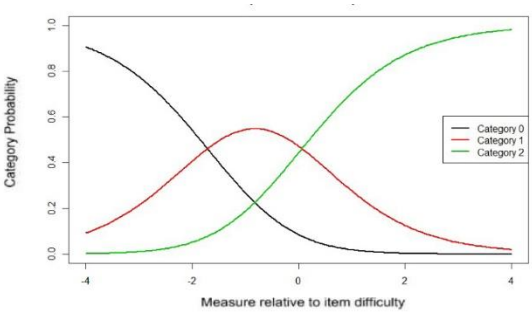
Item 3/4. Do you usually have discomfort with the CL using electronic devices? Categories:

No (0)
Yes (1)



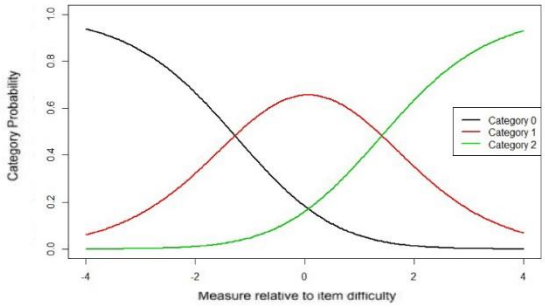
Item 5. Do you usually have problems with your CL in adverse environments? Categories:

No (0)
Yes (1)



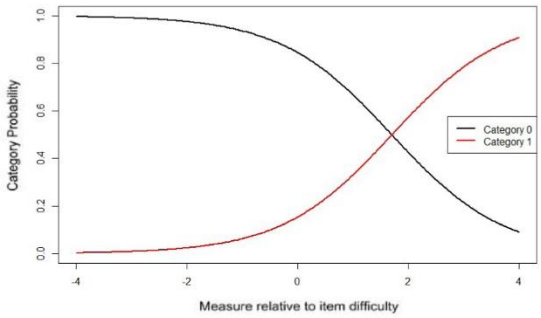
Item 6. During a typical day in the past week, have you experienced dryness? Categories:

No (0)
Yes, with the CL (1)
Yes, with and without the contact lenses (2)



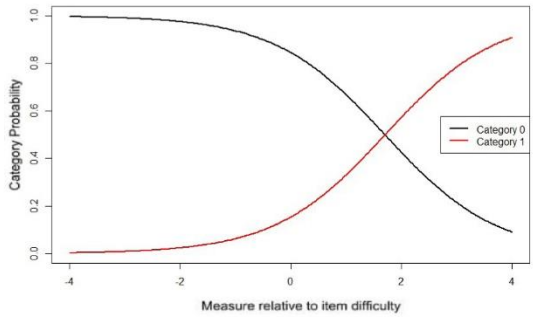
Item 6. During a typical day in the past week, have you experienced discomfort? Categories:

No (0)
Yes, with the CL (1)
Yes, with and without the CL (2)



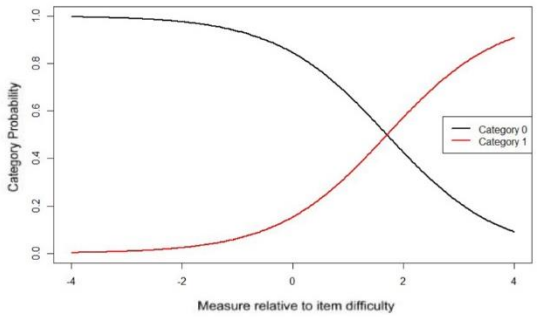
Item 7. During a typical day in the past week, have you experienced red eyes both with and without contact lenses on? Categories:

No (0)
Yes (1)



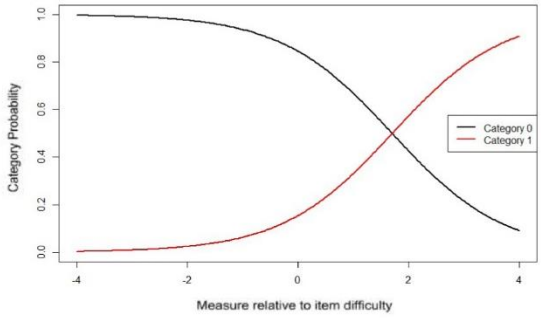
Item 7. During a typical day in the past week, have you experienced itching both with and without contact lenses on? Categories:

No (0)
Yes (1)



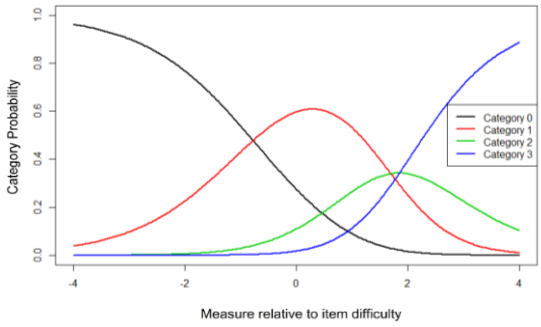
Item 7. During a typical day in the past week, have you experienced poor vision both with and without contact lenses on? Categories:

No (0)
Yes (1)



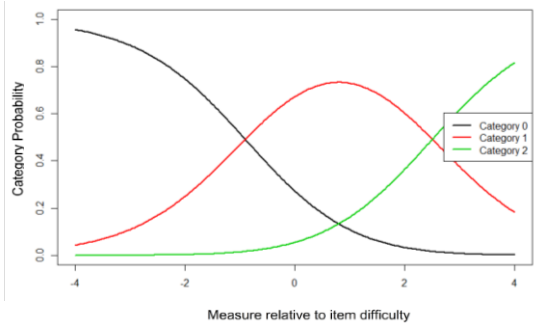
Item 7. During a typical day in the past week, have you experienced watery eyes both with and without contact lenses on? Categories:

No (0)
Yes (1)



Item 8. Describe your level of discomfort at the moment just before removing your CL. Categories:

No discomfort (0)
Somewhat uncomfortable (1)
Uncomfortable (2)
Very uncomfortable (3)

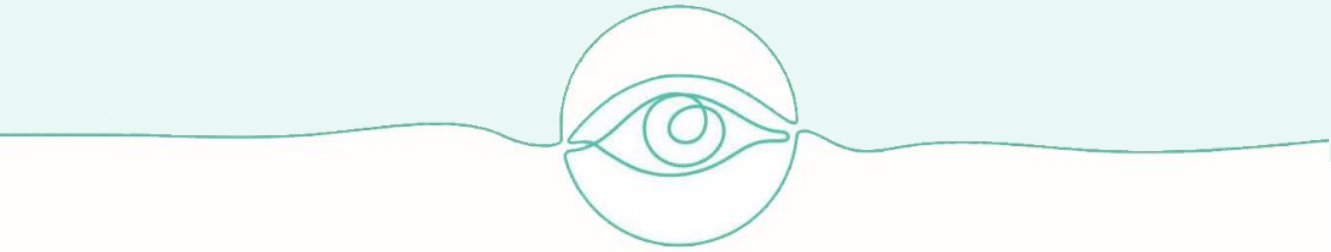


Item 9. Describe your level of general satisfaction with your CL. Categories:

Very satisfied (0)
Satisfied (1)
Unsatisfied (2)

CHAPTER 5

MANAGEMENT OF CONTACT LENS DISCOMFORT: OUTCOMES OF COMMON INTERVENTIONS



This chapter explains the second research project of this thesis. It is focused on analyzing the summative effect of the most common solutions on improving CLD, which are carried out in daily clinical settings. It describes the design of the study as well as the methodology of the experimental procedures, statistical analysis, design of a combined clinical score and the outcomes obtained from the three interventions performed for managing CLD: treatment of MGD, fitting the study-DDCL and use of AT.

Part of this work has been published in a scientific journal: Arroyo-del Arroyo C, Fernández I, Novo-Diez A, Blanco-Vazquez M, López-Miguel A, González- García MJ. Contact lens discomfort management: outcomes of common interventions. Eye Contact Lens. 2020 Jul 7. doi: 10.1097/ICL.0000000000000727. PMID: 32649388.

5.1 BACKGROUND

Currently, the CL market is growing slowly due to the number of wearers suffering from CLD and discontinuing annually from CL wear. [35,202] Different approaches to manage CLD, such as treating MGD, refitting to another CL with a more frequent replacement or using AT, have been evaluated individually in various studies.[137,203,204] However, little is known about the summative effect of these solutions on improving the condition, which is the common practice followed in the daily clinical setting.

Also, clinical signs have been demonstrated to be poorly correlated with symptoms in CLD.[111] In fact, for subjective assessments, the most common instruments are questionnaires able to provide a single final score, which usually is the combination of several items. In the case of clinical assessments, clinicians can perform a wide range of clinical tests. However, there is no one single common sign present in all CL wearers suffering CLD.[107] Therefore, a set of tests combining several clinical assessments (i.e. a combined clinical score) may be more predictive for CLD than a single diagnostic test. [98,205]

The primary purpose of this study was to assess the consecutive implementation of these habitual CLD management strategies, similar to daily clinical practice, using a questionnaire and a combined clinical score.

5.2 MATERIALS AND METHODS

This study is a single-centre, single-masked, open-label, prospective randomised design. It was approved by the East Valladolid Health Area Ethics Committee (Valladolid, Spain) and the Research Committee if the IOBA (Appendix 4, pages 229-230) and in compliance with the Tenets of the Declaration of Helsinki. The nature of the research and protocols were explained to the subjects, and written consent (Appendix 5, pages 231-241) was obtained before entering the study.

5.2.1 SUBJECTS

CL wearers who met the following inclusion criteria were invited to join the study: between 18 and 40 years old, CLDEQ-8 score ≥ 12,[120] astigmatism ≤ 0.75 D, and visual acuity ≤ 0.0 LogMAR. CL wearers had to have been CL users for at least 6 months before being included in the study. Additionally, subjects had to wear their CLs at least 2 days per week and 4 hours a day. Exclusion criteria were extended or continuous CL wear (overnight use), current use of the DDCL used in the study (study-DDCL: delefilcon A), level ≥3 of MGD according to the MGD workshop classification,[206] and dry eye disease patients. Dry eye was defined as OSDI score ≥13[207] and at least two of the following tests altered (in at least one eye): FBUT ≤7 seconds, fluorescein corneal staining extent ≥grade 2 (Cornea and Contact Lens Research Unit (CCLRU) scale) [208] in any of the corneal areas, and Schirmer I test without anaesthesia ≤ 5 mm.

Those volunteers who had any other active ocular disease, ocular allergy, history of anterior ocular surgery, any systemic disease that contraindicated CL wear, and/or used any topical medication other than AT were also excluded.

5.2.2 STUDY VISITS

The primary purpose of this study was to assess the consecutive implementation of habitual CLD management strategies, such as MGD treatment, DDCL fitting and AT supplementation, similar to daily clinical practice. In addition, it was also assessed the placebo effect when the DDCL fitting was performed (Chapter 6). The study protocol was designed based on the common practice followed in the daily clinical setting, consisted of four or five visits: a screening visit, a baseline visit and 2 or 3 follow-up visits separated one month for the assessment of the CLD management depending on the group allocated to evaluate the placebo effect (study vs control).

- **Screening visit:** All subjects were instructed not to wear their CLs for at least 24 hours before the screening visit. Clinical evaluation was performed (see section 5.2.3 and 5.2.4 symptoms and signs evaluation). A Data Collection Logbook was specially designed for the study (Appendix 6, pages 242-251). After eligibility was confirmed, subjects underwent MGD assessment. Those who were diagnosed with MGD were instructed to perform lid hygiene 1 month before starting the study (baseline visit) and throughout the whole study. Only patients suffering from level 1 (subclinical) or 2 (symptomatic minimal) of MGD according to the MGD workshop classification[206] were recruited. Cotton discs and eyelid wipes (Systane Eyelid Cleansing Wipes; Alcon Laboratories, Inc., Fort Worth, Texas, USA) were provided. Instructions were also given on how to perform lid hygiene properly. The instructions consisted of applying warm compresses over 5 minutes (a cotton disk wetted with warm water), followed by a gentle massage of the upper and lower lids, and finally, eyelid wipes.[136]

- **Baseline visit (V0):** This visit was scheduled one week after the screening visit, except for those subjects diagnosed with level 1 or 2 of MGD that were scheduled one month after the screening visit. All subjects wore their current CL for at least 4 to 6 hours. During the visit, a clinical evaluation was

performed (see section 5.2.3 and 5.2.4 symptoms and signs evaluation). The MGD condition was also assessed during all the visits (baseline and follow-up visits). At the end of this visit, half of the habitual monthly CL wearers (study group), randomly selected, and all the habitual daily CL wearers were provided with the study-DDCL for a month (delefilcon A, DAILIES TOTAL1®; Alcon Laboratories, Inc., Fort Worth, Texas, USA) and were asked to change them on a daily basis. For the assessment of the placebo effect, the other half of habitual monthly CL wearers (control group) were provided with a new pair of their habitual monthly CL within a CL case, however, they were informed that these CL were new brand. Subjects were instructed to use the CL at least as much as they were using their habitual CL.

Placebo visit: This visit was scheduled one month after V0 for the control group. Subjects came to the visit wearing the CL provided in V0 (the same monthly masked CL) for about 4 to 6 hours. During the visit, a clinical evaluation was performed and at the end they were provided with the same study-DDCL (delefilcon A, DAILIES TOTAL1®; Alcon Laboratories, Inc., Fort Worth, Texas, USA) for one month. Results of this visit are explained in Chapter 6.

Visit 1 (V1): This visit was scheduled one month after the placebo visit for the control group and one month after V0 for the rest of participants. All subjects wore the study-DDCL for at least 4 to 6 hours. During the visit, clinical evaluation was performed (see section 5.2.3 and 5.2.4 symptoms and signs evaluation). At the end of this visit, the same DDCL was provided for another month, and half of the subjects were also randomly dispensed povidone 2% preservative-free eye drops (Filmabak, Thea, Clermont-Ferrand, France). They were instructed to use the AT at least three times each day, after CL insertion, in the middle of the day and after removing the CL. The other half of participants that did not received AT were instructed not to use any other AT or lubricants.

- **Visit 2 (V2):** This visit was scheduled one month after V1. All subjects wore the study-DDCL for at least 4 to 6 hours, and they were asked not to use AT at least one hour before the visit. During the visit, clinical evaluation was performed (see section 5.2.3 and 5.2.4 symptoms and signs evaluation).

At each visit, compliance with the CLD intervention was evaluated using direct questions about their CL use routine. The study design is shown in Figure 5.1.

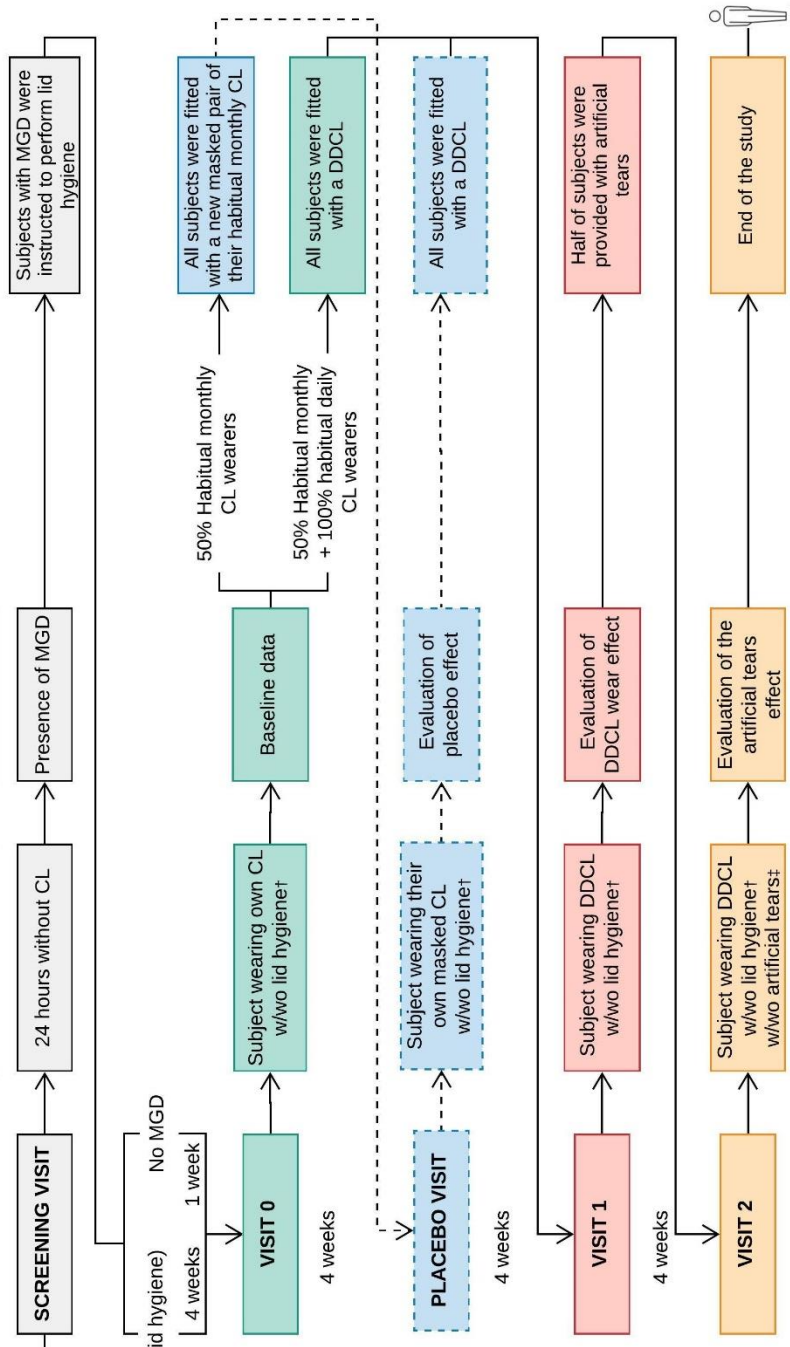


Figure 5.1. Flow chart of the global design of the thesis study.

CL: contact lens; CLD: contact lens discomfort; MGD: Meibomian gland dysfunction; DDCL: daily disposable contact lens; w/wo: with/without. †Participants with MGD underwent lid hygiene during the whole study. ‡After visit 2, half of the participants started using artificial tears. These participants were randomly allocated.

5.2.3 SYMPTOMS EVALUATION

5.2.3.1 Ocular surface disease index

This questionnaire[207] was used to determine if candidates complied with the inclusion criteria. It evaluates symptoms of ocular discomfort and dryness using 12 questions, which are divided in 3 different blocks. The first block evaluates the frequency on a five-point scale (0-4: from “none of the time” to “all of the time”) of 5 ocular symptoms (eyes sensitive to light, gritty eyes, painful or sore eyes, blurred vision, and poor vision); the second block evaluates the limitation of performing 4 visual activities (reading, driving at night, working with a computer or bank machine, and watching television); and third block evaluates the feeling of discomfort under 3 adverse environmental conditions (windy, low humidity, and air conditioned). The total score can range from 0 (no symptoms) to 100 (maximum severity). OSDI scores > 12 points is related to dry eye.[209]

5.2.3.2 Contact Lens Dry Eye Questionnaire-8

Symptoms of discomfort with CL were quantified by administering the CLDEQ-8 (Appendix 3, page 228).[119] CL wearers were instructed to complete the questionnaire considering the symptoms they had commonly suffered in the past 2 weeks while wearing the CL. The CLDEQ-8 consists of 8 questions which evaluate: 1) the frequency (0-4: from never” to “constantly”) and intense at the end of the wearing time (0: “never have it”, or 1-5: from “not at all intense” to “very intense”) of three ocular symptoms during CL wear (discomfort, dryness and blurred vision), 2) the frequency of closing the eye because of the eyes bothering (0-4: from “never” to “constantly”), and 3) the desire of removing the CLs from the eyes (1-6: from “never” to “several times a day”).The CLDEQ-8 total score ranges from 1 to 37, with a diagnostic cut-off of ≥12 points. A clinically important difference is ±3 points.[120]

5.2.3.3 Global Rating of Change Scale

To evaluate the change in comfort during the day and during the month, it was used a 100-units GRCS (-50 meant “extremely worse”, 0 meant “equal” and +50 meant “extremely better”) (Figure 5.2). GRCS are very commonly used in clinical research to quantify a patient's improvement or deterioration over time.[123]

Figure 5.2. Global Rating of Change Scale.

5.2.4 CLINICAL SIGNS

5.2.4.1 Visual acuity

Monocular and binocular visual acuity with habitual correction was performed with high contrast Early Treatment Diabetic Retinopathy Study (ETDRS) charts (CC-100 LCD system; Topcon Corporation, Tokyo, Japan) at 4 meters distance. Measurement was ended when a patient makes three or more mistakes on a line of five letters. Results were recorded in LogMAR units (-0.02 per correct letter).

