PRESBYLASIK VERSUS PSEUDOPHAKIC INTRAOCULAR LENSES IN PRESBYOPIC PATIENTS

DEGREE FINAL PROJECT

CONSORCI SANITARI DE TERRASSA
Facultat de Medicina de la Universitat de Girona
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Als meus tutors, per l'entrega i dedicació.
A en Joan Carles per resoldre tots els meus dubtes tècnics.
A la família, pel recolzament incondicional.
A les meves amistats, per contribuir a fer-ho més fàcil.
Als pacients, sense els quals no seria possible realitzar-ho.
A tot l'equip d'Oftalmologia, per l'acollida durant les pràctiques.

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1. ABBREVIATIONS

BCVA	Best corrected visual acuity
LASIK	Laser in situ keratomileusis
PRK	Photorefractive keratectomy
Presby-LASIK	Presbyopic laser in situ keratomileusis
CK	Conductive keratoplasty
IOL	Intraocular lenses
MfIOLs	Multifocal intraocular lenses
EDOF	Extended Depth of Focus Intraocular Lenses
CEIC	Clinical Research Ethical Committee
CST	Consorci Sanitari de Terrassa
IOP	Intraocular pressure
OCT	Optical coherence tomography
WIOL	Wichterle intraocular lenses
VA	Visual acuity
mmHg	Millimeters of mercury
SD	Standard deviation
IQR	Interquartile range

2. ABSTRACT

BACKGROUND:

Presbyopia is a global problem related to aging that affects over a billion people worldwide, practically all human-beings after the age of 40-45, irrespective of gender. There are many treatment options, such as correction glasses, lenses and so on. In this study we focus on surgical treatment, especially between presbyLASIK and Intraocular lenses, to offer a better option for our patients, because these two techniques are the most commonly used ones, but there are no studies that compare them.

OBJECTIVE:

To compare the two most performed techniques when treating presbyopia, laser's surgery versus intraocular lenses surgery and assess which one provides better results.

Other secondary objectives are comparing the recovery time, residual refractive errors and visual acuity.

STUDY DESIGN:

The study will be a longitudinal, prospective, open, randomized clinical trial. It will be carried out in the hospital Consorci Sanitari de Terrassa.

POPULATION:

Women and men with presbyopia from Terrassa, regardless of whether they have refractive errors or not, between the ages of 45 to 55 years old, according to the inclusion and exclusion criteria.

INTERVENTION AND METHODS:

Our study subjects will be randomly divided into two groups: group A (n=67), where patients will be treated with presbyLASIK surgery, while in group B (n=67), patients will be treated with intraocular lenses surgery. Recruitment of patients will last two years, with a subsequent follow-up for 3 years.

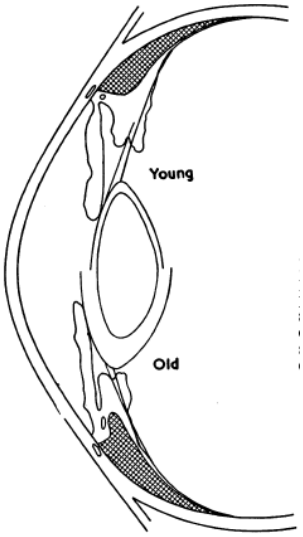
KEY WORDS:

Presbyopia, PresbyLASIK, Intraocular lenses, Refractive error, Diopters, Halos, Dysphotopsies.

3. INTRODUCTION

Presbyopia is a global problem that affects over a billion people worldwide. The accommodation mechanism in younger human eye enables individuals to view targets clearly at various distances. We must differentiate it from myopia, hyperopia or astigmatism.

The youthful accommodation mechanism is what allows the eye to focus on targets at various distances.



The symptoms of presbyopia tend to appear at the age of 40 or older, even so, the decrease in the accommodative response resulting in presbyopia begins in the first ten years of life (1). Nowadays many people want to be operated on when suffering from presbyopia.

Figure 1: Schematic comparison of the anterior parts of the eye in the second and seventh decades respectively (2)*. The shaded parts represent the ciliary muscle.*

3.1. DEFINITION OF PRESBYOPIA

Presbyopia is defined as "the progressive loss of the focusing power of the lens, related to age and that makes it difficult to see nearby objects". It affects the entire population of 40-to-45-year-olds.

Sometimes it is defined as a refractive error or ametropia, though it should not really be considered as such, for ametropies consist of an alteration of the situation of the remote point of the eye from distant vision, whereas presbyopia is a dysfunction of the mechanism that allows the eye to alter the placement of that point, without its position from distant vision being altered(3).

Another more functional definition would be the following: *"Presbyopia is a condition of age rather than ageing and as such is devolved from the lamentable situation where the normal age-related reduction in amplitude of accommodation reaches a point when the clarity of vision at near cannot be sustained for long enough to satisfy an individual's requirements"*(1).

3.1.1. CAUSES OF PRESBYOPIA

The accommodative structures present changes with age, such as a shift in the zonular insertion in the crystalline lens, which affects the anterior displacement of the ciliary body; changes in the thickness and elasticity of the capsule; or even the continued growth of the size and mass of the lens.

The most significant change in presbyopia is the hardening of the crystalline lens.

3.1.2. SYMPTOMS OF PRESBYOPIA

People could experiment difficulty in adjusting to see up-close objects (less than 1m), and thus, they will need to move away from the actual book, mobile phone or object they are looking at, so as to be able to see better.

There is also that feeling when letters from a text have movement or are blurred, headaches may occur when reading for a long time; and eye fatigue is also another symptom, especially at the end of the day or when in poor lighting conditions.

3.1.3. RISK FACTORS FOR PRESBYOPIA

Presbyopia affects practically all human-being after the age of 40-45 and it is believed that both its appearance as well as its manifestations may vary slightly depending on some factors, but this is not a hundred per cent certain. Those factors could be the following:

Both permanent sun exposure in equatorial or tropical countries and high temperatures contribute to a faster aging of the lens and, therefore, to a more rapid onset of presbyopia. Another factor to consider is that, in women, it has been attributed to hormonal factors related to menopause in addition to the body constitution, which can impose more limitations to repel far away objects beyond the near point of vision.

On the other hand, there are other factors: ametropia (presbyopia manifests itself earlier in farsightedness); occupational factors (the strain in near vision makes it necessary to correct before presbyopia); drug use and some diseases which affect the accommodative system (this may require a temporary correction or permanent near vision due to the inability to accommodate normally (3)).

Table 1: Predisposing factors for the appearance of presbyopia (3)

Predisposing factors for the appearance of presbyopia
Age >40 years
Gender (influence of hormonal flow in menopausal women)
History of early onset of presbyopia
Large pupil diameter (shallower depth of focus)
Professional occupation (accommodative demand)
Weather conditions (warmer climates)
Use of drugs with accommodative involvement
Suffering from diseases with accommodative involvement

3.2. REFRACTIVE AND ACCOMMODATION ABNORMALITIES: HYPEROPIA, MYOPIA, ASTIGMATISM

Emmetropia is the state in which parallel light rays are focused on the retina of the eye in a relaxed state (without accommodating). The opposite situation, ametropia, would include: myopia, hyperopia and astigmatism.

The measurement of the refractive state of the eye (refraction) can be carried out objectively or subjectively.

- **Objective method**: we focus a ray of light from a retinoscope on the patient's retina, and by using lenses of different powers and placing them in front of the eye, we neutralize the light reflection of the retina.
- **Subjective method**: we place lenses in front of the eye and ask the patient to tell us with which ones they see the letters of the optotype more clearly.

3.2.1. HYPEROPIA

We speak of hyperopia when parallel light rays are focused behind the retina of the eye in a relaxed state (without accommodation). It may be due to the short anteroposterior diameter of the eye or due to a low refractive power of the cornea or lens.

The power required to focus on far and close-up objects depends on the accommodation mechanism (explained later). When there is a high degree of hyperopia requiring a greater accommodative effort, vision can be blurred and ocular discomfort, headache or visual fatigue (asthenopia) may appear (4).

3.2.2. MYOPIA

In myopia, unlike in hyperopia, parallel rays of light are focused in front of the retina. It may be due to the eye having a long anteroposterior diameter or because of a high refractive power in the cornea or lens. The main symptom is blurred vision of distant objects (4).

Myopia, as a rule, progresses until the eye is fully developed, usually when we reach our early 20s (5).

3.2.3. ASTIGMATISM

In the case of astigmatism, the eye has different refractive powers, either because of irregularities in the corneal curvature or due to alterations of the lens (4).

Astigmatism is a state in which light rays, after refraction, do not converge at a single point (5). Distorted vision may appear when this disorder is more pronounced and the patient ends up squinting his or her eyes, thus suffering from discomfort, headache, or fatigue (4).

3.3. ACCOMMODATION

Accommodation is understood as the process by which the eye changes its optical power to maintain images clearly focused on the retina as the distance changes to the observed object (6).

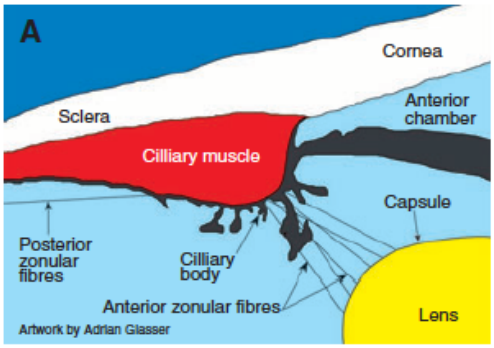


Figure 2: Schematic diagram of the accommodative structures (7)

3.3.1. ANATOMICAL COMPONENTS OF THE ACCOMMODATIVE APPARATUS

- **Ciliary Muscle and Ciliary Body**

It is perhaps the most important accommodative anatomical structure, located within the ciliary body, externally bordering the sclera, and the most superficial layer of pigmented connective tissue of the ciliary body. Its internal face limits both anteriorly with the ciliary processes or pars plicata, and posteriorly with the pars plana of the ciliary body, which provides oxygen and nutrients to the ciliary muscle. It is made up of smooth muscle fibers: longitudinal or meridional fibers, radial or reticular fibers, and circular or equatorial fibers (6).

The ciliary body is divided into the pars plicata anteriorly and the pars plana posteriorly, the latter region extending to the ora serrata.

- **Zonule**

The zonule is the suspensory ligament that attaches the lens to the ocular wall. It consists of both anterior and posterior zonular fibers.

The anterior zonular fibers extend from the equatorial region lens capsule, where they insert forming zonular lamellae, bordering the circumlental space until anchoring in the internal limiting membrane of the unpigmented ciliary epithelium, at the level of the crypts between the ciliary processes of the pars plicata.

Posterior zonular fibers, also called zonule of the pars plana or ciliary zonule, start from the internal limit or from the inferior membrane between the unpigmented and pigmented ciliary epithelium at the level of the posterior insertion of the ciliary muscle, near the ora serrata of the retina. They form an intertwined network of fibers that is directed towards the ends of the posterior ciliary processes (6).

