UNIVERSITY OF LATVIA
FACULTY OF PHYSICS AND MATHEMATICS
DEPARTMENT OF OPTOMETRY AND VISION SCIENCE

EFFECT OF ORTHOKERATOLOGY ON EYE AXIAL LENGTH AND REFRACTION IN MYOPIC CHILDREN

BACHELOR THESIS

Author: **Davide Rizzieri**
Student card number: dr13042
Supervisor: docent, Dr.phys. Pēteris Cikmačs

RIGA 2017

ABSTRACT

Thesis is written in English on 68 pages, contains 17 figures, 10 tables and 73 references.

Study purpose was to compare eye axial length and eye refraction changes in two group’s myopic adolescents. For one group myopia was treated with Orthokeratological contact lenses (OK) and for other group refraction was corrected with spectacles. After 18 months, for myopic subject group corrected with glasses eyes axial length increase was 0,20 mm, in comparison to patients group treated with OK contact lenses only 0,05 mm. Average myopia progression for patients treated with OK contact lenses was -0,04 D and for group corrected with glasses refraction changes was -0,40 D. The refraction changes difference 0,36 D was significant.

KEYWORDS: eye axial length, myopia, myopic progression, orthokeratology, refraction spherical equivalent.

ABSTRAKTS

Darbs uzrakstīts angļu valodā uz 68 lapaspusēm, satur 17 attēlus, 10 tabulas un 73 literatūras atsauces.

Darba mērķis bija salīdzināt acu aksiālā garuma un refrakcijas izmaiņas divām grupām tuvredzīgo jauniešu. Vienai grupai tuvredzība tika koriģēta ar ortokeratoloģiskajām kontaktlēcām (OK), bet otrajai ar brillēm. Pēc 18 mēnešiem tuvredzīgo pacientu grupai koriģētai ar brillēm acs aksiālais garums vidēji palielinājās par 0,20 mm, turpretī pacientiem koriģētiem ar OK kontaktlēcām tas bija tikai 0,05 mm. Pacientu grupai koriģētai ar OK kontaktlēcām tuvredzības pieaugums vidēji bija tikai -0,04 D, bet pacientiem koriģētiem ar brillēm tas bija -0,40 D. Refrakcijas izmaiņu atšķirība 0,36 D bija būtiska.

Atslēgvārdi: acs aksiālais garums, tuvredzība, tuvredzības progresēšana, ortokeratoloģija, refrakcijas sfēriskās ekvivalents.

TABLE OF CONTENT

INTRODUCTION

The purpose of this work is to understand how it is possible to oppose the progression of myopia in young people and, according to the studies conducted so far, controlling it by using of RGP contact lenses for night orthokeratology.

My hypothesis is that the short-sightedness of those treated with lenses for orthokeratology increases less than the degree of refractive subjects which, otherwise, uses spectacles with single-vision lenses for distance. We analyze the data collected through the ocular biometry to assess the eye axial elongation. This prospective study compares the myopia progression of two groups of young Italian shortsighted, one wearing monofocal spectacles lenses and another wearing orthokeratology lenses with a symmetrical design. The main purpose of this study is to compare the differences observed in eyes axial length growth and in myopic refraction measured between the two groups, after a period of 18 months.

Second, we analyze and compare the time spent outdoors, to understand its correlation with myopia progression.

My research and data collection consist in monitoring, with the help of an Ophthalmologist, 60 subjects (young people) from 7 to 16 years, inside of my two clinics (in Northern Italy). 30 subjects with spectacles (monofocal lenses in organic material, n=1,50) and 30 subjects with orthokeratology, all selected from my data base; myopia from 0,75 Diopters to 4,50 D, with maximum cylinder of 1,50 D. The analysis consists in measuring the progression of refractive error by the spherical equivalent calculation.

The work's four main themes are:

- Description of myopia, refractive condition in extraordinary increase, all the factors affecting it and which determine, in most cases, myopia progression.

- After analyzing the orthokeratology approach in the correction of juvenile myopia, we assess a number of mechanisms related to stretching of the posterior segment and involving the retina, choroid and sclera.

Referring to the studies analyzed, we discuss the role of the central and the peripheral vision in emmetropization process and the role of the peripheral hyperopic defocus in the progression of myopia. We talk about prevention, with particular attention to the role of outdoor activities.

- Analysis of previous studies that explain the procedure of axial length measurement with biometrics and others that consider the efficacy of orthokeratology treatment in slowing the growth of the eye and consequently reduce the progression of myopia.

- Discussion about the method used for our study. We investigated the refractive state of both groups. We performed in all subjects a measure of the axial length of the eye at the start of the study and a measure at the end (after 18 months). We detected ocular biometry using a Tomey Biometer AL100 ultrasound. Among the variables considered there is the time spent outdoor.

Various studies, in fact, show scientifically that exposure to outdoor light plays an important role in the myopia control. We discuss our experience in pediatric orthokeratology (it started 15 years ago), about effectiveness, approach and collaboration with doctors, benefits, safety and compliance.

Finally, RESULTS, DISCUSSION AND CONCLUSIONS.

1. REVIEW OF LITERATURE

1.1. Myopia

Myopia is a phenomenon studied for a long time, since it is very common and affects many young people during adolescence. The incidence of myopia is approximately doubled in the last three decades (Wolffsohn et al., 2016). The features and facets of myopia are well known although its etiology is still unknown (Zhu et al., 2014). In the clinical management of myopia, the use of ophthalmic lenses and standard contact lenses, are the most used methods to bring back the image on the retina and thus ensure a clear view. Myopia is the most common refractive error and the incidence is very high, especially in Asian countries such as Korea, Hong Kong, Taiwan, China and Singapore (Chi, 2014). It has also been reported a gradual increase in the incidence of myopia in Western countries. In fact, this condition, especially in the United States of America and in Europe, afflicts about half of young adults (Grigoletto, 2013). By some estimates, a third of the world population could be affected by the short-sightedness at the end of this decade. Therefore, it is possible to speak of a real epidemic. The prevalence of myopia in adolescents, is shown in Figure 1.1.

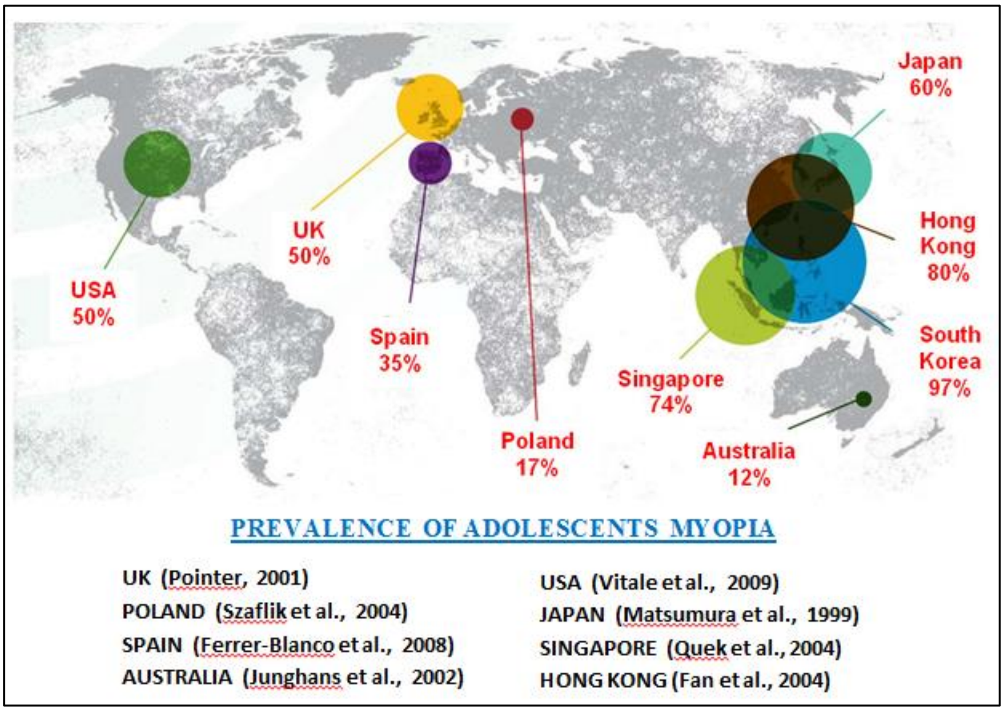


Fig. 1.1. Prevalence of adolescent's myopia (Santodomingo, 2011).

Some factors that contribute to the onset of myopia are: increased school education, prolonged work for near, genetic, hereditary, persistent use of vision to technological instruments, race and reduced time spent outdoors, diet.

High myopia is associated with various problems affecting the ocular health, such as cataracts, glaucoma, retinal detachment, macular degeneration, vitreous disorders, low vision and blindness. Myopia, when it is high, it is also reason to a significant increase in health care costs (Chi, 2014). There are currently three hypotheses that attempt to explain the onset of juvenile myopia (Zhu et al., 2014). It was hypothesized that a high accommodative lag for near induces an abnormal axial growth of the eye, although many studies have found no relationship between accommodative lag and myopia progression (Berntsen et al., 2011; Berntsen et al., 2012). The second hypothesis is based on eye longitudinal growth in emmetropic and myopic children caused by mechanical tension created by the lens or by the ciliary body, which limits the equatorial eye expansion causing an accelerated axial elongation (Mutti, 2010). The third hypothesis, consider that myopic eyes are relatively more hyperopic in the peripheral retina than in the fovea. Contrasting visual signals in the central and peripheral retina cause the axial growth and the development of the central refraction. However, this last hypothesis remains controversial (Zhu et al., 2014).

Generally, it is thought that the progression of juvenile myopia is caused by axial elongation of the eye and that this is not compensate by a reduction in refractive power of the cornea or the lens (Kakita, Hiraoka & Oshika, 2011).

Prevention and control of myopia have affected the studies and research of many clinicians who have considered various approaches, including ophthalmic lenses and contact lenses. The interventions with spectacles, especially with monofocal lenses, have not proven particularly effective to counter and control the progression of myopia (Walline et al., 2011). This is probably due to the hyperopic defocus induced in peripheral retina which stimulates, according to the hypotheses proposed by Zhu et al. (2014), the axial elongation and therefore the myopia progression. Even the under-correction of myopia has been shown to accelerate the rise of myopic progression.

Also the use of ophthalmic bifocal or multifocal lenses showed a modest and clinically insignificant effect on myopia progression control. However, only in cases of children with high accommodative lag and esophoria for near, with close reading distance and low myopia, researchers have seen encouraging results (Li, Ji & Wu, 2011; Gwiazda et al, 2011). Recent evidences show that spherical bifocal soft contact lenses, with concentric geometry, can reduce myopia progression more effectively than monofocal contact lenses (Horner et al. 1999; Walline, Jones & Sinnott, 2008) because equipped a center that corrects the refractive error and concentric zones that create a retinal myopic defocus (favorable during distance vision and near). It is therefore important to create a peripheral myopic defocus in order to slow the progression of myopia (Santodomingo et al., 2012).

Other studies have suggested that modern orthokeratology has the potential to reduce the progression of myopia in children and it is the method that currently has the most efficacy (Swarbrick, 2006).

The behavioral approach considers that the most time spent on outdoor activities is beneficial and has proved effective in delaying the onset of myopia. It is postulated that the increased levels of luminance to which a person is subjected, with more outdoor activities, may facilitate the release of a retinal transmitter, the dopamine, which appear effective in preventing the axial growth and the development of myopia. Furthermore, it is seen that the solar light component can stimulate particularly vitamin D, which could play a potential role in the prevention of eye growth (Grigoletto, 2013).

Since the outdoor viewing distances are typically greater compared to indoors, the accommodative response is reduced and the retinal image quality may improve because the pupil diameter is smaller in the full light, increasing the focus depth (Wolffsohn et al., 2016). However, the hypothesis that the large amount of outdoor light is the main reason for less myopia progression was contradicted by a study that shows the spectral composition of light as a predominant protective factor in development of myopia, and not primarily its intensity (Mehdizadeh & Nowroozzadeh, 2009).

1.2. Orthokertology

Orthokeratology (Ortho-K) is defined as the contact lens technique using rigid contact lenses to reshape the cornea with the purpose of changing or temporarily eliminating the refractive error (Zhu et al., 2014). Orthokeratology, is a non-surgical technique for the correction of vision.

Ortho-K is the ideal alternative to refractive surgery (PRK or Lasik) and for those who not prefer to wear corrective spectacles or contact lenses during the day. It can be used, also, with the aim of preventing the development of myopia progression in children or adolescents and even in cases of regression or residue of the myopic defect, post refractive surgery (Bullimore, N.1 2015). Orthokeratology technique applies through the design and application of custom contact lenses to patients who will use them at night while they sleep. Awakening, the contact lenses are removed, and the reshaped cornea allows a clear view all day long (often for two days), without need traditional glasses or contact lenses.

Ortho-K is a non-invasive and completely reversible procedure. If Ortho-K contact lenses are not worn for several nights, the elastic cornea simply returns to its original shape

(Formenti, 2011). In the next figure 1.2., we can see the central and mid-peripheral corneal epithelium, before Ortho-K treatment and in subsequent steps.

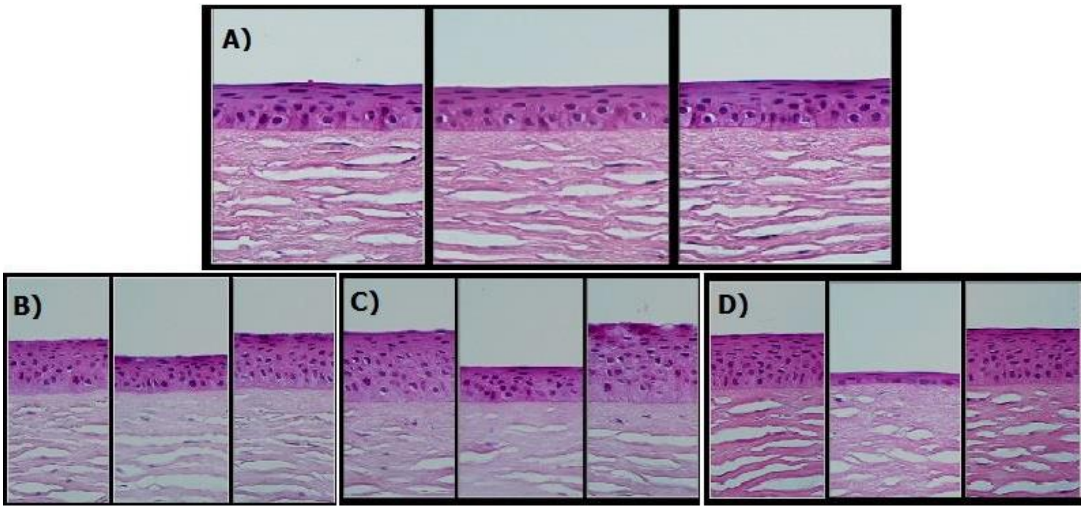


Fig. 1.2. Central corneal epithelium (middle image) and the mid-peripheral (side images) fixed with hematoxylin-eosin: A) Baseline, B) After 4 hours of OK treatment for myopia, C) After 8 hours of OK treatment for myopia, D) After 14 days OK treatment for myopia
(taken and modified by: Choo J.D. et al., 2008)

These lenses have a particular design (inverse geometry) able to modify the shape of the anterior surface of the cornea; in particular, they cause a temporary flattening of the central part and a curvature of the mid-peripheral part of the cornea. These lenses produce a compression and a flattening of the epithelial cells of the central cornea while those of semi-periphery, are less compressed between them, larger and oval (Reinstein et al., 2009). The changes in the corneal profile that follow and that are detectable through corneal topography, are effective for the correction of low and medium myopia (Formenti, 2011).

Historically, since the 1950, specialists had noticed the curvature changes induced by rigid lenses. Only in the early 60s began to exploit this effect to correct refractive errors (Jessen, 1962) but security issues and the unpredictability have limited its use. George Jessen, during the "International Society of Contact Lens Specialists Conference", held in Chicago in 1962, illustrated the "Orthofocus" technique, which consisted in the PMMA lens application in myopic subjects, applied flatter than the K, wearing during the day. However, Swarbrick (2006) reports that, according to some rumors never fully confirmed, since the ancient times, the Chinese usually slept with small weights or bags full of sand on the eyelids to reduce myopia.

In subsequent years, other optometrists including Tabb, Ziff, Nolan, Neilson, May, Grant, have started to use this technique, although considered dangerous at the time by other optometrists and ophthalmologists, developing a personal technique for each application

(Piovanelli, 2013). This application since 1962 will be called "orthokeratology", a term coined by Newton Wesley, and in 1976 will be defined by Kerns as "the reduction, modification or elimination of refractive defect by programmed application of contact lenses" (Mountford, Ruston & Dave, 2004).

The first contact lenses were very flat and with large diameters in order to ensure the effect of flattening on the corneal apex. These lenses, however, had big limitations including the difficulty of centering and consequently excessive dynamic that induced visual disturbances, physiological and tolerability problems. Then were introduced diameters and radii smaller but still sufficient to cause corneal change (Grigoletto, 2013).