5.2.4.2 Tear meniscus area

The inferior tear meniscus was imaged by spectral-domain optical coherence tomography (OCT) (Figure 5.3), using the Topcon 3D OCT 2000 (Topcon Corporation, Tokyo, Japan). The lower tear meniscus area (LTMA) in μm^2 was calculated using the "polygon selections" tool of the ImageJ software (http://imagej.nih.gov/ij/).[210]

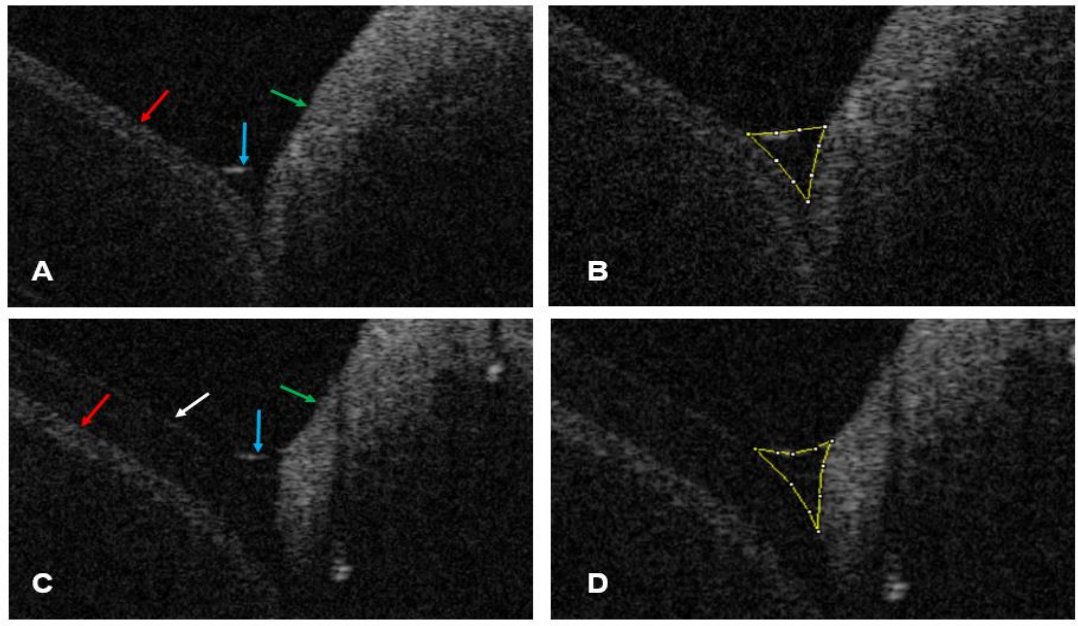


Figure 5.3. Tear meniscus area captures with optical coherence tomography and analysed with ImageJ software.

Image A and C: lower tear meniscus area captured without the contact lens and with the contact lens, respectively. Image B and D: lower tear meniscus area drawn with the polygon selection of the ImageJ software. Red and green arrows indicate the cornea and inferior eyelid, respectively, the blue arrow indicates the lower tear meniscus and the white arrow indicates the contact lens. (From IOBA, University of Valladolid).

5.2.4.3 Tear break-up time

Tear break-up time was measured with two different techniques. During the screening visit (without the CL) fluorescein was instilled (FBUT,

invasive technique), however, during the rest of the visits (with the CL) a non-invasive BUT (NIBUT) was assessed (Figure 5.4). FBUT was evaluated after the instillation of sodium fluorescein (BioFluoro, Tiedra farmacéutica S.L, Madrid, Spain), using a cobalt blue filter over a SL-D7 slit-lamp (Topcon Corporation) and a Wratten #12 yellow filter. NIBUT was measured using the Tearscope Plus instrument (Tearscope Plus; Keeler, Windsor, UK). The mean of the three measurements for both cases (FBUT and NIBUT) was calculated.

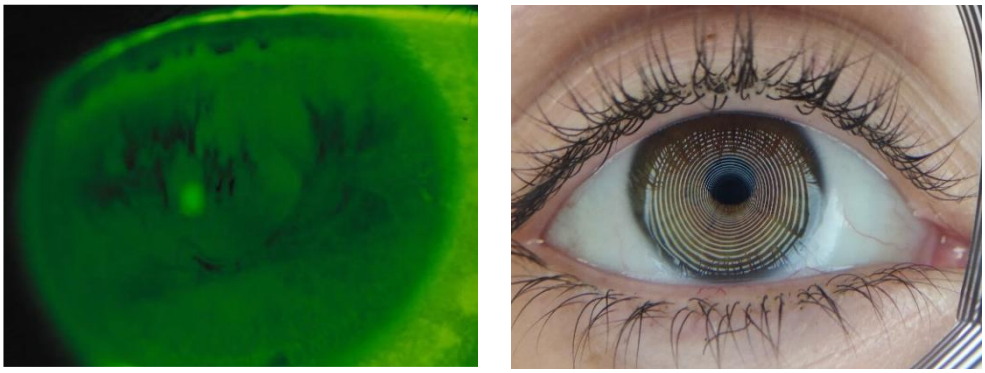


Figure 5.4. Tear break-up time measured with two techniques, one invasive, using fluorescein (left) and one non-invasive, using the Tearscope (right).

(From IOBA. Universidad de Valladolid)

5.2.4.4 Slit-lamp biomicroscopy findings

The ocular surface was examined with a slit lamp (SL-D7; Topcon Corporation, Japan) (http://global.topcon.com/). Bulbar and limbal hyperaemia were graded using the Efron grading scale (0-4, in 1-unit steps),[211] while tarsal hyperaemia was graded using the CCLRU grading scale (0-4, in 1-unit steps).[208]

Sodium fluorescein (BioFluoro, Tiedra farmacéutica S.L, Madrid, Spain) was instilled, and corneal staining was evaluated using the cobalt blue and the Wratten #12 yellow filters (http://www.kodak.de/ek/DE/de/corp/default.htm). The extent of corneal staining was assessed using the CCLRU grading scale (0-4). Finally, lissamine green (I-DEW green Entod Research Cell, UK Ltd. Tottenham, Ln,

London, UK) was instilled, and conjunctival staining was evaluated using the CCLRU grading scale (0-4, in 1-unit steps). LWE was made visible using the lissamine green staining, and evaluated for the upper lid according to Korb et al classification (Table 5.1).[101,102]

Table 5.1. Lid wiper epitheliopathy (LWE) grading score.

Horizontal length	Horizontal grade	Sagittal length	Sagittal grade	Mean of both grades	LWE grade
< 2 mm	0	< 25%	0	0	0
2-4 mm	1	25-50%	1	0,5-1,0	1
5-9 mm	2	50-75%	2	1,25-2,0	2
≥ 10 mm	3	> 75%	3	2,25-3,0	3

In order to detect MGD, lid margin and lipid secretion were evaluated. First, lid margin was scored using a 0-4 scale based on the presence (1) or absence (0) of each of these 4 criteria, irregular lid margin, vascular engorgement, plugging of MG orifices, and shift of the mucocutaneous junction.[26] All points from each sign were summed, thus, the maximum score could be 4. Second, quality and expressibility of lipid secretion was evaluated applying digital pressure through the substance of the lids, and it was assessed on a 0-3 scale: 0= clear meibum, easily expressed; 1= cloudy meibum, easily expressed; 2= cloudy meibum expressed with moderate pressure; 3= meibum not expressible, even with hard pressure.[212]

5.2.4.5 Contact lens fitting evaluation

Centration of the CL was evaluated using a 0 – 3 scale (0=optimum, 1= acceptable deviation, 2= unacceptable deviation); and the movement of the CL with a -2 – 2 scale (-2=unacceptable poor movement, -1= acceptable poor movement, 0=optimum, +1= acceptable loose movement, +2= unacceptable loose movement).[5]

5.2.4.6 Corneal and conjunctival esthesiometry

Sensitivity was measured in the corneal apex and bulbar conjunctiva (2 mm below the limbus) using a Belmonte non-contact esthesiometer prototype.[213,214] This device consists of a tip, placed 5 mm from the corneal apex or bulbar conjunctiva, which expulsed an air jet. The air jet characteristics was selected by the clinician. Mechanical threshold was measured using an airflow ranging between 0 and 200 ml/min.[213,214] Airflow temperature during this stage was calculated to match that of the corneal surface (34ºC) to avoid stimulation of thermal receptors.[213] Esthesiometry outcomes are presented as a mean between corneal and conjunctival measurements.

5.2.4.7 Schirmer test without anesthesia

This clinical test was used to determine if candidates complied with the inclusion criteria. A Schirmer sterile strip (Tearflo; Alcon Laboratories, Inc., Fort Worth, Texas, USA) was inserted into the external canthus of the eyelid margin without topical anesthesia. The length in mm of the moistened strip was measured after five minutes.

5.2.5 MEIBOGRAPHY AND IMAGE ANALYSIS

Meibography provides photographic documentation of the MG under specialized illumination techniques.[215] There are two different types of meibography: transillumination of the everted lid[216,217,218] and direct illumination, named non-contact meibography.[26,219] The method used in this study was the second, using a camera and an infrared light source, without

touching the patient during the meibography procedure. For this purpose, it was used the Easy Tear View Plus (EASYTEAR s.r.l., Trento, Italy) (Figure 5.5). It is a dacryoscope with an infrared light source that allow to investigate the integrity and functionality of the MG (Figure 5.6).

Figure 5.5. Easy Tear View Plus with the infrared device.
(From EASYTEAR®view+)

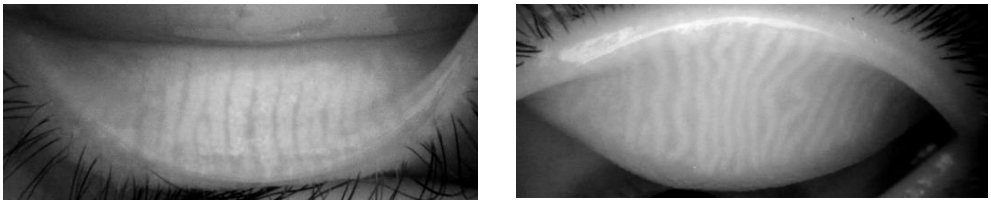


Figure 5.6. Meibography of the lower lid (left) and upper lid (right) taken with the Easy Tear View Plus camera.
(From IOBA. Universidad de Valladolid)

The images obtained were analysed using the Meiboscale[220] (Figure 5.7) to measure the area of loss of the MG.

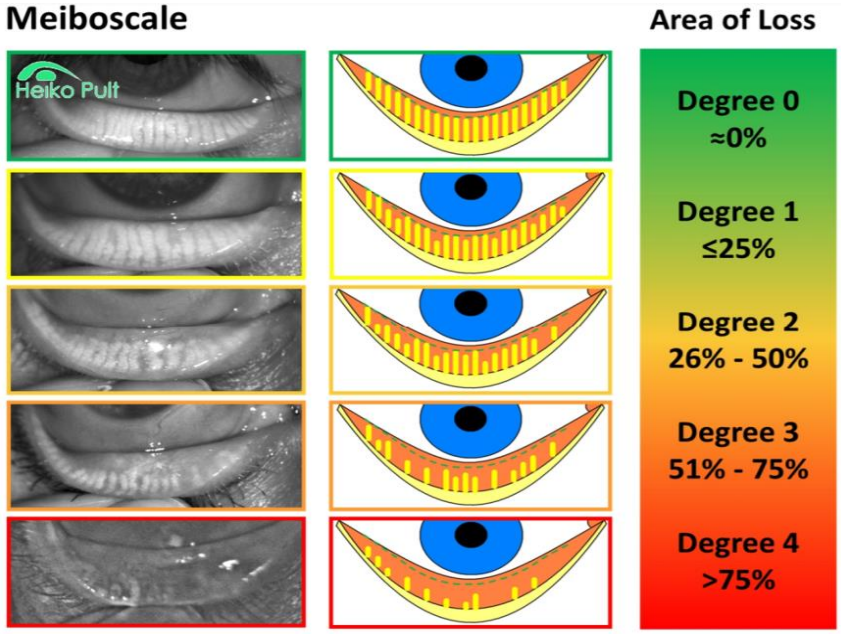


Figure 5.7. Meiboscale. Instrument used to analyse the area of loss of the Meibomian glands.

(From Dr.Heiko Pult – Optometry & Vision Research, www.heiko-pult.de)

5.2.6 STATISTICAL ANALYSIS

5.2.6.1 Sample size calculation

The sample size was calculated considering a significance level of 0.05 and a statistical power of 0.8. It was determined based on a 2.5 odds-ratio of CL wearers reassigned into the asymptomatic group (CLDEQ-8<12 points) by the end of the study. Thus, the resulting sample size was 47 CL wearers, with an expected drop-out rate of 10%.

5.2.6.2 Development of combined clinical scores

To analyse clinical tests results, a weighted combined clinical score was built. This combined clinical score was created using the 7 clinical tests performed in the screening visit to assess the ocular surface (bulbar, limbal and tarsal hyperaemia, NITBUT, LTMA, and corneal and conjunctival staining). LWE was not used for the combined clinical score because it was not performed during the screening visit. Outcomes of the esthesiometry were not included in the combined clinical score either because it might not be considered a purely objective test, which highly depends on the participant response. The goal was to group all the variables in a single clinical score following statistical criteria. Variables were divided as either quantitative or ordinal, and a correlation matrix was performed to observe how the variables correlated with each other. For quantitative variables, Pearson's correlation coefficient was used, and for ordinal variables, Spearman's correlation coefficient was selected.

To create a model for the latent variable called Clinical Score, structural equation models were used. The purpose of structural equation models was to assess unobservable latent variables or factors based on one or more observed variables. Firstly, the number of factors (groups of variables) defining the Clinical Score was determined using the Horn parallel analysis,[221] the Velicer´s Minimum Average Partial,[222] the Very Simple Structure,[223] and the Item Hierarchical Clustering Algorithm.[224] For the clustering algorithm, each variable was added to a cluster if it improved the cluster reliability. Reliability was measured with the Cronbach α and Revelle β. For this analysis, the R package psych was used.[225] Once the initial model was established, it was fitted using structural equation models with a robust maximum likelihood estimation method. Different parameters were added or deleted to improve the goodness of fit based on modification indexes. The goodness of fit was evaluated by the Chi-square test, root mean square error of approximation,

comparative fix index and non-normed fit index. Finally, the normality of distribution of any residuals was checked for all models. Logarithmic transformation (base 2) was applied when the normality assumption was not valid.

5.2.6.3 Analysis of the effect of the interventions

Subjective (CLDEQ-8 outcomes), Clinical Scores and corneal and conjunctival esthesiometry were used to evaluate the possible changes observed after undergoing consecutive CLD management strategies. The paired Wilcoxon test was used to assess changes in MGD signs (lid margin and lipid secretion) and the upper and lower Meiboscore. Linear mixed models were fitted (R package nlme)[226] to evaluate the effect of the different interventions (DDCL and AT) on subjective and clinical scores, and esthesiometry. This analysis provided an appropriate framework for studying the relation between the responses of the subjective and objective scores (dependent variables) and the different interventions performed (independent variables). It allowed us to analyse repeated measurements made on the same participant (longitudinal study) and incorporating random effects and fixed effects. The scores were quantified, estimating the least-square means, and then, post-hoc comparisons were performed. A multivariate-t adjustment was used for multiple comparisons (R package Estimated Marginal Means).[227] Continuous variables are presented as mean± standard deviation and categorical variables are presented as median [interquartile range].

Statistical analyses were conducted using the statistical package for the social sciences software (SPSS 22.0 for Windows) and the R statistical software (version 3.1.1, Foundation for statistical computing, Vienna, Austria).[181]

5.3 RESULTS

5.3.1 SUBJECTS

A total of 47 CL wearers were recruited, with 42 subjects finishing the study. There were 5 drop-outs due to travel and scheduling constraints. Characteristics of the CL used by subjects before recruitment are detailed in Table 5.2.

Table 5.2 Characteristics of the habitual contact lens used by the participants before recruitment.

Material	Subjects (n)	Manufacturer/ supplier	Parameters		Polymer type	FDA group	Frequency replacement
			Base curve (mm)	Diameter (mm)			
comfilcon A	10	CooperVision, Inc.	8.6	14.0	Silicone hydrogel	V	Monthly
lotrafilcon B	7	Alcon Laboratories, Inc.	8.6	14.2	Silicone hydrogel	V	Monthly
nelfilcon A	7	Alcon Laboratories, Inc.	8.7	14.0	Conventional hydrogel	II	Daily
ocufilcon D	6	CooperVision, Inc.	8.6	14.2	Conventional hydrogel	IV	Monthly
omafilcon B	2	CooperVision, Inc.	8.6	14.2	Conventional hydrogel	II	Monthly
omafilcon A	2	CooperVision, Inc.	8.7	14.2	Conventional hydrogel	II	Daily
polymacon	2	Bausch & Lomb	8.4	14.0	Conventional hydrogel	I	Monthly
methafilcon A	2	CooperVision, Inc.	8.7	14.40	Conventional hydrogel	IV	Monthly
fanfilcon A	1	CooperVision, Inc.	8.4	14.2	Silicone hydrogel	V	Monthly
hilafilcon B	1	Bausch & Lomb	8.6	14.2	Conventional hydrogel	II	Monthly
hilafilcon B	1	Bausch & Lomb	8.6	14.2	Conventional hydrogel	II	Daily
somofilcon A	1	CooperVision, Inc.	8.6	14.1	Silicone hydrogel	V	Daily

Demographic data, CL characteristics, wearing habits, and results of the seven clinical tests in the screening visits for the 42 CL wearers are summarised in Table 5.3.

Table 5.3. Demographic data, CL wear characteristics and clinical test data of the CL wearers.

Factor	Survey sample
Age (years) (range)	23.2±4.9 (18-40)
Gender	31 (73.8%) female; 11 (26.2%) male
CL wear length (years) (range)	6.21±4.11 (6 months-21 years)
CL power (RE/LE) (range)	-2.96±1.27D (-1.25D,-5.75D) / -2.84±1.37D (-0.75D,-6.25D)
CL material	23 (54.8%) hydrogel CL 19 (45.2%) silicone hydrogel CL
CL replacement	31 (73.8%) monthly; 11 (26.2%) daily
Days of CL wear per week (range)	5.1±1.7 (2-7 days)
Hours of CL wear per day (range)	7.9±2.4 (4-14 hours)
CLDEQ-8 score (1-37 points) (range)	21.62±3.98 (15-30)
Bulbar hyperaemia (0-4)	1 [1-2]
Tarsal hyperaemia (0-4)	1 [0-1]
Limbal hyperaemia (0-4)	1 [0-1]
Corneal staining (0-20)	0 [0-1]
Conjunctival staining (0-4)	0 [0-1]
Break-up time (s) (range)	10.02±6.79 (3.66-29.67)
Lower tear meniscus area (μm^2) (range)	15003.50±8354.30 (3975.0-41565.0)

Continuous variables are presented as mean± standard deviation and categorical variables are presented as median [interquartile range]. CL: contact lens; RE: right eye; LE: left eye; CLDEQ-8: Contact Lens Dry Eye Questionnaire 8.

CLDEQ-8 scores, Clinical Scores and esthesiometry values obtained during the screening, baseline and the 2 follow-up visits are detailed in Tables 5.4, 5.5 and 5.6, respectively. In the screening visit, 11 subjects were diagnosed with MGD, therefore, they performed lid hygiene for the whole study. In V0, 25 subjects were fitted with the study-DDCL and the other 17 were fitted with the study-DDCL in the placebo visit. Then, in V1, 21 randomly allocated CL wearers used AT. All the subjects who underwent V0 finished the study.

Table 5.4. Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8, clinical tests and esthesiometry in the screening visit.

Test	Screening visit	
	No MGD group (n=31)	MGD group (n=11)
CLDEQ-8 (1-37)	21.61± 4.09	21.64± 3.83
Bulbar hyperaemia (0-4)	1.32 [1-2]	1.36 [1-2]
Limbal hyperaemia (0-4)	0.81 [0-1]	0.91 [0-2]
Tarsal hyperaemia (0-4)	0.81 [0-1]	1.18 [1-2]
Non-invasive tear break-up time (s)	10.21±7.17	9.49±5.85
Lower tear meniscus area (μm^2)	16340.58±9200.60	11235.36±3323.04
Corneal staining (0-20)	0.35 [0-1]	0.82 [0-1]
Conjunctival staining (0-4)	0.32 [0-3]	0.73 [0-1]
Esthesiometry (ml/minute)	120.45± 36.75	132.14± 49.17

Continuous variables are presented as mean± standard deviation and categorical variables are presented as median [interquartile range]. MGD: Meibomian gland dysfunction.

Table 5.5. Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8 score, clinical variables and esthesiometry obtained in baseline (V0) and first visit (V1). Participants were grouped based on their previous contact lens frequency replacement.

Test	Baseline visit (V0)		First visit (V1)	
	Previous monthly CL wearers group (n= 31)	Previous daily CL wearers group (n= 11)	Previous monthly CL wearers group (n= 31)	Previous daily CL wearers group (n= 11)
CLDEQ-8 (1-37) (mean)	19.29±6.64	23.36±2.84	12.16±7.01	13.55±5.43
Bulbar hyperaemia (0-4)	1.52 [1-2]	1.82 [1-2]	1.84 [1-2]	2 [1.75-2.25]
Limbal hyperaemia (0-4)	1.32 [1-2]	1.36 [1-2]	1.32 [1-2]	1.40 [1-2]
Tarsal hyperaemia (0-4)	1.13 [1-2]	1.09 [1-2]	1.32 [1-2]	0.70 [0-1]
Non-invasive tear break-up time (s)	10.67±3.64	9.82±2.88	11.96±3.97	11.55±2.82
Lower tear meniscus area (μm^2)	15053.03± 9790.51	9947.27± 4060.53	14231.38± 6086.34	10.913.10± 4572.91
Corneal staining (0-20)	1.45 [0-2]	2.73 [1-3]	0.94 [0-2]	1.20 [0-3]
Conjunctival staining (0-4)	0.81 [0-1]	1.18 [0-2]	0.61 [0-1]	0.40 [0-1]
Esthesiometry (ml/minute)	120.45± 44.66	95.32± 41.01	113.48± 42.91	92.5± 48.41

Continuous variables are presented as mean± standard deviation and categorical variables are presented as median [interquartile range]. CL: contact lens.

Table 5.6. Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8 score, clinical variables and esthesiometry obtained in first (V1) and second (V2) visit. Participants were grouped randomly based on receiving or not artificial tears.