- **Crystalline lens and its capsule**

The crystalline lens is made up of a number of epithelial cells surrounded by an acellular membrane, also known as the lens capsule. It is not detached from its cells and, like epithelial tissue, it grows throughout life by adding new fibers in the equatorial zone, which translates into a linear increase in mass with age. Its anteroposterior thickness also increases with age (6).

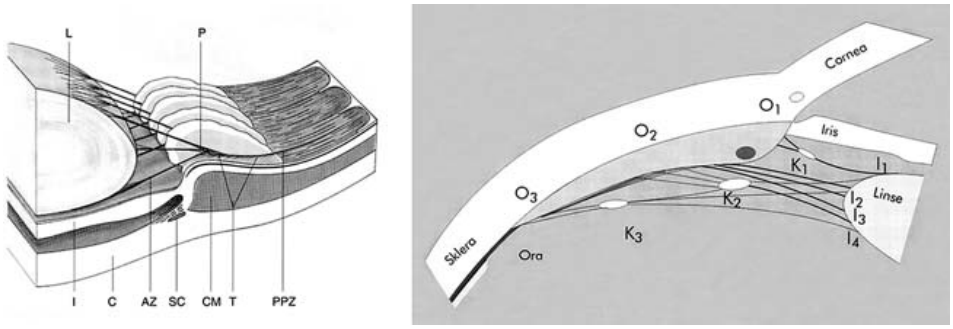


Figure 3: Models of the human zonule (6) *Left: P= zonular plexus, PPZ= posterior zonule, AZ= anterior zonule. Right: O= origins, K= interconnection points, I= sites of insertion in the crystalline lens*

3.3.2. ACCOMMODATIVE MECHANISM

The human eye is emmetropic. In a relaxed state (and under minimally efficient conditions of light or morphoscopic stimulation), rays from a distant object (5m or more) converge on the retina.

Accommodation consists of a process of myopization or increase in the diopter power of the system in order to focus the closest objects. The change in optical power is neuronally linked to pupillary convergence and constriction (6).

The most widely used theory is Helmholtz's theory, according to which, when the eye is in a relaxed state and focusing at a distance, the ciliary muscle is relaxed.

When we try to focus on a nearby object, the ciliary muscle contracts, causing most of the anterior ciliary body to move forward and toward the axis of the eye, releasing the tension of the zonular fibers around the lens equator. The capsule surrounding the lens allows it to mold into a more spherical and accommodating shape.

The disaccommodative mechanism occurs when the contraction of the ciliary muscle ends. The posterior insertion of the ciliary muscle and the posterior zonule fibers causes disarray in the

muscle. This causes an increase in tension in the fibers of the equator of the lens and, in turn, because of the constant pull, it reaches a flattened and non-accommodated state.

The diameter of the lens increases, the thickness of the lens decreases and there is a flattening of the anterior and posterior curvatures.

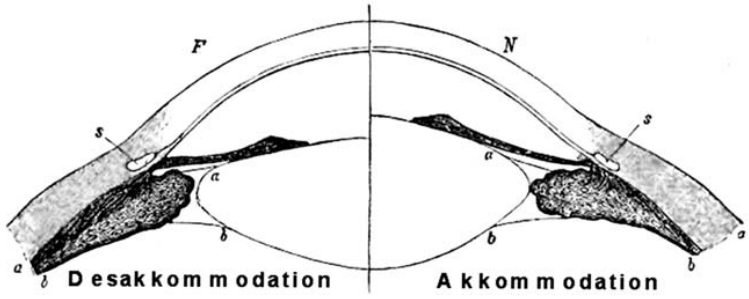


Figure 4: Accommodation model (6)

3.3.3. PHYSIOLOGICAL ASPECTS OF ACCOMMODATION

The ciliary muscle has anterior and posterior tendons and at the ultrastructural level, actin and myosin filaments, cytoplasmic organelles and nerve endings. This muscle lacks spontaneous activity and its structure favours precision when in the accommodative response (6).

Neural control of accommodation: the parasympathetic effector pathway

Control of accommodation is partly reflexive and partly conscious, but in any case, it is exerted on the activity of the ciliary muscle, mainly through the parasympathetic pathway with certain influences of the sympathetic. According to the conventional model, parasympathetic stimulation involves the constriction of the ciliary muscle and when inhibited it reaches a state of relaxation.

The role of the sympathetic system would be to assist in the disaccommodation of the eye (which depends mainly on the inhibition of the parasympathetic), producing the relaxation of the fibers of the ciliary muscle (6).

3.4. EVALUATION OF PRESBYOPIA

Presbyopia is diagnosed with a basic test, which includes an evaluation of refraction, best corrected visual acuity (BCVA) and an lid lamp exam.

Refraction evaluation determines if you have myopia, hyperopia, astigmatism or presbyopia. **Visual acuity is checked with the best corrected lenses possible (BCVA).**

Then there are many other tests to perform when planning a presbyopia surgery, which may be the following:

- **Tonometry**: in order to measure Intraocular pressure (IOP).
- **Topography**: in order to know the curvature, thickness, eccentricity and asphericity of the cornea.
- **Biometry**: for the calculation of intraocular lenses and for obtaining the dimensions (measurements) of the eyeball, like axial length, the size of the anterior chamber or keratometry.
- **Pupillometry**: in order to measure size of the pupil.
- **Endothelial cell count**: in order to detect anomalies.
- **Keratometry**: in order to measure the cornea curvature radius so as to give a value for corneal astigmatism.
- **OCT**: in order to study the histological sections of the retina as well as analysing the posterior retina, the macula, the papilla and the relation with vitreous and choroid.

All this techniques are explained later on in the methodology section.

3.5. SURGICAL TREATMENT OF PRESBYOPIA

Currently, we can find different types of procedures when treating presbyopia:

3.5.1. Monovision:

- *Laser in situ keratomileusis (LASIK)*
- *Photorefractive keratectomy (PRK)*

3.5.2. Presbyopic LASIK (presbyLASIK)

3.5.3. Conductive keratoplasty (CK)

3.5.4. IntraCor femtosecond laser

3.5.5. Corneal inlay

3.5.6. Anterior ciliary sclerotomy

3.5.7. Lenticular approaches:

- *Pseudophakic multifocal intraocular lens:*
  - *Multifocal IOL*
  - *EDOF*
  - *Accommodative IOL*
- *Phakic intraocular lens*

3.5.1. MONOVISION LASIK AND PRK

Patients with presbyopia and myopia may have to endure difficulties with near vision once their refractive error has been corrected. Before the surgery, they were able to read by removing their glasses, and once the actual surgery is done, they may feel frustrated with their decreased near vision (8).

Monovision is used in order to compensate presbyopia by correcting distance vision in one eye and near vision in the other eye. Usually, the non-dominant eye is corrected for near vision and the dominant eye for far vision (9).

In this situation a presbyopic person has the ability, using both eyes simultaneously, to focus on intermediate, far and up-close images without the need of optical compensation (10).

This procedure entails the appearance of anisometropia (*visual problem in which each eye has a different refractive error, for example, one eye being myopic and the other hypermetropic*) in order to provide near and distance vision, somehow managing to reduce the binocular acuity and the stereopsis (*the perception of depth produced by the reception in the brain of visual stimuli from both eyes in combination; binocular vision*) (8).

3.5.2. PRESBYOPIC LASIK (MULTIFOCAL LASER ABLATION)

Multifocal LASIK (PresbyLASIK) is a vision correction surgery which consists of changing the shape of the cone in order to create areas to see from different distances.

Its use in presbyopia consists of the following:

- Excimer laser reshapes the cornea in different areas, irrespective of whether it is used for near, far or intermediate vision. In each area, the light is refracted differently so that people with presbyopia regain good vision in all cases.

There are three main types of multifocal corneal excimer laser profiles:

1) **Multifocal transition profile** (no longer in use)**:** not accepted by surgeons because it induced vertical coma (an aberration where people are not able to see a round point, but the image of a coma).
2) **Central presby-LASIK**
3) **Peripheral presby-LASIK**

Peripheral presby-LASIK: the center of the cornea is left distance wise, the periphery is ablated and a negative asphericity is created to increase the depth. When performing this

method, an efficient excimer laser is required in order to compensate for the loss of energy during the ablation of the peripheral cornea (8)(9).

However, when there is a spherical aberration and the pupil becomes miotic, the refraction of the eye undergoes a change that influences near vision negatively. One of the main disadvantages it that when it is used in myopic patients, it is necessary to remove a considerable amount of corneal tissue, which is why it is mainly performed in hyperopes (11).

Central presby-LASIK: it creates a hyperpositive area in the center, vision wise, while the periphery is left far, vision wise. (8) One of the advantages is that it can be performed in the center of the cornea in myopic and hyperopic profiles, as well as in emmetropes with minimal corneal excision (9).

Although the peripheral presbyLASIK appears to induce less loss of contrast sensitivity and is less pupil-dependent, the central presbyLASIK requires much less ablation and theoretical studies suggest that allows better quality of near vision (12).

One of the main limitations would be the alignment between the central pupil and the corneal vertex, which can induce coma aberrations (11) *(So called because a point image is blurred into a comet shape, is produced when rays from an off-axis object point are imaged by different zones of the lens. In spherical aberration, the images of an on-axis object point that fall on a plane at right angles to the optical axis are circular in shape, of varying size, and superimposed about common centre; in coma, the images of an off-axis object point are circular in shape, of varying size, but displaced with respect to each other. "Coma is alarming because of the significant deterioration of the visual quality. It produces images double, halos and glare around objects; it affects the contour and corners of the images")*(13).

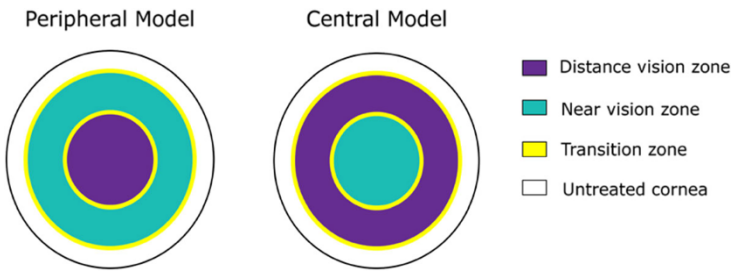


Figure 5: Differences between ablation patterns. In peripheral presbyLASIK, the center of the cornea is treated for distance vision and the periphery for near, while in central presbyLASIK, the center of the cornea is treated for near vision and the periphery for distance vision (11).

3.5.3. CONDUCTIVE KERATOPLASTY

Conductive Keratoplasty (CK) is a procedure based on the use of radiofrequency, a low-frequency energy, with the aim to procedure a sufficient temperature increase in the corneal stroma so as to achieve the contraction of collagen fibers and consequently a modification of the corneal curvature and the refractive power (14). This is generated by a console, a pen-shaped piece held by a removable cable and connector, a pedal that controls the release of energy, and a speculum that provides the electrical return surface.

Significant regression of refractive and keratometric effects of CK has been observed over extended follow-up. Regression has been the main factor limiting the use of thermal keratoplasty treatments"(8). This is one of the reasons why this technique is no longer used nowadays.

