Comparison of Two Contact Lens Fitting Strategies for Keratoconus

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STATEMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity. I confirm that I have not used plagiarism or any form of falsification of results in the process of the thesis elaboration.

I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

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Miguel Romero-Jiménez

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Cree a aquellos que buscan la verdad.
Duda de los que la encuentran.
André Gide

When you make the finding by yourself
– even if you're the last person on Earth to see the light –
you'll never forget it.
Carl Sagan

São os problemas sem resolver, não os resolvidos,
os que mantêm a mente activa.
Erwin Guido Kolbenheyer

Abstract

Purposes: the main goal was to characterize the effect of the two rigid gas-permeable (RGP) contact lens fitting philosophies (apical-touch and three-point-touch) on keratoconus progression by assessing clinical features every 6 months over a 2-year period. The second goal was to assess whether the First Definite Apical Clearance Lens (FDACL) concept is useful for fitting corneal RGP lenses with a variable optic zone diameter and to evaluate which soft contact lens power should be used for piggyback lens fitting in keratoconus. Finally, the relationship between RGP contact lens wear and anterior corneal surface features along the time, in keratoconus was evaluated.

Methods: for the main goal, first trial lens was selected following manufacturer's guidelines and the back optic zone radius (BOZR) was flattened or steepened in 0.10 mm steps until a FDACL was found. Subsequently, subjects were randomly allocated to three-point-touch (BOZR 0.10 mm flatter than FDACL) and apical touch fittings (BOZR 0.40 mm flatter than FDACL). Subsecuently, keratoconus progression was assessed by analyzing clinical features every 6 months over a 2-year period. For piggyback evaluation, six corneal topographies were taken with Pentacam Eye System over the naked eye and successively with soft lens (Senofilcon A) powers of -3.00, -1.50, 0.00, +1.50 and +3.00 D. Several corneal features were then assessed from Pentacam topographies. Finally, to analyse the effect that RGP contact lens had on the cornea, differences between the baseline and post-CL wear on anterior corneal surface features were compared by analyzing Pentacam topographies.

Results: the two years follow-up showed that a greater increase in subjective over-refraction and thus potentially in myopia was found with three-point-touch lens fitting in comparison to apical-touch fitting. Anterior corneal surface higher-order aberrations decreased following RGP contact lens fitting and then they gradually increase along the time, being that increasing greater in the three-point-touch fitting group in comparison to the apical-touch. An increasing on the thinnest corneal thickness right after initial contact lens fitting was also evidenced, followed by progressive decrease along the time. On the other hand, apical-touch fitting approach increases risk of corneal scarring development almost two times in comparison to three-point-touch fitting approach.

The use of the FDACL provides a systematic, reliable and repeatable starting point for a variable diameter RGP contact lens fitting in keratoconus. Apical-touch fitting approach is more difficult to achieve and maintain along the time and it causes an increased number of subjects who discontinued lens wear in comparison to three-point-touch fitting approach. On the other hand, mild negative-powered silicone hydrogel soft contact lenses are more appropriate than positive–powered lenses to use in piggyback lens fittings because they allow the fitting of a flatter and less powered RGP lens.

Finally, RGP contact lens flattens the anterior cornea, reduces corneal asphericity and corneal stigmatism, and reduces anterior corneal surface higher-order aberrations after a short period of wear in keratoconus.

Conclusion: overall, the present work demonstrates objectively that apical-touch fitting approach should be avoided in keratoconus, in order to increased optimal lens fit rate, to decrease number of lens wearers drop-outs and, more important, to reduce corneal scarring incidence. Additionally, corneal RGP contact lens wear in keratoconus causes slight local corneal swelling whose clinical relevance should be ascertained by focused conducted studies.

Resumo

Objetivo: Pretendeu-se com este estudo analisar o impacto das lentes de contacto rígidas de gás permeável (RPG) com 2 filosofias de adaptação (apoio apical e três pontos de apoio) em queratocones em progressão, avaliando as características clínicas em cada seis meses durante um período de dois anos. O segundo objetivo foi avaliar se o método FDACL é útil como ponto de início sistemático para a adaptação de lentes corneais RGP com um diâmetro de zona óptica variável usando duas estratégias de adaptação e avaliar qual é a potência da lente hidrófila adequada quando se adapta com a técnica piggyback em queratocones. Finalmente pretendeu-se avaliar a relação da influência do uso da lente RGP na superfície anterior da córnea em sujeitos com queratocone.

Métodos: No objetivo principal, a primeira lente foi usada seguindo as recomendações do fabricante, com a redução ou o aumento do raio da zona óptica posterior (BOZR) em passos de 0,10mm até encontrar o padrão FDACL. Posteriormente, os indivíduos foram distribuídos aleatoriamente para um dos dois grupos de estudo (adaptação plana ou adaptação de três pontos de apoio) e adaptados com lentes que tinham um BOZR 0,40mm ou 0,10mm maior do que a lente que tinha mostrado inicialmente o padrão FDACL. A progressão do queratocone foi avaliada através da análise das características clínicas, em cada seis meses, durante dois anos. Para avaliar o piggyback, seis topografias corneais com o *Pentacam Eye System* foram realizadas antes da colocação da lente e consecutivamente com lentes hidrófilas de silicone hidrogel com potências de -3.00D, -1.50D, 0.00, +1,50D e +3,00D. Várias características da córnea foram avaliadas a partir das topografias obtidas com o Pentacam. Finalmente, para avaliar qual o efeito que a utilização da lente RGP tinha na superfície corneal em sujeitos com queratocone, as características da superfície da córnea anterior, através da topografia Pentacam foram analisadas por comparação entre a linha de base (sem a utilização de lentes de contacto) e depois de usar as lentes de contato.

Resultados: Os dois anos de monitorização mostraram um incremento miópico da sobre-refração subjetiva, que foi mais significativo com a técnica de três pontos de contacto do que com a técnica de apoio apical. As aberrações de alta ordem na superfície anterior da córnea diminuíram após a adaptação das lentes RGP tendo-se posteriormente verificado um aumento gradual ao longo do tempo, sendo este aumento maior no grupo adaptado com a técnica de três pontos de apoio. Um aumento na zona de espessura mínima da córnea após o uso das lentes RPG foi encontrado, sendo que posteriormente se verificou uma redução da mesma ao longo do estudo. Foi também verificado que a estratégia de adaptação de apoio apical incrementa o risco de desenvolver cicatrização corneana quase duas vezes, em comparação à estratégia de três pontos de apoio. O uso do conceito FDACL proporciona um ponto de início sistemático, fiável e reproduzível para a adaptação de lentes RPG em queratocone. A estratégia de apoio apical é mais difícil de conseguir e manter no tempo e causa um número maior de abandono de uso das lentes de contato, em comparação com a estratégia de três pontos de apoio. As lentes hidrófilas em média com potências negativas demonstraram ser mais apropriadas que as lentes positivas para a adaptação em piggyback ao permitir a adaptação de lentes RGP de menor potência. Por outro lado, os nossos resultados demonstram que as lentes RGP aplanam a córnea central, reduzem a asfericidade e o astigmatismo corneano, e reduzem as aberrações de alta ordem após um curto período de uso.

Conclusão: em resumo, o presente trabalho demonstra que a estratégia de adaptação de apoio apical deveria ser evitada em córneas com queratocone para aumentar a taxa de sucesso na adaptação, reduzir o número de abandonos de usuários de lentes de contato e, mais importante reduzir o risco de desenvolvimento de cicatrização corneana. Por outro lado, o uso de lentes corneais RGP em queratocone causa uma ligeira reação de edema corneal cuja relevância clínica deveria ser abordada em futuros estudos.

Resumen

Objetivo: el objetivo principal era caracterizar el efecto que dos diferentes estrategias de adaptación (plana y tres puntos de apoyo) de lentes de contacto permeables al gas (RPG) tienen sobre la progresión del queratocono, evaluando las características clínicas cada seis meses durante dos años. El segundo objetivo fue evaluar si el concepto de *First Definite Apical Clearance Lens (FDACL)* era útil en la adaptación de lentes RPG con zona óptica de diámetro variable y analizar qué potencia de lente de contacto hidrofílica debería ser usada en piggyback para queratocono. Por último, se analizó la relación entre el uso de lentes de contacto RPG y las características de la superficie anterior de la córnea.

Métodos: para el objetivo principal, la primera lente de prueba fue seleccionada siguiendo las recomendaciones del fabricante, reduciendo o aumentando el radio de la zona óptica posterior (BOZR) en pasos de 0,10 mm hasta que se observaba el patrón de FDACL. A continuación, los sujetos eran aleatoriamente asignados a uno de los dos grupos de estudio (adaptación plana o adaptación en tres puntos de apoyo) y adaptados con lentes que tenían un BOZR 0,40 mm o 0,10 mm mayor que la lente que había mostrado el patrón de FDACL. La progresión del queratocono fue evaluada analizando las características clínicas cada seis meses durante dos años. Para la evaluación del piggyback, se tomó una topografía con Pentacam Eye System sobre la córnea desnuda, y consecutivamente sobre lentes hidrofílicas de hidrogel de silicona con potencias de -3,00, -1,50, 0,00, +1,50 y +3,00. Varias características corneales fueron estudiadas y comparadas. Por último, Para analizar el efecto que el uso de lentes RGP tenían sobre la córnea en queratocono, se analizaron las características de la superficie anterior corneal mediante topografía Pentacam, comparando las mismas entre la situación basal (sin uso previo de lentes de contacto) y después de usar las lentes de contacto.

Resultados: el seguimiento a dos años mostró un incremento en la refracción subjetiva y por lo tanto un aumento potencial de la miopía en el grupo de tres puntos de apoyo en comparación con el de adaptación plana. Las aberraciones ópticas de la cara anterior de la córnea se redujeron inmediatamente después de comenzar a usar las lentes RPG seguido de un aumento progresivo durante el seguimiento, siendo dicho incremento mayor en el grupo de tres puntos de apoyo en comparación con el grupo de adaptación

plana. También se evidenció un incremento del espesor mínimo corneal inmediatamente después de comenzar a usar las lentes de contacto RPG, seguido de una reducción del mismo a lo largo del seguimiento. Por otro lado, el grupo de adaptación plana mostró un riesgo de desarrollar cicatrización corneal más de dos veces mayor que el grupo de tres puntos de apoyo. El uso del FDACL proporciona un método sistemático, fiable y repetible para la adaptación de lentes RPG con diámetro variable en queratocono. La estrategia plana es más difícil de conseguir y mantener a lo largo del tiempo y está asociada a un mayor número de abandonos del uso de las lentes RPG en comparación con la estrategia de tres puntos de apoyo. Por otro lado, las lentes hidrofílicas de potencia negativa media son más apropiadas que las de potencia positiva para la adaptación de piggyback en queratocono, porqué permiten la adaptación de lentes RPG con el BOZR más plano y de menor potencia.

Por último, las lentes RPG aplanan la superficie anterior de la córnea, reducen la asfericidad y el astigmatismo corneal y reducen las aberraciones de alto orden de la cara anterior después de un corto periodo de uso de las lentes.

Conclusiones: el presente trabajo demuestra que la estrategia de adaptación de apoyo apical debería ser evitada en queratocono para aumentar la tasa de éxito en la adaptación, reducir el número de abandonos de usuarios de lentes de contacto y, más importante, reducir el riesgo de desarrollo de cicatrización corneal. Por otro lado, el uso de lentes corneales RGP en queratocono causa un ligero edema corneal local cuya relevancia clínica deberá ser objeto de futuros estudios.

Glossary of terms & Abbreviations

3PT: three-point-touch

a: affected

AC: anterior chamber

ACP: average corneal power

AT: apical-touch

Bc: base curve

BCVA: best corrected visual acuity

BFS: best fit sphere

BL: baseline

BOZD: Back optic zone diameter

BOZR: Back optic zone radius

BSCVA: best spectacle-corrected visual acuity

CL: contact lens

CLEK: Collavorative longitudinal evaluation of keratoconus

CL-W: contact lens wearers

CPV: corneal p value

CS: contrast sensitivity

CXL: cross-linking

D: days

Dia: diameter

Dk: Oxygen permeability

DLK: deep lamellar keratoplasty

Ecc: Eccentricity

FDACL: First definite apical clearance lens

HOA: Higher-order aberrations

ICL: implantable collamer lens

ICRS: intra corneal ring segment

IOL: intra ocular lens

K_m: Average central keratometry

Ksag: maximum sagital keratometry

KSS: keratoconus severity score

LogMAR: Logarithm minimum arc of resolution

M: months

Max: maximum

MCK: mean central keratometry

MFE: maximum front elevation

Min: minimum

N-CL: non-contact lens wearers

PARK: photoastigmatic refractive keratectomy

PKP: penetrating keratoplasty

PRK: photorefractive keratectomy

RGP: Rigid gas-permeable

RMS: root mean square error

SD: standard deviation

Sim K: simulated keratometry

TK: maximum tangential curvature

ua: unaffected

VA: visual acuity

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Publications related with this Thesis

Papers

- Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. *Contact Lens & Anterior Eye.* 2010 33;157-166.

- Romero-Jiménez M, Santodomingo-Rubido J, González-Méijome JM. The thinnest, steepest and maximum elevation locations in non-contact and contact lens wearers in keratoconus. *Cornea.* 2013;32:332-33.

- Romero-Jiménez M, Santodomingo-Rubido J, Flores-Rodríguez P, González-Méijome JM. Which soft contact lens power is better for piggyback fitting in keratoconus? *Contact Lens & Anterior Eye.* 2013;36:45-48.

- Romero-Jiménez M, Santodomingo-Rubido J, González-Méijome JM. An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical-touch fitting approaches with the Rose K2 lens. *Eye Contact Lens.* 2013;39:269-272.

- Romero-Jiménez M, Santodomingo-Rubido J, Flores-Rodríguez P, González-Méijome JM. Short-term corneal changes with gas-permeable contact lens wear in keratoconus subjects: a comparison of two fitting approaches. *Journal of Optometry. September, 2014. Epub Ahead of Print.*

- Romero-Jiménez M, Santodomingo-Rubido J, Flores-Rodríguez P, González-Méijome JM, Cesar Villa-Collar. Which soft contact lens power is better for piggyback fitting in keratoconus? Part II. *Contact Lens & Anterior Eye. October, 2014. Epub Ahead of Print.*

Oral presentations

- Adaptación de lente Rose K2 para queratocono: propuesta de protocolo. CIOCV 2011. Universidade do Minho. Braga. Portugal.

- Estudio de la potencia de la lente hidrofílica en Piggyback para queratocono. Optom 2012. Madrid. Spain.

- Estudio de la potencia de la lente hidrofílica en Piggyback para queratocono. Optom 2012. Madrid. Spain.

- Three-point-touch vs. flat fittings of Rose K2 lenses in keratoconus: an assessment of the success rate. BCLA meeting 2011. Manchester. UK

- Progresión del queratocono y estrategia de adaptación de lentes permeables al gas: signos clínicos. Optom 2014. Madrid. Spain.

- Cambios corneales causados por el uso de lentes permeables al gas en queratocono: comparación de dos estrategias de adaptación. Optom 2014. Madrid. Spain.

Posters

Short-term corneal changes with gas-permeable contact lens wear in keratoconus subjects: a comparison of two fitting approaches. BCLA meeting, Manchester, June 2013.

CHAPTER 1

Introduction and Research Rationale

1.1. Introduction

Keratoconus, which was first described in detail in 1854 [1], derives from the Greek's words *Kerato* (cornea) and *Konos* (conus). Keratoconus is the most common primary corneal ecstasia. [1] It is a progressive corneal disorder with an incidence of 1 per 2,000 in the general population.[1] It is a bilateral and asymmetric corneal degeneration characterized by localized corneal thinning which leads to protrusion of the thinned area.[2] Corneal thinning normally occurs in the inferior-temporal as well as the central cornea. Corneal protrusion causes high myopia and irregular astigmatism, affecting visual quality. Currently, a combination of corneal topographic findings (i.e., inferior corneal steepening and superior-inferior corneal curvature asymmetry) and clinical signs (i.e., Fleischer's ring, Vogt's striae and corneal scarring) are commonly used to diagnose and monitor the disease.[3,4] Though the etiology of keratoconus remains unclear, it is suspected to develop as a combination of genetic and environmental factors.[5]

To date, rigid gas-permeable (RGP) contact lenses represent the most common and successful management option for early to moderate cases of keratoconus, because these lenses can correct relatively high levels of irregular astigmatism and thus substantially improve visual acuity. [6,7] When contact lenses could not be successfully fitted, most keratoconus subjects have been traditionally referred for penetrating keratoplasty surgery. In fact, it has been estimated that around 12% of patients with keratoconus undergo such medical intervention.[8] However, in the last decade, new surgical procedures, including corneal ring segments implantation[9,10] and collagen cross-linking,[11,12] have been developed to treat keratoconus.

The last major review on keratoconus was published in 1998.[1] However our understanding of keratoconus disease has evolved substantially since then with regards its definition, epidemiology, clinical features, classification, histopathology, aetiology, pathogenesis, management and treatment strategies. Therefore, it is mandatory to compile this new knowledge and to provide an updated review of this pathology.

1.2. Contact lens fitting in keratoconus

Rigid gas-permeable contact lenses represent the first management option in keratoconus. However, the fitting of these lenses can be challenging for eye care practitioners, despite the large number of contact lens designs available for fitting the keratoconic eye. The latter might be partly attributed to the lack on consensus on the best contact lens fitting strategy for successfully managing these patients resulting in many contact lens fitters using a "trial-and-error" approach for the fitting of these lenses,[21] leading to increased number of ordered lenses to achieve an optimal lens fit. Furthermore, increased practitioner chair-time also leads to inconveniences for both the practitioner and the patient. Therefore, finding an easy and reliable contact lens fitting approach in keratoconus is both appealing and demanding.

Classically, three RGP contact lens fitting approaches have been described for keratoconus: steep or apical-clearance, flat or apical-touch and three-point-touch or divided support.[13] The differences between these fitting approaches are primarily based in the relationship between the central corneal curvature and the back optic zone radius of the lens. In the apical-clearance fitting approach, the lens back optic zone radius is stepper than central corneal curvature, so the lens vaults the cone apex and bears over the peripheral cornea. [13] In the apical-touch fitting approach, the back optic zone radius of the lens is flatter than the central corneal keratometry, thus the lens mainly bears over the apex of the cone.[13] In the three-point-touch fitting approach, the lens divide its bearing over the cone apex and the mid periphery of the cornea. [13] Currently, there is no a clear understanding whether apical-clearance fitting provides better[16] or worse[14, 15] visual acuity in comparison to apical-touch fitting. Besides, the apical-clearance approach might induce central corneal steepening,[16] which can be misinterpreted as keratoconus progression, so this fitting approach is not regularly used. The apical-touch strategy is thought to induce greater central corneal staining, leading to permanent corneal scarring, than the apical-clearance fitting strategy[18] and this is likely to be attributed to the flatter back optic zone radii relative to the central corneal curvature of the former vs. the latter fitting strategy.[19] Nevertheless, this casual relationship has not been ascertained in a well-conducted, longitudinal, randomized study over a large sample of subjects.[18] Nowadays, three-point-touch is probably the most accepted contact lens fitting approach in keratoconus because it is thought to provide good visual quality while respecting corneal integrity.[13] However, there is not scientific evidence in support of the latter claim and thus some contact lens fitters continue using the apical-touch strategy to manage theirs keratoconus patients.[20]

1.2.1. Corneal rigid gas-permeable contact lens fitting in keratoconus

In 1996, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study group described the concept of the First Definite Apical Clearance Lens (FDACL) as the flattest rigid gas permeable contact lens that exhibited a definite apical-clearance fluorescein pattern contact lens fitting in keratoconus.[21] This group performed a study to validate the FDACL procedure as a tool to measure corneal curvature, assess disease progression in keratoconus beyond that obtainable from keratometry or videokeratography, and to facilitate contact lens fitting in keratoconus. This study group demonstrated that decreasing by 0.20mm and increasing by 0.1 and 0.40 mm the FDACL an apical-clearance, three-point-touch and apical-touch fluorescein patterns, respectively, could be achieved. The study concluded that the use of the FDACL was a valid and reliable method to select the most appropriate contact lens fitting for keratoconus. In this study the CKEK study group used a contact lens design with the same back optic zone diameter, independently of the back optic zone radius. As a final advice, they recommended the use of a lens design with a variable optic zone diameter as more appropriate for keratoconus fitting.[21] However, the utility of the FDACL concept as a systematic starting point for fitting rigid gas permeable contact lens with variable optic zone diameter in keratoconus has not been ascertained. In summary, two questions should be answered about RGP contact lens fitting in keratoconus: 1) is the FDACL concept useful as a starting point for fitting RGP contact lenses with variable optic zone diameter in keratoconus, decreasing the number of ordered lenses?, and 2) are there differences in RGP contact lens fitting success rate with the first lens ordered between apical-touch and three-point-touch fitting approaches?

1.2.2. Piggyback lens system evaluation in keratoconus

Although most keratoconus subjects can be successfully fitted with RGP contact lenses, some of them suffer from intolerance to RGP lens wear. In 1970, Baldone described the piggyback lens system for fitting contact lenses to keratoconus patients who could not tolerate the wear of RGP lenses.[22,23] This system consists in fitting a RGP lens onto a soft lens; the latter acting as a carrier. The soft lens provides a bandage which covers the cornea and protects the cone apex from potential mechanically-mediated complications resulting from wearing RGP lenses alone.[24] The use of a soft contact lens has also been reported to improve the centration of the RGP lens as well as improving visual acuity, comfort, thus increasing dramatically lens wearing time.[24] The percentage of keratoconus subjects that wear piggyback lens systems is estimated to be about 2%.[7] Although the most important concerns related to piggyback lens wear are corneal swelling and neovascularization resulting from wearing low oxygen transmissibility soft lenses,[25] recent studies have probed that the fitting of high oxygen permeability RGP lenses in combination with silicone hydrogels provides enough levels of corneal oxygenation to prevent hypoxic-related complications with daily wear.[26,27] Classically, a low positive-powered soft power has been recommended with piggyback lens fittings as it is thought to create a lenticular bowl which facilitates RPG lens centration.[23] However, the use of a negative-powered soft contact lens has been proposed in cases of relatively steep corneas.[28] Despite of the latter, most fitters use low positive-powered soft contact lenses in piggyback fittings.[29] In a pilot study on a normal subject without keratoconus, O'Donnell and co-workers determined that positive-powered soft lenses facilitated spherical RGP lens centration compared to negative-powered soft lenses, even when negative-powered soft lenses caused a flattening of the anterior corneal surface.[29] In keratoconus, central keratometry is normally steeper in comparison to normal corneas, thus a flatter and easier-to-fit anterior corneal surface might be obtained by fitting negative-powered soft contact powers. Besides, corneal eccentricity is greater in keratoconus in comparison to normal corneas.[30] To the best of our knowledge, there are no studies which have assessed whether positive- or negative-powered soft contact lenses provide a more regular anterior corneal surface to facilitate RGP lens fitting over the soft contact lens. Furthermore, there is no standardized procedure for piggyback lens fitting in keratoconus. In our opinion, there are two important questions to be answered regarding piggyback fitting in keratoconus: 1) it is the FDACL concept useful for piggyback fitting in keratoconus? and 2) which soft lens power is really more appropriate for piggyback fitting in keratoconus?

1.3. Rigid gas-permeable contact lens impact on corneal structure

As it has been discussed above, corneal RGP contact lens wear continue being the most predominant common method to manage keratoconus disease,.[6,7] Nevertheless, little is know with regards to its impact on to understand how the RGP contact lens wear affects the corneal structure. The latter, however, has become crucial for two reasons: 1) because the new surgical procedures for keratoconus treatment (i.e. cross-linking and corneal ring segments implantation) base the surgical indication and procedure on the patients' anterior cornea tangential keratometry values, corneal anterior coma-like aberration as well as and corneal elevation maps,[9,12] and 2) because some imflamatory events, which could be exacerbated by rigid gas-permeable contact lens wearing, has been related with the onset and/or progression of the keratoconus.[31-34]

In the past, RGP contact lens wear has been shown to induce a flattening of the central cornea in both normal[35] and keratoconus subjects.[36] Zadnik and Mutti have previously reported that apical-touch fitting of RGP lenses may flatten the central cornea of keratoconus patients by exerting pressure on the cone apex, thereby forcing the anterior surface to align to a shape similar to that of the RGP lens' back surface.[37] In a 2-years follow-up study of subjects wearing three-point-touch fitted RGP lenses, Hwang et al. found a flattening of the central cornea and a decrease in the thickness of the thinnest point of the cornea.[38] Changes in central corneal curvature and/or thickness may lead to changes in subjective refraction and higher-order aberrations that could potentially impact visual acuity. In summary, two questions should be answered regarding the impact of corneal rigid contact lens wear in keratoconus subjects: 1) is there any difference in anterior corneal features between long-term RGP contact lens wearers and non-contact lens wearers in keratoconus? and 2) how corneal RGP contact lens impact on anterior corneal surface in keratoconus after short-term wearing time comparing apical-touch and three-point-touch fitting approaches?

1.4. Two years clinical outcomes of Rose K2 contact lens fitting in Keratoconus: A comparison of two fitting strategies.

In 1999, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study group stated, "*in spite of the debated risk for increased corneal scarring imposed by flat fitting rigid contact lenses, most CLEK Study patients wear flat-fitting lenses, as prescribed by their practitioners. Because the significance of flat-fitting lenses is unknown, a large-scale randomized clinical trial is required to test the efficacy of apical-touch vs. apical-clearance fitting of rigid contact lenses in the management of keratoconus*".[20] However, nowadays apical-clearance fitting approach is not regularly intended by the practitioners because induces central corneal steepening,[16] which could be interpreted as keratoconus progression. It is necessary to clarify that new surgical procedures for keratoconus (specially cross-linking) base their surgical indications in keratoconus progression which is mostly stated as central corneal keratometry increasing.[39,40] In this thesis author's opinión, fitting corneal RGP lenses with apical-clearance approach would lead to a keratoconus progression diagnostic in most subjects fitted with this approach, and subsequently surgical procedure would be undertaken in all of them, at least in Spain, which is the country where this survey was carried out. On the other hand, despite the fact than three-point-touch fitting approach is considered the most appropriate fitting approach for corneal RGP contact lenses fitting in keratoconus[13] most practitioners continue using apical-touch fittings to manage their keratoconus patients. To the best of our knowledge, no previous studies have compared the incidence of complications in subjects fitted with corneal RGP lenses using apical-touch and three-point-touch contact lens fittings strategies. Furthermore, the impact of these two fitting approaches on corneal structure, visual quality and keratoconus progression, have not been previously compared either in short- or in long-term contact lens wearers with keratoconus. Therefore, the question whether three-point-touch is really better fitting approach, in terms of corneal scarring incidence, compared to apical-touch, remains unanswered beyond practitioners' clinical experiences. Therefore, it seems more interesting to compare apical-touch vs. three-point-touch approaches than apical-touch vs apical-clearance. Additionally, in the past, has been thought that RPG contact lenses could delay keratoconus progression, and the flatter the lens' back optic zone radius, the lesser keratoconus progression.[41,42] Currently, this is not acepted anymore.[43,44] Finally, in 2005, the CLEK study group stated "[…] *it is the investigator´s opinion that true three-point-touch fitting patterns, neither flat or steep, are difficult to achieve and maintain. Years of experience grading of fluorescein patterns at the CLEK Photography Reading Center have borne out that observation (unpublished data)*." [16] However, since then, several longitudinal studies about the use of RGP contact lens in keratoconus using a three-point-touch fitting approach have been published, although none of them have studied, in a strict way, whether the three-point-touch pattern has been maintained along time.[39,45-47]

Therefore, regarding RGP contact lens fitting in keratoconus, three important questions should be studied: 1) is the three-point-touch fitting approach really difficult to achieve and maintain?, 2) is three-point-touch contact lens fitting approach really healthier (i.e. incidence on corneal scarring) than apical-touch? and 3) does the two fitting approaches (i.e. apical-touch and three-point-touch) have different impact on keratoconus progression in a two-years follow-up period?

1.5. Hypothesis, aims and outline of the Thesis

The hypothesis of this thesis is that three-point-touch fitting of corneal RGP lenses is safer, provides better visual quality and delays disease progression in comparison to apical-touch fitting. Therefore, the main goal of this thesis is to compare apical-touch vs. three-point-touch fittings in terms of incidence of complications (i.e. corneal scarring), visual quality and keratoconus progression over a 2-years period. Subjects were randomly assigned to wear Rose K2 lenses fitted using one of the two fitting philosophies under investigation (i.e. apical-touch and three-point-touch).

The thesis has been organized in seven chapters. The aims of each chapter are described below.

Chapter 1.
Introduction and research Rationale.

Chapter 2.
General Methodology of the Thesis.

Chapter 3.
Keratoconus: a review
The aim of Chapter 3 is to provide an updated review on the definition, epidemiology, clinical features, classification, histopathology, aetiology and pathogenesis, management and treatment strategies for keratoconus.

Chapter 4.
Contact Lens Fitting in Keratoconus
Chapter 4 has four different aims:

1. To assess whether the FDACL concept is useful as a systematic starting point for fitting corneal RGP lenses with a variable optic zone diameter (i.e. Rose K2) using two different fitting approaches (i.e. apical-touch and three-point-touch).

2. To compare the optimal lens fit rate obtained with the first lens ordered from the manufacturer between apical-touch and three-point-touch fitting approaches. Additionally, the impact of cone shape (i.e. nipple and oval) in the optimal fit rate was also evaluated.

3. To evaluate how different soft contact lens powers affect anterior corneal surface in terms of central keratometry, corneal eccentricity and anterior corneal surface higher-order aberrations (HOA) in subjects with keratoconus in order to provide a better understanding on which soft contact lens power should be used for piggyback lens fitting.

4. To assess whether the FDACL concept is useful for piggyback lens fitting in keratoconus and to evaluate how soft lens power affects the clinical performance (i.e. fitting and power) of the RGP lens fitted over the soft contact lens.

Chapter 5.
Rigid Gas Permeable Contact Lens Impact on Corneal Structure
Chapter 5 has two specific aims:

1. To assess the relationship between the thinnest corneal location and the steepest and maximum elevation corneal locations in subjects with keratoconus and the effect of long-term RGP contact lens wear on the location of these points.

2. To characterize the biometric characteristics of keratoconic corneas and how these might be affected by a short-term wear of RGP lens fitted using the two fitting philosophies under investigation. Corneal features were assessed using the Pentacam optical instrument, which provides high-resolution measures of corneal curvature and thickness.

Chapter 6.

Two years Clinical Outcomes of Contact Lens Fittings in keratoconus

Chapter 6 has three specific aims as follows:

1. To study the feasibility of achieve and maintain the three-point-touch fitting approach during the study period.
2. To characterize the effect of the two contact lens fitting philosophies on cone progression by assessing changes in corneal topographies taken every 6 months over a 2-year period
3. To evaluate the prevalence, incidence and severity of specific clinical signs of keratoconus disease (i.e. Fleischer's ring, Vogt's striae and corneal scarring) between subjects fitted with apical-touch and three-point-touch strategies. Corneal scarring was assessed using the Gestalt scarring system developed by the CLEK study group.

Chapter 7.

General discussion, conclusions and recommendations for future work

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CHAPTER 2

General Methodology

2.1. Thesis study design.

The present study was designed as a prospective, longitudinal, randomized and single-masked clinical trial. Although a double- or triple-masked design is considered to be the gold standard, it was not possible because author knew the fitting approach assigned to each subject (i.e. apical-touch or three-point-touch). However, the examiner did not review the data collected on the previous visits before each subject visit, so he did not had knowledge about data related to clinical signs, corneal features or contact lenses' parameters at each of the subsequent visit. The main goal of the study was to evaluate differences in clinical features in keratoconus subjects fitted with RGP lenses using apical-touch and three-point touch fitting approaches over a two-years follow-up period.

2.2. Subjects enrolment.

All subjects examined to be included on the present study were referred from ophthalmologist with a keratoconus diagnostic to fit contact lenses. Subjects were both current RGP contact lens wearers as well as non-contact lens wearers. All of them were initially interested on RGP contact lens wearing.

The first visit had two objectives: 1) to perform an ocular examination to check whether the subject matched inclusion/exclusion criteria (**Table 2.1**) and 2) to inform them about the nature and the objective of the study. After a complete explanation, subjects were encouraged to ask as many questions as were necessary to solve all possible questions and doubts about the study. Once the subject stated that he or she had understood everything about the investigation and no doubts remained, the author of the thesis asked him or her whether he or she was interested on participate. If the subject was interested on being enrolled, a complete dossier was facilitate to him or her containing the documents listed bellow which were asked to be read and signed before to begin the study:

- Two copies of "Written Informed Consent about risks and benefits of RGP contact lens wearing in keratoconic corneas".
- Two copies of "Consent Form for Research Participants".
- One copy of "Information Sheet for Research Participants".

These documents are attached at **Appendix 1** of the present document. The documents contained all the information about the project and the commitment that subjects acquired with the principal investigator of the thesis. The commitments were to attend to the scheduled visits, wear the contact lenses that would be fitted by the researcher and using the maintenance solutions prescribed. Subjects were informed they could discontinue the study at any time.

Table 2.1. *Inclusion and exclusion criteria.*

Inclusion Criteria	Exclusion Criteria
Be at least 16 years old.	Non-keratoconic ocular diseases such as cataracts, glaucoma, macular disease, etc.
Diagnosed with keratoconus by corneal topography and/or corneal signs (i.e. Vogt's striae, Fleischer's ring, corneal scarring).	Use of systemic or topical medications that can affect ocular physiology or the performance of the contact lenses.
Neophyte and existing contact lens wearers.	Bilateral corneal transplant, intra corneal ring segments or cross-linking.
	Any lid or anterior segment abnormalities which could contraindicate contact lens wear. Other than those common in keratoconus patients.
Be willing and able to follow instructions and meet the protocol-specified schedule of follow-up visits.	Aphakia or amblyopia.

2.3. Visits schedule.

Once subjects agreed to participate in this study, they were scheduled for initial examination and contact lens fitting. A detailed visits procedure is displayed at **Figure 2.1.**

In subjects who were current RGP contact lens wearers they were asked to avoid the use of their habitual contact lenses a week before the examination, and they must bring their lenses in the storage case to the first visit.

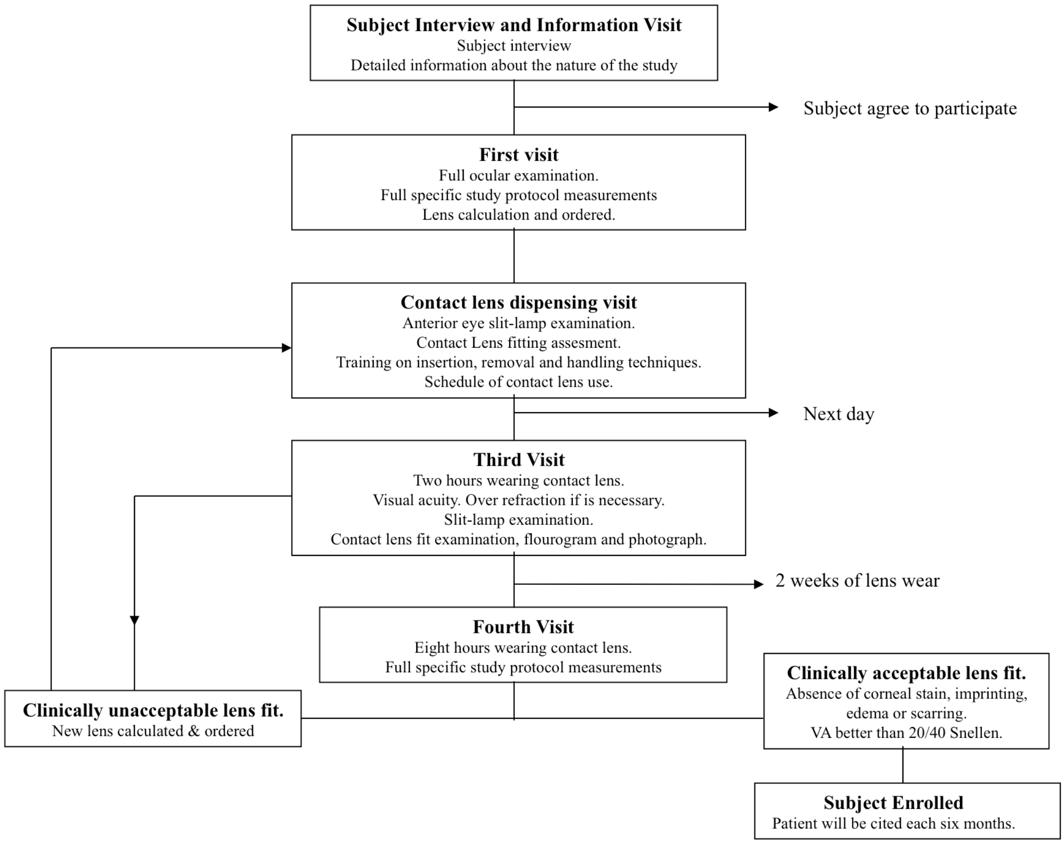

Figure 2.1. Subject enrolment and initial rigid gas-permeable contact lens fitting procedure.

2.4. Specific study measurements and examinations.

The specific study measurements and examinations of the study are the following:

- High contrast visual acuity (Snellen):
    - Monocular and binocular uncorrected.
    - Monocular with pinhole.
    - With habitual spectacles (if available), monocular and binocular.
    - With habitual contact lenses (if available)
- Intraocular pressure.
- Pentacam Topography.
- Javal keratometry.

- Retinoscopy.
- Subjective refraction.
- Anterior segments slit lamp examination.
- Corneal photography.
- Contact lens fitting protocol.
- Data of current RGP contact lens recording (if available).
- Examination of current contact lenses and photography of fluorogram (if available), and record of parameters of these lenses (BOZR, diameter and power).

Once the lenses were dispensed and the subject had been wearing them for at least 8 hours per day for 2 weeks, the following additional measurements were performed at each subsequent visit:

- Full contact lens evaluation
- Evaluation of First Definite Apical Clearance Lens (FDACL).
- Contrast sensitivity (The Mars Letter Contrast Sensitivity Test).

2.5. Visual acuity measure.

At each visit, subjects were asked to read the letters from the biggest to the smallest on a decimal chart until three letters were missed in the same line. Visual acuity scores were recorded as the numbers of letters read correctly. Visual acuity measurements were converted to LogMAR values for statistical analysis.

2.6. Slit lamp examination and clinical signs recording.

Slit lamp biomicroscopy was performed according to standarized protocol and included examination of the adnexa, conjunctiva, and cornea. Graded observations included bulbar and limbal redness, lid roughness and corneal staining (type, depth and/or extend). These clinical events were monitored subjectively in 0.1 units using the Cornea and Contact Lens Research Unit grading scales (CCLRU).[1] Corneal punctate staining was defined as “temporary punctate staining” when it disappeared spontaneously with treatment by the next consecutive visit. The other was defined as “persistent punctate staining”. Additionally, and as a part of the clinical corneal signs evaluation and keratoconus progression, specific keratoconic corneal signs (i.e. Fleischer's ring, Vogt's striae and corneal scarring), were graded according to a custom-made scale (Fleischer's ring and Vogt's striae) based on the Gestal Scarring Scale developed by the CLECK Study Group.[2] This Gestal scale is based on density, size, number and location of corneal scarring. The Gestal Corneal Keratoconus Clinical Signs Scale adapted from CLEK and used in the present work to grade corneal keratoconic clinical signs is showed in **Table 2.2**. To measure the extension if clinical signs with precision an ocular with millimetre graded graticule was inserted on the slit lamp (**Figure 2.2**).

Table 2.2. *Gestal Corneal Keratoconus Clinical Sings Scale. Descriptors for grading in 0.5 steps. LOS: line of sight.*

Grade	Fleischer's Ring	Vogt's Striae	Scarring
1	Trace with slight density. Size less than 90º or length arc around the cone.	Noticeable only wearing RGP contact lens and after blink. Trace and scarce striaes.	Trace and not on LOS, less than 1.5 mm. total size.
2	Easily noticeable. 90º to 180º arc length around the cone. Continuos or in sections.	Easily noticeable. Less than 1.0 mm. of length and less than 0.5 of width.	Easily noticable and approaching LOS, 1.5 to 2.5 mm. total size.
3	Density easily noticable. 180º to 270º. Continuos or in sections.	Noticable striaes on LOS. 1.0 mm to 1.5 mm of length and more than 0.5 mm. of width.	Dense but translucent and impinging on LOS, total size 2.5 mm. or greater.
4	Complete ring around the base of the cone. More than 270º arc length. Continuos.	Dense and large than 2.0 mm. Striae affecting LOS.	Opaque and on LOS, size 2.5 mm. or greater.

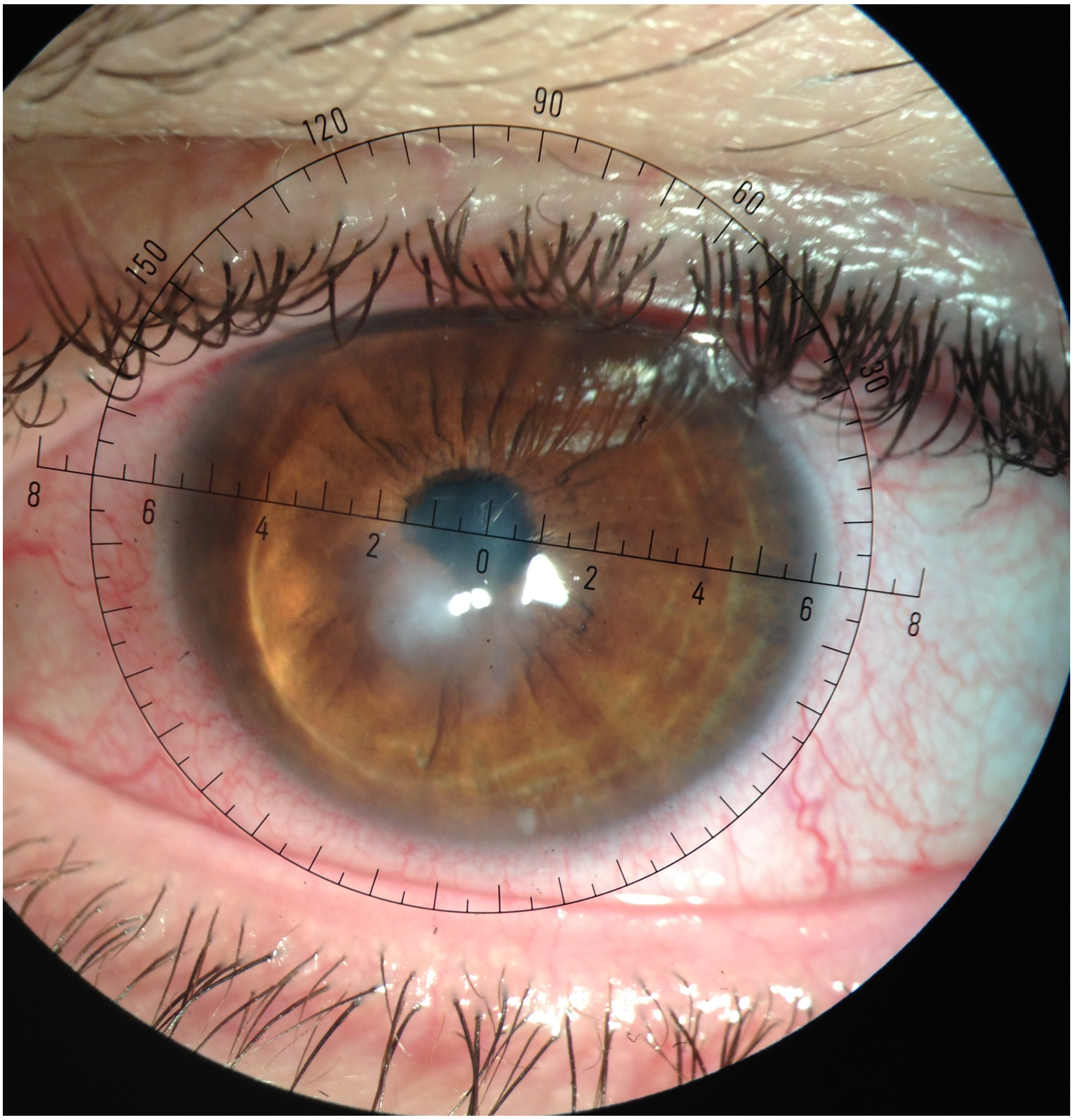

Figure 2.2. Corneal scarring evaluation using an ocular with graded scale graticule.

2.7. Corneal topography examination.

All corneal features, except clinical signs and contact lens performance evaluations, were acquired through corneal topographic using the Pentacam Eye Scanner (Software version 1.16.r:23, Oculus Inc, Wetzlar, Germany). The Pentacam system is based on a rotation Sheimpflug camera that can take 12 to 50 single captures to reconstruct a 3D anterior segment image. In the present study, anterior segment Pentacam examinations were produced with 25 single captures within 2 seconds. The measurement results obtained with Pentacam were checked under the device's quality specification window; only the correct measurements (i.e. "quality specifications" reads OK) were accepted. If the comment was marked yellow or red, the examination was repeated. As it has been previously reported that the Pentacam instrument provides high sensitivity and specificity in keratoconus detection,[3,4] as well as high reproducibility and repeatability in measuring corneal thickness,[5] and corneal power,[6] a single Pentacam examination was acquired for each eye in each visit.

2.8. Contact lens fitting method.

Following manufacturer's recommendations, the first trial lens' BOZR was selected 0.20 mm steeper than the average central keratometry using a Javal Keratometer, and fitted on the eye. Enough time to stop tearing reflex caused by contact lens was allowed, and then sodium fluorescein was instilled for fitting assessment (Haag-Streit, Koeniz, Switzerland). Then, the lens' BOZR was flattened (i.e. increased) or steepened (i.e. decreased) in 0.10 mm steps until the first definite apical clearance lens (FDACL) was found following a method previously described by the CLEK Study Group.[7] Subsequently, subjects were randomly allocated to either the apical-touch or three-point-touch fitting group, and lenses with BOZR of 0.40 mm and 0.10 mm flatter than the FDACL, respectively, were fitted (**Figure 2.3**). Once the subjects were allocated to the group, the selected RGP lens was insert. Following 30 to 60 minutes after lens insertion the overall diameter and edge lift were assessed to ensure the lens was well centered and showed a fluorescein band of 0.5 to 0.7 mm in width along the lens edge. Once an acceptable trial lens fit was achieved, overrefraction was performed and the lens was ordered from the manufacturer. Then, subjects were rescheduled for a dispensing visit. At the dispensing visit, corneal topography was performed in all subjects, prior to lens insertion. Consequently, subjects were trained in procedures for insertion, removal and cleaning/disinfection of contact lenses, and instructed to wear their contact lenses for 2 to 4 hours a day, increasing 1-2 hours for each following days until reaching at least 8 hours of continuous wearing time. Subjects were scheduled for visits at the first day, and fourteenth day. If at the fourteenth day visit contact lens fitting was clinically acceptable and the subject still agreed to wear continue with the study, he/she was enrolled. Contact lenses were replaced on a yearly basis.

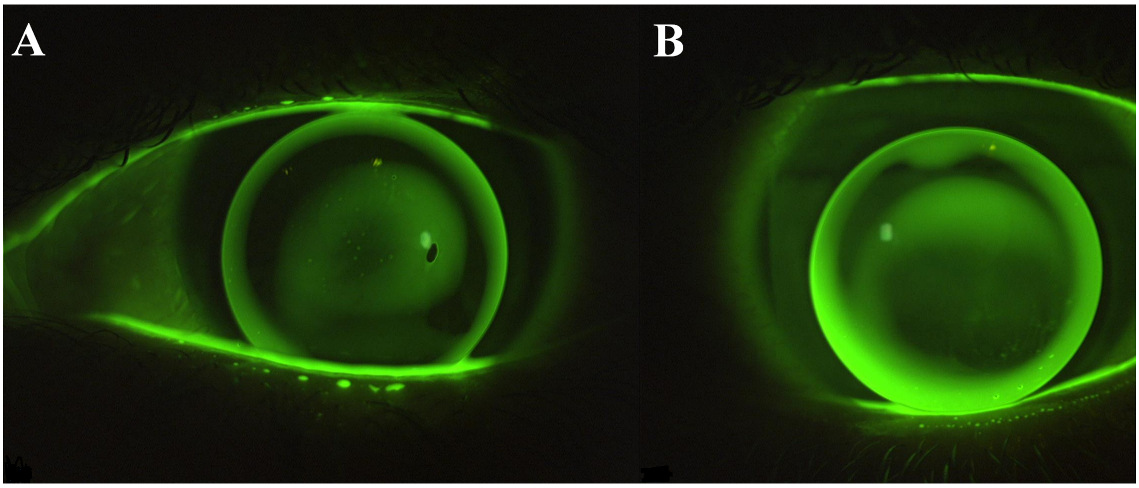

Figure 2.3. Fluorescein patterns of A) three-point-touch and B) apical-touch fitting approaches, respectively.

2.9. Interpretation of contact lens fluorescein patterns.

The examiner washed and wetted the lens with unpreserved saline solution and applied it over the subject's cornea. A sterile fluorescein strip was wetted with one drop of saline solution. The fluorescein strip was gently shaken one time and the strip was gently touched on the subject's superior bulbar conjunctiva. The subject was asked to blink normally. One minute after instilling the fluorescein, the fluorescein pattern was evaluated at the slip lamp biomicroscope with 16X magnification and the cobalt blue filter in place, and the use of a Wratten 12 yellow filter in front of the slit lamp's objective lens.

The subject's current rigid gas-permeable contact lens flourescein pattern was classified as definite apical clearance, apical clearance, apical touch and definite apical touch,[7] in order to analyze lens-cornea relationship (**Figure 2.4**).

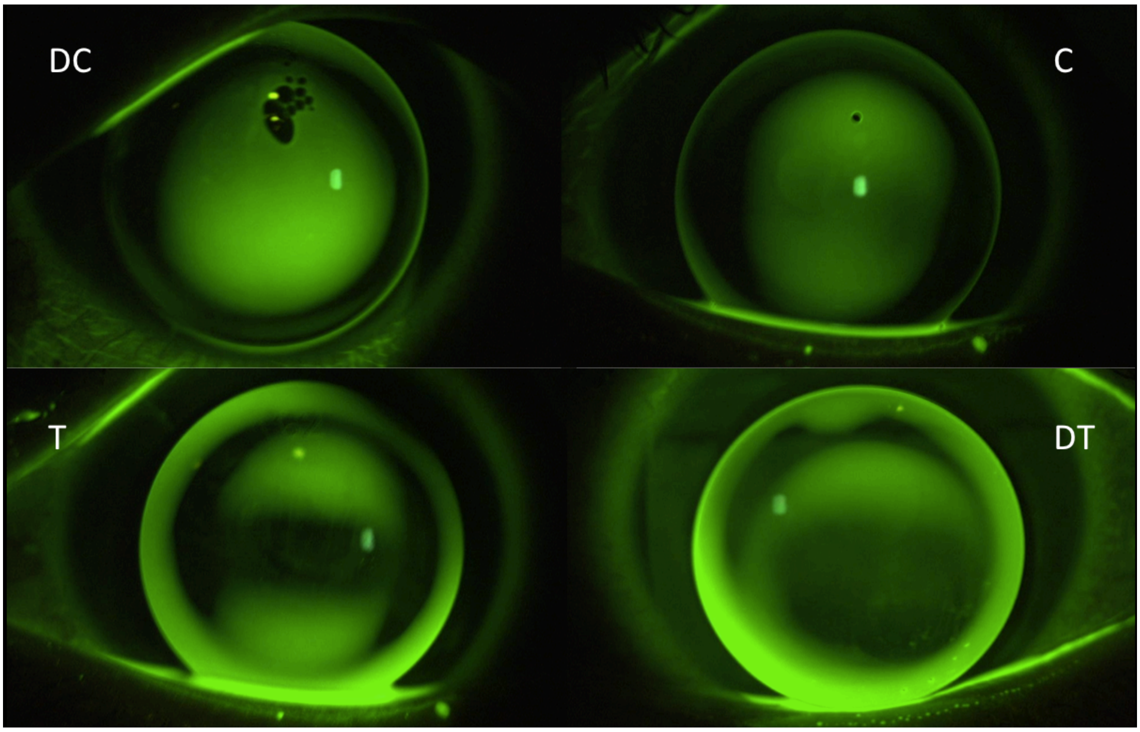

Figure 2.4. Contact lens fitting fluorescein patterns. DC: definite apical clearance. C: apical clearance. T: apical touch. DT: definite apical touch.