Test	First visit (V1)		Second visit (V2)	
	No AT group (n= 21)	AT group (n= 21)	No AT group (n= 21)	AT group (n= 21)
CLDEQ-8 (1-37)	11.62±5.7	13.43±7.43	9.76±5.32	11.38±6.7
Bulbar hyperaemia (0-4)	1.95 [1-3]	1.76 [1-2]	1.62 [1-2]	1.57 [1-2]
Limbal hyperaemia (0-4)	1.43 [1-2]	1.29 [1-2]	1.33 [1-2]	1.19 [1-2]
Tarsal hyperaemia (0-4)	1.10 [1-2]	1.29 [1-2]	1.19 [1-2]	1.24 [1-2]
Non-invasive tear break-up time (s)	11.54±3.89	11.96±3.6	12.27±4.57	13.68±5.87
Lower tear meniscus area (μm^2)	11786.61± 6354.36	14554.52± 5493.93	11158.0± 4248.31	14647.28± 5268.82
Corneal staining (0-20)	0.90 [0-2]	1.05 [0-2]	0.9 [0-1]	0.76 [0-1]
Conjunctival staining (0-4)	0.67 [0-1]	0.43 [0-1]	0.57 [0-1]	0.24 [0-1]
Esthesiometry (ml/minute)	95.81± 40.20	120.16± 46.84	87.77± 40.83	117.31± 51.0

Continuous variables are presented as mean± standard deviation and categorical variables are presented as median [interquartile range]. AT: artificial tears.

5.3.2 CLINICAL SCORES

According to the Horn parallel analysis and the Very Simple Structure test, a model with two factors of the latent variables was determined. Contrastingly, the Velicer´s minimum average partial and the Item hierarchical clustering algorithm proposed a one single factor model. Both models were adjusted using structural equation models to choose the most consistent, which was the model with two factors (two Clinical Scores).

The likelihood-ratio test and goodness of fit of the Clinical Scores are detailed in Table 5.7 and Table 5.8.

Table 5.7 Likelihood ratio test of the different models presented in the structural equation models.

	df	AIC	BIC	Chi square	Chi square dif	df dif	*p*-value
M1	14	814.89	839.22	16.669	7.2943	1	***0.0069***
M2	13	809.60	835.66	9.375	.	.	.

df: degree of freedom; AIC: Akaike information criterion; BIC: Bayesian information criteria; dif: difference; M1: model with one factor; M2: model with two factors.

Table 5.8 Goodness of fit of the different models presented in the structural equation models.

	M1	M2
Chi-square	16.669	9.375
df	14	13
***p*-value**	0.2742	0.7441
Chi-square /df	1.19	0.72
RMSEA	0.067	0
90% CI	0, 0.171	0, 0.111
H_0: RMSEA≤0.05	0.3726	0.8119
CFI	0.926	1
NNFI	0.889	1.163

df: degree of freedom; RMSEA: Root Mean Square Error of Approximation; CI: Confidence interval; H_0: null hypothesis; CFI: Comparative Fix Index; NNFI: Non-Normed Fit Index; M1: model with one factor; M2: model with two factors.

Therefore, two Clinical Scores were obtained (Figure 5.8). The first one (Clinical Score 1) was the weighted combination of the following variables: limbal, bulbar, and tarsal hyperaemia and corneal staining. Clinical Score 2 was the weighted combination of conjunctival staining, NITBUT and LTMA. A 0 score value for both Clinical Scores reflected a healthier clinical condition, while a 100 score value reflected poorer clinical condition.

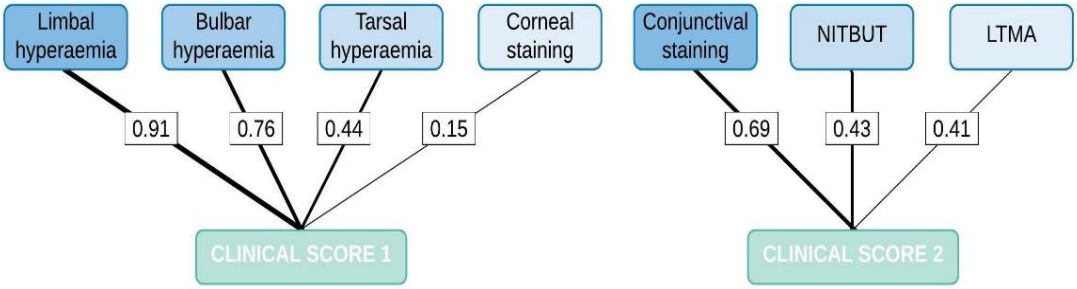


Figure 5.8. Clinical variables included in each Clinical Score. The numbers represent the relative weight of each variable within each Clinical Score.

NITBUT: non-invasive tear break-up time; LTMA: lower tear meniscus area.

For Clinical Score 2, a logarithmic transformation was performed because the residuals of the model showed a lack of normality. Thus, outcomes are detailed as fold changes.

5.3.3 EFFECT OF CLD INTERVENTIONS

Results of the effects of the interventions performed presented in this chapter correspond to the coloured part of the study design (Figure 5.9).

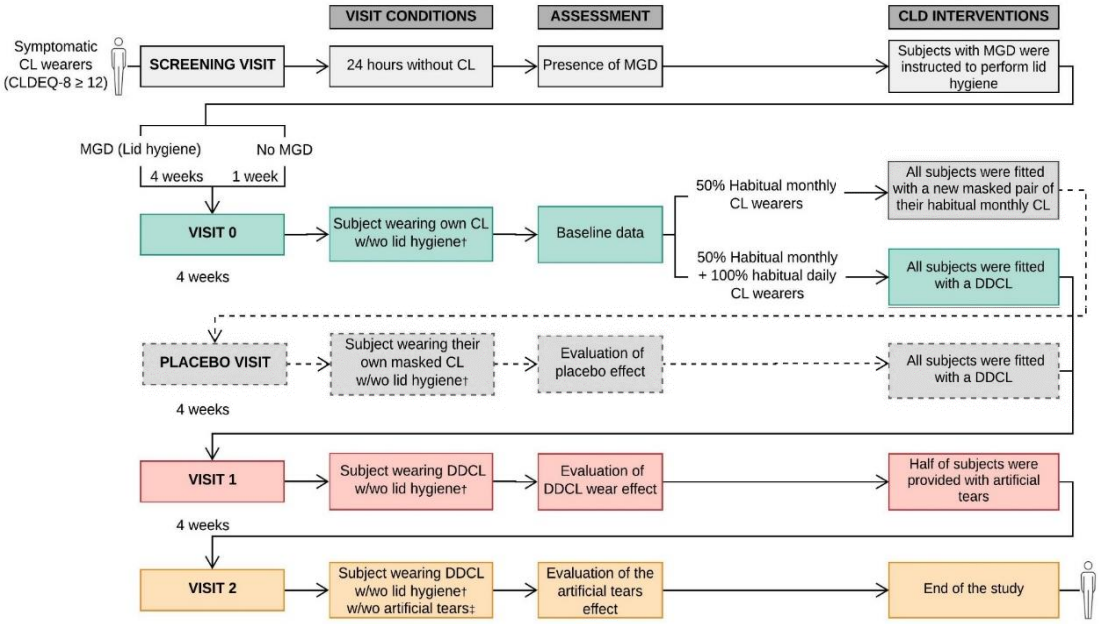


Figure 5.9 Study visits whose outcomes are presented in Chapter 5.
Coloured visits correspond to the three interventions performed. CL: contact lens; MGD: Meibomian gland dysfunction; DDCL: daily disposable contact lens; w/wo: with/without. †Participants with MGD underwent lid hygiene during the whole study. ‡After visit 2, half of the participants started using artificial tears. These participants were randomly allocated.

5.3.3.1 Lid hygiene

Outcomes of the lid margin status, lipid secretion and Meiboscore of the upper and lower lid along the visits after performing lid hygiene is presented in Table 5.9. MGD subjects showed a significant improvement in lid margin status ($p=0.009$) and in lipid secretion ($p=0.007$) after 4 weeks of lid hygiene and maintained the status after the consecutive visits. From the initial 11 CL wearers detected with level 1 or 2 of DGM during the screening visit, only 4 remained having MGD (2 with level 2 and 2 with level 1) at the end of the study. No significant differences ($p>0.05$) were found between visits in terms of MG area of loss according to the Meiboscale.

Table 5.9 Outcomes of the lid margin status, lipid secretion and Meiboscore obtained in subjects with Meibomian gland dysfunction (n=11) during visits.

	Screening visit	4 weeks of lid hygiene (V0)	8 weeks of lid hygiene (V1)	12 weeks of lid hygiene (V2)
Lid margin status	2 [1-3]	1 [1-1]	0 [0-1]	0 [0-1]
Lipid secretion	2 [1-2]	1 [1-1]	0 [0-1]	0 [0-1]
Meiboscore of upper lid	1 [0-2]	1 [1-2]	1 [1-2]	1 [1-2]
Meiboscore of lower lid	0 [0-1]	0 [0-1]	0 [0-1]	0 [0-1]

V: visit; Variables are presented as median [interquartile range].

Evolution of symptoms as measured with the CLDEQ-8, Clinical Scores and esthesiometry after lid hygiene are presented in Table 5.10. Participants who underwent lid hygiene showed a significant (p=0.01) higher decrease on CLDEQ-8 score. After performing lid hygiene, no significant change was found in Clinical Score 1, however, Clinical Score 2 was significantly (p=0.04) higher in MGD participants. Esthesiometry did not show a significant difference between subjects who underwent lid hygiene and subjects who did not.

Table 5.10 Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8 score, Clinical Score 1 and 2 and esthesiometry found after implementing lid hygiene.

Effect	Comparisons	CLDEQ-8			CLINICAL SCORE 1			CLINICAL SCORE 2			ESTHESIOMETRY		
		Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value	Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value	FC (I)/(II)	95% CI FC (Inf/ Sup)	Test; *p*-value	Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value
Lid hygiene performance	(I) Yes (n=11) (II) No (n=31)	-2.74↓	-4.87/ -0.61	t=-2.54; *p=0.012*	1.66↑	-3.60 / 6.93	*t=0.63*; p=0.53	1.25↑	1.00 / 1.55	*t=2.01; p=0.04*	-0.83↓	-16.88/15.22	t=-0.10; p=0.92

Dif: difference; CI: confidence interval. Arrows indicate the direction of changes (downward arrows indicate lower contact lens discomfort for CLDEQ-8 results and better clinical condition for Clinical Scores results).

5.3.3.2 Daily disposable contact lens fitting

The effects of the DDCL fitting on the CLDEQ-8, Clinical Scores and esthesiometry are presented in Table 5.11. Regarding the efficaciousness of fitting the study-DDCL, there was a significant ($p<0.0001$) decrease on the CLDEQ-8 after the first month using the study-DDCL (Table 5.11, 1-month Study-DDCL wear effect). However, CLDEQ-8 was not significantly ($p=0.40$) further reduced after the second month of study-DDCL wear (Table 5.11, 2-month Study-DDCL wear effect). Additionally, we observed that the improvement in CLDEQ-8 scores was not significantly ($p=0.68$) different between previous monthly and daily CL wearers (Table 5.11, replacement frequency change effect).

We did not find any significant ($p=0.75$) change in the Clinical Score 1 after one or two months of study-DDCL (Table 5.11). Likewise, we did not find any difference ($p=0.42$) in the change of Clinical Score 1 between previous monthly or daily CL users. There was a significant ($p=0.04$) decrease in Clinical Score 2 (towards a healthier ocular surface) after one month wearing the study-DDCL (Table 5.11: score decreased 1.35 (1/0.74) times in V1). In contrast, there were no significant differences in Clinical Score 2 neither after the second month wearing the study-DDCL ($p=0.98$), nor between previous monthly and daily CL wearers ($p=0.12$).

Esthesiometry did not show a significant difference after any of the effects evaluated.

Table 5.11 Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8 score, Clinical Score 1 and 2 and esthesiometry found after DDCL wear.

Effect	Comparisons	CLDEQ-8			CLINICAL SCORE 1			CLINICAL SCORE 2			ESTHESIOMETRY		
		Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value	Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value	FC (I)/(II)	95% CI FC (Inf/ Sup)	Test; *p*-value	Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value
1-month Study-DDCL wear	(I) V1-study-DDCL (n=42) (II) V0-habitual CL (n=42)	-10.12↓	-13.66 / -6.58	t=-6.90; *p<0.0001*	-1.12↓	-8.13 / 5.90	*t=-0.38*; p=0.97	0.74↓	0.54 / 0.99	*t=-2.48; p=0.04*	1.29↑	-15.84 / 18.42	t=0.18; p=0.99
2-month Study-DDCL wear	(I) V2-study-DDCL (n=42) (II) V1-study-DDCL (n=42)	-1.60↓	-4.33 / 1.13	t=-1.41; *p*=0.40	-2.17↓	-8.11 / 3.77	*t=-0.88*; p=0.75	0.97↓	0.77 / 1.22	*t=-0.27; p*=0.98	-7.26↓	-19.32 / 4.80	t=-1.46; p=0.38
Replacement frequency change	(I) Yes (n=31) (II) No (n=11)	0.54↑	-2.02 / 3.10	t=0.42; *p*=0.68	-2.65↓	-9.14 / 3.85	*t=-0.81*; p=0.42	0.82↓	0.63 / 1.06	*t=-1.52; p*=0.12	12.21	-2.91 / 27.32	t=1.60; p=0.11

DDCL: daily disposable contact lenses; Dif: difference; FC: fold change; CI: confidence interval. Arrows indicate the direction of changes (downward arrows indicate lower contact lens discomfort for CLDEQ-8 results and better clinical condition for Clinical Scores results).

5.3.3.3 Use of artificial tears

The effects of the AT use on the CLDEQ-8, Clinical Scores and esthesiometry are presented in Table 5.12. There were not significant ($p \geq 0.09$) differences neither in the CLDEQ-8 scores, nor in the clinical scores, nor in the esthesiometry between the group who used the AT and the group who did not.

5.3.4 CLDEQ-8 CLASSIFICATION

According to the CLDEQ-8 classification, none of the CL wearers that performed lid hygiene became categorized as asymptomatic (CLDEQ-8 score<12 points). After fitting the study-DDCL, 20 out of 42 (47.61%) CL wearers became categorized as asymptomatic (Figure 5.10. All subjects V1). After additionally using AT, 5 (4 in the AT group and 1 in the no AT group) out of the 22 subjects that remained classified as symptomatic became categorized as asymptomatic

In summary, at the end of the study, from the 42 CL symptomatic wearers that entered the study, 25 (59.52%) finished classified as asymptomatic (Figure 5.10. All subjects V2). The CLDEQ-8 score at the beginning and the end of the study of these 25 CL wearers who became categorized as asymptomatic was 21.92±3.56 points (range: 15-29) and 6.60±3.40 (range: 1-11) ($p<0.001$), respectively. Regarding the subjects that remained symptomatic during the whole study (17 out of 42, 40.48%), their mean CLDEQ-8 score decreased also significantly ($p<0.001$) from 21.18±4.60 (range: 15-30) to 16.41±3.86 (range: 13-22).

Table 5.12 Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8 score, Clinical Score 1 and 2 and esthesiometry found after artificial tears use.

Effect	Comparisons	CLDEQ-8			CLINICAL SCORE 1			CLINICAL SCORE 2			ESTHESIOMETRY		
		Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value	Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value	FC (I)/(II)	95% CI FC (Inf/ Sup)	Test; *p*-value	Dif. (I)-(II)	95% CI dif. (Inf/ Sup)	Test; *p*-value
Use of artificial tears	(I) Yes (n=21) (II) No (n=21)	-0.71↓	-3.54 / 2.13	t=-0.49; *p*=0.62	-1.29↓	-7.83 / 5.24	*t=-0.39*; p=0.69	0.81↓	0.63 / 1.03	*t=-1.70; p=0.09*	3.64↑	-9.88 / 17.16	t=0.53; p=0.60

Dif: difference; CI: confidence interval. Arrows indicate the direction of changes (downward arrows indicate lower contact lens discomfort for CLDEQ-8 results and better clinical condition for Clinical Scores results).

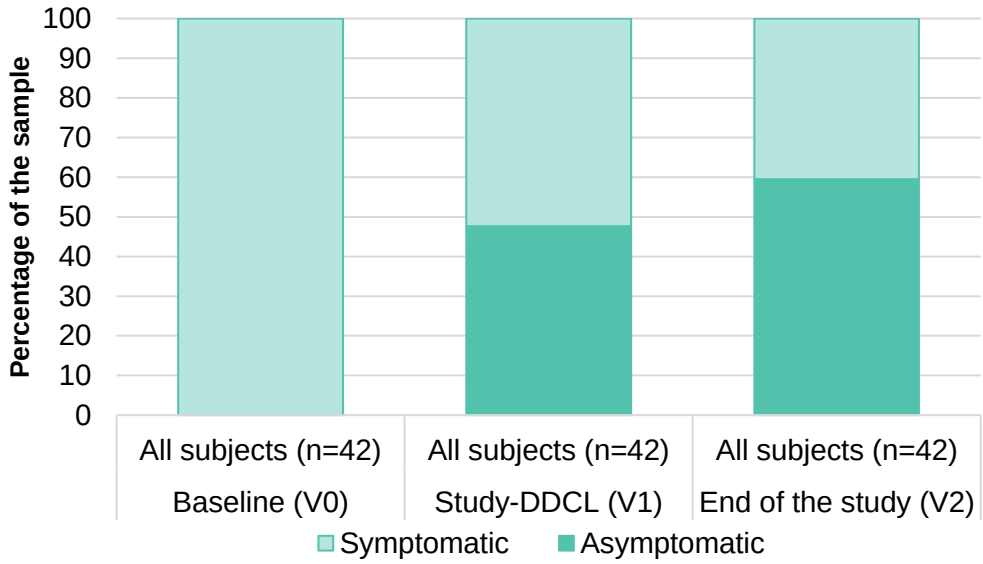


Figure 5.10. Percentage of symptomatic/asymptomatic contact lens wearers (based on the Contact Lens Dry Eye Questionnaire-8 score) after each contact lens discomfort intervention. V0/V1/V2: visit 0/1/2; Study-DDCL: daily disposable contact lens (delefilcon A).

5.4 DISCUSSION

CLD is a challenging condition, affecting the short- and long-term success of CL wear.[54] CL wearers solve these symptoms by reducing their daily wearing time or removing their CL either temporarily or permanently. However, some interventions can be used to manage the condition, such as lid hygiene, DDCL refitting and/or use of AT.[124] Several authors have proven the ability of these interventions to reduce CLD.[171,173, 228] However, literature is scarce regarding the summative effect of undergoing the most common CLD interventions consecutively, as it is performed in clinical settings.[13]

Our results showed that the sequential implementation of commonly used interventions in the clinical setting to manage CLD was effective in managing symptoms and signs. Up to 60% of subjects were finally classified as asymptomatic as measured with CLDEQ-8 and an improvement in ocular surface health after one month of study-DDCL wear was observed. In addition, we have observed that lid hygiene was an effective implementation to reduce MGD signs (Table 5.9). Around 50% of CL wearers with 1-2 level of MGD showed no further signs at the end of the study.

In this study, we used a validated questionnaire (CLDEQ-8) to evaluate CLD symptoms. Additionally, we also included the use of combined clinical scores to improve the analysis of clinical test outcomes. There is a lack of consensus in the literature regarding the possible association between symptoms and clinical observations when wearing CL.[107,111, 229] Consequently, we decided to combine the information obtained with several clinical tests creating a weighted combined clinical score. This newly-designed score could better detect the ocular surface changes observed in our sample of symptomatic CL wearers after undergoing different CLD interventions. Combined clinical scores have been used previously in other fields of the medicine such as general surgery or obstetrics and gynecology.[230,231] In addition it has been also used in the evaluation of treatment for corneal

neovascularization,[232] and to our knowledge, this is the first time that it is used for CLD research purposes. It must be taken into account that this is a statistical approach including the clinical tests evaluated in our study sample. Further research is needed to include other clinical tests that could be related to CLD (such as the presence of LWE or LIPCOF, among others), and to validate this statistical approach.

In our study, the initial seven clinical tests were grouped into two combined clinical scores based on statistical analysis using structural equation models, thus, variables were not grouped following a clinical decision process. Clinical Score 1 gathered information regarding conjunctival (limbal, bulbar and tarsal) hyperaemia and corneal staining, and Clinical Score 2 included NITBUT, LTMA and conjunctival staining data. Clinical Score 2 was able to detect clinical changes when CL users underwent the CLD interventions performed in this study. Data gathered by this Clinical Score appeared to be more precise and might help to reduce the lack of correlation between subjective and clinical tests in CL wearers. As it provides a unique score that allows a more precise way to evaluate clinical changes, overcoming limitations encountered when monitoring multiple clinical test outcomes that may have conflicting results. However, due to the nature of the sample (habitual CL wearers) and the inclusion and exclusion criteria of the study, we were not able to find higher changes in clinical signs, since participants were normal subjects without moderate nor severe ocular surface alterations (Table 5.3). Subjects with more clinical signs, such as dry eye disease patients were not included since aetiology seems to be different from CLD,[54] however subjects with dry eye disease are prone to have CLD secondary to its ocular surface disease.[54] Thus, according to the exclusion criteria, only subjects with evaporative mild dry eye (MGD levels 1 and 2) could have participated in the study.