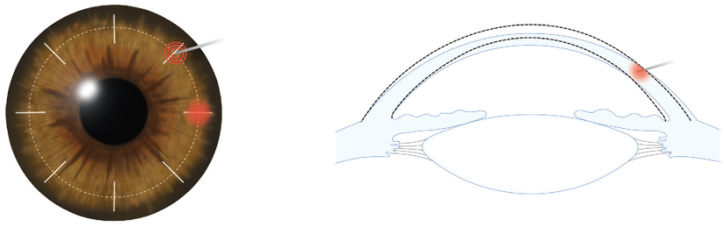


Figure 6: Conductive keratoplasty (CK). Spot algorithm used to predict the effect of CK (15)

3.5.4. INTRACOR FEMTOSECOND LASER

This technique consists of applying femtosecond laser pulses on the corneal stroma to correct refractive errors without the need for cutting the flap or any other corneal incision.

The intracor procedure is performed by using the Technolas femtosecond laser system, using laser pulses on the cornea to induce a local reorganization of biomechanical forces as well as a change in corneal shape.

Some of the advantages are the following: intrastromal delivery without breaking the epithelium, avoidance of pain and inflammation of the exposed ocular surface; speed of recovery due to the absence of healing in the superficial wound; and stability of refractive result preserving the strongest anterior corneal fibers. However, some of the disadvantages would be the diffractive effects from the delivery of laser pulses, alignment, and progression or loss of effect due to changes in corneal biomechanics over time (8).

3.5.5. CORNEAL INLAY

Corneal inlay consists in lenticules that are inserted into the cornea. We can find 3 types:

- **KAMRA**: it uses a pinhole effect; it is a small opaque disc with a smaller aperture in the center which improves near vision. It is only implanted in one eye, specifically on the non-dominant eye. However, one of the drawbacks is that it restricts the entry of light with the small aperture, and in some patients, it can cause glare, halos, reduced contrast and night vision (16).

- **Raindrop**: it is based on changes in the shape of the cornea. It is made of biocompatible hydrogel material and 80% water and it allows the passage of nutrients and oxygen because of its permeability.

  It should be placed in the non-dominant eye, at a depth of minimum 150µm, leaving a residual stromal bed thickness of 300µm and it should be aligned over the center of the pupil. The thickness of the central cornea of the eye should be 500µm or more. Once the inlay has been placed, before the placement of the actual flap, it must be left to dry for 30 seconds (9)**.**

- **Presbia Flexivue Micro-lens**: it consists of a transparent hydrophilic concave-convex disc, which is implanted in the non-dominant eye. There is a central flat area surrounded by peripheral ring segments with different refractive indices. There is a hole in the center of the implant that allows nutritional flow through corneal tissue (17).

  In distant vision, light rays pass through the central area of the inlay, which has no refractive power (plane), and they are sharply focused on the retina, whereas the rays that pass through the peripheral refractive zone will focus in front of the retina.

  In near vision, the rays that pass through the central zone of the inlay will be focused behind the retina, and those that pass through the peripheral refractive zone will focus on the retina (9).

  This technique is reversible and depends on the size of the pupil.

This techniques preserves distant vision in the implanted eye, one of the differences with monovision (15).

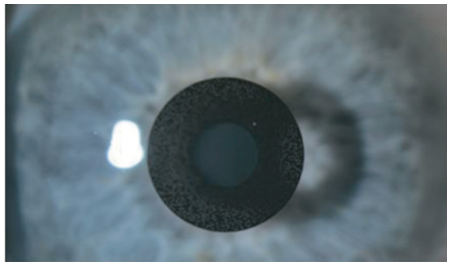


Figure 7: KAMBRA inlay in a light colored eye (9)

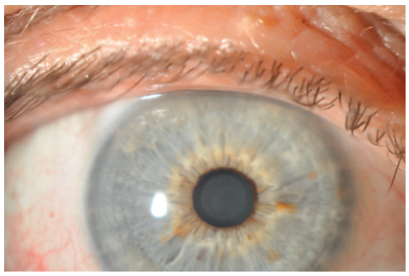


Figure 8: Raindrop corneal inlay (9)

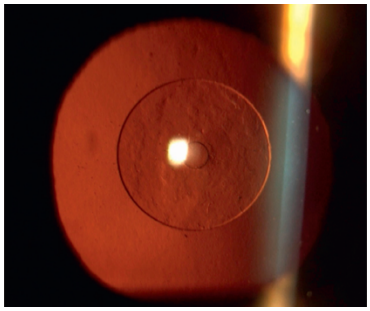


Figure 9: Flexivue inlay (9)

3.5.6. ANTERIOR CILIARY SCLEROTOMY

This technique consists of making radial incisions in the sclera overlying the ciliary muscle. This allows the expansion of the sclera that covers the ciliary body, thus increasing the space between the equator of the lens and the ciliary body.

Unfortunately, the effect of the surgery gradually disappears and this is due to the healing of the sclera. An attempt was made to place silicone plugs in the incisions to prevent scleral healing. However, anterior ciliary sclerotomy is not considered an appropriate treatment for the correction of presbyopia (8).

3.5.7. LENTICULAR APPROACHES

There are a lot of ways to compensate for the loss of accommodation with an intraocular lens. This consists in a process where the crystalline lens is replaced with an intraocular lens (IOL) that simulates the function of the crystalline lens and provides the patients with functional vision for all distances (18).

It is very important to precise biometry, accurate IOL power calculation, good surgical technique as well as patient selection in order to achieve the best visual outcome and patient satisfaction (8).

1) <u>Pseudophakic multifocal intraocular lens:</u>

- **Multifocal IOLs (MfIOLs)**

These lenses use a refractive or diffractive technology that give patients near, distance and intermediate vision. This lenses separate light into different foci, which cause a dispersion of the energy of the light entering into the eye (19).

MfIOLs can be:

- ***Refractive IOLs****:* These lenses consist of concentric rings with different potencies. They have five refractive optical zones (1/3/5 for far vision, and 2/4 for near vision). This design provides adequate intermediate and distance vision, but near vision may not be sufficient or may affect the quality of the retinal image by creating distortion. One of the disadvantages of this lens is dysphotopsia *(Positive: halos, flashes or reflections with the lights; or Negative: the presence of an arc-shaped shadow or dark crescent in the temporary visual field)* (18).
- ***Diffractive IOLs:*** These lenses use microscopic steps (diffractive zones) across the lens surface. "Light is directed towards the distant and near focal points. Diffractive MfIOLs can be subdivided into apodised (gradual reduction in diffractive step heights from centre to periphery) or non-apodised (uniform height): both are designed to reduce the severity of night haloes compared with refractive MfIOLs"(18).

  These lenses provide good reading and distance vision. Intermediate vision is good, but not as good as the others (19)**.**
- ***Rotationally asymmetrical MfIOLs:*** They usually give good results in distance and near vision with minimal dysphotopsia as well as retaining intermediate vision, because they have a larger section for distance vision and a smaller reading segment, with one transition zone (9).

  These lens are shapes in a way that minimizes the loss of light caused by the splitting of the incoming light (18).

- **Accommodative IOLs**

These IOLs are designed to use ciliary muscle contraction, capsular bag elasticity and changes in vitreous cavity pressure to induce change or movement in the shape of the IOL in order to produce an optical change in the eye. So, with ciliary body contraction the optic lens moves forward so as to provide accommodation (15).

“A hinge between the optic and haptics allows the lens to move forwards, as the eye focuses on near objects and backward as the eye focuses on distant objects, thereby increasing the dioptrical power of the pseudophakic eye”(18).

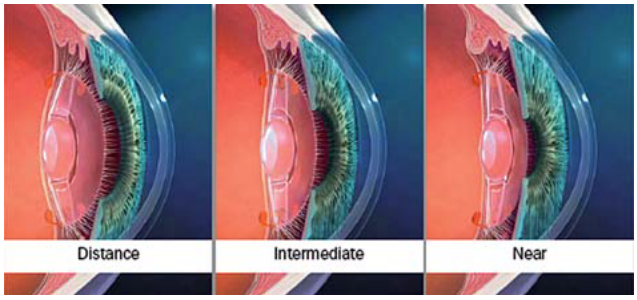


Figure 10: The change that the lens undergoes in its position inside the eye causes its dioptric power to change (20)

- **Extended Depth of Focus Intraocular Lenses (EDOF)**

  The goal of this technique is to create an elongated focus to enhance intermediate and near visual performance, while minimally affecting distance performance. The trade-off with use of EDOF lenses is a reduction in the quality of distance image should the aberration magnitude be too large (21). These lenses provide improved visual acuity at intermediate distances and might also cause fewer or less severe visual disturbances as well as yielding better contrast sensitivity (22).

  Spatial frequency, pupil size and corneal models should all be taken into consideration in order to evaluate diffractive IOL performance in vitro (23).
  These types of lenses are designed to demonstrate functional vision over a range of distances and they can provide a more uniform visual quality between far and intermediate distances, the visual quality is diminished across all distances compared with monofocal IOLs.

  Compared to bifocal and trifocal IOLs, EDOF IOLs are designed to provide less glare and halos and less contrast sensitivity loss. “However, patients should be counselled about possible dysphotopsias and the need consequent for low power reading glasses postoperatively” (23).

Types of EDOF IOLs:

- **Small-Aperture Design:** IC-8 would be an example, and it is basically is a one-piece hydrophobic acrylic posterior chamber IOL. It is implanted in 1 eye through a 3.5mm corneal incision using a single-use injector system; the contralateral eye receives a different type of IOL.
- **Bioanalogic Design:** Wichterle IOL-Continous Focus is a bioanalogic hydrogel IOL designed to emulate the crystalline lens with a similar shape, no haptics and a refractive power that decreases from the center to the periphery. It is implanted via an injector through a 2.5 to 3.2mm incision and pushed inside the posterior capsular bag for 5 seconds in order to allow the IOL to adhere to the capsule.
- **Diffractive Optics**: as Tecnic Symfony and Symfony toric, these ones have a step structure design intended to provide improved visual acuity at intermediate distances. It may be implanted with screw-sytle or syringe-sytle insertion instruments through an approximately 2.3mm corneal incision. Patients might experience a reduction in contrast sensitivity, halos or glare in low-illumination conditions as a result of the IOLs elongated focus design.
- **Nondiffractive Optics:** SIFI Mini WELL is a one-piece aspheric biconvex hydrophilic hydrophobic copolymer IOL implanted via a disposable injector through a 2.4mm incision. The design comprises 3 zones: a central zone with positive spherical aberration, a middle zone with negative spherical aberration and an outer monofocal zone (22)**.**

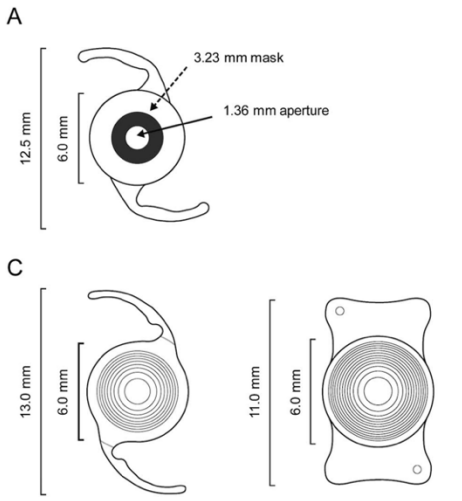


Figure 11: Types of EDOF IOL technology. (22)

A: IC-8 IOL

B: WIOL-CF IOL

C: Tecnis Symfony IOL

D: SIFI Mini WELL IOL

2) Phakic intraocular lens:

These are artificial lenses implanted in the anterior or posterior chamber of the eye in order to correct refractive errors (between the cornea and the natural lens). They are interesting because they preserve accommodation, they yield predictable results and they have lower risk of retinal detachment. We can find 3 types: anterior chamber IOLs, iris-fixated IOLs and posterior chamber IOLs (15). In presbyopia, the anterior chamber is normally used.