2.10. Contact lenses and care solutions.

All contact lenses and care solutions used in this study were provided free of charge by Menicon Company Limited (Nagoya, Japan). The contact lenses were standard Rose K2 manufactured in tisifolcon A material (Menicon Z). The manufacturer facilitated to the researcher two complete fitting sets of this lens design. All the lenses on the trial set were laser marked with the BOZR data in order to avoid mistakes during the trial sessions. The parameters of the trial set employed were displayed at **Table 2.3**. The care solutions using during the study were multipurpose solution Menicare Plus for cleaning, disinfecting, rinsing and storaging lenses on a daily basis, and Menicon Progent for protein removal on a weekly basis. All the lenses and care solutions were dispensed to subjects free of charge during the follow-up period. If a subject abandoned the study before to finish the follow-up (two years) he or she has not had to assume any charge for lenses or care solutions.

Table 2.3. Parameters of the lenses from the Rose K2 trial set.

BOZR	Diameter	Power
7.60	9.2	-2.00
7.50	9.2	-2.00
7.40	9.1	-2.00
7.30	9.1	-3.00
7.20	9.0	-3.00
7.10	9.0	-3.00
7.00	8.9	-4.00
6.90	8.9	-5.00
6.80	8.8	-6.00
6.70	8.8	-7.00
6.60	8.7	-8.00
6.50	8.7	-9.00
6.40	8.7	-10.00
6.30	8.7	-11.00
6.20	8.7	-12.00
6.10	8.7	-13.00
6.00	8.7	-14.00
5.90	8.7	-15.00
5.80	8.7	-16.00
5.70	8.7	-17.00
5.60	8.6	-18.00
5.50	8.6	-19.00
5.40	8.6	-20.00
5.30	8.5	-21.00
5.20	8.5	-22.00
5.10	8.3	-23.00

2.11. Keratoconus grading method election rationale.

Despite keratoconus was described more than a century ago, there is not scientific consensus about the method of grading the severity of the disease. Multiple methods have been previously described based on:

- Visual acuity with contact lens or manifest refraction.[8]
- Repeatability of and changes in refraction and corrected visual acuity.[9-11]
- Tolerance to contact lens wear.[12,13]
- Type of contact lens worn.[14]
- National Eye Institute-Visual Function Questionnaire quality of life scores.[15]
- Age of keratplasty.[16]
- Between-eye asymmetry.[17-19]
- Slit lamp findings (i.e. Fleischer ring, Vogt's striae, corneal staining).[20,21]
- Apical corneal scarring.[12,21-23]
- FDACL lens base curve radius.[24,25]
- Changes in corneal curvature.[26]
- Topographic índices.[23-35]
- Corneal thickness.[36-45]
- Histopathological changes.[46-53]

In 2006, McMahon et al.[54] presented a severity grading system for keratoconus, the Keratoconus Severuty Score (KSS). It uses two corneal topography índices: average corneal power (ACP) and the root mean square (RMS) error for higher-order Zernike terms derived for the first corneal surface wavefront. It also includes clinical signs (i.e. Vogt's striae, fleischer ring and corneal scarring) and a manual interpretation of the topographic map patterns. We consider that this method is the most complete because it combines corneal features and clinical signs. In the KSS index, keratokonus stage is graded based on ACP and higher-order RMS error as:

- Mild (ACP ≤ 52.00 D or RMS >1.50, ≤3.50)
- Moderate (ACP > 52.00 D, ≤ 56.00 D, or RMS > 3.50, ≤ 5.75)
- Severe (ACP > 56,00 D or RMS > 5.75)

The worst of the two variables (i.e. ACP and RMS) carries the greater weight to select the appropriate grade.[54]

2.12. Definition of keratoconus progression rationale.

Progression of keratoconus has been recordered by varying means. The most reproductible method is by keratometric measurements, either using a topographer or a manual keratometer. There are several criteria for keratoconus progression based on central keratometry in scientific literature. For example, Witting-Silva et al.[55] defined keratoconus progression as an increase in corneal keratometric value of at least 1.00 D over 12 months or less. Other authors have defined progression as an increase in kerratometry of 3.00 D in six months,[54] or as little as 1.00 D over 24 months.[57]

Changes in subjective refraction have also been proposed but most clinicians agree that a consistent subjective refraction in a patient with keratoconus may be difficult to achieve. Progression is suggested by an increase in manifest cylinder of more than 1.00 D or an increase in spherical equivalent of at least of 0.50 D over 12 months. Finally, a 0.1 mm decrease in back optic radius of the best fitting contact lens provides further evidence.[55] In the present study, an increase in average central keratometry of 1.5 D during the follow-up period will be defined as keratoconus progression.

2.13. Statistical analysis

2.13.1. Sample size.

The study's sample size was calculated using a statistical power analysis software (SigmaPlot 12.0, Systat Software, Inc., San Jose, California, USA) based on data from previous studies.[55, 58,59] The primary outcome measures for this study was change in central corneal power (ACP) over a 2-year period. Taking a standard deviation (S.D.) of the change in central corneal power of 3.50 D,[58] a sample size of 79 eyes (40 eyes per group) was required to detect a change of 1.75 D assuming a $p=0.01$ and a power of 0.85. In cases of bilateral keratoconus, data from both eyes were included in the analysis, as explained below, and reported as mean ± standard deviation. Assuming 13% of keratoconus subjects present unilateral keratoconus,[60] to ensure the enrolment of at least 79 eyes with keratoconus disease a minimum of 43 keratoconus subjects were needed for this study. In addition, taking into account a potential dropout rate of 10% during the follow-up period,[61] the number of subjects to be recruited in this study was taken to be at least 48 (24 per group).

2.13.2. Eye as within-subject factor.

Currently, there is some controversy in ophthalmology and optometry as to the use or 1 or both eyes of subjects for data analysis.[62,63] However, it is well established keratoconus is an asymmetric disease[17-19] and thus well designed and conducted studies have opted to collect and analyse data from both eyes.[64,65] The use of data from both eyes is recommended in cases where results from both eyes are poorly correlated.[63] The use of the intra-class correlation and Wilcoxon signed rank tests showed that, in our sample, both eyes of subjects with bilateral keratoconus showed a relatively low correlation (all $\mathbf{r}_o < 0.5$) in all the measures of interest of this study (i.e. average corneal power, thinnest corneal thickness, Higher-order aberrations, etc.) and thus eyes were treated as a within-subject factor. In subjects with bilateral keratoconus, the same fitting approach (i.e. the same treatment) was applied to both eyes.

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CHAPTER 3

Keratoconus

Miguel Romero-Jiménez

Introduction

Chapter 3 of this thesis is a comprehensive review of keratoconus disease. The last major review on keratoconus was published in 1998 by Rabinowitz. However our understanding of the disease has evolved substantially since then with regards to its definition, epidemiology, clinical features, classification, histopathology, aetiology, pathogenesis, management and treatment strategies. Therefore, it was mandatory to compile this new knowledge and to provide an updated review of this pathology before to begin this thesis survey. The present chapter was published as a review article, based on available literature and practical experience, in Contact lens and Anterior Eye under the title: "Keratoconus: a review".

Keratoconus: A review

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*(The content included in the present chapter has been updated with studies published from June the 1st 2010 until January the 31st of 2014)

3.1. Abstract.

Keratoconus is the most common primary ectasia. It usually occurs in the second decade of life and affects both genders and all ethnicities. The estimated prevalence in the general population is approximately 54 per 100,000.

Ocular signs and symptoms vary depending on disease severity. Early forms normally go unnoticed unless corneal topography is performed. Disease progression is manifested with a loss of visual acuity, which cannot be satisfactorily compensated with spectacles. Corneal thinning frequently precedes ectasia. In moderate and advance cases, a hemosiderin arc or circle line, commonly known as *Fleischer's ring*, is frequently observed around the cone base. *Vogt's striae*, which are fine vertical lines produced by compression of Descemet's membrane, is another characteristic sign. An important percentage of patients eventually develop corneal scarring. *Munson's sign*, a V-shape deformation of the lower eyelid in downward position; *Rizzuti's sign*, a bright reflection from the nasal area of the limbus when light is directed to the temporal area of the limbus; and breakages in Descemet's membrane causing acute stromal oedema, known as hydrops, are frequently observed in advanced stages.

Several classifications based on morphology, disease evolution, ocular signs and index-based systems of keratoconus have been proposed. Theories into the genetic, biomechanical and biochemical causes of keratoconus have been suggested. Management varies depending on disease severity. Incipient cases are managed with spectacles, mild to moderate cases with contact lenses and severe cases can be treated with keratoplasty. This article provides an updated review on the definition, epidemiology, clinical features, classification, histopathology, aetiology and pathogenesis, and management and treatment strategies for keratoconus.

Keywords: keratoconus, review, epidemiology, classification, aetiology, management.

3.2. Definition.

Keratoconus, which was first described in detail in 1854,[1] derives from the Greek words *Kerato* (cornea) and *Konos* (cone). Keratoconus is the most common primary ectasia. It is a bilateral[2,3] and asymmetric corneal degeneration,[4,5] characterized by localized corneal thinning which leads to protrusion of the thinned cornea, although anecdotic keratoconus onset has been described in thick corneas.[6] Corneal thinning normally occurs in the inferior-temporal as well as the central cornea,[7] although superior localizations have also been described.[8,9] Corneal protrusion causes high myopia and irregular astigmatism, affecting visual quality. It usually becomes apparent during the second decade of the life, normally during puberty,[3,10] although the disease has also been found to develop earlier,[11] and latter in life,[10,12] and it typically progresses until the fourth decade of life, when it usually stabilizes.[10] A recent study has determined that 50% of non-affected eyes of subjects with unilateral keratoconus will develop the disease in 16 years.[13]

3.3. Epidemiology.

The incidence in the general population has been estimated to be between 5 and 23 and the prevalence 5.4 per 10,000 [3,10,14] Differences on the rates reported are attributed to different definitions and diagnostic criteria employed between studies. However, it wouldn't be surprising to expect an increase in the incidence and prevalence rates of this disease over the next few years with the current wide spread use of corneal topography leading to improved diagnosis.

Keratoconus affects both genders, although it is unclear whether significant differences between males and females exit. Some studies have not found differences in the prevalence between genders;[3,15] others have found a greater prevalence in females;[14,16] while other investigators have found a greater prevalence in males.[17-20]

Keratoconus is also known to affect all ethnicities.[10,20-22] In a study conducted in the Midlands area of the United Kingdom, a prevalence of 4:1, and an incidence of 4.4:1 was found in Asians compared to Caucasians.[19] In other study undertaken in Yorkshire, also in the United Kingdom, the incidence was found to be 7.5 times higher in Asians compared to Caucasians. The latter was hypothesized to be attributed to consanguineous relations, especially first-cousin marriages, which commonly take place in the Asian population of the area under assessment. [23]

3.4. Clinical features.

The ocular symptoms and signs of keratoconus vary depending on disease severity. At incipient stages, also referred to as frustre forms, keratoconus does not normally produce any symptoms[24] and thus can go unnoticed by the patient and practitioner unless specific tests (i.e., corneal topography) are undertaken for diagnosis. Disease progression is manifested by a significant loss of visual acuity, which cannot be compensated for with spectacles. Therefore, eye care practitioners should be suspicious about the presence of keratoconus when a visual acuity of 6/6 or better is difficult to achieve with increasing against-the-rule astigmatism.[10] Near visual acuity is generally found to be better than expected from the refraction, distance visual acuity and age of the patient. The appearance of "scissor" shadows while performing retinoscopy, suggest the development of irregular astigmatism. Through retinoscopy it is possible to estimate the location of the cone's apex and its diameter, and the adjustable spectacle corrected visual acuity achievable. The Charleux oil drop that is observed by backlighting the mydriatric pupil also poses a warning sign.[10] Keratometry readings are commonly within the normal range, but may appear irregular. Corneal thinning, where the thinnest part of the cornea is normally located outside the visual axis, is also a common sign preceding ectasia. In moderate and advance cases of keratoconus, a hemosiderin arc or circle line, commonly known as *Fleischer's ring* (**Figure 3.1**), is frequently seen around the cone base.[25,26] This line has been suggested to be an accumulation of iron deposits from the tear film onto the cornea as a result of severe corneal curvature changes induced by the disease and/or due to modification of the normal epithelial slide process.[27] Another characteristic sign is the presence of *Vogt's striae* (**Figure 3.2**),[28] which are fine vertical lines produced by compression of Descemet's membrane, which tend to disappear when physical pressure is exerted on the cornea digitally[15] or to appear by gas permeable contact lens wear.[29] The increased visibility of corneal nerves (**Figure 3.3**) and observation of superficial and deep corneal opacities (**Figure 3.4**) are also common signs, which can be present at different severity stages of the disease.[15] The majority of patients eventually develop corneal scarring. *Munson's sign*, a V-shape deformation of the lower eyelid when the eye is in downward position, and *Rizzuti's sign*, a bright reflection of the nasal area of the limbus when light is directed to the temporal limbal area, are signs frequently observed in advanced stages.[15] Breaks in Descemet's membrane have been described in severe keratoconus, causing acute stromal oedema, known as Hydrops, sudden vision loss and significant pain.[30]

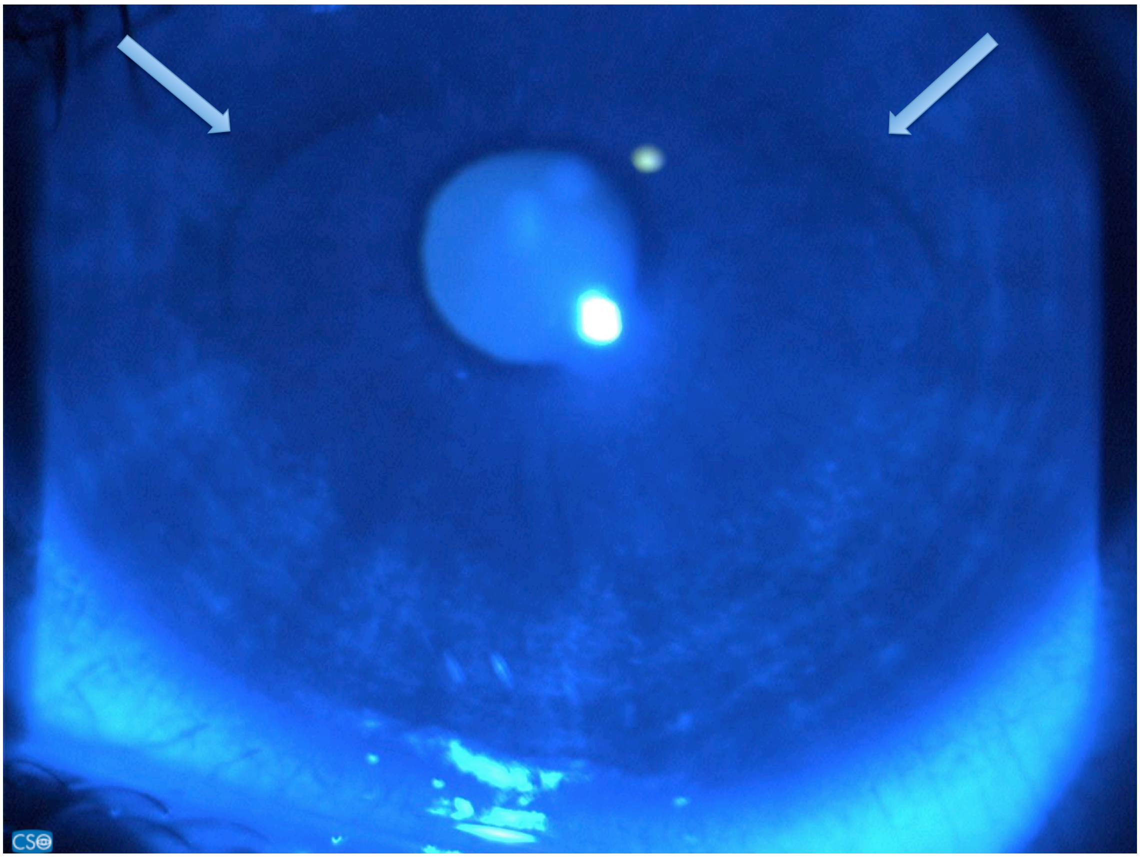

Figure 3.1 Fleischer's ring Sign view under blue cobalt filter.

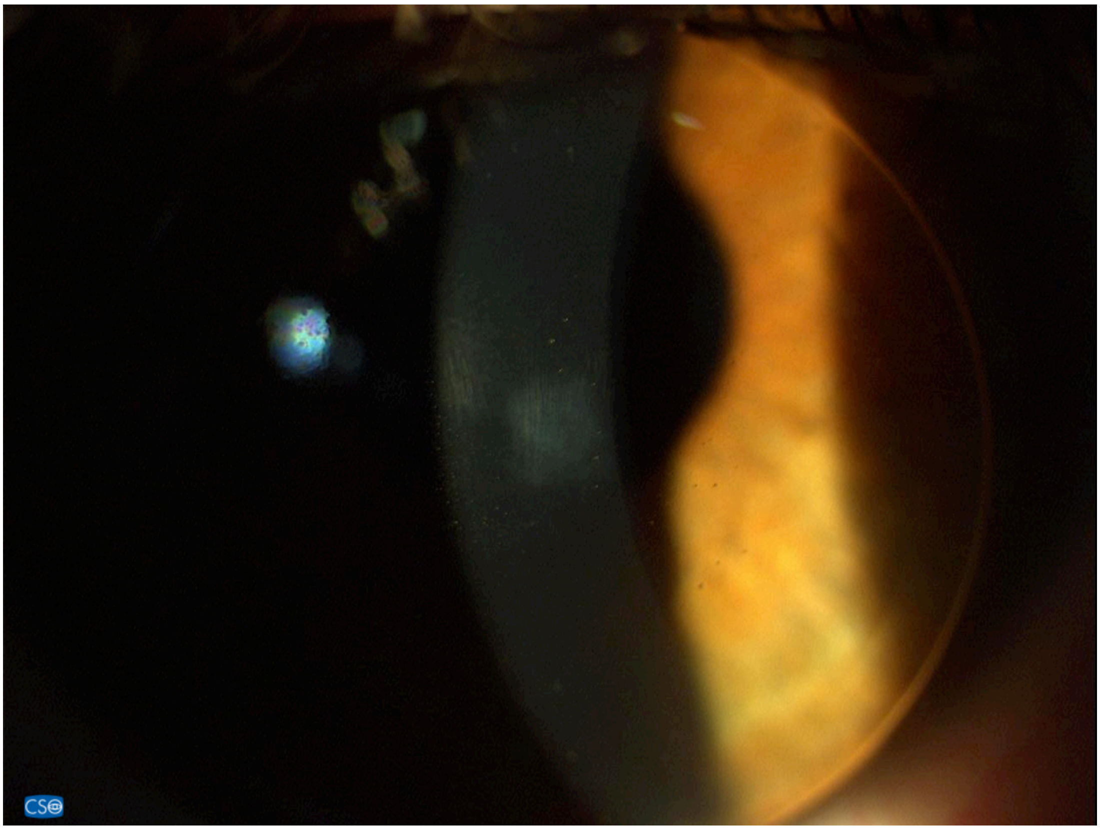

Figure 3.2 Vogt's Striae Sign with corneal rigid gas-permeable contact lens. Vertical lines in Descemet's membrane are noted.

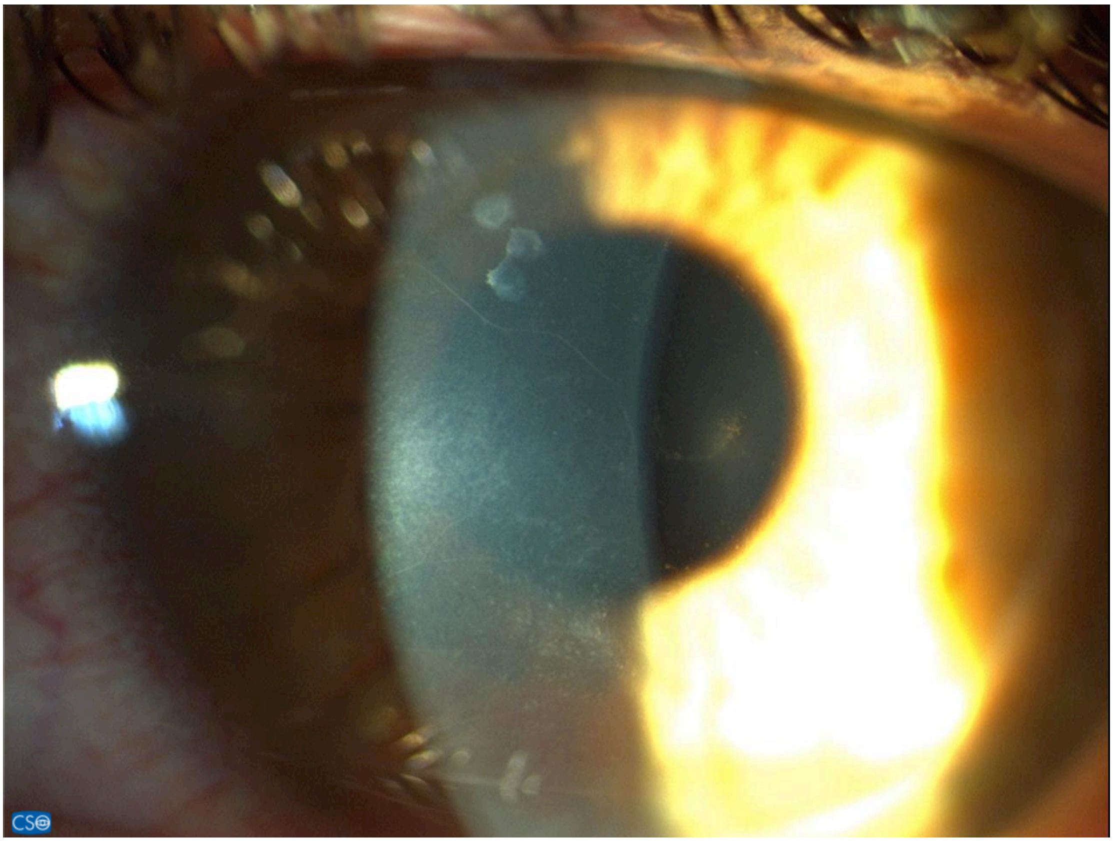

Figure 3.3 Increased visibility of corneal nerves in keratoconus.

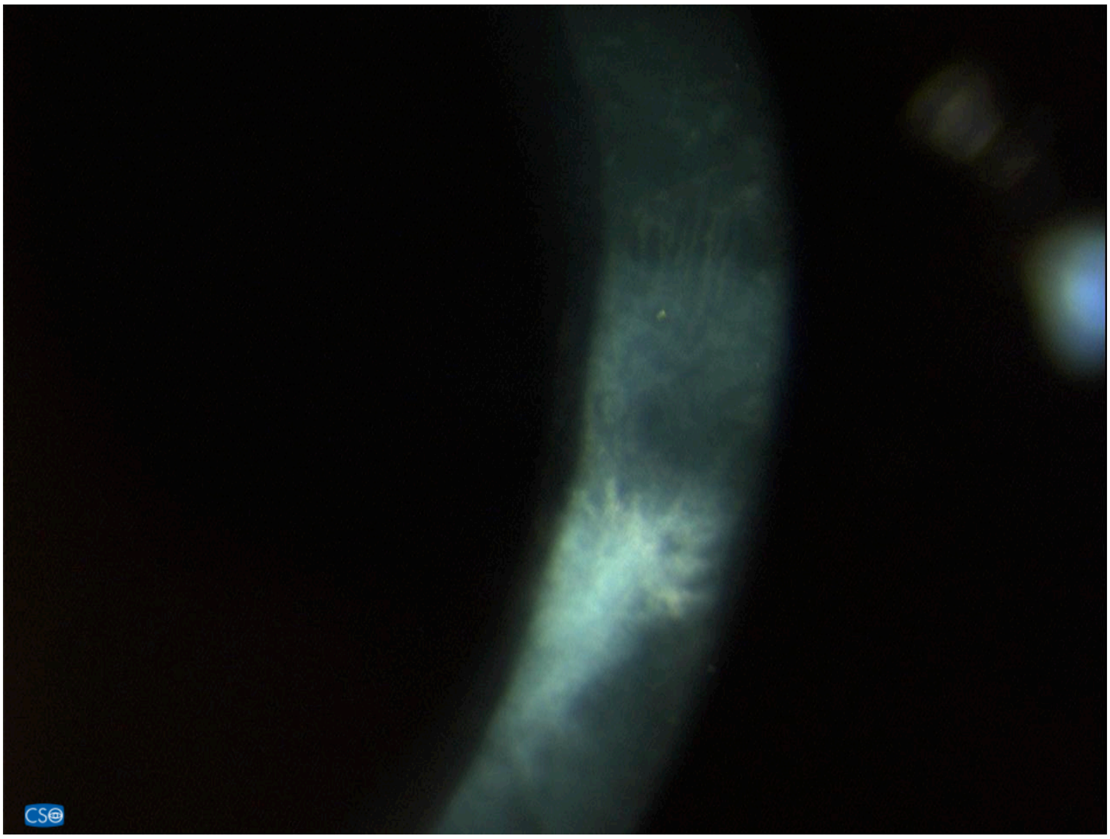

Figure 3.4 Significant corneal scarring induced by contact lens wear.

3.5. Classification.

Several classifications of keratoconus based on morphology, disease evolution, ocular signs and index-based systems have been proposed in the literature:

3.5.1. Morphology.

Classically, keratoconus has been classified into the following categories according to location and size of the ecstatic area: [9,31-33]

Nipple - The cone has a diameter ≤ 5mm, round morphology and is located in the central or paracentral cornea, more commonly in the infero-nasal corneal quadrant. Correction with contact lenses is usually possible and fitting process relatively easy.

Oval - The cone has a diameter > 5mm and a paracentral to peripheral location, more commonly in the infero-temporal corneal quadrant. Contact lens correction is more difficult due to frequent decenttration.

Keratoglobus – The cone is located throughout 75% of the cornea. Contact lens correction is not possible, except in very limited cases or using very large diameter contact lenses

The wide spread use of corneal topography has allowed the detection of new keratoconus patterns affecting the superior, nasal and central cornea.[34] More recently, a new D-shape keratoconus pattern, which affects subjects who have undergone laser assisted in situ keratomileusis (Lasik) refractive surgery procedures, has been described in the literature.[35]

3.5.2. Disease evolution.

The first keratoconus classification based on disease evolution was proposed by Amsler,[36,37] who classified the disease in four different severity stages, similar to that reported by Hom and Bruce (**Table 3.1**).[32]

Table 3.1. Keratoconus Classification. *Keratoconus classification based on disease evolution. VA, visual acuity; D, dioptres.*

Stage	Description
1	Frustre or subclinical form; diagnosed by corneal topography; ~ 6/6 VA achievable with spectacle correction.
2	Early form; mild corneal thinning; corneal scarring absent.
3	Moderate form; corneal scarring and opacities absent; Vogt's striae; Fleischer's ring; < 6/6 VA with spectacle correction, but ~ 6/6 VA with contact lens correction; irregular astigmatism between 2-8 D; significant corneal thinning.
4	Severe form; corneal steepening > 55D; corneal scarring, < 6/7.5 VA with contact lens correction; severe corneal thinning and Munson's sign.

3.5.3. Index-based systems.

Disease detection, even at early stages, has become increasingly important particularly in an attempt to prevent iatrogenic ecstasia formation -the lost of corneal shape- which has been widely documented in patients with subclinical forms of keratoconus who have undergone refractive surgery procedures.[38-40] For this reason, several index-based classification methods have been developed based on corneal topography systems for grading the severity of keratoconus (**Table 3.2**).[41-49] Furthermore, optical coherence tomography instruments have demonstrated their utility in keratoconus detection based on the assessment of corneal thickness.[50]

Recently, several new instruments for assessing different characteristics of the anterior eye have included built-in software for the detection and monitoring of keratoconus disease: the Pentacam (Oculus, Wetzlar, Germany),[51] the Galilei (Ziemer Ophthalmology, Biel, Switzerland),[52] the Schwind Sirius (CSO, Scandicci Firenze, Italy),[53] the SS-1000 Casia (Tomey Co, Nagoya, Japan)[54] for anterior segment tomography using slit-scan technology and Scheimpflug technology, and the Ocular Response Analyzer (Reichert Inc, Depew, NY, USA)[55] and Corvis ST (Oculus, Wetzlar, Germany) to evaluate the biomechanical properties of the cornea.

The Pentacam instrument, which is based on the Scheimplug working principle, takes 12 to 50 images of the cornea at different angles using a rotating camera (**Figure 1.4)** This method evaluates disease severity and progression based on changes in corneal volume and anterior chamber angle, depth and volume. The Pentacam has been found useful in discriminating keratoconic from normal corneas, although a relatively low sensitivity in detecting subclinical forms of keratoconus have been reported. The images provided by the instrument should be interpreted with caution because they do not provide enough data on changes in the posterior corneal surface to make a clinical diagnosis of abnormality. Additionally, interpretation of the posterior corneal surface's higher-order aberrations should be also carried out with caution as reported outcomes show the posterior corneal surface aberrations are negative in sign, which is in contradiction with the theoretical optical properties of the corneal surface.[56] As a result, placido disc-based topographers might be better suited to detecting incipient cases of keratoconus.[57]

Table 3.2. Indices for keratokonus detection. *Index-based system for keratoconus detection. A higher value than the point of cut value suggests the presence of keratoconus.*

Author	Index	Point of Cut	Description
Rabinowitz/ Mc Donnel [41]	K Value I-S Value	47.2 1.4	Diagnosis is performed based on the central keratometry and inferior-superior keratometric dioptric asymmetry.
Maeda/Klyce[42]	KPI KCI%	0.23 0%	KPI is derived from eight quantitative videokeratography index. KCI% derived from KPI and other four described by author index.
Smolek/Klyce[43,44]	KSI	0.25	Keratoconus detection and severity using an artificial intelligent system.
Schwiegerling/ Greivenkamp[45]	Z3	0.00233	Diagnosis is performed based in videokeratoscopic height data decomposed into the set of orthogonal Zernicke polynomials.
Rabinowitz/Rasheed[46]	KISA%	100%	Useful to know if keratoconus is present or absent. It derived from K-value, I-S value, AST and SRAX.
Mc Mahon et al.[43]	KSS	0.5	Diagnosis is performed based on slit-lamp findings, corneal topography, corneal power and higher order first corneal surface wavefront root mean square error.
Mahmoud et al.[48]	CLMI	> 0.45	Diagnosed based in detecting the presence or absence of keratoconic patterns and to determine the location and magnitude of the curvature of the cone.
Mahmoud et al.[49]	CLMI_X	>0.45	Diagnosed based in detecting the presence or absence of keratoconic patterns and to determine the location and magnitude of the curvature of the cone.

The Ocular Response Analyzer allows keratoconus diagnosis and classification by assessing corneal hysteresis and resistance. A previous study has found the latter two values to be significantly lower in keratoconus compared to normal and post-lasik subjects.[58]

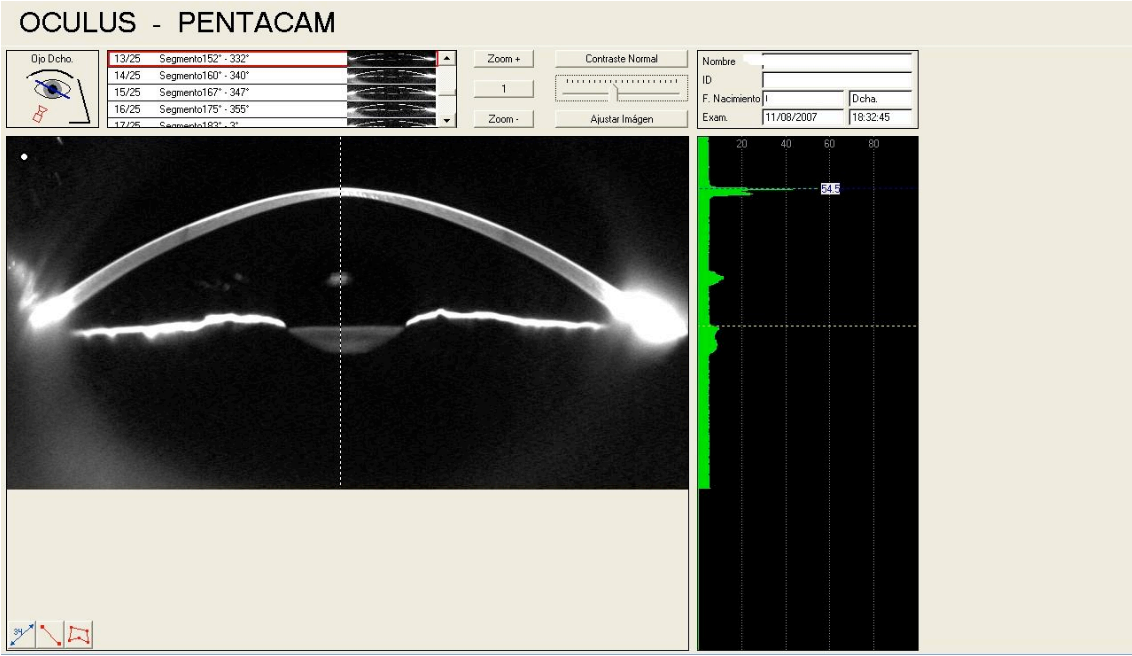

Figure 3.5 Scheimpflug image in severe keratoconus. Significant corneal thinning is appreciated in the central cornea.

3.6. Histopathology.

Histopathologically, there are three signs which typically characterize keratoconus: (1) stromal corneal thinning; (2) Bowman's layer breakage; and (3) iron deposits within the corneal epithelium's basal layer .[10,14]

In general, the keratoconic cornea has decreased tissue volume compared with healthy corneas.[60] In keratoconus disease, the corneal epithelium's basal cells degenerate and grow towards Bowman's layer and this can be noted by observing accumulation of ferritin particles into and between epithelial cells.[60] Basal cell density is also decreased in comparison to normal corneas[61] and particularly in keratoconus subjects who wear contact lenses.[62,63] Bowman's layer often shows breakages, which are filled with collagen from the stroma and positive nodules of Schiff's periodic acid. They form Z-shaped interruptions due to collagen bundles separation.[64] In the stroma, a decrease in the number of lamellae and keratocytes, degradation of fibroblasts,[53] changes in the gross organization of the lamellae, and uneven distribution of collagen fibrillar mass and inter- and intra-lamellae, particularly around the apex of the cone have been observed.[65] Studies carried out using confocal microscopy have demonstrated a reduction in the number of keratocytes in keratoconus compared to normal subjects; the reduction being greater the more advanced the disease:[66,67] This reduction is even greater in patients wearing corneal rigid gas-permeable contact lenses.[62,63] Descemet's membrane is usually unaffected, except in cases of breakages of this tissue, and the endothelium is also generally unaffected by the disease,[61,68] although pleomorphism and elongation of endothelial cells pointing towards the cone have been reported.[64] It has also been demonstrated that corneal nerves in keratoconic corneas have thicker fibre bundles and reduced subepithelial plexus density compared healthy corneas.[70]

3.7. Aetiology and pathogenesis.

Currently, keratoconus is hypothesized to be caused by a combination of genetic and environmental factors.[69] However, despite the intensive research activity into the aetiology and pathogenesis of keratoconus over the last few decades, the cause(s) and possible mechanisms for its development remain unclear. Albeit, there have been several hypotheses proposed into the genetic and biochemical mechanisms. Furthermore, the association of other diseases to keratoconus has also been investigated.

3.7.1. Genetics.

Family, twins and genetic studies have been conducted in an attempt to further understand the genetic nature of keratoconus:

3.7.1.1. Family studies.

Studies carried out before corneal topography techniques became commercially available reported that 6 to 8% of subjects with keratoconus had close relatives affected by the disease.[71] However, studies assisted by corneal topography have shown that up to 50% of subjects with keratoconus have at least one close relative affected by the disease.[72] A recent study estimated that relatives of keratoconics have a risk 15 to 67 times higher of developing keratoconus than those who do not have relatives with keratoconus.[73] An autosomal dominant mode of inheritance with variable expression has been suggested.[72,74]

3.7.1.2. Twin studies.

To date, 32 pairs of monozygotic twins[69,74-79] and five pairs of dizygotic twins,[69] affected with keratoconus have been described in the literature. In most cases of monozygotic twins, both subjects were affected, although with different[74,75] or similar levels of severity.[76] However, the severity of keratoconus is more concordant in monozygotic than in dizygotic pairs of twins, which suggests a strong genetic component of disease development, probably combined with environmental factors.[69] However, another study on two pairs of twins failed to detect keratoconus in both twins.[77]

Other studies have assessed the mode of transmission in keratoconus disease. A study in an 18 year old monozygotic keratoconus twin, their 8 year old sister and parents, who have not been diagnosed with keratoconus,[78] suggests the possibility of a recessive mode of inheritance, although it is possible the sister could develop the disease over time. The first case of twins with keratoconus in opposite eyes but with a similar level of severity and clinical features has been recently reported.[79] This may have resulted as a consequence of the rise in genetic and/or environmental factors during the acquisition of the zygote symmetry, before it divides into two monozygotic embryos.

3.7.1.3. Genetic Analyses.

Linkage studies carried out in families affected with keratoconus to identify the genetic regions (Loci) have reported genetic susceptibility to the disease.[80-87] Several loci, have been associated to keratoconus disease in different studies (Table 1.3).

Heon et al. identified four mutations of the VSX1 gene (i.e., R166W, L159M, D144E and H244R) in different keratoconic patients.[88] Bisceglia et al. also found four mutations of the VSX1 gene (i.e., D144R, G160D, P247R and L17P) in 7 out of 80 keratoconus subjects assessed.[89] Recently, Eran et al. identified the D144E mutation linkage in a Jewish family affected by keratoconus.[90] In contrast, Aldave et al. reported that just 2 out of 100 keratoconus subjects showed any gene mutation.[91] More recently, Liskova et al. have shown that mutation of D144E is not the direct cause of keratoconus development[92] and Tang et al. have identified that mutations L159M, R166W and H244R are not related to keratoconus.[93]

Table 3.3. Identified Loci in Keratoconus disease.

Author	Locus
Fullerton J, et al.[80]	20q-12
Tyynismaa H, et al.[81]	16q22.3-q23.1
Hughes et al.[82]	15q22.33-24.2
Brancati F, et al.[83]	3p14-q13
Hutchings H, et al.[84]	2p24
Tang YG, et al.[85]	5q14.3-q21.1
Li X, et al.[86]	9q
Bisceglia L, et al.[87]	5q21.2

3.7.2. Biochemical factors.

Several biochemical theories for keratoconus development have been proposed to support the hypothesis that corneal thinning occurs as a result of the loss of corneal structural components. Määttä M et al. found differences in collagen types XIII,[94] XV and XVIII[95] between normal and keratoconic corneas, leading to the suggestion that these differences might play an active role in the wound healing process observed between normal and keratoconic corneas. The excessive degradation of the corneal stroma commonly observed in keratoconus might be the result of proteolitic enzyme activity that can be initiated by an increased level of proteases and other catabolic enzymes,[96] or decreased levels of proteinase inhibitors[97] such as ⟨2-macroglobulin and ⟨1-antiprotease).[98]

It has also been found that keratocytes in keratoconus have four times greater numbers of Interleukin-1 receptors compared to normal subjects.[99] As Interleukin-1 has been postulated to be a modulator of keratocytes proliferation, differentiation and death, it has been suggested that the loss of anterior stromal keratocytes might occur due to an excess of apoptotic cell death and stromal mass loss.[100] Furthermore, if epithelial microtrauma leads to an increased release of Interleukin-1, the latter provides support towards the association of keratoconus with eye rubbing, contact lens wear and atopy.[101] Pro-inflammatory markers Interleukin-6, ICAM-1 and VCAM-1 are over-expressed by 2-40 times, whereas anti-inflammatory marker Interleukin-10 is under-expressed by 8 times in keratoconic patients who wear contact lenses compared to normal myopic subjects.[102] Interleukin-6 cytokine is over expressed in early forms of keratoconus, which supports the development of chronic inflammatory events in the pathogenesis cascade of the disease.[103] In addition, tears proteomic profile has been probed to be affected in keratoconus compared with control subjects, which could be related with the onset and evolution of the disease. [104,105]

3.7.3. Biomechanical Factors.

The different distribution and lower number of stromal lamellae in keratoconic compared with normal corneas[64,65] has been proposed as a precursor for corneal rigidity reduction and thinning, ultimately leading to keratoconus development.[106] Furthermore, oxidative damage has been described as a co-factor in keratoconus progression. Keratoconic corneas have decreased levels of aldehyde dehydrogenase Class 3,[107] and superoxide dismutase enzymes.[108] Both of these enzymes play important roles in the reactive oxygen processes of different species. The reactive oxygen accumulation causes cytotoxic deposition of malondialdehyde and peroxynitrites, which could potentially damage corneal tissues.[109] The main factors related to increased oxidative damage are ultraviolet radiation, atopy and mechanical trauma;[109] the latter could occur as a result of chronic eye rubbing and contact lens wear.[109]

Conflicting results have been reported in the literature with regards to whether[110,111] or not[112] atopy is associated with keratoconus development, as keratoconus subjects appear to rub their eyes much more frequently than normal subjects.[113-115] One study found topographic differences,[116] whereas another study reported differences in progression between keratoconus patients with and without atopy.[117] Interestingly, the latter study found that keratoconic patients with atopy tend to have faster keratoconus progression and more frequent refractive and immunologic complications leading to the earlier need of keratoplasty.[117] Contact lens wear has also been associated to keratoconus progression;[118] however, whether contact lens wear could trigger keratoconus development remains unclear.[10]

Protective steps to reduce oxidative damage and potentially prevent keratoconic development include: (1) the use of ultraviolet filters; (2) improvement of ocular comfort with the use of non-steroidal anti-inflammatory medications; (3) the use of preservative-free artificial tears and allergy medications and; (4) improved contact lens fit to minimize corneal microtrauma.[109]

3.7.4. Related Diseases.

Keratoconus commonly develops as an isolated condition, although it has also been described in association with many syndromes and diseases.[10,119] Studies have reported that 0.5% to 15% of subjects with Down's syndrome suffer from keratoconus, leading to an association 10 to 300 times higher than that of the normal population.[14,120,121] This association has been suggested to occur as a result of eye rubbing owing to the increased rate of blepharitis seen in approximately 46% of Down's syndrome individuals.[121] It has also been found that 30% to 41% of subjects with Leber's congenital amaurosis, a rare genetic disorder, also suffer from keratoconus.[122,123] Although keratoconus in Leber's congenital amaurosis has been documented as an oculo-digital sign (i.e., patients rub their eyes with the fingers in a strongly and compulsively manner), genetic rather than eye rubbing mechanisms for keratoconus have also been identified.[122] Other associations between keratoconus and connective tissue disorders, such as Ehlers-Danlos syndrome subtype VI,[124] Osteogenesis Imperfecta[126] and Joint Hypermobility[126] have previously been reported. Additionally, some studies have found an association between advanced keratoconus and mitral valve prolapse[127,128] whereas another has not.[130]

3.8. Management and treatment.

Keratoconus management varies depending on the disease severity. Traditionally, incipient cases are managed with spectacles, mild to moderate cases with contact lenses, and severe cases can be treated with keratoplasty. Other surgical treatment options include intra-corneal rings segments (ICRS), corneal collagen cross-linking (CXL), laser procedures (i.e., photorefractive keratectomy, phototherapeutic keratoctomy, lasik in-situ keratomileusis) intra-ocular lens implants or a combination of these. A summary of the published keratoconus treatments and their combinations are shown in Table 3.4.

Table 3.4 Management and treatment of keratoconus based in disease stage.

Stage I. (Suspect and Frustre)	Stage II. (Early)
Spectacles[10] *Contact lens Hidrophylic*[134] *RGP contact lens*[140,141] *PRK*[201]	*RGP contact lens*[140,141] *Cross-Linking*[187] *Intra Corneal Ring Segmenst*[183] *Combination CXL and ICRS*[189] *PRK*[201] *PARK*[172]
Stage III. (Moderate)	**Stage IV. (Severe)**
All of the Stage II and: *Combination CXL and PRK*[200] *Combination ICRS and Lasek*[202] *Combination ICRS and IOL AC*[191] *Combination ICRS and IOL AC Toric*[192] *Combination ICRS and ICL*[193] *Excimer Laser Assisted Lamellar Keratoplasty*[174] *Epikeratolpasty*[175]	*Penetrating Keratoplasty*[177-179] *Lamellar Keratoplasty*[165-167] *Conductive Keratoplasty*[197,198] *Laser Thermal Keratoplasty*[199]

RGP: rigid gas-permeable, IOL: intra ocular lens, PRK: photorefractive keratectomy, CXL: cross-linking, ICRS: intra corneal ring segments, PARK: photoastigmatic refractive keratectomy, AC: anterior chamber, ICL: implantable collamer lens.

3.8.1. Spectacles.

Spectacles are normally used in early cases of keratoconus only. As the disease progresses, irregular astigmatism develops and adequate visual acuity cannot be achieved with this type of visual correction.[10]

3.8.2. Contact Lenses.

The first to describe the use of contact lenses to manage keratoconus was Adolf Fick in 1888.[130] Since then, contact lens wear has represented the most common and successful treatment method for early to moderate cases of keratoconus. A study which evaluated contact lens prescribing trends in 518 keratoconus patients (1004 eyes) over a 30-years period showed that contact lens wear represented a satisfactory treatment method and delayed the need for surgery in approximately 99% of all fittings. [131] Although contact lenses for keratoconus are manufactured with hydrogel, silicone hydrogel, gas-permeable and hybrid (i.e., rigid centre and soft skirt) materials, corneal gas-permeable contact lenses remain the most commonly used contact lens type,[132,133] as high levels of irregular astigmatism cannot normally be corrected with other contact lens types (**Table 3.5**).

Frustre and early forms of keratoconus can be, in some cases, successfully corrected with hydrogel contact lenses. Several soft contact lens designs for keratoconus are currently available (**Table 3.5**).[134] Features such as the higher oxygen permeability and modulus of rigidity of silicone hydrogels makes them better suited to keratoconus correction than conventional hydrogel contact lenses. Recently, several new custom-made aberration-control soft contact lenses have been developed to improve visual performance of mild to moderate keratoconus.[135,136]

Three fitting strategies of gas permeable contact lenses, including apical-clearance, apical-touch and three-point touch, have been traditionally used for keratoconus fitting. Apical-clearance provides lens support and bearing directed off the apex and onto the paracentral cornea, with clearance (vaulting) of the apex of the cornea; however, this strategy is no longer in current use as it has been associated with poor visual acuity and cone progression control.[137] The apical-touch fitting technique is characterized by providing primary lens support on the apex of the cornea, in which the central optic zone of the lens actually touches or "bears on" the central cornea (**Figure 3.6**). This technique provides good visual acuity and keratoconus progression control; however, an increase in corneal scarring has also been documented.[137] The three-point-touch fitting technique, perhaps the most popular, allows the contact lens to bear at several points on the cornea, including a light touch on the apex and a heavier touch on the paracentral cornea (**Figure 3.6**). This technique has also been associated with good visual acuity and keratoconus progression control. Previous studies have not found differences in contact lens wearing comfort between apical-touch and apical-clearance fittings techniques.[138] Furthermore, although corneal scarring might occur with apical touch compared to three-point-touch fittings,[139] no randomized clinical trial has been carried out to assess which of these two fitting philosophies perform best.

Despite the different keratoconus gas-permeable contact lens designs commercially available, including multicurve and aspheric designs with unique or variable asphericity, the most popular and successful design currently available is probably the *Rose K* lens (Menicon Co., Ltd, Nagoya, Japan);[140] however, other lens designs have also been reported to be successful in treating keratoconus.[141] More recently, reverse geometry contact lens designs for keratoconus management have also been used with relative success.[142]

Hybrid contact lenses, such as *SoftPerm* (Ciba Vision, Duluth, Georgia, USA),[143] *Solotica* (Solotica, Brazil)[144] and more recently, *Synergeyes* (SynergEyes, Carlsbard, CA, USA)[145] have also been used with relative success in keratoconus management. However, these lenses have not been widely accepted as the current designs, generally more expensive than gas permeable lenses, do not normally provide improved visual correction and wearing comfort in comparison with gas permeable contact lenses.

Table 3.5 Contact lenses for keratoconus. *Contact lens types for keratoconus. Bc, Base curve; Dia: Diameter. Power expressed in diopters. * Synergeyes Clear Kone and Ultrahealth designs, and Paragon ICD design provide vault in microns instead of back surface curve in millimetres.*

Lens Type	Propietary name	Manufacturer	Bc (mm)	Dia (mm)	Power (D)
Soft	Kerasoft	Ultravision	8.0-9.0	14-15	±30
	Soft K	Soflex	7.-8.20	14.2	+10/ -20
Gas Permeable	Rose K2	Menicon	4.3-8.6	7.9-10.4	±30
	Rose K2 IC	Menicon	5.7-9.3	9.5-12	±30
	Rose K2 PG	Menicon	5.7-9.3	9.4-12	±30
	IKone	Valley Contax	4.8-7.7	8.8-10.4	±30
	Soper	David Thomas	5.2-7.5	7.5-9.5	±30
	McGuire	David Thomas	5.6-7.4	8.6-9.6	±30
	Dyna Intralimbal	Lens Dymanic	5.9-9.3	10.4-12.0	±25
Corneo-scleral	SoClear	Dakota Science	5.8-7.8	13.3-15.5	+20 -15
	Normal Eyes	Paragon	5.8-10.5	15.5	±30
	Rose K XL	Menicon	5.8-8.4	13.6-15.6	±20
	Digi Form	Truform	Any	13.5-16.0	Any
	Maxim	Aculens	Any	15.4-16.4	Any
Scleral	Innovative	Innovative Sclerals	Any	18.0-24.0	Any
	GelFlex	Ezekiel Optom.	Any	18.0-24.0	Any
	Tru-Scleral	Truform	7.3-9.0	16.0-20.0	Any
	ICD	Paragon	3900-5600*	16.5	±20
	Scleral SW	Procornea	6.6-8.7	18-20	±30
Hybrid	Clear-Cone	Synergeyes	100-600*	14.5	+5/-15
	UltraHealth	Synergeyes	50-550*	14.5	+20/-10
	SoftPerm[a]	CibaVision	6.5-8.1	14.3	+6/-16

[a] discontinued.

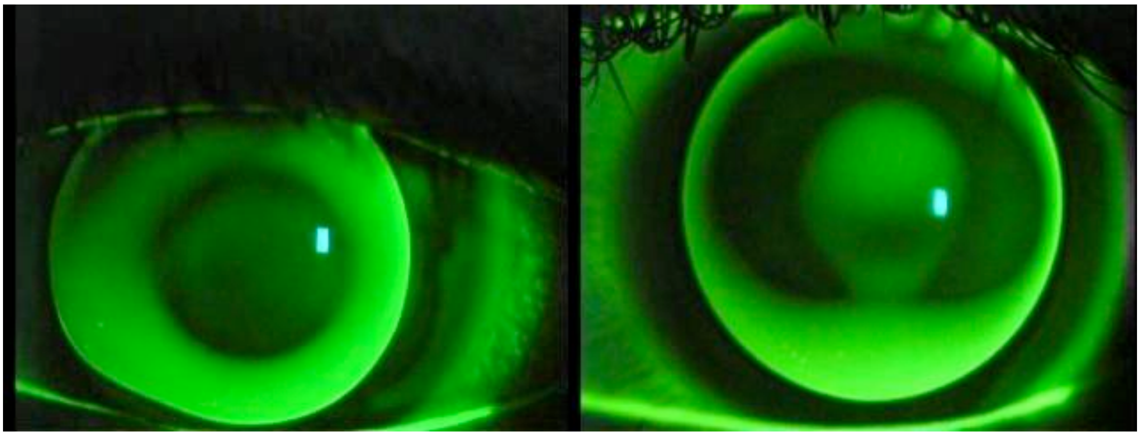

Figure 3.6 Fluorescein patterns of two different gas-permeable contact lens fitting approaches in keratoconus. The figure on the left shows a flat fitting with a significant touch of the lens on the cornea. The figure on the right shows a three-point-touch fitting with slight central touch and peripheral bearing on the cornea.