According to a dry eye report based on a survey performed in 2018 by eye care practitioners in the USA,[130] the majority of clinicians (65%) classified most CL dry eye patients as the evaporative type. In addition, it has been previously estimated that up to 35% of symptomatic CL wearers presented MGD.[132] This study has been designed to evaluate the common interventions followed in daily clinical setting. Therefore, excluding MGD subjects could be not enough representative of the habitual clinical practice. In fact, 26.2% of our CL wearers recruited were diagnosed of mild MGD (Level 1 or 2), thus, our sample might be quite similar to the CL wearers who are consulting in the daily clinic. For this reason, the first stage in our study was to evaluate the MG and recommend lid hygiene in CL wearers with level 1 or 2 MGD. This first stage was performed to obtain a healthier ocular surface status in CL wearers with MGD prior to the baseline visit. Thus, we aimed to reduce the effect of uncontrolled ocular factors that could bias the outcomes of the other CLD interventions performed. In our study, it was observed that lid margin status improved after the lid hygiene (Table 5.9), outcomes that are similar to those reported by Guillon et al.[138] In addition, in our study it was observed that performing lid hygiene provided higher improvement in symptoms (Table 5.10). This improvement in symptoms has been also observed in the study of Paugh et al.[137] Regarding signs, in our study no change in Clinical Score 1 and esthesiometry was observed between MGD and no MGD participants. Other study found no significant differences in MG dropout between high and low corneal or conjunctival thresholds.[233] However, Golebiowski et al,[234] did found a reduced lid margin sensitivity in subjects with higher MGD score. It must be taken into account that differences between studies could be due to different study designs. Results of Clinical Score 2 showed that MGD subjects did not improve so much as no MGD participants did. This difference observed in the Clinical Score 2 could have been observed because MGD participants had a less healthy ocular surface at the beginning of the study in comparison with no MGD participants.

As indicated in the 2018 dry eye report, 52% of the practitioners would refit their CLD patients into a different CL with a more frequent replacement schedule, as the first-line recommendation in CLD management.[130] Indeed, 64% of the clinicians reported that DDCLs based on silicone hydrogel materials were the most efficacious to reduce CLD.[130] Therefore, in this study, the first intervention was to refit CL wearers with a silicone hydrogel DDCL. However, the hydrophobic nature of silicone may also lead to poor wettability, and increase the lens surface coefficient of friction, which may contribute to discomfort with silicone hydrogel CL.[46,235] For this reason, we selected delefilcon A DDCL, because it has a very low silicon content[236] that can provide similar characteristics to both conventional hydrogel and silicone hydrogel lenses.[237] Also, delefilcon A has shown to provide longer NITBUT, and greater wettability than other silicone hydrogel DDCLs,[238] resulting in longer comfortable CL wear time compared to a conventional hydrogel DDCL.[173] Similar to these results, we found a significant improvement in CL symptoms, as measured with the CLDEQ-8, for both monthly and daily CL subjects when fitted with delefilcon A during the first month. A second month with this DDCL was also assessed to evaluate if further time using delefilcon A CL could improve even more symptoms and signs. However, the results obtained during the second month did not show any further improvement, thus, one month is enough to observe changes in the status of CLD after using this CL. These findings showed that changing the CL material into this material and/or the replacement frequency is effective for CLD symptoms management independently of the previous CL. In addition, the Clinical Score 2 (composed of conjunctival staining, NIBUT, and LTMA) decreased significantly when subjects were refitted with study-DDCL (Table 5.11). Ocular surface sensitivity did not change significantly after this intervention. Recent studies investigating silicone hydrogel and disposable hydrogel lenses have shown no reduction in central corneal mechanical sensitivity.[239–241] Although ocular surface

sensitivity has been related to CL wear, the link between ocular surface sensitivity and CLD is still unclear.[242–244]

The second most recommended intervention (11%) among practitioners for CLD subjects is AT.[130] Therefore, the next stage in our study was to evaluate the use of AT in CLD. Tear substitutes were administrated to half of the subjects to evaluate the effect of study-DDCL and AT compared to the study-DDCL only. AT were administered to half of the subjects in a random order, independently of the CLDEQ-8 score to observe if the remaining symptoms could be decreased even further, as it has been showed before.[245–247] The AT selected in this study contained povidone 2%. It is a polymer that acts as a viscosity enhancer, and it can be used by CL wearers and non-wearers to alleviate dry eye symptoms.[170] The use of these preservative-free eye drops has been previously studied in CL wearers suffering from computer visual syndrome, showing a decrease of symptoms of ocular tiredness, dryness, and difficulty in focusing.[170] In contrast, our results showed no subjective (CLDEQ-8 score) or clinical (Clinical Scores 1 and 2), or corneal/conjunctival sensitivity improvements after the use of povidone 2% AT. The absence of significant changes in our study may be because symptoms after wearing the study-DDCL for only one month may not be severe enough to show an improvement in CLD with using AT. Another explanation could be that the combination of the study-DDCL with this AT was not effective enough; other AT could provide better results.

Finally, we observed that from the 42 symptomatic CL wearers initially recruited, 25 ended the study classified as asymptomatic according to the CLDEQ-8 score criteria. We demonstrated that performing these consecutive CLD interventions could result in successful CLD management in at least 60% of CL wearers. The mean reduction of the CLDEQ-8 scores in this 25-group of CL wearers classified as asymptomatic at the end of the study was noteworthy (from 21.92±3.56 to 6.60±3.40 points), taking into account that a 3-point variation is considered to be a clinically important change.[120]

Appropriate CLD management could result in lower CL wear discontinuation, and therefore, lower CL dropout rates. Around 40% of the subjects of the study remained symptomatic, however, these CL users showed a clinically important reduction (from 21.18±4.60 to 16.41±3.86 points) in their symptoms as measured with the CLDEQ-8. Therefore, the CLD interventions administered were not as effective in these CL wearers regarding symptoms.

One of the limitations of this study is that the study-DDCL fitted, the AT provided (povidone 2% preservative-free) or the order of both CLD interventions might not be the best clinical approach. Moreover, there are other factors, such as environmental factors, that have not been considered and could have affected the outcomes obtained in our study. Therefore, despite our results show evidence of effective CLD management after common interventions, they must be interpreted with caution if different DDCL and AT are recommended in the daily clinical setting. Another limitation of the present study concerns compliance. We were not able to know whether the CL wearers recruited adequately performed the lid hygiene or properly used the AT. Subjects were asked about their compliance with our instructions, and the importance of proper compliance was stressed at each visit. Finally, we were not able to mask the study-DDCL blister, therefore, subjects knew what DDCL they were fitted with. Additionally, we do not know if any of the subjective outcomes could be biased, as the improvement that subjects had when the study-DDCL was worn cannot be completely related to the CL fitted itself, factors such as the fact of changing the CL could have affected the results.

In conclusion, our study outcomes show that refitting symptomatic CL wearers with delefilcon A DDCL is an effective intervention for CLD. Additionally, performing other interventions not related to the CL itself, such as MGD management could also improve CL comfort. However, administration of AT to DDCL wearers did not appear to further improve CLD symptoms or signs.

CHAPTER 6

PLACEBO EFFECT IN CONTACT LENS DISCOMFORT MANAGEMENT

This chapter is focused on analyzing the possible placebo effect that could affect the subjective outcomes when new CL are fitted for managing CLD. The study design of this chapter is part of the main study of this thesis, explained in the Chapter 5. The methodology and experimental procedures are detailed in the Chapter 5.

This work has been published in a scientific journal: Arroyo-Del Arroyo C, Novo-Diez A, Blanco-Vázquez M, Fernández I, López-Miguel A, González-García MJ. Does Placebo Effect Exist in Contact Lens Discomfort Management? Cont Lens Anterior Eye. 2020. Doi: 10.1016/j.clae.2020.09.003. Epub ahead of print. PMID: 33071184.

6.1 BACKGROUND

The majority of the practitioners would refit their CLD patients with a different CL with a more frequent replacement schedule, being the first-line recommendation for alleviating CLD.[130]

Multiple, often co-existing, causes contribute to CLD, making it difficult to isolate the causative factor. Thus, when a new CL is fitted, it is difficult to identify the reason for comfort as a single parameter or characteristic of the CL.[124] Moreover, when a clinician provides instructions to manage CLD, the CL wearer can develop a desire to respond to the therapy, even though the CLD intervention itself might not provide any real benefit. This can be considered a placebo effect, which has been studied in dry eye disease clinical trials.[248,249] The placebo effect may be defined as an effect produced by the symbolic dimensions of treatment, beginning with a positive belief that the treatment or procedure will work and an experience of expectancy that the stimulates specific neurochemical processes.[250]

This study aimed to examine the effects of refitting monthly CL wearers who suffer from CLD with DDCLs, and to assess if a placebo effect could affect the subjective outcomes when new CLs are fitted.

6.2 MATERIALS AND METHODS

. The study was approved by the East Valladolid Health Area Ethics Committee (Valladolid, Spain) and the Research Committee if the IOBA (Appendix 4, pages 229-230) and in compliance with the Tenets of the Declaration of Helsinki. The outcomes explained in this chapter correspond to the coloured part of the study design (Figure 6.1)

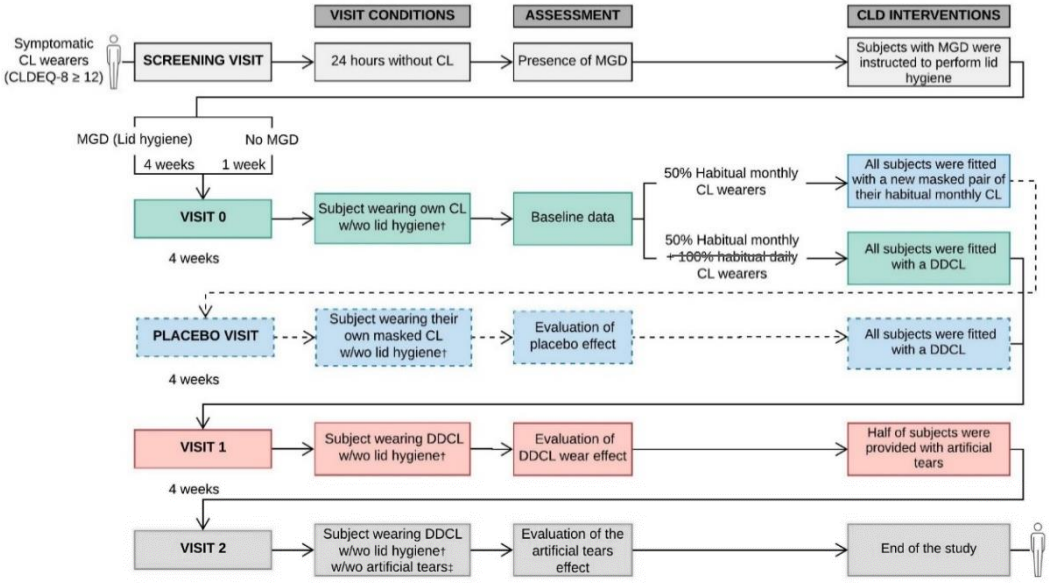


Figure 6.1 Study visits whose outcomes are presented in Chapter 6.

Coloured visits correspond to study of the placebo effect; only monthly contact lens wearers were analysed in this study. CL: contact lens; MGD: Meibomian gland dysfunction; DDCL: daily disposable contact lens; w/wo: with/without. †Participants with MGD underwent lid hygiene during the whole study. ‡After visit 2, half of the participants started using artificial tears. These participants were randomly allocated.

6.2.1 PARTICIPANTS

All participants were monthly CL wearers for at least 6 months who participated in the study described in Chapter 5 and reported CLD based on the cut-off score of the CLDEQ-8 (CLDEQ-8≥12).[120] Inclusion and exclusion criteria are described in Chapter 5.

6.2.2 STUDY VISITS

Study protocol consisted of three or four visits: screening visit for recruitment, baseline visit for refitting a CL, and one or two follow-up visits for the assessment of the CL fitted, depending on the group allocated (study or control). After eligibility was confirmed in the screening visit, monthly CL wearers were randomized to study or control group.

- **Baseline visit (V0):** Participants came to the visit after 4-6 h of their habitual CL wear. At the end of this visit, approximately half of the participants were randomly selected (study group) and given DDCLs for one month (delefilcon A, DAILIES TOTAL1; Alcon Laboratories, Inc., Fort Worth, Texas, USA), and participants were asked to change them on a daily basis. The other half of the participants (control group) were provided a new pair of their habitual monthly CLs in a CL case; however, participants were informed that these CLs were from a new brand. Participants who belonged to the control group were instructed to use them until the following visit. Participants were also instructed to clean and disinfect the CLs with the same system and follow the same routine used previously.

- **Placebo visit:** This visit was schedule four weeks after V0 for subjects who belong to control group. Subjects came to the visit wearing the habitual masked CLs provided in V0 for about 4-6 h. At the end of this visit, participants of the control group were provided with the same DDCLs given to the study group (delefilcon A) for one month and were asked to change them daily. In this visit the placebo effect was assessed in the control group.

- **Visit 1 (V1):** This visit was scheduled four weeks after V0 for the study group and four weeks after placebo visit for control group. All participants came to the visit wearing the study-DDCLs for about 4-6 h. In this visit the DDCL effect was assessed in both groups.

6.2.3 SYMPTOMS EVALUATION

At each visit, the patient's symptoms were recorded with the CLDEQ-8 (Appendix 3, page 224). In addition, to evaluate the change in comfort one month after the CL fitting, a 100-units GRCS was used (-50 meant "extremely worse", 0 meant "equal", and +50 meant "extremely better") (Figure 5.2).

6.2.4 CLINICAL EVALUATION

The tests included in the clinical evaluation (described in the section 5.2.4 Clinical Signs) were: NITBUT, bulbar, limbal and tarsal hyperemia, corneal staining, conjunctival staining and LWE.

6.2.5 STATISTIC ANALYSIS

To calculate the sample size, a Student's t-test was used for two paired samples to detect any large effect (Cohen's d = 0.7), with a power of 80% and a significance level of 0.05. Thus, at least 14 participants were necessary in each group. The data were analysed using IBM SPSS statistical software (version 24).

The percentage of change was calculated for each variable, except for the GRCS (as it already provides a relative score), to compare the magnitude of the effect of each intervention (DDCL and placebo effect). These effects were defined as relative changes between visits. The formula used to calculate the relative change for quantitative variables was the following:

$$Relative\ change\ (\%) = \frac{Final\ value - Initial\ value}{Initial\ value}\ x\ 100$$

The following formula was used for qualitative variables.[251]

If final value > initial value:

$$Relative\ change\ (\%) = \frac{Final\ value - Initial\ value}{Max\ value - Initial\ value} \times 100$$

If final value < initial value:

$$Relative\ change\ (\%) = \frac{Final\ value - Initial\ value}{Initial\ value - Min\ value} \times 100$$

If final value = initial value:

$$Relative\ change\ (\%) = 0.0$$

A Student's t-test was used to determine if the relative change differed significantly from 0 (one-sample t-test). It was also used to determine if the treatment groups showed different average changes (two independent samples t-test).

In addition, normality of the relative change was analysed using a Shapiro-Wilk test, and the correlation analysis between the relative change of CLDEQ-8, GRCS, and clinical tests was performed using a Spearman test. The correlation was classified as follows: 0.00–0.20, poor; 0.21–0.50, fair; 0.51–0.70, moderate; 0.71–0.90, very strong, and >0.90, almost perfect correlation.[252]

6.3 RESULTS

6.3.1 SUBJECTS

Thirty-one (8 male and 23 female) volunteers with a mean age of 23.2 ± 5.3 years were recruited (study group, n = 14; control group, n = 17). None of the participants used artificial tears before or during the study. The demographic data, CL characteristics, and wearing habits for both study and control groups are described in Table 6.1. No significant ($p > 0.05$) differences were found between groups regarding baseline data, except for the CL material used before recruitment ($p = 0.002$).

Table 6.1. Demographic data and characteristics of contact lens wearers of the placebo group and the study group.

Factor	Study group (n=14)	Control group (n=17)	P-value
Age (range)	24.6±6.6 years (18-40)	22.1±3.7 years (18-32)	0.20
Gender	9 (64.3%) female 5 (35.7%) male	14 (82.3%) female 3 (17.7%) male	0.27
CL wear length (years)	7.3±5.2 (range: 6 months-21 years)	5.5±3.5 (range: 6 months-15 years)	0.30
CL power (RE/LE)	-2.91±1.13 D (range -1.75D, -5.75D) -2.84±1.05 D (range -1.25D, -4.75D)	-3.21±1.43 D (range -1.25D, -5.25D) -2.89±1.58 D (range -1.00D, -6.25D)	0.53/ 0.91
CL material	10 (71.43%) hydrogel CL 4 (28.57%) silicone hydrogel CL	3 (17. 7%) hydrogel CL 14 (82.3%) silicone hydrogel CL	**0.002**
Days of CL wear per week (range)	5.4±1.5 (4-7 days)	5.7±1.4 (3-7 days)	0.60
Hours of CL wear per day (range)	7.9±2.5 (4-13 hours)	7.9±2.3 (4-14 hours)	0.96
CL symptoms (CLDEQ-8)	23.07±4.78	22.35±5.01	0.69
NITBUT (s)	9.8±2.3	11.4±4.4	0.46

Factor	Study group (n=14)	Control group (n=17)	P-value
Bulbar hyperemia (0-4)	1 [1–2]	1 [1–2]	0.61
Limbal hyperemia (0-4)	1 [1–2]	1 [1–2]	0.43
Tarsal hyperemia (0-4)	1 [0–1]	1 [1–2]	0.15
Corneal staining (0-20)	0 [0–2]	2 [1–3]	0.06
Conjunctival staining (0-4)	0 [0–1]	1 [0–2]	0.14
LWE (0-3)	0 [0–0]	0 [0–1]	0.17

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as median [interquartile range]. CL: contact lens; RE: right eye; LE: left eye; CLDEQ-8: Contact Lens Dry Eye Questionnaire 8; NITBUT: non-invasive tear break-up time; LWE: lid wiper epitheliopathy.

Participants came to the different visits with a similar number of CL wearing hours (range: 5.92-6.60), without significant (p=0.57) differences between visits. The results of the CLDEQ-8 and clinical tests for both groups during V0, placebo visit and V1 are detailed in Table 6.2.

Table 6.2 Outcomes of the Contact Lens Dry Eye Questionnaire (CLDEQ)-8 and clinical tests for both groups during V0, placebo visit and V1.

Test	STUDY GROUP (n=14)		CONTROL GROUP (n=17)		
	Habitual monthly CL (visit 0:baseline)	DDCL (visit 1: 1-month use)	Habitual monthly CL (visit 0:baseline)	Masked monthly CL (placebo visit)	DDCL (visit 1: 1-month use)
CLDEQ-8 (1-37) (mean)	23.1 ± 4.8	13.4 ± 5.5	22.4 ± 5.0	15.9 ± 5.9	10.9 ± 7.5
NITBUT (s)	9.7 ± 2.4	10.6 ± 3.0	11.4 ± 4.4	11.2 ± 5.9	13.8 ± 4.1
Bulbar hyperaemia (0-4)	1 [1–2]	2 [1–2]	1 [1–2]	2 [1–3]	2 [1–2]
Limbal hyperaemia (0-4)	1 [1–2]	1 [1–2]	1 [1–2]	1 [1–2]	2 [1–2]
Tarsal hyperaemia (0-4)	1 [0–1]	1 [0–2]	1 [1–2]	1 [1–2]	1 [1–2]
Corneal staining (0-20)	0 [0–2]	0 [0–1]	2 [1–3]	1 [0–2]	1 [0–2]
Conjunctival staining (0-4)	0 [0–1]	0 [0–1]	1 [0–2]	1 [0–2]	0 [0–1]
LWE	0 [0–0]	0 [0–0]	0 [0–1]	0 [0–0]	0 [0–0]

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as median [interquartile range]. CL: contact lens; DDCL: daily disposable contact lens; NITBUT: non-invasive tear break-up time; LWE: lid wiper epitheliopathy.

6.3.2 STUDY GROUP

DDCL wear

After one month of wearing the DDCLs (V0 vs. V1, first column, Table 6.3), CLD symptoms significantly improved in the study group as measured with the CLDEQ-8 (relative change of -39.6 ± 25.8%; $p < 0.001$) as well as with the GRCS (improvement of 31.3 ± 14.6; $p < 0.001$).

However, none of the clinical signs showed significant ($p > 0.05$) relative changes after one month of DDCL usage (Table 6.3, first column).

Table 6.3 Comparison of the DDCL wear effect and placebo effect in the control and study groups. Relative changes (%) are provided for CLDEQ-8 and clinical tests.

Tests	DDCL effect (study group)	Placebo effect (masked monthly CL) (control group)	p-Value (DDCL vs. placebo effect)	DDCL effect (control group)	p-Value (DDCL effect: study vs. control group)
CLDEQ-8	-39.6 ± 25.8*	-26.1 ± 31.0*	0.20	-26.5 ± 58.5	0.42
GRCS	31.3 ± 14.6*	14.9 ± 17.0*	**0.008**	20.5 ± 25.5*	0.17
NITBUT	12.7 ± 33.6	2.9 ± 47.17	0.52	37.9 ± 42.3*	0.08
Bulbar hyperaemia	23.8 ± 46.5	26.5 ± 40.0*	0.87	-11.8 ± 51.6	0.06
Limbal hyperaemia	-9.5 ± 39.06	21.6 ± 34.7*	**0.03**	0.0 ± 55.0	0.59
Tarsal hyperaemia	16.7 ± 45.8	-3.9 ± 53.5	0.27	3.9 ± 47.0	0.45
Corneal staining	-6.5 ± 56.8	-14.2 ± 74.5	0.75	-18.1 ± 66.0	0.61
Conjunctival staining	-1.2 ± 44.6	-5.9 ± 64.5	0.82	-47.1 ± 59.9*	**0.02**
LWE	1.8 ± 39.8	-19.1 ± 37.0*	0.14	-14.7 ± 42.4	0.28

CL: contact lens; DDCL: daily disposable contact lenses; CLDEQ-8: Contact Lens Dry Eye Questionnaire-8; NITBUT: non-invasive tear break-up time; LWE: lid wiper epitheliopathy; GRCS: global rating of change scale; GRCS values > 0 indicate less symptoms; Negative percentage values mean a decrease in the test score, and positive percentage values mean an increase in the test score; *: relative change significantly ($p \leq 0.05$) different from 0.