But there are some complications like surgically induced astigmatism, corneal endothelial cell loss, pupil distortion, chronic uveitis, pupillary block glaucoma, pigment dispersion syndrome and cataracts (18).

4. JUSTIFICATION

Presbyopia is the gradual loss of near vision, which begins to be noticed approximately when reaching the age of 40-45 and it progresses over the years. In some people it can appear earlier on or take even longer to take place (3).
Presbyopia is a process related to aging and therefore, it has become very a rather common condition in our community.

This process occurs due to the changes that the crystalline lens undergoes over the years, which goes from being flexible to rigid and loses its ability to accommodate (6).
As it is so frequent and affects both men and women, without a preference of sex, more and more people decide to undergo eye surgery due to the fact that vision loss has an important impact on the person's quality of life.

Therefore, there are different treatment options: Monovision (with LASIK or PRK), Presbyopic LASIK, Conductive keratoplasty, Intracor femtosecond laser, Corneal inlay, Anterior ciliary sclerotomy, and IOLs (multifocal/accommodative-edof), bearing in mind the fact that some are more used than others for they obtain better results and fewer side effects. Even so, nowadays it is not possible to give a clear answer as to which the best treatment is, although it is true that the surgery with laser and with IOLs is the most used. However, there is nothing clear about these two techniques and even if it is true that during the last years the IOLs are becoming more common, we cannot guarantee for certain which may be the best.

For these reasons above mentioned in our study we will try to answer this question as well as trying to propose what the best option would be as far as presbyopia treatment is concerned, that is, laser or IOLs, taking into account the side effects and residual refractive errors each technique entails in an experimental clinical trial.

5. HYPOTHESIS AND OBJECTIVES

5.1. HYPOTHESIS

When it comes to treating presbyopia in patients aged 45-55, we believe that surgery with intraocular lenses will give us better results than presbyLASIK treatment.

5.2. OBJECTIVES

The main objective here is to compare the two most performed techniques for treating presbyopia, laser versus surgery with intraocular lenses, and then assess which one is better, considering side effects.

Other objectives we wish to achieve are the following:

- To compare the recovery time with the technique used
- To compare residual refractive errors
- To compare visual acuity

6. METHODOLOGY

6.1. STUDY DESIGN

We will design a longitudinal, prospective, open, randomized clinical trial in order to analyse which the best technique in the treatment of presbyopia is and how it affects the patient's vision; it will be carried out in the Consorci Sanitari de Terrassa.

6.2. STUDY POPULATION

The population we will be studying will consist of women and men with presbyopia from Terrassa, who will be recruited according to the inclusion and exclusion criteria.

A target population of 134 people, aged between 45 and 55 years of age.

6.2.1. INCLUSION CRITERIA

To be enrolled in this study the subjects had to accomplish the following criteria:

- To be 45-55 years of age.
- Refractive state: presbyopia in emmetropic, myopic, hyperopic patients and/or astigmatism.
- Refractive error from 0 to +4.00D, and astigmatism not exceeding 2.00D, because the presbyLASIK technique cannot be performed on patients with very high prescriptions.
- High motivation: patients who wish to improve their near vision situation without optical correction for any reason (labor, etc).

6.2.2. EXCLUSION CRITERIA

- Cornea with alterations or scars, irregular astigmatisms or other pathologies in the cornea (such as Fuch's dystrophy, keratoconus).
- Thin corneas of less than 520 microns, since these patients cannot undergo presbyLASIK surgery.
- Cataracts, as it can induce changes in graduation. Contraindicate direct action in the corneal plane, since it is known that within a brief period the crystalline lens will have to intervene, so it makes it more difficult for LASIK.
- Suffer from an eyelid or tear disease, such as blepharitis or a severe dry eye that does not respond to classic artificial tear treatment.

- Defects or diseases in the iris. To prevent the lens from contacting it.
- Patients with ocular hypertension (PIO), may contraindicate action on the cornea (as in Glaucoma, especially narrow-angle).
- Retinopathies and maculopathies in general are contraindications for most of the usual techniques of presbyopia surgery.
- Diabetic patients: hyperglycemia or rapid changes in blood sugar level often cause blurred vision. Eye problems that can occur in people who suffer from diabetes include cataracts, glaucoma, retinal detachment and macular edema.

6.3. SAMPLING

6.3.1. SAMPLING SIZE

The sample size has been calculated using the free online software called GRANMO.

To calculate the sample size, we've assumed an alpha risk of 0.05 and a beta risk of less than 0.2 in a bilateral contrast, 67 subjects will be taken into account in the first group (presbyLASIK) and 67 in the second (IOLs) in order to detect a difference equal to or greater than 0.5 units. The common standard deviation is assumed to be 1. A loss of follow-up rate of about 5% has been estimated (24).

6.3.2. SAMPLING METHOD AND ENROLMENT

Both women and men diagnosed with presbyopia who meet the inclusion and no-exclusion criteria will attend the centre participating in the study.

They will be informed about the study and the possibility to participate in it in order to ensure a good comprehension of the study, its implications and risks. The information will be explained to them orally and some time will be spent on solving the patients' questions. Moreover, an information sheet with all the information detailed will be given to them. If they agree to participate, they will have to sign the informed consent (Annex 1) to be able to enrol the study.

6.3.3. ESTIMATED TIME OF RECRUITMENT

Patients will be recruited from the ophthalmological consultation in the hospital Consorci Sanitari de Terrassa (CST). Basing on clinical practise, we could recruit about 60-70 patients/year in CST. Considering that, the recruitment will last two years so as to achieve a sample of 134 patients and thus, complete our study.

6.4. RANDOMIZING AND MASKING

Each time that a patient with presbyopia accepts participating in the trial data is entered in a program which assigns every patient in a part of the study: either A or B. Thus, this trial is going to achieve an optimised informatics randomness.

Nevertheless, this randomized clinical trial cannot be masked at double blind or single blind, it will be open-label, since the presbyopia surgical techniques applied may be utterly different and, moreover, the physicians who perform them and evaluate their results and complications must be concerned about the surgery which is to be carried out. The patients will also know what treatment is being used on them.

They will have to sign a consent form after reading the informative document which explains that they will undergo a presbyLASIK surgery randomly or an intraocular lenses surgery. They will have to sign the consent form for both, accepting to participate in one of those two techniques.

6.5. STUDY VARIABLES

Independent variable: nominal qualitative variable

- Surgery treatment for presbyopia. There will be 2 groups randomly distributed, with different administration treatment, the first one (group A) will have presbyLASIK surgery, while the other group (group B) will have IOLs surgery.

Dependent variable:

- Residual refractive error (quantitative normal variable), it will be analysed by using the auto refractor, a machine that is used to obtain the objective graduation that a patient has and that does not depend on the patient's responses. It should also be measured manually by the optotype test (Annex 2), the optician-optometrist or ophthalmologist places lenses of different graduations on the patient's eyes, who must say the numbers and letters that he/she is able to distinguish on a panel placed in front of him/her out loud. This way visual acuity is accurately measured.
- Side effects (qualitative variable): as presence of halos, dysphotopsies, dry eyes, will be an important fact to take into account when evaluating the success of the two surgeries we are comparing.

Co-variables:

- Age (continuous quantitative variable): expressed in years. It is an important factor because presbyopia increases with the age.
- Gender (dichotomous nominal qualitative variable): as mentioned in the introduction, certain hormonal factors are related to the risk of presbyopia in women.
- Presence of refractive errors from the beginning (quantitative variable): myopia, hypermetropia, astigmatism, as they will affect the final result of the actual presbyopia surgery, because some will obtain better results with laser and others with IOLs.
- Visual requirements: it is important to take into account their type of work, since some will have more accommodative demand when it comes to near vision and others with the exact opposite, distant vision.

6.6. DATA COLLECTION, MEASURE INSTRUMENTS AND PROCEDURES IN CHRONOLOGICAL ORDER

All patients treated in the medical ophthalmologic department of Consorci Sanitari de Terrassa involved in this study will be asked to meet all the inclusion and non-exclusion criteria so as to be able to participate in this study. The patient must accept and give written consent after he/she has read the information sheet.

Patients will come to us after noticing worsening of vision when looking up-close (such as reading the newspaper, a menu from a restaurant and so on).

FIRST VISIT: Preoperative visit

On the first visit we will analyse the entire medical history, asking for personal and family history, bearing in mind it is important to rule out diabetes, hypertension and other ocular pathologies that are exclusion criteria in our study.

Once the anamnesis is finished, we must carry out a proper eye examination and perform a series of tests in order to determine the type of lens to use, as well as assess whether the patient is a candidate for the laser.

- **Ocular Refraction and Visual Acuity**:

  Ocular refraction refers to the refraction that occurs in light from objects as it passes through different parts of the eye, causing the images to concentrate on the retina. In case of presbyopia, myopia, hyperopia, astigmatism, we have refractive errors and it is important

to know this before IOLs surgery so as to choose the best lenses option. To detect refractive errors we have different gadgets:

- Auto Refractor: a machine that helps the optometrist to measure automatically the graduation presented in the eye of the patient in an objective way. The patient should place his/her chin on the chin rest of the equipment and bring his/her eye closer to the instrument without actually touching it. Then, the auto refractor will display an image that will move away from the eyeball while automatically measuring refraction. Finally, will print a paper with the tests results expressed in diopters (the refractive capacity of a lens) (25).
- Phoropter: the device used for the subjective graduation of sight and here the patient intervenes in the process by saying if he/she sees better or not with one lens or another. It is like "super-test glasses" that has all the lenses inside and the optician-optometrist, rather than putting on and taking off lenses, simply turns a disk or a button that places the lenses in front of the eye, thus making the actual test faster (26).

  The phoropter has incorporated a series of filters, colored, polarized lenses and prism systems, which make it possible to carry out a complete battery of optometric tests, thus evaluating not only the refractive state (graduation), but also the accommodative and binocular state of the eyes (phoria-deviations, latent strabismus, etc.).

Visual Acuity (VA) is the ability of the visual system to differentiate two points close to each other and separated by a certain angle. We use the optotypes in order to calculate it (Annex 2), which is a set of letters, signs or figures of various sizes which are projected in decreasing size so as to be able to determine how well and far the patient can see (27).