At the end of the 1980s it was proposed a new type of lenses for orthokeratology with a special design called "reversed" geometry, characterized by a transition zone between the optical zone and the peripheral flange, more curve than the optical zone. Therefore, this lens allowed to have a flat application in the central area and better support in the paracentral area. This is due to the closure of the transition zone favoring therefore the centering on the cornea (Grigoletto, 2013).

Since the mid ‘90s, orthokeratology acceptance has increased significantly thanks to technological developments in the field of contact lenses, the availability of highly permeable materials and the instrumentation advent for the study of the corneal profile, design and the realization of the lenses (Lum & Swarbrick, 2011; Zhu et al., 2014).

Orthokeratology, especially in children, is becoming a popular corrective technique for the correction of myopia. Children are very active and orthokeratology allows them the freedom to play and participate in sports without the traditional contact lenses or spectacles.

Orthokeratology contact lenses are permeable (RGP) and are universally recognized as the healthiest type and more physiological contact lenses. They have in fact demonstrated the lowest risk of complications. With OK, the risk of MK is similar to that of soft lenses even though it occurred a higher incidence of microbial keratitis (MK) among young than adults (Bullimore, N.2 2015; Mirsayafov, 2015). The reason is that young people are less responsible and the parents, sometimes, underestimate the problem and give low priority to their role as controllers.

The effectiveness of this technique is subjective; among the factors that influence the reshaping action of the lenses is the resistance presented by the cornea. A cornea easier to mold can quickly acquire the desired corrective effect but, until the stabilization of the treatment, even a quick recovery of the initial condition (Reinstein et al., 2009).

About the vision, studies have shown a reduction in contrast sensitivity and an increase in high order aberrations (especially in those with higher myopia and decentralized treatment).

A possible decentralization of lenses, can produce monocular double vision and perception of halos (Sammarco, 2013). It is necessary, therefore, to continue in the search of ideal parameters and get the best lens centering. From our experience, usually the cornea returns to its initial shape after 1-8 weeks of treatment conclusion. Clinically, we can attend to complications such as corneal staining, corneal imprinting, reduction of intraocular pressure, the reduction of corneal sensitivity and the risk of microbial keratitis. This risk may be caused by: lens design, not suitable material, response of corneal epithelial cells and inadequate maintenance (do not use water and clean hands!).

The optometrist, applicator specialist, will use advanced technologies such as the digital slit lamp, the mapping of the cornea (topography) and imaging techniques to develop a three-dimensional map of the corneal surface. The procedures are performed in a few seconds and they are completely non-invasive and painless.

1.2.1 Benefits

We said previously, Ortho-K can slow and stop the progression of myopia in children. It has a very high degree of security, but must be respected all the protocols for the application and for the maintenance. Ortho-K, if practiced with competence and supported by a good compliance from the patient, it has proved to be a completely safe practice.

In a pilot study of 16 teenagers conducted by Mika et al. (2007), the majority of staining observed in some subjects during the different checks was acceptable (Grade 1 CCLRU Grading Scales), while more complicate staining all resolved in the period follow-up without any complications. This is guaranteed thanks to new materials for RGP CL which reached values of Dk/t > 125 X 10-9 (cm · mL O2) / (sec · mL · mmHg), the minimum value to avoid anoxia of all corneal layers (Harvitt & Bonanno, 1999).

Also recommended for many professions who work in environments where contact lenses and glasses may not be suitable; dusty environments or climates unsuitable for example.

From our clinical experience, we have found that orthokeratology is often a good choice when the daily use of traditional contact lenses become intolerable because of dry eye. Orthokeratology provides excellent vision in case of dry eyes, without compromising their health or comfort. Drop out of this technique, therefore, is very low and there are few serious complications, easily manageable. The protocol must be, however, very selective and highly accurate.

1.2.2 Disadvantage

It’s necessary perform several optometric controls at pre and post application (generally a minimum of 4-6 visits in a period of 3-6 months, depending on the complexity of the case) and it requires more trial lenses to obtain good results. It is certainly a longer and more complicated work for optometrist, especially if the subject to be treated is a child. The lenses used for Ortho-K are more expensive than standard contact lenses. The price for the Ortho-K is based on the orthokeratologist competence, refractive error of the patient and the complexity of the individual case. Wear the lenses is always necessary, otherwise the cornea returns to its original shape. Then, it’s a treatment with transient effect and not definitive. The success to reach acuity of 20/20 feet (0,00 logMAR) is high, but cannot be always guaranteed, in particular for the more complex cases.

Sometimes we have medium-high myopia, with large pupil diameters, and then our patient has to make compromises. In these cases, in fact, we will have greater presence of halos and disturbing aberrations. There are limits in the correction of some refractive defects. Our experience shows that the symmetric myopia without astigmatism is easily solved up to 5 diopters (although the possibility of correction extends up to approximately 8 diopters).

With the presence of astigmatism, the more difficulties are when the spherical base is particularly low compared to the value of the cylinder, or, in the case of against the rule and oblique astigmatism. The cylindrical limit is around three diopters, more easily when it is central and not limbus to limbus.

1.2.3 Important details for the selection of candidates

Important during the consultation is to establish and understand the patient's expectations for lifestyle, comfort, vision, safety and much more will be discussed in detail to ensure the achievement of results. Candidates will be evaluated for age, eye health, refractive degree, employment, the size of the pupil and expectations. It’s possible to fit the lenses to children under six years of age.

Even the refractive surgery is possible after orthokeratology. In this case, it is important to stop wearing the lenses for a period of time (usually several months), so the eyes return to original form and stabilize.

The orthokeratology practice requires great technical ability, continuous professional updating, specialized equipment, the collaboration between optometrist and ophthalmologist (optometrist for the technical part and ophthalmologist for the annual monitoring of ocular health).

1.3. Myopic peripheral defocus theory

The central refractive error is determined by the error of the eye focus respect to the fovea. However, in addition to the foveal region, which corresponds only to a small part of the visual field (1 degree against 104 monocular), in the overall refractive eye condition, the peripheral retinal areas are very important.

Studies in animals and humans have shown that the peripheral retina plays an important role in increasing the axial length of the eye and in the emmetropization process (Sammarco, 2013). The peripheral hyperopic defocus, or the peripheral blur caused by a focus over the retina, is presented together with a shape of the eyeball prolate (axial length greater than the equatorial). Functionally and anatomically there are several components involved in the development and progression of myopia: the accommodation, the retina, choroid and sclera. The contraction of the ciliary muscle in the activation of the accommodative mechanism can produce a tension on the sclera and a potential stretching resulting in axial elongation. According to this hypothesis, a prolonged accommodative activity can produce a progressive myopia.

According to another hypothesis, the accommodation would play a positive role in the progression of myopia because it reduces the peripheral hyperopic defocus (Sammarco, 2013). When the eye accommodates precisely to focus objects placed in the next point, thanks to the increase in power of the lens, the image plane falls on the retina and the defocus is reduced by eliminating the stimulus for axial elongation. Then, the eyes that are able to accommodate properly, should remain emmetropic. On the contrary, a wrong accommodation and the presence of peripheral defocus, stimulate the bulbar elongation.

The hypothesis, according to which the accommodation is not responsible of myopic progression, is coherent with the results of some studies on the proximal activity as risk factors for myopia, which suggest to read in bright lighting conditions for reduce the pupil size and increase the depth of field, thereby reducing the peripheral hyperopic defocus (Sammarco, 2013).

Animal studies showed a direct communication between the retina and the sclera.

Wildsoet & Wallman, (1992) in a study on chickens, found that the emmetropization continues even after surgical interruption at the optic nerve. Then, the retinal origin signals that normally induce an axial elongation, are transmitted directly to the sclera without “leaving” the eye. Although, embryologically there isn’t an explanation for this phenomenon, several studies suggest the presence of this direct communication retina / sclera so, the visual stimuli (including blurring), passing from the retina to the epithelium and then, through the choroid, they reach the sclera.

In support of the model that the vision determines the refractive status and the visual impairment and consequently influence the anatomical condition of the eye, numerous studies have been conducted on laboratory animals (Zhu & Wallman, 2009). In a study conducted on a group of chicks, the researchers altered the normal emmetropization process inducing a temporary refractive error, by the application of power lenses + 7 and - 7 D. In chicks which they applied positive lenses, the increase in axial length is reduced resulting in a myopic peripheral defocus, while, in chicks which they applied negative lenses, they obtained a peripheral hyperopic defocus and a consequent increase of the axial length (Zhu & Wallman, 2009).

In a previous study, Norton, Siegwart and Amedo (2006), have verified the competition between hyperopic and myopic defocus in a group of young monkeys always through the application of negative power lenses to induce a hyperopic defocus, and gradually more positive to induce a myopic defocus. Analyzed the results, the authors concluded that the hyperopic defocus is the stimulus that produces a bulbar elongation, and if this stimulus is reduced with the lenses that cause the least amount of defocus, the myopic progression can be stopped. Figure 1.3. shows a representation of the peripheral defocus.

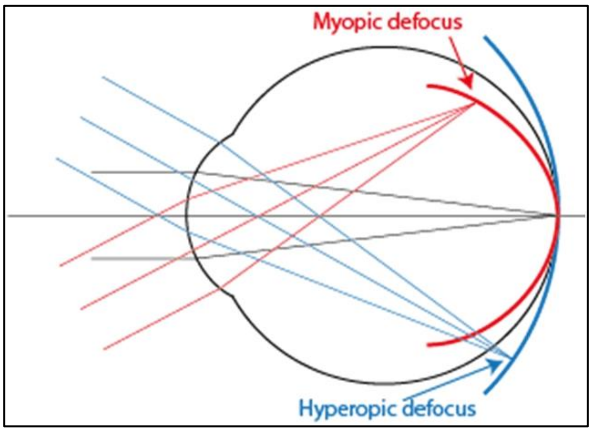


Fig. 1.3. Representation of the peripheral myopic defocus (red) and hyperopic (blue) when an object, place at infinity optical, is observed and its image falls in the fovea (from www.contactlensupdate.com).

Peripheral refraction means the focal point position of light rays, off the primary visual axis arriving to the eye when the horizontal light rays are focused on the fovea.

The hypothesis currently more confirmed is that peripheral hyperopia constitutes a predisposing factor to the development of myopia, and so, the correction of peripheral error would result in a lower rate of myopic progression. In myopic subjects, the spherical correction of refractive error, using traditional contact lenses or monofocal lenses, increases the hyperopic defocus. It would be necessary to correct the central refractive error and also the peripheral error. If this is not possible, the eye continues its extension in order to focus more clearly on the retina also objects projected on the peripheral part, resulting in a progressive increase of myopia (Sammarco, 2013).

The following figure 1.4., shows a diagram of a myopic eye with prolate shape and an axial length in excess, and are proposed corrections with a negative ophthalmic lens and ortokeratologic contact lens. In the first case we can see the presence of the peripheral hyperopic defocus, while with the Ortho-K lenses, there is a great improvement and the defocus control.

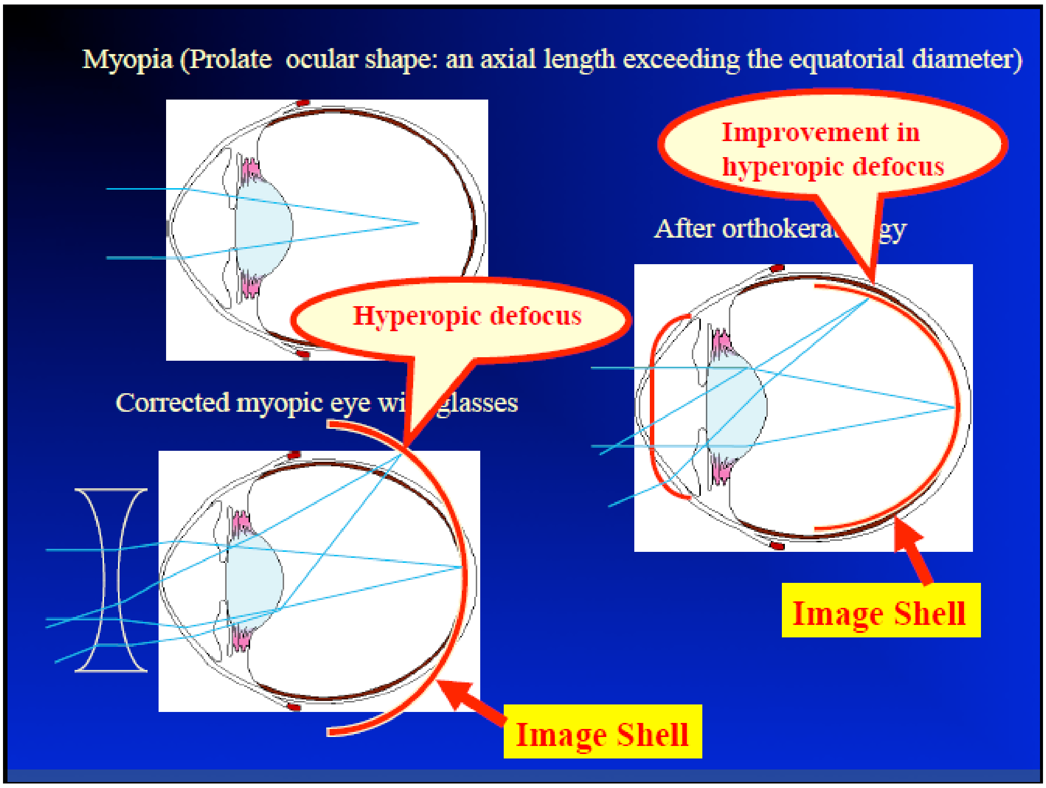


Fig. 1.4. Myopic eye (axial length in excess), and the image obtained with a negative ophthalmic lens and orthokeratology contact lens. (Hiraoka, 2013)

In a study on a group of monkeys, Smith, Hung and Huang (2009), have verified if the central myopic progression is influenced by peripheral hyperopic defocus. First, they used on eyes non-surgically treated, spherical lenses which caused a central myopia and a peripheral hyperopic defocus. Later, they removed the fovea by photo ablation; however, this technique showed no efficacy to prevent the progression of myopia. The authors concluded that the peripheral refractive error is determinant in the development of the central refractive error. It is known that the eye growth and development of the refractive condition are regulated by visual feedback mechanisms. The latest research confirm that are the optical error or peripheral defocus to adjust the central refractive condition (Charman & Radhakrishnan, 2010).

Currently there are several treatments that, according to the studies, are effective to slow and sometimes block the axial elongation: the corneal reshaping (orthokeratology and refractive surgery) and the control of accommodation (progressive ophthalmic lenses, vision training, atropine).

In the topography (post OK) shown in Fig. 1.5., it's possible to observe the central flattening (dark green area) which allows the subject to get a clear central vision and the semi peripheral bending (red ring area).

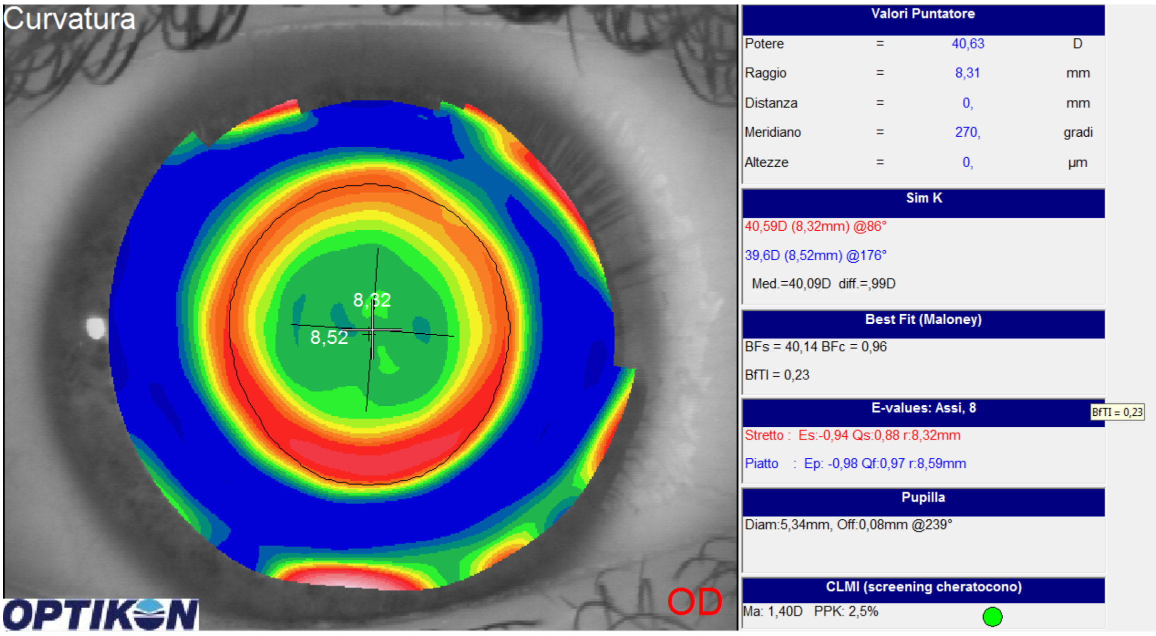


Fig. 1.5. Corneal topography after orthokeratology treatment (Rizzieri D., 2016)

The increase of the curvature between 3 and 4 mm from the center of the cornea, produces peripheral myopic defocus useful for axial elongation and myopia progression control. Therefore, the results from the studies on myopia control support the hypothesis that treatment techniques which reduce the peripheral defocus are more successful (Kang, Gifford & Swarbrick, 2013). In this study, Pauline Kang, Gifford and Swarbrick (2013), assessed if the change in two parameters for Ortho-K lenses (optic zone diameter and point of alignment of the peripheral curve) could produce changes in the peripheral refraction, corneal topography and the aberrations. From the results obtained they found that to increase the diameter of the optical zone or to change the peripheral curve alignment on the cornea it was not enough to significantly change the peripheral refraction or the topographic values;

however, the changed parameters were only two. In the future they could analyze different design, able to vary the peripheral refraction and aberrometric profile of the cornea.