6.3.3 CONTROL GROUP

6.3.3.1 Masked monthly CL wear

After one month of wearing the masked monthly CLs (V0 vs. Placebo visit, second column, Table 6.3), CLD symptoms showed a significant improvement in the control group as measured with the CLDEQ-8 (-26.1±31.0%; p=0.03) and the GRCS (14.9±17.0; p=0.002). In contrast, bulbar hyperaemia and limbal hyperaemia showed significant worsening of 26.5±40.0% (p=0.02) and 21.6±34.7% (p=0.02), respectively, after wearing the masked monthly CLs. However, LWE showed a significant (p=0.049) improvement of -19.1±37.0%. The remaining clinical tests did not show significant (p>0.05) relative changes.

6.3.3.2 Study-DDCL wear

After one month of wearing the DDCLs (Placebo visit vs. V1, fourth column, Table 6.3), there was no significant (p=0.07) decrease in symptoms in the control group as measured with the CLDEQ-8; however, the GRCS was able to find a significant improvement in symptoms (20.5±25.5; p=0.02). A significant improvement in terms of relative change was observed in the NITBUT (37.9±42.3%, p=0.002) and conjunctival staining (-47.1±59.9%, p=0.005). The remaining clinical tests did not show significant (p>0.05) relative changes.

6.3.4 STUDY VS. CONTROL GROUP

Comparing the effect of both interventions (third column, Table 6.3), the CLDEQ-8 improvement in terms of relative change was not different between the DDCL and the masked monthly CL wears (p=0.20). However, the GRCS did find a significant (p=0.008) difference between the improvement observed after DDCL use (DDCL effect) and masked monthly CL use (placebo effect). Regarding the clinical signs, when comparing both interventions, only a significant (p=0.03) worsening of the limbal hyperaemia was found with the masked monthly CLs.

Comparing the DDCL effect in the study and control groups (fifth column, Table 6.3), the relative improvements in CLDEQ-8 (p=0.42) and GRCS (p=0.17) after DDCL wear were not significantly different between them. In addition, the relative improvement of the conjunctival staining in the control group was significantly (p=0.02) higher than that observed in the study group when the DDCLs were fitted. No significant (p>0.05) differences were found for the rest of the clinical variables evaluated.

Comparing the evolution of symptoms for both groups through the different visits using the CLDEQ-8 (Figure 6.2), the mean reduction at the end of the study in CLDEQ-8 outcomes did not show significant differences between the study and the control groups (9.7±7.3 vs. 11.4±6.8 points; p=0.42).

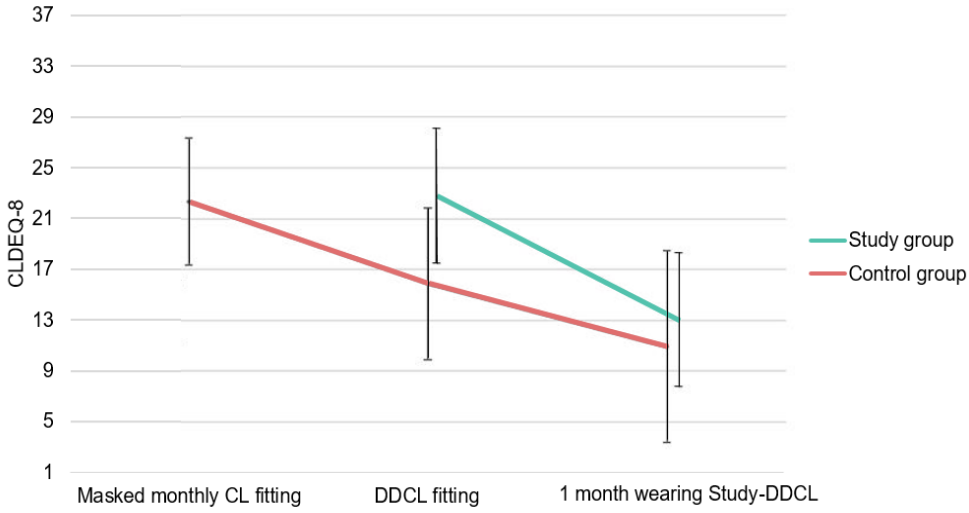


Figure 6.2. Outcomes of the CLDEQ-8 scores in study and control group during the interventions.

CLDEQ-8: Contact Lens Dry Eye Questionnaire-8; DDCL: daily disposable contact lens. DDCL fitting was performed during visit 0 in the study group and placebo visit in the control group.

6.3.5 CORRELATION BETWEEN CHANGES IN SYMPTOMS AND SIGNS

There were no significant (p>0.05) correlations between the relative changes observed in symptoms (CLDEQ-8 and GRCS) and signs, except for the one found (r=0.57, p=0.03) between the GRCS and conjunctival staining in the study group after wearing the DDCLs. The data are detailed in Tables 6.4, 6.5 and 6.6.

Table 6.4. Outcomes of the correlations between the relative change in symptoms and clinical signs for the study group (n = 14) after wearing the daily disposable contact lens.

Relative change		NITBUT	Bulbar hyperaemia	Limbal hyperaemia	Tarsal hyperaemia	Corneal staining	Conjunctival staining	LWE
CLDEQ-8	Correlation (r)	0.28	-0.10	0.26	0.09	0.41	-0.24	0.10
	p-value	0.33	0.73	0.37	0.76	0.15	0.41	0.73
GRCS	Correlation (r)	-0.18	0.02	-0.06	0.12	-0.03	0.57	0.32
	p-value	0.53	0.94	0.84	0.68	0.93	**0.03**	0.27

CLDEQ-8: Contact Lens Dry Eye Questionnaire-8; GRCS: global rating of change scale; NITBUT: non-invasive tear break-up time; LWE: lid wiper epitheliopathy.

Table 6.5. Outcomes of the correlations between the relative change in symptoms and clinical signs for the control group (n = 17) after wearing the masked monthly contact lens.

Relative change		NITBUT	Bulbar hyperaemia	Limbal hyperaemia	Tarsal hyperaemia	Corneal staining	Conjunctival staining	LWE
CLDEQ-8	Correlation (r)	0.36	-0.37	-0.15	-0.35	0.12	0.30	0.07
	p-value	0.16	0.14	0.58	0.17	0.65	0.24	0.80
GRCS	Correlation (r)	-0.34	0.38	0.20	0.36	-0.08	-0.21	0.15
	p-value	0.18	0.14	0.45	0.16	0.76	0.43	0.58

CLDEQ-8: Contact Lens Dry Eye Questionnaire-8; GRCS: global rating of change scale; NITBUT: non-invasive tear break-up time; LWE: lid wiper epitheliopathy.

Table 6.6. Outcomes of the correlations between the relative change in symptoms and clinical signs for the control group (n = 17) after wearing the daily disposable contact lens.

Relative change		NITBUT	Bulbar hyperaemia	Limbal hyperaemia	Tarsal hyperaemia	Corneal staining	Conjunctival staining	LWE
CLDEQ-8	Correlation (r)	-0.20	0.03	0.10	-0.08	-0.27	0.10	-0.09
	p-value	0.45	0.89	0.69	0.77	0.29	0.70	0.72
GRCS	Correlation (r)	-0.24	0.29	0.17	0.33	0.20	-0.46	-0.21
	p-value	0.35	0.27	0.51	0.20	0.45	0.07	0.43

CLDEQ-8: Contact Lens Dry Eye Questionnaire-8; GRCS: global rating of change scale; NITBUT: non-invasive tear break-up time; LWE: lid wiper epitheliopathy.

6.4 DISCUSSION

The results of the present study showed that refitting monthly CL wearers with DDCLs is an effective intervention for managing symptoms of CLD, according to the outcomes of the questionnaires administered. In addition, the existence of a placebo effect was detected when refitting monthly CL wearers with DDCLs.

According to the literature review, this was the first study to characterise the placebo effect in CLD interventions. However, other study designs included several arms receiving different CLD interventions, and used one of them as a control group to be compared against the others.[69,87] Therefore, the current study used a control group that was masked to the initial CLs fitted, to thoroughly analyse the effect of the most common intervention for CLD (i.e., DDCL refitting). This study was designed to observe whether changing the habitual monthly CLs as an intervention for CLD had a placebo effect. Thus, the use of new and masked pairs of the habitual CLs was considered the appropriate first intervention for the control group.

In this study, both groups (study and control) were fitted with delefilcon A DDCLs. This DDCL was selected because it has low silicon content and has greater wettability than other silicone hydrogel DDCLs,[236,237] better clinical response (longer NITBUT), and longer comfortable wearing time when compared with other DDCLs.[173,238] However, other DDCL materials could provide different results.

To assess DDCL wear and placebo effect on symptoms, two different questionnaires were used. The CLDEQ-8 is one of the most commonly used questionnaires to measure CLD.[119,121] This questionnaire is a validated instrument that can estimate CLD during the medium term (two weeks).[119] In addition, participants were assessed using GRCS as it is very commonly used in clinical research to quantify a patient's improvement or deterioration over time, because it is simple, short, easy to score, reproducible, validated, and

sensitive to change.[123] In addition, different signs were evaluated to assess the effect of both interventions from a clinical point of view. The variation in the relative change observed in CLDEQ-8 and GRCS scores was assessed after fitting the masked CLs and the DDCLs. This was necessary because the absolute score improvement that could be expected after fitting a DDCL depends on the initial CLDEQ-8 value obtained before DDCL fitting.[173] Moreover, the control group could have a lower initial CLDEQ-8 score after the masked CL fitting (placebo effect) but before the DDCL refitting, as was observed later.

This study found a significant improvement in symptoms in both questionnaires in the study group after a month of wearing the DDCLs. These results are in line with the decrease in the CLDEQ-8 score that was reported when delefilcon A CLs were refitted in habitual monthly or bi-weekly CL wearers.[173] However, none of the signs observed changed significantly in this group. When the DDCLs were assessed in the control group, the GRCS showed a significant improvement. In contrast, the CLDEQ-8 improvement did not reach significance, despite being higher than the CLDEQ-8 clinically important difference (±3 points)[120] (Table 6.3). However, it is important to note that the placebo effect before the DDCL wear in the control group had already decreased the CLDEQ-8 score. In the control group, significant improvement of NITBUT and conjunctival staining was found after DDCL wear. This is similar to previous studies that reported better NITBUT outcomes with the use of delefilcon A CLs.[235,238,253] In the case of conjunctival staining, the study group could not show improvement because the median value in the baseline visit was already 0 (Table 6.2). In addition, the well-known variability of the clinical tests must be taken into account when assessing the ocular surface signs.[97,101] The DDCL effect in terms of relative changes in CLDEQ-8 scores was similar for both groups, indicating that switching symptomatic CL wearers to delefilcon A may be helpful in reducing CLD symptoms. It was also observed that the level of comfort after a month of using this DDCL was similar

irrespective of the initial level of comfort before the DDCL was refitted (Figure 6.2, DDCL fitting). In addition, it has been studied (Chapter 5) that a second month with this DDCL did not show any further improvement in either symptoms or signs. Thus, one month should be enough to observe changes in the status of CLD after using DDCL.[254]

This study also found that the severity of symptoms within the control group decreased significantly over a month after using a masked monthly CL wear as measured with both the CLDEQ-8 (Mean: -6.5 points, Table 6.2) and GRCS (Mean: 14.9 points). These findings showed the existence of a placebo effect when refitting DDCLs to symptomatic monthly CL wearers. A significant improvement of LWE was found after wearing the masked monthly CLs; some studies have already reported an association between decreased LWE and improved CLD symptoms.[97,103] However, in this study, it could be considered clinically irrelevant because LWE score changed from 0 (interquartile range [IQR]: 0–1) to 0 (IQR: 0–0) (Table 6.2). In contrast, a significant worsening of bulbar and limbal hyperaemia was detected. However, from a clinical viewpoint, changes in the bulbar and limbal hyperaemia were also minor (Table 6.2). Both findings can be attributed to the nature of the sample recruited (habitual CL wearers) and the inclusion and exclusion criteria of the study. Relevant changes in clinical signs were not found because participants were normal subjects without moderate or severe ocular surface alterations.

In the present study, it was observed that both effects, the DDCL and placebo (masked monthly CL wear), were similar according to the CLDEQ-8 relative changes found (Table 6.3). However, the GRCS did show that the DDCL achieved better results and was more effective in managing CLD than the masked monthly CL, in terms of CL wearing symptoms. Thus, it is recommended to use not only the CLDEQ-8 but also other instruments like GRCS, to better evaluate symptoms when assessing the effectiveness of fitting new CLs.

Regarding correlations between the changes in symptoms and signs, no association was found except for the one between GRCS and conjunctival staining, solely in the study group. The absence of associations between symptoms and signs in CLD has already been reported.[54] The only association found indicated that a change to higher conjunctival staining is related to lower symptoms. This finding might be the result of the inherent variability of the clinical tests used for assessing the ocular surface signs and the low scores typically observed in normal CL wearers. Therefore, the use of questionnaires seems to be a better alternative to evaluate CLD.

Based on this study's results, it should be mandatory to control the placebo effect in clinical studies and trials assessing CLD, otherwise, outcomes could be biased. This finding is supported by the Imanaka et al. study outcomes.[249] These authors observed that, in dry eye disease patients who had previously participated in clinical trials, placebo response was more pronounced in patients with severe symptoms. Therefore, these authors indicated that the symptoms score during baseline should be considered when analysing the data and interpreting the results to avoid bias. A placebo arm is commonly used in clinical trials to assess the effectiveness of the therapy; however, a positive response to a placebo does not necessarily mean that a certain treatment does not work, but rather that another mechanism may be present. This effect works on symptoms, which are modulated by the brain, similar to pain perception. As CLD is a condition primarily diagnosed according to symptomatology, this effect should be considered when evaluating different CLD interventions. In addition, due to the variability of the scales and the difficulty in measuring subjective outcomes, the use of different instruments will allow clinicians and researchers to properly assess the effect of the interventions on comfort.

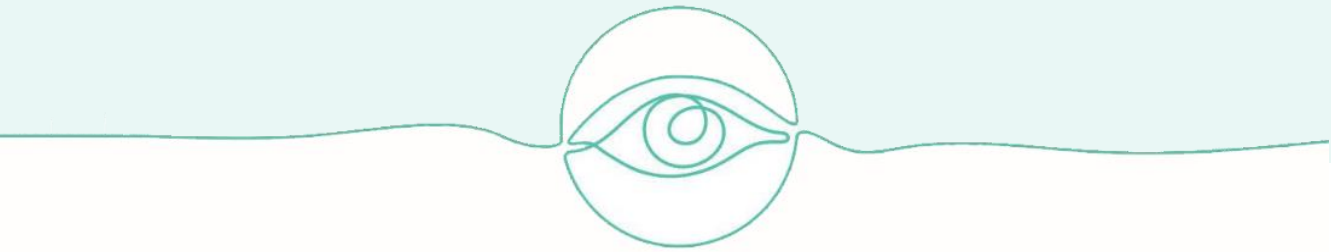
The results from this study highlight the existence of a placebo effect in the management of CLD; however, the findings are not without limitations.

One limitation of this study is the difference in the current CL material that volunteers of each group used before being recruited. The control group mainly used silicone hydrogel CLs (82.3%), whereas, in the study group, only 28.57% of the participants were silicone hydrogel CL wearers. Thus, when the DDCL participants of the study group were refitted, not only the frequency of replacement was changed, but also the type of material. This could result in better outcomes in the study group than in the control group in terms of the DDCL effect. However, switching wearers from hydrogels to silicone hydrogel may not necessarily help to reduce CLD.[39] In addition, although the participants were younger compared to the average age of CL wearers,[7] in general, sample characteristics during the screening visit were considered appropriate, as there were no differences in age, gender, CL wear habits, CL comfort and clinical signs between groups. Further studies with larger sample sizes are needed to confirm these findings.

In conclusion, outcomes from the present study showed that refitting symptomatic monthly CL wearers with DDCLs (delefilcon A) is an effective intervention for reducing symptoms related to CLD. In addition, the results also showed that clinicians and researchers must consider that there is a placebo effect when assessing the subjective effectiveness of DDCL refitting.

CHAPTER 7

CONCLUSIONS



This chapter includes the conclusions achieved in the present doctoral thesis. The following **conclusions** were achieved:

The general conclusion of the thesis is that the use of adequate subjective and objective instruments is crucial for detecting and evaluating contact lens discomfort properly. However, owing to its nature, the use of subjective instruments allows a better evaluation and monitoring of the condition after implementing different management strategies.

Conclusion 1: the Contact Lens Discomfort Index (CLDI) questionnaire is a well-structured and reliable instrument that is able to detect contact lens discomfort based on the currently established definition. The English translation of the CLDI has acceptable psychometric properties, however, a review of some items should be done to ensure a better design.

Conclusion 2: the combined clinical score designed in this study is a precise instrument able to detect changes in the ocular surface of symptomatic contact lens wearers. It is the result of gathering several clinical tests, overcoming limitations encountered when looking at the outcomes of several clinical test that may lead to inconsistent conclusions.

Conclusion 3: refitting symptomatic contact lens wearers with delefilcon A contact lenses was the most effective intervention evaluated in this study for improving symptoms as well as signs. Implementing lid hygiene in symptomatic wearers with Meibomian gland dysfunction helped to ameliorate contact lens discomfort symptoms and signs associated with the Meibomian gland dysfunction. On the other hand, the administration of the study-artificial tears did not appear to further improve symptoms or signs of contact lens discomfort.

Conclusion 4: the presence of a placebo effect when monitoring symptoms after refitting a contact lens for contact lens discomfort management, must be always taken into account when assessing its effectiveness. Otherwise, outcomes can mislead decision-making processes in clinical and research scenarios.

CAPÍTULO 8

RESUMEN

La presente tesis se ha realizado en el Instituto de Oftalmobiología Aplicada (IOBA) de la Universidad de Valladolid (Valladolid, España) y ha sido dirigida por la Dra. María Jesús González García y el Dr. Alberto López Miguel. Así también, opta a la mención internacional tras haber realizado una estancia de tres meses en la Glasgow Caledonian University bajo la supervisión de la Dra. Suzanne Hagan.

Este apartado presenta un resumen en español de la tesis doctoral, cumpliendo así con los requisitos establecidos por la Universidad de Valladolid para la defensa de la tesis con mención internacional.

1. INTRODUCCIÓN

Se estima que, aproximadamente, el 50% de los usuarios de lentes de contacto (LC) sufre con cierta frecuencia síntomas de incomodidad con sus LC.[1] Este problema se denomina incomodidad con LC (ILC). Además, esta condición es la primera causa de abandono del uso de LC.[36,55,80] La etiología de la ILC es aún desconocida, lo que la hace una condición difícil de detectar y de manejar. Por tanto, la ILC supone un importante impacto tanto para fabricantes, como para los clínicos y los propios usuarios.[1] La sociedad *Tear Film and Ocular Surface* (TFOS) definió esta condición como "una afección caracterizada por sensaciones oculares adversas, episódicas o persistentes, relacionadas con el uso de LC, ya sea con o sin alteración de la visión, resultado de la reducción de compatibilidad entre la LC y el entorno ocular, que puede llevar a la disminución del tiempo de uso y al abandono del uso de lentes de contacto".[32] También se definieron los factores asociados a la ILC, como los factores asociados a la propia LC (material, diseño, cuidado, etc.) o aquellos asociados al ambiente (características del usuario o de sus propiedades oculares o el ambiente que le rodea).[32]

Esta condición se detecta principalmente mediante la medida de los síntomas, debido a la ausencia de correlación entre síntomas y signos.[1,108] Los cuestionarios son instrumentos comunes que se han considerado apropiados para la medida y diagnóstico de síntomas de sequedad ocular. Varios estudios han utilizado cuestionarios para evaluar la ILC, aunque fueron originalmente diseñados para diagnosticar ojo seco, como son el *Ocular Surface Disease Index* (OSDI)[113] o el cuestionario McMonnies.[115] Sin embargo, el cuestionario más utilizado es el *Contact Lens Dry Eye Questionnaire* (CLDEQ),[83] creado específicamente para usuarios de LC. Este cuestionario cuenta con una versión de 8 preguntas (CLDEQ-8) y un punto de corte que discierne entre usuarios sintomáticos o asintomáticos.[119,120] No obstante, el CLDEQ-8 no contempla alguna de las características de la ILC

establecidas en el Workshop sobre incomodidad con lentes de contacto elaborado por la TFOS en el 2013.