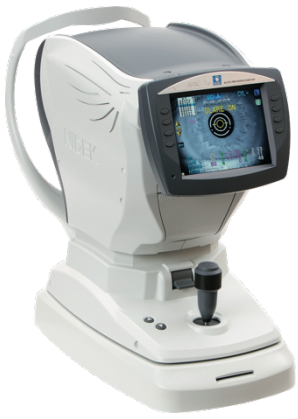


Figure 12: Auto Refractor (25)

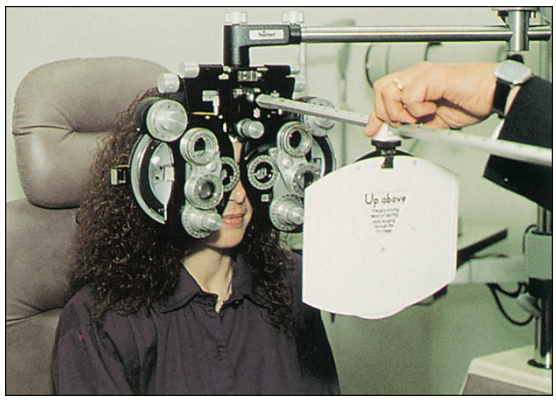


Figure 13: Phoropter (26)

- **Intraocular pressure (IOP):** it is the pressure of the fluid inside the eye. Normal eye pressure is generally between 10-20 mmHg (millimeters of mercury), if it is too low or too high it can damage vision. One of the most used techniques used to measure it in consultation is flattening tonometry, in which the ophthalmologist places an anesthetic drop in each eye and fluorescein dye is used during the test. The patient must remain seated, avoiding any kind of movement and when leaning on the slit lamp he/she must avoid blinking., This test takes place in a semi-dark room (28).

- **Funduscopic Examination:** it allows the specialist to examine posterior eye structures and detect alterations of the retina and optic nerve (29).

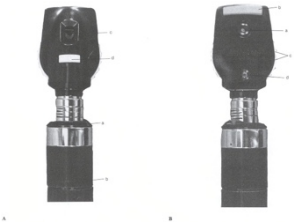


Figure 14: Ophthalmoscope (30)

- **Biometry** (Annexe 3)**:** accurate biometry is of vital importance in achieving a IOLs power calculation so as to choose the best option of lens before the surgery (31).

  This technique measures the following:

  - Length of the eye: it measures the distance between the central point of the most anterior surface of the cornea and the central point of the retina or macula.
  - Curvature of the anterior face of the cornea: the measurement of different axes is crucial for the calculation of the lens.
  - Amplitude of the anterior chamber: it measures the distance between the inner part of the cornea and the anterior capsule of the lens.
  - Horizontal diameter of the visible iris or white-to-white diameter of the eye.

- **Topography and Keratometry:** the measurement of corneal curvature can be done by using these two techniques:

  Keratometry: it measures the radius of curvature of the cornea so as to give a value for corneal astigmatism. In most corneas, is accurate enough to fit contact lenses or calculate intraocular lens power (important to know before the surgery). It is also useful to detect irregular astigmatism, which would be an exclusion criterion in our study.

  Corneal topography (Annex 4): it provides a detailed map of the corneal surface based on the study of reflected light after a previous projection on the anterior surface of the cornea.

It allows to know the curvature of the cornea, detect pathologies, quantify aberrations of the anterior surface, adapt contact lenses and plan surgeries (32).

- **Endothelial cell count** (Annex 5): it allows assessment of endothelial cell density, size, and shape. This cells make up the deepest layer of the cornea, also known as the endothelium. From the total amount of 5,000 cells per mm^2 that we have at birth, the number of cells decreases to 1,500 and 2,500 cells per mm^2 in adult life. The minimum level necessary for normal function is between 600 and 900 cells per mm^2. When the level is below 500 cells per mm^2, the cornea accumulates water in its interior and loses transparency.

- **Pupillometry:** it allows us to know the size of the pupil and its response to certain stimuli. During the examination the patient should be in a dark room, sitting with a straight back, with his/her eyes open, head steady and, most importantly, avoid blinking at all times. The infrared pupillometer is then placed in the line of sight of the patient while keeping his/her eyes on a fixed and distant point.

- **Pachymetry:** a painless test that allows us to measure the thickness of the cornea, which is gently placed in the front of the eye (the cornea) and measures its thickness. It is important to carry out this technique before a refractive laser surgery, because the laser will remove part of the thickness of the cornea in order to rectify the myopia, astigmatism or hyperopia that the patient could suffer from, and therefore, it is a test that must be taken into account. In case of not having the necessary thickness, it will be unsafe and thus, for these cases it is better to use intraocular lenses (33).

- **Visual field** (Annex 6)**:** a non-invasive monocular test that allows us to obtain the information of the entire visual pathway from the retina to the calcarine cortex, by presenting light stimuli from the periphery to the center (34).

  It is carried out in a room with dim lighting, the patient seated and with a duration of 5-8 minutes per eye. One eye is covered and before starting the test, the patient will have to stare at the central orange lights. By doing so, the device takes the reference of the central gaze and fixation, which the patient would have to maintain throughout the test. Various points of light will appear on the screen in the form of small lightning bolts or flashes, in different areas and with different intensity.

- **Optical coherence tomography (OCT)** (Annex 7)**:** it is a non-invasive, contact free, diagnostic imaging technique that is used for detailed exploration of the parts of the retina, specifically the macula and the optic nerve. It allows us to control and monitor future problems. With OCT the ophthalmologist can map and measure the thickness of each distinctive layer of the retina. The ophthalmologist puts in drops that widen the pupil and facilitate the examination of the retina. The patient sits in front of the machine and supports his/her head on a support to keep it still. The device then performs an eye scan for 5 to 10 minutes (35).

Once all these techniques have been carried out, we can know for sure whether the patients will be candidates for our study or not, with laser or intraocular lenses, as well as the type of lens that would suit them better. Later, we will explain what the treatment consists of, the method procedure and an approximation of how near, intermediate and distant vision would be like at the end.

Next, we will fully explain to the patients what our study consists of and the beneficial effects of both possible surgeries, the risks, options, laser and IOLs, and possible complications. After that we would give them an information sheet with all the information of our study. Should they agree to enter our study, they would have to sign a written consent and the patient will be given an appointment a week later in order to be operated on.

SURGICAL TREATMENT

There will be two groups of presbyopic patients, distributed randomly and homogeneously, those who are emmetropic or those who suffer from myopia, hyperopia or astigmatism associated.

- Group A: will be treated with presbyLASIK surgery (explain in pages 15-16)
- Group B: will be treated with IOLs surgery (explain in pages 19-23)

The surgery will take about 15-20 minutes, depending on whether any problems or complications arise and also taking into account the previous preparation of the patient, topic anesthesia, etc. Once the surgery is finished, patients can go home, with this type of surgery there is no need to spend the night in hospital.

POSTOPERATIVE VISIT

Once the surgery is performed, the first postoperative visit would be the day after the operation. In that visit, the ophthalmologist will carry out an ocular examination, to make sure the surgery was successful and to compare the recovery time with both surgeries.

The doctor will measure the IOP and do a check-up with biomicroscope in order to assess the state of the cornea, the anterior chamber of the eye and, in cases of surgery with IOLs, check if the lens is properly placed.

FOLLOW-UP

A week later after the first postoperative visit, the patients will have their next appointment, where the specialist will do a check-up with biomicroscope (as in the first postoperative visit), and will assess visual acuity without refraction, funduscopic examination and, finally, measure the IOP, all this taking into account the possible appearance of side effects (halos, dysphotopsies, dry eyes and so on).

The next visit, will be six weeks later, and like in the previous one, the ophthalmologist will check the IOP, funduscopic examination, and explore with biomicroscope, always considering there may be side effects. Unlike in the previous visit, in this one the specialist will assess visual acuity with refraction and perform an Auto Refractor and OCT.

Then, the following visits during the first year will be every 6 months, where the most important thing to evaluate will be the Auto Refractor. Once the first year has passed, the visits will be yearly for the next 3 years after the surgery. In these visits, the ophthalmologist will examine the same as in the visit made 6 weeks after the operation.

7. STATISTICAL ANALYSIS

7.1. DESCRIPTIVE (UNIVARIATE) ANALYSIS

In order to describe sample characteristic groups, we will analyse variables using the following criteria:

- Categorical variables (qualitative): expressed by percentage (%)
- Numerical variables (quantitative): expressed by mean +/- standard deviation (SD) if the variable follows a normal distribution, or expressed by median +/- interquartile range (IQR) if the variable follows a non-normal distribution.

To summarize the dependent variable, residual refractive error, I will perform it by median, stratifying by laser and IOLs groups.

The other dependent variable, side effects, will be taken into account when assessing the outcome of both surgeries, but due to the size of the sample, we will focus on the diopters (residual refractive error).

7.2. BIVARIATE ANALYSIS

To determine differences between study groups (participants with laser surgery or IOLs) we used the following:

- **Categorical variables** (qualitative): will be compared using Xi^2 test
- **Numerical variables** (quantitative):
    - will be compared using T-Student test for normal distribution
    - will be compared using Mann-Whitney test for non-normal distribution

The analyses between the dependent and the independent variables will be stratified by the covariables. Should these covariables be quantitative, they will be categorized.

7.3. MULTIVARIATE ANALYSIS

Finally, we will use multivariate models to adjust for possible confounding. The association between the dependent variable in both interventions will be adjusted in a log-lineal regression, controlled by covariables.

8. LIMITATIONS OF THE STUDY

One limitation that we should consider is patient withdrawal, as with the improvement of symptoms, patients may not come to the appointments or they could easily forget about it or even change the date.

Another would be the budget, the high price of the treatment also represents a limitation when performing the study. It is important to take this into account, due to the fact that IOLs surgery is more expensive than laser and this could condition the decision of our patients and make them rethink about the study.

It should also be taken into account that in presbyLASIK surgery we have both central and peripheral techniques, and one of the limitations of the peripheral one would be the fact that in myopic patients it requires moving a considerable amount of corneal tissue, which has better results in hypermetropic patients and thus, this is something to bear in mind when analysing the results, because depending on the technique used, they will have better results in myopic, hypermetropic or emmetropic patients.
The same happens with the surgery with IOLs, since there are many types and depending on the ocular characteristics of each person, analysed with the preoperative tests, one type of lens or another will be chosen. In the study we do not distinguish between different types of lenses, we make a global comparison between laser versus IOLs, so it may happen that in the results we have a lot of variability, and therefore, some lenses may give very good results and perhaps others not so much, compared to laser techniques and vice versa.

LASIK laser surgery is not a reversible process as it affects the very structure of the eye and the cornea, making it impossible to return to the former state. On the other hand, although a change in the structure of the eye is also made by removing the lens with intraocular lenses, the lens we implant in its place could be removed or exchanged for others lenses if necessary.