Piggyback contact lens systems, consisting on the fitting a gas permeable on top of a soft contact lens, have also been used for keratoconus management. The soft contact lens is used to improve wearing comfort and provide a more regular area for the gas permeable contact lenses to sit, whereas the gas permeable contact lens is primarily used for providing adequate visual acuity (**Figure 3.7**).[146] The use of high oxygen permeability soft (i.e., silicone hydrogel) and gas permeable contact lenses is highly recommended for keratoconus management as these corneas are well known to be compromised.[147]

In the last decade, some new designs of large diameter gas-permeable contact lenses have been developed to manage keratoconus showing their utility,[148-152] although some concerns about oxygen permeability with this large-diameter contact lenses have been discussed.[153] The fitting of this large-diameter contact lenses is based in allowing some vault between lens and corneal apex avoiding direct contact. This vault is intended to be from 50 microns in corneo-scleral lenses (**Figure 3.8**)[151,152] and up to 400 microns in mini-scleral and full-scleral lenses (**Figure 3.9**).[148-150]

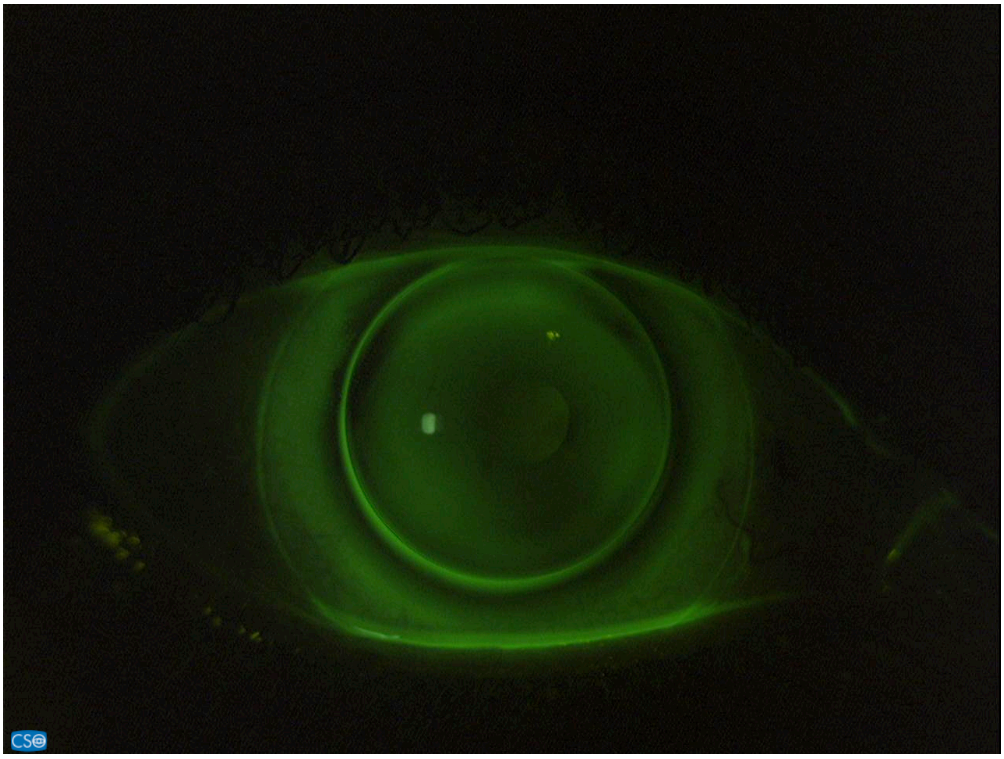

Figure 3.7 Piggy-back fitting in keratoconus.

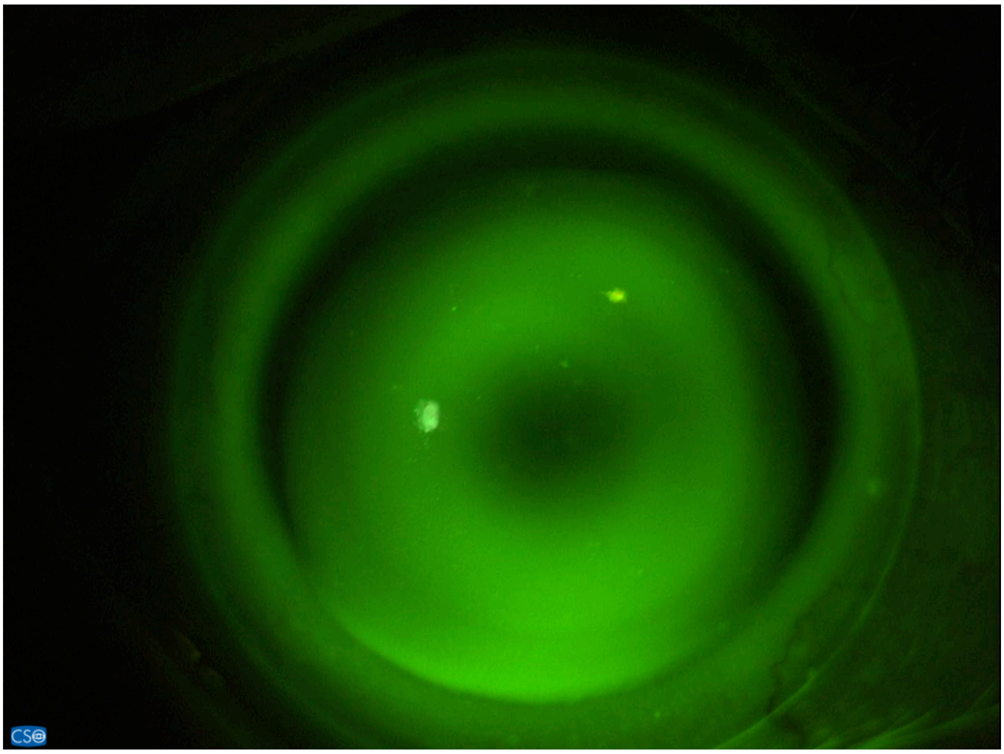

Figure 3.8 Rose K2 XL corneo-scleral contact lens fluorogram in keratoconus, with slight apical bearing.

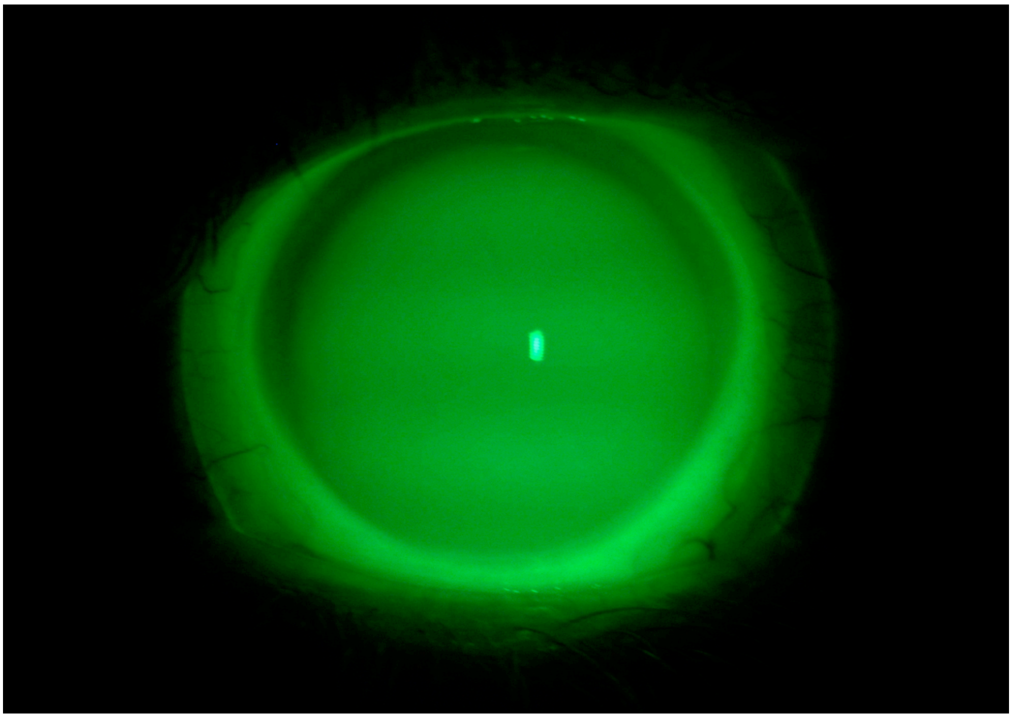

Figure 3.9 ICD mini-scleral contact lens fluorogram in keratoconus. The lens vaults completely the cornea and all bearing has place on conjunctiva.

3.8.3. Surgical procedures.

Although penetrating keratoplasty (PKP), in which the entire thickness of the cornea is removed and replaced by transparent corneal tissue, is perhaps the most commonly used surgical option for advanced cases of keratoconus which cannot be successfully managed with contact lenses,[10,154] it's use is limited to a relatively low number of cases. A recent study has shown that just 12% of 1065 keratoconus subjects who were followed-up for 8 years required PKP.[155] Another study in which keratoconus subjects were followed-up for 48 years reported that less than 20% of them required PKP intervention.[3] In a 7 years follow-up study of 2363 keratoconus subjects, 21.6% required PKP.[156] The risk factors reported to increase the likelihood of keratoconic patients having to undergo PKP are the presence of corneal scarring, visual acuity worse than 6/12 (20/40) with contact lens correction, corneal keratometry steeper than 55 D, corneal astigmatism > 10 D, early age of keratoconus development and poor contact lens tolerance.[154,155,157] **Table 3.6** shows the percentage of penetrating keratoplasty led by keratoconus in different countries.[158-164]

Deep Lamellar Keratoplasty (DLK), in which superficial corneal layers are removed (descement's layer and endothelium remain intact) and replaced with healthy donor tissue has been employed in keratoconus management in recent years.[165-167] However, eyes undergoing PKP are more likely to achieve 6/6 (20/20) vision than those undergoing DLK.[165] On the other hand, a higher risk of endothelial cells loss and graft rejection has been reported with the use of PKP in comparison with DLK.[165,167]

Table 3.6 Percentage of penetrating keratoplasty led by Keratoconus in different countries.

Country	Period	Total eyes PKP.	%KC eyes
China[158]	1997-2002	1702	13%(4 rd)
Spain[159]	1995-2000	60	16.6% (3 rd)
New Zeeland[160]	1991-1999	1308	45,6% (1st)
EEUU[161]	1985-1996	4217	11,4% (3rd)
Iran[162]	1994-2004	19668	34,51% (1st)
Canada[163]	1996-2004	777	12% (4rd)
Taiwan[164]	1987-1999	770	2.5% (6th)
France[177]	1980-1999	3736	28,8% (1st)

Radial keratotomy, in which longitudinal incisions along the peripheral cornea are performed, has been used for the treatment of keratoconus with very limited success. Thus, the technique is no longer conventionally performed for the treatment of keratoconus.[168,169]

Photorefractive keratectomy (PRK), a technique which permanently changes the shape of the anterior central cornea using an excimer laser to ablate (i.e., remove by vaporization) a small amount of tissue from the corneal stroma has been used in the treatment of keratoconus with modest success. Although some studies have reported a significant reduction in cone progression in subjects with early keratoconus[170] as well as an increase in visual acuity and a decrease in higher-order aberrations,[171,172] the technique has been frequently associated with the development of ectasias post-treatment and thus, this procedure is not longer commonly used.

Other corneal surgical procedures for the treatment of moderate keratoconus include Excimer laser-assisted anterior lamellar keratoplasty,[173] Epikeratoplasty[174] and Laser-assisted in-situ keratomileusis.[174] Although laser refractive surgery procedures following PKP and DLK have been commonly used to correct high levels of surgery-induced astigmatism,[165-168,176-178] a higher risk of ectasia has been reported following the use of these surgical techniques.[39,40]

Intra corneal rings segments, a surgical technique originally developed for the treatment of low myopia,[180] has been recently adapted for the treatment of keratoconus.[181] The technique consist in the implantation of one or two polymethyl methacrylate segments in the corneal stroma to reshape its abnormal shape in an attempt to improve visual acuity, contact lens tolerance[182] and prevent or, at least, delay the need for corneal graft.[183] It is commonly used to treat mild to moderate cases of keratoconus, as normal corneal transparency and a minimum corneal thickness of 450 microns at the site of the incision are required.[183] This surgical option has been associated with an improvement in uncorrected and best corrected visual acuity,[183,184] and a decrease in high-order corneal aberrations, especially coma.[185]

Corneal cross-linking is a technique, which aims to increase corneal rigidity and biomechanical stability. The procedure involves removing the corneal epithelium in a 6-7 mm diameter central zone followed by rivoflavin 0.1% solution application and corneal radiation with ultraviolet-A light at 370 nm. Ultraviolet-A light radiation activates riboflavin generating reactive oxygen species that induce covalent bonds between collagen fibrils in the corneal stroma. The irradiation level at the corneal endothelium, lens and retina is significantly smaller than the damage threshold.[186] It has been recommended not to perform this technique in corneas thinner than 400 microns[186] as toxic reactions could take place in the corneal endothelium. Several long-term studies on subjects who underwent corneal cross-linking have reported an improvement in best corrected visual acuity, a flattening of keratometric readings and a significant reduction in cone progression.[187,188] Also, this technique has been successfully used in combination with other surgery techniques, such as corneal intacts.[189] The use of corneal cross linking, however, has been associated with a decrease in the number of keratocytes immediately after treatment, followed by a progressive recovery postoperatively reaching baseline levels six months after treatment, accompanied by an increase in the density of stromal fibers.[190]

The implantation of an intraocular lens for the management of keratoconus is normally undertaken in combination with other types of corneal refractive surgery techniques, such as corneal rings or keratoplasty, as intraocular lens implantation does not normally affect corneal shape and cone progression. Furthermore, the combination of these techniques, which allows the correction of high levels of astigmatism by placing an intraocular lens in the anterior or posterior chamber, has been used with relative success in a limited number of subjects, normally intolerant contact lens wearers, who has shown significant improvement in visual acuity.[191-193]

Thermal therapy, a surgical technique consisting of the application of heat at the cone, gained some popularity in the mid-1970s;[194] however, its wide use was abandoned as a result of its poor predictability[164] and induced adverse effects such as corneal scars and opacities.[196] Recently, radiofrequency techniques, consisting of the application of radiofrequency energy through the corneal stroma using a probe tip, have been used for keratoconus treatment.[197,198] The energy heats the collagen fibrils causing them to shrink. Eight or 16 thermal spots are normally applied around a 5 mm optical zone, inducing a flattening of the cone and subsequent improvement in visual acuity.[197] Additionally, the use of thermal therapy in conjunction with infrared diode lasers have been shown to reduce irregular astigmatism in keratoconus by improving corneal shape regularity.[199]

3.9. Conclusion.

Keratoconus is the most common corneal ectasia. It usually appears in the second decade of the life and affects both genders and all ethnicities. The prevalence in the general population has been estimated to be approximately 54 per 100,000. The ocular symptoms and signs of keratoconus vary depending on disease severity. Despite the intensity of research activity over the last few decades into its aetiology and pathogenesis, the cause(s) and possible mechanisms for development remain poorly understood. There have been, however, several hypotheses proposed into the genetic, environmental, biomechanical and biochemical causes and mechanisms. Keratoconus treatment and management has improved substantially in recent times. While contact lens wear remains the most successful option for managing mild to moderate cases of keratoconus, new surgical options, such as corneal rings and cross linking procedures, have been developed to treat moderate to severe cases. The substantial amount of research currently being conducted is promising for further understanding this disease.

Conflict of interest

MR-J and JS-W report no conflicts of interest. JS-R is a full-time employee of Menicon Company Limited. The Rose K contact lens for keratoconus and irregular corneas is own by Menicon Company Limited.

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CHAPTER 4

Contact Lens Fitting in Keratoconus

Miguel Romero-Jiménez

Introduction:

Chapter 4 of this thesis is an introduction to RGP contact lens fitting in keratoconus and it is divided in two different parts.

The first part of this chapter (section 4.1) tries to answer the question: is the FDACL concept useful as a starting point for fitting RGP contact lenses with variable optic zone diameter in keratoconus, decreasing the number of ordered lenses? And if so, are there differences in RGP contact lens fitting success rate with the first lens ordered between apical-touch and three-point-touch fitting approaches? This section was published as a paper in Eye & Contact Lens under the title: "An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical-touch fitting approaches with the Rose K2 lens".

The second part (section 4.2) tries to answer the questions: which soft lens power is really more appropriate for piggyback fitting in keratoconus? And it is the FDACL concept useful for piggyback fitting in keratoconus? This part was divided in two different sections (4.2.1 and 4.2.2). Section 4.2.1 was published as a paper in Contact Lens and Anterior Eye under the title: "Which soft contact lens power is better for piggyback fitting in keratoconus?" Section 4.2.2 has been published as a paper in Contact Lens and Anterior Eye under the title: "Which soft contact lens power is better for piggyback fitting in keratoconus? Part II".

SECTION 4.1

Rigid gas-permeable contact lens fitting in keratoconus

Miguel Romero-Jiménez

An assessment of the optimal lens fit rate in keratoconus subjects using three-point-touch and apical-touch fitting approaches with the Rose K2 lens

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4.1.1. Abstract.

Objectives: To compare the number of ordered lenses required to achieve an optimal lens fit between three-point-touch and apical-touch fittings in keratoconus subjects with nipple and oval cones using the First Definite Apical Clearance Lens (FDACL) as a starting point.

Methods: First trial lens was selected following manufacturer's guidelines and the back optic zone radius (BOZR) was flattened or steepened in 0.10 mm steps until a FDACL was found. Subsequently, subjects were randomly allocated to three-point-touch (BOZR 0.10 mm flatter than FDACL) and apical-touch fittings (BOZR 0.40 mm flatter than FDACL). Changes were made solely in total lens diameter, edge lift and/or back vertex power until an optimal lens fit was achieved. Differences between fitting approaches were compared in terms of optimal lens fit rates defined as the percentage of subjects successfully fitted with the first lens ordered from the manusfacturer.

Results: Sixty-one subjects (109 eyes) were randomly allocated to three-point-touch and apical-touch fitting approaches. An average of 2.3 trial lenses were necessary to achieve the FDACL. An optimal lens fit rate was achieved with the first lens in 84 out of 109 eyes (77%). No statistically significant differences in optimal lens fit rates were found between three-point-touch and apical-touch fitting approaches (83% and 71%, respectively; p=0.12) and between nipple and oval cones (81% and 68%, respectively; p=0.12).

Conclusions: The use of the FDACL provides a systematic, reliable and repeatable starting point for Rose K2 contact lens fitting in keratoconus. Eye care practitioners should anticipate higher optimal lens fit rates when using three-point-touch (83%) in comparison to apical touch contact lens fittings (71%).

Key words: keratoconus, contact lens fitting, cornea, RGP, contact lenses.

4.1.2. Introduction.

Rigid gas-permeable (RGP) contact lenses represent the most common and successful management option for early to moderate cases of keratoconus.[1] However, the fitting of these lenses can be challenging for eye care practitioners, particularly because many of them do not follow a standardized fitting approach[2] leading to an increased number of ordered lenses, increased practitioner chair-time and inconveniences for practitioners and patients. Classically, three RGP contact lens fitting approaches have been described in the literature for keratoconus: steep or apical-clearance, flat or apical-touch and divided support or three-point-toucch.[3] Differences between fitting approaches are based in the relationship between the central corneal curvature and the contact lens' back optic zone radius (BOZR). In the apical-clearance approach, lens bearing takes place over the peripheral cornea. In the apical-touch approach, lens bearing occurs at the apex of the cone. In the three-point-touch approach, lens bearing is distributed between the apex and the mid-periphery of the cornea. Although the three-point-touch fitting approach has been proposed as safest modality of contact lens fitting in keratoconus, patients are frequently fitted using the apical-touch approach.[4]

In 1996, the collaborative longitudinal evaluation of keratoconus (CLEK) study group described the concept of the first definite apical clearance lens (FDACL) as the flattest lens that exhibited a definite apical clearance fluorescein pattern in keratoconus.[5] This study found that the use of the FDACL was a valid and reliable standardized method to select the most appropriate contact lens fit in keratoconus and recommended the use of a lens design with a variable optic zone diameter for keratoconus fittings.[6]

The Rose K2 contact lens (Menicon Co., Ltd., Nagoya, Japan) features an aspherical back optic zone of variable back optic zone diameter (BOZD), which changes with the lens' base curve (i.e. the BOZD increases with increasing BOZR and vice versa). The company claims an optimal lens fit rate with the first ordered lens of around 80%. The latter value is in contrast with an independent study which reported a 33% optimal lens fit rate with the first ordered lens.[6]

The purpose of the present study is to compare the number of ordered lenses required to achieve an optimal lens fit between three-point-touch and apical-touch fittings in keratoconus subjects with nipple and oval cones using the FDACL as a starting point.

4.1.3. Materials and methods.

Sixty-six subjects (117 eyes) with keratoconus participated in the study. Comprehensive optometric and ophthalmic examinations were performed in all subjects which included the assessment of uncorrected and corrected logMAR visual acuities, anterior segment biomicroscopy, fundus examination, keratometry and corneal topographic analyses using the Pentacam Eye Scanner (Software version 1.16.r:23, Oculus Inc, Wetzlar, Germany).

Keratoconus diagnosis was performed according to the keratoconus severity score described by the CLEK study group.[7] Cone shape was classified into nipple and oval cones following previous reported criteria.[8] A nipple cones was defined as that having a diameter ≤5 mm, a round morphology and central or paracentral corneal location. An oval cone was considered that having a diameter >5mm and a paracentral to peripheral corneal location. Eyes with a previous history of acute corneal hydrops, corneal surgery or any other ocular disease were excluded from the study. All subjects were older than 18 years of age. Informed consent was obtained from all subjects prior to the start of all experimental work and data collection. The study followed the Tenets of the Declaration of Helsinki and was approved by the Institutional Ethical Committee Review Board of MGR Doctores ophthalmology clinic and the scientific committee of the School of Sciences at the University of Minho.

All contact lenses used in the study were standard Rose K2 lenses manufactured in tisilfocon A material (Menicon Z, Menicon Co., Ltd. Nagoya, Japan). The lens design features a variable BOZD and aspherical geometry, and it is available in several peripheral curves. The trial set employed consists of 26 lenses having an overall diameter ranging from 9.2 to 8.3 depending on the BOZR (i.e. the flatter the BOZR the bigger the overall diameter). In subjects with bilateral keratoconus, lens fitting was performed on both eyes using the same fitting approach[5,6] as it is well established keratoconus is an asymmetric condition.[9,10]

4.1.3.1. Fitting method

In eligible subjects, the average keratometry (K_m) of the flattest and steepest corneal meridians were calculated and rounded to the closest 0.10 mm step. Following manufacturer's recommendations, the first trial lens was selected 0.20 mm steeper than K_m and inserted on the eye. Five to 10 minutes were allowed for the lens to settle on the eye and then sodium fluorescein was instilled for lens fitting assessment (Haag-Streit, Koeniz, Switzerland). Then, the BOZR of the lens was flattened (i.e. increased) or steepened (i.e. decreased) in 0.10 mm steps until a FDACL was found (**Figure 4.1.1**) and the number of trial lenses needed were recorded.

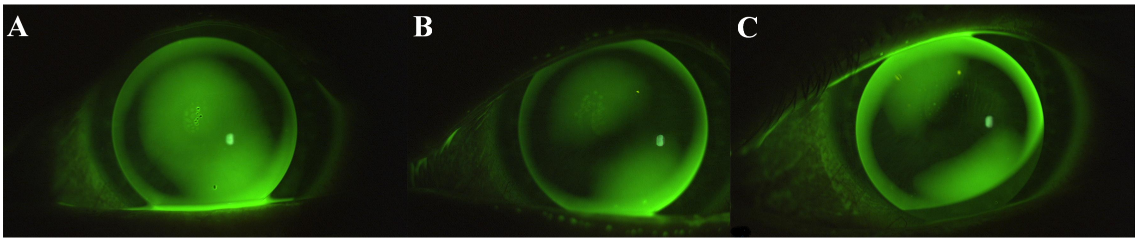

Figure 4.1.1. Contact lens fitting fluorescein patterns showing: (A) First Definite Apical Clearance Lens (FDALC); (B) Light touch; and (C) Definitive touch. Lens B is 0.10 mm flatter than lens A, and lens C is 0.30 mm flatter than lens B.

Subsequently, subjects were randomly allocated to three-point-touch and apical-touch fitting approaches and lenses with base curves 0.10 mm and 0.40 mm flatter than FDACL, respectively, were fitted (**Figure 4.1.2**). Following 30 to 60 minutes after lens insertion, the overall diameter and edge lift were assessed to ensure the lens was well centered and that the edge lift shows a fluorescein band of 0.5 to 0.7 mm in width along the horizontal meridian. Once an acceptable trial lens fit was achieved, the lens was ordered from the manufacturer and subjects were scheduled for a dispensing visit. At the dispensing visit, if the lens provided an acceptable fit, subjects were rescheduled for another follow-up visit two weeks later. An optimal lens fit was considered that in which at the one-month follow-up visit subjects demonstrated at least 20/30 high contrast distance visual acuity and 8 hours of comfortable wearing time. Also, the lens fit was required not to induce any corneal physiology changes ≥ 1 unit using the CCLRU grading scale.[11] Suboptimal lens fits were remedied by changing the contact lens' specifications (i.e. edge lift, diameter and/or power). The BOZR always remained unchanged to ensure subjects were fitted using three-point-touch and apical-touch fitting approaches.

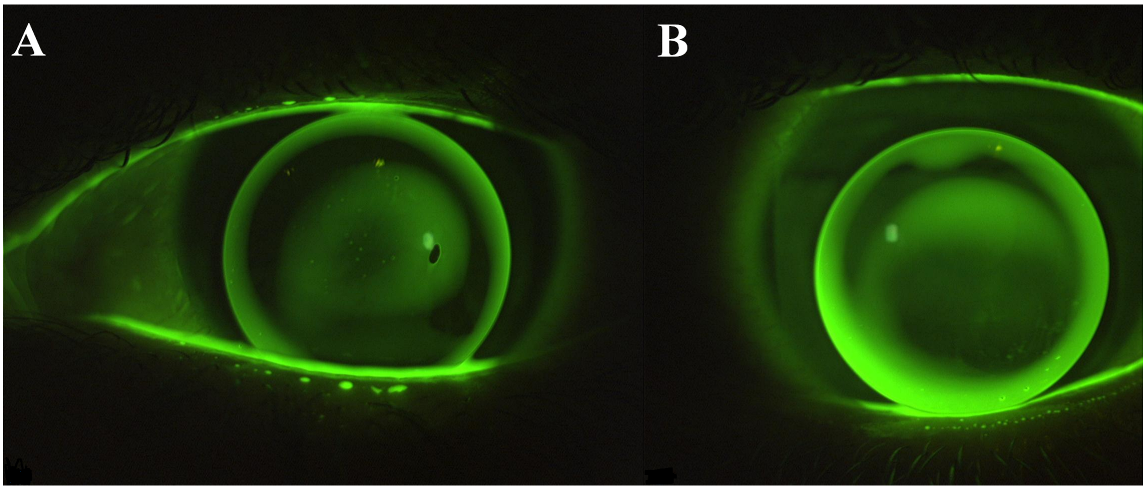

Figure 4.1.2. A: Three-point-touch fitting fluorescein pattern showing a light touch of the lens over the cone apex. B: Flat fitting fluorescein pattern showing a definite touch of the lens over the cone apex.

This process was repeated as many times as necessary until an optimal lens fit was achieved. Differences between fitting approaches were compared in subjects with nipple and oval cones in terms of optimal lens fit rates defined as the percentage of subjects successfully fitted with the first ordered lens from the manufactured.

4.1.3.2. Statistical analysis.

Normality of data distribution was checked using the Kolmogorov-Smirnov test. Differences in BOZR between the first trial lens recommended by the manufacturer (K_m - 0.2mm) and FDACL for all eyes as well as between fitting approaches (i.e. three-point-touch vs. apical-touch), cone types (i.e. nipple and oval) and for the different combinations of fitting approaches and cone types were evaluated using paired and unpaired t-tests as appropriate.

Differences in the number of lenses required to achieve an optimal lens fit with the first ordered lens from the manufacturer between fitting approaches, cone types and for the different combinations of fitting approaches and cone types were assessed using the Chi-square and Fisher Exact tests as appropriate.

Statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). The level of statistical significance was taken as 5%.

4.1.4. Results.

Thirty-seven males (56%) and 29 females (44%) with unilateral or bilateral keratoconus were recruited for the study (117 eyes). The mean age ± standard deviation was 34.6 ± 9.3 years (range 18.3-56.2). Of these, five subjects (8 eyes) were not enrolled because unbearable discomfort experienced during the fitting process and thus were not included in the statistical analysis. Sixty-one subjects (109 eyes) were successfully dispensed contact lenses. In the three-point-touch group, 36 eyes had nipple cones and 18 eyes had oval cones. In the apical-touch group, 39 and 16 eyes had nipple and oval cones, respectively.

Statistically significant differences were found in BOZR between the first trial lens recommended by the manufacturer (Km-0.2mm) and the FDACL for the entire sample as well as between fitting approaches and cone types (all $p \leq 0.05$, **Table 4.1.1**). Additionally, statistically significant differences were also found in BOZR between the first trial lens recommended by the manufacturer (Km-0.2mm) and the FDACL for the three-point-touch fitting approach in oval cones as well as for the apical-touch fitting approach in nipple and oval cones (all $p \leq 0.05$, **Table 4.1.1**). An average of 2.3 ± 1.7 trial lenses per eye was necessary to obtain the FDACL for the entire sample.

In the entire sample, 84 eyes (77%) achieved an optimal lens fit with the first lens ordered. Twenty-three (21%) and 2 eyes (2%) required a second and a third additional ordered lens, respectively, to obtain an optimal lens fit. A greater, although not statistically significant, number of lenses were required to obtain an optimal lens fit in oval in comparison to nipple cones ($p=0.12$). Similarly, the number of lenses required to obtain an optimal lens fit was also greater for the apical-touch in comparison to the three-point-touch fitting approach, although this difference was not statistically significant ($p=0.12$). **Table 4.1.2** shows the number of lenses required to achieve an optimal lens fits as well as the reasons for lens reordering.

Table 4.1.1. *Comparison between of the first trial lens curvature recommended by the manufacturer (Km -0.20mm) and the FDACL for the different fitting approaches, cone types and fitting approach/cone type combinations.*

Measurement	Entire Sample	Fitting approach		Cone Type		Fitting approaches/cone types combinations.			
						Three-point-touch		Apical-touch	
		3pt n=54	Apical n=55	Nipple n=75	Oval n=34	Nipple n=36	Oval n=18	Nipple n=39	Oval n=16
Km-0.2	6.82	6.94	6.69	6.77	6.91	6.99	6.84	6.55	7.0
FDACL	6.69	6.85	6.53	6.71	6.65	6.97	6.64	6.47	6.68
p-value	<0.001	0.003	<0.001	0.041	<0.001	0.532	<0.001	0.042	<0.001

Km, Average central keratometry; FDACL, First definite apical clearance lens radius; Km-0.2 and FDACL are expressed in millimeters.

4.1.5. Discussion.

In the present study, we have used the FDACL concept as a starting point to achieve three-point-touch and apical-touch fitting approaches using a RGP lens design which incorporates a variable BOZD and aspherical back surface geometry (i.e. Rose K2). An average of 2.3 trial lenses were necessary to achieve the FDACL, which is in relative agreement with previous studies that reported 2 to 5 trial lenses per eye to obtain an optimal lens fit.[12,13] According to the manufacturer, the lens should be fitted to achieve a three-point-touch fluorescein pattern. It has been previously reported that a lens with a BOZR 0.10 mm flatter than the FDACL normally generates a three-point-touch lens fitting.[5] Therefore, that the manufacturer's recommended initial trial lens was solely 0.13 mm flatter than the FDACL in the entire sample indicates the fitting protocol proposed by the manufacturer is accurate in achieving a three-point-touch lens fitting.

Table 4.1.2. Number and reasons for lens reordering.

Cause	Cone Type		Three-point-touch (n=54)		Apical-touch (n=55)	
	Nipple (n=75)	Oval (n=34)	Nipple (n=36)	Oval (n=18)	Nipple (n=39)	Oval (n=16)
Steep BOZR.	1	1	1	-	-	1
Increased Diameter	1	1	-	-	1	1
Increased Power	2	-	-	-	2	-
Flat Edge Lift	3	-	2	-	1	-
Decreased Power	3	5	1	3	2	2
Flat BOZR.	1	-	-	-	1	-
Steep Edge Lift	2	4	-	2	2	2
Toric Periphery	1	-	-	-	1	-
Total number (percentage)[1]	14 (19%)	11 (32%)	4 (11%)	5 (28%)	10 (27%)	6 (38%)
p-value	0.12		0.12			

BOZR: Base optical zone radius. [1]Number and percentage of reordered lens for each cone type and fitting approaches combined with cone types. The cell on the bottom right shows the statistical p-value for the comparison between fitting approaches (i.e. three-point touch vs. apical-touch)

That we have found a 77% optimal lens fit rate with the first lens ordered for the entire sample is in contrast with a previous study from Betts et al.[6] which reported an optimal lens fit rate of 33% using also the Rose K2 lens in keratoconus subjects. The latter discrepancy between studies might be attributed to differences in the methodologies employed. In the Betts et al. study, lens fittings were carried out to achieve a "light feather-touch" fluorescein pattern on the central cornea, following manufacturer's guidelines.[6] Although the latter fitting approach might be assumed to be a three-point-touch fitting, it is still subject to subjective interpretation. In our study, however, we employed a more systematic, reliable and repeatable approach for lens fitting as subjects were randomly allocated to three-point-touch and apical-touch fitting approaches using

BOZR 0.10 mm and 0.4 mm flatter than FDACL, respectively. The latter methodology might be more likely to lead to higher optimal lens fit rates.

Although not statistically significant, clinically meaningful differences were found in optimal lens fit rates between three-point-touch (83%) and apical-touch (71%) lens fitting approaches. Optimal lens fit rate differences between fitting approaches might be attributed to differences in mean corneal curvatures between groups as it is well established that the more advanced the disease the more challenging the lens fit. In fact, the BOZR of the first trial lens recommended by the manufacturer (Km-0.2) was steeper for the apical-touch (6.69 mm) in comparison to the three-point-touch (6.94 mm) lens fitting approach. Additionally, apical-touch fittings are normally associated to looser, less stable and worse centered lenses in comparison to three-point-touch fittings, which could ultimately lead to lower optimal lens fit rates, independently of keratoconus disease severity. Nevertheless, optimal lens fit rates found for both three-point-touch (83%) and apical-touch fittings (71%) are in relatively good agreement with that reported by the manufacturer (80%).

In nipple and oval cones, the differences between the first trial lens recommended by the manufacturer and the FDACL were 0.06 and 0.26 mm, respectively. These differences on BOZR were expected due to corneal morphological differences between cone types. The apex of oval cones has been reported to be located further away from the geometrical center of the cornea in comparison to nipple cones.[7] In nipple cones, the cone tends to be round, small and centrally or para-centrally located, whereas in oval cones, the cone apex has been reported to be normally infero-temporally located.[8] Therefore, the fitting protocol used in this study is likely to be more successful in nipple in comparison to oval cones.

Considering both fitting approaches and cone types together, we found that the fitting protocol used in this study requires fewer numbers of contact lenses to achieve an optimal lens fit in subjects with nipple cones fitted using the three-point-touch fitting approach in comparison to the other possible combinations of fitting approaches and cones types (i.e. three-point-touch/oval cones, apical-touch/nipple cones and apical touch/oval cones). The latter is likely to be attributed to the posterior surface design of the Rose K2 lens, which might better mimic the corneal shape of nipple in comparison to oval cones. Higher optimal lens fit rates might be achieved in oval cones using larger overall lens diameters or different contact lens designs.

In conclusion, the use of the FDACL provides a systematic, reliable and repeatable starting point for Rose K2 contact lens fitting in keratoconus. Eye care practitioners should anticipate higher optimal lens fit rates when using three-point-touch (83%) in comparison to apical-touch fittings (71%). Nevertheless, the optimal lens fit rate found in this study (77%) is in good agreement with that reported by the manufacturer (80%).

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The results of this study were presented at 35th British Contact Lens Association Clinical Conference held in Manchester (UK) May, 26-29, 2011.

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SECTION 4.2

Piggy back evaluation in keratoconus

Miguel Romero-Jiménez

SECTION 4.2.1

Which soft contact lens power is better for piggyback fitting in keratoconus?

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Contact Lenas & Anterior Eye 2013;36:45-48

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4.2.1.1. Abstract.

Objectives: To evaluate anterior corneal surface regularity with soft contact lenses of different powers in subjects with keratoconus.

Methods: Nineteen subjects (30 eyes) with keratoconus were included in the study. Six corneal topographies were taken with Pentacam Eye System over the naked eye and successively with soft lens (i.e. Senofilcon A) powers of -3.00, -1.50, 0.00, +1.50 and +3.00 D. Corneal measurements of mean central keratometry (MCK), maximum tangential curvature (TK), maximum front elevation (MFE) and eccentricity (Ecc) at 6 and 8 mm chord diameters as well as anterior corneal surface high order aberrations (i.e. total RMS, spherical- and coma-like and secondary astigmatism) were evaluated.

Results: Negative- and plano-powered soft lenses flattened ($p<0.05$ in all cases), whereas positive-powered lenses did not induce any significant changes ($p>0.05$ in all cases) in MCK in comparison to the naked eye. The TK power decreased with negative lenses ($p<0.05$ in both cases) and increased with +3.00 D lenses ($p=0.03$) in comparison to the naked eye. No statistically significant differences were found in MFE with any soft lens power in comparison to the naked eye ($p>0.05$ in all cases). Corneal eccentricity increased at 8 mm diameter for all lens powers ($p<0.05$ in all cases). Not statistically differences were found in HOA RMS and spherical-like aberrations. Statistically differences were found in coma-like and secondary astigmatism.

Conclusions: Negative-powered soft contact lenses provide a flatter anterior surface in comparison to positive-powered lenses in subjects with keratoconus and thus they might be more suitable for piggyback contact lens fitting.

Key words: piggyback, contact lens, cornea, keratoconus.

4.2.1.2. Introduction.

Keratoconus is a progressive, bilateral and asymmetric corneal disorder with an incidence of 1 per 2,000 in the general population.[1,2] This corneal degeneration is characterized by localized corneal thinning which leads to protrusion of the thinned cornea, high myopia and irregular astigmatism, thus affecting visual quality. Corneal thinning normally occurs in the inferior-temporal as well as the central cornea.[3] Although the etiology of keratoconus remains unclear, it is suspected to develop as a combination of genetic and environmental factors.[4] Currently, a combination of corneal topographic findings (i.e. inferior corneal steepening and superior-inferior corneal curvature asymmetry) and clinical signs (i.e. Fleischer's ring, Vogt's striae and corneal scarring) are commonly used to diagnose and monitor the disease.[5]

New surgical procedures to treat keratoconus have emerged in the last decade, including corneal ring segments implantation[6] and collagen cross-linking.[7] However, corneal rigid gas-permeable (RGP) contact lenses still represent the most common and successful treatment option for early to moderate cases of keratoconus. Nevertheless, the use of these lenses might be associated to increased on-eye lens discomfort in comparison to soft contact lens wear ultimately leading to reduced wearing time and eventually contact lens wear discontinuation.

Piggyback lens systems were first described by Baldone in the early 1970s for improving contact lens comfort in keratoconus subjects fitted with RGP lenses alone.[8,9] The technique consists in fitting a RGP lens onto a soft lens (**Figure 4.2.1.1**). The soft lens is used to improve comfort, RGP lens centration and to protect the cone apex from potential corneal scarring induced by the RGP lens.[10] Although piggybacking has been associated to corneal swelling and neovascularization,[11] recent studies have shown that current high Dk RGP lenses in combination with silicone hydrogel contact lenses provide sufficient oxygen transmissibility to avoid hypoxic-related complications during daily wear.[12,13] Current generations of silicone hydrogel lenses have a lower modulus of rigidity than earlier generations of silicone hydrogel and thus they are more likely to provide enhanced comfort to keratoconus ubjects fitted using the piggyback technique.

Classically, the use of a low positive-powered soft contact lens has been recommended for piggyback fittings as it is believed to create a lenticular bowl which facilitates RGP lens centration, although the use of a negative-powered lens has been suggested perhaps as more appropriate for fitting steep corneas (i.e. mean K >47.5 D).[14] In fact, most studies report the use of positive-powered lenses in piggyback fittings.[15,16] In a pilot study on non-keratoconic eyes, O'Donnell and co-workers found that positive-powered lenses facilitated spherical RGP lens centration, despite negative-powered lenses generated a flatter anterior corneal surface for lens fitting.[15] As keratoconus is associated to corneal steppening in comparison to normal corneas, it might be expected that the use of negative-powered soft lenses over the keratoconic cornea might generate a flatter surface onto which the RGP lens might fits better. On the other hand, corneal eccentricity is normally increased in keratoconus in comparison to normal corneas.[17] Therefore, positive-powered soft lenses might reduce corneal eccentricity, thus facilitating RGP lens fitting. To the best of our knowledge, however, no previous study has evaluated which soft contact lens power provides a more regular anterior corneal surface to facilitate the fitting of a RGP lens over the soft contact lens. Therefore, the purpose of this study is to evaluate how different soft lens powers affect anterior corneal surface in terms of central keratometry, corneal eccentricity and anterior corneal surface higher-order aberrations (HOA) in keratoconic eyes.

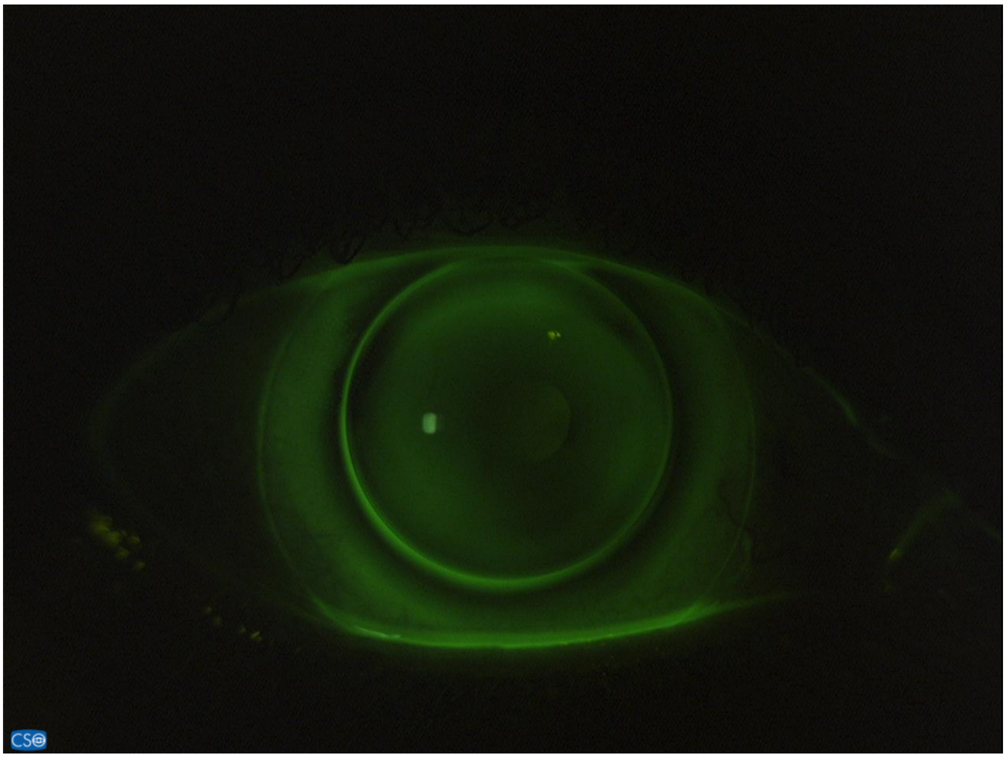

Figure 4.2.1.1. On-eye piggyback lens fitting

4.2.1.3. Methods.

Subjects of at least 18 years of age diagnosed with keratoconus according to the keratoconus severity score were recruited for the study.[4] Full informed consent was obtained from all subjects prior to the start of all experimental work and data collection. The study followed the Tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of MGR Doctores Ophthalmology Clinic.

In eligible subjects, comprehensive optometric and ophthalmologic examinations were performed in all subjects. The examination included Snellen uncorrected and corrected visual acuity tests (with manifest refraction and over the contact lens), biomicroscopy examination, fundus evaluation, keratometry and corneal topographic analysis using the Pentacam Eye Scanner (Software version 1.16.r:23, Oculus Inc, Wetzlar, Germany). Eyes with a previous history of acute corneal hydrops, pellucid marginal degeneration, corneal surgery or any other ocular disease were excluded from the study. Corneal topography assessments were taken over the naked eye. Subsequently, a soft contact lens with a base curve of 8.40 and a power of -3.00 D was fitted, and new topography assessments were recorded with the lens over the cornea (Senofilcon, Acuvue Oasys, Johnson & Johnson, Jacksonville, FL). The same process was repeated consecutively with lenses of -1.50, 0.00, +1.50 and +3.00 D.

We analyzed mean central keratometry, maximum tangential curvature, maximum front elevation, and corneal eccentricity at 6 and 8 mm chord diameters. Additionally, HOA coefficients (i.e. 3rd to 6th order) and total HOA root mean square (RMS) were calculated for a 6.0 mm pupil. The corresponding RMS values were evaluated for the following types of optical aberrations: from 3rd HOA up to the 27th term; spherical-like aberrations for 4th and 6th order Zernike terms; coma-like aberrations for 3rd and 5th order Zernike terms; and secondary astigmatism aberrations for 4th and 6th order Zernike terms.

4.2.1.3.1 Statistical analysis.

Normality of data distribution was assessed using the Kolmogorov-Smirnov test. Differences in mean keratometry and maximum tangential curvature for each of the contact lens powers in comparison to the naked eye were evaluated using the Paired Student's t-test. Differences in maximum elevation, eccentricity and HOA values for each of the contact lens powers in comparison to the naked eye were evaluated using the Wilcoxon Singed Rank test. Statistical analyses were carried out using SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). The level of statistical significance was taken as 5%.

4.2.1.4. Results.

Thirty eyes from 10 males (53%) and 9 females (47%) diagnosed with keratoconus were included in the study. The mean age (± SD) was 26.4 (± 6.2), ranging from 18 to 43 years. The mean flattest central K was 48.10 (± 4.84) and the mean steepest central K was 51.67 (± 5.39). According to the keratoconus severity score, the stage of keratoconus was mild in 20 eyes, moderate in 7 eyes and severe in 3 eyes. All subjects were current RGP contact lens wearers.

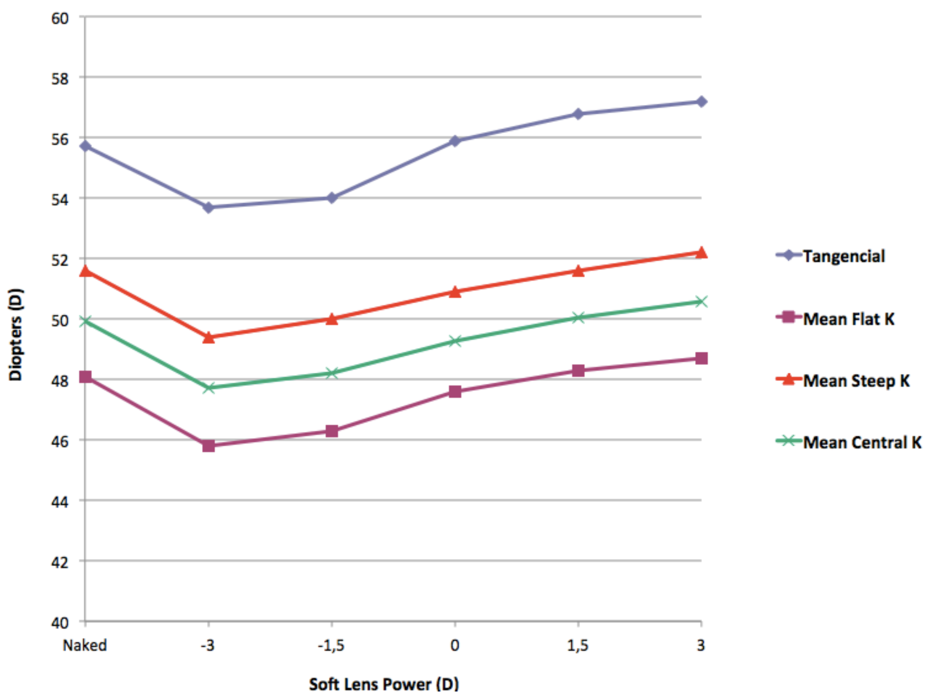

Figure 4.2.1.2 Mean, flattest and steepest central keratometry (K) and maximum tangential curvature on the naked eye as well as with different soft contact lens powers. D: diopters.

Mean central keratometry flattened significantly with negative- and plano-powered soft lenses (all $p<0.05$), but did not change significantly with positive-powered lenses (all $p>0.05$). Maximum tangential curvature flattened significantly with negative-powered lenses (all $p<0.05$); did not change with the plano or +1.50 D lenses; and steepened significantly with +3.00 D lenses (**Figure 4.2.1.2**). No statistical significant differences were found in maximum front elevation with any of the soft lens powers assessed in comparison to the naked eye (**Table 4.2.1.1**).

Table 4.2.1.1. *Mean central keratometry, tangential curvature and maximum front elevation.*

	Mean Central Keratometry		**Tangential Curvature**		**Maximum Front Elevation**	
Condition	Power (D)	p*	Power (D)	p*	Distance (microns)	p*
Naked-eye	49.95 ± 5.03		55.72 ± 7.19		36.21 ± 22.20	
-3.00 D	47.72 ± 4.60	<0.001	53.70 ± 6.56	<0.001	33.69 ± 18.01	0.255
-1.50 D	48.21 ± 4.61	<0.001	<0.001	<0.001	34.45 ± 17.94	0.353
0.00 D	49.28 ± 4.54	0.002	55.93 ± 8.27	0.696	37.41 ± 19.77	0.588
+1.50 D	50.04 ± 4.21	0.712	56.28 ± 7.83	0.211	34.69 ± 15.85	0.502
+3.00 D	50.59 ± 4.66	0.127	57.22 ± 8.11	0.031	31.90 ± 13.97	0.106

**p–value is calculated by comparing each lens power against the naked eye.*

Similar corneal eccentricities at the 6 mm chord diameter were found with the different contact lens powers assessed (all p>0.05). However, statistically significant differences were found between all soft contact powers in comparison to the naked eye at the 8 mm chord diameter. A trend for increasing corneal eccentricity with increasing lens power was found for the 8mm chord diameter (**Table 4.2.1.2.**).

Table 4.2.1.2. Corneal eccentricities at 6 and 8 mm chord diameters.

	6 mm diameter		**8 mm diameter**	
Condition	**Ecc**	**p***	**Ecc**	**p***
Naked-eye	0.63 ± 0.41		0.78 ± 0.32	
-3.00 D	0.64 ± 0.47	0.799	0.89 ± 0.27	0.001
-1.50 D	0.55 ± 0.40	0.171	0.88 ± 0.26	0.007
0.00 D	0.57 ± 0.39	0.367	0.91 ± 0.25	0.003
+1.50 D	0.56 ± 0.43	0.355	0.93 ± 0.26	0.005
+3.00 D	0.56 ± 0.49	0.488	0.95 ± 0.27	0.004

* p-value is calculated by comparing each lens power against the naked eye. Ecc= eccentricity

No statistically significant differences were found between the different lens powers in HOA RMS, except for -3.00 soft lens power (p=0.012). No significant differences were found for spherical-like aberration for all lens powers (all p>0.05). Significant differences were found in coma-like aberrations for all lens powers, except for the +3.00 D lens (p=0.358), and for secondary astigmatism aberrations for all lens powers, except with -3.00 D lens (p=0.117). The results of the anterior corneal surface aberrations are summarized in **Table 4.2.1.3**.

Table 4.2.1.3. Anterior corneal surface aberrations for 6.0 mm pupil diameters.