El manejo de la ILC puede ser un desafío en la práctica clínica habitual, debido a que puede ser una condición episódica, con síntomas variables y que desaparecen con la retirada de las LC. Algunas de las intervenciones más comunes, aunque no necesariamente definitivas, incluyen el cambio de la LC (cambio del material y/o de la frecuencia de reemplazo), el cambio de los sistemas de limpieza y mantenimiento, el uso de lágrimas artificiales o, en última instancia, la retirada de las LC.[124] Sin embargo, antes de atribuir los síntomas de la ILC a los factores asociados a la propia LC, deben tratarse primero las alteraciones coexistentes de la superficie ocular que puedan estar influyendo, como puede ser la presencia de disfunción de las glándulas de Meibomio (DGM).[124] El tratamiento más común para estos usuarios es la realización de higiene de párpados. [134,135]

Con respecto a los factores propios de la LC, la intervención más común es la readaptación a una LC con mejores propiedades del material o con una mayor frecuencia de reemplazo.[130,160] En concreto, la adaptación de LC desechables diarias (LCDD) es la primera intervención más recomendada para mejorar la ILC, mostrando mejor humectabilidad, mayor comodidad y mejor comportamiento en la superficie ocular que otras LC.[130] Además, el uso de lubricantes oculares o lágrimas artificiales también ha mostrado buenos resultados en el manejo de la ILC,[83] siendo esta intervención la segunda más recomendada entre los profesionales.[130]

A fin de profundizar en este tema, esta tesis se ha dirigido a la creación de un cuestionario para la detección de la ILC, así como la evaluación de la aplicación consecutiva de las diferentes intervenciones para manejar la ILC y al estudio de un posible efecto placebo cuando se aplica un cambio en la adaptación de LC.

2. HIPÓTESIS Y OBJETIVOS

2.1 HIPÓTESIS

La hipótesis de esta tesis es que el diagnóstico y manejo de la incomodidad con lentes de contacto puede mejorar mediante el diseño de instrumentos subjetivos y objetivos basados en el conocimiento que se ha ido desarrollando durante los últimos años.

2.2. OBJETIVOS

El objetivo principal de esta tesis fue estudiar el diagnóstico y el manejo de la incomodidad con lentes de contacto mediante el uso de instrumentos tanto subjetivos como objetivos. Se han establecido los siguientes objetivos con el fin de diseñar y desarrollar un instrumento subjetivo (cuestionario) y otro objetivo (índice clínico ponderado) que permitan la detección de la incomodidad con lentes de contacto y la evaluación de cambios en la superficie ocular en sujetos que la sufren.

Objetivo 1: crear un nuevo cuestionario específicamente diseñado para usuarios de lentes de contacto capaz de detectar la incomodidad con lentes de contacto de acuerdo la definición actualmente establecida.

Objetivo 2: diseñar un índice clínico ponderado capaz de analizar mejor los cambios producidos en los signos clínicos observados tras el manejo de la incomodidad con lentes de contacto, evitando el análisis de múltiples puntuaciones de diferentes pruebas clínicas.

Objetivo 3: analizar la variación de los síntomas y signos tras la implementación consecutiva de las diferentes intervenciones para el manejo de la incomodidad con lentes de contacto (higiene de párpados, readaptación de lentes de contacto desechables diarias y el uso de lágrimas artificiales).

Objetivo 4: estudiar la existencia del efecto placebo en el manejo de la incomodidad con lentes de contacto.

3. DISEÑO Y CREACIÓN DE UN CUESTIONARIO PARA LA DETECCIÓN DE LA INCOMODIDAD CON LENTES DE CONTACTO

3.1 JUSTIFICACIÓN

Aunque el cuestionario CLDEQ-8 ha sido considerado el mejor instrumento validado para la evaluación de la ILC, algunos factores asociados a esta condición, como el entorno ocular o el tiempo de uso de las LC no se recogen en este cuestionario. Consecuentemente, en este estudio se ha diseñado y creado un cuestionario para detectar la ILC basado en su actual definición. Además, en esta tesis también se ha llevado a cabo la traducción de este cuestionario en inglés para una mayor difusión y uso del mismo.

Este estudio incluye dos proyectos, uno llevado a cabo en el IOBA de la Universidad de Valladolid, donde se diseñó y creó el cuestionario desarrollado; y otro llevado a cabo en la Glasgow Caledonian University, donde se realizó la traducción y análisis del cuestionario en inglés.

PARTE I: DESARROLLO DEL CUESTIONARIO CONTACT LENS DISCOMFORT INDEX (CLDI)

3.2 MATERIALES Y MÉTODOS

3.2.1 Diseño de la encuesta

En primer lugar, se diseñó y administró una encuesta para caracterizar a los usuarios de LC y estudiar los principales factores que podían afectar a la ILC. Para ello, se tuvieron en cuenta las opiniones y experiencias de usuarios de LC y de optometristas con experiencia clínica en la adaptación de LC; así mismo se revisó la literatura científica para elegir las preguntas que conformaron el primer borrador de la encuesta.

Se realizó un estudio piloto donde los usuarios de LC participaron de forma voluntaria rellenando la encuesta dos veces en un periodo de 15 días

en una plataforma online. Al final, se les invitó a comentar cualquier aspecto referido a la dificultad para completar la encuesta. Se evaluaron los comentarios y se implementaron las mejoras para obtener la versión definitiva de la encuesta. Se analizaron las respuestas de ambas rondas mediante el test Chi-cuadrado y el test de Wilcoxon.

La versión definitiva de la encuesta se envió a la comunidad universitaria de la Universidad de Valladolid (trabajadores y estudiantes) mediante un e-mail masivo con el enlace a la plataforma online donde se dispuso la encuesta.

3.2.2 Cuestionario para evaluar la incomodidad con lentes de contacto

Las respuestas obtenidas de la encuesta fueron la base para definir la variable latente de interés (ILC).

a) Primero se redujo el número de preguntas determinando qué preguntas de la encuesta permitían medir y detectar la ILC de forma más precisa. Para ello se tuvo en cuenta la definición y características determinadas en el *Workshop* del TFOS en 2013.[32] Las respuestas a estas preguntas se ordenaron en categorías, asignando valores bajos a respuestas menos asociadas con la presencia de ILC y valores más altos a respuestas más asociadas con la ILC.
b) El cuestionario se analizó mediante la teoría de respuesta al ítem, que expresa la asociación entre una respuesta a un ítem o pregunta y una variable latente. En concreto se utilizó el análisis de Rasch,[182] que permitió medir esta variable latente a partir de las puntuaciones obtenidas de cada sujeto. Este análisis permite la eliminación o modificación de las preguntas según la relación entre las respuestas de los sujetos y el nivel de ILC que el sujeto presenta, comprobando que los sujetos con mayor ILC tuvieran más posibilidad de seleccionar respuestas con puntuaciones más altas. Para comprobar la dificultad de cada pregunta se estiman los estadísticos *infit* y *outfit*, los cuales deben estar entre los valores 0,7 y

1,3.[184] Como medida global del ajuste del modelo se utilizó el test de Andersen. Además, para comprobar la asunción de que únicamente había una dimensión (una sola variable latente a medir) se hizo un análisis de componentes principales con los residuos del modelo. Preguntas con autovalores >2 fueron considerados como evidencia de multidimensionalidad. Tras este proceso se obtuvo el cuestionario final con las preguntas ajustadas al modelo.

c) Para definir una puntuación capaz de clasificar a los usuarios entre sintomáticos (con ILC) o asintomáticos (sin ILC) se creó una escala continua de puntuación, obtenida a través de la suma de puntuaciones de cada pregunta. Primero se realizó un análisis *cluster* no supervisado en el que se calculó la distancia entre los individuos (medida de similitud entre los sujetos), se eligió un algoritmo de agrupación (cuántos individuos son representativos de cada grupo) y se seleccionó el número de grupos a considerar. Para ello se utilizó la distancia de Gower, el algoritmo *k-medoids* y el ancho de silueta, respectivamente.[186-188]

d) Por último, se analizó la repetibilidad del cuestionario, administrándolo a una muestra de usuarios de LC dos veces en un periodo de 10 días. Los tests realizados para ello fueron el coeficiente de correlación intraclase (CCI) y la k de Cohen (k). Se consideró como apropiado un CCI mayor de 0,70 y un k mayor a 0,61.[190,191]

3.2.3 Administración del cuestionario

Se desarrolló un estudio con el fin de administrar el cuestionario desarrollado junto con el CLDEQ-8 en una muestra de usuarios de LC. Se comparó la cantidad de sujetos clasificados como sintomáticos o asintomáticos según ambos cuestionarios. Se analizaron más profundamente las respuestas de los sujetos clasificados de forma diferente por cada cuestionario.

3.3 RESULTADOS

3.3.1 Encuesta

La encuesta creada para caracterizar a los usuarios de LC consistió en 31 preguntas, incluyendo preguntas demográficas, asociadas a factores que influyen en la ILC, relacionadas con el tipo de LC, hábitos de uso y síntomas con las LC. El pilotaje de la encuesta se realizó a 25 sujetos y tras su análisis, 8 preguntas fueron modificadas, añadiendo alguna respuesta o aclaración.

La versión definitiva de la encuesta (la versión en inglés se incluye en el Capítulo 4, páginas 105-109) se envió a través de un correo electrónico a toda la población de la Universidad de Valladolid y fue respondida por 1104 usuarios de LC (746 mujeres y 358 hombres con una media de 27,2±10,4 años).

3.3.2 Cuestionario CLDI

Se seleccionaron 10 preguntas y, tras el análisis de Rasch, 9 preguntas conformaron el cuestionario que se denominó Contact Lens Discomfort Index (CLDI) (la versión en inglés y en español se encuentra en las Figuras 4.3 and 4.4, respectivamente). El análisis de componentes principales mostró unidimensionalidad del cuestionario.

La puntuación total (A) consistió en la suma de las puntuaciones de cada pregunta (rango: 0-18). El ancho de silueta mostró que el número de clusters o grupos fue dos, uno con puntuaciones ≤5, conformando el grupo de sujetos con menos síntomas (asintomáticos) y otro con puntuaciones ≥11, conformando el grupo con más síntomas (sintomáticos). Estas puntuaciones ya corresponderían con la puntuación definitiva (C). Sin embargo, hubo 564 sujetos que no se asociaban adecuadamente a ningún grupo (puntuaciones entre 6 y 10) y fueron evaluados más profundamente utilizando una subescala (B) con las preguntas 4, 7 (opciones picor, mala visión y ojos rojos) y 9. Si sumando las puntuaciones de esta subescala se obtenía un valor menor o

igual a 2 (B≤2), había que restar el número de preguntas de esta sub-escala B, cuyo valor era “0” a la puntuación total (A) para obtener la puntuación definitiva (C). Si la puntuación de la sub-escala B era mayor a 2 (B>2), había que sumar la puntuación de la sub-escala B a la puntuación total (A) para obtener la puntuación definitiva (C). Finalmente, si la puntuación definitiva era mayor que 8 (C>8), el sujeto era clasificado como un usuario de LC sintomático, y si era menor o igual que 8 (C≤8) como usuario de LC asintomático.

Treinta y un sujetos participaron en el estudio de la repetibilidad del cuestionario. Se obtuvo un CCI de 0,88 (95% intervalo de confianza (IC), 0.75–0,94), y k fue 0.67 (95% IC, 0,41-0,93).

3.3.3 Administración y comparación del cuestionario CLDI

Se administraron los cuestionarios CLDEQ-8 (Anexo 3) y CLDI a 58 usuarios de LC. El 70,7% (Intervalo de confianza (IC) del 95%: 57,1%, 81,5%) de la muestra fue igualmente clasificada por ambos cuestionarios, sin embargo, hubo 17 sujetos (29,3%, IC 95%: 57,1%, 81,5%) que fueron clasificados como sintomáticos según el CLDEQ-8, pero como asintomáticos por el CLDI (tabla 8.1).

Tabla 8.1 Distribución de la muestra acorde a la clasificación de los cuestionarios Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8) y Contact Lens Discomfort Index (CLDI)

	CLDEQ-8: Asintomáticos	CLDEQ-8: Sintomáticos	Total
CLDI: Asintomáticos	16	17	33
CLDI: Sintomáticos	0	25	25
Total	16	42	58

Tras analizar más profundamente las respuestas del CLDI en estos 17 sujetos (grupo A) y comparándolos con los 25 sujetos clasificados sintomáticos por ambos cuestionarios (grupo B) se vieron diferencias significativas en algunas preguntas (tabla 8.2).

Tabla 8.2 Comparación de las respuestas de algunas preguntas del CLDI que difirieron entre sujetos diferentemente clasificados por el CLDI y el CLDEQ-8.

Preguntas CLDI	Grupo A (Si, %)	Grupo B (Si, %)	P-valor
2. Uso mis LC tanto como deseo o necesito	82,3	48,0	**0,05**
4.2 Tengo problemas cuando uso dispositivos electrónicos	47,1	88,0	**0,01**
7.3. Me pican los ojos con y sin las LC	23,5	60,0	**0,04**
9. Estoy satisfecho/a con las LC	35,3	0,0	**0,01**

CLDI: contact lens discomfort index; CLDEQ-8: contact lens dry eye questionnaire 8; LC: lentes de contacto.

PARTE II: TRADUCCIÓN AL INGLÉS DEL CLDI

3.4 MATERIALES Y MÉTODOS

Para la traducción del cuestionario se siguió el método de traducción directa e inversa.[176,192] En primer lugar, el cuestionario fue traducido y adaptado al inglés por dos optometristas bilingües nativos ingleses, familiarizados con las ciencias de la visión. El resultado de ambas traducciones lo evaluó el equipo de personas que lo creó y eligió la versión más adecuada. Posteriormente, el cuestionario en inglés fue traducido de nuevo al español por dos optometristas bilingües nativos españoles que desconocían la versión original del cuestionario. Por último, el mismo equipo aseguró que esta última traducción era equivalente a la original.

La versión en inglés del cuestionario se envió mediante una plataforma *online* a estudiantes o trabajadores de la Glasgow Caledonian University, así como pacientes que acudían a la clínica de dicha universidad.

a) Se realizó una correlación entre las diferentes preguntas para identificar aquellas que pudieran resultar confusas. Se consideró mala correlación entre preguntas aquella que fuera menor a 0,4.[193] Así mismo se comprobó la correlación entre cada pregunta y la puntuación del cuestionario obtenida, en este paso el umbral se estableció en 0,3.
b) La fiabilidad del cuestionario se determinó con el alpha de Cronbach, que describe en qué medida las respuestas altas de una pregunta se correlacionan con las respuestas altas del resto de preguntas.
c) Para explicar las correlaciones entre el conjunto de las variables medidas a través de un conjunto reducido de variables latentes se realizó un análisis factorial confirmatorio.
d) Las propiedades psicométricas del cuestionario se evaluaron mediante un análisis de Rasch.[197] Se definió si las categorías de las respuestas eran adecuadas, la precisión de la medición, la unidimensionalidad y el ajuste al modelo del cuestionario. Este análisis fue similar al realizado para la versión en español del cuestionario.
e) Se realizó, de igual manera, la repetibilidad del cuestionario mediante el CCI y el k de Cohen.

3.5 RESULTADOS

El cuestionario CLDI se tradujo (Figura 4.3) y analizó en una muestra de 164 usuarios de LC (130 mujeres y 34 hombres con una media de 34,21±12,92 años). Las características demográficas y de uso de LC de la muestra inglesa difirieron significativamente de la muestra española original de creación del cuestionario.

Las preguntas del cuestionario en general se correlacionaron bien, salvo las preguntas 5, 6 y 7 (respuestas ojos rojos, ojos llorosos y mala visión). Especialmente, esta última pregunta también mostró una mala correlación con la puntuación total del cuestionario. El coeficiente alpha de Cronbach fue de 0,763 (IC 95%: 0,711-0,8) y el análisis factorial confirmatorio mostró que las cargas factoriales de todas las preguntas fueron altas, salvo las relacionadas con los síntomas ojos rojos, llorosos y la mala visión, aunque todas fueron estadísticamente distintas de 0. El análisis de Rasch fue satisfactorio para todas las preguntas, excepto el síntoma mala visión que no se ajustaba bien al modelo.

En el estudio de repetibilidad participaron 48 sujetos y se obtuvo un CCI de 0,84 (IC 95%: 0,73-0,91) y k fue 0,62 (IC 95%, 0,41-0,93).

4. EVALUACIÓN DE LAS INTERVENCIONES MÁS COMUNES PARA EL MANEJO DE LA INCOMODIDAD CON LENTES DE CONTACTO

4.1 JUSTIFICACIÓN

Numerosos estudios han evaluado previamente diferentes intervenciones para el manejo de la ILC, como el tratamiento de la DGM, la readaptación a una LCDD o el uso de lágrimas artificiales.[43,203,204] Sin embargo, estas intervenciones se han evaluado de forma individual, pero no en su conjunto y de forma consecutiva, como se aplican normalmente en la práctica clínica habitual. Por ello, el objetivo de este estudio fue evaluar el efecto de la implementación consecutiva de estas 3 intervenciones, tanto en síntomas como en signos, en usuarios de LC que presenten ILC.

4.2 MATERIALES Y MÉTODOS

El proyecto llevado a cabo en el IOBA incluyó 42 usuarios habituales de LC hidrofílicas que sufrían ILC según el criterio del cuestionario CLDEQ-

8.[120] Los sujetos fueron excluidos si padecían ojo seco o cualquier otra patología que contraindicara el uso de LC o un grado ≥3 de DGM.[206,207]

4.2.1 Visitas de estudio

Todos los participantes acudieron a una visita de inclusión, una visita basal y a 2 o 3 visitas de seguimiento según el grupo donde fueran incluidos (estudio vs control).

- **Visita de inclusión**: los sujetos acudieron sin haber usado las LC al menos durante 24 horas. Se comprobó que cumplieran los criterios de inclusión y exclusión. A los sujetos diagnosticados con grados 1 o 2 de DGM se les instruyó para realizar higiene de párpados.
- **Visita basal (V0):** se evaluó a los sujetos con sus LC habituales puestas. A todos los usuarios de LCDD y a la mitad de los usuarios de LC mensuales (grupo de estudio) se les adaptó las LCDD del estudio (delefilcon A). Como grupo control y para evaluar el efecto placebo, a la otra mitad de los usuarios de LC mensuales se les adaptó su misma LC mensual enmascarada, aunque a los sujetos se les indicó que era una LC diferente.
- **Visita placebo:** al grupo control se le evaluó tras un mes de uso de la LC habitual mensual enmascarada y, posteriormente, se les adaptó la LCDD del estudio.
- **Visita 1 (V1):** a todos los sujetos se les evaluó tras un mes de uso de la LCDD. Posteriormente, se les proporcionó otro mes de uso de las mismas LCDD y, además, de forma aleatoria, a la mitad de la muestra se les pautó el uso de lágrimas artificiales (Filmabak, Povidona 2%, Thea).
- **Visita 2 (V2):** a todos los sujetos se les evaluó tras un mes de V1 y finalizaron el estudio.

4.2.2 Evaluación clínica

En estas visitas se evaluó el confort ocular mediante el CLDEQ-8 (Anexo 3)[119] y una escala relativa de 100 puntos (-50 significa extremadamente peor y +50 extremadamente mejor) (Figura 5.2).[123] Además, se realizaron una serie de pruebas clínicas: medida del área del menisco lagrimal, tiempo de ruptura lagrimal no invasivo (NIBUT por sus siglas en inglés, non-invasive tear break-up time), hiperemias bulbar y limbar, tinción corneal y conjuntival con fluoresceína, epiteliopatía en parabrisas (LWE por sus siglas en inglés, Lid Wiper Epitheliopaty), y sensibilidad corneal y conjuntival. Además, se les evaluó la calidad y expresión de las glándulas de Meibomio, así como el área de pérdida usando la Meiboscale.

4.2.3 Análisis estadístico

Para el análisis de la evaluación subjetiva (CLDEQ-8) y clínica se realizó un modelo lineal mixto. Para el análisis de los signos de las glándulas de Meibomio se utilizó el test pareado de Wilcoxon.

Desarrollo del índice clínico ponderado: para analizar de forma conjunta las diversas variables clínicas se creó un índice clínico ponderado que aunara las puntuaciones de todas ellas en dos escalas sencillas mediante modelos de ecuaciones estructurales. Para ello, siguiendo un criterio estadístico, se agruparon las variables hiperemia bulbar, limbar y tarsal y tinción corneal que conformaron el índice clínico 1; y el menisco lagrimal, NIBUT y tinción conjuntival, que conformaron el índice clínico 2. Ambos índices clínicos puntuaban de 0-100, donde puntuaciones bajas significaban un mejor estado de la superficie ocular y puntuaciones altas un peor estado de la superficie ocular. El LWE no fue incluido en el índice clínico debido a que esta prueba no se realizó en la visita de inclusión usada para su creación. Tampoco se incluyó la estesiometría en el índice clínico debido a no ser una prueba del todo objetiva, ya que depende de la respuesta del participante.

4.3 RESULTADOS

De los 42 sujetos que participaron en el estudio (31 mujeres, 11 hombres con una media de 23,2±4,9 años), 11 fueron diagnosticados con nivel 1 o 2 de DGM y realizaron higiene de párpados durante todo el estudio. Además, 11 eran usuarios habituales de LCDD y 31 de LC mensuales.

4.3.1 Efecto de la higiene de párpados

Los sujetos con DGM mostraron una mejoría significativa tanto en los signos del borde palpebral (p=0,009) como en la calidad de la secreción lipídica (p=0.007) tras 4 semanas de higiene de párpados y a lo largo del estudio. No hubo diferencias en el área de pérdida de glándulas de Meibomio tras la higiene de párpados. Al final del estudio, solo 4 sujetos seguían teniendo DGM (2 con grado 1 y 2 con grado 2).

Con respecto al CLDEQ-8, se observó que aquellos sujetos que realizaron la higiene de párpados tenían menos síntomas con las LC (2,74 puntos menos en el CLDEQ-8) de forma significativa (p=0,01) con respecto a los que no siguieron esta higiene. Así mismo, no se observaron diferencias en el índice clínico 1, sin embargo, el índice clínico 2 estaba 1,25 veces más elevado significativamente (p=0,04) en estos sujetos. No hubo diferencias en la estesiometría en estos sujetos.