Although the role of the peripheral hyperopic defocus in the genesis of myopia is not entirely clear, the research laboratory results on animals and human clinical trials are clear: to induce a peripheral myopic defocus through the ortho-k can slowing the progression of myopia (Smith III, Campbell & Irving, 2013). In terms of myopic control, orthokeratology treatment creates a myopic peripheral defocus, minimizing eye growth and thereby slowing the progression.

1.4. Time outdoor theory

Several important theories concerning the myopia prevention supports the importance of children's outdoor activities. Many studies agree on the prevalence of short-sighted in children spending less time outdoors than non-myopic. Also they show these activities have a preventive effect on the onset of myopia (Jones et al., 2007; Dirani et al., 2009).

The analysis of the recent scientific literature supports the hypothesis that the time spent in activities outdoors has a beneficial effect in reducing the prevalence of myopia in children and adolescents (Sherwin et al., 2012). The mechanism has not been clarified. It is proved that myopic subjects have lower serum concentrations of vitamin D than non-myopic. The production of vitamin D is related to sun exposure, however, it is not clear if vitamin D is protective for myopia or if the concentration of this vitamin is only a marker of some other biological effect connected to sun exposure (Yazar et al., 2014). In addition to the spectral composition, some researchers studied the distribution of light within the day: the exposure to constant light, as to the constant darkness, alters the growth of the eye causing more refractive errors. The alternation of light and dark, however, causes a modulation of the melatonin production and retinal dopamine, which play a vital role in the control the eye growth (Siegwart & Norton, 2013). The retina is a tissue distinctly circadian, showing rhythms in a variety of functions, including the sensitivity, the electrophysiological response, phagocytosis of outer segments of the photoreceptors, the expression of melanopsin, the synthesis of melatonin and retinal dopamine (Tosini et al., 2008). The alteration of the natural alternation between light and dark, such as the use of lights by night in the bedrooms of children under the age of two years, has been associated with the development of myopia in later years (Quinn et al. 1999).

A study conducted in Sydney in 2008, show that children who spent more than 15 hours a week in outdoor activities presented less or no myopia progression than children who spent

less time in these activities and remained committed in proximal visual activities. After studying more than 4.000 children in Sydney in primary and secondary schools, for three years, the authors found that children who spent less time outdoors, were more likely to develop myopia (Rose et al., 2008). Rose's team eliminated any other interference and explained the results obtained. Children who spent more time outside not necessarily spent less time with books, digital screens and prolonged close work. The thing most important and decisive was the eye exposure to bright light (Rose et al., 2008). They identified some of the environmental factors that explain this influence on myopic control.
Some of these are the following:

- Exposure to sunlight stimulates the production of vitamin D by the skin and in the retinal level are release some substances, including dopamine, that is, a neurotransmitter that helps to inhibit or to slow the eye elongation.

Dopamine, a neurotransmitter released by the inner retina, is an important chemical messenger for amacrine cells and retinal ganglion cells processing. It is involved in the retinal adaptation process to the luminance.

Amacrine cells of the retina showed to play an important role in the modulation and control of eye growth (Yi & Li, 2011).

The best evidence for the light-dopamine hypothesis, derived from tests on chicks. In 2010, Ashby and Schaeffel showed that injection into the eyes of the chicks of a drug inhibiting dopamine, called spiperone, could eliminate the protective effect of bright light. Retinal dopamine is normally produced in the diurnal cycle, and "communicates" to the eye the transition from night vision to daylight vision. Researchers now suspect that in low light conditions (typically covered), the cycle is canceled, with consequences for the eye growth (Ashby & Schaeffel, 2010).

- An open field of view and bright during any reduced work distance, is considered the ideal condition in order not to create a peripheral hyperopic defocus.
- Exposure to beneficial microorganisms, such as Mycobacterium Vaccae, which has systemic antidepressant properties (American Society of Microbiology, 2010).

He et al. (2015) evaluated the efficacy of the time spent outdoors increase in school for the prevention and incidence of myopia. This was a randomized clinical trial of children in Guangzhou, China, conducted between October 2010 and October 2013. They entered an increase of 40 minutes of outdoor activities for every day at school. Parents invited to involve their children in outdoor activities after school hours, especially weekends. 952 children were in the treatment group and 951 in the control group, with an average age of 6,6 years. The incidence rate of myopia was 30,4% in the treatment group and 39,5% in the control group (difference of -9,1%). There was also a significant difference in the change of refractive (spherical equivalent): -1,42 D for the treatment group, compared to the control group (-1,59 D), with a difference of 0,17 D. The axial length elongation was not significantly different between the treatment group (0,95 mm) and the control group (0,98 mm) with a difference of -0,03 mm. It's not yet entirely clear what are the factors that reduce the development of myopia in children who spend more time outdoors.

The real relationship between light and myopia is probably very complex, with intricate interactions between the circadian cycle and time, the intensity and spectral composition of light exposure. For example, it should still understand if, even the accommodative relaxation can influence this condition (Jones et al., 2007).

The role of the outdoor activities is offering many opportunities for researchers and, though the presence of many question, the research considers correct the prescription by the practitioner of these activities to young patients. In fact, even the visual training, which provides procedures and programs for the myopic control, consider this principle. In addition to exercises, that train the accommodative and convergence abilities, the procedures that allow “to open the periphery" that is, train your peripheral vision, have great importance.

Thus, ideal would be to plan the visual training procedures and perform them outdoor. In this way you could benefit at the same time, of both.

1.5. Analysis of Previous Studies

1.5.1 Biometrics and axial length of the eye in myopia progression

The axial length (AL) is the measure of the eyeball taken along the axis of symmetry and represent the distance from the cornea to the retinal surface. It is generally accepted that the myopic progression is given mainly by the AL.

A large number of authors, such as Grosvenor and Scott (Grosvenor & Scott, 1993), reported that myopia is always axial. Myopia caused by an increase of the corneal or lens refractive power without increase of AL, it is almost non-existent. The longer AL, the greater myopia. We mention a short-term study, made by Cheung and Cho, (2013), where they investigated in the validity measurement of axial length for monitoring the myopia progression. In this interesting study, the researchers compared the changes in the individual eye components, and the overall change of the anterior segment length in subjects with orthokeratology and in those with single-vision glasses for a period of 6 months. Since ASL (anterior segment length) was not affected by the Ortho-k treatment, the total measured axial length reflects the real growth of the eyeball and it's a valid parameter for monitoring the progression of myopia in the eye treated with Ortokeratologic lenses (Number Clinical Trials .gov, NCT00962208). Finally, this study showed that the axial length is a valid parameter for monitoring the progression of myopia since Ortho-k lenses caused negligible variations (Cheung & Cho, 2013).

The ocular biometry ultrasound is an objective method for the measurement of AL. It is an invasive technique that requires the use of an anesthetic and the contact on the cornea with a detection sonde. In our study, we used Novesina 0,4% (Oxybuprocaine Hydrochloride) but in no case occurred burning, irritation or allergic reaction to medication. One possible source of error, in the ultrasonic measurement, can be excessive contact with the cornea (excessive pressure). Another source of error is the non-alignment of the probe respect to ocular axis of symmetry.

In several previous studies, it was analyzed repeatability and reliability of AL measures performed with biometer A scan ultrasound. For example, in the study by Chan, Cho and Cheung (2006), it was found that among children, measurements of AL, performed with three different instruments (two biometer ultrasound and IOL Master), were not significantly different between them ($p > 0,05$) and were comparable in both groups (Ortho-K subjects and subjects with glasses). The measurements with the IOL Master, however, have greater repeatability and accuracy. Unfortunately, the cost of the IOL Master is still very high compared to biometer ultrasound and clinical optometric practice does not always allow to have a sophisticated instrument. In this study, measurements of AL and ACD (anterior chamber depth) performed with all the instruments, were not affected by the following flattened cornea using ortokeratologic lenses.

Even in the study by Sheng, Bottjer and Bullimore (2004), they demonstrated the correlation between the AL measures with the IOLMaster and biometer A-scan ultrasound.

In support of our measurements using the biometer A-scan ultrasound, we report as described in the study of Santodomingo-Rubido et al. (2002): "the study evaluates the validity and repeatability of these measurements and compares the findings with those obtained from instrumentation currently used in clinical practice. IOLMaster measurements of anterior chamber depth and axial length were compared with applanation A-scan ultrasonography (StorzOmega)". The results are reported below.

Axial length: the difference between IOLMaster and ultrasound measures was insignificant. This study has found a closer agreement between PCI (partial coherence interferometry) and applanation ultrasonography than most of the previous reports.

We can therefore say that biometrics ultrasound, when performed by expert hands, can still be used to monitor the elongation of the eye in patients treated with orthokeratology (Chan, Cho & Cheung, 2006).

1.5.2 Orthokeratology, axial length of the eye and refraction

In terms of myopic control, orthokeratology treatment would create a myopic peripheral defocus, minimizing eye growth and thereby slowing the myopia progression. In this regard, we found several investigations published in recent years: the first study was written by Cho, Cheung and Edwards, in 2005, then in 2009 Walline, Jones and Sinnott; Kakita, Hiraoka and Oshika in 2011, Santodomingo et al. and Hiraoka et al. in 2012, and finally, in 2013 Chen, Cheung and Cho, and then Charm and Cho, with the partial correction. This study, conducted by Charm and Cho in Hong Kong in 2013, compared the reduction of axial elongation of the eye in a group of children following the orthokeratology treatment and a group of children with simple monofocal corrective glasses. The children of both groups were aged between 8 and 11 years and a myopia greater than -5.00 D. After two years it resulted in a decrease of 63% in the increase of the axial length for children with orthokeratology treatment than children with single-vision glasses ($p = 0.005$) (Charm & Cho, 2013).

Now we analyze in more detail, three prospective studies that evaluated the effect of orthokeratology on myopia progression in children. Cho, Cheung and Edwards (2005), evaluated the changes of axial length in 35 Chinese children from 7 to 12 years of age, with orthokeratology lenses (for 2 years) and compared the change in axial length with a control group 35 children who used single-vision glasses. At the end of 24 months, the axial length has increased 0,25 mm more in the group of subjects with spectacle lenses compared to the group with orthokeratology.

In a subsequent study conducted in the United States, Walline, Jones and Sinnott (2009) compared the growth of the eye in 35 myopic children (8 to 11 years) who used contact lenses for orthokeratology with a control group which used soft contact lenses. After 2 years, the axial length of the group of soft contact lenses is increased by 0,32 mm more than the orthokeratology group.

Kakita, Hiraoka and Oshika (2011) compared the axial length growth in myopic children from 8 to 16 years, users of ortokeratologic contact lenses, relative to others of the control group with single-vision glasses. After 2 years of follow-up, the axial length in the group with eyeglass lenses, was increased by 0,22 mm more than in orthokeratology group. The study involved children with higher refractive errors (from -0,50 D to -10,00 D) than in previous studies (Kakita, Hiraoka & Oshika, 2011).

Myopia in children, increased more rapidly between 6 and 13 years the age (Cho, Cheung & Edwards, 2005; Walline, Jones & Sinnott, 2009).

It also appears that, in the study of Kakita, Hiraoka and Oshika (2011), the range of the selected myopic children could be too large and therefore have affected the data, also because manufacturers recommend a limit to -5,00 D, to better correct the defect.

These three studies were different in methodology. Cho, Cheung and Edwards (2005), and Walline, Jones & Sinnott (2009), have not considered the prospective control groups and, in both studies, several biometer ultrasound was used to measure the axial length of the prospective groups and in the historical control groups. On the contrary, Kakita, Hiraoka and Oshika (2011), to measure the axial length, they used a laser interferometry (Zeiss IOLMaster), without contact and with a resolution of 0,03 diopters (D).

Cho, Cheung and Edwards (2005) and Kakita, Hiraoka and Oshika (2011), selected Chinese and Japanese subjects, whereas Walline, Jones and Sinnott (2009), made the study in the United States and 86% of subjects completed the study, were classified as white.

Since the initial myopia and the progression in East Asian children are generally significantly higher that children from western countries, the results must consider the ethnic differences. Also the researchers observed in previous studies, corneal responses differences induced by contact lenses depending if they were Asian or non-Asian subjects (Hamano, Jacob & Senft, 2002).

Now we will describe in more detail, the study of Santodomingo which conducted in Spain in 2012 and, in my opinion, very well executed. Comparing the growth of the axial length of the eye into two groups, between 6 and 12 years of age, in a 2-year time. 31 children recruited for the orthokeratology treatment, while 30 children with simple single-vision glasses (Santodomingo-Rubido et al., 2012). All candidates were subjected to the anterior biomicroscopy, indirect microscopy fundus, evaluated the ability of binocular vision and analysis of visual refraction. Measurements were performed with the auto-refrattometer in cycloplegic (after instillation in both eyes of three drops of Cyclopentolate Hydrochloride 1%). Three evaluations with auto-refractometer for obtain an average refraction. Finally, the researchers detected the axial length measurements, and performed the corneal topography. Subjects in the SV (single vision) group used monofocal glasses, for distance, with the highest positive and negative lower power to achieve an optimal visual acuity. The OK subjects group used contact lenses Menicon Z NIGHT, and for the calculation of the design, the optometrists used the Menicon Professional Software Easy Fit (Menicon Co., Ltd., Nagoya, Japan). The subjects provided the MeniCare solution for disinfection, for daily cleaning and rinsing. Every week, Menicon Progent, intensive cleaner (Menicon Co., Ltd., Nagoya, Japan). After delivery of the lenses, subjects were monitored at intervals of 1, 6, 12, 18, and 24 months. The follow-up visits will be completed within two hours after waking. During the different visits, they replaced contact lenses or glasses only when it is presented a decrease of visual acuity line. Measurements of axial length were taken with the Zeiss IOLMaster (Carl Zeiss Jena GmbH, Jena, Germany). Three separate measures made, and wrote the average score. Corneal topography made with the Wavelight Allegro Topolyzer (Wavelight Laser Technologies AG, Erlangen, Germany). For the study recorder the first measurements in each eye. All subjects had a myopia between -0,50 D and -4,00 D and astigmatism was accepted no more than 1,00 D. Every six months was measured axial length and corneal topography and finally a refractive error in cycloplegia.

After two years recorded an average increase of the bulbar axial length of 0,47 mm for the orthokeratology group, versus 0,69 mm in the group of children with single-vision glasses (p=0,001). About the refraction, however, the effect on the spherical component was significant with a greater increase of negative refractive error in glasses group than the Ortho-K (the SV group showed an increase in myopia over 1 D). No significant changes on the value of the cylinder (see Figure 1.6.), (Santodomingo-Rubido et al., 2012).

	Baseline	6 Months	12 Months	18 Months	24 Months
Refractive components					
Sphere (D)					
OK	−2.20 ± 1.09	−0.19 ± 0.23	−0.22 ± 0.27	−0.21 ± 0.27	−0.34 ± 0.29
SV	−2.35 ± 1.17	−2.58 ± 1.24	−2.97 ± 1.24	−3.26 ± 1.28	−3.60 ± 1.38
Cylinder (D)					
OK	−0.29 ± 0.29	−0.31 ± 0.29	−0.33 ± 0.33	−0.30 ± 0.31	−0.24 ± 0.37
SV	−0.35 ± 0.34	−0.30 ± 0.33	−0.32 ± 0.33	−0.32 ± 0.40	−0.38 ± 0.35
Biometric components					
Axial length (mm)					
OK	24.49 ± 0.78	24.61 ± 0.79	24.71 ± 0.81	24.91 ± 0.79	24.96 ± 0.86
SV	24.26 ± 1.01	24.44 ± 1.01	24.63 ± 1.02	24.79 ± 0.98	24.95 ± 0.99

Fig. 1.6. Mean (+- SD) Refractive and Biometric Values for the Orthokeratology and Single Vision Spectacle Groups (Santodomingo-Rubido et al., 2012)

Another study, where 128 patients fitted with ortokeratology or glasses, is Zhu et al. (2014) study. The subjects were divided into groups of low, moderate and high myopia, and the analysis was periodically compare the axial length between the groups and subgroups with different degrees of ametropia. In two years of study we saw a reduction in the progression of myopia in children with low, moderate and high myopia. The axial elongation was slower in the group with orthokeratology. Similar results are found in the subgroups. In the group with low and moderate myopia, the annual increase in axial length was significantly different between the Ortho-K and the control groups (during both years). In the group of high myopia, significant differences were found only in the first year. In the two years, the axial length was significantly associated with young age and early treatment.