	Higher-Order Aberrations (RMS)		**Spherical-like**		**Coma-like**		**Secondary Astigmatism**	
Condition	Value	p*	Value	p*	Value	p*	Value	p*
Naked-eye	2.22 ± 1.13		0.42 ± 0.28		1.98 ± 1.07		0.40± 0.28	
-3.00 D	2.02 ± 0.96	0.012	0.40 ± 0.33	0.642	1.70 ± 1.00	0.001	0.49 ± 0.32	0.117
-1.50 D	2.08 ± 1.06	0.082	0.39 ± 0.22	0.294	1.74 ± 0.94	0.009	0.53 ± 0.41	0.037
0.00 D	2.12 ± 1.19	0.284	0.40 ± 0.31	0.705	1.76 ± 0.91	0.019	0.54 ± 0.37	0.031
+1.50 D	2.18 ± 0.99	0.117	0.42 ± 0.36	0.417	1.76 ± 0.86	0.007	0.56 ± 0.34	0.039
+3.00 D	2.21 ± 0.90	0.854	0.45 ± 0.39	0.888	1.85 ± 0.79	0.358	0.60 ± 0.45	0.007

*p-value is calculated by comparing each soft lens power against the naked eye

4.2.1.5. Discussion.

The fitting of RGP contact lenses is normally the most widely accepted option for managing keratoconus patients, because these lenses can effectively mask corneal irregularity and thus improves visual acuity. However, some patients might not tolerate the discomfort associated with the use of RGP lenses. In these cases, piggyback fitting is usually recommended. However, the fitting of a RGP onto a soft contact lens can be challenging to the eye care practitioner. Such fittings require soft and RGP lenses to move independently from each other with blinking and appropriate RGP centration over the soft contact lens. Although it is commonly recommended the use of a low-positive powered soft contact lens for piggyback fittings, little is known about the most appropriate soft contact lens power to be employed in these fittings. To the best of our knowledge, this is the first study to assess the most adequate soft contact lens power for piggyback lens fitting. Against commonly accepted practice, the use of a negative-powered soft contact lens provides a better surface for the RGP lens to fit over the soft lens. In fact, we found a decrease in corneal keratometry and maximum tangential curvature with negative-powered lens powers, which aids at regularizing the anterior corneal curvature and shape. A flatter surface as a result of fitting a negative-powered soft lens powers over the cornea will require a less negative and thus lighter and more stable RGP lens to fit over the soft contact lens. On the contrary, the fitting of a positive-powered soft lens would require a RGP contact lens of stronger power.

The elevation topography map has been proposed as the one which more accurately represents the true corneal shape, because it is independent of axis, orientation and position.[18] In our study, we did not find any significant differences in the maximum front elevation of the cornea between the different soft contact lens powers assessed, suggesting that soft contact lens power has little effect over the true anterior corneal shape. The latter is surprising because a -3.00 D lens is likely to have differences in thickness across the optic zone of the order of several dozens of microns. Although the Pentacam instrument might not be able to detect such small differences in lens thickness, the fitting of a soft contact lens over the keratoconic eye is expected to regularize areas of lower elevation surrounding the cone. Taking the latter into account, a negative soft lens power may be more suitable than a positive lens for piggyback fitting because of its thinner central thickness, which will allow greater corneal oxygenation.[12] In fact, measurements of thickness undertaken in our lab (ET-3, Rehder Development Company, Castro Valley, CA) on a plano-powered Senofilcon A lens revealed a value of 70 μm at the center of the lens, with values increasing up to 80 μm at 4 mm chord and decreasing to 15 μm at 8 mm chord. Despite these differences in thickness, it seems that soft contact lens power does not affect anterior shape of the surface resultant from fitting a soft lens over the keratoconic cornea and, consequently, it might not affect RGP lens centration.

The eccentricity of the normal cornea normally ranges between 0.35 and 0.45, but keratoconus disease is associated to greater corneal eccentricity. In our sample, we have found mean corneal eccentricities of 0.63 and 0.78 at 6 mm and 8 mm chord diameters, respectively. A previous study found positive-powered soft lenses to improve centration of back-surface spherical RGP lens designs fitted over the soft lens in comparison to negative-powered soft lenses.[15] However, since keratoconus disease is associated with increased corneal eccentricity, back-surface spherical RGP lenses (eccentricity = 0) might not be the most appropriate RGP design for piggyback fitting. Back-surface aspherical RGP lenses with eccentricities of around 0.8 are more likely to better conform the ecstatic cornea of keratoconus subjects. Alternatively, spherical RGP contact lens designs with multiple peripheral curves are also likely to better mimic the corneal shape in keratoconus. In our study, soft lens power had no influence on corneal eccentricity at 6 mm chord diameter. However, all soft lens powers increased surface eccentricity at 8 mm of diameter chord, particularly with positive-powered soft lenses. Therefore, negative-powered soft lenses might be a better option for piggyback fitting in keratoconus in terms of reducing corneal eccentricity.

In keratoconus, corneal asymmetry and irregularity induce an increase of higher-order aberrations, specially coma- and spherical-like aberrations, in comparison to normal corneas,[19] and these aberrations together with vertical coma have been proposed as the major aberrations adversely affecting visual quality in keratoconus subjects.[20] In our study, no statistical differences were found in HOA RMS except with the -3.00 D lens, being the value of the RMS lower with this lens power. Spherical-like aberration did not change, irrespective of the soft lens power fitted, which it is in agreement with a previous study.[21] However, we found that coma-like aberration reduces with soft lenses, being greater with the more negative the lens power, and secondary astigmatism increases for all soft lens powers, except with the -3.00 D lens, being higher with the positive the lens power. Therefore, negative-powered soft lenses seem to be more suitable in terms of anterior higher-order corneal aberrations for piggyback lens fitting in keratoconus. The results related to anterior corneal HOA presented in this study should be interpreted with caution as a previous study reported questionable repeatability in measuring corneal wavefront aberrations with the Pentacam instrument.[22] Furthermore, another study reported Zernike coefficients measured by the Pentacam device to be higher than those provided by other measuring devices.[23] Nevertheless, it is of interest the reduction in coma-like aberrations with negative soft lens powers found in this study as coma-like aberrations measured with the Pentacam have been reported to be more accurate than other coefficients measured with the same device.[24]

A limitation of this study was the theoretical approach undertaken to assess the most appropriate soft contact lens power for piggyback fitting, as we did not fit RGP lenses over the different soft lenses employed in this study. Therefore, the findings of this study need to be confirmed with a clinical study in which different RGP designs are fitted over different soft contact lens powers in keratoconus subjects. And, in addition to assessing surface curvature and aberrations, it would be also desirable to assess lens centration, movement and comfort.

In summary, the results of this study show that negative-powered soft contact lenses are likely to be more suitable for piggyback fitting than positive-powered lenses in subjects with keratoconus as they provide a flatter and less aberrated corneal surface.

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SECTION 4.2.2

Which soft contact lens power is better for piggyback fitting in keratoconus? Part II

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4.2.2.1. Abstract.

Objectives: To evaluate how soft lens power affects rigid gas-permeable (RGP) lens power and visual acuity (VA) in piggyback fittings for keratoconus.

Methods: Sixteen keratoconus subjects (30 eyes) were included in the study. Piggyback contact lens fittings combining Senofilcon-A soft lenses of -6.00, -3.00, +3.00 and +6.00 D with Rose K2 RGP contact lenses were performed. Corneal topography was taken on the naked eye and over each soft contact lens before fitting RGP lenses. Mean central keratometry, over-refraction, RGP back optic zone radius (BOZR) and estimated final power as well as VA were recorded and analysed.

Results: In comparison to the naked eye, the mean central keratometry flattened with negative-powered soft lenses ($p<0.05$ in all cases), did not change with the +3.00 soft lens power ($p=1.0$); and steepened with the +6.00 soft lens power ($p=0.02$). Rigid gas-permeable over-refraction did not change significantly between different soft lens powers (all $p>0.05$). RGP's BOZR decreased significantly with positive-powered in comparison with negative-powered soft lenses (all $p<0.001$), but no significant differences were found among negative- or positive-powered lenses separately (both $p>0.05$). Estimated RGP's final power increased significantly with positive-powered in comparison with negative-powered soft lenses (all $p<0.001$), but no significant differences were found among negative- or positive-powered lenses separately (both $p>0.05$). Visual acuity did not change significantly between the different soft lens powers assessed (all $p>0.05$).

Conclusions: The use of negative-powered soft lenses in piggyback fitting reduces RGP lens power without impacting VA in keratoconus subjects.

Key words: piggyback, contact lens, cornea, keratoconus.

4.2.2.2. Introduction.

Rigid gas-permeable (RGP) contact lenses represent the most common and successful management option for early to moderate cases of keratoconus,[1] despite the development of surgical treatments that aim to regularize the anterior corneal surface (i.e. intrastromal corneal ring implantation)[2] or to stabilize the progression of the disease (i.e. cross-linking).[3] Currently, a number of contact lens designs and materials are available to fit irregular corneas, particularly keratoconus as it is the most common primary ectasia.[1,4] Corneal RGP,[5] semi-scleral,[6,7] scleral,[8] hybrid[9] or custom-made soft contact lenses[10] are commonly used to manage keratoconus patients. However, corneal RGP lenses are probably the most widely prescribed contact lens design in keratoconus subjects worldwide. Discomfort or recurrent anterior corneal surface erosions are sometimes associated with the use of these lenses leading to reduced wearing time and sometimes to discontinuation from lens wear. In cases of unbearable discomfort with RGP lens wear, a soft lens can be used as a carrier of the RGP lens; the fitting of a RGP lens onto a soft contact lens is known as piggyback system and was first described by Baldone in the early 1970's.[11,12] It is estimated that piggyback is used by about 2% of keratoconus contact lens wearers.[13] Furthermore, VA is similar with piggyback systems in comparison to RGP lens wear alone.[14]

Piggyback fitting is normally recommended using a low-positive powered soft contact lens because it shifts the highest elevation of the cornea to a more centered location and hypothetically facilitates RPG lens centration, although the use of a negative-powered lens was recommended by Baldone in steeper corneas.[15] However, despite of the latter and that central keratometry is steeper in keratotconus in comparison to normal corneas, most practitioners continue using a low positive-powered soft lens in piggyback fittings for the keratoconic cornea.[16,17] In a previous study, we demonstrated that negative-powered soft lenses create a flatter and less powerful anterior corneal surface, which reduces coma-like aberration potentially leading to an improvement in visual acuity, thus making them more suitable for piggyback contact lens fittings.[18] However, the results of the latter study were derived using a theoretical approach as no RGP lenses were actually fitted over soft contact lenses of different powers. Furthermore, as a result of the latter, we were unable to assess the impact of negative-powered soft lenses on visual acuity or RGP lens fitting (i.e. centration, movement and power). On the contrary, in a very recent study performed on regular corneas, the use of a low positive-powered soft contact lens was recommended for piggyback fitting in all cases (i.e. regular and irregular corneas) because: (1) it is believed to facilitate RGP lens centration; and (2) it does not contribute to the total power of the piggyback lens system.[19] Based in all the above, the purpose of the present study was to evaluate whether postive- or negative-powered soft lenses are more suitable for piggyback fitting in keratoconus with regards to the RGP's lens fitting and visual acuity.

4.2.2.3. Methods.

This was a prospective non-dispensing, single-masked study. Sixteen subjects (30 eyes) of at least 18 years of age with keratoconus were enrolled. A comprehensive optometric and ophthalmologic examination was performed in all subjects which included the assessment of uncorrected and corrected visual acuities with and without contact lens wear, biomicroscopy examination, fundus evaluation, and keratometry and corneal topographic analysis (Pentacam Eye Scanner, software version 1.16.r:04, Oculus Inc, Wetzlar, Germany). Subjects had to be current RGP lens wearers to be enrolled in the study. Exclusion criteria were previous history of acute corneal hydrops, corneal surgery or other ocular disease. All subjects were provided written informed consent to participate in the study. The study followed the Tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of MGR Doctores Ophthalmology Clinic Madrid, Spain and the scientific committee of the School of Sciences at the University of Minho and European University on Madrid.

The soft contact lenses used in the study were made of senofilcon A material and all had BOZRs of 8.40 mm (Acuvue Oasys, Johnson & Johnson Vision Care Inc., Florida, USA). The RGP lenses fitted in this study were Rose K2 lenses manufactured in tisilfocon A material (Menicon Co., Ltd., Nagoya, Japan). In subjects with bilateral keratoconus, the study was performed on both eyes as it is well established keratoconus is a bilateral and asymmetric condition.[20,21]

4.2.2.3.1. Fitting method.

Corneal topography was obtained over the naked eye (i.e. without contact lens) in all eligible subjects. Then, one of the soft lenses were fitted and allowed to settle down on the eye for 10min before taking a new corneal topography with the soft lens over the cornea (**Figure 4.2.2.1**).

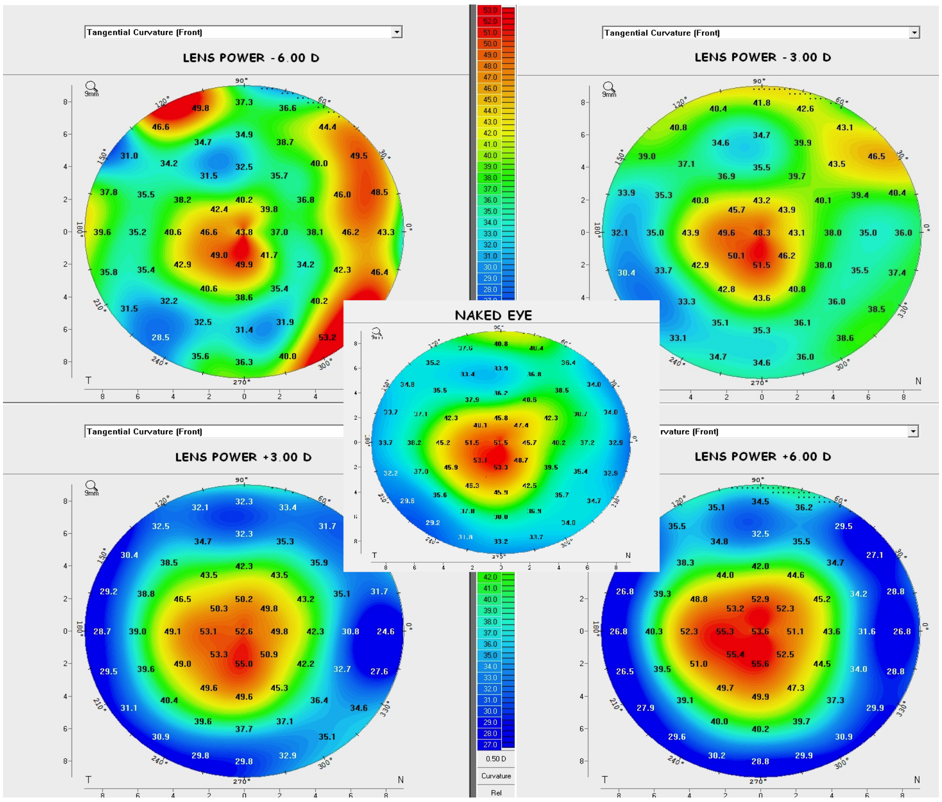

Figure 4.2.2.1. Anterior corneal topographies over the naked eye (central) as well as with soft contact lenses of -6.00 D (top left), -3.00 D (top right), +3.00 D (bottom left) and -6.00 D (bottom right). Cone size increases with positive-powered and decreases with negative-powered soft lenses.

Then, a RGP contact lens was fitted over the soft contact lens with a BOZR equal to the mean central keratometry measured over the soft lenses minus 0.2 mm, accordingly to the manufacturer's fitting guide. Then, the BOZR was flattened or steepened in 0.10 mm steps until the first definite apical clearance lens (FDACL) was observed following previous reported methodology.[5,22] Once the FDACL was achieved, the BOZR was flattened 0.10 mm to obtain a three-point-touch fitting approach.[5] The RGP lens was allowed to settle on the eye for 30 to 45 min and the lens fitting was assessed using low molecular weight fluorescein (Haag-Streit, Koeniz, Switzerland). The soft lens was required to cover the entire cornea without overpassing the limbus, whereas the RGP lens must be well-centered whithin the limbal area. A RGP lens was considered well-centered when the pupil was covered by the lens' back optic zone without touching the limbus on primary eye gaze (**Figure 4.2.2.2**).

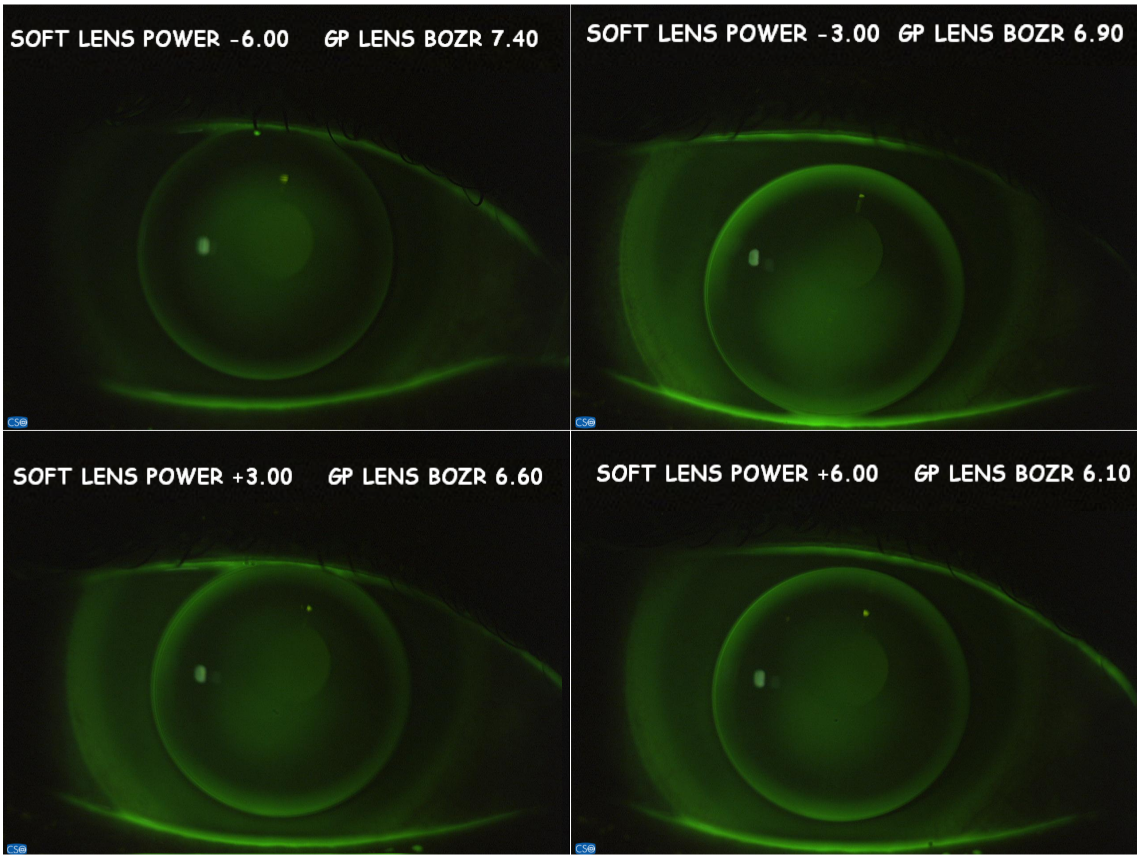

Figure 4.2.2.2 Piggyback lens system's flourograms of soft contact lenses of different powers. All images show the first definite apical clearance lens for each soft lens power.

Rigid gas-permeable lens movement was required to be between 0.5 and 1.5 mm with blink. When RGP lens centration and/or movement were inappropriate, changes to the edge lift were performed to improve the lens fitting (i.e. excessive movement or upper lens decentration was remedied by decreasing the edge lift, whereas insufficient movement or downward lens decentration was solved by increasing the edge lift). Once an optimal lens fitting was achieved, over-refraction was performed. The procedure described above was repeated with soft lenses of -6.00, -3.00, +3.00 and +6.00D, consecutively. The same investigator (M R-J) carried out all the lens fittings and assessments.

4.2.2.3.2. Statistical analysis.

Differences in mean central keratometry and RGP's over-refraction, BOZR and final estimated power as well as best contact lens visual acuity (BCLVA) between the naked eye and the different soft lens powers were analyzed using a repeated measures analysis of variance (ANOVA) followed by post-hoc tests, if necessary. Equality of variances and sphericity were tested using the Levene and Mauchly tests, respectively, to select appropriate p-values. Statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). The level of statistical significance was taken as 5%.

4.2.2.4. Results.

Eleven males (69%) and 5 females (31%) current corneal RGP contact lens wearers with keratoconus were included in the study. The mean age (± SD; range) of the subjects was 34.9 (± 8.8; 21.3-49.4) years. Thirty eyes (16 right eyes and 14 left eyes) were fitted. According to the keratoconus severity score,[23] 21 and 9 eyes had mild and moderate keratoconus, respectively. No subjects were previous fitted using a piggyback contact lens system.

An average of 2.6 ± 0.8 RGP trial lenses were necessary to achieve an optimal piggyback lens fitting. No clinically significant differences on RGP lens centration or movement were found between the different soft lens powers fitted in this study (**Figure 4.2.2.2**). Significant differences were found in mean central keratometry between the naked eye and the different soft lens powers ($p<0.001$). In comparison to the naked eye, the mean central keratometry flattened with negative-powered soft lenses ($p<0.05$ for the -3.00 and -6.00 D soft lenses); did not change with the +3.00 D soft lens ($p=1.0$); and steepened with the +6.00 D soft lens ($p=0.02$) (**Table 4.2.2.1**).

Table 4.2.2.1 Mean (± SD) central keratometry, back optic zone radius, over refraction and visual acuity measures for the naked eye and for the differen soft contact lens powers.

Measure	MCK (mean±SD) (mm)	RGP Over Rx (mean±SD) (D)	RGP Lens' BOZR (mean±SD) (mm)	VA (mean±SD) Log MAR
Naked	6.83±0.80	--	--	--
-6.00D	7.75±0.77	0.05±5.35	7.54±0.66	0.07±0.10
-3.00D	7.32±0.75	-1.44±5.19	7.22±0.62	0.06±0.08
3.00D	6.69±0.66	-3.10±5.51	6.64±0.50	0.06±0.08
6.00D	6.42±0.62	-3.31±5.90	6.38±0.37	0.05±0.08

MCK: mean central keratometry; RGP: rigid gas-permeable; BOZR: back optic zone radius; Rx: refraction; VA: visual acuity.

Although the difference in RGP over-refraction between the -6.00 and +6.00 D soft lenses was 3.26 D, being greater (more negative) with positive-powered lenses in comparison with negative-powered lenses (**Table 4.2.2.1**), such differences were not statistically significant (p=0.91).

Statistically significant differences were found in RGP's BOZR fitted on top of each of the 4 different soft contact lens powers (p<0.001). The BOZRs were steeper with positive-powered in comparison with negative-powered lenses (**Table 4.2.2.1**). However, the BOZR was not statistically different among negative-powered (-3.00 vs -6.00D) or positive-powered (+3.00 vs +6.00D) lenses (**Table 4.2.2.2**).

***Table 4.2.2.2**. Statistical and Post-Hoc Analyses between soft lenses.*

Measure	P-value	Post-hoc -6.00 D			Post-hoc -3.00 D		Post-hoc +3.00D
		-3.00	**+3.00**	**+6.00**	**+3.00**	**+6.00**	**+6.00**
RGP final estimated power	<0.001	1.0	<0.001	<0.001	0.019	<0.001	1.0
BOZR	<0.001	0.176	<0.001	<0.001	<0.001	<0.001	0.505

RGP: rigid gas-permeable; BOZR: back optic zone radius

The more positive the soft contact lens fitted, the smaller the difference between mean central keratometry and BOZR (**Figure 4.2.2.3**).

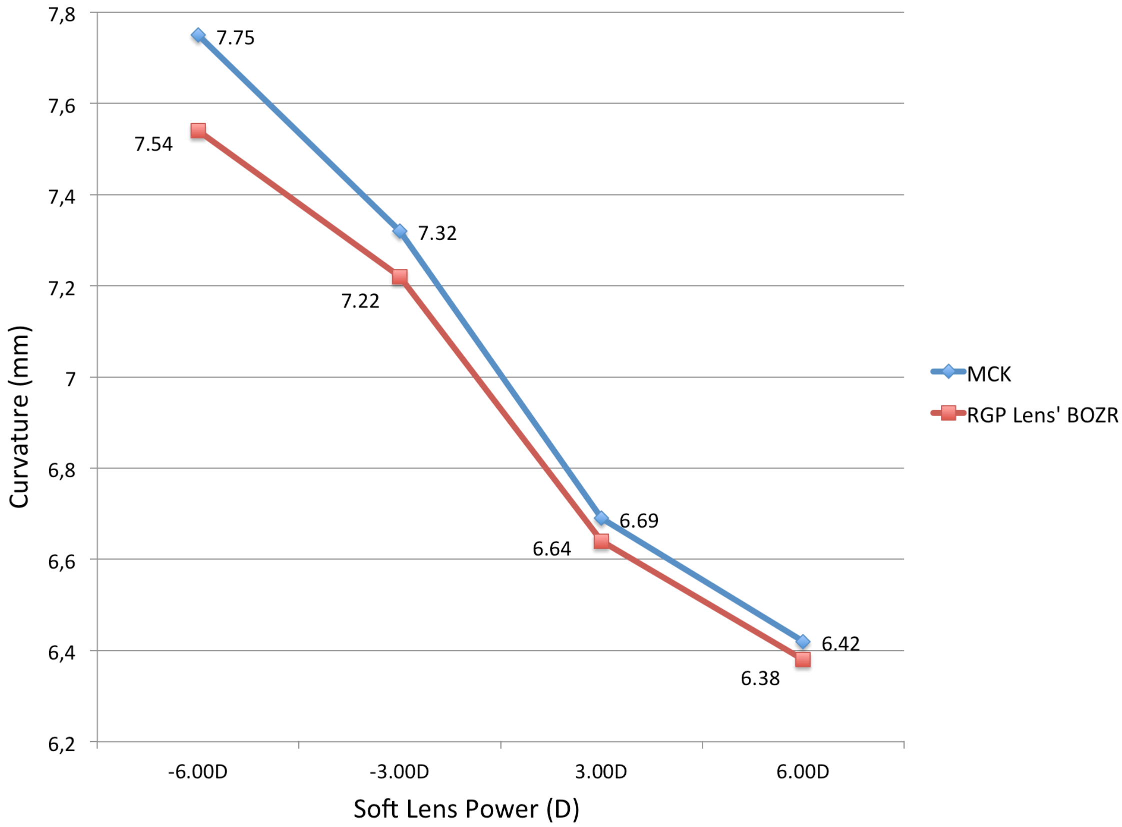

Figure 4.2.2.3. Comparison between the mean central keratometry and the final rigid gas-permeable lens' back optic zone radius. MCK: mean central keratometry; RGP: rigid gas-permable; BOZR: back optic zone radii. Mm: millimeters. D: diopters.

Statistically significant differences were also found in estimated RGP's final power ($p<0.001$, **Figure 4.2.2.4**). The estimated final power of the RGP lens increased significantly with positive-powered in comparison with negative-powered soft lenses (all $p<0.001$), but no significant differences were found among negative- or positive-powered lenses separately (both $p>0.05$).

Best corrected visual acuities (**Table 4.2.2.1**) did not varied significantly between the different soft lens powers employed (all $p>0.05$).

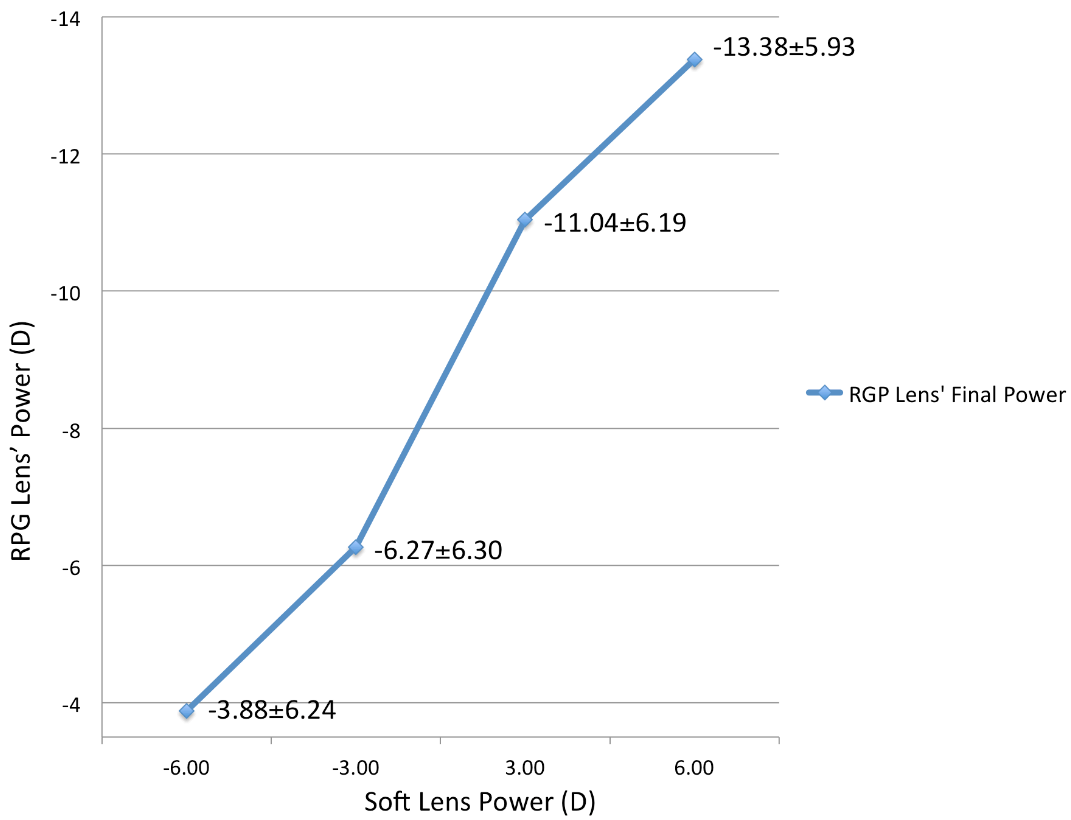

Figure 4.2.2.4. Estimated final power of the RGP lens. RGP: rigid gas-permable. D: diopters.

4.2.2.5. Discussion.

Piggyback contact lens fitting in keratoconus is challenging for eye care practitioners because it requires a wide knowledge of the different contact lens designs and materials currently available in the marketplace, as well as of the corneal shape of the keratoconic eye. This study aimed at understanding how soft lens power affects the fitting of an RGP lens onto a soft contact lens, particularly taking into account that most practitioners are likely to use low positive-powered soft lens in piggyback lens fittings in keratoconus. In fact, the latter has been recommended in a very recent study, although performed on regular corneas.[19] However, the central keratometry of keratoconus subjects is normally much steeper than that of normal corneas and thus the results obtained in normal corneas might not be extrapolated for fittings carried out on keratoconus corneas. In fact, we found similar RGP centration and movement for all soft lens powers assessed in this study using the FDACL concept as a first step to a obtain a three-point-touch fitting.[5,22]

We have found that negative-powered soft lenses flatten mean central keratometry and the +6.00D soft lens power steepen mean central keratometry, which it is in agreement with previous studies.[16,18,19] Therefore, fitting negative-powered soft contact lenses for piggyback in keratoconus provides a flatter and less powerful anterior corneal surface, which will necessarily impact the resultant piggyback lens system's power.

The absence of differences found in RGP's over-refraction between the different soft lenses is likely to be attributed to the RGP lens' design. The Rose K2 contact lens features a variable power related to the BOZR (i.e. as the BOZR increases, the power decreases and vice versa). In the present study, the latter might be considered as an advantage because the RGP lenses used were very similar in power to the theoretical final ordered lenses, which allowed a reliable fitting evaluation with regards to lens movement and centration.

That the BOZR of the RGP lens lens became steeper the more positive the power of the soft contact lens used is likely to impact the RGP lens' power and weight and thus on-eye lens stabilization and flexure. The difference between BOZR and mean central keratometry was greater with negative-powered in comparison to positive-powered soft lenses. The latter might be attributed to the fact that the cone becomes wider in extension with positive in comparison to negative soft lenses (**Figure 4.2.2.1**). In fact, the use of postitive-powered soft lenses creates a bowl that better mimics the central back surface of the Rose K2 lens used in this study as well as providing a better centration of the the highest elevation point of the cornea, which it is typically inferiorly-located in keratoconus corneas. This could be interpreted as it would be easier to fit a RGP lens over a positive-powered soft contact lens. However, modern RGP contact lens designs for keratoconus (i.e. Rose K2) allows easy modifications on lens' edge lift, which might be the most essential factor to contract for successful fitting of RGP lenses in keratoconus, particularly with regards to lens' movement and centration.

The final estimated power of the RGP lens was significantly more negative with positive-powered in comparison to negative-powered soft contact lenses, which it is expected to be due to the change in mean central keratometry over the soft contact lens and the subsequent steepening of the lens' BOZR. In regular corneas, it has been recently reported that only 21% of the labelled soft lens' power is transferred to the piggyback lens system for soft contact lens powers ranging from -6.00 to +6.00.[19] Thus, theoretically, a difference of 2.5 D might be found on the estimated final power of the RGP lens for soft contact lens powers from -6.00 to +6.00. However, the final estimated power of the RGP found in this study was, on average, -9.5 D more negative when fitted over a +6.00 soft lens in comparison to that fitted over a -6.00 soft lens. This might be explained by the difference on mean central keratometry found with negative- in comparison to positive-powered soft lenses. The flattening caused by a mild (e.g. -3.00 D) negative soft lens on the effective anterior corneal surface is likely to lead to a decrease on the effective refractive power of the ocular system. When a RGP lens is fitted over a negative-powered soft lenses, a flatter BOZR is necessary to achieve an optimal lens fit in comparison to a RGP lens fitted over positive-powered soft lenses, which leads to a reduction in the RGP' lens power. On the other hand, for the same overall lens diameter, the greater the lens' power (both negative or positive), the heavier the lens. A heavier lens is likely to experience greater decentration on the cornea with blink in comparison to a lighter lens. Furthermore, the RGP lens' central thickness becomes thinner the more negative the power of the RGP lens. In the case of the Rose K2 lens design used in this study, the central thickness varies from 0.17 mm to 0.13 mm for BOZR ranging from 7.55 to 6.40 mm, respectively (manufacturer's data). It has been previously reported that the thinner the center of a RGP lens, the greater the lens flexure and thus the induction of residual astigmatism.[24] Thus, a less powerful RGP lens would decrease the likelihood of lens flexure and the potential induction of residual astigmatism leading to an improvement in visual quality.

Best-corrected visual acuity was similar with the different combinations of soft contact lens powers and RGP lenses tested in this study. However, the use of negative- or positive-powered soft contact lenses might impact the high order aberrations of anterior corneal surface, as spherical- and coma-like aberrations have been reported to increase in keratoconus in comparison to normal subjects.[25] Furthermore, positive-powered soft lenses induce positive spherical aberration whereas negative-powered soft lenses induce negative spherical aberration with, the greater the lens power the higher the spherical-aberration induced.[26] Keratoconus subjects normally display positive spherical-like aberration. Our group has previously found a significant reduction in coma-like aberration with the use of negative-powered soft lenses in comparison to positive-powered soft contact lenses fitted in keratoconus eyes.[18] Awwad and co-workers also found a reduction in spherical aberration with the use of negative-powered soft lenses.[26] Thus, the use of negative-powered lenses in piggyback lens fittings in keratoconus is likely to reduce spherical- and coma-like aberrations and thus improve visual quality.

An additional issue to consider is that the use of negative-powered soft lenses in piggyback lens fittings are likely to provide higher oxygen transmissibility to the piggyback system at the center of the cornea.[27,28] The latter is important to consider for a better oxygen availability around the cone area. The corneal epithelium, which is usually affected from its basal membrane to the more superficial cells, might benefit from this strategy from a physiological point of view.

In conclusion, despite low positive-powered soft contact lenses have been traditionally used for piggyback fitting in keratoconus, the results of this study as well as our previous study[22] confirms that the use of a mild negative-powered soft contact lens might be more appropriate to use in piggyback lens fittings as it allows the fitting of a flatter and less powered RGP lens. Furthermore, the lighter weight of a lens powered RGP lens is likely to result in better on-eye lens centration and movement. In addition, a more negative-powered soft lens might reduce spherical- and coma-like aberrations, leading to an improvement in visual quality. Finally, the use of a negative-powered lens in piggyback lens fittings is likely to provide a better overall performance in terms of oxygen transmissibility at the center of the piggyback system. Considering all the above, eye care practitioners should consider the use of a low negative-powered silicone hydrogel contact lens for piggyback in keratoconus.

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CHAPTER 5

Rigid Gas-Permeable Contact Lens Impact on Corneal Structure

Miguel Romero Jiménez

Introduction

Chapter 5 of this thesis is an assessment of the RGP contact lens impact on keratoconus corneas and it is divided in two different parts.

The first part of this chapter (section 5.1) tries to answer the question: is there any difference in anterior corneal features between long-term RGP contact lens wearers and non-contact lens wearers in keratoconus? This section was published as a paper in *Cornea* under the title: "The thinnest, steepest and maximum elevation locations in non-contact and contact lens wearers in keratoconus".

The second part of this chapter (section 5.2) tries to answer the questions: how corneal RGP contact lens impact on anterior corneal surface in keratoconus after short-term wearing time comparing apical-touch and three-point-touch fitting approaches? This section has been published as a paper in *Journal of Optometry* under the title: "Short-term corneal changes with gas-permeable contact lens wear in keratoconus subjects: a comparison of two fitting approaches".

SECTION 5.1

The thinnest, steepest and maximum elevation locations in non-contact and contact lens wearers in keratoconus

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5.1.1. Abstract

The thinnest, steepest and maximum elevation locations in non-contact and contact lens wearers in keratoconus

Objectives: To assess the relationship between the thinnest corneal location and the steepest and maximum elevation corneal locations in subjects with keratoconus, as well as the effect of corneal rigid gas-permeable contact lens wear on the location of these points.

Methods: Sixty-one consecutive subjects (98 eyes) with keratoconus. Thirty-one (49 eyes) and 30 (49 eyes) subjects were corneal rigid gas-permeable contact lens (CL-W) and non-contact lens wearers (N-CL), respectively. Thinnest, steepest and maximum elevation corneal locations were evaluated from topographies collected with Pentacam Eye Scanner.

Results: In the entire sample as well as in N-CL and CL-W, the thinnest location does not overlap with the steepest or maximum elevation corneal locations (all $P>0.05$). The thinnest and maximum tangential curvature locations were found to be located further away from the geometrical centre of the cornea in CL-W vs. N-CL ($P<0.05$).

Conclusion: The thinnest corneal location does not overlap with maximum axial and tangential curvatures nor with the front and back elevation locations in keratoconus subjects. Contact lens wear does not affect this lack of overlapping.

Keywords: cornea, keratoconus, contact lenses.

5.1.2. Introduction

Keratoconus is a progressive corneal disorder with an incidence of 1 per 2,000 in the general population.[1,2] It is a bilateral and asymmetric corneal degeneration characterized by localized corneal thinning which leads to protrusion of the thinned cornea. Corneal thinning normally occurs in the inferior-temporal as well as the central cornea. Corneal protrusion causes high myopia and irregular astigmatism, affecting visual quality. Currently, a combination of corneal topographic findings (i.e., inferior corneal steepening and superior-inferior corneal curvature asymmetry) and clinical signs (i.e., Fleischer's ring, Vogt's striae and corneal scarring) are commonly used to diagnose and monitor the disease.[3,4] Though the etiology of keratoconus remains unclear, it is suspected to develop as a combination of genetic and environmental factors.[5]

To date, corneal rigid gas-permeable contact lenses represent the most common and successful treatment option for early to moderate cases of keratoconus, because these lenses can correct relatively high levels of irregular astigmatism and thus substantially improve visual acuity. When contact lenses cannot be successfully fitted, most keratoconus subjects undertake penetrating keratoplasty surgery. In fact, it has been estimated that around 12% of keratoconus patients eventually require penetrating keratoplasty.[6] However, in the last decade, new surgical procedures, including corneal ring segments implantation[7,8] and collagen crosslinking[9,10] have been developed to treat keratoconus.

Although previously studies have assessed the location of the steepest and thinnest corneal locations in keratoconus subjects,[11,12] no previous studies have investigated in detail whether the thinnest corneal location overlaps with steepest and maximum elevation corneal locations in keratoconus. Additionally, previous studies have been undertaken using Placido-based corneal topography instruments. Currently, sophisticated instruments based on Scheimpflug principles allow precise three-dimensional reconstruction of the entire cornea shape.[13-17] Furthermore, it is not known whether rigid gas-permeable contact lens wear affects these corneal locations. Therefore, the purpose of this study is to assess whether the thinnest corneal location overlaps with the steepest and maximum elevation corneal locations in keratoconus subjects, and whether contact lens wear affects these corneal locations.

5.1.3. Materials and methods

5.1.3.1. Patient selection

Ninety-eight eyes from 61 consecutive subjects were included in the study: 49 eyes from 31 subjects who have been wearing corneal rigid gas-permeable contact lenses for a minimum period of 6 months (mean 27.5 months, SD±4.3), and 49 eyes from 30 subjects who had never worn contact lenses. All subjects included in the study were diagnosed of keratoconus according to the Keratoconus Severity Score.[3] Eyes with a previous history of acute corneal hydrops or corneal surgery were excluded from the study. All subjects provided written informed consent to participate in the study. The study followed the Tenets of the Declaration of Helsinki and was approved by the Institutional Ethical Committee Review Board of MGR Doctores Ophthalmology Clinic.

5.1.3.2. Data Collection

Corneal topographies were taken and evaluated using the Pentacam Eye Scanner (Software version 1.16.r:23, Oculus Inc, Wetzlar, Germany). Anterior segment reconstructions were produced with 25 single captures. Upon completion of every scan, the Pentacam software analyzed 12,500 points from the front and back corneal surfaces to generate a three-dimensional image of the anterior segment.

The thinnest corneal location is automatically calculated by the instrument and represented in terms of x and y coordinates. To evaluate the steepest corneal location, axial and tangential front curvature maps were used. The maximum corneal elevation location was recorded from front and back elevation best-fit sphere topography maps. To determine the x and y coordinates of the steepest corneal location in the axial and tangential curvature maps and the highest location in maximum front and back elevation maps, three consecutive measurements were recorded manually and a mean calculated. Additionally, minimum corneal thickness, maximum axial and tangential curvature powers, maximum front and back heights, mean central keratometry, corneal thickness at the maximum tangential curvature location, corneal volume, anterior chamber depth and anterior chamber volume were also evaluated in order to ascertain whether rigid gas-permeable contact lens wear affects the entire or just the anterior cornea.

Axial and tangential curvature front maps were evaluated using the American style map display setting with a relative scale of 61 colors and 1 dioptre steps. Front and back elevation maps were also evaluated using the American style map display setting with a relative scale of 61 colors and a sphere reference shape with float and auto diameter options, and 2.5 micron steps. All x and y coordinates were transformed into vectors and angles to carry out the statistical analysis and to describe the distance and orientation of the different locations with regards to the instrument's measurement axis (i.e., the point where the topography map shows the (0,0) coordinate).

Superior and inferior as well as nasal and temporal corneal locations in right eyes were given positive and negative values, respectively, in relation to the instrument's measurement axis. Cones from left eyes have been horizontally inverted so that all cones are represented as if for the right eye.

In contact lens wearers group, corneal topographies were taken immediately after lenses were removal. All measurements were performed by the same investigator (MR-J).

5.1.3.3 Statistical Analyses

Normality of data distribution was checked using the Kolmogorov-Smirnov test. The mean and standard deviations were calculated for each vector and angle. Differences in each parameter were assessed separately. Two locations were considered different if statistically significant differences were found in vector, angle or both of them. Paired sample t-tests were employed to assess differences in vectors and angles between the different variables measured for the entire sample group as well as in non-contact (N-CL) and contact lens wearers (CL-W). Independent sample t–tests were used to assess differences in vectors and angles between N-CL vs. CL-W. Pearson's product moment correlations were used to assess relationships between the distance to the instrument's measurement axis and the distances from the thinnest to the other reference points. Statistical analyses were performed using SPSS 15.0 software (SPSS Inc, Chicago, IL, USA). The level of statistical significance was taken as 5%.

5.1.4. Results

5.1.4.1. Subjects' Demographics

The entire sample consisted of 98 eyes (49 N-CL and 49 CL-W) of 61 subjects, 42 of which were males (69%). Thirty-two and 29 subjects were CL-W and N-CL, respectively. The mean age (± SD) for the entire sample was 35.4 ± 10.0 (range 12.2-67.5). The mean ages (± SD) in N-CL and CL-W were 35.8 ± 9.1 (range 22.3-65.1) and 35.0 ± 11.9 (range 12.2-67.5), respectively (P=0.758).

5.1.4.2. Entire Sample

The thinnest corneal location was found to be located in a different point of the cornea in comparison with both the maximum curvature (axial and tangential) and the maximum elevation (front a back) corneal locations (**Table 5.1.1 and Figure 5.1.1**)

A strong correlation was found between the distance from the vertex normal and: (1) the distance between the thinnest and the axial (r=0.963, p<0.001); (2) the thinnest and the tangential (r=0.937, p<0.001); (3) the thinnest and the front elevation (r=0.881, p<0.001); and (4) the thinnest and the back elevation (r=0.855, p<0.001) corneal locations.

5.1.4.3. Effects of CL Wear

The thinnest corneal location did not overlap with maximum curvature (axial and tangential) and maximum elevation (front and back) corneal locations in both N-CL and CL-W groups, when assessed separately (all P > 0.05). (**Tables 5.1.2 and 5.1.3**)

Table 5.1.1 *Comparison between the thinnest location and maximum curvature and elevation locations for entire sample.*

<table>
<tr><th colspan="6">Vectors</th></tr>
<tr><th colspan="2">Coordinate 1 (C1)</th><th colspan="2">Coordinate 2 (C2)</th><th>C1-C2[a]</th><th>P</th></tr>
<tr><td rowspan="4">Thinnest</td><td rowspan="4">0.84 (±0.29)</td><td>Axial</td><td>1.44 (±0.96)</td><td>0.62</td><td>0.001</td></tr>
<tr><td>Tangential</td><td>1.23 (±0.71)</td><td>0.57</td><td>0.001</td></tr>
<tr><td>Front Elevation</td><td>1.31 (±0.51)</td><td>0.47</td><td>0.001</td></tr>
<tr><td>Back Elevation</td><td>1.15 (±0.41)</td><td>0.31</td><td>0.030</td></tr>
<tr><th colspan="6">Angles</th></tr>
<tr><th colspan="2">Coordinate 1</th><th colspan="2">Coordinate 2</th><th colspan="2">P</th></tr>
<tr><td rowspan="4">Thinnest</td><td rowspan="4">220º (±32)</td><td>Axial</td><td>231º (±70)</td><td colspan="2">0.127</td></tr>
<tr><td>Tangential</td><td>197º (±54)</td><td colspan="2">0.001</td></tr>
<tr><td>Front Elevation</td><td>216º (±29)</td><td colspan="2">0.389</td></tr>
<tr><td>Back Elevation</td><td>221º (±28)</td><td colspan="2">0.855</td></tr>
</table>

Vectors are expressed in millimeters. [a]C1-C2 represents the vectorial difference (expressed in millimeters) between the thinnest location and maximum curvature and maximum elevation locations.

When comparing N-CL vs. CL-W, the locations of the thinnest, maximum axial curvature and maximum elevation (front and back) were found to be similar between groups (all $P > 0.05$), but the maximum tangential curvature locations were found to be different between these two groups ($P < 0.05$). However, CL-W showed the thinnest, maximum tangential curvature and maximum front elevation locations to be positioned further away from the instrument's measurement axis in comparison to N-CL (**Figures 5.1.2 and 5.1.3**).

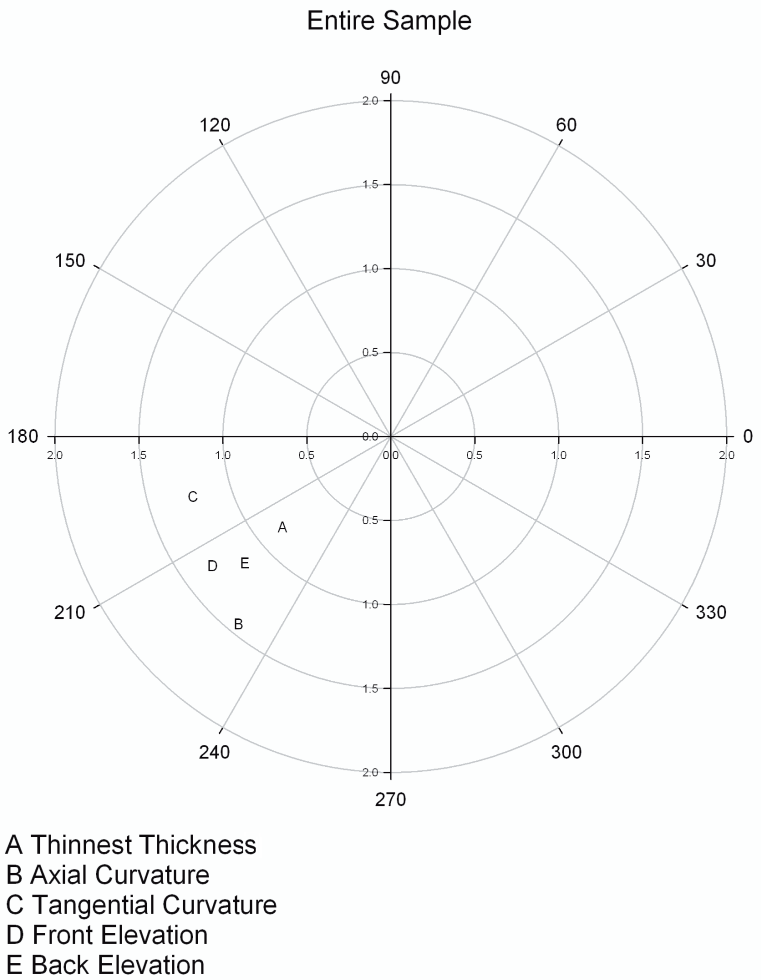

Figure 5.1.1. Position (angle and distance) of the reference points for the entire sample with regards to the instrument's measurement axis. Angles and distances are expressed in degrees and millimetres, respectively.

Table 5.1.2. *Comparison between the thinnest location and maximum curvature and elevation locations for N-CL.*

Vectors					
Coordinate 1 (C1)		**Coordinate 2 (C2)**		**C1-C2**[a]	**P**
Thinnest	0.76 (±0.30)	**Axial**	1.22 (±0.96)	0.69	0.001
		Tangential	0.93 (±0.71)	0.54	0.034
		Front Elevation	1.14 (±0.51)	0.42	0.001
		Back Elevation	1.04 (±0.41)	0.31	0.001
Angles					
Coordinate 1		**Coordinate 2**		**P**	
Thinnest	214º (±38)	**Axial**	236º (±63)	0.041	
		Tangential	224º (±56)	0.002	
		Front Elevation	212º (±23)	0.801	
		Back Elevation	214º (±23)	0.952	

Vectors are expressed in millimeters. [a]Vectorial difference between the thinnest location and the maximum curvature and elevation locations.

No significant differences were found in the thickness at the maximum tangential curvature location, corneal volume, anterior chamber volume or the anterior chamber depth between N-CL and CL-W (all $P > 0.05$) (**Table 5.1.5**)

Table 5.1.3. *Comparison between the thinnest location and maximum curvature and elevation locations for CL-W.*

Vectors					
Coordinate 1 (C1)		**Coordinate 2 C2**		**C1-C2[a]**	**P**
Thinnest	0.82 (±0.29)	**Axial**	1.51 (±0.96)	0.61	0.001
		Tangential	1.33 (±0.71)	0.59	0.001
		Front Elevation	1.31 (±0.51)	0.53	0.001
		Back Elevation	1.16 (±0.41)	0.31	0.001

Angles				
Coordinate 1		**Coordinate 2**		**P**
Thinnest	223º (±24)	**Axial**	227º (±76)	0.829
		Tangential	210º (±48)	0.089
		Front Elevation	218º (±33)	0.285
		Back Elevation	228º (±32)	0.830

Vectors are expressed in millimeters. [a]Vectorial difference between the thinnest location and the maximum curvature and elevation locations.