4.3.2 Efecto del uso de la LCDD del estudio

Se observó una disminución significativa (p<0,0001) de 10,12 puntos en el CLDEQ-8 tras el primer mes de uso de las LCDD del estudio (V1). Sin embargo, no hubo diferencias en el CLDEQ-8 ni tras el segundo mes de uso de estas LCDD (V2), ni entre los sujetos que eran usuarios habituales de LC mensuales y los usuarios de LCDD.

El índice clínico 1 no mostró diferencias en ningún caso, mientras que el índice clínico 2 disminuyó de forma significativa (p=0,04) 1,35 veces tras

un mes de uso de la LCDD del estudio (V1). La estesiometría tampoco mostró ninguna diferencia tras las visitas o los grupos evaluados.

4.3.3 Efecto del uso de lágrimas artificiales

No se encontró ninguna diferencia significativa tras el uso pautado de lágrimas artificiales ni en el CLDEQ-8, ni en los índices clínicos o en la estesiometría.

4.3.4 Clasificación de los usuarios de LC según el CLDEQ-8

De acuerdo a la clasificación del CLDEQ-8 entre usuarios sintomáticos y asintomáticos, de los 42 sujetos que comenzaron siendo sintomáticos, 20 pasaron a ser asintomáticos tras el primer mes de uso de las LCDD del estudio y 5 más tras el uso de lágrimas artificiales. La puntuación del CLDEQ-8 de estos 25 sujetos disminuyó una media de 15,32 puntos ($p<0,001$). Respecto de los 17 sujetos que permanecían siendo sintomáticos, su puntuación también disminuyó significativamente ($p<0,001$) 4,77 puntos de media.

5. EFECTO PLACEBO EN EL MANEJO DE LA INCOMODIDAD CON LENTES DE CONTACTO

5.1 JUSTIFICACIÓN

La intervención más común para el manejo de la ILC es la readaptación a una LCDD,[130] sin embargo, son muchos los factores que intervienen en hacer que esta intervención resulte exitosa.[124] Entre ellos, el deseo del propio usuario de sentirse más cómodo con esa LC. Por ello, el control del efecto placebo en este tipo de intervenciones debería tenerse en cuenta a la hora de medir sus resultados. De hecho, el efecto placebo ya ha sido probado en ensayos clínicos sobre la enfermedad de ojo seco.[248,249]

Por este motivo, uno de los objetivos de este estudio fue evaluar el efecto de la readaptación de una LCDD sobre la ILC y determinar si existe un efecto placebo cuando se aplica esta intervención.

5.2 MATERIALES Y MÉTODOS

Se incluyeron en esta parte del estudio los 31 usuarios habituales de LC mensuales y se analizaron los datos del CLDEQ-8 (Anexo 3) y la escala relativa -50/+50 (Figura 5.2), así como la hiperemia bulbar, limbar y tarsal, el NIBUT, la tinción corneal y conjuntival y el LWE en las visitas V0, visita de placebo y V1 (metodología detallada en el apartado 4.2). Los sujetos fueron divididos, de forma aleatoria, en un grupo de estudio, al cual se les readaptó la LCDD del estudio (delefilcon A) y un grupo control, al cual se les adaptó primero la misma LC mensual de forma enmascarada y, después la LCDD del estudio.

5.2.1 Análisis estadístico

Para la comparación entre visitas y grupos de la magnitud del efecto de cada intervención se calculó el cambio relativo para todas las variables, excepto para la escala relativa, que ya proporciona información de cambio. Para comprobar si este cambio relativo era significativamente distinto de 0 se usó el test t-Student de una muestra y para comprobar si había diferencias entre grupos se usó el test t-Student para muestras independientes. Además, se analizó la correlación entre los cambios de signos y síntomas mediante el test de Spearman.

5.3 RESULTADOS

El grupo de estudio se compuso de 14 usuarios de LC y el grupo control de 17 usuarios. No hubo diferencias significativas ni en sexo, edad, hábitos de uso de las LC, síntomas con sus LC ni en los signos clínicos entre ambos grupos, estudio y control.

5.3.1 Grupo de estudio

Tras un mes de uso de la LCDD del estudio, los síntomas medidos con ambos cuestionarios disminuyeron de forma significativa (CLDEQ-8: -39,6±25.8%, p<0,001; Escala relativa: mejoría de 31,28±14,59 puntos; p<0,001). No hubo cambios en los signos clínicos.

5.3.2 Grupo control

Tras un mes usando la misma LC mensual enmascarada, los síntomas medidos con ambos cuestionarios disminuyeron de forma significativa (CLDEQ-8: -26,1±31.0%, p=0,03; escala relativa: mejoría de 14,94±16,95; p=0,002). Por otro lado, hubo un empeoramiento significativo de la hiperemia bulbar y limbar de 26,5±40.0% (p=0,02) y de 21,6±34.7% (p=0,02), respectivamente; y una mejora significativa del LWE (-19,1±37.0%, p=0,049).

Tras el siguiente mes usando la LCDD del estudio, los síntomas mejoraron según ambos cuestionarios (CLDEQ-8: -26,5±58,5%; p=0,07; escala relativa: mejoría de 20,53±25,46; p=0,02). También se observó una mejora significativa del NIBUT (37,9±42,3%, p=0,002) y de la tinción conjuntival (-47,1±59,9%, p=0,005).

5.3.3 Grupo de estudio vs. grupo control

Comparando el efecto de ambas intervenciones se observó que el cambio relativo del CLDEQ-8 fue similar (p=0,20) tras el uso de la LCDD y la LC mensual enmascarada. Sin embargo, la escala relativa sí mostró una mejoría significativa (p=0,008) en los síntomas tras el uso de la LCDD con respecto al uso de la LC mensual enmascarada (efecto placebo). Con respecto a los signos clínicos, solo se encontró un empeoramiento significativo (p=0,03) de la hiperemia limbar en el efecto placebo en comparación con el efecto de la LCDD.

En la comparación de la LCDD entre ambos grupos, no se encontraron diferencias en la mejoría de los síntomas con ambos cuestionarios (CLDEQ-8: p=0,42 y Escala relativa: p=0,17). Sin embargo, el grupo control mostró una mejora significativamente mayor en la tinción conjuntival (p=0,02) que el grupo de estudio.

Tras un mes de uso de la LCDD del estudio, ambos grupos obtuvieron valores similares del CLDEQ-8 (grupo de estudio 9,71±7,30 y grupo control 11,41±6,84; p=0,42).

5.3.4 Correlación entre los cambios de signos y síntomas

Solo se observó una correlación moderada significativa (r=0.57, p=0.03) entre el cambio encontrado en la escala relativa y la tinción conjuntival en el grupo de estudio tras el uso de las LCDD. El resto de correlaciones no fueron significativas.

6. CONCLUSIONES

Las siguientes conclusiones han sido obtenidas en esta tesis doctoral:

La conclusión general de esta tesis es que el uso de instrumentos subjetivos y objetivos adecuados es crucial para una correcta detección y evaluación de la incomodidad con lentes de contacto. Sin embargo, debido a la naturaleza de esta condición, el uso de instrumentos subjetivos permite una mejor evaluación y seguimiento de esta condición cuando se implementan diferentes estrategias para su manejo.

Conclusión 1: el cuestionario Contact Lens Discomfort Index desarrollado en esta tesis es un instrumento fiable y bien estructurado capaz de detectar la incomodidad con lentes de contacto de acuerdo a la definición actualmente establecida. La versión en inglés de este cuestionario tiene buenas propiedades psicométricas, sin embargo, es necesario revisar algunos de los ítems incluidos para asegurar un diseño mejor.

Conclusión 2: el índice clínico ponderado desarrollado en este estudio es un instrumento preciso que puede detectar cambios en la superficie ocular de usuarios sintomáticos de lentes de contacto. Es el resultado de combinar diferentes pruebas clínicas, eliminando las limitaciones encontradas cuando se observan los resultados de una batería de pruebas clínicas pudiendo llevar a conclusiones inconsistentes.

Conclusión 3: readaptar las lentes de contacto desechables diarias delefilcon A a usuarios sintomáticos de lentes de contacto es la intervención más eficaz evaluada en esta tesis, mejorando tanto síntomas como signos. La realización de higiene palpebral en usuarios que además tienen disfunción de glándulas de Meibomio ayuda a reducir los síntomas relacionados con el uso de lentes de contacto y los signos asociados a la disfunción de las glándulas. Por otra parte, el posterior uso pautado de las lágrimas artificiales evaluadas parecer no mejorar más allá los síntomas o los signos de la incomodidad con lentes de contacto.

Conclusión 4: debe tenerse en cuenta la presencia de un efecto placebo cuando se evalúan los síntomas tras la readaptación de una lente de contacto como manejo de la incomodidad con lentes de contacto. De lo contrario, los resultados obtenidos pueden inducir a error en los procesos de toma de decisiones en un ámbito clínico y de investigación.

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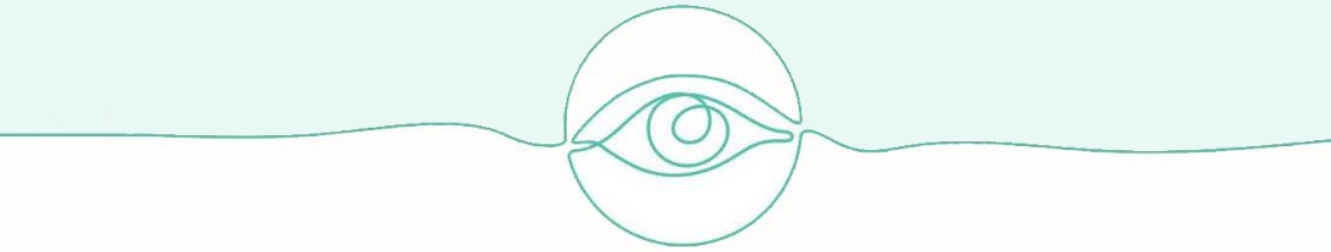
APPENDIX



APPENDIX 1. RESEARCH ETHICS APPROVALS OF THE CLDI STUDY

COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA
ÁREA DE SALUD VALLADOLID – ESTE (CEIC-VA-ESTE-HCUV)

Valladolid a 26 de Febrero de 2015

En la reunión del CEIC ÁREA DE SALUD VALLADOLID – ESTE del 26 de Febrero de 2015, se procedió a la evaluación de los aspectos éticos del siguiente proyecto de investigación.

PI 15-222	CARACTERIZCIÓN DE LA POBLACIÓN CON INCOMODIDAD CON LENTES DE CONTACTO	IOBA I.P.: CRISTINA ARROYO DE ARROYO EQUIPO: Mª JESUS GONZALEZ, ALBERTO LOPEZ RECIBIDO: 06-02-2015

A continuación les señalo los acuerdos tomados por el CEIC ÁREA DE SALUD VALLADOLID – ESTE en relación a dicho Proyecto de Investigación:

Considerando que el Proyecto contempla los Convenios y Normas establecidos en la legislación española en el ámbito de la investigación biomédica, la protección de datos de carácter personal y la bioética, se hace constar el **informe favorable** y la **aceptación** del Comité Ético de Investigación Clínica del Área de Salud Valladolid Este para que sea llevado a efecto dicho Proyecto de Investigación.

Un cordial saludo.

F. Javier Alvarez

Dr. F. Javier Álvarez.
CEIC Área de Salud Valladolid Este –
Hospital Clínico Universitario de Valladolid
Farmacología
Facultad de Medicina,
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Universidad de Valladolid

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Instituto Universitario de Oftalmobiología Aplicada

COMISION DE INVESTIGACION

Dña. Mª Paz García García como **Secretaria de la Comisión de Investigación** del Instituto Universitario de Oftalmobiología Aplicada (IOBA) de la Universidad de Valladolid,

CERTIFICA

Que el TFM titulado **"Caracterización de la población con incomodidad con lentes de contacto"** con número de registro 01/2015 de Dña. Cristina Arroyo del Arroyo, se encuentra en el momento de la última reunión de la Comisión de Investigación de 22 de enero de 2015

X Aprobado

□ Pendiente de

Y para que así conste expido el presente certificado.

En Valladolid, a 23 de enero de 2015

Fdo.: Mª Paz García García
Secretaria de la Comisión de Investigación

APPENDIX 2. INFORMED CONSENT OF THE CLDI PILOT STUDY

IOBA CONSENTIMIENTO INFORMADO

TÍTULO ESTUDIO:

Caracterización de la población con incomodidad con lentes de contacto

INVESTIGADOR RESPONSABLE: María Jesús González García

Está usted siendo invitado a participar en el proyecto de investigación arriba señalado, cuya finalidad última es determinar los factores responsables de provocar incomodidad durante el porte de lentes de contacto. Con el objeto de diseñar el modelo definitivo de encuesta, se va a realizar una fase piloto que es en la que usted participará.

Su colaboración consistirá en rellenar la encuesta que le entregaremos en dos ocasiones distintas en el tiempo, y los datos obtenidos serán utilizados para perfilar el cuestionario definitivo que se empleará en la segunda fase del estudio, pero no formarán parte de esta.

En ningún momento podrá accederse a sus datos personales o clínicos si no es por parte del equipo investigador y para los fines únicamente especificados en el presente documento.

Confirmo que he comprendido las características del estudio y he tenido tiempo suficiente para poder formular aquellas dudas y preguntas que me hayan surgido al respecto, que me han sido solucionadas por parte del equipo investigador y que se me entrega copia firmada por ambas partes del presente documento.

Por lo anterior, yo …… doy mi consentimiento para participar en el estudio, con fecha ……

Firma del participante

Nombre del investigador ……

Fecha ……

Firma

Yo, ……..… revoco el consentimiento dado para el presente estudio y no deseo que los datos obtenidos sean empleados en el mismo.

Firma y Fecha ..……

APPENDIX 3. CONTACT LENS DRY EYE QUESTIONNAIRE 8

Patient/Subject #:_____
Date:__/___/____Time:_____

CONTACT LENS QUESTIONNAIRE-8
(CLDEQ-8)

1. Questions about **EYE DISCOMFORT**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel discomfort while wearing your contact lenses?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your eyes felt discomfort with your contact lenses, **how intense was this feeling of discomfort…**

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:

   a. During a typical day in the past 2 weeks, **how often** did your eyes feel dry?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your eyes felt dry, **how intense was this feeling of dryness**…

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

3. Questions about **CHANGEABLE, BLURRY VISION:**

   a. During a typical day in the past 2 weeks, **how often** did your vision change between clear and blurry or foggy while wearing your contact lenses?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

   When your vision was blurry, **how noticeable was the changeable, blurry, or foggy vision** …

   b. At the end of your wearing time?

Never have it	Not at All Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

4. Question about **CLOSING YOUR EYES:**
   During a typical day in the past 2 weeks, **how often** did your **eyes bother you so much that you wanted to close them**?

   0 Never
   1 Rarely
   2 Sometimes
   3 Frequently
   4 Constantly

5. Question about **REMOVING YOUR LENSES:**
   How often during the past 2 weeks, did your eyes *bother you so much* while wearing your contact lenses that you felt as if you needed to stop whatever you were doing and **take out your contact lenses**?

   1 Never
   2 Less than once a week
   3 Weekly
   4 Several times a week
   5 Daily
   6 Several times a day

APPENDIX 4. RESEARCH ETHICS APPROVAL OF THE CONTACT LENS DISCOMFORT MANAGEMENT STUDY

COMITÉ ÉTICO DE INVESTIGACIÓN CLÍNICA
ÁREA DE SALUD VALLADOLID – ESTE (CEIC-VA-ESTE-HCUV)

Valladolid a 27 de Octubre de 2016

En la reunión del CEIC ÁREA DE SALUD VALLADOLID – ESTE del 27 de octubre de 2016, se procedió a la evaluación de los aspectos éticos del siguiente proyecto de investigación.

PI 16-492 **IOBA**	DETECCIÓN DE LOS CAMBIOS A NIVEL MOLECULAR TRAS LA REALIZACIÓN DE PROCEDIMIENTOS CLÍNICOS PARA LA RESOLUCIÓN DE LA INCOMODIDAD CON LENTES DE CONTACTO	IOBA IP: ALBERTO LOPEZ MIGUEL, MARÍA JESÚS GONZÁLEZ EQUIPO: CRISTINA ARROYO DEL ARROYO IOBA RECIBIDO: 07-10-2016

A continuación les señalo los acuerdos tomados por el CEIC ÁREA DE SALUD VALLADOLID – ESTE en relación a dicho Proyecto de Investigación:

Considerando que el Proyecto contempla los Convenios y Normas establecidos en la legislación española en el ámbito de la investigación biomédica, la protección de datos de carácter personal y la bioética, se hace constar el **informe favorable** y la **aceptación** del Comité Ético de Investigación Clínica del Área de Salud Valladolid Este para que sea llevado a efecto dicho Proyecto de Investigación.

Un cordial saludo.

F. Javier Alvarez

Dr. F. Javier Álvarez.
CEIC Área de Salud Valladolid Este –
Hospital Clínico Universitario de Valladolid
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Universidad de Valladolid

ioba Instituto Universitario de Oftalmobiología Aplicada

COMISION DE INVESTIGACION

Dña. Mª Paz García García como **Secretaria de la Comisión de Investigación** del Instituto Universitario de Oftalmobiología Aplicada (IOBA) de la Universidad de Valladolid,

CERTIFICA

Que el proyecto de tesis doctoral titulado **"DETECCIÓN DE LOS CAMBIOS A NIVEL MOLECULAR tras la realización de PROCEDIMIENTOS CLÍNICOS PARA LA RESOLUCIÓN DE LA INCOMODIDAD CON LENTES DE CONTACTO"** de **Cristina Arroyo del Arroyo**, se encuentra en el momento de la última reunión de la Comisión de Investigación de 18 de noviembre de 2016

X Aprobado

□ Pendiente de

Y para que así conste expido el presente certificado.

En Valladolid, a 18 de noviembre de 2016

Fdo.: Mª Paz García García
Secretaria de la Comisión de Investigación

APPENDIX 5. INFORMED CONSENT OF THE CONTACT LENS DISCOMFORT MANAGEMENT STUDY

IOBA CONSENTIMIENTO INFORMADO

TÍTULO DEL ESTUDIO

Detección de los cambios a nivel molecular tras la realización de procedimientos clínicos para la resolución de la incomodidad con lentes de contacto

Promotor: Instituto Universitario de Oftalmobiología Aplicada – Pº de Belén 17 47011 – Valladolid

Equipo Investigador: Cristina Arroyo del Arroyo

Mª Jesús González García

Alberto López Miguel

PROPÓSITO DEL ESTUDIO

Está siendo usted invitado a participar en un estudio de investigación cuyo objetivo es analizar los cambios en la concentración de moléculas inflamatorias en la película lagrimal tras la aplicación de distintas soluciones clínicas aplicadas en la práctica diaria para reducir la sintomatología con las lentes de contacto. Las soluciones elegidas serán la realización de higiene palpebral, el uso de lentes de contacto desechables diarias y la aplicación de lágrimas artificiales de forma pautada.

PARTICIPACIÓN VOLUNTARIA

Debe saber que su participación en este estudio es voluntaria y que puede decidir no participar o cambiar su decisión y retirar el consentimiento en cualquier momento.

CONDICIONES DEL ESTUDIO

Si decide participar, usted accede a que se le realicen pruebas oculares, las cuales a veces requieren la instilación de colirios tópicos oculares (tinciones vitales). Además, accede a que se le tomen muestras de lágrima, se le realice citología por impresión conjuntival y microscopía confocal. La muestra de lágrima se toma sin anestesia porque no es un procedimiento doloroso ni molesto. La citología y la microscopía confocal, si bien son también mínimamente invasivas se realizarán bajo anestesia tópica ocular a fin de evitar posibles molestias. Todas las muestras serán recogidas bajo un código alfanumérico para asegurar la protección de sus datos personales.

DESCRIPCIÓN DE LAS VISITAS

Se estima que su participación en este estudio tenga una duración total de entre 1 y 4 meses (dependerá de su evolución en el estudio y de su disponibilidad para realizar las visitas) durante los cuales tendrá que realizar un total de 1 ó 2 visitas al mes, con una duración aproximada de entre una hora y una hora y media cada una, en función de las pruebas de cada visita.

Su permanencia en el estudio dependerá de la mejoría o no de sus síntomas a lo largo del mismo.

Las 24 horas previas a la primera visita del estudio, usted no podrá usar ningún tipo de lente de contacto. En caso de que use lágrimas artificiales tampoco podrá hacer uso de ellas durante la semana previa a tal día.

Visita de inclusión (visita 0)

Se le hablará sobre el estudio; se le responderá a todas las preguntas que tenga y se le pedirá que firme este formulario de consentimiento antes de iniciar su participación.

Se le preguntará sobre su actual estado de salud, general y ocular y el uso de lentes de contacto y se le pedirá que cumplimente unos cuestionarios sobre sus síntomas oculares.

Y se realizarán las siguientes pruebas (las pruebas clínicas marcadas con un asterisco son opcionales, según el criterio del investigador principal).

- Medida de la agudeza visual.
- OCT: obtención de imágenes del menisco lagrimal (central).
- Recogida de una muestra de lágrima por capilaridad, utilizando un capilar apoyado en el canto externo del ojo.
- Biomicroscopía de polo anterior: evaluación del estado de la superficie ocular con una lámpara de hendidura, y tras instilar tinciones vitales (fluoresceína y verde de lisamina).
- BUT: medida del tiempo que tarda la lágrima en desestabilizarse (con fluoresceína).
- Evaluación de las glándulas de Meibomio con una lámpara de hendidura.
- Test de Schirmer: medida de la producción lagrimal.
- Estesiometría corneal y conjuntival: evaluación de la sensibilidad mecánica de estas estructuras oculares utilizando como estímulo un flujo de aire.
- Citología por impresión de la conjuntiva tarsal* aplicando un pequeño fragmento de filtro en el tarso del párpado. Dicho filtro se retirará posteriormente y se analizará la expresión genética y de micro-ARN de las células adheridas mediante la técnica RT-PCR.