The data from the current study remarks the idea that Ortho-K can decrease progression of myopia by approximately half compared with spectacle lenses. The major strength of this study is the inclusion of a greater number of subjects with moderate and high myopia compared to previous studies (Zhu et al., 2014). This study, therefore, is agree with Cho and Cheung (2012). Both agree that younger myopic children, will benefit most from the ortho-k treatment, compared to older children. There was no relationship with sex, the initial refractive error, the initial axial length, the initial curvature of the cornea (Cho & Cheung, 2012).

To integrate this exhibition part of previous international studies, I remember the study by Wen et al. (2015), which were included eight studies involving 769 subjects average 10 years of age (±1,52). The studies included were subjected to a meta-analysis. The meta-analysis is a more authoritative work than the individual analyzed, because allows a greater statistical power. A 2-year follow-up, a statistically significant difference was observed in the change of the axial length between the Ortho-K and control groups, with a weighted mean difference (WMD) -0,25 mm. The progression of axial elongation is decreased about 50% and the rate of abandonment of treatment (drop out) was similar like in the control group. Also from this meta-analysis, it is concluded that the Orthokeratology, if done with care and precise monitoring, is effective and fully accepted by young users. The analyzed data showed no statistically significant differences between Asians and Caucasians children both for efficacy and acceptability, and the results do not substantially contradict the original results including orthokeratology and control. In both groups, measurements with A-scan and IOL Master, showed no significant differences. It's reported no case of serious complication with a result of permanent damage to the eyes (Wen et al., 2015).

In Fig.1.7., the table shows the axial length efficacy, in millimeters, and the orthokeratology acceptability for each study analyzed, for a period of 2 years. The studies selected are the most important made in recent years (since 2005) for the myopic control with orthokeratology.

Efficacy (mean AL change) and acceptability (dropout rate) in each study at 2-year follow-up.

	Mean AL change (mm)		Dropout rate (dropouts/total)	
	Treatment group	Control group	Treatment group	Control group
Cho et al. (2005)	0.29 ± 0.27	0.54 ± 0.27	8/43	NA
Walline et al. (2009)	0.25 ± 0.27	0.57 ± 0.40	12/40	NA
Kakita et al. (2011)	0.39 ± 0.27	0.61 ± 0.24	3/45	10/60
Cho and Cheung (2012)	0.36 ± 0.24	0.63 ± 0.26	14/51	10/51
Hiraoka et al. (2012)	0.45 ± 0.21	0.71 ± 0.40	7/29	9/30
Santodomingo-Rubido et al. (2012)	0.47 ± 0.20	0.69 ± 0.30	2/31	6/30
Charm and Cho (2013)	0.19 ± 0.21	0.51 ± 0.32	14/26	10/26
Chen et al. (2013)	0.31 ± 0.27	0.64 ± 0.31	8/43	14/37

AL = axial length; NA = not available.

Fig.1.7. Efficacy (mean AL change) and acceptability (dropout rate) in all analyzed studies (Wen et al., 2015)

In a randomized prospective study of 26 Eastern Asia children, 10.8 - 17 years of age, for a period of 12 months, subjects were fitted with Ortho-K lenses overnight in one eye, and conventional lenses rigid gas permeable (GP) for the day, in the contralateral (Swarbrick et al., 2015). The axial length was monitored from the baseline, every 3 months, with a biometer IOL Master, corneal topography performed with Medmont E300 and the objective refraction made with auto-refractometer Shin-Nippon NVision-K 5001. The purpose was to verify the effect of night Orthokeratology, on the growth of axial length in the East Asian children with progressive myopia. After 6 months of treatment, the axial length was increased by 0,04 ± 0,06 mm (mean ± standard deviation) in the eye with a GP ($p=0,011$), but showed no change (-0,02±0,05 mm) in the eye with OK ($p=0,888$). During the second phase (after other 6 months) of lens wear, in the eye OK there was no change compared to the baseline axial length (at 12 months -0,04±0,08 mm; $p=0,218$). However, in the eye with GP, the axial length increase (at 12 months), was significant (0,09±0,09 mm, $p<0,001$). During the study, the eye with daytime GP lens, showed a progressive increase in axial length. These results show that, at least in the first months, with the nocturnal orthokeratology, it inhibits the axial growth of the eye and also the progression of myopia than conventional GP lenses.

From a recent Chinese study (He et al., 2016), it appears again the orthokeratology effective in reducing the development of myopia in Chinese children with low to moderate myopia.

The axial elongation, which is an important parameter reflecting the progression of myopia, was measured with IOL Master, every time from the same masked examiner and was compared between the groups after 1 year. The subjects were divided into two subgroups according to age, to study the development of myopia at different ages. After one year, the average axial elongation was 0,27±0,17 mm in the Ortho-K group and 0,38±0,13 mm in the control group, with a significant difference between the two groups ($p < 0.001$). In conclusion it is clear that the Ortho-K lenses are effective in controlling the progression of myopia in Chinese children, especially in younger children and children with higher myopia (He et al., 2016).

The Orthokeratology, compared to single-vision glasses, demonstrated an effective treatment option to slow the axial elongation in older children who early onset of myopia, were female, had low myopia beginning of the treatment, had greater power of the cornea, had the cornea shape more prolate, larger iris and pupil diameter, and had parents with low myopia (Santodomingo-Rubido et al., 2013).

2. RESEARCH

2.1. Aim and tasks of research

This prospective study will compare the myopic progression of two groups of children, one wearing single vision spectacle lenses and one wearing orthokeratology lenses. The primary measure will be axial length.

A prospective study of 120 eyes, for eighteen months, comparing Ortho-K wearing group and spectacles wearing control-group, matched for myopic refraction, outdoor activities, time not at school and axial length.

Variable: Time spent outdoor (the average time performing the activity will be calculated as time spent during school year × 8/12 + time spent in vacations × 4/12).

2.2. Participants

The duration of the study was 18 months, from January 2015 to June 2016. I selected from my database children and adolescents from 7 to 16 years, 30 subjects (already OK treatment) users of Ortho-k contact lenses with symmetrical design (average years: 13.01±2.14) and 30 subjects with spectacles vision (SV) organic lenses (n=1.5) as control group (average years: 14.01±1.61). In the initial period of recruitment (Jan 2015) all subjects selected for the study were subjected to slit lamp examination, to exclude issues to the corneal anterior segment.

2.3. Methods

There are several lens designs that can help better control the progression of myopia, even in cases of medium and high astigmatism. Toric lenses in the periphery and bitoric, definitely get a better centering on corneal toric profiles. Despite the different technical possibilities, available to the orthokeratology expert, we considered only spherical design to speed up the application and to simplify the selection of candidates.

We performed a corneal topography to exclude dystrophies of the cornea and finally, we excluded amblyopic subjects. All examinations and consultations were provided free of charge and in every meeting for follow-up tests, we honored patients with products for the maintenance of Ortho-k lenses (for the OK group) and with a voucher (for the SV group).

Figure 2.1. shows candidates recruited for the study.

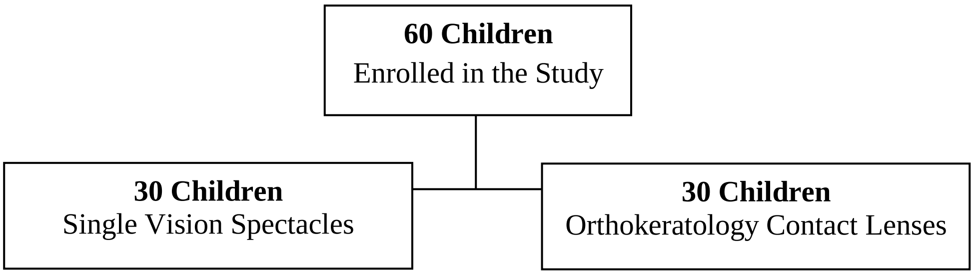


Figure 2.1. Subjects recruited for the study.

2.3.1 Inclusion / Exclusion criteria

The selection of subjects was made according to the following inclusion criteria:

- **Age range:** from 7 to 16 years old;
- **Refraction:** SF from -0,75D to -4,50D and CYL≤1,50 D with the rule astigmatism (AX 180° ± 30°);
- **Intraocular pressure:** not exceeding 21 mm/Hg;
- **Absence of Amblyopia and/or Congenital cataracts**;
- **Regular attendance to office appointments**;
- They did **not discontinue the use of Ortho-k lenses more than 3 nights a month (only for the OK group)**;
- **Caucasian** (Italian);

The exclusion criteria were:

- Presence of eye disease: Keratoconus, Anterior segment Dystrophies, Outcomes of Herpetic Keratitis, Keratoplasty, Systemic Disease;
- Use of drugs, which may interfere with ocular physiology and compromise lens performance;
- Refractive astigmatism > 1,50 D;
- Limbus to limbus astigmatism;
- Contraindications presence: severe hypolacrimia, blepharitis, allergies, incomplete winking, chronic fatigue, significant anemia (microcythemia);

2.3.2 Instruments for the researches:

- We used a single spherical design for OK Lenses. A set of trial lenses in Boston XO.
- Auto-refractometer TOPCON RM A3000: to determine precise refractive errors we used techniques of standard subjective refraction, auto-refractometry and retinoscopy;
- LCD digital optotype MOS by TECNOVISION (Trento – Italy): we used targets presented in the traditional way and according to the most used standards (LogMAR measurement system);
- Phoropter L-7040 by INAMI & Co. Ltd. 24-2, Hongo 3-chome, Bunkyo-ku, Tokyo 113-0003, Japan;
- Heine BETA 200 SPOT retinoscope;
- Slit lamp SL 980 by CSO (Florence – Italy): the slit lamp was used to monitor the health and integrity of the cornea at each follow-up session;
- Fluorescein: corneal integrity was evaluated by topical application of sodium fluorescein;
- Corneal Topographer Keratron Piccolo by OPTIKON 2000 S.p.a. (Rome – Italy);
- Ultrasound SCAN Biometer AL 100 by TOMEY CORPORATION (figure 2.2.) (Noritakeshinmachi, Nishi–Ku, Nagoya, Aichi, Japan): three measurements were taken at each visit and the average of 3 was used as the representative value;

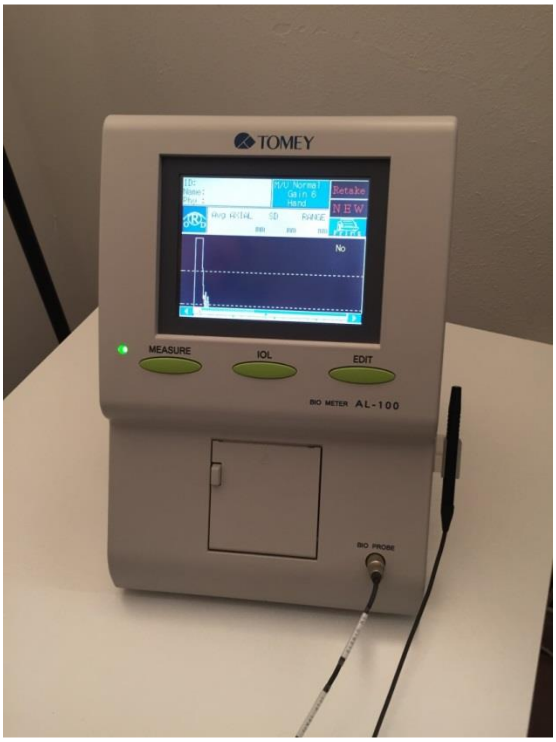


Fig. 2.2. Ultrasound SCAN Biometer AL 100 by TOMEY CORPORATION.

2.3.3 Informed Consent and Permission for Research - Questionnaire

We calculated the time spent outdoors (the average time performing the activity will be calculated as time spent during school year × 8/12 + time spent in vacations × 4/12) by our candidates from each group.

We did sign to all parents a permission for the realization of this research; such research is supervised by the Ethics Commission for Scientific Research of the University of Latvia.
The parents of Ortho-K group subjects signed an informed consent with the benefits and the risks of such research, and where it was indicated the optometrist's private telephone number (figure 2.3.).

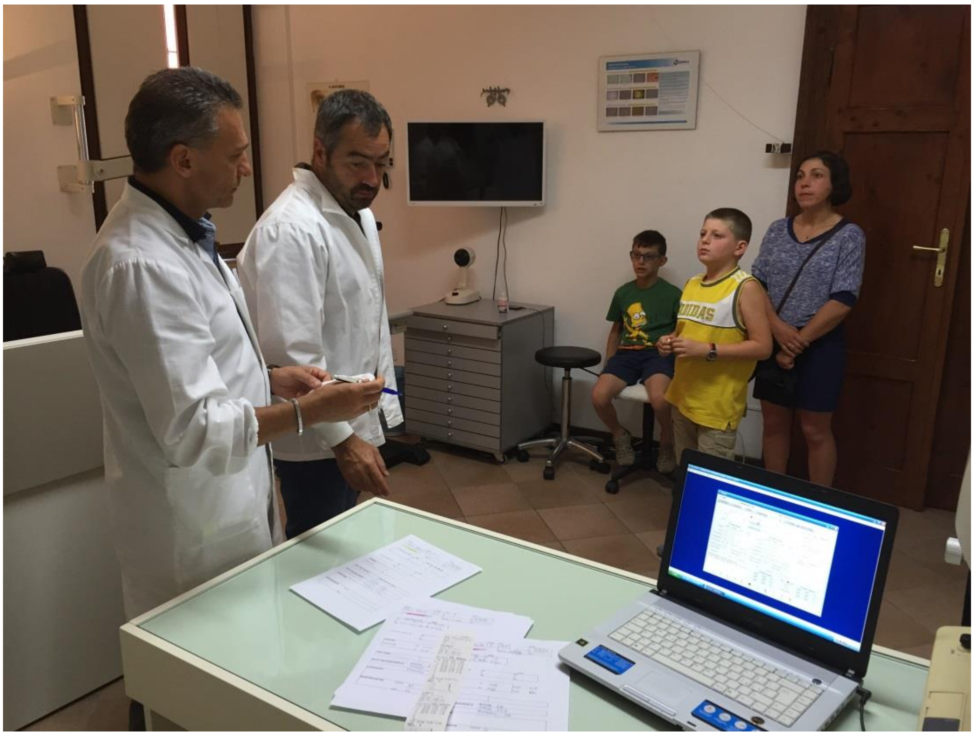


Fig. 2.3. Informed consent.

2.3.4 First data collecting in the SV control group

The reference initial measurements were the following:

- Auto-refractometry without cycloplegy;
- Retinoscopy for distance and for near;
- Optometric examination using a phoropter, trial lenses and trial spectacles;

We prescribed a correction for distance using the maximum positive or minimum negative criteria, to obtain an optimal visual acuity. It was asked to them to use spectacles all the time.

A digital optotype system was used for the assessment of monocular visual acuity, this to ensure accuracy and reproducibility (MOS System). Then we performed corneal topography with previous instillation of “Contopharma Lens & Lid” tear substitute (five minutes before measurements) for the best tear quality and distribution. Finally, the ocular biometry was performed to each eye after instillation of Novesina (Oxybuprocaine hydrochloride). While waiting before the examination, we did the questions relating to the questionnaire.

2.3.5 OK lens application criteria and Protocol for an effective and safe treatment in Children / Adolescent

After the first meeting with the child and parents, in which the orthokeratologic technique was explained in great detail, some demonstration videos were shown and the benefits, the risks and the protocol were analyzed, we set the next appointment (about 90 minutes).

In this occasion, the process is:

- Determine the **Myopic Refractive Power** to compensate with the maximum positive or minimum negative power technique;
- **Biomicroscopy** for the pre-application evaluation;
- **Corneal Topography** with previous instillation (five minutes before measurement) of “Contopharma Lens & Lid” tear substitute. The technique used to define the lens for the treatment (in pre Ortho-k phase) is to produce at least 8 maps for each eye and to extrapolate the best one (the average map). This map was used to read the average parameters of each eye: flat radius Sim K, average eccentricity flat radius at 8 mm from the center. We detected the corneal diameter with two techniques (caliber function and extrapolation to three points) and we did average. At this point trial lens was selected from the set, taking the one that showed the base radius of curvature, the corrective power and the right diameter (it is recommended the lower one, of about 1,2 mm with respect to the total corneal diameter).