In addition, not all people are suitable to undergo LASIK surgery, those who have large refractive errors, such as very high myopia or those with an excessively thin cornea would be discarded, because our study is random and in these cases the laser would not be suitable, which would condition our actual randomization.

9. ETHICAL CONSIDERATIONS

This project complies with the ethical principles of the *Helsinki Declaration of 1965* (respect for people or autonomy, beneficence, maleficence and justice) about research involving human subjects established by the World Medical Association (WMA).
Before beginning our study, corresponding protocol will be sent to the *Clinical Research Ethical Committee (CEIC) of Hospital Consorci Sanitari de Terrassa (CST)*, who will have to approve it prior to starting the study.

All personal and clinical information will remain confidential and anonymous, only to be used for the purpose of the research according to the "*Ley Orgánica 3/2018, del 5 de diciembre, de Protección de Datos de Carácter Personal y garantía de los derechos digitales*" published on BOE 294, 6th December 2018, and by the "*Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos*".

The patients must be informed about all the details in the protocol and they must sign the consent form to enrol the trial (Annex 1). Participants have the right to access, modify, oppose or remove their personal data.

This clinical trial will have an insurance contracted with an insurance company.

The investigators of this project declare that there are no conflicts of interest, and that they did not receive any economic compensation to collaborate in the study.
All the research team commit to all data being published with transparency and they will not exclude unfavourable events or data, whatever the results of the trial may be.

10. FEASIBILITY

We determine that this study is feasible because it will be carried out in CST hospital that already have all the means and resources available in order to accomplish the study.

All the ophthalmologists and investigators involved in the trial have enough experience in their specialty, in the case of ophthalmologists, treating refractive errors, myopia, hypermetropia, astigmatism as well as presbyopia surgery with both presbyLASIK and IOLs techniques.

The number of expected patients to participate in the study is affordable logistics wise. Moreover, for the time calculated, according to our estimations, we can recruit the necessary sample to obtain a good representation of the proposed study population.
The main obstacle in the execution of this protocol is the cost, because of the price difference between laser and IOLs surgery.
The work plan explains the steps that makes this trial feasible.

11. WORK PLAN AND CHRONOGRAM

11.1. PERSONAL OF THE RESEARCH TEAM

The research team will consist of ophthalmologists participating in the trial of the Consorci Sanitari de Terassa.

11.2. STUDY STAGES

STAGE 1. COORDINATION AND PROJECT DESIGN

- **Protocol elaboration:** during the months of August and September 2020 this protocol was designed, with the help of expert ophthalmology doctors from the Consorci Sanitari de Terassa.
- **Protocol approbation:**
  - *CEIC's authorization:* the protocol will be presented to the Comitè d'Ètica d'Investigació Clínica (CEIC) of CST (two month before the start of the study, that is, October and November 2020) as the coordinating hospital of the study in order to receive the authorization to start it. Should any recommendations be proposed, they will be considered and introduced to the protocol.
  - *CST Director's authorization:* the director of the hospital must approve the study.

- **Organization meeting:** before starting the study an organizational meeting will take place in order to coordinate all the investigators of the center, and they will designate a person who will be in charge of organizing and ensuring the optimum coordination among everybody participating in the study, as well as making sure that the protocol is being followed and that patient's data is properly gathered.

STAGE 2. STUDY TIMELINE

- **Participants recruitment:** two years will be necessary (from January 2021 to January 2023) in order to recruit the 134 required patients for the study.
- **Intervention:** it will take a few minutes or an hour maximum, during the morning assigned.
- **Participant's evaluation; follow up routine:** during the 3 years after the operation has taken place.
- **Data collection**: from the moment the patient enters the ophthalmologic center until the last monitoring visit, 3 years after the surgery.

- **Data monitoring and quality control**: it will be carried out by an external service during and at the end of the data collection process so as to ensure all data is properly registered in the database.

STAGE 3. DATA ANALYSIS AND INTERPRETATION

- **Statistical analysis:** Once all data is collected from the last patient recruited, a statistical analysis will be carried out by an external service during January 2026.
- **Interpretation and discussion of the results:** data will be analysed during a month by an external statistic and then results will be discussed.
- **Final report:** a final report will be written during the month of March 2026 by the maximum authority in the center, who will have participated voluntarily and been elected by the investigators via vote in the last meeting. Finally, it will be read by the other investigators who will propose possible modifications and/or give their approval.

STAGE 4. DIVULGATION

- **Publication of the results:** a final report will be presented in journal articles in April or May 2026.
- **Dissemination of the results:** the coordinating investigators team will attend a congress to present the results of the study during June and July 2026.

Table 2: Chronogram

STEPS		2020					2021 to 2023		2024	2025	2026						
		A	S	O	N	D					J	F	M	A	M	J	J
1) COORDINATION AND PROJECT DESIGN																	
Protocol elaboration																	
Protocol approbation	CEIC's authorization																
	Director's authorization																
Organization meeting																	
2) STUDY TIMELINE																	
Patients recruitment																	
Surgery intervention																	
Participants evaluation, follow-up																	
Data collection																	
Data monitorization and quality control																	
3) DATA ANALYSIS AND INTERPRETATION																	
Statistical analysis																	
Interpretation and discussion of the results																	
Final report																	
4) DIVULGATION																	
Publication of the results																	
Dissemination in congress																	

12. BUDGET

Table 3: Budget

	QUANTITY	COST PER UNIT	SUBTOTAL
MATERIAL			
Printing: - Protocol information sheets for participants - Informed consents	804 sheets (6 per patient)	0'03€	24.12€
OCT	6/patient x 134 patients	50€	40.200€
CV	1/patient x 134 patients	35€	4.690€
Topography	1/patient x 134 patients	35€	4.690€
Biometry	1/ patient x 134 patients	35€	4.690€
Pupillometry	1/patient x 134 patients	35€	4.690€
Pachymetry	1/patient x 134 patients	35€	4.690€
PROCEDURES			
Medical Visit (including Funduscopic examination, VA, IOP)	7/patient x 134 patients	30€	28.140€
Intraocular lenses	1/patient x 67 patients	1.200€	80.400€
PresbyLASIK surgery	1/patient x 67 patients	1.000€	67.000€
PERSONAL COSTS			
Ophthalmologist's fees	1/patient x 134 patients	800€	107.200€
Operating room rights (including anesthesiologist and +50€ of instrumentalist)	1/patient x 134 patients	650€	87.100€
Statistical expert for randomization and data analysis	142h	40€/h	5680€
Data monitorization and quality control	4h/patient x 134 patients	40€/h	21.440€
Insurance policy	1	5.000€	5.000€
PUBLISHING EXPENSES AND TRAVELS			
Publication in a journal	1	2.000€	2.000€
Congresses	1	1.000€	1.000€
		TOTAL BUDGET	**468.634,12€**

Material

To schedule the surgery it is necessary to perform a series of tests to see the state of the eye, the refraction, etc, and if it is suitable for presbyLASIK or IOLs, we must take into account the cost of the material for each of the tests that are to be performed, both in the preoperative visit and throughout the whole study.

Procedures

Apart from the tests, the cost of the operating room must also be calculated, both for the surgery with presbyLASIK and for IOLs.

Personal costs and services

The research team will consist of an ophthalmologist who will perform the follow-up explorations and data collection. The rest of the services will have to be hired:

- A statistic will be hired to take care of the patients' randomization and also the statistical analysis.
- Data monitoring and quality control.

13. CONFLICT OF INTERESTS

Authors declare no conflict of interest in any step of this trial.

14. IMPACT

Sooner or later everyone will develop presbyopia, some before others, but it is an inevitable part of life. Based on our hypothesis, if the study we propose confirms that the intraocular lenses surgery has better results for treating presbyopia than presbyLASIK, this will entail a great economic impact, because the surgery has a very high cost. In the end, however, it is an investment for the future, as it will be for the benefit of the patients, because it will improve their quality of life, for vision plays an important role in patients' day-to-day life. Moreover, if we stop to think about it and start taking into account the cost of changing glasses every so often or the purchase of daily or monthly lenses, this particular surgery would be more economical in the long run.

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16. ANNEXES

16.1. ANNEX 1 - INFORMED CONSENT

CST: CONSORCI SANITARI DE TERRASSA

FECHA Y HORA DE REALIZACIÓN: / / :

NOM. Y APELL.:

FECHA NACIM.: TELEFONO:

NHC: CIP:

DIRECCIÓN:

DOCUMENTO DE CONSENTIMIENTO INFORMADO
AUTORIZACIÓN
INTERVENCIÓN / EXPLORACIÓN / TRATAMIENTO

Sr./Sra. con D.N.I.

en calidad de: Paciente

Manifiesto voluntariamente que:

El Dr./Dra. que me atiende, me ha informado:

- De la conveniencia de practicarme una intervención de
- De la preparación que debo hacer antes de la prueba, así como de la necesidad de avisar de posibles alergias a medicamentos, alteraciones de la coagulación, enfermedades cardiopulmonares, existencia de prótesis, marcapasos, medicaciones actuales o cualquier otra circunstancia. A causa de mi estado actual (diabetes, obesidad, anemia, hipertensión, edad avanzada, etc.), pueden aumentar los riesgos o complicaciones como:

- De los riesgos más frecuentes, descritos en la hoja informativa que se me entregado.
- Que si aparecen complicaciones, puede ser necesario tratamiento adicional.
- Que la realización del procedimiento puede ser filmada con motivos científicos o didácticos, preservando siempre mi intimidad.
- Que no existen garantías de que se puedan conseguir los resultados previstos.
- De la utilización de la anestesia más adecuada en mi caso. En caso de anestesia tópica (gotas anestésicas en el ojo), ésta será aplicada per el oftalmólogo y supervisada por el anestesiólogo que, en caso necesario, administrará los fármacos necesarios.

Otras informaciones:

Asimismo, doy mi consentimiento para que se realicen procedimientos de cualquier índole (moleculares, inmunohistoquímicos o los que se precisen necesarios en cada momento) que puedan tener implicaciones para el tratamiento o seguimiento de mi enfermedad y/o que puedan sugerir una posible predisposición hereditaria a neoplasias u otras enfermedades. Autorizo a los profesionales responsables del seguimiento de mi enfermedad que el material biológico que sea necesario para hacer estos estudios pueda ser derivado a centros concertados o específicos.

En el caso de que alguno de estos resultados tenga implicaciones clínicas para usted o sus familiares, será informado del resultado.

La información me ha sido dada de forma comprensible y mis preguntas han sido contestadas, por tanto:

TOMO LIBREMENTE LA DECISIÓN DE AUTORIZAR al equipo médico que me atiende a realizar la intervención de , firmando este documento.

Si durante este proceso surgiera alguna situación imprevista, autorizo al equipo médico a que haga lo que en ese momento se considere más conveniente, siempre y cuando no sea posible mi consentimiento previo. También entiendo que en cualquier momento, y sin necesidad de dar ninguna explicación, puedo revocar el consentimiento que ahora presto.

Terrassa,

Firma del médico:
Dr./Dra.
Núm. colegiado:
Servicio: OFTALMOLOGIA

Firma del paciente o responsable:

Revoco el consentimiento dado en fecha .....
Sr./Sra. ..... con D.N.I. .....