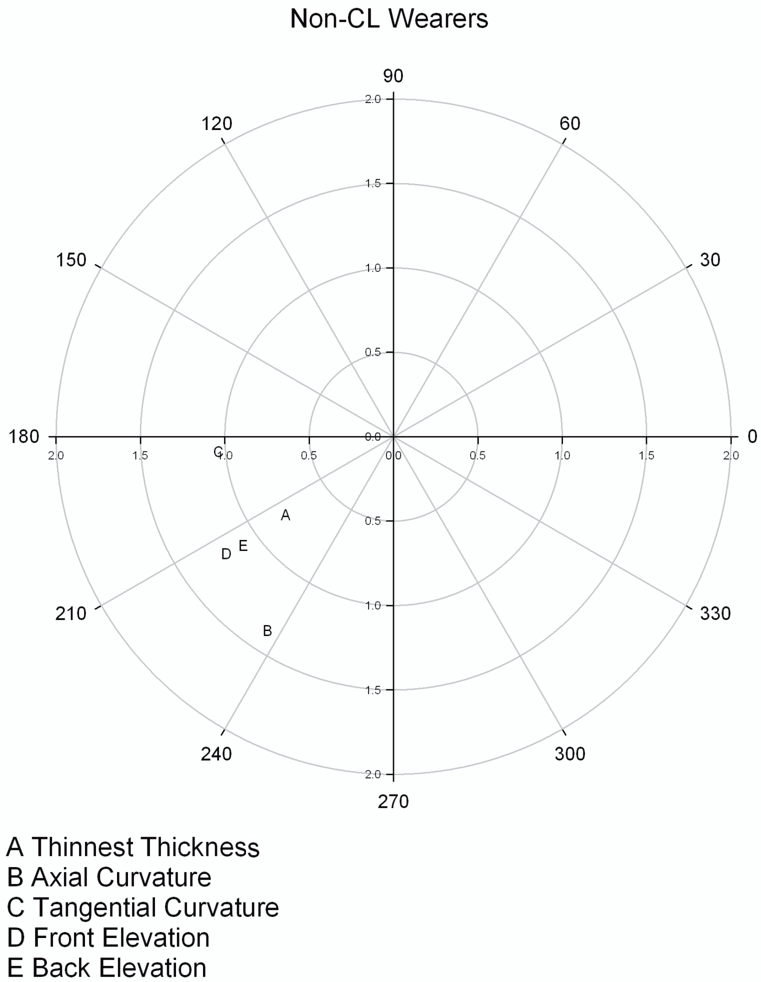

Figure 5.1.2. Position (angle and distance) of the reference points in non-contact lens wearers (N-CL) with regards to the instrument's measurement axis. Angles and distances are expressed in degrees and millimetres, respectively.

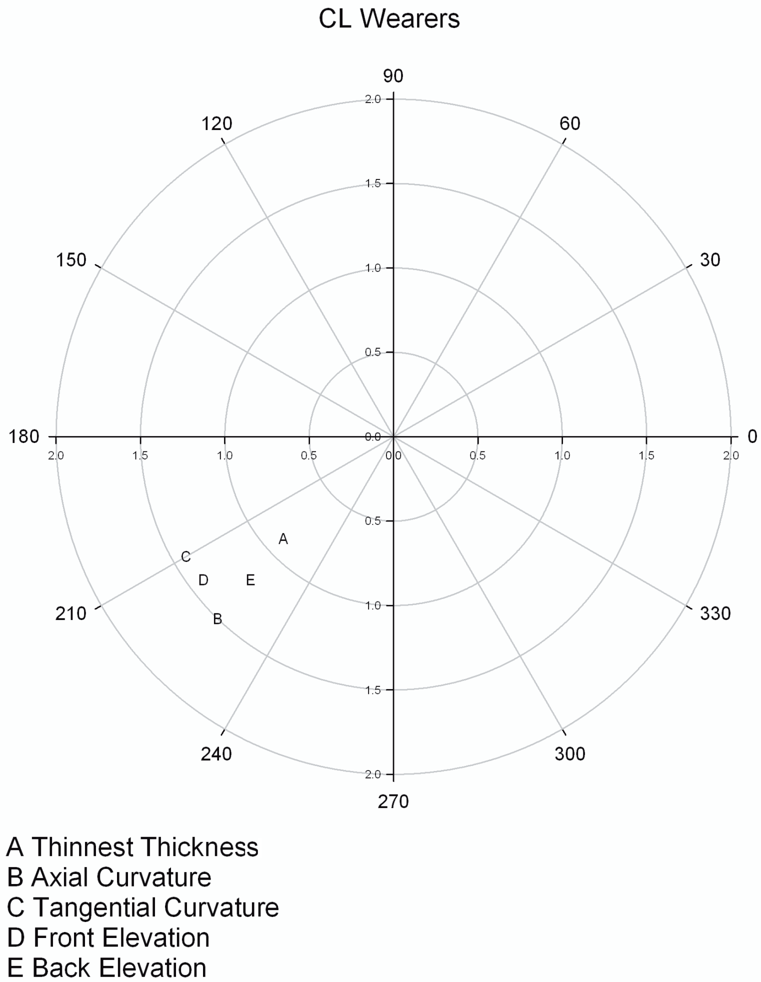

Figure 5.1.3. Position (angle and distance) of the reference points in contact lens wearers (CL-W) with regards to the instrument's measurement axis. Angles and distances are expressed in degrees and millimetres, respectively.

Table 5.1.4. *Thinnest corneal thickness, mean central keratometry, maximum axial and tangential curvatures and maximum front and back elevation values in N-CL and CL-W.*

Measurement	Value				P
	N-CL[a] (n=49)		CL-W[b] (n=49)		
	Mean	±SD	Mean	±SD	
Thickness	450.73	51.91	454.86	51.82	0.695
CK[c]	49.38	5.46	48.64	3.55	0.430
Max[d]. K Axial	56.71	8.00	53.68	5.16	0.028
Max. K Tang[e]	57.95	7.74	55.14	5.81	0.045
Max Elev[f] Front	39.29	22.10	31.33	21.22	0.072
Max Elev Back	65.37	30.45	62.29	35.49	0.646

Curvature is expressed in diopters. Thickness and elevations are expressed in microns. [a]Non-contact Lenses wearers, [b]Contact Lens Wearers, [c]central keratometry, [d]Max= Maximum, [e]Tangential, [f]Elevation.

Table 5.1.5. *Thinnest thickness at the maximum tangential curvature point, corneal volume and anterior chamber volume and depth.*

Measurement	N-CL[a] n=49		CL-W[b] n=49		P
	Mean	±SD	Mean	±SD	
Tangential Thickness	464.12	51.44	483.53	51.08	0.064
CV[c]	57.66	3.84	59.16	4.75	0.090
ACV[d]	199.57	35.84	187.35	35.03	0.091
ACD[e]	3.41	0.352	3.34	0.348	0.327

All values are expressed in microns. [a]No-contact Lenses wearers, [b]Contact Lens Wearers, [c]Corneal Volume, [d]Anterior Chamber Volume, [e]Anterior Chamber Depth.

5.1.5. Discussion

It has been previously reported that the Pentacam instrument provides high sensitivity and specificity in keratoconus detection[13,14] as well as high reproducibility and repeatability in measuring corneal thickness,[15] power[16] and posterior elevation.[17] Therefore, the device used in this study is well suited for assessing corneal shape in keratoconus subjects.

5.1.5.1. Entire sample

The thinnest corneal location did not overlap with the maximum axial and tangential curvature or with the maximum front and back elevation corneal locations in this study. The latter is in agreement with previous reports in normal[18] and keratoconus subjects.[11,12]

We found that the greater the distance between the thinnest location and the other reference points (i.e., axial, tangential, front and back elevations), the greater the distance between the reference points and the normal corneal vertex, and vice versa. The latter suggests that the reference locations are closer and further away from each other in central and peripheral cones, respectively.

5.1.5.2. Effects of contact lens wear

The lack of overlapping between the thinnest and the maximum curvature (axial and tangential) and maximum elevation (front and back) locations found in the entire sample as well as in both N-CL and CL-W suggests that this is likely to be an anatomical feature of keratoconus disease and that rigid gas-permeable contact lens wear does not affect this lack of overlapping.

Some differences, however, were found between N-CL and CL-W in our study. The thinnest and maximum tangential curvature locations were found to be positioned slightly further away from the instrument's measurement axis in CL-W in comparison to N-CL. Additionally, a 3.00D difference was found in the maximum tangential curvature power between N-CL and CL-W. It has been previously reported that corneal rigid gas-permeable contact lenses can flatten the central cornea, and more particularly the corneal epithelium, ultimately leading to a potential displacement of the cone apex.[19,20] Therefore, it is possible that the physical pressure exerted by the contact lens over the keratoconic cornea modifies the anterior corneal curvature and power and perhaps the thinnest corneal location as well. The latter is supported by a previous study which reported that keratoconus subjects fitted with corneal rigid gas-permeable contact lenses showed greater corneal irregularity and higher central curvature power than non-contact lens wearers keratoconus subjects.[21] It is also known that the cone apex gets displaced towards the corneal periphery with the normal progression of the disease, and higher central keratometric powers are commonly associated to more advanced stages of keratoconus disease. [1, 2] In our study, N-CL and CL-W were well matched in terms of age, corneal thickness and central curvature power, however it is unclear whether the further away corneal locations of the thinnest and maximum tangential found in CL-W in comparison to N-CL in this study are attributed to contact lens wear or the normal evolution of the disease.

No significant differences in front and back elevations were found in this study between N-CL and CL-W wearers, neither in location nor in height. It has been shown that front and back elevation maps provide a more accurate representation of the anterior corneal surface than curvature maps because they are independent of axis, orientation and position.[14] Furthermore, elevation maps have been reported to be useful in the diagnosis and monitoring of keratoconus disease.[22] Although corneal rigid gas-permeable contact lens wear is commonly associated to flattening of the anterior central cornea, the use of these lenses is unlikely to change the true shape of the cornea (i.e., front and back corneal elevations). However, our results are in contrast with a recent cross-sectional study which evaluated the effects of corneal rigid gas-permeable contact lens wear in keratoconus subjects.[23] After close to 2-years of follow-up, a lower front and higher back corneal elevations, respectively, were found with rigid gas-permeable contact lens wear in comparison to baseline, but no significant changes were observed on corneal elevation or curvature in non-contact lens wearers in comparison to baseline.[23] Although contact lens wearers showed reduced corneal thickness and increased central curvature power in comparison to non-contact lens wearers after 2-years, the latter might be attributed to differences in disease severity between the groups in that study.[23]

To assess the true effect of corneal rigid gas-permeable contact lens wear on the corneal shape of keratoconus, it would have been ideal to discontinue contact lens wear for a relative long period of time (e.g., 1 month) and then compare the results with those collected a few minutes after lens removal. However, the latter was not possible because keratoconus subjects rely on their contact lenses to achieve adequate visual function.

No statistical differences in corneal volume, anterior chamber depth, anterior chamber volume and corneal thickness at the maximum tangential curvature corneal values were found between N-CL and CL-W. Although we were expecting a slightly reduction in corneal thickness at the maximum tangential corneal location in CL-W in comparison to N-CL as a result of contact lens-induced corneal flattening, an increase in corneal thickness was found. Furthermore, we observed smaller anterior chamber depth and anterior chamber volume in CL-W vs. N-CL. Despite keratoconus has been typically described in the literature as a non-inflammatory disease, recent studies have shown it is accompanied by an increase of pro-inflammatory cytokines in the tears in comparison to normal subjects,[24] being the inflammatory response even greater with contact lens wear.[25] It is, therefore, possible that the physical pressure induced by contact lens wear causes a local, slight and superficial inflammation of the anterior cornea leading to an increase in local thickness and volume.

In summary, the thinnest corneal location does not overlap with the steepest and maximum elevation corneal locations in keratoconus, and contact lens wear does not seems to affect this lack of overlapping. We suggest that contact lens wear in keratoconus flatten the corneal apex displacing the thinnest and maximum tangential curvature corneal locations, and increasing corneal thickness on cone apex. However, longitudinal studies are required to ascertain whether the change found in these corneal locations is attributed to contact lens wear *per se* or to the normal progression of the disease.

5.1.6. References

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SECTION 5.2

Short-term corneal changes with gas-permeable contact lens wear in keratoconus subjects: a comparison of two fitting approaches

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5.2.1. Abstract

Short-term corneal changes with gas-permeable contact lens wear in keratoconus subjects: a comparison of two fitting approaches

Objectives: To evaluate changes in anterior corneal topography and higher-order aberrations (HOA) after 14-days of rigid gas-permeable (RGP) contact lens (CL) wear in keratoconus subjects comparing two different fitting approaches.

Methods: Thirty-one keratoconus subjects (50 eyes) without previous history of CL wear were recruited for the study. Subjects were randomly fitted with either an apical-touch or three-point-touch fitting approach. The lens' back optic zone radius (BOZR) was 0.4 mm and 0.1 mm flatter than the first definite apical clearance lens, respectively. Differences between the baseline and post-CL wear for steepest, flattest and average corneal power (ACP) readings; central corneal astigmatism (CCA); maximum tangential curvature (KTag); anterior corneal surface asphericity, anterior corneal surface HOA and thinnest corneal thickness measured with Pentacam were compared.

Results: A statistically significant flattening was found over time on the flattest and steepest SimK and ACP, in apical-touch group (all $p<0.01$). A statistically significant reduction in KTag was found in both groups after contact lens wear (all $p<0.05$). Significant reduction was found over time in CCA ($p=0.001$) and anterior corneal asphericity in both groups ($p<0.001$). Thickness at the thinnest corneal point increased significantly after CL wearing ($p<0.0001$). Coma-like and total HOA RMS error, reduced significantly following CL wearing in both fitting approaches (all $p<0.05$).

Conclusion: Short-term rigid gas-permeable CL wear flattens the anterior cornea, increases the thinnest corneal thickness and reduces anterior surface HOA in keratoconus subjects. Apical-touch was associated with greater corneal flattening.

Keywords: cornea, keratoconus, contact lenses.

5.2.2. Introduction

Corneal rigid gas-permeable (RGP) contact lenses still represent the most common and successful management option for mild to moderate cases of keratoconus because these lenses can mask relatively high levels of irregular astigmatism and thus substantially improve visual acuity.[1] Additionally, most keratoconus subjects report wearing these lenses comfortably along the day.[1,2]

Three fitting approaches have been described to fit corneal RGP in keratoconus: 1) apical-touch (lens bears on corneal apex), 2) three-point-touch (lens' bearing is shared between corneal apex and mid periphery) and 3) apical-clearance (lens bears on mid periphery without apical-touch).[3]

The use of corneal RGP contact lenses has been shown to induce topographical changes on the cornea in normal control subjects[4,5] as well as in subjects with keratoconus.[6] In normal subjects, corneal curvature changes observed following RGP contact lens wear are related to the type of contact lens worn and the number of years of lens wear.[5] It has been reported that apical-touch fitting causes central corneal flattening in keratoconus,[7] whereas apical-clearance fitting causes central corneal steepening,[8] which could be confounded with the normal progression of keratoconus disease, so apical-clearance fitting approach is not usually intended. Zadnik and Mutti,[9] previously discussed that apical-touch fitting RGP lenses might 'mold' the keratoconic cornea by exerting pressure on the cone apex, thereby forcing the anterior surface to conform with the RGP lens' back surface. Hwang et al. have reported RGP contact lens wear fitted with three-point-touch fitting approach in keratoconus subjects caused corneal flattening after two years of wear.[2] More recently, Jinabhai and co-workers reported that both visual acuity and thickness at the thinnest corneal point decreased and corneal curvature and corneal higher-order aberrations (HOA) increased, after ceasing RGP contact lens wear for 1 week in keratoconus subjects who had been wearing these lenses, mostly fitted with apical-touch fitting approach, for an average of 7 years.[10] Therefore, corneal curvature, shape, thickness and anterior surface higher-order aberrations are altered following RGP lens wear in keratoconus subjects who have been wearing corneal RGP contact lens for a long period. However, to the best of our knowledge, no previous studies have reported corneal changes induced by a short period of corneal RGP lens wear in neophyte contact lens wearers with keratoconus in a clinical context. Those changes might have implications in the lens-to-cornea relationship, lens parameters and lens power prescribed. To clarify this question it is necessary to know whether corneal changes observed after short periods of time within the initial period of fitting and adaptation are similar to the changes reported by other authors. Thus, the present study assessed the changes in the anterior corneal surface induced by RGP lenses fitted according two different approaches, over a period of 14 days. This time of contact lenses adaptation was decided because subjects were neophyte contact lens wearers. As it is known, some subjects experienced some discomfort when they begin to wear RGP contact lenses and it takes longer for them to be able to wear lenses 8 or more hours a day. In order to be sure that subjects were wearing contact lenses at least eight hours a day, we decided to give them two weeks to get used to contact lenses and wearing them at least 8 hours a day before to acquire a new topography.

5.2.3. Materials and Methods

Subjects with keratoconus and no previous history of contact lens wear were included in the study. Comprehensive optometric and ophthalmic examinations were performed in all subjects including the assessment of uncorrected and corrected logMAR visual acuities, anterior segment biomicroscopy, fundus examination, and keratometry. In addition a corneal topographic examination was performed using the Pentacam Eye Scanner (Software version 1.16.r:23, Oculus Inc, Wetzlar, Germany). All topographic examinations were taken by the same examiner (M R-J). The Pentacam system is based on a rotation Sheimpflug camera that can take 12 to 50 single captures to reconstruct a 3D anterior segment image. In the present study, anterior segment Pentacam examinations were produced with 25 single captures within 2 seconds. The results obtained with Pentacam were checked under the device's quality specification window; only the correct measurements (i.e. "quality specifications" reads OK) were accepted; if the comment was marked yellow or red, the examination was repeated. As it has been previously reported that the Pentacam instrument provides high sensitivity and specificity in keratoconus detection,[11,12] as well as high reproducibility and repeatability in measuring corneal thickness,[13,14] and corneal power[15] a single Pentacam examination was acquired for each eye.

Keratoconus diagnosis was performed according to the keratoconus severity score described by the CLEK study group.[16] The keratoconus grading was based on average central corneal power (ACP) and HOA Root Mean Square error (RMS) as mild (ACP ≤ 52.00 D or RMS >1.50, ≤3.50), moderate (ACP > 52.00 D, ≤ 56.00 D, or RMS > 3.50, ≤ 5.75) and severe (ACP > 56,00 D or RMS > 5.75) The worst of the two variables (i.e. ACP and RMS) carries the greater weight to select the appropriate grade.[11] Eyes with a previous history of acute corneal hydrops, corneal surgery or any other ocular disease were excluded from the study. All subjects were older than 18 years of age. Informed consent was obtained from all subjects prior to the start of all experimental work and data collection. The study protocol followed the Tenets of the Declaration of Helsinki and was approved by the Institutional Ethical Committee Review Board of MGR Doctores ophthalmology clinic and the scientific committee of the School of Sciences at the University of Minho.

All contact lenses used in the study were standard Rose K2 lenses manufactured in tisilfocon A material (Menicon Z, Menicon Co., Ltd. Nagoya, Japan). In subjects with bilateral keratoconus, lens fitting was performed on both eyes using the same fitting approach.

5.2.3.1. Fitting method

Following manufacturer's recommendations, the first trial lens' BOZR was selected 0.20 mm steeper than the average central keratometry and fitted on the eye. Enough time to stop reflex tearing caused by contact lens was allowed, and then sodium fluorescein was instilled for fitting assessment (Haag-Streit, Koeniz, Switzerland). Then, the lens' BOZR was flattened (i.e. increased) or steepened (i.e. decreased) in 0.10 mm steps until the first definite apical clearance lens (FDACL) was found following the methodology previously described by the CLEK Study Group.[17] Subsequently, subjects were randomly allocated to either the apical-touch or three-point-touch fitting group, and lenses with BOZR 0.40 mm and 0.10 mm flatter than the FDACL, respectively, were fitted (**Figure 5.2.1**) accordingly with a method previously described by the authors.[18] Once the subjects were randomly allocated to a group (apical-touch or three-point touch), the selected RGP lens was inserted. Following 30 to 60 minutes after lens insertion the overall diameter and edge lift were assessed to ensure the lens was well centered and showed a fluorescein band of 0.5 to 0.7 mm in width along the lens edge. Once an acceptable trial lens fit was achieved, the lens was ordered from the manufacturer, and subjects were rescheduled for a dispensing visit. At the dispensing visit, corneal topography was performed in all subjects, previously to lens insertion. Subsequently, subjects were trained in procedures for insertion, removal and cleaning/disinfection of contact lenses, and instructed to wear their contact lenses for 2 to 4 hours a day, increasing 1-2 hours for each following days until reaching at least 8 hours of continuous wearing time. Subjects were scheduled for visits after 1, 7, and 14 days of contact lens wearing. Patients were required to attend the follow-up visits wearing their lenses A new topography over the naked eye was taken following 14 days of contact lens wear. This topography was taken within one minute after RGP lens removal.

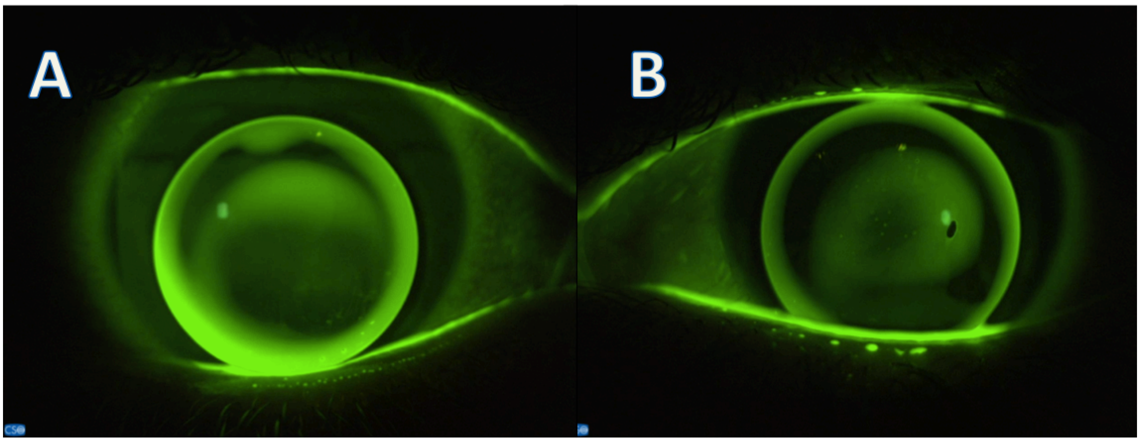

Figure 5.2.1. Contact lens fitting fluorescein patterns showing: (A) apical-touch fitting approach and (B) three-point-touch fitting approach.

All measurements reported are from the anterior corneal surface. Differences between baseline and 14-days of RGP lens wear in maximum and minimum simulated keratometry (Steepest SimK and Flattest SimK, respectively), average corneal power, maximum tangential curvature, central corneal astigmatism, anterior corneal surface asphericity for an 8 mm chord diameter and in the thinnest corneal thickness were compared between fitting approaches. Additionally, differences between groups following contact lens wear were also assessed in anterior corneal surface HOA coefficients (3rd to 6th order) and total HOA RMS. The corresponding RMS error values were evaluated for the following types of optical aberrations: HOA from the 3th- to the 6th-order Zernike terms inclusive; spherical-like aberrations for the 4th and 6th order Zernike terms; coma-like aberrations for the 3rd and 5th order Zernike terms; and secondary astigmatism aberrations for the 4th and 6th order Zernike terms.· Although Pentacam is capable to measure until the term 10th of Zernike terms, the analysis of corneal aberrations takes normally until term 6th.[10,19] All corneal HOA were calculated for a 6.0 mm. of diameter.[19]

5.2.3.2. Statistical analysis

In the present study, in subjects with bilateral keratoconus, contact lens fitting was performed on both eyes with the same fitting approach. So, the randomization of fitting approach was undertaken on subjects instead of eyes. Despite keratoconus is normally defined as a bilateral and asymmetric condition,[20,21] and although many previous reports have used data from both eyes in keratoconus for statistical analysis,[1,2,7-9] we followed recent recommendations of Karakosta A et al.[22] and Armstrong RA.[22] to elucidate whether in the present study data form both eyes could be use as within-subjects factor. An Intraclass Correlation test was carried out to compare data from the most and less advanced keratoconus eyes of subjects with bilateral keratoconus. All studied parameters showed a weak correlation (all ICC $r_o < 0.5$), thus, in subjects with bilateral keratoconus, data from both eyes were treated as within-subject factor.[22,23] Normality test were performed for all data collected using the Shapiro-Wilk test with a level of significance of 5%. All normally distributed data were analyzed using 1-way repeated-measures analysis of variance (RM-ANOVA). Fitting approach (i.e. apical-touch vs. three-point-touch) was designated as the factor of interest and study visits (i.e. baseline vs. 14 days) as the repeated measure. Equality of variances and sphericity were tested using the Levene and Mauchly tests, respectively to select appropriate p-values. Non-parametric variables were evaluated using Wilcoxon signed-rank test for each group separately, and U Mann-Whitney test for comparison between groups. Non-continuous variables were assessed with Chi-square test. Statistical analyses were performed using SPSS software (version 15.0, SPSS Inc.; Chicago, IL, USA). The level of statistical significance was taken as 5%.

5.2.4. Results

Thirty-one subjects (50 eyes) with keratoconus were included in the study. Sixteen subjects (25 eyes) and 15 subjects (25 eyes) were fitted with an apical-touch fitting approach and with a three-point-touch fitting approach, respectively.

Grade of severity did not show statistically significant differences between groups either at baseline or over the follow-up period (all p>0.05) (**Table 5.2.1**). However, the KSS range decreased in apical-touch group after contact lens wearing (**Table 5.2.1**).

Table 5.2.1. *Severity of the groups based on the Keratoconus Severity Score.*

KSS	Baseline			Day Fortieth		
	Apical-Touch	Three-point-touch	p-value*	Apical-Touch	Three-point-touch	p-value*
Mild	15	21	0.115	20	21	0.713
Moderate	8	4		5	4	
Severe	2	0		0	0	

* Chi-square test. KSS: Keratoconus Severity Score range.

The flattest SimK was found to be flatter following CL wear in the apical-touch group (p=0.030), but no significant differences were found in the three-point-touch group or between groups either at baseline or after 14 days of CL wearing (all p>0.05) (**Table 5.2.2**) The steepest SimK was found to be flatter following contact lens wear in comparison to baseline in apical-touch group (p<0.0001), but no significant differences were found in the three-point-touch group or between groups either at baseline or after the follow-up period (all p>0.05) (**Table 5.2.2**). Average corneal power was found to be significantly flatter following contact lens wear in comparison to baseline in apical-touch group (p=0.003), but no statistically significant differences were found in three-point-touch group or between groups and visits (all p>0.05) (**Table 5.2.2**). A statistically significant difference in maximum tangential curvature power was found between groups at baseline (p=0.026) but not after 14 days of CL wear (p=0.118). The maximum tangential curvature power was significant reduced with 14 days of contact lens wear in comparison to baseline in both groups (all p<0.001) (**Table 5.2.2**).

Table 5.2.2. *Comparison of the flattest, steepest and average corneal power and maximum tangential keratometry.*

Measurements (D)	Apical-touch				Three-point-touch				Comparison Between groups p^+	
	Baseline	14 days	Dif.	P*	Baseline	14 days	Dif.	P*	Baseline	14 days
Flattest SimK	46.61±3.41	46.31±2.86	0.29	0.030	45.88±3.10	45.92±3.23	-0.04	0.190	0.665	0.662
Steepest SimK	50.65±4.24	49.79±3.57	0.77	<0.0001	49.43±3.60	49.13±3.28	0.30	0.010	0.399	0.607
ACP	48.53±3.73	47.98±3.11	0.51	0.003	47.56±3.18	47.46±3.16	0.10	0.227	0.372	0.535
KTag	56.79±4.90	54.56±4.28	1.8	<0.0001	53.68±3.81	52.61±3.37	1.07	0.001	0.026	0.118

*Wilcoxon signed rank test. $^+$ U Mann-Whitney test. Dif: difference; D: diopters; SimK: simulated keratometry; ACP: average corneal power; KTag: maximum tangential curvature.

Contact lens wear induced a statistically significant reduction in central corneal astigmatism in comparison to baseline in both groups (p<0.0001, **Table 5.2.3**). However, no statistically significant differences were found between groups in the value of central corneal astigmatism (p=0.808) or in the time*group interaction (p=0.176, **Table 5.2.3**).

Corneal asphericity was found to be significantly reduced following contact lens wear ($p<0.0001$), but no significant differences were found between groups ($p=0.337$) or in the time*group interaction ($p=0.114$) (**Table 5.2.3**).

Table 5.2.3. Comparison of central corneal astigmatism and corneal asphericity for apical-touch and three-point-touch fitting approaches. (RM-ANOVA test).

	Apical-touch			Three-point-touch			p-value		
	Baseline	**14 days**	**Dif.**	**Baseline**	**14d ays**	**Dif.**	**Time**	**Group**	**Time*group**
CCA (D)	3.60±2.04	3.28±1.76	0.32	3.90±1.58	3.21±1.54	0.69	<0.0001	0.808	0.176
Corneal asphericity	-0.87±0.63	-0.72±0.46	0.15	-0.70±0.37	-0.64±0.35	0.06	<0.0001	0.337	0.114

CCA: central corneal astigmatism. D: diopters

The thickness at the thinnest point was significant thinner in the apical-touch group in comparison to the three-point-touch group at both baseline and after 14 days of CL wear visits (RM-ANOVA test, $p=0.010$). A statistically significant increase in thickness at the thinnest corneal point was found over time ($p<0.0001$), but no statistically significant differences were found for the time*group interaction ($p=0.134$), (**Figure 5.2.2**).

No statistically significant differences were found in spherical-like anterior corneal aberration either over time within each group (Wilcoxon signed rank test all $p>0.05$) or between groups at any visit (U Mann-Whitney test all $p>0.05$) (**Figure 5.2.3**). Statistically significant reduction in secondary astigmatism aberration in apical-touch group and in coma-like aberration and in higher-order RMS in both groups was found following contact lens wear in comparison to baseline (Wilcoxon test all $p<0.05$) (**Figure 5.2.3**). However, no significant differences were found between groups at any visit in secondary astigmatism, coma-like or higher-order RMS anterior corneal aberrations (U Mann-Whitney test all $p>0.05$) (**Figure 5.2.3**).

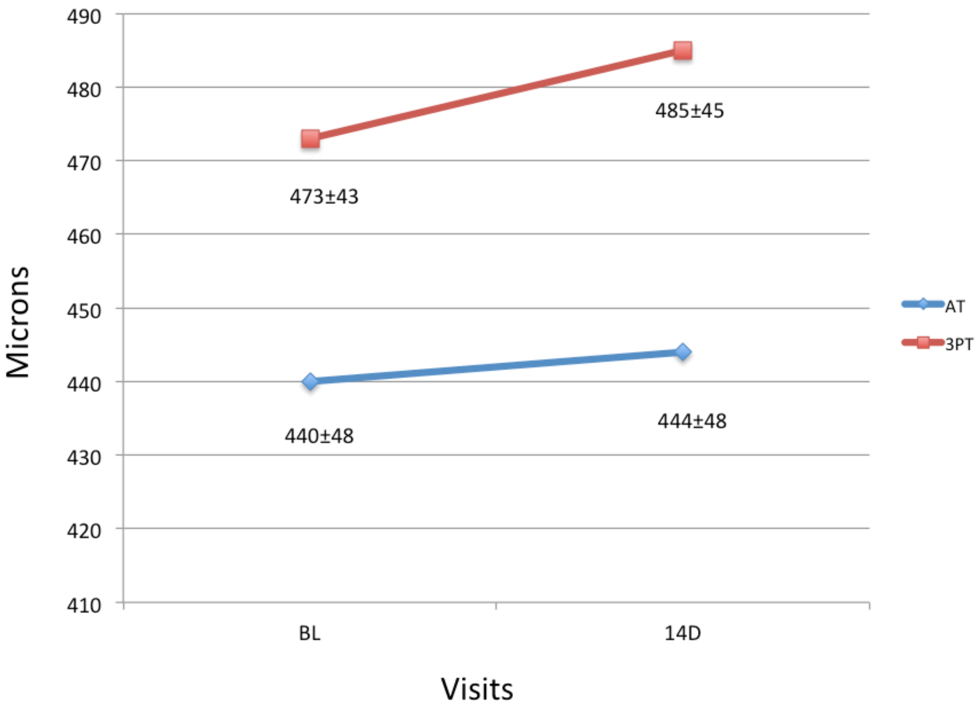

Figure 5.2.2. Comparison of the Thinnest Corneal Thickness both fitting approaches. BL: Baseline; AT: apical-touch fitting approach; 3PT: three-point-touch fitting approach.

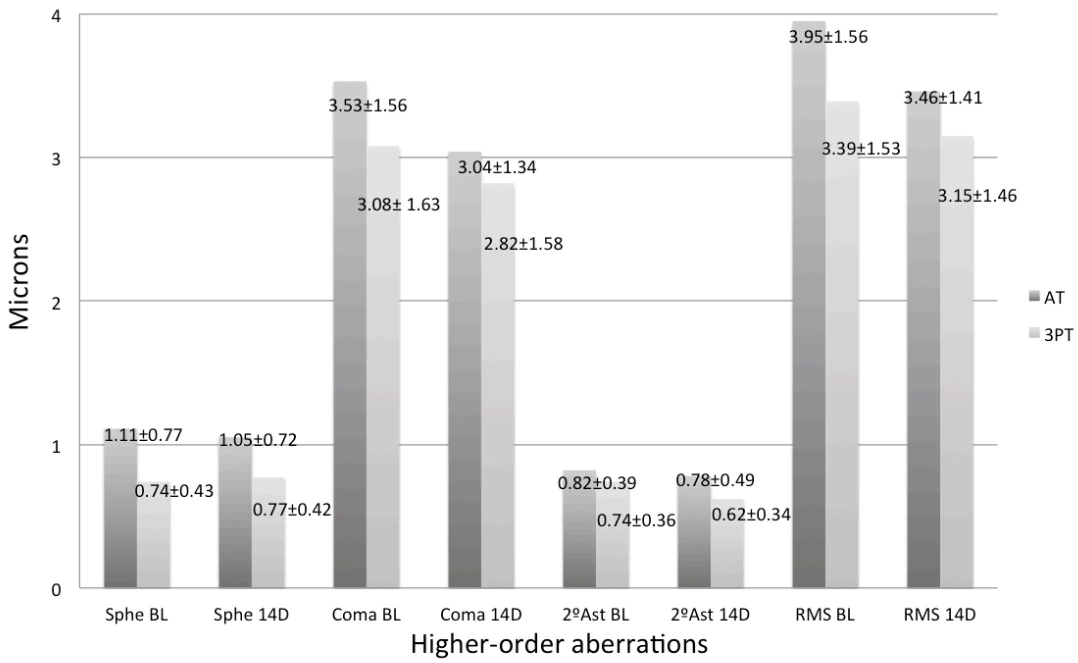

Figure 5.2.3. Analysis of anterior corneal higher-order aberrations for both fitting approaches. Sphe: spherical-like aberration; 2º Ast: secondary astigmatism; RMS: root mean square error; BL: baseline; AT: apical-touch fitting approach; 3PT: three-point-touch fitting approach.

5.2.5. Discussion

To the best of our knowledge, this is the first study to assess short-term corneal changes caused by apical-touch and three-point-touch RGP contact lens fittings approaches in neophyte contact lens wearers with keratoconus. As expected, this study found RGP contact lens wear to induce corneal flattening. In the apical-touch group, significant anterior corneal surface flattening was found on average corneal power. This flattening was greater in the steepest in comparison to the flattest corneal meridian, which is in agreement with previous reports.[10,24] This is favorable to a reduction in corneal toricity and can be attributed to how RGP lenses settle on eyes with keratoconus. Rigid gas-permeable contact lenses tend to move towards the direction of the steepest (and more elevated) axis leading to increased lens' bearing and thus greater flattening on this corneal meridian. In the three-point-touch group, although these changes were not statistically significant, the steepest corneal meridian flattened and the flattest meridian steepened, which is in agreement with a previous report.[24] A significant flattening in the maximum tangential curvature was also found in both groups following RGP lens wear, that was greater in the apical-touch group in comparison to the three-point-touch group. The flattening in maximum tangential curvature was found to be greater, in magnitude, than the flattening in average corneal power. This is attributed to greater lens' bearing on the cone apex in comparison to other corneal locations. In the present study, anterior corneal surface flattening was found to be greater in apical-touch group in comparison to the three-point-touch group. This greater reduction in anterior corneal surface curvature in apical-touch group caused the improvement on the KSS staging in this group. This reduction in corneal curvature with RGP contact lens wearing could be misinterpreted as an improvement on keratoconus staging, but once the subject discontinues contact lens wearing, corneal curvature increases.[10,26]

We found that central corneal astigmatism was reduced with contact lens wear and this is attributed to the fact that the steepest meridian flattened more than the flattest meridian in both groups after contact lens wearing. A greater, not statistically significant but clinically significant, reduction of corneal astigmatism was found with the three-point-touch fitting approach compared to the apical-touch fitting approach. The amount of central corneal astigmatism reduction in three-point-touch group was 0.69 D. Hwang et al. found a reduction in central corneal astigmatism of 0.70 D after two years of RGP contact lens wearing in keratoconus subjects fitted with three-point-touch fitting approach.[2] In the three-point-touch approach, lens' bearing on the cone apex tends to be slight and it mainly occurs over the steepest and more elevated corneal axis, which may imply lens clearance over the flattest corneal axis. It has been reported apical-clearance fitting approach to cause corneal steepening,[8] so the flattest axis in three-point-touch approach probably remains unchanged or becomes steeper.[24]

Corneal asphericity was also found to reduce with contact lens wear and this might be also related to the corneal flattening induced by contact lens wear. This corneal asphericity reduction with RGP contact lens wear in keratoconus was previously reported.[10] A flattening of the mean central curvature reduces the difference between central and peripheral corneal curvatures thus reducing corneal asphericity.[25] Clinically greater reduction in corneal asphericity was found in apical-touch group in comparison to three-point-touch group, which is presumably related with the greater corneal curvature flattening in the apical-touch group.

The significant difference found between groups in thinnest corneal thickness is likely to be related to baseline differences between groups in thickness despite randomization of subjects into the two different groups. Interestingly, an increase in thickness at the thinnest point was found following contact lens wear. This finding is in agreement with Jinabhai et al. who reported a decrease in thinnest corneal thickness after discontinuation of RGP contact lens wear for 1-week in long-term contact lens wearers with keratoconus in two previous studies,.[10,26] More recently, Romero-Jiménez et al. found greater thickness at the thinnest corneal point in a group of keratoconus subjects who had been wearing RGP lenses for at least six months compared with a control group of non-contact lens wearers with keratoconus.[27] Thinnest corneal thickness increase with RGP contact lens wearing might be the result of lens-induced corneal inflammation from mechanical effect. This thickness increasing seems to be present since the very first time of contact lens wearing and along the time that subjects wear the lenses, as a chronic slight inflammation. The increasing in thinnest corneal thickness was found to be greater in three-point-touch group in comparison to apical-touch group. This might be caused because in apical-touch group the pressure of the lens over the corneal epithelium is greater than in three-point-touch group, which lead to a geater reduction of corneal epithelium layer which mask the possible local corneal inflammation caused by RGP contact lens wearing. Despite keratoconus has been classically described in the literature as a non-inflammatory disease, recent studies have shown it is accompanied by an increase of pro-inflammatory cytokines in the tears in comparison to normal subjecs,[28] with the inflammatory response being even greater with contact lens wear.[29] The mechanical rubbing of the RGP lens over the cornea might cause a subtle inflammatory response on the cornea leading to increased corneal thickness. However, studies should be conducted to corroborate the latter.

The reduction in anterior surface corneal aberrations found following RGP lens wear is attributed to the corneal flattening induced by lens wear. In addition, the reduction of higher-order corneal aberrations was greater in the apical-touch group, in comparison to three-point-touch group, a finding in agreement with a previous report which found that the flatter the BOZR, the greater the reduction in higher-order ocular aberrations.[30]

In conclusion, our study shows RGP contact lens wear to flatten the anterior cornea, to reduce corneal asphericity and corneal stigmatism, and to reduce anterior corneal surface higher-order aberrations in keratoconus subjects after a short period of wear. The greater contact lens bearing, the greater corneal curvature flattening. Three-point-touch fitting approach causes a greater reduction in central corneal astigmatism in comparison to apical-touch. In addition, RGP contact lens wear might cause a local and slight chronic corneal inflammation whose clinical relevance should be ascertained. Changes found on anterior corneal surface with short period of RGP contact lens wear are clinically relevant in terms of corneal curvature flattening, especially in apical-touch fitting approach, because they could be misinterpreted as a keratoconus improvement. On the other hand, it is necessary to evaluate whether changes on anterior corneal surface observed after a short period of time are maintained or they evolve along the time. Differences found between apical-touch and three-point-touch fitting approaches after a short period of RGP contact lens wear on corneal surface are not clinically relevant, except on central corneal curvature. Therefore, is not possible to state that one of the RGP contact lens fitting approach evaluated is better than the other in terms of corneal impact.

5.2.6. References

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CHAPTER 6

Two-Year Clinical Outcomes of Rigid Gas-Permeable Contact Lens Fitting in Keratoconus

Miguel Romero-Jiménez

Introduction

Despite the current surgical options for keratoconus treatment (i.e. corneal cross-linking, Intrastromal Corneal Ring Segment (ICRS) implantation and corneal keratoplasty), rigid gas-permeable (RGP) contact lenses still represent the first method for keratoconus management. Although semi-scleral, mini-scleral and scleral contact lenses have experienced a renaissance in the last decade,[1] mainly due to the improvements in gas-permeable materials and computer-assisted manufacturing technology, corneal RGP contact lenses continue to be the gold standard for the optical management of keratoconus.

Three RGP contact lens fitting approaches have classically been described for keratoconus: steep or apical-clearance, flat or apical-touch and three-point-touch or divided support.[2] The differences between these fitting approaches are primarily based on the relationship between the central corneal curvature and the back optic zone radius of the lens. In the apical-clearance fitting approach, the back optic zone radius of the lens is steeper than the central corneal curvature, so that the lens vaults the cone apex and bears on the peripheral cornea. In the apical-touch fitting approach, the back optic zone radius of the lens is flatter than the central corneal keratometry, thus the lens mainly bears on the apex of the cone. In the three-point-touch fitting approach, the lens bearing is distributed between the cone apex and mid-peripheral cornea.[2]

Rigid gas-permeable contact lens wear and corneal scarring in keratoconus

In 1982 Korb et al. published a paper comparing apical-touch and apical-clearance fitting approaches in keratoconus subjects.[3] Seven patients were fitted with apical-clearance lens on one eye and apical-touch lens on the other. With regard to the flattest meridian of corneal curvature, the apical-touch fittings were between 0.1 and 0.9 mm flatter, and the apical-clearance fittings were between 0.1 and 0.6 mm steeper. The two lens designs were randomly fitted to the right or left eye. Therefore, the apical-touch fitting approach was fitted to the more advanced eye in four patients and to the less advanced eye in the remaining three. In 1 year, four of the seven eyes wearing the apical-touch fitting approach developed corneal scarring, whereas no scarring developed in the eyes fitted with the apical-clearance technique. In spite of the limited sample, the fitting of early keratoconus with gas-permeable lenses was recommended in order to achieve minimal clearance or minimal apical bearing.[3]

In 1991 Edrington et al. presented the results from the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study, which also suggested the increased risk of scarring with apical-touch fitting.[4] Observations were made on 741 keratoconic patients. Seventy-five per cent of the eyes were fitted with apical-touch, 24% were fitted with apical-clearance and 1% in piggyback lens systems. Twenty-five percent of 233 eyes fitted with apical-clearance were scarred in comparison with 46% of 732 eyes fitted with the apical-touch fitting approach.[4] However, the magnitude of central touch was not quantified, and thus the apical-touch, apical-clearance and the three-point-touch fitting approaches could not be differentiated. In addition, the causal relationship could not be ascertained with cross-sectional data as it depended on fitting techniques and disease severity.[4]

Later, in 1996 Gundel et al., from the CLEK study group, reported the results of a pilot study consisting of 13 subjects (22 eyes) fitted with the apical-clearance fitting approach.[5] After a year of follow-up, 1 of 22 eyes presented early central corneal scarring in 12 months. In addition, changes in the flat and steep keratometric readings between the baseline and 12-month visits showed an average steepening of 2.29 D and 1.28 D, respectively, for 14 of 22 completing eyes, from which reliable keratometric readings could be obtained both at baseline and in 12 months.[5]

Also, in 1996 Edrington et al., from the CLEK study group, published the results of a pilot study comparing the feasibility of apical-clearance and apical-touch fitting approaches in keratoconus, based on the concept of first definite apical-clearance lens (FDACL).[6] Seventeen subjects were randomly assigned to apical-clearance and 13 to apical-touch fitting approaches, respectively. Unfortunately, as some patients were missed to follow-up for this study, the evaluation of possible effects of these two different fitting approaches on corneal scarring was not possible.

In 1999 Edrington et al., also from the CLEK study group, published the analysis of this large cohort regarding RGP contact lens relationships in 808 keratoconus subjects, who wore this type of contact lenses. The results revealed that 12% and 88% of eyes were fitted with apical-clearance and apical-touch fitting approaches, respectively.[7] Thus, the authors reached the conclusion that "*in spite of the debated risk for increased* *corneal scarring imposed by flat fitting rigid contact lenses, most CLEK Study patients wear flat-fitting lenses, as prescribed by their practitioners. Because the significance of flat-fitting lenses is unknown, a large-scale randomized clinical trial is required to test the efficacy of apical-touch vs. apical-clearance fitting of rigid contact lenses in the management of keratoconus".*[7]

In 2000 Barr et al., from the CLEK study group, reported the factors associated with corneal scarring in keratoconus. Analyzing the data of the contact lens fitting relationship in 1576 eyes with keratoconus, 31% and 9% of eyes fitted with apical-touch and apical-clearance, respectively, presented corneal scarring. However, the relationship between the apical-touch fitting approach and corneal scarring could not be ascertained with cross-sectional data from this study. On the other hand, the authors discovered a relationship between RGP contact lens wear and corneal scarring in keratoconus (odd ratio of 3.51).[8]

Later, in 2005 Zadnik et al. published a paper evaluating the safety and efficacy of apical-touch and apical-clearance fitting approaches in 761 subjects with keratoconus, who wore RGP contact lenses.[9] Data showed a greater number of scarred corneas in the apical-touch fitting approach than in the apical-clearance fitting approach (43% vs. 26%, respectively). However, after controlling the corneal curvature, the association of the RGP contact lens fitting approach and corneal scarring did not persist. With regard to the data reported, these authors concluded that "*after controlling disease severity in the form of corneal curvature, keratoconic eyes fitted with a RGP contact lens resulting in apical-touch fluorescein pattern did not have an increased risk of being scarred centrally. The "natural history" of corneal scarring in keratoconus with apical-touch fitting approach, cannot determine casual proof that one method of fitting lenses is safer than another.*" Finally, they stated that a randomized clinical trial was needed to ascertain which RGP contact lens fitting approach is safer.[9]

In summary, apical-touch fitting has a bad reputation due to apical scarring. The only literature to support this argument is the one reported by Korb et al., whose sample size was nevertheless very small.[3] Results obtained from the largest cross-sectional study on keratoconus (CLEK) concluded twice[7,9] that a randomized clinical trial was necessary to ascertain if the apical-touch RGP contact lens fitting approach has a higher risk for incidence of scarring than the apical-clearance fitting approach in keratoconus. To the best of our knowledge, such a clinical trial has not been conducted yet. Finally, and in spite of the bad reputation of the apical-touch fitting approach, most keratoconus subjects, who wore contact RGP contact lenses, showed an apical-touch fluorescein pattern.[10]

Longitudinal surveys of RGP contact lens wear in keratoconus

Despite of the CLEK study group's recommendations, there is still a lack of longitudinal, randomized clinical trials comparing apical-touch and apical-clearance RGP fitting approaches in keratoconus. The main reason for this may lie in the fact that, in spite of the weak scientific evidence, apical-touch RGP contact lens fitting approach is often considered as the cause of central corneal scarring in keratoconus and, consequently, this contact lens fitting approach is avoided nowadays. On the contrary, the apical-clearance fitting approach has been published to induce central corneal steepening,[9] which could be interpreted as keratoconus progression. It is necessary to clarify that new surgical procedures for keratoconus (especially cross-linking) base their surgical indications on keratoconus progression, which is mostly stated as central corneal curvature steepening.[11,12]

The third proposed RGP contact lens fitting approach in keratoconus is defined as three-point-touch.[2] Currently, this is the most recommended fitting approach in keratoconus, because it is thought to be safer than the other fitting approaches in terms of corneal health. However, there is a lack of scientific evidence that supports it since the effect of three-point-touch versus other fitting approaches has not been studied. To complicate things, in 2005 the CLEK study group stated that "[…] *it is the investigator´s opinion that true three-point-touch fitting patterns, neither flat or steep, are difficult to achieve and maintain. Years of experience grading of fluorescein patterns at the CLEK Photography Reading Center have borne out that observation (unpublished data).*" [9]

To date, two retrospective studies have been published using the three-point-touch RGP contact lens fitting approach in keratoconus .[11,13] None of them have compared the three-point-touch fitting approach with other fitting approaches (i.e. apical-touch or apical-clearance). Lee et al. analyzed retrospectively data of 60 keratoconic eyes fitted with multicurve RGP contact lenses, worn for an average of 11.4 months.[13] A reduction (in millimeters) on the steepest SimK was reported. On the contrary, an increase (in millimeters) in the flattest SimK was found.[13] Incidence of corneal scarring was not reported.[13] On the other hand, Hwang et al. published retrospective data of 77 keratoconic eyes fitted with a multicurve RGP contact lens design, worn for an average of 22.4 months in comparison with 30 keratoconic eyes that did not wear contact lenses. Reduction in both average corneal power and thinnest corneal thickness was found in the contact lens wearer group.[11] In addition, 3 of 77 eyes (3.9%) in the contact lens wearer group developed corneal scarring during the follow-up in comparison with 2 of 30 eyes (6.9%) in the non-contact lens wearer group.[11]

Summary of RGP contact lens fitting in keratoconus

In summary, the apical-touch fitting approach has the bad reputation of causing central corneal scarring in keratoconus, and it is recommended to be avoided, despite of the weak scientific evidence. On the other hand, three-point-touch fitting approach is recommended as the best RGP fitting approach on keratoconus, because it is argued to be safer than apical-touch, although there is a lack of scientific support. In spite of the aforementioned, most keratoconus subjects who wore RGP contact lenses showed an apical-touch RGP contact lens fluorescein pattern. Finally, no longitudinal clinical trials comparing apical-touch and three-point-touch fitting approaches have so far been published. Thus, the main goal of this thesis was to undertake a prospective, longitudinal, randomized and single-masked clinical trial, comparing apical-touch and three-point-touch RGP contact lens fitting approaches in keratoconus subjects for a period of two years.

Aims and structure of this chapter

Chapter 6 of this thesis shows the outcomes of a two-year follow-up in two groups of keratoconus subjects fitted with either the apical-touch fitting approach or three-point-touch fitting approach, trying to answer the following questions:

1. Is the three-point-touch fitting approach really difficult to achieve and maintain?
2. Is the three-point-touch contact lens fitting approach really healthier (i.e. incidence of corneal scarring) than apical-touch?

3. Do both fitting approaches (i.e. apical-touch and three-point-touch) have different impact on keratoconus progression in a two-year follow-up period?

This chapter is divided in eight different sections:

- Section 6.1. Subject demographics, visits and dropouts
- Section 6.2. Contact lens fitting characteristics.
- Section 6.3. Anterior Corneal Curvature, Asphericity and Anterior Best-Fit Sphere Reference Surface.
- Section 6.4. Anterior corneal surface higher order aberrations.
- Section 6.5. Visual quality.
- Section 6.6. Corneal Thickness.
- Section 6.7. Corneal clinical signs.
- Section 6.8. Keratoconus severity score.

SECTION 6.1

Subject demographics, Visits and Dropouts.

6.1.1. Introduction

This section summarizes the results of the demographical data, number and causes of unscheduled visits and dropouts.

6.1.2. Demography at baseline

Subject recruitment began on November 1, 2009, and finished on December 30, 2010. During this period, 66 keratoconus subjects were examined as eligible candidates to be included in this study. Five subjects (8%) were excluded after contact lens (CL) fitting trials because they refused to wear RGP contact lens due to unbearable discomfort with the lenses. Three additional subjects decided not to participate in the study after being fitted with contact lenses. Therefore, 58 subjects (99 eyes) were enrolled and fitted with Rose K2 lenses. Subjects were randomly allocated to the apical-touch (29 subjects, 49 keratoconic eyes) and three-point-touch contact lens fitting groups (29 subjects, 50 keratoconic eyes). Seven and 3 subjects presented unilateral keratoconus at baseline, so 92 eyes of 52 subjects were fitted with contact lenses and data of them included in statistical analysis. One and 3 eyes presented ICRS in the apical-touch and three-point-touch fitting groups, respectively. Additionally, 1 and 2 eyes presented corneal keratoplasty in the apical-touch and three-point-touch fitting groups. Eyes with ICRS or corneal keratoplasty were not fitted with contact lenses and data of them were not included in the statistical analysis. No significant differences were found in subjects' eye conditions between the two groups at baseline (**Table 6.1.1**).