We applied the trial lens (set it for 15 minutes), we have instilled fluorescein and using a slit lamp we observed the fluoresceinic pattern (alignment of the lens curves). The ideal lens is the one centered with good position, with vertical motion range of 0,5 mm, the slightest touch in the optical zone, suitable lifting in the "reservoir area" and subsequent alignment on average outskirts with last curve that ensures a sufficient tear replacement and that it does not lock in the epithelium. The corrective effect, lens applied, must ensure a monocular visual acuity of at least 0,00 logMAR.

After choosing the final lens, we provided to the subject instructions for the insertion and the removal. In the case of younger children, we decided to ask parents to leave the study and wait in the waiting room, then they were called up once the child was able to insert and remove the lens. Several precautions are used to facilitate the process and create less anxiety to little patient. To facilitate the impact of the lens on the eye and avoid air bubbles, it is necessary to put a drop of unit dose saline solution in the inner part of the lens, then apply horizontally (parallel to the table). Only in the case of hypersensitivity, it is allowed to use a solution based on cellulose (I Confort – Conto Pharma). To improve the application practice, we taught to put a drop of I Confort on the forefinger and apply it in the eye. This solution of high concentration cellulose, is particularly viscoelastic and helps to keep the lens in equilibrium on the finger during insertion into the eye. At the first meeting, the optometrist inserts the lens and possibly applies a cryogenic patch to reduce discomfort. We taught the subject to hold with his thumbs the upper eyelids and look down, or to close the eye and place his palms of the hand on the eyeball. Then we taught to lay the forefinger directly on the lens, to reduce fear and increase confidence with the lens inserted. Subsequently we have provided instructions for the removal with a small rubber suction cup. If the lens, in the morning, is too adherent to the corneal epithelium, we teach to push (with the help of the lower eyelid) the lens upwards to admit fluid under the lens or, with closed eyes, directing the glance to the right and left. This facilitates the removal.

Knowing that the suction cup is the tool that can be fully contaminate, as highlighted in the study by Cho, Boost and Cheng (2009), where it is seen that 85% of the subjects does not regularly replace them and that 59% of the subjects does not regularly disinfect them, in our protocol it is written and recommended to replace it every three months (it is inserted in the quarterly pack of solutions for disinfection). Subsequently, in the same session, the child should be able to apply the lens and only at great difficulty, it requires the intervention of a parent to help him. Finally, it shows parents the procedure for the correct cleaning of the lenses. After the first trial night, the next morning (the first control), the subject must go to the optometric clinic, even with lenses inserted. The post application control has the purpose to verify the compliance of the wearer and to observe the lens position at slit lamp examination. After removing the lens, we look at the health of the cornea in biomicroscopy, we check it by instilling fluorescein, we analyze the visual acuity and perform a corneal map to monitor the accuracy of the obtained molding.

If, during the control, no problems appear, we proceed with the order of the final lenses and the trial are returned, interrupting the application. After delivering the final lenses, we set additional appointments for post-controls, after one week, after one month, after 3 months, then the protocol provides optometric controls every six months; it is also planned an annual ophthalmologic evaluation. In this regard, in our practice, it is routine practice to deliver the OK-candidate a written request where it requires a specific survey ophthalmologist to rule out any problems, the absence of contraindications and for a confirmation to continue the application work.

2.3.6 Basic Data collection in the OK group, for research

At the time of the initial data collection, the subjects of the OK group already used orthokeratologic lenses with reverse geometry, all symmetrical, spherical geometry (no toric or bitoric) with standardized curves produced by an Italian company: TS Lac - Milan. These lenses (we use for 15 years) have special geometry that ensure very good centering.

The lenses were calculated with a fixed average eccentricity (in the corneal area to 8 mm) of 0,41. At the beginning of our study, in the subject of the OK group, being wearers of night lenses from more time, in the first meeting the auto-refractometry was not performed. This, in fact, is an unreliable examination due to the shape of the cornea obtained by the molding. Subjects came in the clinic during the morning (within three hours after the removal of the lenses) and, to everybody, we evaluated the monocular visual acuity for distance (with a translucent occluder on the other eye) with the digital MOS system to ensure accuracy and reproducibility; it is observed the ocular anterior segment with biomicroscope.

We performed the corneal topography after instillation (five minutes before the survey) of “Contopharma Lens & Lid” tear substitute. Only in the case of insufficient visual acuity, it was decided to apply the lenses and re-check visual acuity in the over-refraction. Considering that the lenses allowed to see perfectly for distance, the way to check any deterioration was given by the over-refraction. The lens necessary to insert in over-refraction to obtain the visual acuity of 0,00 LogMar showed worsening myopic. In these cases we have provided for the replacement of the lenses updating the corrective effect. Then we instilled Novesina for ocular biometry examination. While the waiting before the exam we submitted the questionnaire.

Variables that can influence the application are: eyelid tension, tear density, corneal hardness (resistance). The tear density has alimentary and chemical/pharmacological origins. Usually children have high eyelid tension, perfect tear density and low corneal hardness. It’s more difficult to treat the eyes with low corneal eccentricity and with very flat radii.

2.3.7 Measurement Techniques

All follow-up visits were performed in the morning not later than three hours after the removal of the contact lenses (for the OK group), with the aim to evaluate more precisely the parameters (molding with corneal topography, visual acuity and ocular biometry). All the subjects of the study were followed for 18 months (from January 2015 to June 2016). The visits were performed with the following frequency: the start of the study, 6th months, 12th months, and finally 18th month. In the intermediate visits we only evaluated the visual acuity, retinoscopy, biomicroscopy, topography (only for OK group), and (only for the control group) we performed the autorefractometry

2.3.8 Visual acuity and subjective refraction

The monocular refractive error in each eye was determined using the phoropter and trial lenses. We asked all subjects to read the letters proposed with MOS system and we recorded the monocular visual acuity. In SV group, only in the case where the visual acuity had decreased by one line, the new lenses for spectacles were provided. If, in the OK group, it is a decrease in visual acuity by one line, we re-examined the visual acuity with lenses applied (after cleaning and rinsing). Only in this way, working in over-refraction, we reached new corrective effect to be ordered on the new contact lenses. Contact lenses have been replaced anyway at the 12th month. It has never been necessary to replace them before the deadline.

2.3.9 Anterior ocular health and Corneal Topography

Slit lamp was used to evaluate the anterior ocular health and detect any changes caused by OK lenses.

Corneal topography was performed by the Keratron topographer (OPTIKON 2000, Rome, Italy). This model has a small cone measuring 28 Placido rings with a corneal coverage up to 90%. We always have the instrument calibrated with the calibration ball, before each measurement cycle. During the periodic inspections the topography is needed to monitor and control the shaping of the cornea (OK group). We should always ensure centering to reduce aberrations, avoid warpage, islands or anything else.

2.3.10 Axial length (AL)

Measurements of axial length were collected with AL 100 SCAN biometer (figure 2.4.). The axial length (AL) is the measurement of the axial length of the eyeball taken along the symmetry axis and it is the distance from the cornea to the retinal surface. It is generally accepted that the myopic progression is given mainly by the AL. The higher AL, the higher the myopia. We took a minimum of 10 readings for measurement (we performed at least two average measurements for each eye) and recorded the average score.

Fig. 2.4. Measurements of axial length with AL 100 SCAN biometer.

To validate the accuracy of this instrument, we measured the ocular axial length of a volunteer subject not included in this study, and then we compared the measurements taken at the same person with a Zeiss IOL Master biometer (Germany, Jena) available in Vista Vision Eye Clinic in Verona. Then, we made a further test interfacing biometric measurements taken to another subject (not included in the study) with our Tomey biometer, comparing them with those taken with a Topcon instrument "ALADIN" made available by the Harmony Clinic in Mantova. We concluded that the Tomey biometer used for our study is reliable and accurate, only if used wisely. For this, measurements were always performed by the same experienced operator, ophthalmologist, collaborator in our clinics, to ensure maximum reliability and repeatability. The instrument has been set to "automatic" mode, which means that the measurement is blocked and obtained when the probe is perpendicular to the ocular surfaces traversed by the wave, which specifically impacts on the cornea, crystalline lens, retina. An involuntary eye movement of the subject, during the measurement, may affect the accuracy of the survey. The subjects were instructed to observe a target set on the wall and they were advised not to change the look direction. The measurement precision was achieved thanks to the expert hands of the medical examiner that uses in its daily practice and for some time, the biometer in question.

2.3.11 Materials

The control group used spectacles with monofocal lenses (spherical design) of Opto IN (San Giovanni Lupatoto - Verona - Italy), in organic material n=1,50 (CR-39). The ophthalmic lenses were modified according to the visual acuity determined in the follow-up sessions. The lenses used in Ortho-k treatment were built in Boston XO (Polymer Technology - USA) with a nominal Dk value of 100×10^{-11} (cm2 / sec) [ml O2 / (ml x mmHg)].

2.3.11.1 Specification for the OK lenses

Name	ESA ORTHO6
Producer	TS LAC
Material	BOSTON XO
Design	REVERSE GEOMETRY ESACURVA
DK	100×10^{-11} (cm2 . mLO2) / (sec . ml . mmHg)
Nominal Base Curve	from 7,00 to 9,00 mm (0,05 mm step)
	correction effect from -0,25 to -8,00 (step 0,25 D)
Optic Zone Diameter (mm)	from 5,00 to 7,00 mm (0,10 mm step)
Total Diameter (mm)	from 10,00 a 12,00 mm (0,20 mm step)
Thickness at the center	from 0,15 a 0,32 (standard 0,22 mm)

2.3.11.2 Solutions for the maintenance of the OK Lenses

All subjects were instructed not to use the tap water to avoid the risk of acantameba keratitis. We communicated patients not to rinse the containers with water, but to use saline solution. All subjects of the OK group used the following products for daily care of the lenses:

- I-Clean ContoPharma (ContoPharma AGEichzun 7-CH-3800 Interlaken) for daily cleansing (rub each lens surface for at least 10 seconds);
- Peroxide Tab in One, ContoPharma, with chlorophyll catalase (used for daily disinfection - replace every day);
- Saline single-dose solution without preservatives, Salisin of Shalcon (Schalcon S.p.A. Rome). To rinse lens before insertion;
- Tears of humectants ContoPharma Drop & See for corneal re-epithelialization and as supplement. One drop to be applied to each eye before and after removal;
- Lens case for daily storage. Rinse the case with saline, then air dry without closing the caps. Replace the case with every new bottle of Tab in One solution;

- Rubber suction cup to facilitate the removal of the lenses;
- Periodic Enzyme, Progent Menicon (Menicon Co., Ltd. Aoi 3, Naka-ku, Nagoya 460-0006 Japan) for the intensive cleaning of the lenses (1 treatment per month, for the first half and after the 6th month, 1 treatment every 15 days). This allows to remove even microscopic deposits inside of the lens, which can affect the corneal moulding impair vision and ocular health.

2.4. Results

Statistical analyses were conducted using Microsoft Excel and Quick Statistics Calculators. Below there is table 2.1. summarizing descriptions, units of measurements and acronyms used to produce charts and histograms.

DESCRIPTION		Units of measure	Acr
PROGR			
CODE			CODE
SURNAME			SU
NAME			NA
BORN			BO
AGE Y		Year	Y
GENDER			M or F
DATE OF EXAM			DATE
GROUP			
SPECTACLES VISION			SV
ORTHO K			OK
RIGHT SPHERICAL EQUIVALENT		D	RSE
LEFT SPHERICAL EQUIVALENT		D	LSE
RIGHT BIOMETRICS		mm	RB
LEFT BIOMETRICS		mm	LB
STANDARD ERROR			SEr
STANDARD DEVIATION			SD
AVERAGE VALUES			(Mean±SD)

Tab. 2.1. Legend.

In Table 2.2. the data collected for the SV group glasses at the beginning of the study (2015) are grouped. From the elaboration it detects an average myopia of -2,47±1,16 D (SE) for the right eye and -2,45±1,18 D (SE) for the left eye. The average for biometrics in the right eyes was 24,12±0,98 mm and for left eye was 24,09±0,98 mm.

progr	Code	BORN	AGE Y	GENDER	DATE	GROUP	R S E (D)	L S E (D)	R BIO (mm)	L BIO (mm)
1	AGF	16/06/2000	14,6	F	02/01/2015	GLASSES	-3,25	-3,25	23,45	23,36
2	BMF	04/03/2003	11,8	F	02/01/2015	GLASSES	-1,38	-0,88	21,65	21,77
3	BSM	03/06/2005	9,6	M	02/01/2015	GLASSES	-1,63	-1,88	23,38	23,39
4	BFM	11/12/2001	13,1	M	02/01/2015	GLASSES	-2,13	-2,63	24,40	24,27
5	BDM	08/01/2001	14	M	02/01/2015	GLASSES	-4,00	-4,00	24,57	24,21
6	BFM	19/09/2005	9,3	M	02/01/2015	GLASSES	-1,38	-1,88	24,46	24,52
7	BAM	23/05/2006	8,6	M	02/01/2015	GLASSES	-4,50	-4,50	24,80	24,66
8	BAF	02/01/1999	16	F	02/01/2015	GLASSES	-2,25	-2,00	23,76	23,68
9	BLF	24/07/2000	14,5	F	02/01/2015	GLASSES	-4,25	-4,50	23,98	24,93
10	BAF	22/12/2000	14,1	F	02/01/2015	GLASSES	-1,88	-2,38	24,46	24,85
11	BLM	26/11/2000	14,1	M	02/01/2015	GLASSES	-3,50	-3,25	25,15	25,03
12	BAM	29/03/2002	12,8	M	02/01/2015	GLASSES	-1,25	-1,13	25,32	25,09
13	CAF	12/01/2000	15	F	02/01/2015	GLASSES	-3,00	-3,25	22,96	22,90
14	CGF	24/03/2000	14,8	F	02/01/2015	GLASSES	-2,50	-2,63	23,01	23,29
15	CDM	17/09/2000	14,3	M	02/01/2015	GLASSES	-4,50	-4,50	25,68	25,66
16	GLM	03/10/2000	14,3	M	02/01/2015	GLASSES	-1,00	-1,25	24,82	24,86
17	GLF	05/10/2000	14,3	F	02/01/2015	GLASSES	-1,63	-1,13	23,15	22,39
18	LCM	27/10/2000	14,2	M	02/01/2015	GLASSES	-2,00	-2,25	23,91	24,08
19	LAF	09/09/2000	14,4	F	02/01/2015	GLASSES	-1,88	-2,13	25,09	24,75
20	LSF	06/01/2003	12	F	02/01/2015	GLASSES	-3,50	-3,13	24,57	25,05
21	MVF	15/02/2001	13,9	F	02/01/2015	GLASSES	-4,50	-4,13	25,29	24,78
22	MAF	12/05/2005	9,7	F	02/01/2015	GLASSES	-1,38	-1,38	23,34	22,99
23	MAF	23/12/2000	14,1	F	02/01/2015	GLASSES	-2,13	-1,50	24,38	23,83
24	PGM	21/08/2000	14,4	M	02/01/2015	GLASSES	-3,25	-3,50	26,26	26,17
25	PRM	13/12/2000	14,1	M	02/01/2015	GLASSES	-1,25	-1,25	23,68	23,45
26	PTM	20/05/2008	6,7	M	02/01/2015	GLASSES	-2,50	-2,50	23,73	24,02
27	RNF	04/08/2001	13,5	F	02/01/2015	GLASSES	-1,13	-1,13	22,93	22,94
28	SEF	15/12/2002	12,1	F	02/01/2015	GLASSES	-1,25	-1,00	23,62	23,40
29	VEF	14/11/2001	13,2	F	02/01/2015	GLASSES	-4,13	-3,88	24,88	24,78
30	TAF	29/03/2002	12,8	F	02/01/2015	GLASSES	-1,25	-0,75	22,93	23,46
Mean			**13,01**				**-2,47**	**-2,45**	**24,12**	**24,09**
SD			**2,14**				**1,16**	**1,18**	**0,98**	**0,98**
SEr							**0,22**	**0,22**	**0,18**	**0,18**

Tab. 2.2. SV group, at the beginning of the study (2015).