Firma del paciente o responsable:

Firma del médico:
Dr./Dra. .....
Núm. colegiado .....
Servicio .....

Se adjunta información complementaria.

16.2. ANNEX 2 – OPTOTYPE TEST

16.3. ANNEX 3 – BIOMETRY

Apellido:
No. ident.:
Fecha nacim.:
Fecha medición:
Cirujano: **Lentes Monofocales**

Fórmula:
Refr. aspirada:
n:

ZEISS

Se deberá verificar la plausibilidad de los valores de medición AL ya que podrían existir modificaciones patológicas.

OD derecho

AL: 23.40 mm (SNR = 152.5)
K1: 44.70 D / 7.55 mm x 144°
K2: 45.18 D / 7.47 mm x 54°
R / EE: 7.51 mm / 44.94 D
Cil.: -0.48 D x 144°
ACD ópt.: 3.19 mm

Estado: Fáquico

OS izquierdo

AL: 23.16 mm (SNR = 98.3)
K1: 44.82 D / 7.53 mm x 30°
K2: 45.12 D / 7.48 mm x 120°
R / EE: 7.51 mm / 44.97 D
Cil.: -0.30 D x 30°
ACD ópt.: 3.35 mm

Estado: Fáquico

Physiol FineVision		**ZEISS CT LUCIA 611P**	
Const. A:	119.40	Const. A:	120.10
IOL (D)	REF (D)	IOL (D)	REF (D)
22.0	-0.94	23.0	-0.96
21.5	-0.61	22.5	-0.64
21.0	-0.28	22.0	-0.33
20.5	**0.04**	**21.5**	**-0.01**
20.0	0.36	21.0	0.29
19.5	0.68	20.5	0.60
19.0	0.99	20.0	0.90
Emet. IOL: 20.57		Emet. IOL: 21.48	

Physiol FineVision		**ZEISS CT LUCIA 611P**	
Const. A:	119.40	Const. A:	120.10
IOL (D)	REF (D)	IOL (D)	REF (D)
23.0	-1.10	24.0	-1.10
22.5	-0.77	23.5	-0.77
22.0	-0.44	23.0	-0.45
21.5	**-0.11**	**22.5**	**-0.14**
21.0	0.21	22.0	0.18
20.5	0.53	21.5	0.48
20.0	0.85	21.0	0.79
Emet. IOL: 21.33		Emet. IOL: 22.28	

Hoya iSert PC-60AD(+)		**Hanita BunnyLens MF**	
Const. A:	118.50	Const. A:	118.90
IOL (D)	REF (D)	IOL (D)	REF (D)
21.0	-1.04	21.5	-1.04
20.5	-0.70	21.0	-0.70
20.0	-0.35	20.5	-0.37
19.5	**-0.02**	**20.0**	**-0.03**
19.0	0.32	19.5	0.30
18.5	0.65	19.0	0.62
18.0	0.98	18.5	0.94
Emet. IOL: 19.48		Emet. IOL: 19.95	

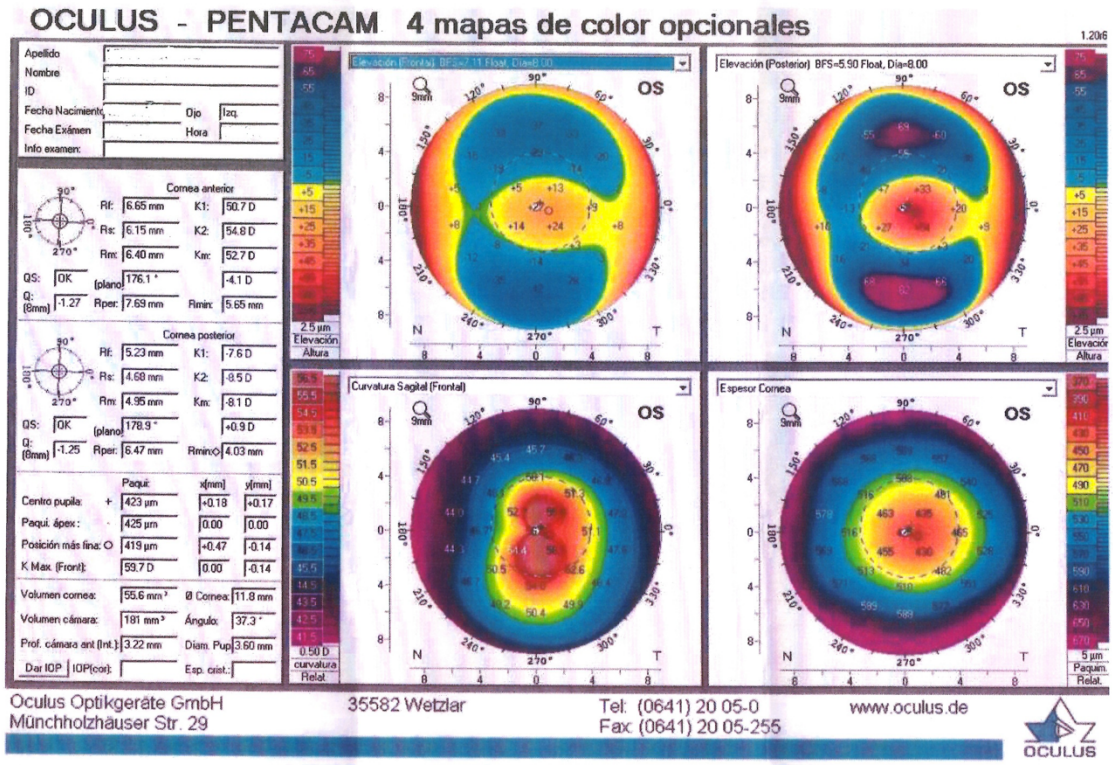
Hoya iSert PC-60AD(+)		**Hanita BunnyLens MF**	
Const. A:	118.50	Const. A:	118.90
IOL (D)	REF (D)	IOL (D)	REF (D)
21.5	-0.90	22.0	-0.88
21.0	-0.55	21.5	-0.54
20.5	-0.21	21.0	-0.21
20.0	**0.13**	**20.5**	**0.13**
19.5	0.47	20.0	0.46
19.0	0.80	19.5	0.78
18.5	1.13	19.0	1.10
Emet. IOL: 20.20		Emet. IOL: 20.69	

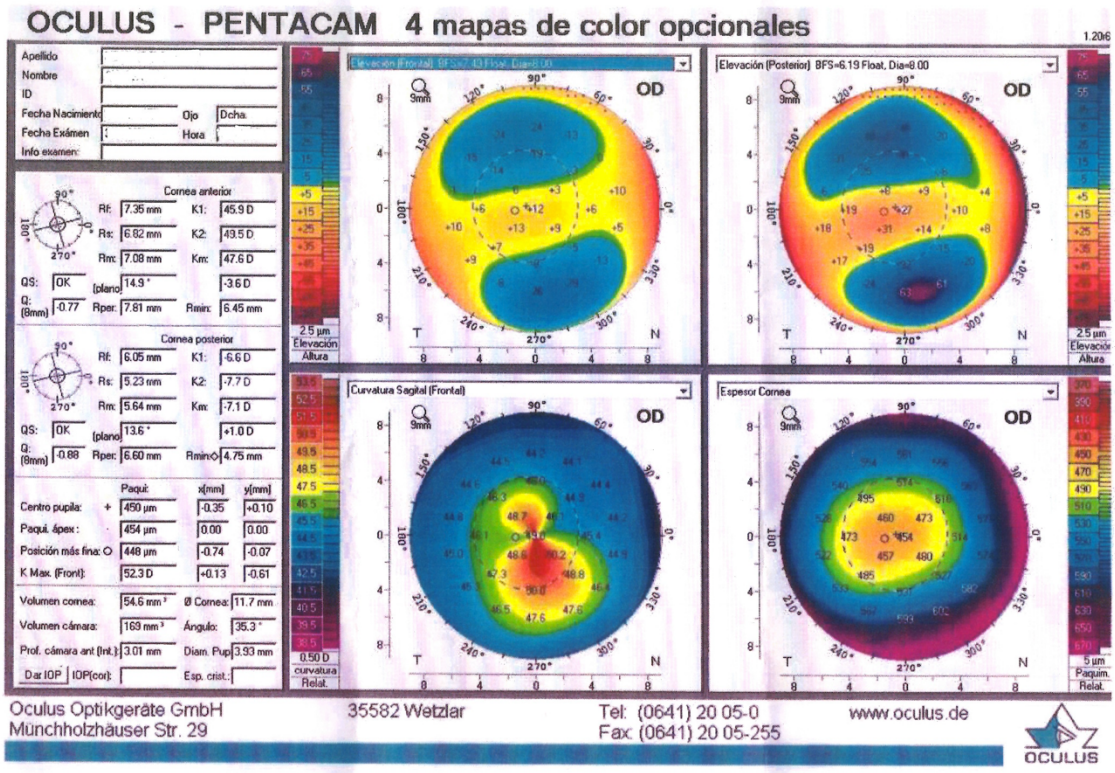
(* = Cambiar manualmente, ! = Valor inseguro)

Carl Zeiss IOLMaster® Advanced Technology V. 7.5
Calibración verificada el: 05/04/2019

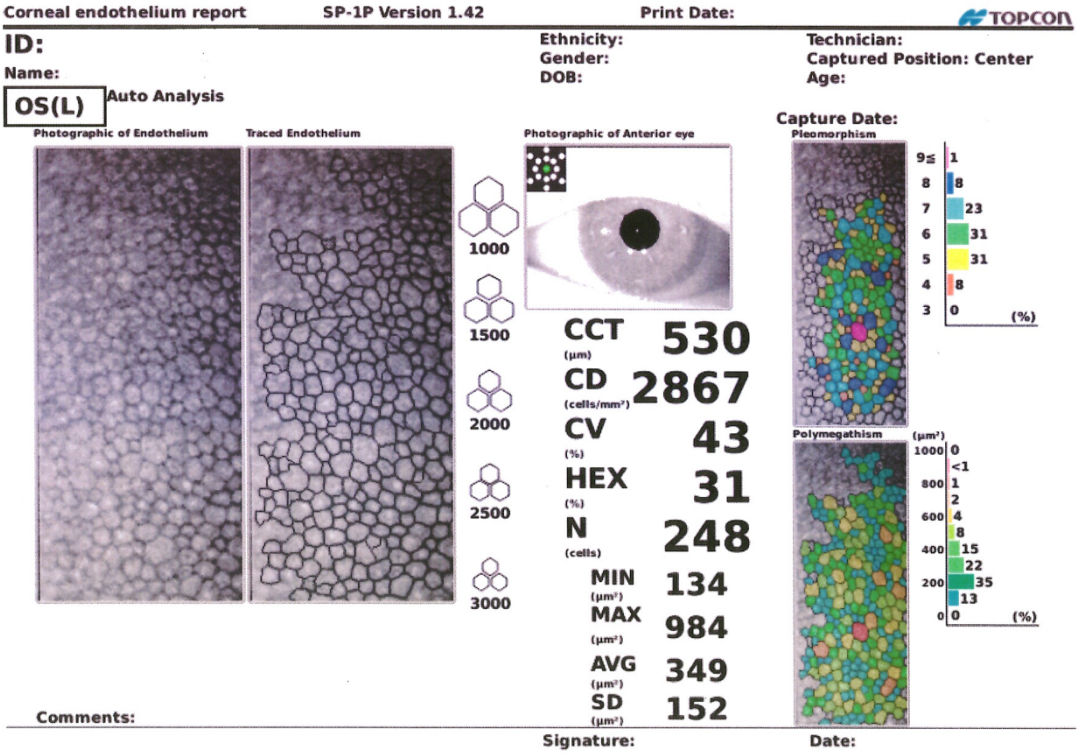
Impreso el: 12/04/2019 a las 11:42 horas.