Table 6.1.1. *Subjects' eye conditions at baseline.*

Eye condition	Apical-touch	Three-point-touch	p*
Bilateral Keratoconus	40	42	0.396
Unilateral Keratoconus	7	3	
ICRS	1	3	
Keratoplasty	1	2	

*Chi-square test. ICRS: Intrastromal Corneal Ring Segment.

6.1.2.1. Subjects' baseline gender

Thirty-three men (57%) and 25 women (43%) were initially enrolled in this study. Seventeen men (59%) and 12 women (41%) were randomly allocated to the apical-touch group and 16 men (55%) and 13 women (45%) to the three-point-touch group. No significant differences were found in the male-female ratio between the two groups (Chi-square test, p=0.50).

6.1.2.2. Subjects' baseline age

Mean (±SD) age of the whole sample at baseline was 35.0±7.8 years (range 18.0-55.9). In the apical-touch group, age at baseline was 33.5±8.2 years, whereas in the three-point-touch group it was 36.5±7.1 years (Unpaired-t test, p=0.54).

6.1. 3. Demography of subjects that completed two-year follow-up

6.1.3.1. Subjects' gender

Twenty-seven men (57%) and 20 women (43%) completed a two-year follow-up. Thirteen men (59%) and 9 women (41%), and 14 men (56%) and 11 women (44%) completed the study in the apical-touch and the three-point-touch fitting groups, respectively (Chi-square test, p=0.506).

6.1.3.2. Subject's age

Mean age of the whole sample at baseline was 35.8±7.6 years (range 1.8.0-55.9). In the apical-touch group, age at baseline was 34.2±8.5 years, whereas in the three-point-touch group it was 37.0±6.6 years (Unpaired-t test, p=0.104).

6.1.4. Subject dropouts

Eleven subjects (19%) abandoned the study at different stages, 7 in the apical-touch group (24%) and 4 in the three-point-touch group (14%) (Chi-square test, p=0.504). In the apical-touch group, 5 subjects (9 eyes) abandoned CL wear before the 6-month follow-up visit, and 2 subjects (3 eyes) before the 18-month follow-up visit. Five of 7 subjects of this subgroup were neophyte contact lens wearers, and the other 2 were soft contact lens wearers before they enrolled. In the three-point-touch group, 3 subjects (5 eyes) abandoned CL wear prior to the 6-month follow-up visit, and 1 subject (2 eyes) before the 12-month follow-up visit. Three subjects of this subgroup were neophyte contact lens wearers, and 1 subject was an RGP contact lens wearer. The latter subject wore the lenses of the study 12 months before dropping out from it. The reasons for subjects to drop out from the study are displayed in **Table 6.1.2**.

Table 6.1.2. Reasons of dropout

Cause of dropout	Apical-Touch Subjects (eyes)	Three-point-touch Subjects (eyes)	p*
Discomfort	6 (11)	3 (5)	0.308
No reason	1 (1)	0	
Bad VA after CL removal	0	1 (2)	

* Chi-square test. VA: Visual Acuity. CL: Contact Lens

6.1.5. Unscheduled subject visits

6.1.5.1. Unscheduled visits for all subjects

After the contact lens dispensing visit, subjects had follow-up visits 1, 7 and 14 days, and 1, 6, 12, 18 and 24 months after baseline. In addition, 93 unscheduled visits occurred during the study for all subjects (58). This means that each enrolled subject appeared on average 1.60±1.53 times for an unscheduled visit (range 0-6). The apical-touch group (29 subjects) experienced 54 unscheduled visits (1.9±1.6 on average, range 0-6), whereas the three-point-touch group (29 subjects) experienced 39 unscheduled visits (1.3±1.5 on average, range 0-6). Causes and number of unscheduled visits for the whole sample, and the comparison between groups are shown in **Table 6.1.3**.

Table 6.1.3. Reasons and number of unscheduled visits

Causes	Apical-touch No. of visits (54)	Three-point-touch No. of visits (39)	p* (causes)	p+ (number)
Lens breakage	17	18	0.129	0.124
Lost lens	3	6		
Discomfort	16	10		
Corneal abrasion	3	2		
Visual complaints	14	3		
Lens entrapped	1	0		

* Chi-square test. + U Mann-Whitney test

6.1.5.2. Subjects who discontinued contact lens wear

In the apical-touch group, subjects who discontinued contact lens wear wore contact lenses for 4.1±5.4 months on average (range 1-12 months), and had 8 unscheduled visits (1.1±1.8 on average, range 0-5). All unscheduled visits in this subgroup were caused by discomfort. Three subjects in this subgroup did not have an unscheduled visit prior to their discontinuity in contact lens wear. In the three-point-touch group, subjects who discontinued contact lens wear wore contact lenses for 3.8±5.5 months on average (range 1-12 months), and had 6 unscheduled visits (1.50±1.29 on average, range 0-3). Three of them discontinued contact lens wear, because of the discomfort and 1 due to reduced visual quality following contact lens removal. Comparison of number of unscheduled visits between these subgroups was not statistically significant (Unpaired-t test, p=0.840).

6.1.5.3. Subjects who completed two-year follow-up

Subjects that completed the two-year follow-up (47) had 79 unscheduled visits. Therefore, each subject experienced a mean (±SD) of 1.7±1.5 unscheduled visits (range 0-6). In the apical-touch group, the 22 subjects that completed the two-year follow-up had 46 unscheduled visits (2.1±1.5 on average, range 0-6). In the three-point-touch group, the 25 subjects that completed the two-year follow-up had 33 unscheduled visits (1.3±1.6). The comparison between both groups regarding the reasons and number of unscheduled visits of the subjects that completed the two-year follow-up are shown in **Table 6.1.4**.

Table 6.1.4. . Comparison between groups regarding the reasons and number of unscheduled visits for the subjects that completed follow-up

Causes	Apical-touch No. of visits (46)	Three-point-touch No. of visits (39)	p* (reasons)	p+ (number)
Lens breakage	17	17	0.157	0.033
Lost lens	3	6		
Discomfort	8	6		
Corneal abrasion	3	2		
Visual complaints	14	3		
Lens entrapped	1	0		

* Chi-square test. + U Mann-Whitney test

6.1.6. Discussion

In this study, 5 of 66 eligible subjects (8%) refused RGP contact lens wear due to unbearable discomfort during contact lens trials, and thus they were not included in the study. Three additional subjects decided not to participate in the study after being fitted with contact lenses for different reasons, and they were excluded from the statistical analysis. The 58 remaining subjects (92%) were successfully fitted with Rose K2 lenses and enrolled. However, 11 of 58 enrolled subjects (19%) discontinued RGP contact lens wear, 9 of them due to unbearable discomfort in the first months after wearing them. Our results are in agreement with a previous study, which reported that 18 of 21 keratoconus subjects (90%) could be successfully fitted with Rose K2 lenses, and that only 16 subjects (76%) were able to wear lenses for the entire follow-up period.[14] Furthermore, comfortable RGP lens wear with spherical and multicurve lens designs has been reported in 73%[15] and 87%[2] of keratoconus subjects, respectively. Therefore, approximately 80% of keratoconus subjects are able to wear RGP contact lens comfortably.

Keratoconus affects both genders, although it is unclear whether significant differences between males and females exist. Some studies have not found differences in the prevalence between genders;[16,17] others have found a greater prevalence in females,[18,19] while other investigators have found a greater prevalence in males.[20-23] In this study no statistically significant differences were found between males and females either in the whole sample or between different fitting approaches, especially between the subjects that completed the two-year follow-up.

Although keratoconus usually appears during the second decade of one's life, normally during puberty,[16] most studies report RGP contact lens fitting for keratoconus management in subjects in their twenties[23] and thirties.[15] In this study, mean age for the whole sample was 35 years and no significant differences were found between both groups.

Eleven subjects were missed to follow-up (19%). A previous study reported that 2 of 21 (9.5%) keratoconus subjects fitted with Rose K2 lenses using the three-point-touch fitting approach were missed to follow-up.[14] However, another study reported a dropout rate of 23% in keratoconus subjects fitted with spherical RGP contact lens using the apical-clearance fitting approach.[5] Despite no significant differences were found in this study in the dropout rate between fitting approaches, the percentage of subjects that discontinued contact lens wear was greater in the apical-touch group (24%) than in the three-point-touch group (14%). Discomfort with contact lens was the main reason for contact lens dropout in both groups, and most subjects that abandoned contact lens wear had not worn contact lenses before they were enrolled in this study (72%), and they ceased contact lens wear after the 14th-day visit and before the 6th-month visit (72%). Discomfort has been reported as the main reason for RGP contact lens wear discontinuation,[25] which is in agreement with our results. In summary, cessation of RGP contact lens wear is more likely to happen in the first weeks after the initial contact lens wear. Therefore, practitioners should carefully follow up neophyte contact lens wearers reporting reduced comfort during the first few weeks of lens wear to minimize potential discontinuation.

There were 79 unscheduled visits during the 2-year follow-up, which leads to an average of 1.7 unscheduled visits per subject who completed the follow-up period. A previous study reported an average of 2.5 unscheduled visits in 30 keratoconus subjects randomly fitted with apical-touch and apical-clearance fitting approaches, using spherical tricurve RGP contact lenses.[6] Differences between our findings and the above study might be due to the different contact lens design employed as the Rose K2 lens is a specific lens design for keratoconus fitting. On the other hand, a greater number of unscheduled visits were found in the apical-touch group than in the three-point-touch group. This might be due to the greater number of visual acuity complaints found in the apical-touch group than in the three-point-touch group. Apical-touch contact lens fittings are commonly associated with greater lens movement, which can cause blurry vision, in contrast with three-point-touch lens fittings.

Five central corneal abrasions were found during this study, leading to a rate of 0.03 corneal abrasions per eye per year. Past studies have reported a rate of corneal abrasions of 0.07 per eye per year in a group of 30 keratoconus subjects fitted with either apical-clearance or apical-touch fitting approaches, using tricurve spherical RGP contact lenses.[6] The difference between the above study and our study is likely to be attributed to differences between lens designs.

In summary, approximately 80% of keratoconus subjects are able to wear Rose K2 contact lenses comfortably. Apical-touch contact lens fittings were found to be less comfortable than the three-point-touch fitting, leading to an increased number of subjects that discontinued lens wear. Practitioners should carefully follow up neophyte contact lens wearers reporting reduced comfort during the first few weeks of lens wear to minimize potential discontinuation. The apical-touch fitting approach showed an increased number of unscheduled visits in comparison with the three-point-touch fitting approach.

SECTION 6.2

Contact Lens Fitting Characteristics

Miguel Romero-Jiménez

6.2.1. Introduction

This section analyzes data from the whole sample of previous contact lens wearers and compares both studied groups, as well as contact lens characteristics of fitted contact lenses during follow-up. Additionally, contact lens fluorescein pattern (i.e. fitting approach) maintenance over time was evaluated, as well.

Currently, the most commonly accepted contact lens fitting approach for keratoconus is the three-point-touch.[9] In spite of that, in 2005 the CLEK study group stated the following: "[…] *it is the investigator´s opinion that true three-point-touch fitting patterns, neither flat or steep, are difficult to achieve and maintain. Years of experience grading of fluorescein patterns at the CLEK Photography Reading Center have borne out that observation (unpublished data)*".[9] In order to evaluate the statement above, and as a part of the present study, we evaluated central contact lens fluorescein pattern for all subjects in every visit with slit lamp examination to ascertain if subjects continue being fitted with the fitting approach randomly allocated at baseline. However, and as fluorescein pattern interpretation could depend on observer's subjectivity, we analyzed the relation between the average corneal power (ACP), obtained from Javal keratometry, and the FDACL to assess whether or not central contact lens fluorescein patterns (i.e. apical-touch and three-point-touch) can be maintained over time.

6.2.2. Enrolled subjects and previous contact lens wear

At the time of enrolment, 16 (27 eyes) out of 29 and 13 (24 eyes) out of 29 subjects had not had been wearing RGP contact lenses in apical-touch and three-point-touch fitting groups, respectively. Thirteen (21 eyes) and 16 (26 eyes) subjects wore RGP of different designs in the apical-touch and three-point-touch fitting groups (Chi-square test for subjects, p=0.300; Chi-square test for eyes, p=0.269). In the apical-touch group, one subject presented bilateral keratoconus but only wore RGP contact lens in one eye. For the study's purpose, the subject was fitted with contact lenses in both eyes. In the three-point-touch group, two subjects wore RGP contact lenses only in one eye (the fellow eye had either ICRS or KP), but it was impossible to collect data from their habitual RGP contact lenses. In addition, in the latter group one subject wore lens only in the left eye as the fellow eye was intolerant to contact lens. However, the subject was successfully fitted with RGP contact lenses in both eyes for the sake of the study.

6.2.3. Habitual RGP contact lens data and central fluorescein pattern

To analyze contact lens fluorescein patterns of subjects that wore RGP contact lens before enrolment, these subjects were asked to insert their lenses after all examinations had finished on the first day, and fluorescein pattern was observed and graded with slit lamp. In addition, measurements of back optic zone radius (Shin-Nippon RG-300, Rexxam Co.; Ltd. Japan), diameter and power of the lenses were recorded.

6.2.3.1. Contact lens specifications

Data of the habitual RGP contact lenses were collected from 21 and 24 eyes in the apical-touch and three-point-touch fitting groups, respectively. Two eyes of the three-point-touch group were missed to follow-up, and therefore excluded from the statistical analysis.

For the entire sample, the mean ± SD of habitual contact lens power was -5.4±4.5 D (range -16.50 to +1.25 D). Habitual contact lens power was on average -4.4±2.5 D (range -10.5 to -1.25 D) and -6.5±5.7 D (range -16.50 to +1.25 D) in the apical-touch and three-point-touch fitting approaches, respectively (Unpaired-T test, p=0.130).

For the whole sample, habitual contact lens diameter was 9.5±0.4 mm (range 8.70 to 10.0). Habitual contact lens diameter was 9.5±0.4 D (range 9.0 to 10.0 mm) and 9.5±0.4 D (range 8.70 to 10.0 mm) in the apical-touch and three-point-touch fitting approaches, respectively (Unpaired-T test, p=0.59).

For the whole sample, habitual contact lens back optic zone radius (BOZR) was 7.17±0.49 mm (range 5.80 to 8.40). Habitual contact lens BOZR was 7.10±0.35 mm (range 6.40 to 7.50 mm) and 7.2±0.60 mm (range 5.80 to 8.40 mm) in the apical-touch and three-point-touch fitting approaches, respectively (Unpaired-T test, p=0.420).

6.2.3.2. Habitual central contact lens fluorescein pattern

Habitual central contact lens fluorescein pattern was graded as definite apical-touch, apical-touch, apical-clearance and definite apical-clearance following a previously reported method (**Figure 2.4**).[15] In addition, the lens BOZR was compared with the average FDACL value. The distribution of the fluorescein patterns of the habitual contact lens wearers is shown in **Table 6.2.1**.

The RGP contact lens BOZR was 0.62±0.47 mm (3.0 D; range -0.10 to 1.65 mm) flatter than FDACL, on average. However, habitual RGP contact lens BOZR was 0.75±0.42 mm (3.75 D; range 0.00-1.65 mm) and 0.50±0.48 mm (2.5 D; range -0.10-1.55 mm) flatter than FDACL, on average, in the apical-touch and three-point-touch fitting groups, respectively (Unpaired-t test, p=0.081).

Table 6.2.1. *Habitual central contact lens fluorescein pattern distribution*

Fluorescein pattern	**Baseline**			
	Apical-touch n=21	**Three-point-touch n=22**	**Total % n= 43**	**p-value***
Definite apical-touch	19	14	77%	0.111
Apical-touch	1	5	14%	
Apical-clearance	1	3	9%	
Definite apical-clearance	0	0	0%	

* Chi-square test.

6.2.4. Rose K2 contact lenses

6.2.4.1. Number of contact lenses used during the study

All RGP contact lenses used during the study were Rose K2, manufactured with Tilsificon A material (Menicon Company Limited, Nagoya, Japan).

After initial lens fitting visit, contact lenses were ordered to the manufacturer and dispensed to the subjects. Contact lens replacement was planned on a yearly basis right in the beginning. Ideally, 2 contact lenses should have been necessary for each eye during the study. However, a number of additional lenses had been ordered for different reasons (i.e. lost lens, breakages, changes in one or more parameters, etc.). Reasons and total number of ordered contact lenses during the study (for subjects that completed the two-year follow-up), discriminated by fitting groups, are shown in **Table 6.2.2.**

During the two-year follow-up, 48 (1.33±1.15 per eye, range 0-4) and 34 (0.79±1.19 per eye, range 0-5) additional contact lenses were delivered to the apical-touch (36 eyes) and three-point-touch (43 eyes) fitting groups, respectively (U Mann-Whitney test, p=0.012).

Table 6.2.2. *Reasons and number of ordered Rose K2 contact lenses during the study for subjects that completed the two-year follow-up*

Cause of delivered lens	Apical-touch n=36	Three-point-touch n=43	p*
First Fitting	72@	86@	0.020
Breakages	17	17	
Lost lens	3	6	
Power change	12	1	
BOZR change+	15	8	
Edge lift change	0	2	
Diameter change	1	0	

* Chi-square test. @ Necessary lenses (they have been excluded from the statistical analysis). + BOZR changes were made to maintain prescribed fitting approach.

6.2.4.2. Contact lens' power variations during follow-up

No statistically significant changes were found in contact lens power either during follow-up (RM-ANOVA test, F=2.541, p=0.068) in the time*group interaction (p=0.462, F=0.904) or between fitting groups (F=0.531, p=0.468).

Mean negative contact lens power increased 0.69 D in the apical-touch group in two years. In the three-point-touch group, the mean negative contact lens power increased 2.23 D in two years. At the time of first contact lens fitting, the difference between both groups in contact lens power was 0.07 D. However, this difference increased to

1.47 D after two years. The changes in contact lens power during the study for the two groups are shown in **Figure 6.2.1.**

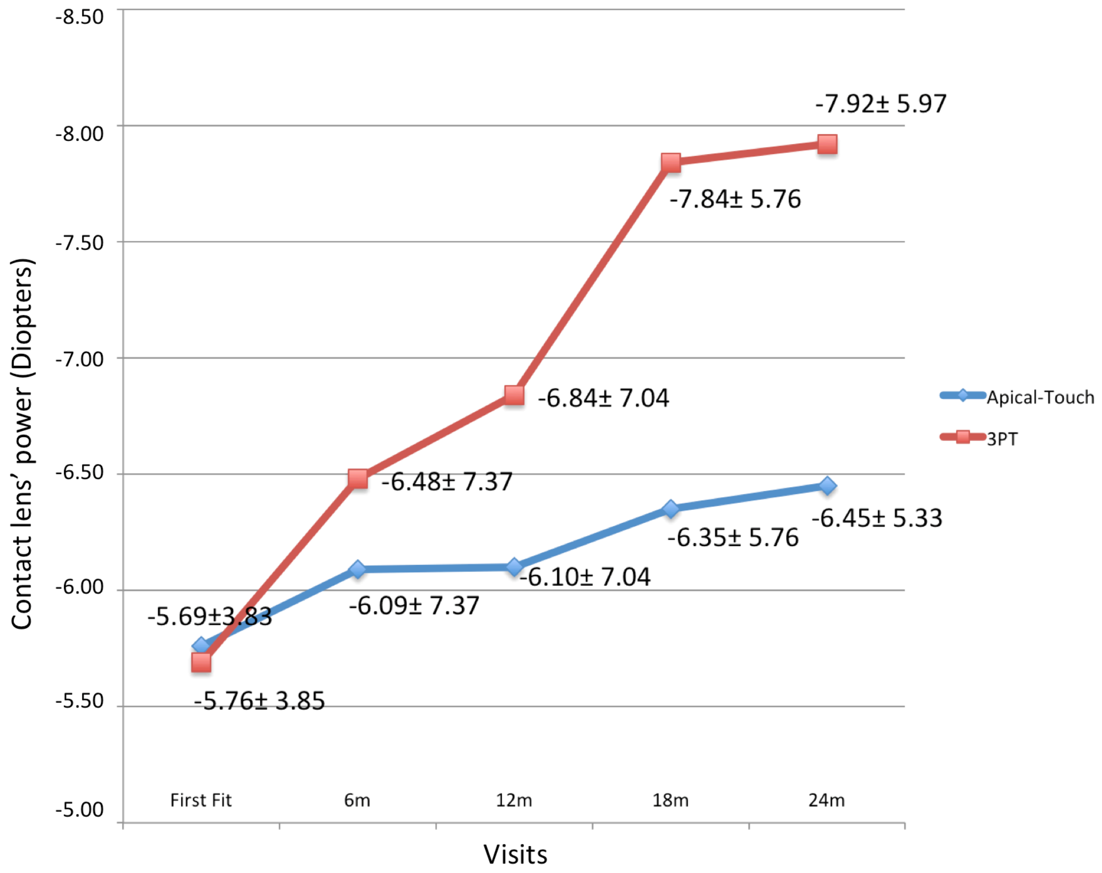

Figure 6.2.1. Contact lens power change during follow-up. 3PT: Three-point-touch.

6.2.4.2. Changes in contact lens BOZR during the study

No statistically significant differences were found in contact lens BOZR either during the two-year follow-up (RM-ANOVA test, F=0.048, p=0.877) in the time*group interaction (F=0.158, p=0.749) or between fitting groups (F=0.015, p=0.904). (**Table 6.2.3**).

Table 6.2.3. Prescribed contact lens BOZR at different visits for subjects that completed the two-year follow-up

Group	First Fitting	6m	12m	2nd Fit*	18m	24m
Apical-touch	6.91±0.47	6.91±0.48	6.91±0.48	6.91±0.50	6.90±0.50	6.91±0.51
Three-point-touch	6.92±0.47	6.92±0.47	6.92±0.47	6.91±0.47	6.92±0.48	6.93±0.49

* 2nd Fit: new contact lens fitting in the 12-month visit to replace all RGP contact lenses.

6.2.5. Subjective refraction

To facilitate statistical analysis, all subjective refraction data were converted into power vector coordinates M, J0 and J45 as outlined by Thibos et al.[26] Power vector term M represents the mean spherical equivalent, and J0 and J45 represent the amplitude and the harmonic phase, respectively.[26] Subjective refraction was undertaken in the first visit before contact lens fitting and in the 24-month visit.

Statistically significant changes were found in power vector M between the first and 24-month visit (RM-ANOVA, $F=18.406$, $p<0.0001$), but no significant changes were found in the time*group interaction ($F=3.79$, $p=0.055$) and between both groups ($F=1.316$, $p=0.255$). No statistically significant changes were found in power vectors J0 and J45 either between visits, groups or time*group interaction (RM-ANOVA, all $p>0.05$). At the time of first visit, differences in power vector M between the apical-touch and three-point-touch groups was 0.94 D, being more negative in the latter. In the 24-month visit, differences in power vector M between both groups was 1.75 D. In the apical-touch group, power vector M increased 0.5 D in two years, whereas in the three-point-touch it increased 1.31 D.

Table 6.2.4. summarizes the results of the power vector components M, J0 and J45, measured at baseline and in the 24-month visit. **Figure 6.2.2.** shows box and whisker plots displaying differences in the M component between groups and visits.

Table 6.2.4. Summary of the power vector components, measured at baseline and in the 24-month visit.

Vector Term	Apical-touch		Three-point-touch	
	First visit	**24 month**	**First visit**	**24 month**
M	-5.74±3.95	-6.24±3.86	-6.68±6.15	-7.99±6.19
J0	0.28±0.10	0.44±1.01	-0.08±0.91	0.11±0.87
J45	-0.08±1.4	-0.03±1.41	0.03±1.06	-0.07±0.92

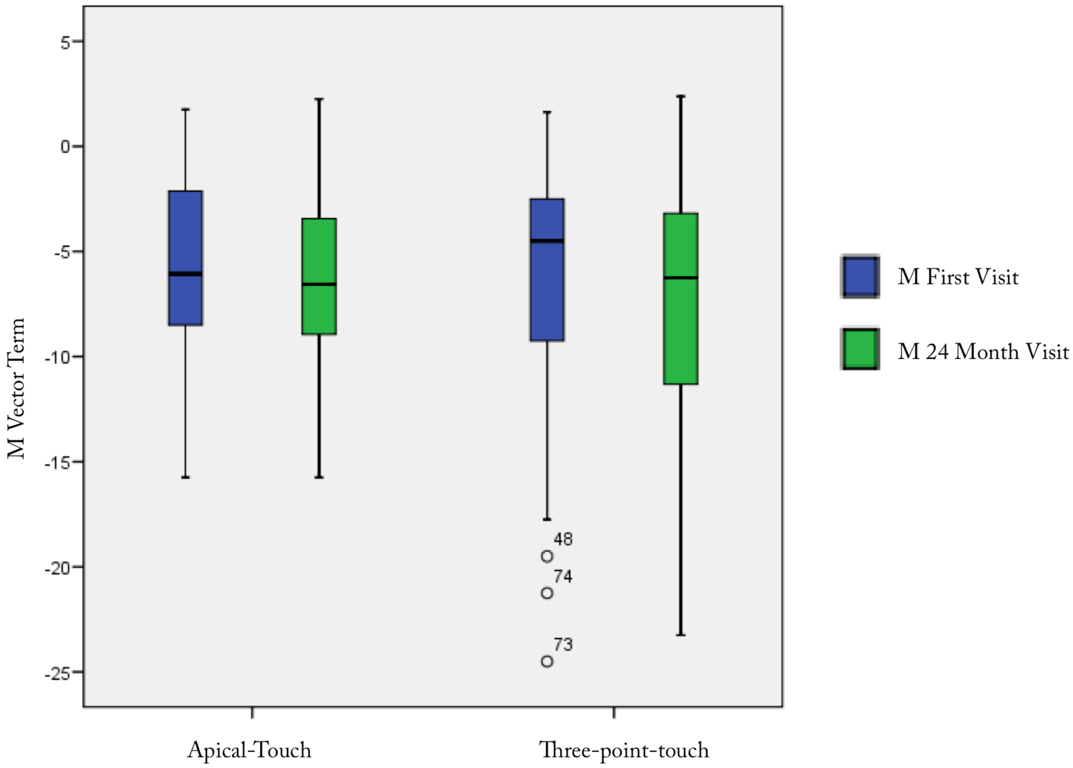

Figure 6.2.2. Box and whisker plots showing the M component of the refraction in both studied groups and studied visits.

6.2.6. Contact lens fluorescein patterns maintenance over time

6.2.6.1. Average corneal power

No statistically significant differences were found on average corneal power (ACP) between visits (RM-ANOVA test, F=0.514, p=0.684). However, we found significant differences not only in the time*group interaction (F=2.882, p=0.033) but also between fitting groups (F=4.427, p=0.039) (**Table 6.2.5**).

6.2.6.2. First definite apical clearance lens

No statistically significant differences were found on FDACL either during the two-year follow-up (RM-ANOVA test, F=2.558, p=0.082) or in the time*group interaction (F=2.335, p=0.101). However, significant differences were found between fitting groups (F=8.001, p=0.006) (**Table 6.2.5**).

6.2.6.3. Differences between ACP and FDACL

In the apical-touch group, differences between ACP and FDACL remained clinically stable over time (**Table 6.2.5**). In the three-point-touch group, these differences were smaller but they were still clinically equivalent (**Table 6.2.5**).

Table 6.2.5*. ACP and FDACL data. All values are expressed in millimeters.*

Group	Apical-touch			Three-point-touch		
	ACP	FDACL	ACP-FDACL	ACP	FDACL	ACP-FDACL
First Fitting	6.81±0.53	6.51±0.49	0.30	7.08±0.45	6.82±0.47	0.26
6 months	6.88±0.50	6.55±0.45	0.33	7.01±0.44	6.80±0.46	0.21
12 months	6.83±0.45	6.51±0.49	0.32	7.03±0.47	6.83±0.48	0.20
18 months	6.79±0.49	6.50±0.48	0.29	7.04±0.45	6.81±0.47	0.23
24 months	6.81±0.54	6.48±0.51	0.33	7.04±0.45	6.80±0.49	0.24

ACP: Average Corneal Power; FDACL: First Definite Apical-Clearance Lens

6.2.6.4. Number of lenses needed to maintain fitting approaches

Throughout 2 years of contact lens wear, 15 and 8 contact lenses were needed to maintain the apical-touch and three-point-touch fitting approaches allocated at baseline, respectively (Chi-square test, p=0.023). All the ordered lenses compromised changes solely in the lens BOZR.

6.2.7. Discussion

In this study, subjects were very well matched with regard to previous RGP wearing experience as no statistically significant differences were found between groups in the number of subjects wearing RGP contact lenses before the beginning of the study. Furthermore, the contact lens parameters (i.e. power, BOZR and diameter) were similar between groups.

When we analyzed the habitual central contact lens fluorescein pattern observed with RGP contact lenses, which subjects wore before enrolment, 77%, 14% and 9% showed definite apical-touch, apical-touch and apical clearance fluorescein patterns, respectively. The mean difference in BOZR between habitual RGP contact lenses and FDACL obtained at baseline was 3.0 D, on average. Edrington et al. reported that in 808 keratoconus subjects that wore RGP contact lenses 88% and 12% showed apical-touch and apical-clearance fluorescein patterns, respectively, and a difference of 2.86 D was found comparing habitual lens BOZR and FDACL.[7] Most recently, Jinabhai et al. reported 60%, 33% and 7% of definite apical-touch, apical-touch and apical-clearance fluorescein patterns, respectively, in 15 keratoconus eyes that wore RGP contact lenses.[10] Although all grades of apical-touch fluorescein patterns should be avoided in RGP contact lens fitting in keratoconus, following a recommendation made for more than 30 years ago,[3] most keratoconus subjects continued showing a clear apical-touch fluorescein pattern. Additionally, the average difference between FDACL and habitual lens BOZR in keratoconus is approximately 0.60 mm, which is 0.20 mm flatter than the apical-touch fitting approach of the present study.

In the apical-touch group a greater number of contact lenses had to be reordered than in the three-point-touch group. This was mainly due to two reasons: 1) a great number of visual complaints in the apical-touch group, which forced to change contact lenses, and 2) a great number of lenses which needed to be changed to maintain the apical-touch fitting approach in comparison with the three-point-touch fitting approach. As reported in chapter 4 of this thesis (section 4.1), a great number of reordered lenses were necessary to achieve a successful contact lens fitting in the apical-touch design in comparison with the three-point-touch design. The analysis of the total number and reasons of additional ordered contact lenses throughout the two years of follow-up corroborates that the apical-touch fitting approach is more difficult to achieve and less reliable in terms of final contact lens power and BOZR when compared with the three-point-touch fitting approach.

Although no statistically significant differences were found between both groups in contact lens power over 2 years of contact lens wear, it is the author's opinion that these differences might be clinically meaningful. At baseline, the average contact lens power was practically equal in both groups. However, a difference was expected, because at baseline the difference between groups in the M component of the refraction was 0.94 D, being more negative in the three-point-touch group. In addition, the apical-touch group is expected to require a lower negative contact lens power since part of the refraction is likely to be compensated by tear meniscus under the lens. Using the approximation of 0.10 mm in the lens BOZR, which corresponds to a change in contact lens power of 0.5 D, the tear meniscus under the lens is expected to compensate 1.5 D more than in the apical-touch group in comparison with the three-point-touch group. Therefore, considering the differences in the M component of the refraction as well as the contribution in power by the tear meniscus, the difference in initial contact lens power between groups should approximately be 2.44 D. This difference was not found because average central power (measured with Javal keratometer) was 0.27 mm (≈1.35 D) steeper in the apical-touch group than in the three-point-touch group, compensating the power of tear meniscus in the former. The remained 0.94 D is probably to be compensated by tear meniscus, because the power vector component M represents the mean spherical equivalent, so this 0.94 D might be part of the refractive cylinder.

At the end of the study, the difference in contact lens power between groups was 1.47 D. This difference was due to contact lens power variation in the three-point-touch group. Rate of contact lens power variation over time was 0.35 D/year and 1.12 D/year in the apical-touch group in comparison with the three-point-touch group. The increase in contact lens power could be due to two reasons: 1) increase of average corneal power, and/or 2) increase in myopia. However, since the average corneal power did not change during this study in neither groups, the increase in contact lens power might be attributed to an increase in myopia. Furthermore, subjective over-refraction increased by 1.31 D in the three-point-touch and by 0.50 D in the apical-touch over the course of the study. Therefore, it appears that the three-point-touch fitting approach causes a greater increase in myopia than in the apical-touch fitting approach.

The fact that no significant differences were found in contact lens BOZR over time and between groups might be attributed to baseline differences between groups in average central corneal power. Although apical-touch and three-point-touch fitting approaches were performed with BOZRs 0.40 and 0.10 mm flatter than FDACL, respectively, the average central power in the apical-touch group was 0.30 mm steeper than in the three-point-touch group.

Differences between ACP and FDACL remained stable throughout the follow-up period in both groups, being on average 0.32 mm and 0.23 mm in the apical-touch and three-point-touch fitting approaches, respectively. This difference between groups might be due to the apical-touch group presenting a steeper ACP than the three-point-touch group. Past studies have reported that the steeper the ACP, the more difficult to achieve an apical-clearance fitting approach, because it is difficult to vault the cone apex without generating a contact lens with edges too steep to gracefully glide over the relatively normal, much flatter peripheral cornea.[2,5] The FDACL is, in fact, the first lens that shows an apical-clearance fitting pattern. Therefore, it seems reasonable that the greater the ACP, the greater the difference between ACP and FDACL.

As aforementioned, differences between ACP and FDACL remained stable in both groups during follow-up. To achieve this, 15 and 8 contact lenses were changed to modify the lens BOZR in the apical-touch and three-point-touch fitting groups, respectively. Zadnik et al. stated that a real three-point-touch fitting approach was difficult to achieve and maintain.[9] However, this fitting approach is argued to be the best one to fit keratoconus. In fact, in the present study, the apical-touch fitting approach was more difficult to achieve (more ordered lenses were necessary to achieve a successful fitting in this group) and maintain (more lenses needed to be changed during follow-up) in comparison with the three-point-touch fitting approach. Therefore, it is the author's opinion that the three-point-touch fitting approach is both easy to achieve and maintain over time, and the results of this study support this statement.

In summary, although avoiding apical-touch RGP contact lens fluorescein pattern is recommended since 1982, most keratoconus subjects continue to show a clear apical-touch fluorescein pattern. In fact, habitual lens BOZR is on average 3.0 D flatter than FDACL in keratoconus subjects that wear RGP contact lenses. Apical-touch fitting approach is more difficult to achieve and maintain over time than the three-point-touch fitting approach. However, when a greater increase in subjective over-refraction and thus potentially in myopia is found in the three-point-touch lens fitting than in the apical-touch fitting, there is a great need for further studies to clarify the potential relationship between fitting approaches and myopia progression.

SECTION 6.3

Anterior Corneal Curvature, Asphericity and Anterior Best-Fit Sphere Reference Surface

6.3.1. Introduction

This section analyzes changes in corneal shape during a two-year period and compares both groups. Anterior surface corneal shape can be defined by corneal curvature, asphericity and elevation data.

Corneal curvature assessment was carried out by analyzing the following measurements:

- Javal keratometry (flattest and steepest meridians, and ACP).
- Pentacam simulated keratometry (SimK-min, SimK-max, SimK-ACP and maximum sagittal curvature (Ksag)).

The agreement in ACP assessment between these two methods was evaluated using Pearson correlation coefficients, and the bias between the two measuring techniques was calculated and presented graphically.

To calculate the measurements of the anterior corneal surface asphericity, the Pentacam internal software was used. It was calculated in an 8-mm diameter peripheral ring zone. Corneal surface asphericity will be referred to as the corneal P value (CPV). The CPV gives an index of peripheral flattening and describes the degree to which an aspheric surface differs from the equivalent spherical form by indicating how rapidly the surface flattens from the apex.[27] The CPV is the current American National Standards Institute standard for representing the corneal shape within a conic section.[28]

It has been shown that front and back elevation maps provide a more accurate representation of the anterior corneal surface than curvature maps, because they are independent of axis, orientation and position.[29] Furthermore, elevation maps have been reported to be useful in the diagnosis[30] and monitoring of keratoconus disease.[31]
Anterior corneal best-fit sphere (BFS) reference surface data represents the total curvature of the cornea with a numeric value obtained by a least-squares adjustment, and it is not sensitive enough to detect differences between different stages of keratoconus,[32] but it could be useful to monitor keratoconus progression.[31] BFS data were acquired from the front elevation map by Pentacam by choosing auto-diameter in order to follow published recommendations.[33,34]

6.3.2. Anterior surface corneal curvature

6.3.2.1. Javal Keratometry

Javal keratometric measurements were acquired and recorded in the initial visit and in the 6, 12, 18 and 24-month visits (Javal Keratometer KJ1000, INDO S.A. Spain).

No statistically significant differences were found in the flattest keratometric measurement either during the two-year follow-up (RM-ANOVA test; F=1.165, p=0.325) in the time*group interaction (F=1.198, p=0.312) or between fitting groups (F=2.071, p=0.154). Similarly, no statistically significant differences were found in the steepest keratometric measurement either during the two-year follow-up (F=0.767, p=0.528) in the time*group interaction (F=1.670, p=0.167) or between fitting groups (F=6.11, p=0.160). Finally, no statistically significant differences were found in the keratometric measurements of the average corneal power (K-ACP) during the two-year follow-up (F=0.514, p=0.684). However, significant differences were found in the time*group interaction (F=2.882, p=0.033) and between both fitting groups (F=4.427, p=0.039). Data from the keratometric measurements are shown in **Table 6.3.1.**

Table 6.3.1. Data of keratometry

Group	Measurement	BL	6m	12m	18m	24m
Apical-Touch	Flattest K	7.07±0.59	7.09±0.62	7.05±0.47	7.04±0.54	7.07±0.59
	Steepest K	6.55±0.54	6.67±0.47	6.62±0.48	6.57±0.49	6.62±0.57
	K-ACP	6.81±0.53	6.88±0.50	6.83±0.45	6.79±0.49	6.81±0.54
Three-point-touch	Flattest K	7.29±0.47	7.16±0.47	7.20±0.48	7.21±0.47	7.24±0.46
	Steepest K	6.88±0.49	6.85±0.49	6.86±0.51	6.88±0.50	6.88±0.50
	K-ACP	7.08±0.45	7.01±0.44	7.03±0.47	7.04±0.45	7.04±0.45

K: Keratometry; BL: baseline; m: months; ACP: Average Corneal Power.

6.3.2.2. Pentacam simulated keratometry

Pentacam simulated keratometric measurements were acquired and recorded in the initial visit, on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

Statistically significant differences were found in the Pentacam minimum simulated keratometric (SimK-min) measurement during the two-year follow-up (RM-ANOVA test; F=2.809, p=0.043). However, no statistically significant differences were found in SimK-min either in the time*group interaction (F=1.406, p=0.243) or between fitting groups (F=2.512, p=0.117). In the Pentacam maximum simulated keratometric measurement (SimK-max) statistically significant differences were found either during the two-year follow-up (F=4.083, p=0.013) and between fitting groups (F=6.698, p=0.012), but no statistically significant differences were found in SimK-max in the time*group interaction (F=1.126, p=0.333). Finally, no statistically significant differences were found in the Pentacam simulated average corneal power (P-ACP) either during the two-year follow-up (F=2.777, p=0.58) or in the time*group interaction (F=1.358, p=0.260). However, significant differences were found in SimK-ACP between fitting groups (F=4.569, p=0.036). Data of the Pentacam simulated keratometric measurements are shown in **Table 6.3.2.**

Table 6.3.2. *Data of Pentacam simulated keratometry*

Group	Measurement	BL	14 D	6m	12m	18m	24m
Apical-Touch	SimK-min	7.11±0.52	7.17±0.46	7.13±0.51	7.11±0.51	7.09±0.53	7.06±0.57
	SimK-max	6.52±0.48	6.61±0.50	6.60±0.49	6.60±0.48	6.56±0.50	6.53±0.52
	P-ACP	6.81±0.48	6.89±0.46	6.87±0.48	6.85±0.48	6.83±0.50	6.79±0.53
Three-point-touch	SimK-min	7.32±0.46	7.29±0.47	7.29±0.47	7.29±0.49	7.26±0.52	7.27±0.48
	SimK-max	6.82±0.48	6.86±0.49	6.86±0.47	6.86±0.49	6.86±0.49	6.85±0.50
	P-ACP	7.07±0.45	7.07±0.47	7.07±0.46	7.07±0.47	7.06±0.50	7.06±0.47

SimK: Simulated Keratometry; BL: baseline; m: months; ACP: Average Corneal Power; P: Pentacam; D: Days.

6.3.2.3. Agreement of two corneal curvature assessments: Javal keratometry and Pentacam simulated keratometry

The purpose of this section is to investigate the agreement of corneal curvature assessment for keratoconic eyes by using the Javal keratometer and the Pentacam Eye Scanner. The index of the association between corneal curvature data obtained from different acquisition methods was computed using Pearson correlation coefficients. To carry out this statistical analysis, data from the first visit were used. A strong correlation was found between correspondent values of keratometry and Pentacam simulated keratometry. The strongest correlation was found between K-ACP and P-ACP. The Pearson correlation coefficients for keratometry and Pentacam simulated keratometry are shown in **Table 6.3.3.**

Table 6.3.3. *Pearson correlation coefficients for keratometry and Pentacam simulated keratometry.*

Measurements	Pearson Coefficients	
	r	p
Flattest keratometry vs. SimK-min	0.889	<0.0001
Steepest keratometry vs. SimK-max	0.937	<0.0001
K-ACP vs P-ACP	0.950	<0.0001

SimK: Simulated Keratometry; min: minimum; max: maximum; K: Keratometry; P: Pentacam; ACP: Average Corneal Power.

The bias between the two measuring techniques was calculated. Flattest keratometry, measured with Javal Keratometer, was similar to that measured with Pentacam instrument (difference between devices -0.02±0.25 mm, p=0.929) (**Figure 6.3.1**). Steepest keratometry, measured with Javal Keratometer, was similar to that measured with the Pentacam instrument (difference between devices 0.05±0.19 mm, p=0.473) (**Figure 6.3.2**).

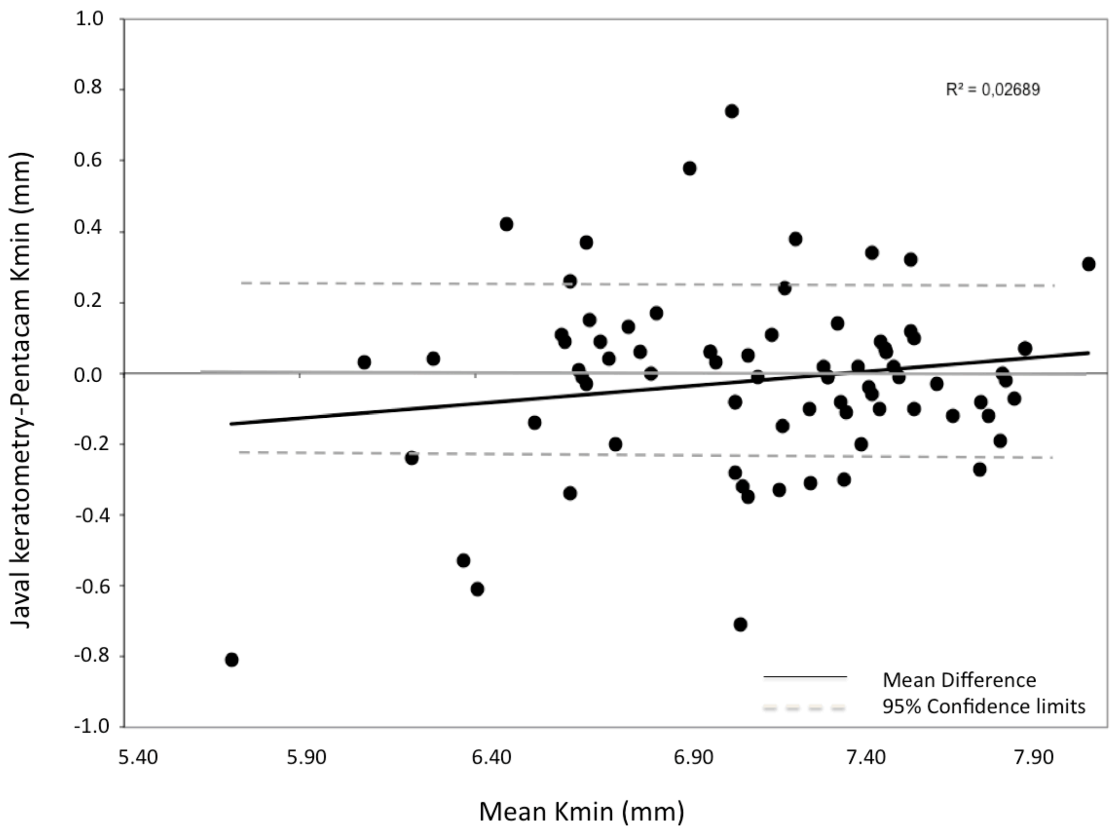

Figure 6.3.1. Differences between minimum keratometry, measured with Javal Keratometer and Pentacam instrument.

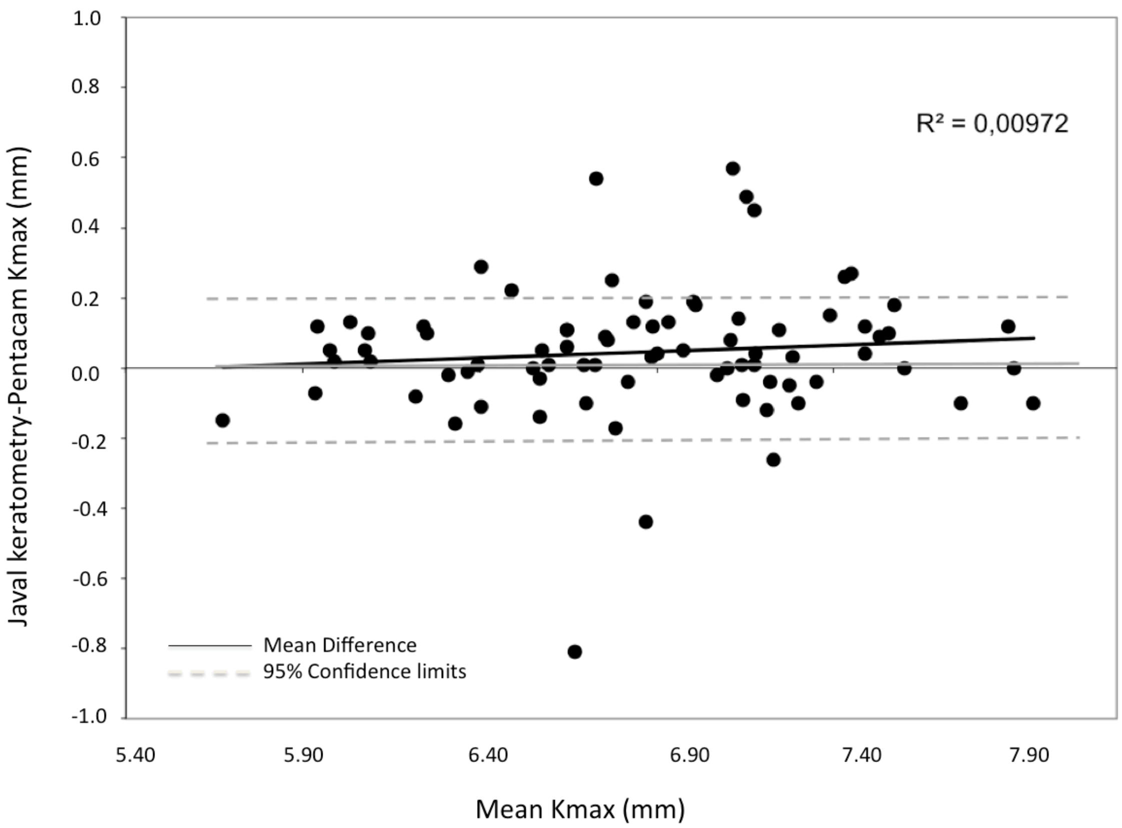

Figure 6.3.2. Differences between maximum keratometry, measured with Javal Keratometer and Pentacam instrument.

6.3.2.4. Maximum sagittal curvature

Pentacam maximum sagittal curvature (Ksag) measurements were acquired and recorded in the initial visit, on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

Statistically significant differences were found in Ksag during the two-year follow-up ($F=6.696$, $p<0.0001$) and between fitting groups ($F=9.815$, $p=0.002$), but no statistically significant differences were found in SimK-max in the time*group interaction ($F=0.556$, $p=0.65$). The Ksag data are shown in **Figure 6.3.2**.

Figure 6.3.2. Maximum sagittal curvature (Ksag) variations over time in both groups. D: days; mm: millimeters; m: months.

6.3.3. Anterior corneal asphericity

Anterior corneal asphericity (CPV) measurements were acquired and recorded in the initial visit, on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

Statistically significant differences were found in CPV measurement during the two-year follow-up (RM-ANOVA test; F=3.388, p=0.015). However, no statistically significant differences were found in CPV either in the time*group interaction (F=1.573, p=0.191) or between fitting groups (F=0.11, p=0.741). The anterior corneal asphericity data are shown in **Figure 6.3.3**.

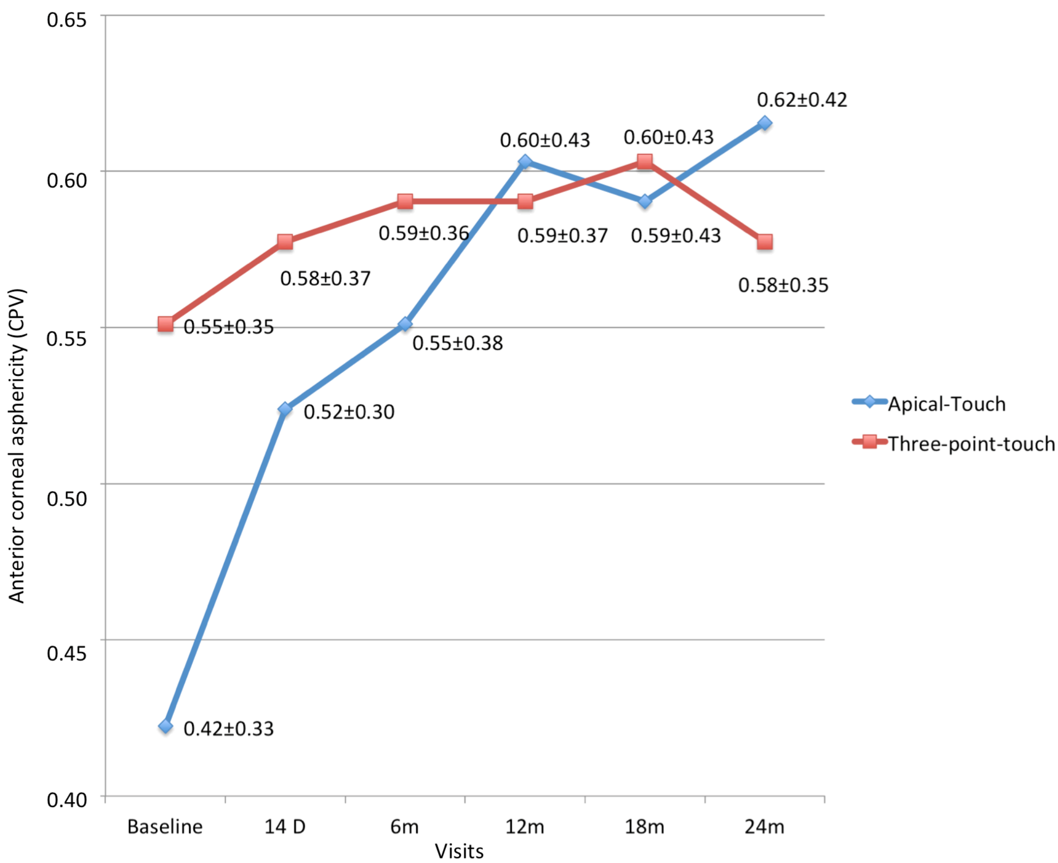

Figure 6.3.3. Anterior corneal asphericity variations over time in both groups. D: days; mm: millimeters; M: months.