In Table 2.3. the data collected for the ORTHO-K group at baseline (2015) are grouped. From the elaboration it detects an average myopia of -2,76±1,07 D (SE) for the right eye and -2,69 ±0,93 D (SE) for the left eye. The average for biometrics in the right eyes was 24,26±0,88 mm and for left eye was 24,23±0,93 mm.

progr	Code	BORN	AGE Y	GENDER	DATE	GROUP	R S E (D)	L S E (D)	R BIO (mm)	L BIO (mm)
1	BLF	26/11/2001	13,1	F	02/01/2015	ORTHO K	-2,25	-2,25	22,37	22,92
2	BRF	10/03/2001	13,8	F	02/01/2015	ORTHO K	-2,88	-3,13	24,59	24,20
3	BAM	01/01/2000	15	M	02/01/2015	ORTHO K	-3,13	-2,38	24,65	24,35
4	BFM	18/08/2000	14,4	M	02/01/2015	ORTHO K	-4,00	-4,00	25,58	25,65
5	BNM	19/01/2000	15	M	02/01/2015	ORTHO K	-2,00	-2,25	25,06	25,67
6	BAF	06/10/2003	11,2	F	02/01/2015	ORTHO K	-3,25	-3,00	23,61	23,61
7	BCF	15/01/1999	16	F	02/01/2015	ORTHO K	-2,00	-2,00	25,12	25,18
8	BAM	16/06/2000	14,6	M	02/01/2015	ORTHO K	-1,00	-2,00	22,77	22,81
9	BGF	16/03/2001	13,8	F	02/01/2015	ORTHO K	-4,50	-3,88	25,29	24,43
10	CMM	23/04/2000	14,7	M	02/01/2015	ORTHO K	-1,00	-3,00	23,97	25,16
11	CLF	27/05/2002	12,6	F	02/01/2015	ORTHO K	-2,75	-2,63	23,68	23,71
12	CGF	12/05/2000	14,6	F	02/01/2015	ORTHO K	-4,00	-2,63	23,93	23,55
13	CBF	04/06/2005	9,6	F	02/01/2015	ORTHO K	-1,75	-1,50	23,49	23,44
14	FAM	01/10/2005	9,3	M	02/01/2015	ORTHO K	-1,25	-1,00	24,54	23,79
15	FRM	19/05/2000	14,6	M	02/01/2015	ORTHO K	-2,25	-2,50	24,56	24,44
16	FCF	17/07/2000	14,5	F	02/01/2015	ORTHO K	-2,75	-2,13	23,87	23,24
17	FDM	07/07/2000	14,5	M	02/01/2015	ORTHO K	-3,25	-1,25	24,03	23,09
18	GGF	21/09/2000	14,3	F	02/01/2015	ORTHO K	-2,25	-1,75	24,63	24,34
19	GDM	01/02/2000	14,9	M	02/01/2015	ORTHO K	-2,50	-2,88	23,95	23,90
20	MLF	07/05/2000	14,7	F	02/01/2015	ORTHO K	-3,38	-3,50	23,51	23,87
21	MIF	21/10/2000	14,2	F	02/01/2015	ORTHO K	-4,00	-4,13	24,18	24,54
22	NMF	17/12/2000	14	F	02/01/2015	ORTHO K	-2,50	-3,50	23,69	24,36
23	NCF	12/07/2001	13,5	F	02/01/2015	ORTHO K	-4,50	-4,50	24,97	25,23
24	RAF	28/01/1999	15,9	F	02/01/2015	ORTHO K	-3,25	-2,50	25,74	24,80
25	SMM	05/07/2001	13,5	M	02/01/2015	ORTHO K	-4,50	-4,13	26,14	26,69
26	SSF	25/07/2002	12,4	F	02/01/2015	ORTHO K	-3,75	-3,75	24,06	24,18
27	SAM	28/04/2000	14,7	M	02/01/2015	ORTHO K	-1,00	-1,25	22,71	22,45
28	TDF	22/01/1999	16	F	02/01/2015	ORTHO K	-2,63	-3,25	23,60	23,62
29	ZAM	26/03/2000	14,8	M	02/01/2015	ORTHO K	-1,00	-2,25	24,41	25,01
30	TLM	17/01/1999	16	M	02/01/2015	ORTHO K	-3,50	-1,88	25,23	24,56
Mean			**14,01**				**-2,76**	**-2,69**	**24,26**	**24,23**
SD			**1,61**				**1,07**	**0,93**	**0,88**	**0,93**
SEr							**0,20**	**0,17**	**0,16**	**0,17**

Tab. 2.3. OK group, at the beginning of the study (2015).

Table 2.4. shows the data collected for the SV spectacles group at the end of the study (2016). From the elaboration, we found an average myopia of -2,89±1,08 D (SE) for the right eye and -2,84±1,07 D (SE) for the left eye. The average for the biometry in right eyes was 24,34±0,98 mm and in left eyes is 24,27±0,97 mm.

progr	Code	BORN	AGE Y	GENDER	DATE	GROUP	R S E (D)	L S E (D)	R BIO (mm)	L BIO (mm)
1	AGF	16/06/2000	16	F	30/06/2016	GLASSES	-3,25	-3,25	23,46	23,40
2	BMF	04/03/2003	13,3	F	30/06/2016	GLASSES	-2,50	-2,25	21,98	21,77
3	BSM	03/06/2005	11,1	M	30/06/2016	GLASSES	-2,25	-2,25	23,37	23,34
4	BFM	11/12/2001	14,6	M	30/06/2016	GLASSES	-2,38	-3,13	24,52	24,47
5	BDM	08/01/2001	15,5	M	30/06/2016	GLASSES	-4,25	-4,00	24,57	24,21
6	BFM	19/09/2005	10,8	M	30/06/2016	GLASSES	-2,13	-2,63	24,56	24,77
7	BAM	23/05/2006	10,1	M	30/06/2016	GLASSES	-4,50	-5,00	24,80	25,11
8	BAF	02/01/1999	17,5	F	30/06/2016	GLASSES	-3,00	-2,25	23,76	23,67
9	BLF	24/07/2000	15,9	F	30/06/2016	GLASSES	-4,75	-4,50	23,98	24,93
10	BAF	22/12/2000	15,5	F	30/06/2016	GLASSES	-2,38	-2,88	25,43	25,27
11	BLM	26/11/2000	15,6	M	30/06/2016	GLASSES	-3,88	-3,88	25,73	25,68
12	BAM	29/03/2002	14,3	M	30/06/2016	GLASSES	-2,00	-1,75	25,32	25,08
13	CAF	12/01/2000	16,5	F	30/06/2016	GLASSES	-3,00	-3,25	22,96	22,90
14	CGF	24/03/2000	16,3	F	30/06/2016	GLASSES	-2,75	-2,75	23,50	23,68
15	CDM	17/09/2000	15,8	M	30/06/2016	GLASSES	-4,75	-5,00	26,07	25,72
16	GLM	03/10/2000	15,8	M	30/06/2016	GLASSES	-1,00	-1,25	24,82	24,86
17	GLF	05/10/2000	15,7	F	30/06/2016	GLASSES	-1,63	-1,13	23,23	22,87
18	LCM	27/10/2000	15,7	M	30/06/2016	GLASSES	-2,25	-2,50	23,99	24,33
19	LAF	09/09/2000	15,8	F	30/06/2016	GLASSES	-1,88	-2,13	25,09	24,72
20	LSF	06/01/2003	13,5	F	30/06/2016	GLASSES	-4,00	-3,38	25,39	25,05
21	MVF	15/02/2001	15,4	F	30/06/2016	GLASSES	-4,50	-4,13	25,37	24,95
22	MAF	12/05/2005	11,1	F	30/06/2016	GLASSES	-2,25	-2,00	23,95	23,73
23	MAF	23/12/2000	15,5	F	30/06/2016	GLASSES	-2,75	-2,00	24,57	24,39
24	PGM	21/08/2000	15,9	M	30/06/2016	GLASSES	-3,25	-3,75	26,26	26,17
25	PRM	13/12/2000	15,6	M	30/06/2016	GLASSES	-1,25	-1,50	23,64	23,42
26	PTM	20/05/2008	8,1	M	30/06/2016	GLASSES	-3,50	-3,38	23,79	24,48
27	RNF	04/08/2001	14,9	F	30/06/2016	GLASSES	-2,00	-2,25	23,71	23,36
28	SEF	15/12/2002	13,6	F	30/06/2016	GLASSES	-1,75	-1,50	23,68	23,47
29	VEF	14/11/2001	14,6	F	30/06/2016	GLASSES	-4,75	-3,88	25,10	24,78
30	TAF	29/03/2002	14,3	F	30/06/2016	GLASSES	-2,25	-1,63	23,57	23,63
Mean			**14,48**				**-2,89**	**-2,84**	**24,34**	**24,27**
SD			**2,14**				**1,08**	**1,07**	**0,98**	**0,97**
ESr							**0,20**	**0,20**	**0,18**	**0,18**

Tab. 2.4. SV group, at the end of the study (2016).

Table 2.5. shows the data collected for the ORTHO-K group at the end of the study (2016). From the elaboration, we found an average myopia of -2,81±1,07 D (SE) for the right eye and -2,72±0,88 D (SE) for the left eye. The average for the biometry in right eyes was 24,32±0,86 mm and in left eyes is 24,27±0,92 mm.

progr	Code	BORN	AGE Y	GENDER	DATE	GROUP	R S E (D)	L S E (D)	R BIO (mm)	L BIO (mm)
1	BLF	26/11/2001	14,6	F	30/06/2016	ORTHO K	-2,25	-2,25	22,86	22,82
2	BRF	10/03/2001	15,3	F	30/06/2016	ORTHO K	-2,88	-3,13	24,59	24,20
3	BAM	01/01/2000	16,5	M	30/06/2016	ORTHO K	-3,88	-2,38	24,65	24,35
4	BFM	18/08/2000	15,9	M	30/06/2016	ORTHO K	-4,00	-4,00	25,61	25,59
5	BNM	19/01/2000	16,5	M	30/06/2016	ORTHO K	-2,00	-2,25	25,06	25,72
6	BAF	06/10/2003	12,7	F	30/06/2016	ORTHO K	-3,50	-3,25	23,74	23,50
7	BCF	15/01/1999	17,5	F	30/06/2016	ORTHO K	-2,00	-2,00	25,06	25,26
8	BAM	16/06/2000	16	M	30/06/2016	ORTHO K	-1,00	-2,00	22,81	22,81
9	BGF	16/03/2001	15,3	F	30/06/2016	ORTHO K	-4,50	-3,88	25,31	24,36
10	CMM	23/04/2000	16,2	M	30/06/2016	ORTHO K	-1,00	-2,25	24,20	24,73
11	CLF	27/05/2002	14,1	F	30/06/2016	ORTHO K	-2,75	-2,63	23,70	23,74
12	CGF	12/05/2000	16,1	F	30/06/2016	ORTHO K	-4,00	-2,63	23,78	23,55
13	CBF	04/06/2005	11,1	F	30/06/2016	ORTHO K	-1,75	-1,75	23,50	23,69
14	FFM	04/09/2004	11,8	M	30/06/2016	ORTHO K	-1,88	-1,75	24,87	24,69
15	FRM	19/05/2000	16,1	M	30/06/2016	ORTHO K	-2,25	-2,50	24,56	24,44
16	FCF	17/07/2000	16	F	30/06/2016	ORTHO K	-2,75	-2,38	23,86	23,33
17	FDM	07/07/2000	16	M	30/06/2016	ORTHO K	-3,25	-1,25	24,03	23,09
18	GGF	21/09/2000	15,8	F	30/06/2016	ORTHO K	-2,25	-1,75	24,63	24,49
19	GDM	01/02/2000	16,4	M	30/06/2016	ORTHO K	-2,50	-2,88	23,95	24,09
20	MLF	07/05/2000	16,2	F	30/06/2016	ORTHO K	-3,38	-3,50	23,52	23,87
21	MIF	21/10/2000	15,7	F	30/06/2016	ORTHO K	-4,00	-4,13	24,06	24,54
22	NMF	17/12/2000	15,5	F	30/06/2016	ORTHO K	-2,50	-3,50	24,15	24,36
23	NCF	12/07/2001	15	F	30/06/2016	ORTHO K	-4,50	-4,50	24,84	25,27
24	RAF	28/01/1999	17,4	F	30/06/2016	ORTHO K	-3,25	-2,50	25,74	25,10
25	SMM	05/07/2001	15	M	30/06/2016	ORTHO K	-4,50	-4,13	26,36	26,66
26	SSF	25/07/2002	13,9	F	30/06/2016	ORTHO K	-3,75	-3,75	24,06	24,21
27	SAM	28/04/2000	16,2	M	30/06/2016	ORTHO K	-1,00	-1,25	22,71	22,55
28	TDF	22/01/1999	17,4	F	30/06/2016	ORTHO K	-2,63	-3,25	23,61	23,62
29	ZAM	26/03/2000	16,3	M	30/06/2016	ORTHO K	-1,00	-2,25	24,40	24,98
30	TLM	17/01/1999	17,5	M	30/06/2016	ORTHO K	-3,50	-1,88	25,23	24,56
Mean			**15,53**				**-2,81**	**-2,72**	**24,32**	**24,27**
SD			**1,51**				**1,07**	**0,88**	**0,86**	**0,92**
SEr							**0,20**	**0,16**	**0,16**	**0,17**

Tab. 2.5. OK group, at the end of the study (2016).

In the following representation (Tab. 2.6.) are shown the average delta, then the change occurred from the beginning to the end of the study, for the myopic progression in terms of spherical equivalent and for the axial elongation in terms of biometry, for both eyes of the SV group: we observed an average decrease of -0,42±0,36 D (R.E.) and -0,39±0,37 D (L.E.); average axial elongation of 0,22±0,30 mm for R.E. and 0,19±0,24 mm for L.E.

progr	Code	Delta R SE (D)	Delta L SE (D)	Delta R BIO (mm)	Delta L BIO (mm)
1	AGF	0,00	0,00	0,01	0,04
2	BMF	-1,13	-1,38	0,33	0,00
3	BSM	-0,63	-0,38	-0,01	-0,05
4	BFM	-0,25	-0,50	0,12	0,20
5	BDM	-0,25	0,00	0,00	0,00
6	BFM	-0,75	-0,75	0,10	0,25
7	BAM	0,00	-0,50	-0,01	0,45
8	BAF	-0,75	-0,25	0,00	-0,01
9	BLF	-0,50	0,00	0,00	0,00
10	BAF	-0,50	-0,50	0,97	0,42
11	BLM	-0,38	-0,63	0,58	0,65
12	BAM	-0,75	-0,63	0,00	-0,01
13	CAF	0,00	0,00	0,00	0,00
14	CGF	-0,25	-0,13	0,49	0,39
15	CDM	-0,25	-0,50	0,39	0,06
16	GLM	0,00	0,00	0,00	0,00
17	GLF	0,00	0,00	0,08	0,48
18	LCM	-0,25	-0,25	0,08	0,25
19	LAF	0,00	0,00	0,00	-0,03
20	LSF	-0,50	-0,25	0,82	0,00
21	MVF	0,00	0,00	0,08	0,17
22	MAF	-0,88	-0,63	0,61	0,74
23	MAF	-0,63	-0,50	0,19	0,56
24	PGM	0,00	-0,25	0,00	0,00
25	PRM	0,00	-0,25	-0,04	-0,03
26	PTM	-1,00	-0,88	0,06	0,46
27	RNF	-0,88	-1,13	0,78	0,42
28	SEF	-0,50	-0,50	0,06	0,07
29	VEF	-0,63	0,00	0,22	0,00
30	TAF	-1,00	-0,88	0,64	0,17
Mean		**-0,42**	**-0,39**	**0,22**	**0,19**
SD		**0,36**	**0,37**	**0,30**	**0,24**
SEr		**0,07**	**0,07**	**0,05**	**0,04**
Values		**30**	**30**	**30**	**30**
Improvement/Shortening		**0**	**0**	**3**	**5**
Stable		**9**	**9**	**8**	**8**
Worsening/Elongation		**21**	**21**	**19**	**17**

Tab. 2.6. SV group: Myopia and Biometry Delta after 18 months.

In Table 2.7. we highlight the average delta for the myopic progression in terms of spherical equivalent and for the axial elongation in terms of biometry, for both eyes of OK group: we observed a worsening average myopic -0,05±0,18 D (R.E.) and -0,03±0,21 D (L.E.); the delta of the average axial length is positive, which means a slight elongation of the eyeball: 0,05±0,15 mm for R.E. and 0,05±0,20 mm for L.E.

progr	Code	Delta R SE (D)	Delta L SE (D)	Delta R BIO (mm)	Delta L BIO (mm)
1	BLF	0,00	0,00	0,49	-0,10
2	BRF	0,00	0,00	0,00	0,00
3	BAM	-0,75	0,00	0,00	0,00
4	BFM	0,00	0,00	0,03	-0,06
5	BNM	0,00	0,00	0,00	0,05
6	BAF	-0,25	-0,25	0,13	-0,11
7	BCF	0,00	0,00	-0,06	0,08
8	BAM	0,00	0,00	0,04	0,00
9	BGF	0,00	0,00	0,02	-0,07
10	CMM	0,00	0,75	0,23	-0,43
11	CLF	0,00	0,00	0,02	0,03
12	CGF	0,00	0,00	-0,15	0,00
13	CBF	0,00	-0,25	0,01	0,25
14	FAM	-0,63	-0,75	0,33	0,90
15	FRM	0,00	0,00	0,00	0,00
16	FCF	0,00	-0,25	-0,01	0,09
17	FDM	0,00	0,00	0,00	0,00
18	GGF	0,00	0,00	0,00	0,15
19	GDM	0,00	0,00	0,00	0,19
20	MLF	0,00	0,00	0,01	0,00
21	MIF	0,00	0,00	-0,12	0,00
22	NMF	0,00	0,00	0,46	0,00
23	NCF	0,00	0,00	-0,13	0,04
24	RAF	0,00	0,00	0,00	0,30
25	SMM	0,00	0,00	0,22	-0,03
26	SSF	0,00	0,00	0,00	0,03
27	SAM	0,00	0,00	0,00	0,10
28	TDF	0,00	0,00	0,01	0,00
29	ZAM	0,00	0,00	-0,01	-0,03
30	TLM	0,00	0,00	0,00	0,00
Mean		**-0,05**	**-0,03**	**0,05**	**0,05**
SD		**0,18**	**0,21**	**0,15**	**0,20**
SEr		**0,03**	**0,04**	**0,03**	**0,04**
Values		**30**	**30**	**30**	**30**
Improvement/Shortening		**0**	**1**	**6**	**7**
Stable		**27**	**25**	**11**	**11**
Worsening/Elongation		**3**	**4**	**13**	**12**

Tab. 2.7. OK group: Myopia and Biometry Delta after 18 months.