- Microscopía confocal de la córnea central*: técnica de contacto (a través de un medio de inmersión) que realiza tomografías de las capas corneales a nivel celular.

Tras la evaluación pertinente y en caso de tener disfunción de las glándulas de Meibomio, se le darán las instrucciones necesarias para la realización de la higiene palpebral, que sirve para mejorar el estado del borde palpebral y evitar la evaporación de la lágrima. Consiste en la aplicación de calor en el párpado, presión con el dedo y retirada de la grasa expresada con un gel limpiador. Dicha higiene palpebral deberá realizarla a lo largo de todo el estudio.

La hora de las siguientes visitas se concretará con usted en la visita de inclusión.

Visita 1

En esta visita se pretende conocer el comportamiento de la superficie ocular durante el uso de sus lentes de contacto habituales, así como la evolución de la higiene palpebral (si la ha estado realizando). Para ello, este día deberá acudir a consulta con sus lentes de contacto habituales puestas entre 4 y 6 horas.

Y se realizarán las siguientes pruebas (las pruebas clínicas marcadas con un asterisco son opcionales, según el criterio del investigador principal).

- Escala de valoración visual de 0 a 10 sobre la comodidad con las lentes de contacto.
- Cuestionarios sobre los síntomas y uso de sus lentes de contacto
- Medida de la agudeza visual
- NIBUT: medida no invasiva del tiempo que tarda la lágrima en desestabilizarse.
- OCT: obtención de imágenes del menisco lagrimal (central).

- Recogida de una muestra de lágrima por capilaridad, utilizando un capilar apoyado en el canto externo del ojo.
- Evaluación de las hiperemias bulbar y limbar (enrojecimiento ocular).
- Evaluación de la adaptación de las lentes de contacto.
- Evaluación de los pliegues conjuntivales mediante biomicroscopía.
- Evaluación de la hiperemia tarsal.
- Evaluación de las tinciones vitales tras instilar colirios (fluoresceína y verde de lisamina).
- Evaluación de la epiteliopatía por efecto parabrisas del párpado superior (con fluoresceína y verde de lisamina).
- Estesiometría corneal y conjuntival: evaluación de la sensibilidad mecánica de estas estructuras oculares utilizando como estímulo un flujo de aire.
- Citología por impresión de la conjuntiva tarsal* aplicando un pequeño fragmento de filtro en el tarso del párpado. Dicho filtro se retirará posteriormente y se analizará la expresión genética y de micro-ARN de las células adheridas mediante la técnica RT-PCR.
- Microscopía confocal de la córnea central*: técnica de contacto (a través de un medio de inmersión) que realiza tomografías de las capas corneales a nivel celular.

Al finalizar esta visita se le adaptarán unas lentes de contacto específicas del estudio, las cuales tendrá que usar durante el mes siguiente hasta la próxima visita. Las lentes de contacto que se adaptarán tendrán una frecuencia de reemplazo mensual, quincenal o diario según sus lentes de contacto habituales. De forma que si usa lentes de contacto desechables diarias le daremos lentes de contacto desechables diarias, mientras que si utiliza mensuales o quincenales podrán adaptarse unas lentes de contacto mensuales, quincenales o desechables diarias, elegido de forma aleatoria. Si ha estado realizando higiene palpebral deberá continuarla de igual forma.

Visita 1.1

Esta visita será necesaria para todos los sujetos excepto para aquellos que han estado portando lentes de contacto desechables diarias en el mes anterior. Para ello acudirá a la visita, acordada previamente, con las lentes de contacto puestas tantas horas como se haya estipulado.

En esta visita evaluaremos dichas lentes de contacto y comprobaremos si existe o no incomodidad con ellas. Las pruebas realizadas serán las mismas que en la visita anterior.

Al finalizar esta visita se le adaptarán lentes de contacto desechables diarias y se le darán las suficientes para un mes.

Visita 2

El objetivo de esta visita es evaluar su sintomatología tras un mes con el uso de las lentes de contacto proporcionadas en la visita anterior. Para ello acudirá a la visita, acordada previamente, con las lentes de contacto puestas tantas horas como se haya estipulado. Las pruebas realizadas serán las mismas que en la visita anterior.

Al finalizar la visita se le proporcionarán unas lentes de contacto desechables diarias suficientes para un mes, y se le pautará, de forma aleatoria, el uso o no de lágrima artificial. Aquellos que usen lágrima artificial se las administrarán los días que usen sus LC: al menos en la inserción y en la retirada, y durante las horas de uso un mínimo de 1 vez a mitad de uso y un máximo de una instilación cada dos horas.

Visita 3

Será la última visita del estudio y se pretende evaluar el efecto, tras un mes, del uso de las lentes de contacto y de la lágrima artificial proporcionadas en la visita anterior. Para ello acudirá a la visita, acordada

previamente, con las lentes de contacto puestas tantas horas como se haya estipulado.

Las pruebas realizadas serán las mismas que en la visita anterior.

RIESGOS Y MOLESTIAS PREVISIBLES PARA EL PACIENTE

No se ha reportado ningún daño derivado de los procedimientos utilizados en este estudio. Ninguno de los procedimientos que se le van a realizar durante las visitas resulta doloroso. No obstante, es posible que al día siguiente de la toma de la citología y la microscopía confocal, tenga una pequeña sensación de molestia en el ojo.

SUS RESPONSABILIDADES

Usted deberá usar las lentes de contacto y las lágrimas artificiales el día de las visitas de estudio durante las horas que el investigador le indique. También deberá acudir a las visitas del estudio y avisar al centro, tan pronto como pueda, si por cualquier motivo no pudiera acudir a alguna de ellas, así como de la rotura o pérdida de las lentes. Se le pedirá que comunique al personal investigador del estudio cualquier cambio de salud o en su medicación (con o sin prescripción médica) que experimente.

CONFIDENCIALIDAD

De acuerdo a la Ley 15/1999, de 13 de diciembre, de protección de datos de carácter personal, se le informa de que sus datos se incluirán en un fichero de datos personales cuyo responsable y titular es el IOBA. Puede publicarse un informe de los resultados de este estudio o enviarse a las autoridades sanitarias pertinentes, pero su nombre no aparecerá en estos documentos.

Su nombre puede ser revelado a las autoridades sanitarias gubernamentales como la AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) o a los Comités Éticos de Investigación Clínica (CEICs)

en caso de que necesiten inspeccionar sus archivos clínicos. Se tomarán las medidas oportunas para mantener la confidencialidad de los archivos clínicos y de la información personal.

DESTINO DE LAS MUESTRAS

En cumplimiento del Real Decreto 1716/2011 de 18 de noviembre, si el paciente acepta, la muestra sobrante, de lágrima y de células conjuntivales, será incluida en la colección de muestras biológicas indicada que el IOBA tiene dada de alta en el Registro Nacional de Biobancos: Investigación en Ciencias de la Visión (C.0001417). Podrá solicitar que se destruyan sus muestras dirigiéndonos una solicitud con copia de su DNI a La Fundación General de la Universidad de Valladolid en Plaza de Santa Cruz, 5 bajo del 47002 de Valladolid o al mail protecciondatos@funge.uva.es.

En el caso de que el paciente no acceda al almacenamiento de las muestras, éstas serán conservadas durante tres meses después de finalizado el estudio, con el propósito de ser utilizado solo si hubiese que repetir alguno de los análisis. Pasados tres meses, las muestras serán destruidas.

PERSONAS DE CONTACTO

Se le anima a que consulte con el personal encargado del estudio cualquier duda que tenga debiendo recibir respuestas satisfactorias a todas sus preguntas. Puede ponerse en contacto con:

Cristina Arroyo del Arroyo: carroyoa@ioba.med.uva.es - teléfono: 983 184761

Mª Jesús González García: mjgonzalez@ioba.med.uva.es - teléfono: 983 184756

Alberto López Miguel: alopezm@ioba.med.uva.es– teléfono: 983 186371

Se le entregará una copia firmada y fechada de este formulario de consentimiento para sus propios archivos antes de su participación en el estudio.

CONSENTIMIENTO INFORMADO POR ESCRITO

Título del estudio: Detección de los cambios a nivel molecular tras la realización de procedimientos clínicos para la resolución de la incomodidad con lentes de contacto.

Al firmar abajo, yo declaro que:

1. He leído, o me han leído, y entiendo completamente el contenido del formulario de información adjunto.
2. He tenido la oportunidad de preguntar y obtener respuestas satisfactorias a cada una de mis preguntas.
3. Acepto de forma voluntaria participar en este estudio de investigación y sé que puedo retirarme en cualquier momento sin que se vea afectada la continuidad de mi tratamiento.
4. Personal del equipo investigador: _____, Dirección: Instituto Universitario de Oftalmología Aplicada, Valladolid; Número de Teléfono: 983 184761; me ha explicado la información para el paciente y el formulario de consentimiento y comprendo lo que implica la investigación.
5. He comprendido completamente que los representantes del patrocinador, el Comité Ético Independiente o los representantes de las autoridades regulatorias pueden examinar mis registros clínicos donde aparece mi nombre para verificar la exactitud de la información obtenida y entiendo que estas personas tendrán el deber de manejar esta información con confidencialidad utilizándola solamente con un objetivo legítimo para la salud pública.

6. Acepto comunicar al personal clínico del estudio todos los efectos secundarios u otros cambios en mi salud y todos los cambios de mi tratamiento médico.
7. Se me entregará una copia firmada y fechada de este formulario de consentimiento para mis propios archivos.

☐ Además de lo anterior, autorizo a que la muestra sobrante en caso de que la haya pueda ser incluida en la Colección de muestras nº1417 (denominada “Investigación en Ciencias de la Visión” dada de alta por el IOBA en el registro nacional de Biobancos) y que sea utilizada en estudios posteriores de naturaleza similar dentro de la línea de investigación en Inflamación de la Superficie Ocular.

PACIENTE	**REPRESENTANTE LEGAL AUTORIZADO** (si aplica)
Nombre: _____	Nombre: _____
NIF: _____	NIF: _____
	En calidad de: _____
Firma: _____	Firma: _____
Fecha: _____	Fecha: _____

Persona que explicó el consentimiento informado	**INVESTIGADOR PRINCIPAL**
Nombre: _____	Nombre: _____
NIF: _____	NIF: _____
Firma: _____	Firma: _____
Fecha: _____	Fecha: _____

APARTADO PARA LA REVOCACIÓN DEL CONSENTIMIENTO (CONTACTAR CON EL INVESTIGADOR PRINCIPAL)

Yo _____ revoco el consentimiento de participación en el estudio, arriba firmado con fecha _____

Firma:

APPENDIX 6. DATA COLLECTION LOGBOOK

VISITA 0 **Paciente:** [ ] **HC:**

Nombre y apellidos: _____ Fecha: ___/___/___
Fecha de nacimiento: __/___/__ Sexo: □ M □ F Hora: ____:____

Ojo de estudio (peor ojo): ☐ Dcho. ☐ Izq.

Historia médica (fecha inicio / status)

Tiene o ha padecido: ☐ diabetes, ☐ infecciones frecuentes de oído o garganta, ☐ sinusitis, ☐ artritis, ☐ reumatismo, ☐ trastorno de la tiroides, ☐ hipertensión arterial, ☐ enfermedades de la piel, ☐ enfermedades del colágeno.

¿Padece alguna alergia? ☐SI ☐NO ¿Cuál?

¿Es fumador? ☐SI ☐NO ¿Desde cuándo? Cigarrillos/día:

Si es mujer, ¿Está embarazada? ☐SI ☐NO ¿Está en lactancia? ☐SI ☐NO

Otros:

Medicación concomitante (fecha inicio / status)

Si es mujer, ¿está tomando anticonceptivos orales? ☐SI ☐NO

Otros:

Procedimientos médico quirúrgicos de relevancia (fecha inicio / status)

Historia oftalmológica (fecha inicio / status)

¿Ha tenido o tiene alguno de los siguientes procesos oculares? (tache lo que proceda)

	OD	OI	¿Hace cuánto tiempo?
Ojo vago	☐	☐	.....
Estrabismo	☐	☐	.....
Enfermedad de retina	☐	☐	.....
Úlcera corneal	☐	☐	.....
Conjuntivitis frecuentes	☐	☐	.....
Defecto epitelial recurrente	☐	☐	.....
Queratocono	☐	☐	.....
Ojo seco severo	☐	☐	.....
Enfermedad superficie ocular	☐	☐	.....
Glaucoma	☐	☐	.....
Cataratas	☐	☐	.....
Cirugía ocular (especificar)	☐	☐	.....
Otros (especificar)	☐	☐	.....

Historia de lentes de contacto

¿Usa actualmente lentes de contacto? ☐ SI ☐ NO

¿Acude con las lentes de contacto retiradas más de 24 horas? ☐ SI ☐ NO

¿Cuánto tiempo las ha usado?

Días semanales de uso: Horas diarias de uso:

Marca: Parámetros:

¿Cada cuánto tiempo cambia sus lentes de contacto?

¿Qué tipo de líquidos utiliza para limpiarlas?

☐ Peróxido ☐ Sol. Única ☐ Jabón ☐ Sol. Salina ☐ Desinfectante ☐ Conservante

¿Usa las pastillas limpiadoras de proteínas? ☐ SI ☐ NO ¿Cada cuánto tiempo?

¿Le ha dado problemas algún líquido en especial? (especificar)

¿Usa lágrimas artificiales? Frecuencia

Cuestionario sobre la discapacidad de la superficie ocular

(Versión española homologada del "Ocular Surface Disease Index" –OSDI-)

¿Ha experimentado algunos de los siguientes síntomas durante la pasada semana?

	Siempre (4)	Casi siempre (3)	La mitad del tiempo (2)	Algunas veces (1)	Nunca (0)
1. Ojos sensibles a la luz					
2. Sensación de tener arena en los ojos					
3. Ojos doloridos (dolor/escozor)					
4. Visión Borrosa					
5. Mala Visión					

¿Los problemas con sus ojos le han limitado a la hora de realizar alguna de las siguientes actividades?

	Siempre (4)	Casi siempre (3)	La mitad del tiempo (2)	Algunas veces (1)	Nunca (0)	No procede
6.Lectura						
7. Conducir de noche						
8. Usar un ordenador o un cajero automático						
9.Ver la televisión						

¿Ha sentido molestias en los ojos en alguna de las siguientes situaciones, durante la pasada semana?

	Siempre (4)	Casi siempre (3)	La mitad del tiempo (2)	Algunas veces (1)	Nunca (0)	No procede
10. Cuando hacía viento						
11. En lugares con una humedad baja (muy secos)						
12. En lugares con aire acondicionado						

$$\text{Puntuación final: } \frac{\text{Puntos}}{\text{Preguntas contestadas}} \times 25 =$$

CUESTIONARIO CLDI

CUESTIONARIO CLDEQ-8

Escala Valoración Visual confort

Extrema incomodidad

Extrema comodidad

Agudeza visual en gafa

	AV gafa	
OD		binocular
OI		

Refracción con gafas y lentes de contacto

	Refracción gafa	Refracción LC
OD		
OI		

OCT para menisco lagrimal

Ojo de estudio	

Contralateral	

Muestra de lágrima

Ojo de estudio	Cantidad	Tiempo

Cantidad	Tiempo

Cantidad	Tiempo

Biomicroscopía de polo anterior

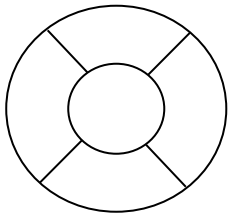
	Ojo derecho					Ojo izquierdo				
	0	1	2	3	4	0	1	2	3	4
Hiperemia conjuntiva bulbar										
Hiperemia limbar										
Hiperemia tarsal										
Papilas										
Folículos										
Edema epitelial										
Edema estromal										
Infiltrados corneales										
Regularidad endotelial										
Vascularización corneal										
Inflamación del segmento anterior										

Tiempo de ruptura lagrimal

	1	2	3	**Media**
OD				
OI				

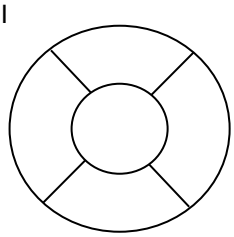
Tinción corneal

OD



Puntuación global:

OI



Puntuación global:

Tinción conjuntival

	Ojo derecho										Ojo izquierdo									
	Nasal					Temporal					Nasal					Temporal				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Verde de lisamina																				

Evaluación de las glándulas de meibomio

	Ojo derecho					Ojo izquierdo				
	0	1	2	3	4	0	1	2	3	4
Expresión										
Calidad de la secreción										
Obstructiva (O) / seborreica (S)										

Meibografía □0 (0%) □1 (±25%) □2 (±50%) □3 (±75%) □3 (>75%)

¿Glándulas obstruidas? ☐SI ☐NO Número:

¿NHP? □SI (próxima visita 28-35 días) □NO (próxima visita7 días)

Signos inflamación (0-4)

Estesiometría

Ojo de estudio	Umbral corneal	Umbral conjuntival
	ml/min	ml/min

Test de Schirmer

OD		OI	

Citología por impresión

¿Eres alérgico al grupo para?

Ojo de estudio		Contralateral	

Criterios de inclusión y exclusión

	✓/×
Sujeto de edad entre 18 y 40 años	
Astigmatismo hasta 0,75 D/ Miopía hasta 8,00 D	
Usuario de LCH esféricas durante al menos 6 meses	
AV monocular en lejos con LC igual o mejor a AV monocular en lejos con su corrección en gafa	
Buena adaptación de las LC según el criterio ISO 11980:2010	
Si usa al menos las LC 2 días/semana y 4 horas/día	
No usuario de uso prolongado o no más de 14 horas de uso habitual	
Sin ojo seco. OSDI ≥ 13 y alterada al menos una de las siguientes pruebas en al menos un ojo: BUT ≤ 7 seg., tinción corneal ≥ 2 (extensión) en alguna de las áreas de la córnea, Schirmer ≤ 5 mm	
Sin Diagnóstico y/o sospecha clínica de queratoconjuntivitis atópica	
Sin otra patología ocular activa de la superficie ocular que contraindique el uso de LC	
Sin historia de cirugía ocular o irregularidad corneal	
Sin enfermedades sistémicas que pudieran afectar a la superficie ocular	
Sin historia de alergia estacional con efecto sobre la SO que pueda afectar al uso de LC	
Sin alteraciones de la visión binocular: estrabismos y ambliopías	
Sin uso de medicación habitual tópica ocular y sistémica, excepto lágrimas artificiales, desde 3 meses antes del estudio	

¿El sujeto es candidato al estudio? ☐ SI ☐ NO

Disponibilidad (según NHP)

VISITA 1 (Con sus LC)

VISITA 1.1 (Placebo)

VISITA 2 (Con las LCDD)

VISITA 3 (LCDD ± LA) **Paciente:**

Nombre y apellidos: ———————— Fecha: ___/___/___

Hora visita: ____:____ Ojo de estudio (peor ojo): □ Dcho. □ Izq.

¿A qué hora se adaptó las LC? ____:____

¿Cambios de salud o medicación?

Días de las LC: NHP ☐SI ☐NO

Rellenar cuestionarios online y papel (CLDEQ-8, CLDI Y ESCALA RELATIVA)

OCT para menisco lagrimal

Ojo de estudio		Contralateral	

Agudeza visual con lentes de contacto

	AV lente de contacto	
OD		binocular
OI		

Tiempo de ruptura lagrimal no invasivo

	1	2	3	**Media**
OD				
OI				

Muestra de lágrima

Ojo de estudio	Cantidad	Tiempo

Cantidad	Tiempo

Cantidad	Tiempo

Evaluación de las lentes de contacto

	OD	OI
Posición de la lente (0, 1, 2)		
Movilidad de la lente (-2, -1, 0, +1, +2)		

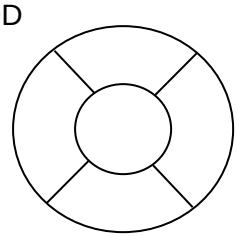
Hiperemia conjuntival

	Ojo derecho					Ojo izquierdo				
	0	1	2	3	4	0	1	2	3	4
Hiperemia conjuntiva bulbar										
Hiperemia limbar										

RETIRAR LAS LC

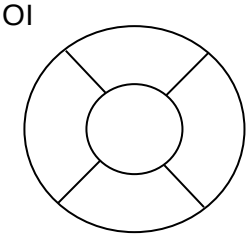
Tinción corneal

OD



Puntuación global:

OI



Puntuación global:

Tinción conjuntival

	Ojo derecho										Ojo izquierdo									
	Nasal					Temporal					Nasal					Temporal				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Verde de lisamina																				

Lid wiper epitheliopathy

	Ojo derecho					Ojo izquierdo				
	0	1	2	3	4	0	1	2	3	4
Longitud horizontal										
Severidad										
FINAL										

Evaluación de las glándulas de Meibomio

	Ojo derecho					Ojo izquierdo				
	0	1	2	3	4	0	1	2	3	4
Expresión										
Calidad de la secreción										
Obstructiva (O) / seborreica (S)										

Meibografía □0 (0%) □1 (≤25%) □2 (26-50%) □3 (51-75%) □4 (>75%)

¿Glándulas obstruidas? ☐SI ☐NO Número:

¿NHP? □SI (próxima visita 28-35 días) □NO (próxima visita7 días)

Signos inflamación (0-4)

Estesiometría

Ojo de estudio	Umbral corneal	Umbral conjuntival
	ml/min	ml/min

Citología por impresión ☐