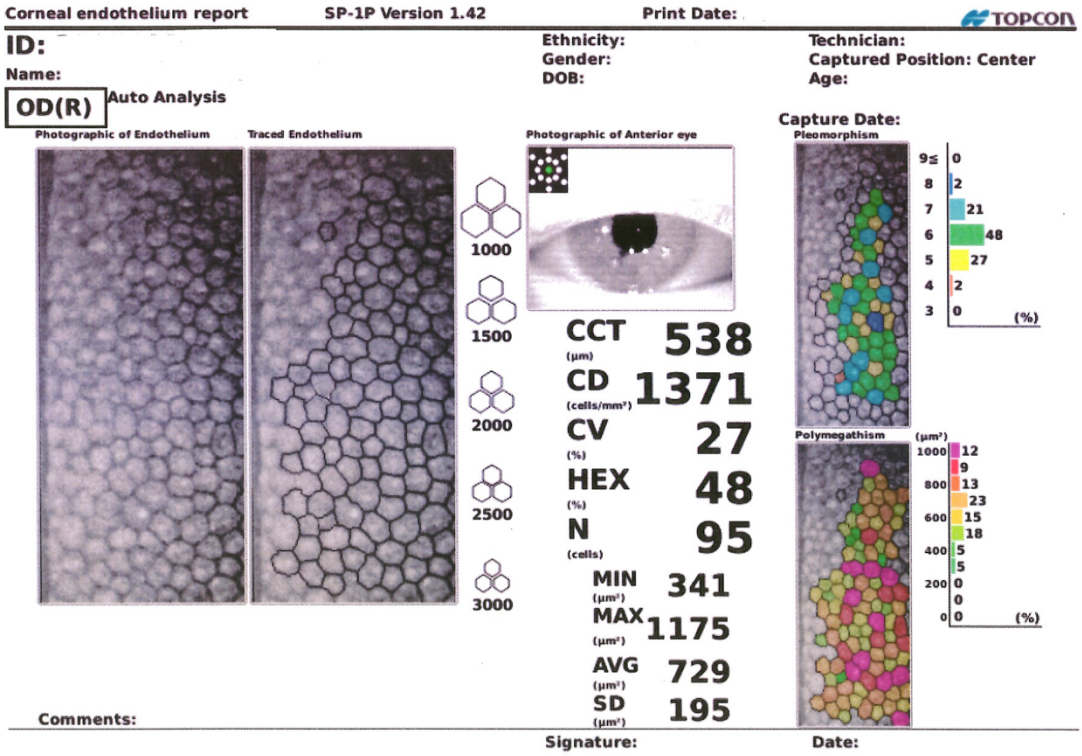
16.4. ANNEX 4 – TOPOGRAPHY



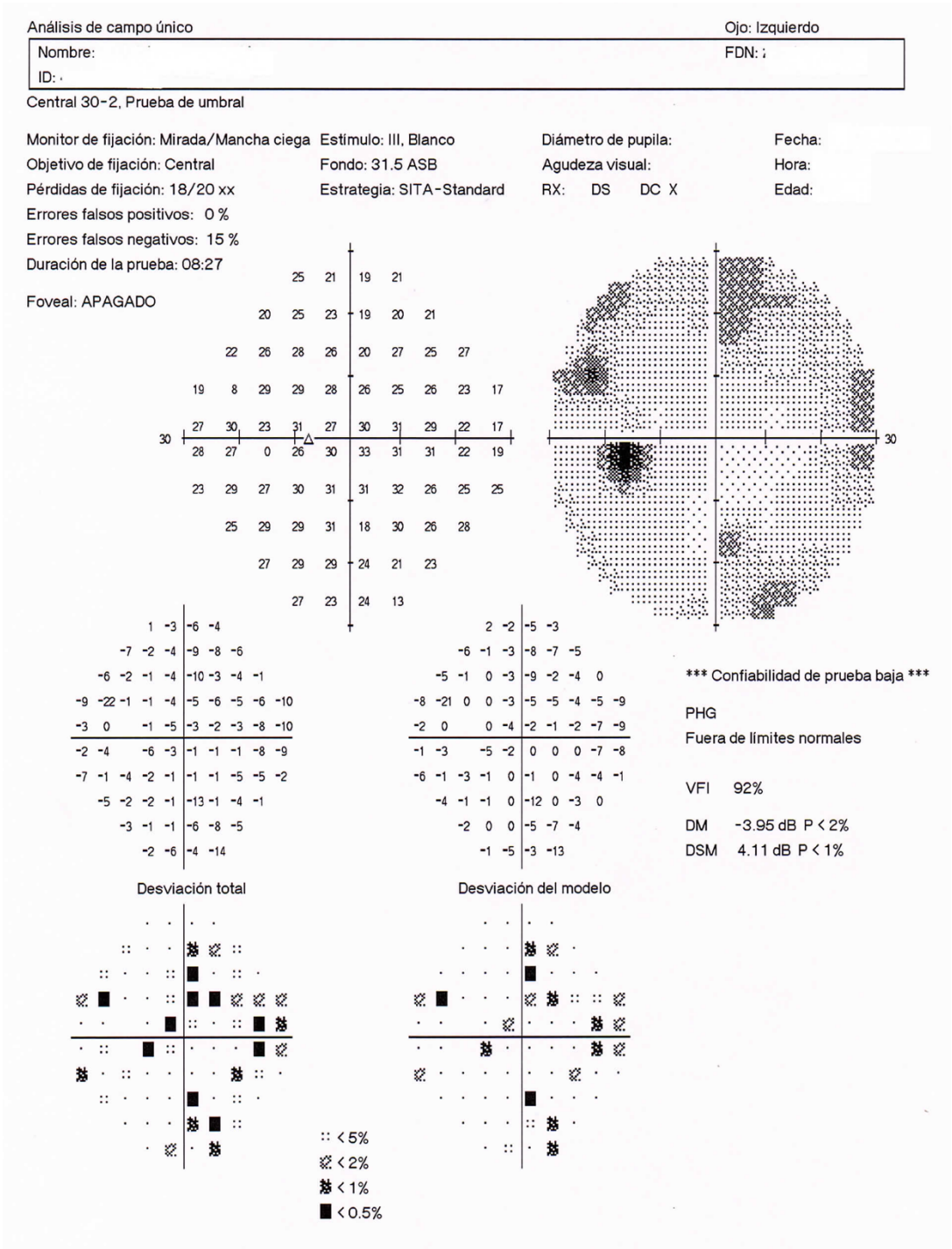


16.5. ANNEX 5 – ENDOTHELIAL CELL COUNT





16.6. ANNEX 6 – VISUAL FIELD



Análisis de campo único | Ojo: Derecho

Nombre: | FDN:

ID:

Central 30-2, Prueba de umbral

Monitor de fijación: Mirada/Mancha ciega | Estímulo: III, Blanco | Diámetro de pupila: | Fecha:

Objetivo de fijación: Central | Fondo: 31.5 ASB | Agudeza visual: | Hora:

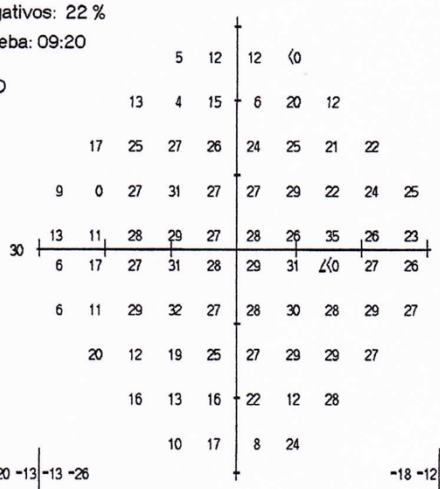
Pérdidas de fijación: 7/21 xx | Estrategia: SITA-Standard | RX: DS DC X | Edad:

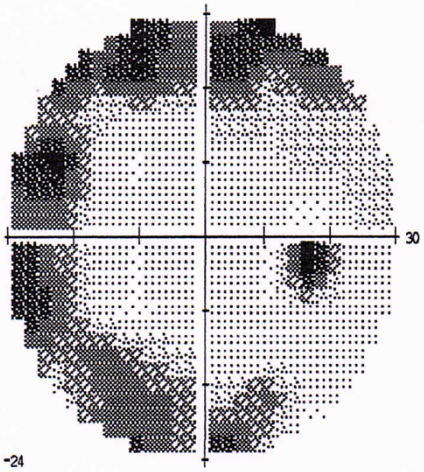
Errores falsos positivos: 5 %

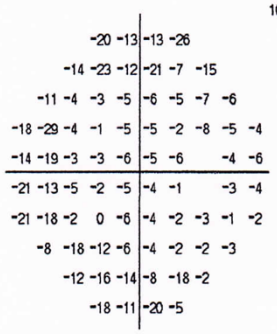
Errores falsos negativos: 22 %

Duración de la prueba: 09:20

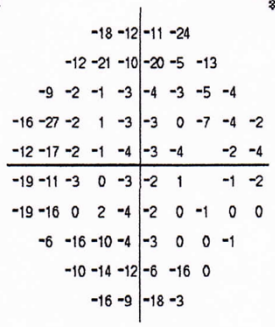
Foveal: APAGADO







Desviación total



Desviación del modelo

*** Confiabilidad de prueba baja ***

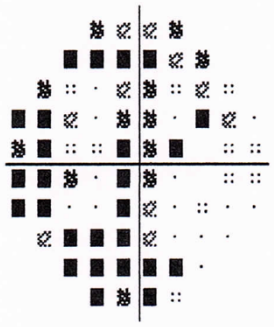
PHG

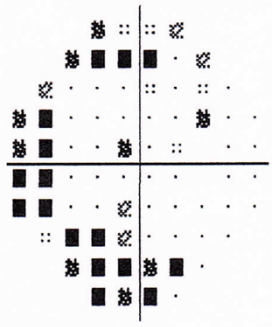
Fuera de límites normales

VFI 86%

DM -7.16 dB P < 0.5%

DSM 7.35 dB P < 0.5%





:: < 5%

▒ < 2%

▓ < 1%

■ < 0.5%

16.7. ANNEX 7 – OPTICAL COHERENCE TOMOGRAPHY