Considering all the 60 eyes of the SV group at the end of the study, we observed an average worsening of myopia of SE -0,40±0,36 D and an axial elongation worsening of 0,20±0,27 mm. Instead, considering the 60 eyes of the group treated with Ortho-K, we observed that in 18 months, myopia worsened on average by SE -0,04±0,19 D and the axial elongation worsened by an average of 0,05±0,18 mm. These data demonstrate the effectiveness of the Ortho-K contact lenses for the control of myopic progression compared to the use of single-vision spectacles. Graphs of figures 2.5. and 2.6. shown respectively Delta SE and Delta Bio mean values for both right and left eyes (R&L eyes, i.e. 60 eyes in each groups) of the two groups (Glasses and Ortho-K).

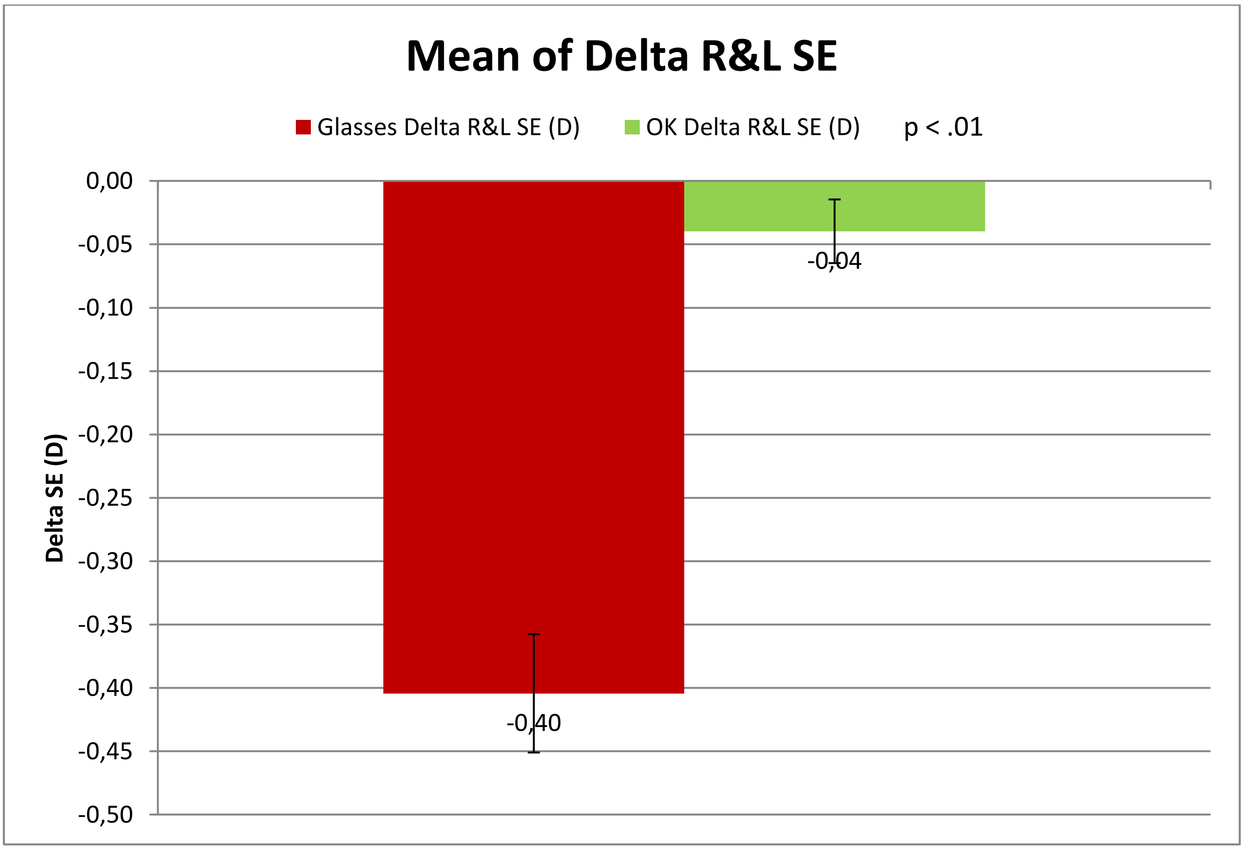


Fig. 2.5. Comparison between Delta SE mean values of SV and OK groups, considering both R&L eyes.

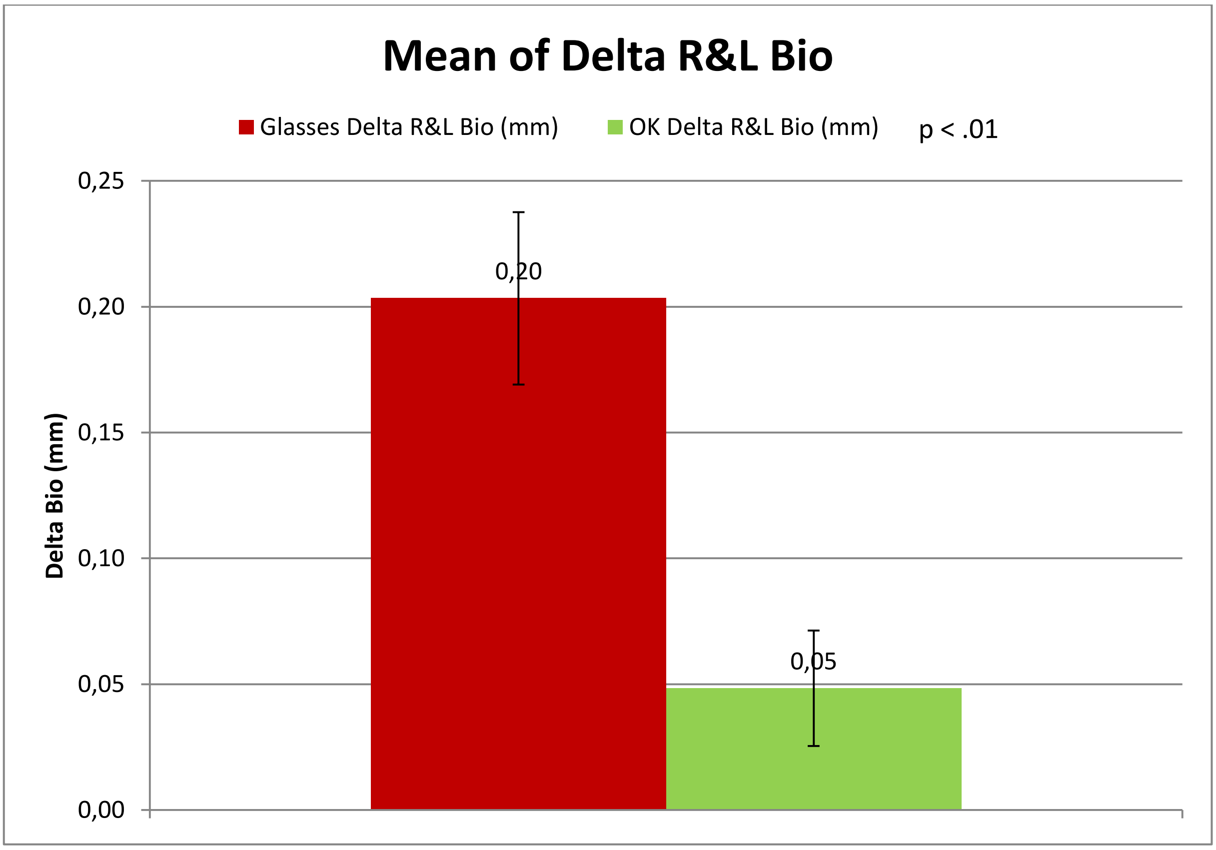


Fig. 2.6. Comparison between Delta Bio mean values of SV and OK groups, considering both R&L eyes.

Table 2.8. Summarizes respectively SV groups and Ortho-K data.

	Glasses				Ortho-K			
Description	**Delta R SE (D)**	**Delta L SE (D)**	**Delta R BIO (mm)**	**Delta L BIO (mm)**	**Delta R SE (D)**	**Delta L SE (D)**	**Delta R BIO (mm)**	**Delta L BIO (mm)**
Mean	-0,42	-0,39	0,22	0,19	-0,05	-0,03	0,05	0,05
SD	0,36	0,37	0,30	0,24	0,18	0,21	0,15	0,20
SEr	0,07	0,07	0,05	0,04	0,03	0,04	0,03	0,04
Values	30	30	30	30	30	30	30	30
Improvement/Shortening	0	0	3	5	0	1	6	7
Stable	9	9	8	8	27	25	11	11
Worsening/Elongation	21	21	19	17	3	4	13	12

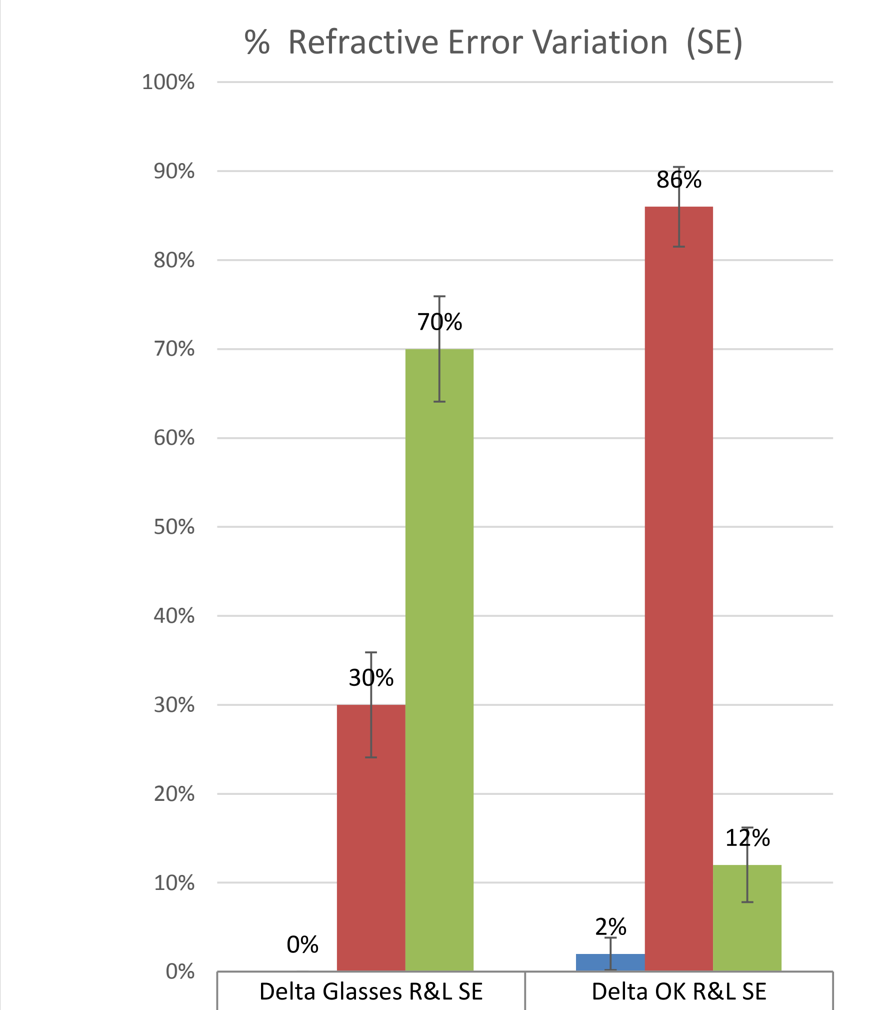
Tab. 2.8. Summary of Data for right and left eye.

The next Table 2.9. shows Data for each group considering the total amount of eyes, R&L as for Delta SE as for Delta Bio.

	Glasses		Ortho-K	
Description	**Delta R&L SE (D)**	**Delta R&L BIO (mm)**	**Delta R&L SE (D)**	**Delta R&L BIO (mm)**
Mean	**-0,40**	**0,20**	**-0,04**	**0,05**
SD	**0,36**	**0,27**	**0,19**	**0,18**
SEr	**0,05**	**0,03**	**0,03**	**0,02**
Values	**60**	**60**	**60**	**60**
Improvement/Shortening	**0**	**8**	**1**	**13**
Stable	**18**	**16**	**52**	**22**
Worsening/Elongation	**42**	**36**	**7**	**25**

Tab. 2.9. Summary, Glasses and Ortho-K group for R&L eyes.

Graph in figure 2.7. represents the percentage values of eye Improvement, Stabilization and Worsening in term of spherical equivalent (SE) registered in each group considering the total amount of eyes (R&L).



	Delta Glasses R&L SE	Delta OK R&L SE	
Improvement	0%	2%	p >.05
Stable	30%	86%	p <.01
Worsening	70%	12%	p <.01

Fig. 2.7. Refractive error variation expressed by eyes percentage on total.

The percentage of eyes improved in the OK group is not significant (p = 0,31732); the percentage of stable eyes in the OK group is statistically higher than the % of the SV group (p <0,01); the percentage of worsened eyes with OK is statistically lower than that recorded for the SV group (p<0,01).

Graph in figure 2.8. represent the percentage values of eye Shortening, Stabilization and Elongation in term of axial length (Bio) registered in each group considering the total amount of eyes (R&L).

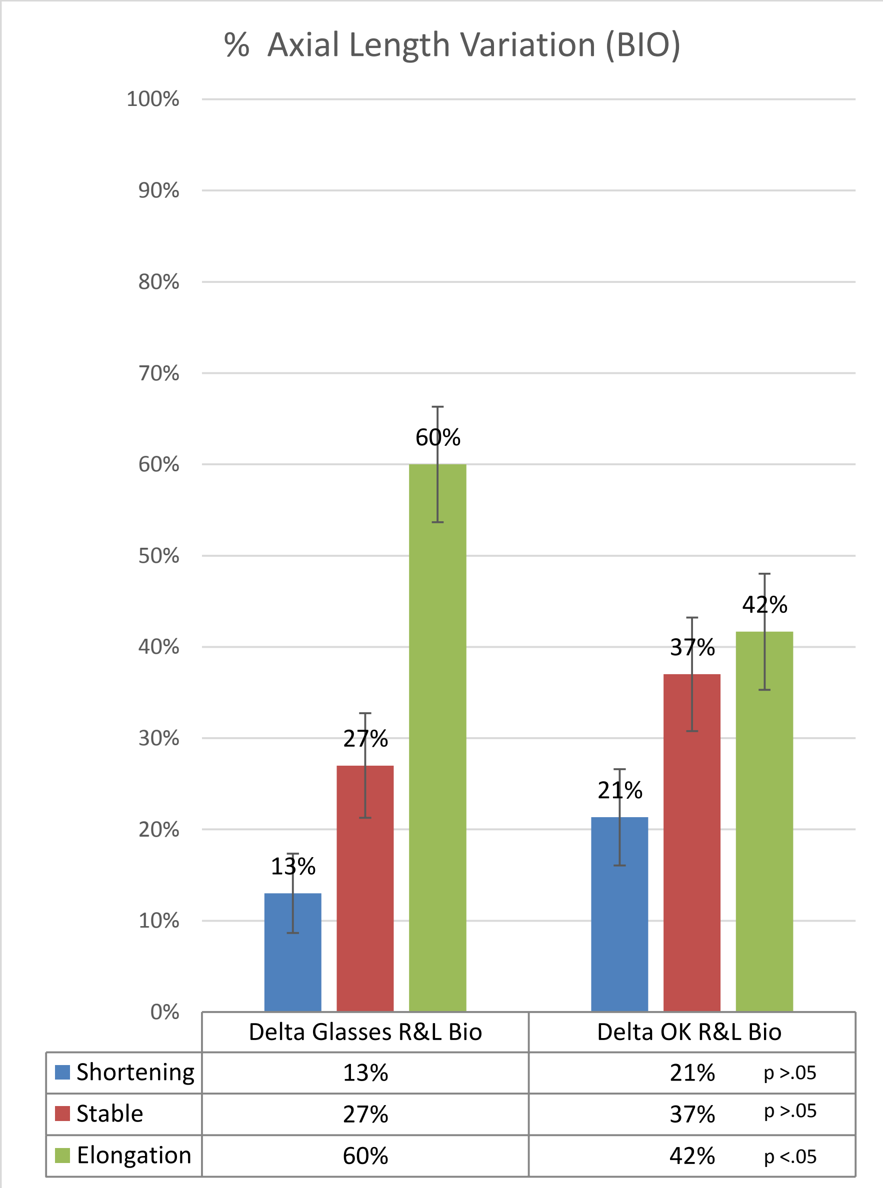


Fig. 2.8. Axial Length variation expressed by eyes percentage on total.