6.3.4. Anterior best-fit sphere reference surface

Anterior corneal BFS surface measurements were acquired and recorded in the initial visit, on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

Statistically significant differences were found on anterior corneal BFS surface during the two-year follow-up (RM-ANOVA test, F=2.995, p=0.018) and in the time*group interaction (F=3.612, p=0.006). However, no significant differences were found between both fitting groups (F=2.542, p=0.115). The anterior corneal BFS surface data are shown in **Figure 6.3.4.**

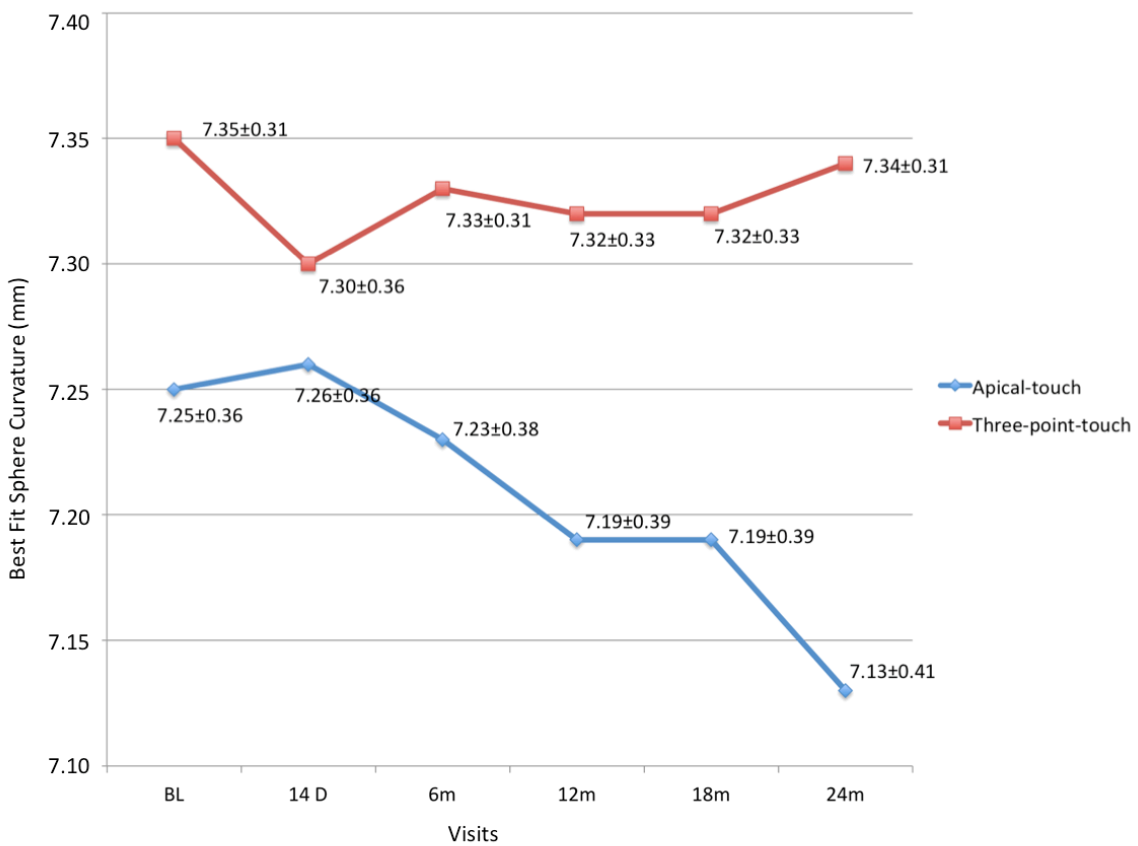

Figure 6.3.4. Curvature variations of anterior best-fit sphere reference surface over time in both groups. D: days; mm: millimeters; M: months.

6.3.5. Discussion

Two different methods were used to assess central corneal curvature in the present study: Javal keratometry and Pentacam simulated keratometry. The analysis of differences and correlation between devices have shown that agreement between them was strong, so they can be used as equivalents to evaluate central corneal curvature in keratoconus. To the best of our knowledge, this is the first time the agreement between Javal keratometry and Pentacam simulated keratometry has been evaluated.

Keratometric data were acquired and recorded in every visit, except on the 14-day visit. The flattest and steepest corneal meridians evaluated with the Javal keratometer did not show any differences or variations over time or between groups. However, the ACP obtained by averaging these two measurements showed differences between both groups at baseline and after follow-up, which could be interpreted as a different keratoconus staging between groups. Besides, the ACP flattened between the first and the 6-month visits in the apical-touch group, whereas it steepened in the three-point-touch group in the same period. However, in the following visits ACP values presented similar values to those found in the first visit, which suggests that RGP contact lens wear does not avoid central corneal curvature steepening.

Pentacam simulated keratometric measurements were obtained and recorded initially, on the 14-day visit, and in the 6, 12, 18 and 24-month visits. Minimum simulated keratometry flattened in the apical-touch between the first and 14-day visit, but it steepened slightly after two years of contact lens wear. In the three-point-touch group, SimK-min steepened after contact lens wear. Similarly, SimK-max flattened in the apical-touch between the first two visits, and in the three-point-touch group it steepened and flattened slightly with contact lens wear. This is in agreement with the presented data in Chapter 5, Section 5.2. of this thesis. Finally, SimK-ACP did not change over time, but it was steeper in the apical-touch group than in the three-point-touch fitting group, suggesting that, in agreement with keratometric data, the apical-touch fitting group presented different keratoconus staging at the baseline. Pentacam simulated keratometry flattened in the apical-touch immediately after contact lens fitting, but it steepened on the visits thereafter, which is in agreement with data obtained by Javal keratometry.

The analyzed corneal curvature data obtained from Javal keratometer and Pentacam (all together) allowed us to conclude that they are congruent between them. Our results confirm that RGP contact lens wear initially flattens the anterior corneal curvature (more in the apical-touch group than in the three-point-touch group), but they do not avoid corneal curvature steepening over time. In 2010 Hwang et al. reported central corneal flattening in 77 keratoconus eyes after two years of wearing a multicurve RGP contact lens design fitted with three-point-touch fitting approach.[11] However, we have found that central corneal curvature remained stable in the same period. This difference might be due to the different follow-up protocol, because the contact lens fitting approach was evaluated and maintained every six months in this study, whereas Hwang et al. only presented data at baseline and in the last visits.

Maximum sagittal curvature decreased after contact lens wear, and this flattening is greater in the apical-touch fitting approach than in the three-point-touch fitting approach. However, this difference was not statistically significant, which suggests that RGP contact lens bearing in keratoconus takes place on the cone apex leading to apical flattening, no matter the fitting approach. These findings are congruent with those presented in Chapter 5, Section 5.2 of this thesis. Maximum sagittal curvature behavior over time followed a similar pattern than central corneal curvature: it flattened immediately after RGP contact lens fitting, and then it steepened slowly. On the other hand, significant differences in the Ksag values were found between groups, being steeper in the apical-touch than in the three-point-touch, which can be explained by the fact that the apical-touch group was presented with advanced keratoconus.

Corneal asphericity reduced similarly in both fitting groups with contact lens wear. This reduction is in agreement with the results presented in Chaplet 5, Section 5.1 of this thesis, as well as with the changes in corneal asphericity reported by Jinabhai et al. after RGP contact lens wear cessation in keratoconus subjects.[10] The discovered corneal asphericity reduction was not in agreement with changes in central corneal curvature. Corneal asphericity describes how rapidly the corneal surface flattens from apex to the periphery. Therefore, a flattening of central corneal curvature or a steepening of mid-peripheral corneal curvature must take place in order to find a reduction in corneal asphericity. As aforementioned, central corneal curvature did not change or steepened slightly after two years of follow-up. Thus, some degree of mid-peripheral corneal steepening might occur with RGP contact lens wear.

The BFS reference surface value decreased after contact lens wear, mainly in the apical-touch fitting approach. Anterior corneal BFS reference surface data represent the total curvature of the cornea with a numeric value obtained by a least-squares adjustment. Therefore, total corneal curvature in the apical-touch decreased after contact lens wear. Since central corneal curvature did not change significantly, some increasing in mid-peripheral corneal curvature should be expected, being greater in the apical-touch group than in the three-point-touch group. The variations found in BFS values are congruent with changes in anterior corneal asphericity. Findings in anterior corneal asphericity and BFS suggest that corneal molding caused by RGP contact lens wear in keratoconus affect not only the central but also the peripheral cornea.

In summary, RGP contact lens wear causes central corneal curvature and maximum sagittal curvature flattening in keratoconus in the first months with both apical-touch and three-point-touch fitting approaches, but they do not avoid curvature steepening over time. A greater degree of flattening is caused by the apical-touch fitting approach in comparison with the three-point-touch fitting approach. Corneal asphericity and BFS decreased after RGP contact lens wear (more in the apical-touch fitting group), suggesting some molding of mid-peripheral cornea with the use of lenses.

SECTION 6.4

Anterior Corneal Surface Higher Order Aberrations

Miguel Romero-Jiménez

6.4.1. Introduction

This section analyzes changes in anterior corneal surface higher order aberrations (HOA) in RGP lens wearers using apical-touch and three-point-touch contact lens fitting approaches for a 2-year period. Higher order aberrations were obtained from Pentacam and expressed as Zernike polynomial terms. Measurements were performed at baseline, on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

Total HOA root mean square (RMS) aberration was calculated from the 3rd to the 6th-order Zernike terms inclusive, because the analysis of corneal aberrations is normally performed up to the 6th term,[10] although Pentacam instrument is capable of measuring until the 10th term. The HOA RMS values for the 3rd and 4th order were also calculated. Spherical-like RMS aberration (including Zernike polynomials Z_4^0 and Z_6^0), coma-like RMS aberration (including Zernike polynomials Z_3^{-1}, Z_3^1, Z_5^{-1} and Z_5^1) and secondary astigmatism (including Zernike polynomials Z_4^{-2}, Z_4^2, Z_6^{-2}, and Z_6^2) were analyzed too. Additionally, 3rd order vertical coma term (Z_3^{-1}), 3rd order horizontal coma term (Z_3^1) and 4th order spherical term (Z_4^0) were analyzed separately. All corneal HOA were calculated for a 6.0 mm of diameter.[10]

6.4.2. Total higher order RMS aberration

Statistically significant differences were found between both groups in total HOA RMS in the initial visit (Friedman test, p=0.035). No significant differences were found in any other visit between both groups (Friedman test, all p>0.05) (**Figure 6.4.1**). Changes in HOA RMS aberration were found after RGP contact lens wear not only in the apical-touch group (U Mann-Whitney test, p<0.0001, Post-hoc analysis **Table 6.4.1**) but also in the three-point-touch group (U Mann-Whitney test, p<0.0001, Post-hoc analysis **Table 6.4.2**).

Figure 6.4.1. Higher order RMS data from both groups.

Table 6.4.1. *Post-hoc analysis of HOA RMS regarding the apical-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	**BL-6m**	**BL-12m**	**BL-18m**	**BL-24m**	**14D-6m**
p-value	<0.0001	0.001	0.001	0.013	0.008	0.001

BL: baseline; m: months; D: days.

Table 6.4.2. Post-hoc analysis of HOA RMS regarding the three-point-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).

	BL-14D	BL-6m	BL-12m	BL-18m	BL-24m	14D-6m	14D-12m	14D-18m	14D-24m
p-value	<0.001	<0.001	<0.001	0.001	<0.001	0.002	0.008	0.003	<0.001

BL: baseline; m: months; D: days.

6.4.3. Third order RMS aberration

No statistically significant differences were found between both groups in the 3rd order RMS aberration in any visit (Friedman test, all $p>0.05$) (**Figure 6.4.2**). Changes in 3rd order RMS aberration were found with contact lens wear not only in the apical-touch group (U Mann-Whitney test, $p<0.0001$, Post-hoc analysis **Table 6.4.3**) but also in the three-point-touch group (U Mann-Withney test, $p<0.0001$, Post-hoc analysis **Table 6.4.4**).

Figure 6.4.2. Third order RMS aberration data from both groups.

Table 6.4.3. *Post-hoc analysis of 3rd order RMS aberration regarding the apical-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	BL-6m	BL-12m	BL-18m	BL-24m	14D-6m
p-value	<0.0001	0.007	0.001	0.017	0.031	0.004

BL: baseline; m: months; D: days.

Table 6.4.4. *Post-hoc analysis of 3rd order RMS aberration regarding the three-point-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	BL-6m	BL-12m	BL-18m	BL-24m	14D-6m	14D-12m	14D-18m	14D-24m
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	0.004	0.001	<0.001

BL: baseline; m: months; D: days.

6.4.4. Fourth order RMS aberration

No statistically significant differences were found between both groups in the 4th order RMS aberration in any visit (Friedman test, all p>0.05) (**Figure 6.4.3**). No statistically significant changes were found over time in the 4th order RMS aberration in any of the groups (U Mann-Whitney test, all p>0.05).

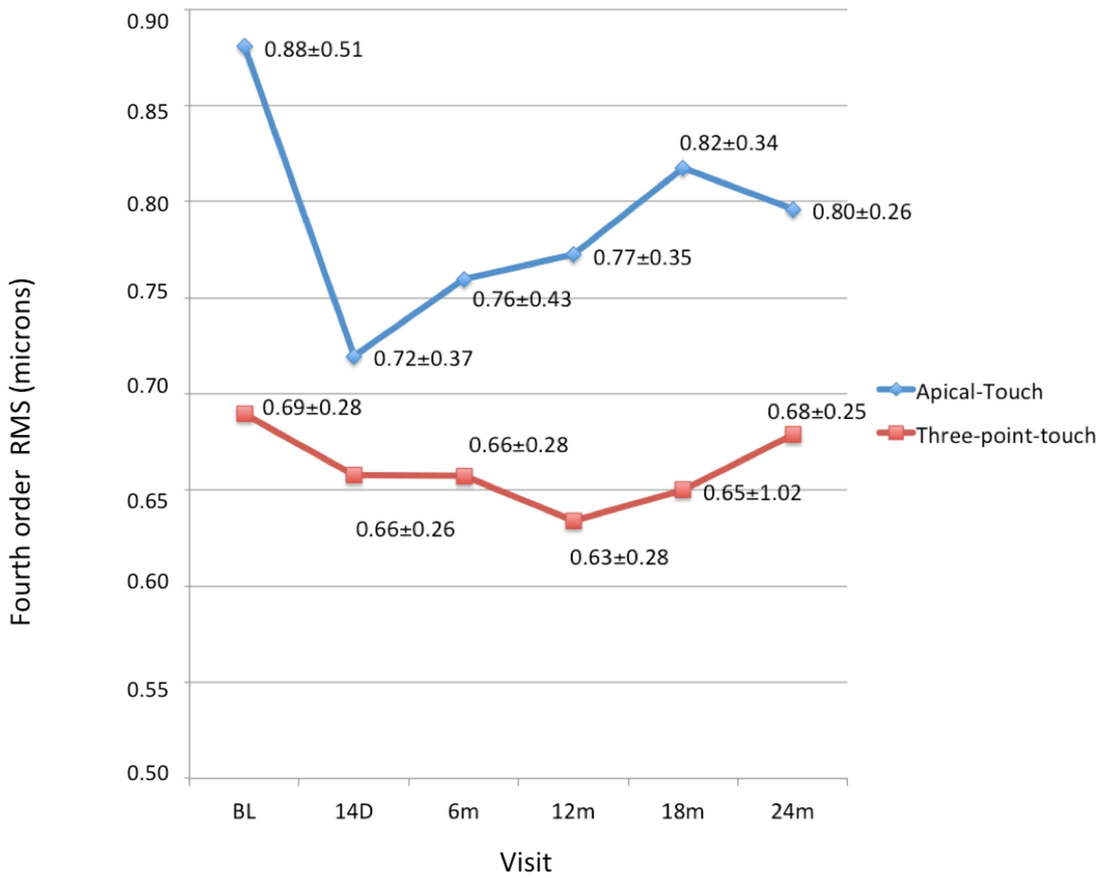

Figure 6.4.3. Fourth order RMS aberration data from both groups

6.4.5. Spherical aberrations

6.4.5.1. Spherical-like RMS aberration

No statistically significant differences were found between groups in spherical-like aberration in any visit between both groups (Friedman test, all p>0.05). No significant differences were found in spherical-like aberration between any pair of studied visits for either the apical-touch group or three-point-touch group (U Mann-Whitney test, all p>0.05) (**Figure 6.4.4**).

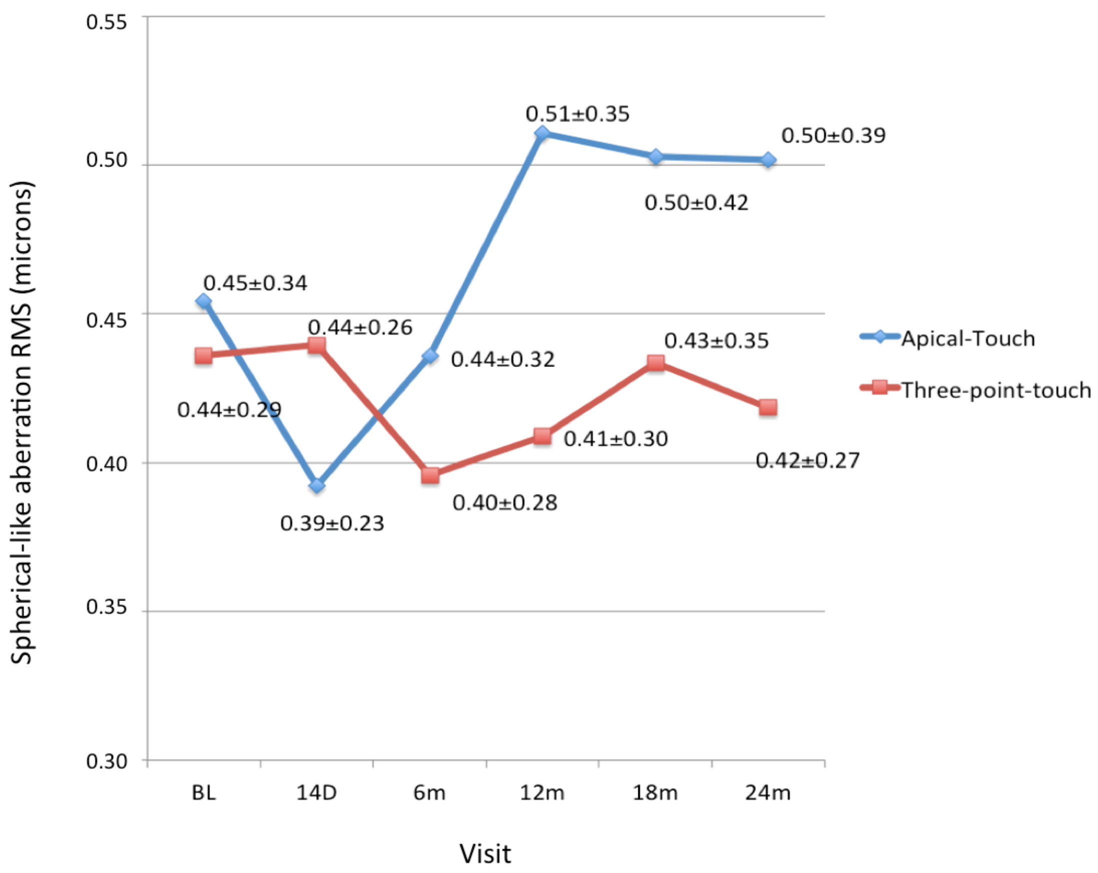

Figure 6.4.4. Spherical-like RMS aberration data from both groups.

6.4.5.2. Fourth order spherical term (Z_4^0)

No statistically significant differences were found in the 4th order spherical Zernike term over a 2-year period of contact lens wear (RM-ANOVA test, F=5.929, p=0.09) between both groups (F=0.255, p=0.615) or for the time*group interaction (F=3.821, p=0.08) (**Figure 6.4.5**).

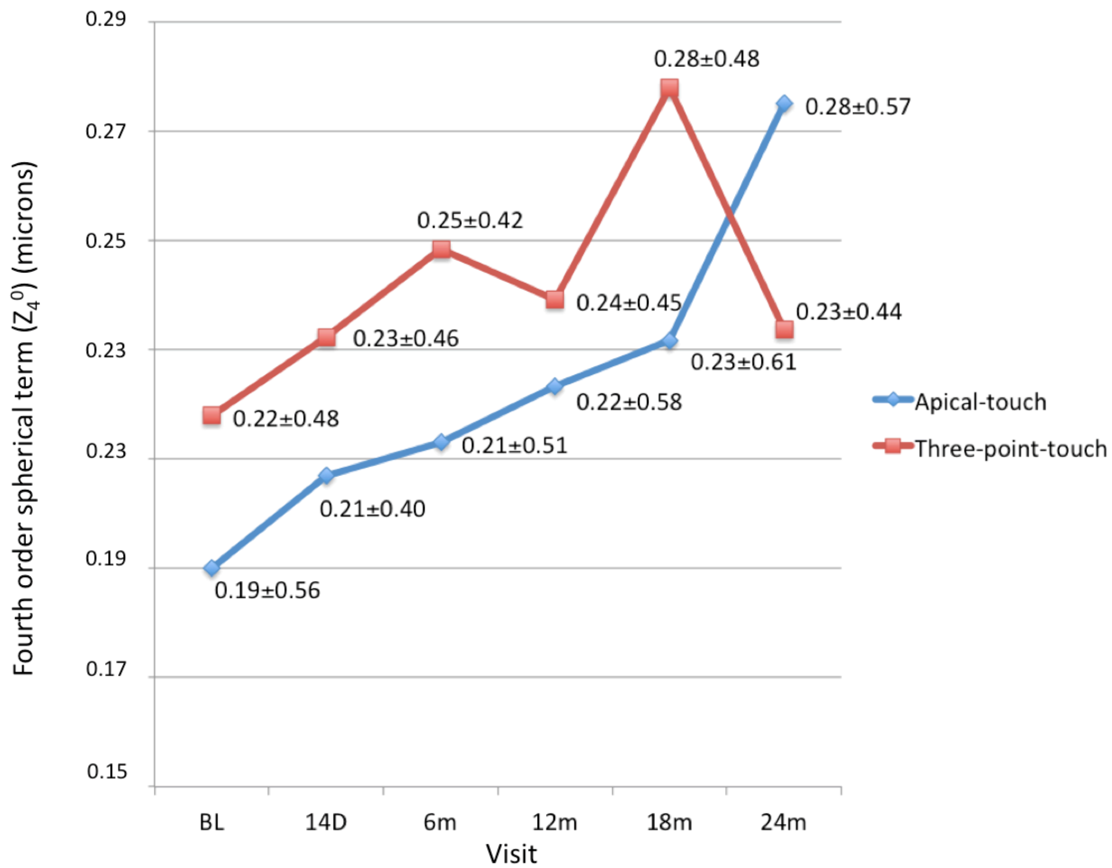

Figure 6.4.5. Fourth order spherical term (Z_4^0) data from both groups.

6.4.6. Coma aberration

6.4.6.1. Coma-like RMS aberration

No statistically significant differences were found between groups in coma-like aberration in any visit (Friedman test, all p>0.05) (**Figure 6.4.6**). However, statistically significant changes in coma-like aberration were found not only in the apical-touch group (U Mann Whitney test, p<0.0001, Post-hoc analysis **Table 6.4.5**) but also in the three-point-touch group (U Mann Whitney test, p<0.0001, Post-hoc analysis **Table 6.4.6**) over time.

Figure 6.4.6. Coma-like aberration data from both groups.

Table 6.4.5. *Post-hoc analysis of coma-like aberration regarding the apical-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	BL-6m	BL-12m	BL-18m	BL-24m	14D-6m
p-value	<0.0001	0.01	0.001	0.02	0.036	0.002

BL: baseline; m: months; D: days.

Table 6.4.6. *Post-hoc analysis of coma-like aberration regarding the three-point-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	BL-6m	BL-12m	BL-18m	BL-24m	14D-6m	14D-12m	14D-18m	14D-24m
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	0.003	0.001	<0.001

BL: baseline; m: months; D: days.

6.4.6.2. Third order vertical coma term (Z_3^{-1})

No statistically significant differences were found between both groups in the 3rd order vertical coma term (Z_3^{-1}) in any visit (Friedman test, all $p>0.05$) (**Figure 6.4.7**). Changes in 3rd order vertical coma term were found not only in the apical-touch group (U Mann Whitney test, $p<0.0001$, **Table 6.4.7**) but also in the three-point-touch group (U Mann Whitney test, $p<0.0001$, **Table 6.4.8**) over time.

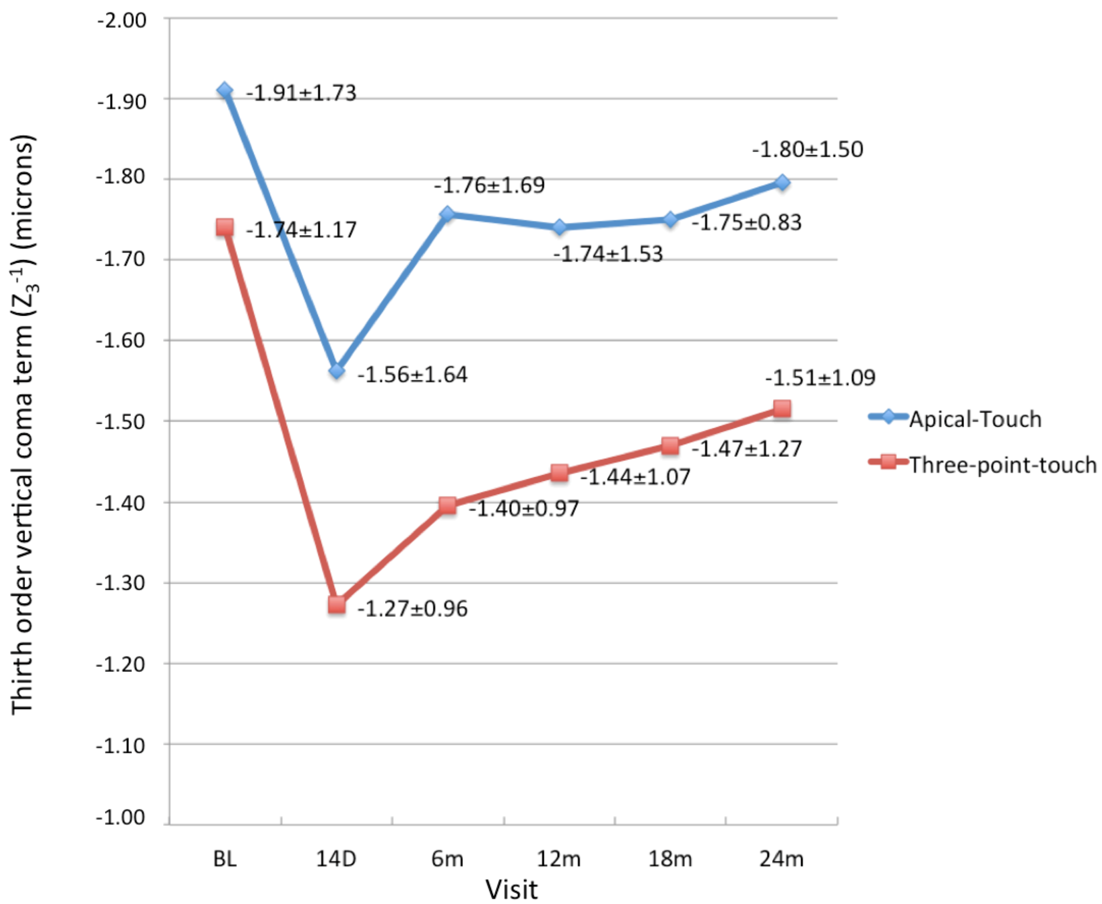

Figure 6.4.7. Third order vertical coma term data from both groups.

Table 6.4.7. *Post-hoc analysis of* 3rd *order vertical coma term regarding the apical-touch group. (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	BL-6m	BL-12m	BL-18m	14D-6m	14D-12m	14D-18m	14D-24m
p-value	<0.001	0.035	0.023	<0.001	0.003	0.047	<0.001	0.048

BL: baseline; m: months; D: days.

Table 6.4.8. *Post-hoc analysis of* 3rd *order vertical coma term regarding the three-point-touch group. (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	BL-6m	BL-12m	BL-18m	BL-24m	14D-6m	14D-12m	14D-18m	14D-24m
p-value	<0.001	<0.001	<0.001	<0.001	0.005	0.014	0.01	0.04	0.001

BL: baseline; m: months; D: days.

6.4.6.3. Third order horizontal coma term (Z_3^1)

No statistically significant differences were found in the 3rd order horizontal coma Zernike term during the two-year follow-up (RM-ANOVA test, F=1.577, p=0.194) in the time*group interaction (F=1.243, p=0.295) or between fitting groups (F=2.165, p=0.145) (**Table 6.4.9**).

Table 6.4.9. *Third order horizontal coma term data from both groups.*

Group	BL	14 D	6m	12m	18m	24m
Apical-touch	-0.39±0.99	-0.19±0.80	-0.27±0.85	-0.21±0.85	-0.25±0.83	-0.34±0.85
Three-point-touch	0.03±1.01	0.01±0.92	0.05±0.97	0.03±0.95	0.02±1.06	-0.01±0.94

BL: baseline; m: months; D: days.

6.4.7. Secondary astigmatism higher order RMS aberration

Statistically significant differences were found between both groups in secondary astigmatism aberration at the baseline visit (Friedman test, p=0.03). However, no significant differences were found between groups in any of the other visits (Friedman test, all p>0.05) (**Figure 6.4.9**). Changes in secondary astigmatism aberration were found in the apical-touch group (U Mann-Whitney test, p=0.014, Post-hoc analysis **Table 6.4.10**) over time. However, no statistically significant changes were found in the three-point-touch group (U Mann-Whitney test, p=0.141) over time.

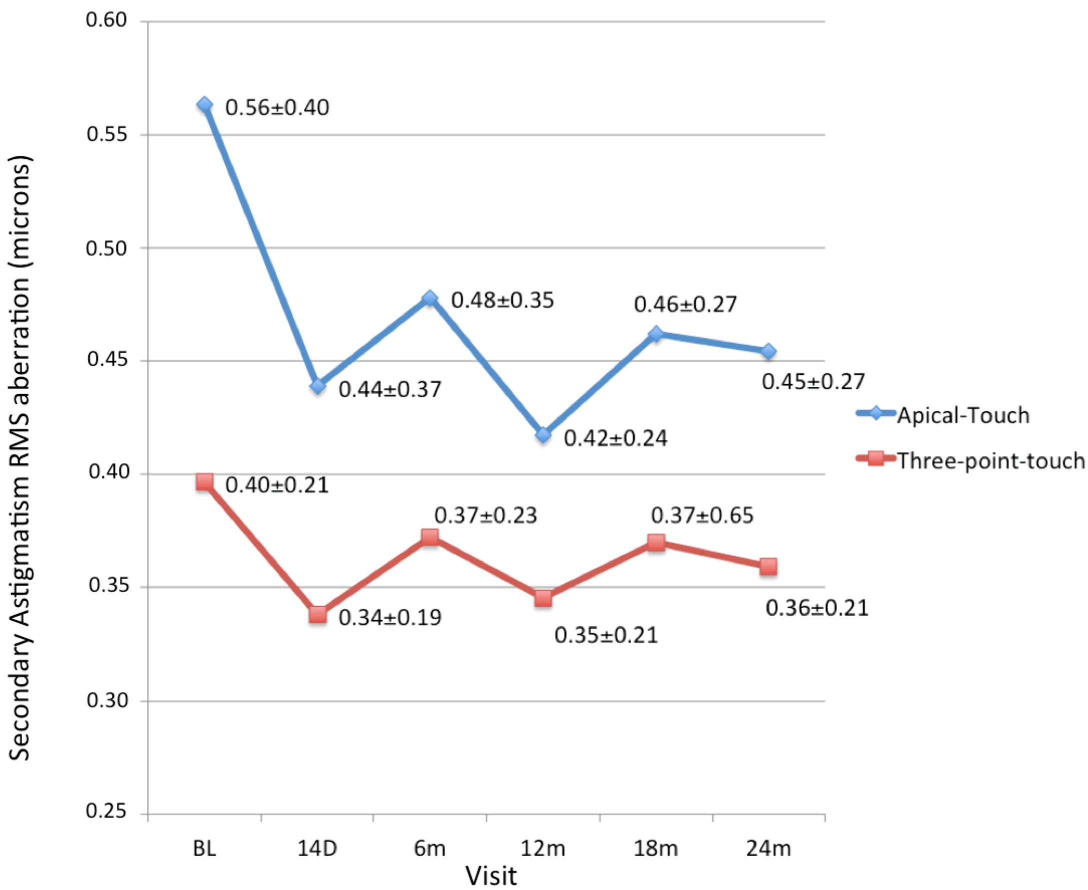

Figure 6.4.8. Secondary astigmatism HOA RMS data from both groups.

Table 6.4.10. *Post-hoc analysis of secondary astigmatism HOA RMS regarding the apical-touch group (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	**BL-12m**	**BL-18m**	**BL-24m**
p-value	0.003	0.007	0.008	0.022

BL: baseline; m: months; D: days.

6.4.8. Discussion

In keratoconus corneal asymmetry and irregularity induce an increase of high order aberrations, especially coma and spherical-like aberrations in comparison with normal corneas.[35] These aberrations and vertical coma have been proposed as the major aberrations affecting visual quality in keratoconus subjects.[36] RGP contact lens wear masks corneal asymmetry and irregularity, and thus reduce HOA in keratoconus during contact lens wear.[37-40] This reduction could be greater when the lens BOZR is flatter than the central corneal curvature in comparison with steeper fitting contact lenses.[41] Recently, Jinabhai et al. reported that corneal HOA increased after ceasing RGP contact lens wear for 1 week in keratoconus subjects that had been wearing these lenses for an average of 7 years. This suggests that RGP contact lenses flatten and mold the irregular corneal, giving the anterior corneal surface a more regular curvature profile by exerting pressure on the apex.[10] In this thesis, we found a greater reduction of higher order corneal aberrations in the apical-touch group than in the three-point-touch group, after neophyte contact lens wearers with keratoconus wore RGP contact lenses for 14 days (**Chapter 5, Section 2**).

Total HOA RMS was greater in the apical-touch group than in the three-point-touch group in the initial visit. However, such difference was not found in subsequent visits, suggesting that the apical-touch RGP contact lens fitting approach has a greater effect over the anterior corneal surface regarding total HOA RMS reduction than the three-point-touch RGP contact lens fitting approach. A similar reduction was also found in the 3rd order RMS after 14 days in comparison with the baseline. Our results are in accordance with those published by Jinabhai et al.,[10] in which RGP contact lens wear leads to a reduction in total HOA RMS and 3rd order RMS, probably as a result of molding the anterior corneal surface. Furthermore, a greater reduction in total HOA RMS was found in the apical-touch group than in the three-point-touch group as this is attributed to the great flattening effect induced by the former fitting approach in comparison with the latter fitting approach. On the other hand, it seems that, once RGP contact lens are fitted, the reduction in total HOA RMS is initially greater in the apical-touch group, but then the gradual increasing is similar in both groups.

The 4th order RMS did not show any change during follow-up either in the apical-touch group or in the three-point-touch group, which is in agreement with the results presented in a previous study, where authors did not find any change in this parameter after ceasing contact lens wear for a week in a group of keratoconus subjects.[10]

Spherical-like aberration and the 4th order spherical term (Z_4^0) did not show any variation over time or differences between both groups in any visit. These results are in agreement with those presented in **Chapter 5**, **Section 2** of this thesis. Spherical-like aberration was not found to be affected by RGP contact lens wear in keratoconus subjects, despite of the employed fitting approach.

Coma-like RMS aberration and 3rd order vertical coma term (Z_3^{-1}) showed a significant reduction in 14 days in comparison with the baseline in both studied groups, and remained stable thereafter. No differences were found between groups in any visit in both coma-like and 3rd order vertical coma term (Z_3^{-1}). These parameters were similarly reduced in both groups in the initial and 14-day visit, and then both parameters showed a gradual increase in the following visits. This behavior is similar to that found in the total HOA RMS and 3rd order RMS. These findings support the published idea that vertical coma is the most important aberration that affects visual quality in keratoconus subjects.[36] Vertical coma impairment in keratoconus is related with the location of the cone apex, which is normally positioned at the inferior-temporal quadrant of the cornea (**Chapter 5, Section 1**). Changes found in coma-like RMS aberration and 3rd order vertical coma term (Z_3^{-1}) in this thesis are in agreement with those published by

Jinabhai et al.[10] Thus, RGP contact lens wear reduced anterior corneal surface coma-like RMS aberration by probably molding the anterior corneal surface. Nevertheless, this does not prevent the increase in coma-like RMS aberration commonly found in keratoconus progression, independently of RGP contact lens fitting approach. On the other hand, no significant differences were found either between both groups or over time in the 3rd order horizontal coma term (Z_3^1), and this is likely to be attributed to the cone apex location, proving that 3rd order horizontal coma term contributes very little to total HOA RMS and it is not affected by RGP contact lens wear in keratoconus subjects.

Secondary astigmatism RMS aberration was greater in the apical-touch group in comparison with the three-point-touch group at baseline. However, such difference was not found in subsequent visits, suggesting that the apical-touch RGP contact lens fitting approach had initially a greater effect over this aberration reduction in comparison with the three-point-touch RGP contact lens fitting approach. In the apical-touch group, a reduction of secondary astigmatism was found after contact lens fitting, and then this parameter remained stable during the remaining follow-up visits. In contrast, in the three-point-touch group no changes were found in secondary astigmatism either after initial contact lens fitting (i.e. 14 days vs. baseline) or between any of the subsequent follow-up visits. The latter advances the idea that the flatter the lens BOZR that is employed in the fitting, the greater the flattening of the anterior corneal surface, and thus the greater the reduction in corneal aberrations in keratoconus (**Chapter 5, Section 2**).

In summary, anterior corneal surface HOA decreased following RGP contact lens fitting, with the latter effect being more profound in the apical-touch fitting approach than in the three-point-touch fitting approach, but then they gradually increased over time, probably as a consequence of the normal progression of the illness. A greater increase in anterior corneal surface HOA was found in the three-point-touch fitting group in comparison with the apical-touch fitting group, and this is attributed to corneal molding differences induced by these two different fitting approaches.

SECTION 6.5

Visual Quality

Miguel Romero-Jiménez

6.5.1. Introduction

This section reports the results of high contrast distance visual acuity and near distance contrast sensitivity with contact lens wear and their evolution during follow-up, and compares both groups.

Visual acuity (VA) was recorded and measured using a projected high contrast decimal chart at 4 m. The chart is composed of 11 lines of 5 letters each. For statistical analysis purposes, the decimal VA was converted to LogMAR VA. Functional measurements of the visual performance were obtained under photopic conditions at 95-85 cd/m2 using a standard hand-held light meter. Best spectacle-corrected visual acuity (BSCVA) was measured 10 to 20 minutes after contact lens removal. Best corrected visual acuity (BCVA) was calculated with RGP contact lens and over-refraction.

Contrast sensitivity (CS) was measured using the Mars Letter Contrast Sensitivity Test (The Mars Perceptrix Corporation, USA). The Mars Letter Contrast Sensitivity Test follows the principles of many of the same design as the Pelli-Robson test,[42] and it has been published to be a useful alternative to the latter.[43-46] This test is printed on resin-coated paper by halftone screening methods. It measures 22.8 x 35.6 cm, and is mounted on plastic board. Three forms of the chart are supplied (for left eye, right eye, and binocular testing, or for repeated testing). The test is intended for testing at 0.5 m, at which distance each letter subtends 2° of arc. It was hand-held by subjects at distance of 50 cm. Following the manufacturer recommendations, the chart was illuminated with an instrument stand lamp angled at 45°, calibrated to the recommended illumination of 85 cd/m2. The Mars Letter Contrast Sensitivity Test uses the same Sloan letter forms which are presented from top to bottom in declining contrast. The Mars test, however, uses much smaller contrast decrements (0.04 log unit) than the Pelli-Robson test (0.15 log unit); these are applied letter by letter, and thus there are no triplets. The test stops when the patient makes two consecutive errors. The score is the log CS of the final correct letter, minus 0.04 for any errors prior to that. Contrast sensitivity measurements were performed with RGP contact lens and over-refraction.

6.5.2. Uncorrected visual acuity

No statistically significant differences in LogMAR uncorrected VA were found between apical-touch (1.73±1.22) and three-point-touch (1.66±1.19) at the baseline (U Mann-Whitney, p=0.98).

6.5.3. Best spectacle-corrected visual acuity

Best spectacle-corrected visual acuity was recorded at baseline visit as well as on the 14-day visit and in the 24-month visit. No statistically significant differences were found in BSCVA between both groups at baseline or on the 14-day visit (U Mann-Whitney test, both p>0.05). However, a statistically significant difference was found in the 24-month visit between both groups (U Mann-Whitney test, p=0.048) (**Table 6.5.1**).

Table 6.5.1. *Best spectacle-corrected visual acuity data.*

Group	Baseline visit	14-day visit	24^{th} month
Apical-touch	0.31±0.36	0.27±0.33	0.42±0.25
Three-point-touch	0.25±0.25	0.23±0.24	0.31±0.22

Statistically significant differences were found between visits in BSCVA in the apical-touch (Friedman test, p<0.0001) and the three-point-touch groups (Friedman test, p=0.032). Post-hoc analysis of BSCVA is shown in **Table 6.5.2**.

Table 6.5.2. *Post-hoc analysis of best spectacle-corrected visual acuity regarding both groups (Wilcoxon Signed Rank test).*

	Baseline-14^{th} day	Baseline-24^{th} month	14^{th} day-24^{th} month
Apical-touch	0.007	0.011	0.001
Three-point-touch	0.723	0.143	0.038

6.5.4. Best corrected visual acuity

Best corrected visual acuity data was assessed on every visit while subjects were wearing RGP contact lenses. No statistically significant differences were found in BCVA between groups in any visit (U Mann-Whitney test, all $p>0.05$) (**Table 6.5.3**).

Table 6.5.3. Best corrected visual acuities found in both studied groups in each studied visit.

Group	BL	14 D	6m	12m	18m	24m
Apical-touch	0.04±0.10	0.03±0.19	0.04±0.06	0.05±0.07	0.06±0.06	0.04±0.05
Three-point-touch	0.06±0.10	0.05±0.08	0.06±0.10	0.05±0.09	0.06±0.08	0.06±0.08

BL: baseline; m: months; D: days.

No statistically significant differences were found in BCVA between visits either in the apical-touch group (Friedman test, $p=0.174$) or in the three-point-touch group (Friedman test, $p=0.714$).

6.5.2. Contrast Sensitivity

Contrast sensitivity was measured in each studied visit, except at the baseline visit, while subjects were wearing RGP lenses. No statistically significant differences were found in CS between groups in any visit (U Mann-Whitney test, all $p>0.05$) (**Table 6.5.4**).

Table 6.5.4. Contrast sensitivity results regarding both studied groups and all visits.

Group	14th day	6th month	12th month	18th month	24th month
Apical-touch	1.55±0.10	1.54±0.12	1.50±0.13	1.47±0.13	1.48±0.13
Three-point-touch	1.52±0.13	1.49±0.15	1.46±0.17	1.44±0.14	1.44±0.16

Statistically significant differences were found in CS in the apical-touch between visits (Friedman test, $p=0.005$), and in the three-point-touch group (Friedman test, $p<0.0001$). The statistical analyses of the differences between pairs of studied visits for each group are shown in **Table 6.5.5**.

Table 6.5.5. *Post-hoc analysis of contrast sensitivity regarding both groups (Wilcoxon Signed Rank test).*

Group	14D-6m	14D-12m	14D-18m	14D-24m	6m-12m	6m-18m	6m-24m	12m-18m	18m-24m	18m-24m
Apical-touch	0.624	0.051	<0.001	0.002	0.156	<0.001	0.019	0.069	0.484	0.567
Three-point-touch	0.094	0.002	<0.001	<0.001	0.021	0.004	0.007	0.222	0.370	0.836

D: days; m: months

6.5.2. Discussion

In keratoconus visual function impairment has been related with both disease progression[15] and deterioration of self-perceived quality of life.[47] Two of the earliest clinical indicators for keratoconus disease are fluctuations on visual acuity and equivocal endpoint on subjective refraction. Furthermore, repeatability of subjective refraction in keratoconus has been published to be lower in comparison with non-diseased eyes, even under the best test conditions.[48] On the other hand, the measurement of high contrast visual acuity has shown to be very repeatable in keratoconus subjects.[49] In the present work, uncorrected VA was similar in both studied groups at baseline.

Although keratoconus subjects mostly rely their visual function on RGP contact lenses, the best subjective refraction should be performed in order to provide them with spectacles for use after contact lens removal or when contact lens wear is contraindicated (e.g. conjunctival infections, corneal abrasion, etc.). Best spectacle-corrected visual acuity did not show statistically significant differences between groups at baseline and on the 14-day visit. However, in the 24-month visit, BSCVA showed statistically, but not clinically, significant differences between groups: the apical-touch group had a loss of a line of decimal BSCVA in comparison with the three-point-touch group. In past literature, less than two lines of VA differences were not considered clinically relevant,[50,51] so self-perceived visual-related quality of life deterioration is associated with a 10-letter (two lines) decline in high contrast binocular VA.[47] The apical-touch group showed a statistically, but not clinically, significant improvement of BSCVA between the initial and 14-day visit, which could be related to the improvement of

HOA RMS. On the contrary, the three-point-touch group did not show any improvement in BSCVA on the 14-day visit in comparison with the baseline. Following two years of contact lens wear, both groups showed a statistically significant reduction in BSCVA of less than two lines of decimal visual acuity, and thus were not considered clinically meaningful.

No statistically significant differences were found between both groups in high contrast BCVA in any of the visits. Davis et al. reported a mean reduction of 0.29 of correctly read letters per year in 953 keratoconus subjects over a period of 7 years.[51] In the present work, we have found the same number of correct letters read after two years. Taking into consideration data from the work of Davis et al., the loss of correct letters should be of 0.58 in our study, which is somewhat unmeasurable. Nevertheless, two years of RGP contact lens wear is unlikely to be enough to find differences in BCVA impairment between fitting approaches, and thus further studies with longer periods of follow-up are recommended.

Although keratoconus eyes suffer from a decrease in contrast sensitivity in comparison with non-diseased eyes,[52] contrast sensitivity measured in keratoconus subjects properly fitted with RGP lenses has been reported to be within the values expected in normal subjects.[53] In our study, no significant differences were found between both groups in contrast sensitivity over the course of the study, suggesting that neither of the fitting approaches studied had an impact on CS. Although statistically significant changes were found between visits in both groups, such differences were not considered clinically meaningful, suggesting that RGP contact lens wear masks any potential decrease in CS, expected from the progression of keratoconus disease.

In conclusion, no clinically meaningful changes were found in visual quality over 2 years of RGP contact lens wear, independently of the assessed lens fitting approach. However, further studies with longer periods of follow-up are recommended to investigate if longer periods of RGP lens wear induce clinically meaningful changes in both VA and CS.

SECTION 6.6

Corneal Thickness

Miguel Romero-Jiménez

6.6.1. Introduction

The objective of this section is to evaluate how the thinnest corneal thickness changes from baseline through two years of RGP lens wear, and if the two RGP fitting approaches under investigation (i.e. apical touch vs. three-point-touch) affect this thickness.

Keratoconus is characterized by a corneal thickness decrease in comparison with non-diseased eyes.[54] This corneal thickness decrease causes keratoconus progression leading to corneal deformation and subsequent visual impairment.[54]

6.6.2. Thinnest corneal thickness assessment

Thinnest corneal thickness measurements were acquired and recorded at baseline, on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

Statistically significant differences were found between both groups in the thinnest corneal thickness value in every visit (U Mann-Whitney test, all $p<0.001$) (**Figure 6.6.1**). Furthermore, statistically significant differences were found over time in the thinnest corneal thickness value in both the apical-touch (Friedman test, $p<0.001$, Post-hoc analysis is shown in **Table 6.6.1**) and three-point-touch groups (Friedman test, $p<0.001$, Post-hoc analysis is shown in **Table 6.6.2**).

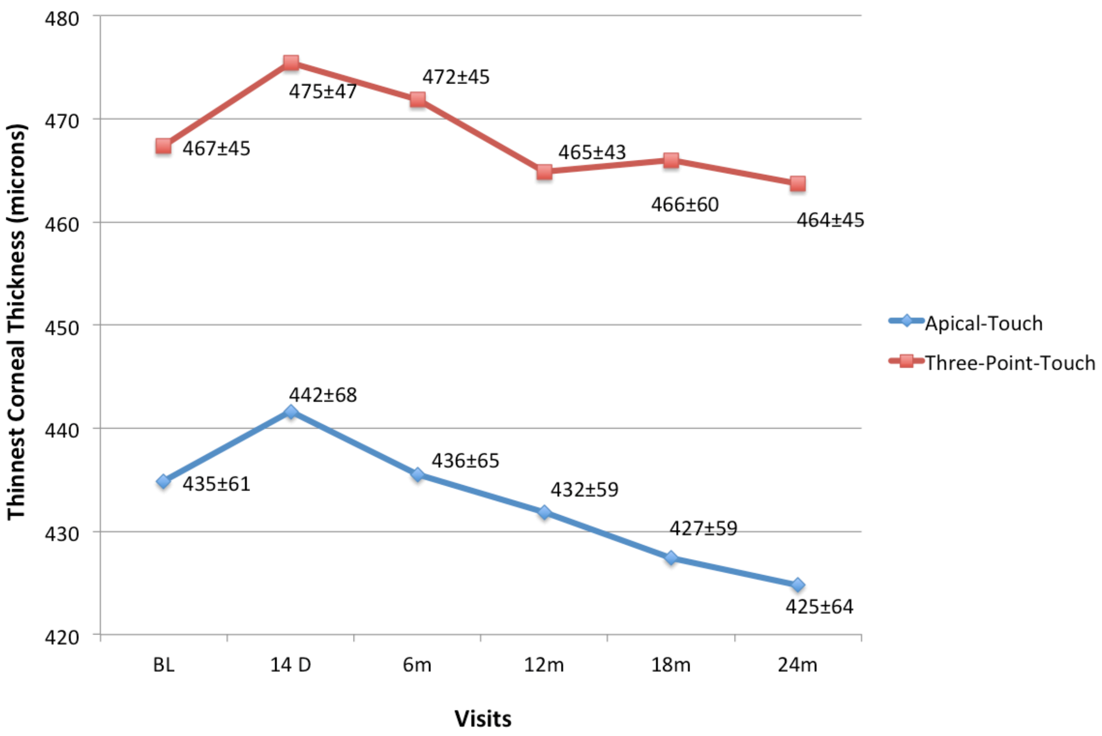

Figure 6.6.1. Changes in thinnest corneal thickness over time in the apical-touch (blue rhombus and line) and three-point-touch (red squares and line) groups. m: months; BL: baseline; D: days.

Table 6.6.1. *Post-hoc analysis of the thinnest corneal thickness regarding the apical-touch group. (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant interactions are shown).*

	BL-18m	BL-24m	14D-6m	14D-12m	14D-18m	14D-24m	6m-18m	6m-24m	12m-24m
p	0.025	0.024	0.08	0.004	0.0001	<0.0001	0.019	0.013	0.022

BL: baseline; m: months; D: days.

Table 6.6.2. *Post-hoc analysis of the thinnest corneal thickness regarding the three-point-touch group. (Wilcoxon Signed Rank test) (Only the pair of studied visits that were statistically significant are shown).*

	BL-14D	14D-12m	14D-18m	14D-24m	6m-12m	6m-18m	6m-24m
p	0.003	<0.001	<0.001	<0.001	0.003	0.007	<0.001

BL: baseline; m: months; D: days.

6.6.3. Discussion

Corneal thickness is thinner in keratoconus in comparison with non-diseased eyes.[54] Besides, corneal thickness decreased with keratoconus progression leading to corneal deformation and subsequent visual impairment.[54] However, the system to grade the severity of keratoconus disease used in this thesis, the Keratoconus Severity Score ranging scheme, does not take into account corneal thickness as a parameter for keratoconus staging.[55]

Statistically and clinically significant differences were found between both groups in the thinnest corneal thickness in every studied visit. At baseline, the apical-touch group showed a corneal thickness 32 microns thinner than the three-point-touch group, which might be attributed to an uneven distribution in the severity of keratoconus between groups, although subjects were randomly allocated to the two fitting approaches.

The thinnest corneal thickness behavior showed similar patterns in both groups. Immediately after RGP contact lens fitting, the thinnest corneal thickness increased, which is in agreement with our results discussed in Chapter 5, Section 2 of this thesis. This suggests a local and slight corneal swelling caused by RGP contact lens wear. Subsequently, a progressive reduction in the thinnest corneal thickness is observed in both groups during the two-year follow-up, and the reduction is greater in the apical-touch group than in the three-point-touch group. This corneal thickness reduction could be caused by either normal disease progression or the molding effect of RGP contact lenses. Jinabhai et al. reported a reduction of 9 microns in the thinnest corneal thickness after one week of RGP contact lens wear cessation in 15 keratoconus eyes, mostly fitted with the apical-touch fitting approach.[10] Therefore, we could expect a similar reduction if the subjects in this thesis had discontinued RGP contact lens wear for one week. Unfortunately, it was not possible to carry out such study. On the other hand, Hwang et al. reported a reduction in the thinnest corneal thickness of 11 microns in a group of 67 keratoconus subjects fitted with the three-point-touch fitting approach after two years of contact lens wear.[11] Nevertheless, we have found a reduction of 3 microns in the same fitting group. Differences between studies could be due to the different devices employed to measure corneal thickness (Orbscan vs. Pentacam).

Despite keratoconus has been classically described in the literature as a non-inflammatory disease, recent studies have shown it is accompanied by an increase of pro-inflammatory cytokines in the tears in comparison with normal subjecs,[57] with the inflammatory response being even greater with contact lens wear than in non-lens wear.[58] The mechanical rubbing of the RGP lens over the cornea might cause a subtle inflammatory response on the cornea leading to an increase in corneal thickness. However, the clinical implications of such increase are not clear. Results presented in Chapter 5, Sections 1 and 2 of this thesis, and in the present section support the idea that RGP contact lens wear causes a chronic, local and slight corneal inflammation in keratoconus. Nevertheless, whether such inflammation has implications on a potential degradation of the corneal surface or different fitting approaches induce different levels of corneal swelling, it is unknown. Further specific studies should be conducted to ascertain such issues.

In summary, the thinnest corneal thickness increased right after initial contact lens fitting, perhaps as a result of corneal swelling, followed by progressive decrease, which might be the result of either corneal flattening induced by contact lens wear or natural disease progression. In addition, the apical-touch fitting group shows a greater reduction in thinnest corneal thickness than in the three-point-touch fitting group after two years of follow-up.

SECTION 6.7

Corneal Clinical Signs

Miguel Romero-Jiménez

6.7.1. Introduction

This section summarizes the results of the clinical signs (i.e. Fleischer's ring, Vogt's striae and corneal scarring) during follow-up and compares both groups. The statistical analysis studies prevalence, incidence and severity regarding each group individually and as a whole. In addition, the possible correlation of clinical signs with total anterior corneal HOA RMS error and ACP is also assessed.

6.7.2. Fleischer's Ring

6.7.2.1. Prevalence

No statistically significant differences were found in Fleischer's ring prevalence in any visit between groups (Fisher's Exact test, all p>0.05). Neither apical-touch nor three-point-touch groups showed statistically significant differences in Fleischer ring's prevalence between different visits (Fisher's Exact test, all p>0.05) (**Table 6.7.1**).

Table 6.7.1. Prevalence of Fleischer's ring in every visit regarding both groups.

Group	Baseline		6th month		12th month		18th month		24th month	
	a	ua	a	ua	a	ua	a	ua	a	ua
Apical-touch	35	1	36	0	36	0	36	0	36	0
Three-point-touch	40	3	41	2	42	1	42	1	42	1

a: number of affected eyes; ua: number of unaffected eyes.

6.7.2.2. Incidence

After two years of follow-up, 1 and 2 eyes developed Fleischer's ring in apical-touch and three-point-touch fitting approaches, respectively.

6.7.2.3. Severity

Statistically significant differences were found at the severity level of Fleischer's ring between groups in the first visit (Chi-square test, p=0.025), being higher in the three-point-touch group than in the apical-touch group. No differences were found between groups in the following visits (Chi-square test, all p>0.05). Neither apical-touch nor three-point-touch groups showed statistically significant differences in Fleischer's ring severity between different visits (Chi-square test, all $p>0.05$) (**Figure 6.7.1**).

6.7.2.4. Correlation with ACP and total HOA RMS

Spearman correlation between Fleischer's ring severity and HOA RMS was (r_s=-0.254, p=0.024) and between Fleischer's ring severity and ACP was (r_s=-0.285, p=0.011).

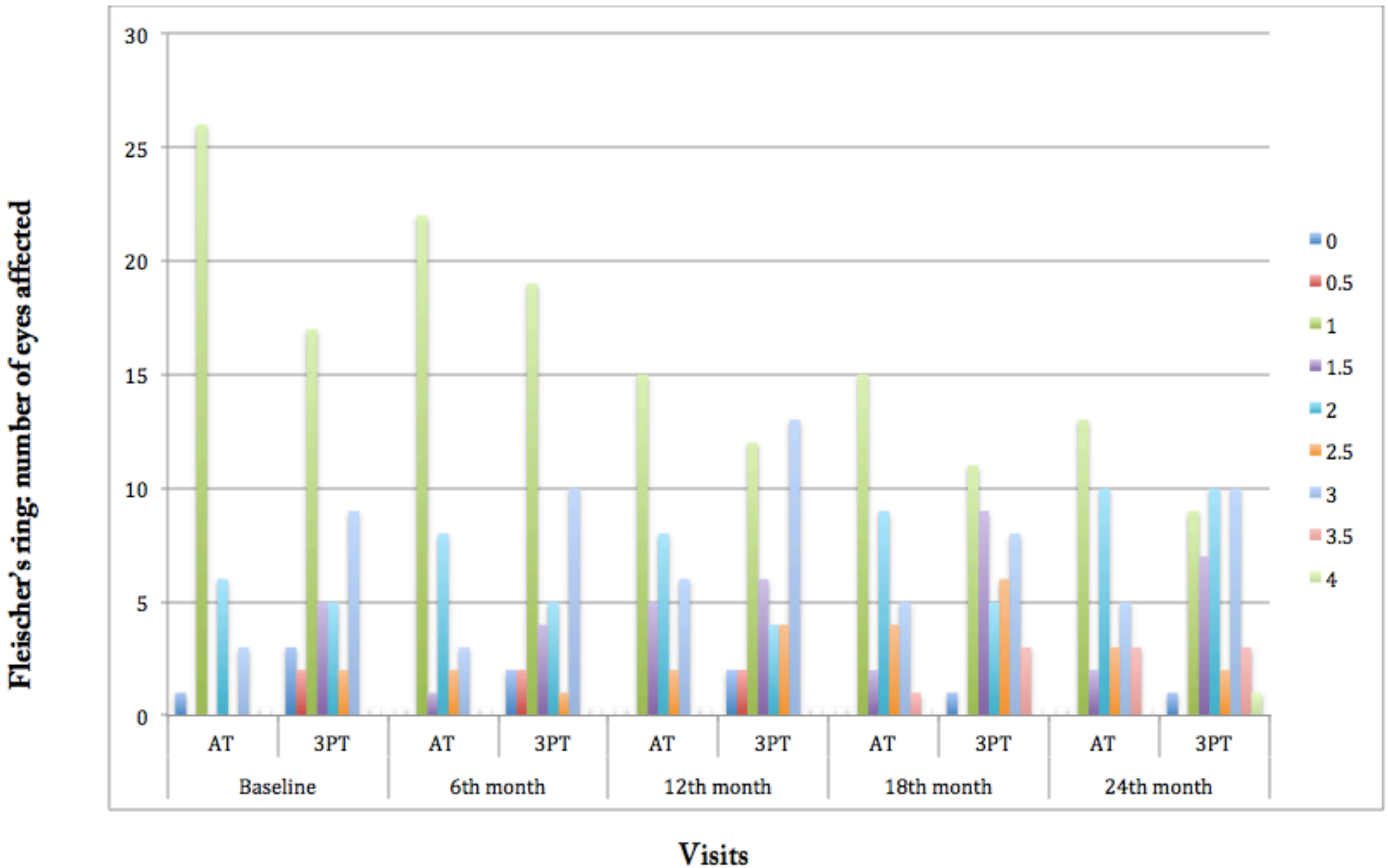

Figure 6.7.1. Number of eyes affected for every level of affectation of Fleischer's ring at different visits. Comparison between groups. Color squares on the right side show steps of the affectation scale. AT: apical-touch,; 3PT: three-point-touch.

6.7.3. Vogt's striae

6.7.3.1. Prevalence

No statistically significant differences were found in Vogt's striae prevalence in any visit between groups (Fisher's Exact test, all p>0.05). Neither apical-touch nor three-point-touch groups showed statistically significant differences in Vogt's striae prevalence between different visits (Fisher's Exact test, all p>0.05) (**Table 6.7.2**).

Table 6.7.2. *Prevalence of Vogt's striae in every visit regarding both groups.*

Group	Baseline		6th month		12th month		18th month		24th month	
	a	ua	a	ua	a	ua	a	ua	a	ua
Apical-touch	14	22	16	20	18	18	18	18	19	17
Three-point-touch	10	33	12	31	14	29	14	29	16	27

a: number of affected eyes; ua: number of unaffected eyes.

6.7.3.2. Incidence

After two years of follow-up, 5 and 6 eyes developed Vogt's striae in the apical-touch and three-point-touch fitting approaches, respectively. The unadjusted odds ratio of eyes fitted with apical-touch and having Vogt's striae is practically the same as in eyes fitted with the three-point-touch (unadjusted OR =1.32, 95% CI 0.40–5.02).

6.7.3.3. Severity

Statistically significant differences were found at the severity level of Vogt's striae between groups in the initial, and 6 and 18-month visits (Chi-square test, all p<0.05), being higher in the apical-touch group than in the three-point-touch group. No differences were found between groups in the following visits (Chi-square test, all p>0.05). Neither apical-touch nor three-point-touch groups showed statistically significant differences in Vogt's striae severity between different visits (Chi-square test, all p>0.05) (**Figure 6.7.2**).

6.7.3.4. Correlation with ACP and total HOA RMS

Spearman correlation between Vogt's striae severity and HOA RMS was (r_s=0.402, p<0.0001) and between Vogt's striae severity and ACP was (r_s=-0.310, p=0.005).

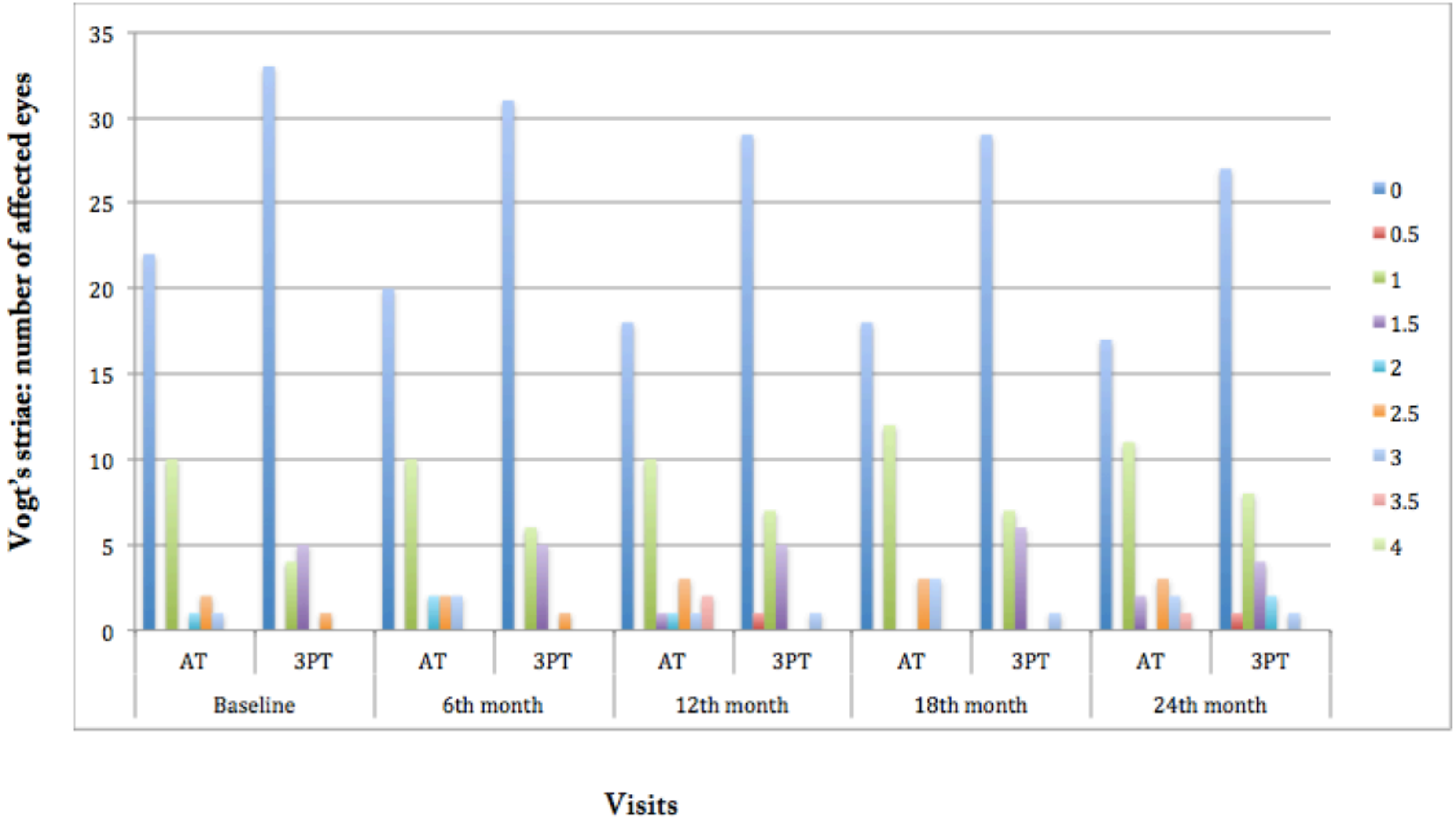

Figure 6.7.2. Number of affected eyes for every level of affectation of Vogt's striae regarding different visits. Comparison between groups. Color squares on the right side show steps of the affectation scale. AT: apical-touch; 3PT: three-point-touch.

6.7.4. Corneal scarring

6.7.4.1. Current RGP contact lens wearers vs. non-contact lens wearers

At baseline, 29 subjects (47 eyes) were current RGP contact lens wearers and 18 subjects (32 eyes) were non-contact lens wearers. In RGP contact lens wearers group, 31 eyes did not present corneal scarring, while 16 eyes did present corneal scarring at baseline. In the non-contact lens wearers group, 27 eyes did not present corneal scarring, while 5 eyes did present corneal scarring (Fisher's Exact test, p=0.077). The unadjusted odds ratio (OR) of eyes wearing contact lenses and having corneal scarring is more than two times that of eyes not wearing contact lenses (unadjusted OR =2.79, 95% CI 0.90–8.62).

6.7.4.2. Prevalence

No statistically significant differences were found in corneal scarring prevalence in any visit between groups (Fisher's Exact test, all p>0.05). Neither apical-touch nor three-point-touch groups showed statistically significant differences in corneal scarring prevalence between different visits (Fisher's Exact test, all p>0.05) (**Table 6.7.3**).

Table 6.7.3. *Prevalence of corneal scarring in every visit regarding both groups.*

Group	Baseline		6th month		12th month		18th month		24th month	
	a	ua	a	ua	a	ua	a	ua	a	ua
Apical-touch	11	25	11	25	13	23	15	21	15	21
Three-point-touch	10	33	10	33	10	33	12	31	13	30

a: number of affected eyes; ua: number of unaffected eyes.

6.7.4.3. Incidence

After two years of follow-up, 4 and 3 eyes developed corneal scarring in apical-touch and three-point-touch fitting approaches, respectively. The unadjusted odds ratio of eyes fitted with apical-touch and having corneal scarring is almost two times than that of eyes fitted with three-point-touch (unadjusted OR =1.91, 95% CI 0.39–9.41).

6.7.4.4. Severity

No statistically significant differences were found at severity level of corneal scarring between groups in any visit (Chi-square test, all $p>0.05$). Neither apical-touch nor three-point-touch groups showed statistically significant differences in corneal scarring severity between different visits (Chi-square test, all $p>0.05$) (**Figure 6.7.3**).

6.7.4.5. Correlation with ACP and total HOA RMS

Spearman correlation between corneal scarring severity and HOA RMS was ($r_s=0.402$, $p<0.0001$) and between corneal scarring severity and ACP was ($r_s=-0.558$, $p<0.0001$)

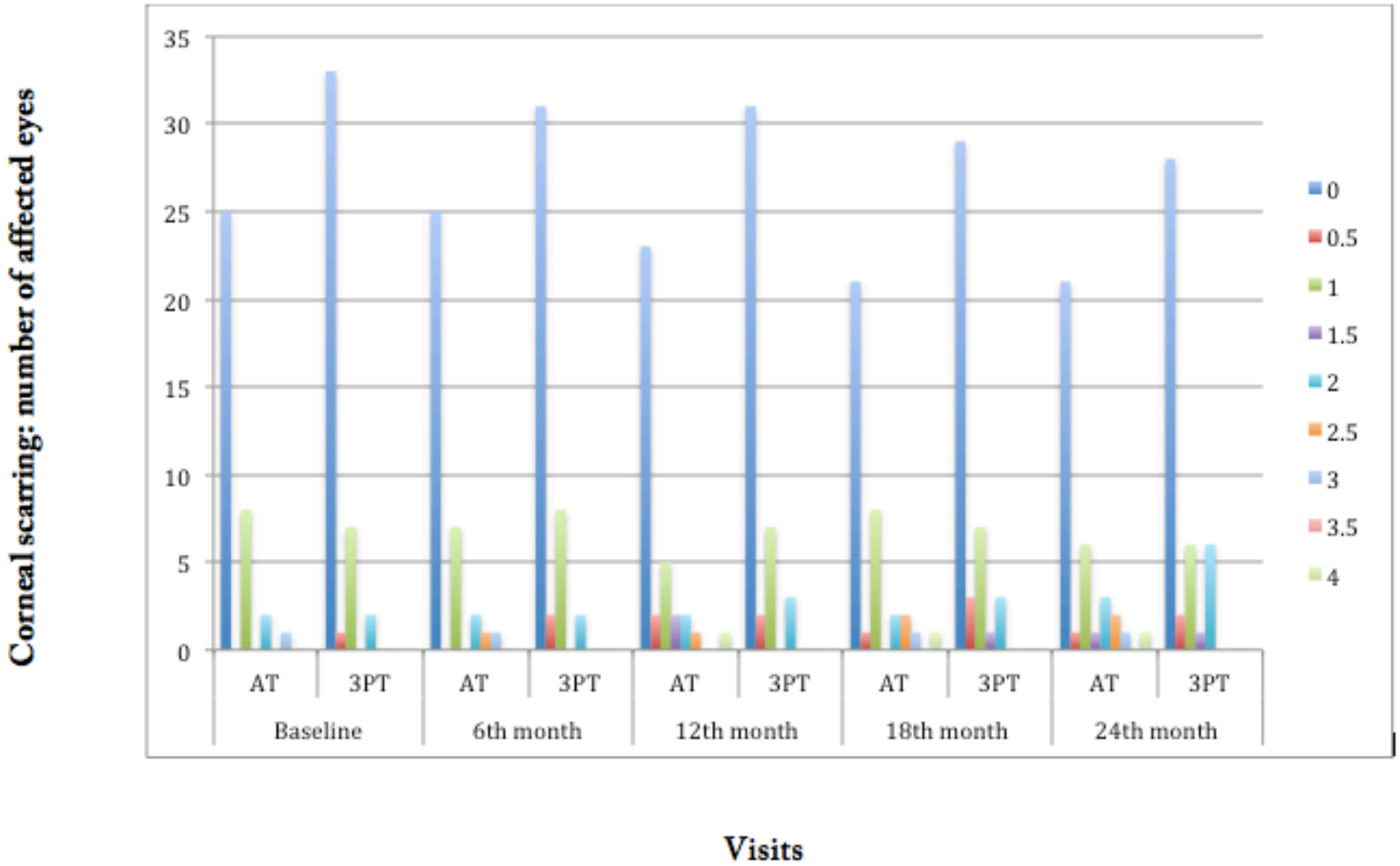

Figure 6.7.3. Number of affected eyes for every level of affectation of corneal scarring regarding different visits. Comparison between groups. Color squares on the right side show steps of the affectation scale. AT: apical-touch; 3PT: three-point-touch.

6.7.5. Discussion

Keratoconus disease is described as a combination of topographic findings and pathognomonic clinical signs (i.e. Fleischer's ring, Vogt's striae and corneal scarring).[55] Only one study has evaluated the prevalence and possible relationship of Fleischer's ring and Vogt's striae with disease severity in keratoconus in the past, discovering that the steeper the central corneal curvature, the greater the presence of clinical signs.[58] Prevalence and severity of corneal scarring in keratoconus have been studied profusely due to its impact on visual function.[2-4,8]

In moderate and advanced cases, a hemosiderin arc or circle line, commonly known as Fleischer's ring, is frequently observed around the cone base. This finding has no impact on visual function. We did not find statistical differences between groups on prevalence, incidence or severity of Fleischer's ring, except at baseline severity: the three-point-touch group presented a slightly greater severity than the apical-touch group, however, such difference was not clinically significant. Zadnik et al. reported that 64% of keratoconus subjects presented Fleischer's ring.[58] In our study, 95% and 98% of keratoconus subjects presented Fleischer's ring at baseline and after 24 months of RGP contact lens wear, respectively. In this study, a positive clinical sign (i.e. Fleischer's ring, Vogt's striae and/or corneal scarring) must be at least present at baseline to diagnose keratoconus, and Fleischer's ring is the most frequent of clinical signs associated with this disease. This methodology might be the reason for the different percentages found between studies. Apical-touch and three-point-touch groups showed similar ratio of Fleischer's ring incidence, so the RGP contact lens fitting approach is not related with this clinical sign incidence. On the other hand, Fleischer's ring severity is weakly correlated with HOA RMS and ACP.

Vogt's striae, which are fine vertical lines produced by compression of Descemet's membrane, is another characteristic sign of keratoconus. A 30% and 44% of eyes presented Vogt's striae at the baseline visit in this study. Zadnik et al. reported a 51% of Vogt's striae prevalence in keratoconus.[58] Vogt's striae prevalence has been related with more advanced disease severity, so it is possible that in the Zadnik et al. report keratoconus severity (based on average corneal power) was greater than in the present work. On the other hand, incidence of Vogt's striae was similar in both groups throughout the follow-up, so this clinical sign incidence is not related with the RGP contact lens fitting approach. Finally, we have found a weak correlation between Vogt's striae severity and HOA RMS or ACP.

One of the main goals of this thesis was to assess the incidence of corneal scarring in keratoconus subjects fitted with RGP contact lens, comparing two fitting approaches (i.e. apical-touch vs three-point-touch) throughout two years of follow-up. In past literature, it has been argued that the apical-touch fitting approach is related with the onset and development of corneal scarring in keratoconus,[3] and therefore a three-point-touch fitting approach has been recommended.[2] Several surveys have assessed the possible putative risk of corneal scarring development in keratoconus with RGP contact lens fitted with the apical-touch fitting approach, and all have concluded that this relationship could not be ascertained with cross-sectional data.[4,8,9] One study showed that RGP contact lens wear in keratoconus increases the risk of developing corneal scarring 3.51 times in comparison with non-RGP contact lens wear.[8] Finally, two studies on keratoconus and RGP contact lens wear recommended a longitudinal study to ascertain whether or not apical-touch caused a higher rate of corneal scarring incidence in comparison with other fitting approaches.[7,9]

We have found that RGP contact lens wearers have an odds ratio of 2.79 of corneal scarring development in comparison with non-contact lens wearers, which is a lower odds ratio than the previous study (3.51).[8] This reduction might be caused by: 1) the sample size differences (1091 keratoconus subjects in previous study vs. 48 keratoconus subjects in this study) and/or 2) the improvement of RGP contact lens design for keratoconus and/or the improvement of fitting approaches (practitioners are currently more aware about the possible relation between excessive apical bearing RGP contact lens and corneal scarring onset and development). Anyway, corneal RGP contact lens wear in keratoconus is, itself, a risk for corneal scarring onset.

No differences in corneal scarring prevalence or severity were found between fitting approaches in any visit. On the other hand, we found a moderate correlation between corneal scarring severity and average corneal power.

In this study, the incidence of corneal scarring was 12% (7 of 58 eyes) overall. In the past, Barr et al. reported a 5-year incidence of corneal scarring of 16.7% of RGP contact lens wearers in keratoconus.[59] Sixteen percent and 9% of eyes fitted with apical-touch and three-point-touch fitting approaches developed corneal scarring in two years, respectively. In this study, the odds ratio of eyes fitted with apical-touch to develop corneal scarring was 1.91 times than of eyes fitted with three-point-touch. Corneal scarring has been related with high and low contrast visual acuity and increased patient-reported symptoms of glare in keratoconus.[60] On the other hand, current surgical keratoconus treatment includes cross-linking and intra corneal ring segment implantation, and corneal scarring is an exclusion criteria for both. Thus, all efforts should be conducted by practitioners in order to avoid corneal scarring onset. Three-point-touch fitting approach should be intended in keratoconus, fitted with RGP contact lenses, in order to reduce corneal scarring incidence.

In summary, most keratoconus eyes have positive Fleischer's ring and/or Vogt's striae, and their severity is not correlated with HOA RMS or ACP. Keratoconus RGP contact lens wearers have increased risk of developing corneal scarring more than two times in comparison with non-contact lens wearers. The apical-touch fitting approach increases risk of developing corneal scarring almost two times in comparison with the three-point-touch fitting approach, thus it should be avoided in keratoconus.

SECTION 6.8

Keratoconus Severity Score

Miguel Romero-Jiménez

6.8.1. Introduction

This section analyzes changes on the Keratoconus Severity Score (KSS) during follow-up and compares both groups. KSS data were analyzed at baseline and on the 14-day visit, and in the 6, 12, 18 and 24-month visits.

6.8.2. Keratoconus severity score

Statistically significant differences were found in KSS between both groups at baseline (Chis-square test, p=0.014). However, no statistically differences in KSS were found between both groups in the following visits (Chi-square test, all p>0.05) (**Table 6.8.1**).

Table 6.8.1. Keratoconus Severity Score frequency regarding both groups.

KSS	Baseline			6m			12m			18m			24m		
	AT	3PT	p*	AT	3PT	p*	AT	3PT	p*	AT	3PT	p*	AT	3PT	p*
Mild	22	38	0.014	24	38	0.054	25	38	0.07	25	35	0.209	24	35	0.104
Mod	12	5		11	5		11	5		9	8		9	8	
Seve	2	0		1	0		0	0		2	0		3	0	

- Chi-square test. KSS: Keratoconus Severity Score range.

No statistically significant differences were found in KSS in apical-touch (Chis-square test, p=0.839) and three-point-touch (Chis-square test, p=0.729) groups between visits.

6.8.3. Discussion

The KSS was developed by the CLEK study group as a keratoconus severity scale and is based on slit lamp findings (including corneal scarring), corneal topography map characteristics and 2 topographic indexes: ACP and higher order anterior corneal surface wavefront RMS error.[55] As aforementioned in Section 1 of this chapter, corneal scarring onset and progression assessment was one of the goals of this thesis, by comparing the two RGP contact lens fitting approaches (apical-touch and three-point-touch). The KSS scheme was chosen for this thesis not only taking into account the corneal scarring presence and severity, but also for its easiness in applying and completing a keratoconus severity scale.

Despite that randomization of subjects into apical-touch and three-point-touch fitting groups, KSS was found to show statistically significant differences at baseline: the apical-touch group initially showed a slightly more advanced staging than the three-point-touch group. This difference is attributed to the high ACP and HOA RMS values, which are higher on the apical-touch group than in the three-point-touch group. However, no differences in corneal scarring severity or incidence were found between groups, as shown in Section 6.7. In the following visits, KSS showed similar levels of severity in both groups, which was caused by a decrease of HOA RMS in the apical-touch group.

When groups were analyzed separately, no statistically significant differences were found in KSS in any group (i.e. apical-touch or three-point-touch). However, KSS slightly increased in both groups when compared between the 14-day and 24-month visits, showing that RGP contact lenses do not avoid keratoconus progression.

In summary, KSS decreased right after apical-touch RGP contact lens fitting due to a HOA RMS reduction, while in the three-point-touch fitting approach such fact was not verified. Thereafter, KSS slowly increased, probably as a natural disease progression.

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CHAPTER 7

General Overview of Results, Conclusions and Future Work

7.1. General overview of results

Keratoconus is the most common primary corneal ecstasia,[1] whose etiology remains unclear, although it is suspected to develop as a combination of genetic and environmental factors.[2] In the last decade, two surgical techniques for keratoconus treatment have been developed (i.e. corneal cross-linking, Intrastromal Corneal Ring Segment implantation). However, corneal rigid gas-permeable (RGP) contact lenses still represent the first method for keratoconus management.

Three RGP contact lens fitting approaches have classically been described for keratoconus: steep or apical-clearance, flat or apical-touch and three-point-touch or divided support.[3] The differences between these fitting approaches are primarily based on the relationship between the central corneal curvature and the back optic zone radius of the lens. The apical-touch fitting has a bad reputation due to its relation to corneal scarring onset;[4] an idea based on the work of Korb et al., whose sample size was very small.[4] Results obtained from the largest cross-sectional study on keratoconus (CLEK) concluded twice[5,6] that a randomized clinical trial was necessary to ascertain whether the apical-touch RGP contact lens fitting approach has a higher risk for scarring incidence when compared with apical-clearance in keratoconus. However, apical-clearance is not currently intended on a routine basis, because it causes central corneal curvature steepening[7], which might be interpreted as keratoconus progression.[2] These two facts together have leaded to the recommendation that the three-point-touch fitting approach is the most appropriate for keratoconus, because it is thought to reduce corneal scarring incidence in comparison with the apical-touch fitting approach.[2] However, to the best of our knowledge, there is no scientific evidence provided by a prospective, longitudinal, randomized and single-masked clinical trial which could support such recommendation. On the other hand, and in spite of the very first recommendation to use negative-powered soft contact lenses for piggyback fittings on relatively steep corneas (i.e. keratoconus),[8] most practitioners use positive-powered soft lenses for piggyback fittings in keratoconus, because it is argued to facilitate RGP lens centration.[9] However, an exhaustive study about which soft contact lens power is better for piggyback fittings in keratoconus has not been conducted yet.

In order to analyze some of these aspects, this thesis was developed by covering the following main issues:

- Assess if the first definite apical-clearance lens (FDACL) concept is useful as a systematic starting point for fitting corneal RGP lenses with a variable optic zone diameter, using two different fitting approaches (i.e. apical-touch and three-point-touch), and evaluate the optimal lens fit rate obtained with the first lens ordered to the manufacturer between the two studied fitting approaches.
- Evaluate how different soft contact lens powers impact on anterior corneal surface in keratoconus in order to provide a better understanding on which soft contact lens power the piggyback lens fitting should be used.
- Assess the relationship between RGP contact lens wear and anterior corneal surface features in keratoconus, and evaluate short-term corneal changes with RGP contact lens wear in keratoconus subjects by comparing between the two fitting approaches under investigation.
- Characterize the effect of the two contact lens fitting philosophies on keratoconus progression by assessing clinical features every 6 months over a 2-year period, paying special attention to the prevalence, incidence and severity of corneal scarring.

The FDACL was developed by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study group as a method to evaluate central corneal curvature and as a starting point for corneal RGP contact lens fitting in keratoconus.[10] To date, the usefulness of this method was not assessed with corneal RGP with variable optic zone diameter. The results obtained in this thesis prove that fitting corneal RGP contact lens with a variable optic zone diameter, using FDACL, provides a systematic, reliable and repeatable starting point for contact lens fitting in keratoconus, and high rates of success with the first lens ordered to the manufacturer. Overall, the three-point-touch fitting approach has shown a greater optimal lens fit rate and a lower number of unscheduled visits and lens wearers dropouts than the apical-touch fitting approach. Thus, three-point-touch fitting approach should be the first option for corneal RGP contact lens fitting in keratoconus.

Despite the extended idea that low positive-powered soft lens is better for piggyback fittings in keratoconus,[9] the outcomes of this thesis have evidenced that mild negative-powered silicone hydrogel soft contact lenses are more appropriate than positive–powered lenses for piggyback lens fittings, because they allow the fitting of a flatter and less powered RGP lens.

The assessment of corneal features by comparing between RGP contact lens wearers and non-contact lens wearers has evidenced that the thinnest corneal location does not overlap with the steepest and maximum elevation corneal locations in keratoconus, and RGP contact lens wear does not seem to affect this lack of overlapping. On the other hand, our study shows RGP contact lens to flatten the anterior cornea in order to reduce corneal asphericity and corneal astigmatism, and to reduce anterior corneal surface higher order aberrations after a short period of wear in keratoconus, which is in agreement with previous reports.[11] In addition, and despite keratoconus being classically described as a non-inflammatory disease,[12] our results have shown that RGP contact lens wear might cause a local and slight chronic corneal inflammation, whose clinical relevance should be ascertained. Finally, differences found between apical-touch and three-point-touch fitting approaches after a short period of RGP contact lens wear on corneal surface are not clinically outstanding, except on central corneal curvature.

Two years of follow-up assessing differences in RGP contact lens wear between both studied groups have evidenced that the apical-touch fitting approach is more difficult to achieve and maintain over time, leading to an increased number of subjects that discontinued lens wear in comparison with the three-point-touch fitting approach. However, a greater increase in subjective over-refraction, and thus potentially in myopia was found with three-point-touch lens fitting in comparison with the apical-touch fitting. Therefore, specific studies are needed to clarify the potential relationship between fitting approaches and myopia progression. Another important find was that anterior corneal surface higher order aberrations decreased following RGP contact lens fitting, and then gradually increased over time, more profoundly in the three-point-touch fitting group than in the apical-touch fitting group, which is attributed to corneal molding differences induced by these two different fitting approaches. An increase on the thinnest corneal thickness right after the initial contact lens fitting was also evidenced, perhaps as a result of corneal swelling, followed by progressive decrease over time. On the other hand, RGP contact lens wear increases the risk of developing corneal scarring more than two times in comparison with non-contact lens wear in keratoconus, which is in agreement with a previous report.[13] And the most important finding lies in the fact that the apical-touch fitting approach increases risk of developing corneal scarring almost two times more than in the three-point-touch fitting approach, confirming the extended idea that the apical-touch fitting approach should be avoided in keratoconus subjects.[3] Finally, keratoconus severity decreased right after initial RGP contact lens wear, but it slowly increased over time, proving that this type of contact lenses does not avoid keratoconus progression.

Overall, this work objectively demonstrates the that apical-touch fitting approach should be avoided in keratoconus in order to increase optimal lens fit rate, decrease the number of lens wearer dropouts and, more importantly, reduce corneal scarring incidence. On the other hand, corneal RGP contact lens wear increases the risk of corneal scarring incidence, so other RGP contact lens design alternatives should be studied. Finally, corneal RGP contact lens wear in keratoconus causes local corneal swelling, whose clinical relevance should be ascertained by conducting specific studies.

Study limitations

The main limitation of this thesis is the different keratoconus severity stages between groups at baseline. Despite that, subjects were randomly allocated to the apical-touch and three-point-touch groups, and statistically significant differences were found at baseline in average corneal power (ACP), total higher order aberration (HOA) root mean square (RMS), thinnest corneal thickness and keratoconus severity score (KSS) staging. The apical-touch group presented a more advanced stage than the three-point-touch group at baseline. Therefore, a comprehensive analysis of the data is mandatory to ascertain the clinical implications of such differences found between groups. The keratoconus severity of this thesis is calculated using the KSS index, as mild, moderate and severe, based on ACP, HOA RMS and presence of corneal scarring.[14]

At baseline, apical touch and three-point-touch groups presented an ACP of 49.50 and 47.75 diopters, respectively. The ACP for mild severity stage, following the KSS severity scheme, must be lower than 52 diopters. So, in terms of ACP, both groups were on average in the same keratoconus severity stage. On the other hand, at baseline, apical-touch and three-point-touch groups presented HOA RMS values of 2.24 and 2.80 microns, respectively. The value of HOA RMS in KSS for mild severity stage must be between 1.50 and 3.50 microns, so, in terms of HOA RMS, both groups were on average in the same severity stage. However, the apical-touch group had a greater number of eyes starting at a moderate severity stage (12) than the three-point-touch group (5) at baseline.

Thinnest corneal thickness measurements showed less 34 microns in the apical-touch group in comparison with the three-point-touch group at baseline. However, none of the more employed indexes for keratoconus severity staging takes into account thinnest corneal thickness among corneal and topographic features, which are included in such indexes.[14-25] Thus, even when there is a difference in this parameter, the clinical importance of such difference is relative.

Finally, no significant differences were found in corneal scarring prevalence or severity between groups at baseline. One of the mains goals of this thesis was to evaluate the incidence of corneal scarring after two years of RGP contact lens wear by comparing it between the groups under study. The most important longitudinal study of keratoconus is the CLEK study.[13] In this survey, the increased risk of corneal scarring incidence was presented in eyes with high corneal curvature of 52 diopters, and the ACP was under this value in both studied groups. Therefore, the odds ratio of corneal scarring incidence found in this thesis is unlikely to be affected by baseline differences discovered in the ACP, HOA RMS and the thinnest corneal thickness.

7.2. Conclusions

The work developed and presented in this thesis proves that fitting corneal RGP contact lens in keratoconus is easy to achieve by following the systematic method proposed. With this work, we have acquired a more exhaustive knowledge of differences in clinical performances between the two studied fitting approaches. The main outcomes of this work can be summarized as follows:

- The use of the FDACL provides a systematic, reliable and repeatable starting point for Rose K2 contact lens fitting in keratoconus, and the three-point-touch fitting approach provides a higher optimal lens fit rate in comparison with the apical-touch approach.

- Mild negative-powered silicone hydrogel soft contact lenses are more appropriate than positive–powered lenses for piggyback lens fitting in keratoconus, because they allow the fitting of a flatter and less powered RGP lens.

- The thinnest corneal location does not overlap with the steepest and maximum elevation corneal locations in keratoconus, and corneal RGP contact lens wear does not affect this lack of overlapping.

- Corneal RGP contact lens causes flattening of the anterior cornea, and reduces corneal asphericity, corneal astigmatism and anterior corneal surface higher order aberrations after a short period of wear in keratoconus.

- The apical-touch fitting approach is more difficult to achieve and maintain over time, and leads to an increased number of subjects that discontinued contact lens wear in comparison with the three-point-touch fitting approach.

- Anterior corneal surface higher order aberrations decreased following corneal RGP contact lens fitting, and then gradually increased over time, more profoundly in the three-point-touch fitting group than in the apical-touch fitting group, which is attributed to corneal molding differences induced by these two different fitting approaches.

- An increase in the thinnest corneal thickness right after the initial contact lens fitting was also evidenced, perhaps as a result of corneal swelling, followed by progressive decrease over time.

- Corneal RGP contact lens wear increases the risk of developing corneal scarring more than two times in comparison with non-contact lens wear in keratoconus.

- The apical-touch fitting approach increases the risk of developing corneal scarring almost two times more than in the three-point-touch fitting approach.

- Overall, this work objectively demonstrates that the apical-touch fitting approach should be avoided in keratoconus in order to increase optimal lens fit rate, decrease the number of lens wearer dropouts and, more importantly, reduce corneal scarring incidence.

7.3. Future Work

From the discussion of the contents of this work and the main outcomes and conclusions aforementioned, new questions have arisen that should be addressed in the future, using the knowledge acquired during the preparation of this thesis. They primarily arise from the application of the presented routine examinations. Examples of areas of interest to clinicians and the industry include:

- Assessment of corneal scarring incidence in keratoconus, using different and currently available RGP contact lens designs (i.e. corneo-scleral, semi-scleral, mini-scleral and full-scleral) in comparison with corneal RGP lenses.

- Prove if different RGP contact lens designs provide different rates of optimal lens fitting, contact lens wearer dropouts and complications in comparison with corneal RGP contact lens designs.

- Evaluation of clinical importance of local corneal inflammation caused by corneal RGP contact lens wear in keratoconus.

- Study if the three-point-touch fitting really causes a greater increase in myopia in keratoconus in comparison with the apical-touch fitting by measuring ocular biometry for a long period of time.

- Extend the follow-up of this work up to five years to ascertain if the outcomes and clinical differences found between the studied groups remain over time.

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APPENDIX 1.

CONSENTIMIENTO INFORMADO PARA LA ADAPTACIÓN DE LENTES DE CONTACTO PERMEABLES A LOS GASES EN QUERATOCONO.

El uso de lentes de contacto rígidas permeables a los gases (RPG) en queratocono tiene como fin el proporcionar al paciente la mejor agudeza visual posible, ya que crea, entre la lente y la cornea, una capa de lágrima que regulariza la superficie corneal irregular típica de estos casos. El porte de lentes de contacto, en general, supone por parte del usuario la asunción de responsabilidades para evitar la aparición de efectos no deseados, tales como infecciones o alergias. En casos especiales, está responsabilidad debe ser aun mayor, por cuanto el riesgo de complicaciones se incrementa, al tratarse de corneas que presentan una sensibilidad deprimida, espesores bajos y otras alteraciones que las hacen más vulnerables a las agresiones externas. Es de máxima importancia que el usuario adquiera un fuerte compromiso con el adaptador, respetando escrupulosamente las instrucciones referentes al uso y cuidado de las lentes de contacto, en especial las referidas al régimen de revisiones, el reemplazo de las lentes y las horas de uso de las mismas.

Riesgos del uso de lentes de tipo permeable.
Aunque las lentes de contacto se han usado desde los años 60, en la actualidad se han desarrollado materiales y geometrías que reducen drásticamente el tiempo de adaptación y los riesgos potenciales para la salud ocular. No obstante, todas las lentes de contacto, mientras se están usando provocan riesgo de irritación ocular transitoria, ya sea causada por alergia, reducción de la cantidad de oxígeno o estimulación mecánica. Estos efectos suelen cesar en cuanto se extraen las lentes de los ojos y no requieren tratamiento en la mayoría de los casos, aunque en ocasiones es necesaria la instauración de un tratamiento con antibiótico y/o antiinflamatorio. El riesgo más importante es la infección o ulcera corneal, la cual ocurre en un bajo porcentaje de casos de usuarios de lentes de contracto rígidas (aproximadamente 1 de cada 10.000) y cuya incidencia esta normalmente relacionada con una baja higiene o un mal uso de las lentes. En la rara situación en la que ocurre una infección corneal, es inusual, aunque posible, la pérdida permanente de agudeza visual. Esta probabilidad es tanto menor cuanto más rápidamente sea tratada. En casos extremos es incluso posible la pérdida del globo ocular.
Las lentes permeables, al ser de material semirrígido, pueden provocan daños corneales importantes en el caso de recibir un golpe en el globo ocular durante el porte de las mismas. Por lo tanto no deben ser utilizadas durante la práctica de deporte o actividades de riesgo.
En situaciones especiales, como queratoconos, queratoglobos, ectasias post-cirugía refractiva, herpes corneal, accidentes corneales, degeneración marginal pelucida y otras, es frecuente encontrar queratitis superficiales por roce de la lente o sequedad del ojo, que si bien deben ser controladas, no suponen riesgos importantes para la salud ocular. En todo caso, en estas situaciones extremas, las alternativas del paciente para tener una agudeza visual suficientemente buena para realizar una vida normal, son el uso de lentes de tipo permeable o la cirugía corneal, bien queratoplastias, implante de anillos intraestromales o fotoqueratectomía terapéutica.

El uso de lentes RPG en situaciones especiales, en las que la cornea no presenta una forma regular, suponen el riesgo de aparición de opacidades corneales (leucomas) que pueden llevar a una pérdida irreversible de agudeza visual si se producen en el eje óptico.

Reconocimiento de información.

He tenido la oportunidad de informarme sobre la adaptación y sus riesgos con mi Optometrista y dirigirle todas las cuestiones que he considerado oportunas, que me han sido contestadas satisfactoriamente. Estoy de acuerdo en seguir el programa de adaptación y los consejos e instrucciones que se me proporcionen, incluido el cuidado correcto de las lentes. Entiendo que mi adaptador va a asegurarse de que yo obtenga de la adaptación el mejor resultado posible y que yo debo comunicarle todo lo concerniente a problemas y complicaciones que aparezcan durante la misma. Si durante el uso de las lentes aparece dolor ocular, ojo rojo o secreciones oculares (legañas) me quitaré inmediatamente las lentes y contactare con mi Optometrista en el teléfono 915919737 ó en el mail mrjlentes@gmail.com . En el caso que no sea posible, entonces me dirigiré al servicio de oftalmología de urgencia.

Consentimiento de adaptación.
Doy mi autorización para que se me realice la adaptación de lentes de contacto de tipo permeable, asumo los riesgos que conlleva, y me comprometo a seguir las instrucciones que me sean dadas por mi Optometrista.

Madrid a .... de .... de 200 .

Nombre y firma.

D/Dña ....,

DOO. Col. ....
D. ....,

Si el paciente tiene menos de 18 años, el padre o tutor;

Nombre y firma.
D/Dña. ....

INFORMACIÓN PARA LOS VOLUNTARIOS DEL ESTUDIO.

Título:
Comparación de dos estrategias de adaptación de lentes de contacto en queratocono.

Invitación.
Está siendo invitado a participar en una investigación sobre lentes de contacto y queratocono. Antes de decidirse a participar es importante que entienda porque se quiere llevar a cabo el estudio y lo que se pretende. Por favor tomese el tiempo necesario para leer esta información cuidadosamente.

¿Cual es el propósito de este estudio?

Este estudio pretende probar que estrategia de adaptación de lentes de contacto es más segura, proporciona mejor calidad de visión y retrasa le progresión del queratocono, la adaptación plana o la adaptación con tres puntos de apoyo.
La estrategia de adaptación plana consiste en adaptar la lente de contacto con un radio base mucho más plano que el radio corneal más plano, para apoyar la lente sobre el ápex del cono. Esta forma de proceder se piensa que retrasa la progresión del cono y proporciona mejor calidad visual.
La estrategia de adaptación en tres puntos de apoyo consiste en repartir el peso de la lente entre la periferia de la cornea y el ápex del cono, adaptando una lente con el radio más cerrado que en la estrategia plana. Esta forma de proceder se piensa que es más segura.

¿Por qué he sido elegido?
Ha sido elegido para tomar parte en el estudio porque sus ojos son representativos de la enfermedad de queratocono.

¿Qué me pasará si acepto participar en el estudio?
Antes de las medidas

Si está de acuerdo en tomar parte en el estudio deberá firmar el consentimiento informado que le será presentado por el investigador principal que resolverá todas las preguntas que se le puedan plantear. Después de firmar usted tendrá el derecho de revocar el consentimiento en cualquier momento durante el estudio sin tener que dar ninguna razón.
Este estudio no le beneficiará directamente y no forma parte de ningún estudio médico.
Sin embargo se le regalarán las lentes y los líquidos de limpieza.
Usted podrá formular las preguntas que considere oportunas en todo momento durante el estudio.

¿Existe algún riesgo si participo en el estudio?

No existen riesgos adicionales a los que existen con el uso de lentes de contacto en queratocono. Estos son:

- Infecciones.
- Erosiones corneales.
- Ulceras corneales.
- Irritación ocular.
- Reacción adversa a los líquidos de mantenimiento de las lentes de contacto.
- Aparición de leucomas corneales.

¿Sera mi participación en el estudio confidencial?
Si. La información obtenida con el estudio permanecerá almacenada de manera segura y nunca será publicada unida a su nombre.

¿Qué ocurrirá con los resultados obtenidos en el estudio?
Los hallazgos clínicos encontrados en este estudio serán enviados para su publicación en reconocidas revistas científicas. Usted no será identificado en ninguna publicación.

¿Qué organismos están involucrados en esta investigación?
El investigador principal es Miguel Romero Jiménez, Optometrista colegiado, y sera dirigido por el Dr. J. Wolffsonh, de la Aston University (School of Life and health Sciences, Birmingham B4 7ET, y por el Dr. J. Santodomingo, de Menicon Co. Ltd., Nagoya, Japan.

¿Quien ha revisado este estudio?
Este estudio ha sido aprobado por Aston University's Ethics Committee.

¿Con quién debo contactar si no entiendo algo o necesito información adicional?
Debería contactar con Miguel Romero, en el número de teléfono 915919737 o en el mail mrjlentes@gmail.com

Explicacion y Consentimiento informado para los voluntarios del estudio.

Descripción del proyecto.

Título: **Comparación de dos estrategias de adaptación de lentes de contacto en queratocono.**

Explicación de los procedimientos:

Este estudio examinará los efectos de dos diferentes estrategias de adaptación (plana y tres puntos de apoyo) en corneas con queratocono durante dos años. Si está interesado en participar en el estudio debe cumplir los siguientes requisitos:

- Diagnosticado de queratocono por topografia corneal y/o signos clínicos en al menos un ojo.
- Usuario o no usuario de lentes de contacto.
- Ser capaz de llevar lentes de contacto permeables al gas.
- Estar dispuesto a cumplir dos años de seguimiento.
- Ser mayor de 12 años.

Si está de acuerdo en participar en el eestudio será adaptado con lentes permeables a los gases Rose K (Menicon CO. Ltd.) con una de las dos estrategias (plano o tres puntos de apoyo) para uso diario. Las lentes de contacto serán reemplazadas una vez al año o antes si fuera necesario. La estrategia de adaptación será asignada de manera aleatoria. Los participantes en el estudio no podrán elegir qué estrategia quieren que les sea adaptada. Los participantes en el estudio recibirán las lentes de contacto y las soluciones de mantenimiento gratis durante el periodo de estudio.

Las medidas de los parámetros oculares serán:

- Evaluación del error refractivo subjetivo.
- Topografía corneal Pentacam.
- Paquimetria corneal Pentacam.
- Examen del polo anterior con lámpara de hendidura.
- Gradación de la salud del polo anterior con Lámpara de hendidura.
- Cuestionario.
- Medidas de la cantidad y calidad de la película lagrimal.

Todas las medidas se realizan sin necesidad de tocar la superficie ocular y se realizan sin la instilación de colirios oculares. Para pacientes que no están familiarizados con estos procedimientos se ofrecerá más información posteriormente si es necesario.

El paciente deberá acudir a consulta:

- Antes de comenzar a usar las LC.
- A las dos semanas.
- A los seis meses.
- A los 12 meses.
- A los 18 meses.
- A los 24 meses.

Los riesgos que podrían afectar a la salud, seguridad y bienestar de los participantes incluyen reacciones a las soluciones de mantenimiento, infecciones oculares o reacciones adversas como resultado de mala higiene, erosiones corneales, ulceras corneales o cicatrización corneal. Para minimizar los riesgos los pacientes con historia previa de reacción a las lentes de contacto o a las soluciones de mantenimiento, o aquellos que parezcan incapaces de cumplir con los protocolos de cuidado y limpieza serán excluidos del estudio. Si ocurre una reacción adversa, el paciente será revisado cuidadosamente hasta que la agudeza visual vuelva a valores normales y la reacción haya cesado.
El uso de lentes de contacto permeables al gas que están comercialmente disponibles y que son expecificamente diseñadas para corneas con queratocono reduce el riesgo de complicaciones. Los pacientes que sufran alguna reacción adversa deberán interrumpir el uso de las lentes de contacto y ser revisados hasta que la situación se normalice. La integridad corneal será revisada al final de cada visita con la lámpara de hendidura y el uso de fluoresceína sódica. La agudeza visual será evaluada con un test estándar de Snellen.

Todos los datos concernientes a los pacientes así como la identidad de los mismos será confidencial.

Declaración de voluntariado.

He leido y entendido las explicaciones anteriores. He tenido oportunidad de hablar con el investigador y preguntarle todas las cuestiones que se me han planteado y he entendido que soy libre de retirarme del estudio cuando quiera. Entiendo que si renuncio a continuar en el estudio en cualquier momento no tendrá consecuencias económicas para mí. El consentimiento de participación no compromete mis derechos legales.
Estoy de acuerdo en participar en este estudio.

Nombre:…………………………………………

Firma:…………………………………………………..

Fecha:……………………………………………………