The percentage of eyes treated with OK where we recorded a shortening is not significant (p = 0,23014) than that observed for the SV group; the percentage of eyes with stable axial length in the OK group is not statistically higher than the % observed in the SV group (p = 0,238); the percentage of eyes that are elongated with OK is statistically lower than that recorded for the SV group (p = 0,04444).

The graphs of the Figure 2.9. and 2.10. show on the abscissa axis the initial myopia, dividing the subjects of each group in the membership classes for refractive degree; on the ordinate show respectively the average spherical equivalent and the average axial elongation recorded for each class. The aim is to relate the initial myopia with both the spherical equivalent and the axial length variation.

From the graph of Figure 2.9. it should be noted that the variation of the sphere equivalent in the group treated with OK, for all initial myopia classes considered, is less than the variation observed for the same classes of the SV group. The differences highlighted in the OK group and the SV are significant for all initial myopia classes considered, except for classes from 0,00 to -1,00 (p = 0,122874; p>0,05) and from -3,01 to -4,00 (p = 0,103122; p>0,05).

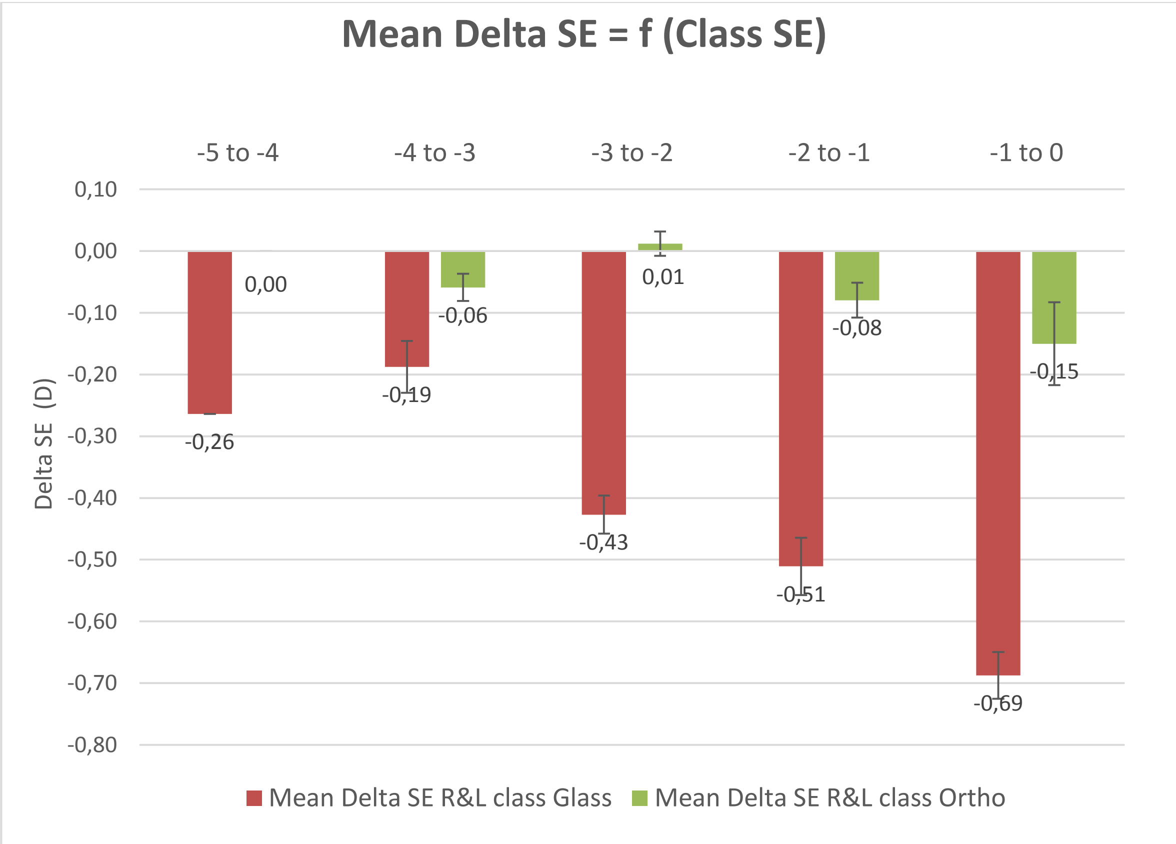


Fig. 2.9. Initial myopia divided into classes of membership and SE variation in each Group.

Similarly, from the graph of Figure 2.10. we can deduce that the change in axial length recorded in the group treated with OK, for all initial myopia classes considered, is less than that recorded for the same classes in the SV group, except for a class: it is shown a greater variation in the direction of elongation of the bulb in the axial OK group for class from -1,00 to 0,00 D (keep in mind that this class includes only 9 eyes, 5 OK and 4 SV). The differences highlighted between OK and the SV group were not significant (p>0,05) for all initial myopia classes considered, except for classes from -2,01 to -3,00 (p = 0,022943; p<0,05) and from -3,01 to -4,00 (p = 0,022315; p<0,05).

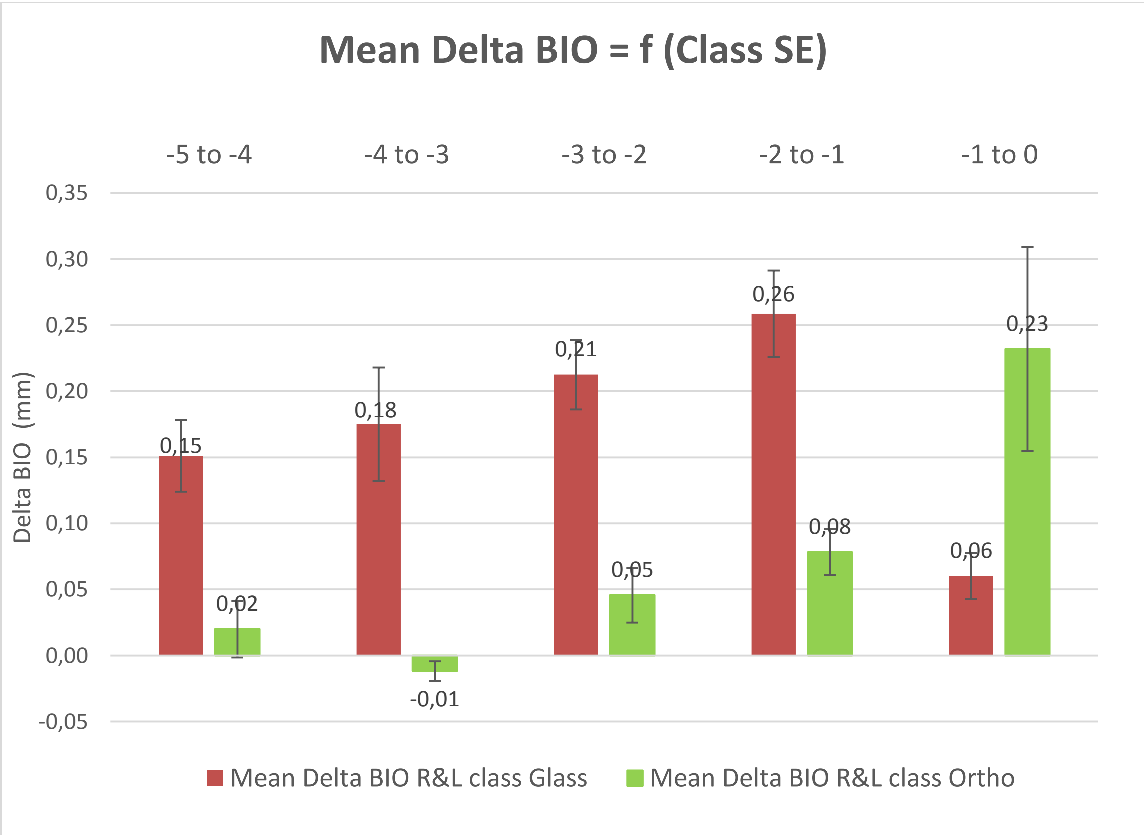


Fig. 2.10. Initial myopia divided into classes of membership and BIO variation in each Group.

2.4.1 Discussion

Data emerging from international studies, and confirmed in our research, suggest that OK lenses may reduce the progression of myopia in children through an eye axial elongation inhibition.

Significant differences in the delta spherical equivalent refraction were highlighted at the end of the study between the two groups, in agreement with the results of previous studies, for example Won et al. (2011) where the average myopic progression was $-0{,}25 \pm 0{,}31\ D$ in the OK group and $-0{,}62 \pm 0{,}39\ D$ in subjects with SV respectively. Won et al. (2011) showed statistically significant differences between subjects with OK and those with SV (t-test, $p<0{,}01$). Our research concluded that the OK group average of myopic progression was $-0{,}04 \pm 0{,}19\ D$ and SV group of $-0{,}40 \pm 0{,}36\ D$, obtaining a difference (p = 0,00001; $p<0{,}01$) similar to that obtained by Won et al. in 2011 (0,36 D against 0,37 D).

The axial growth reduction found with the OK lenses use was compared with the reduction of single vision spectacles. The differences in axial length growth were detected between the two groups and are reasonably consistent with those reported in previous studies (see Table 2.10.).

Study	Intervention	6 Months	12 Months	18 Months	24 Months
Cho et al.	OK vs. SV	0.21	0.18	0.28	0.25
Walline et al.	OK vs. SCL	…	0.15	…	0.32
Kakita et al.	OK vs. SV	…	…	…	0.22
MCOS	OK vs. SV	0.06	0.15	0.11	0.22

Tab. 2.10. Differences in Growth in Axial Length with Time Compared to Baseline for Orthokeratology and Control Groups (mm).

Legenda: OK, orthokeratology; SV, single-vision spectacles; SCL, soft contact lenses.

The difference between the growth of axial length in our two groups, after a period of 18 months, was found to be 0,15 mm (p = 0,000272; $p<0{,}01$). So it’s fully on average with the studies examined. The percentage of eyes treated with OK where we recorded a shortening (21%) was not significant ($p>0{,}05$) than that observed for the SV group (13%); the percentage of eyes with stable axial length in the OK group (37%) was not statistically higher than the percentage observed in the SV group (27%) ($p>0{,}05$); the percentage of eyes that are elongated with OK (42%) is statistically lower than that recorded for the SV group (60%) ($p<0{,}05$).

Several studies have shown that the application of lenses in front of the eyes, induce a hyperopic defocus and cause a rapid increase in axial length in many animal species. The peripheral hyperopic defocus plays a decisive role in the development of refractive error.

Some authors report that the retina most curve is associated with an easier myopization and this is supported by the fact that the shape of the eye, at the posterior pole, is one of the factors that affect the ocular axis growth also in correlation with the peripheral defocus.

Recent reports show that OK lenses, compared to the glasses, reduce peripheral hyperopic defocus. The gas permeable contact lenses with classical geometry (standard design) have no effect on refraction in the periphery. It can be assumed, therefore, that the reduction of the peripheral defocus, created by the OK lenses, support the axial elongation reduction.

We recorded a 13% of eyes in which the axial length was reduced in the SV group and 21% of eyes showed a shortening in the OK group. Although the shortening that occurred (in 8 eyes) in the SV group, is only about 0,02 mm in average, we looked for an explanation in the literature. In a previous study, Read and Collins (2011) have seen a small but significant reduction of AL in a group of young adults after physical activity. A short period of dynamic exercise leads to significant changes in a number of ocular parameters such as biometrics.

The reduction of AL can be related to induced changes in intraocular pressure and blood flow and may have implications for the development of refractive errors. Although 10 minutes after the exercise, AL had returned to baseline, a temporary change of biometrics (in default) was recorded.

In a recent Optometry and Ostheopaty meeting, I asked about the topic to some osteopathic professionals, who have given me their interpretation regarding the shortening of the eyeball. According to osteopathic theory, there would be some pulsatility of brain mass and then the eyeball (extroversion of the brain mass). This pulsatility is transmitted to the bones of the skull, which minimally move. Because of this phenomenon, the eye would change. The cranial movement (8/12 cycles per minute) in extension phase would lead to an anterior-posterior eye elongation, while in flexion the eye will shorten.

As for the axial length was reduced in the treated OK eyes, we report an interesting study of 2016 presented at the annual meeting of the American Academy of Optometry where Fromstein, Chaglasian and Pang (2016), concluded that, over 12 months, AL was elongated in the control group (change of 0,03 mm) while shortened in the Ortho-K group (change of -0,04 mm) (P=0,053), close to but not statistically significant.

Zhu et al. (2013) established that eyes of young animals of various species (chick, tree shrew, marmoset, and rhesus macaque) can shorten in the axial dimension in response to myopic defocus.

Read, Collins and Sander (2010), conclude that significant changes in optical axial length occurred in human subjects after 60 minutes of monocular defocus. The bi-directional optical AL changes observed in response to defocus, implied the human visual system is capable of detecting the presence and sign of defocus and altering optical axial length to move the retina toward the image plane.

Finally, interesting are the results obtained by Swarbrick et al (2014), where the results show that in the first initial months of orthokeratologic lenses use, occurs inhibition of axial elongation growth and inhibits also the myopic progression compared with conventional lenses GP.

Apparent shortening of AL early in OK lens wear, may reflect the contribution of Ortho-K induced central epitelial thinning, combined with choroidal thickening or recovery due to a reduction or neutralization of the myopiogenic stimulus to eye growth in these myopic children (Swarbrick et al., 2014).

3. CONCLUSIONS

- Although the OK contact lenses cannot totally arrest AL elongation in myopic children, they can retard it to a certain measure, which suggests that this treatment is a perfect choice for myopic children for whom the Ortho-K wear is suitable. We confirmed the inhibitory effect of orthokeratology on axial length elongation.
- Our study has clearly shown that the Ortho-K contact lenses are effective to reduce the progress of myopia in children and young teenagers, through the control of the refractive state and axial elongation, in such a way stronger than the glasses SV.
- The increase in myopia was lower in OK group, in all classes considered, for both low and for medium grade.
- The axial elongation recorded for the OK group is 75% less than that of subjects with glasses, at the end of 18 months.
- In full agreement with the literature, we are fully satisfied with the results and the work carried out in collaboration with the physician ophthalmologist. It remains certain our belief according to which the orthokeratology method is, to date, the most suitable strategy in the treatment of juvenile myopia and in the control of its progression.

4. FINAL WORDS

The new inverse geometry design of contact lenses, the accuracy of corneal measurements obtained thanks to the sophisticated instrumentation available to the optometric clinics, the high oxygen permeability of the lens materials, the high technical preparation of the optometrists applicators, have made orthokeratology a safe and effective procedure for the temporary reduction of myopia, up to -6,00 D approximately. In some cases, with great difficulty, we can correct higher myopia (up to -8,00 D). Today is also possible to compensate small astigmatic values (preferably, with the rule astigmatism) up to -2,50 D approximately.

Among the various methods of optometric competence aimed at treatment of myopia progression, such as ophthalmic lenses, contact lenses and some behavioral techniques, it seems to recognize in orthokeratology the most effective and profitable system. Firstly because it involves the use of CL during sleep and allows the subject to be able to support their daily activities without any help. It allows young people to better interface to the outside world, without giving up social or sports activities, thus making it much easier and effective all the outdoor activities benefits.

Nevertheless, we cannot express an opinion on the optimal duration of treatment: it is unknown if a slower rate of axial length will be maintained even after the OK lenses use cessation or whether a rebound phenomenon will occur. Further studies, with appropriate follow-up after discontinuation of treatment are necessary to answer these questions.

It is essential to keep in mind that in order to make sure that orthokeratology be fully effective, it is necessary:

- Better identify the children candidates to treat
- For younger children, to have on our side a collaborative family and which respects the lens cleaning / disinfection criteria
- Better identify the time when starting the orthokeratological treatment
- Avoid interruption of treatment in the critical period of children growth

Obviously, all this, in combination with a very precise application optometric protocol, high professional experience in Orthokeratology and constructive cooperation with ophthalmologists.

A questionnaire was submitted to all participants in order to record how many hours they spend outdoors, in school period and in the summer. The data were analyzed and processed appropriately, establishing 4 classes of membership: from 0 to 2 hours, from 2 to 4 hours, from 4 hours to 6 hours, more than 6 hours. In all cases the data in our possession were not sufficiently reliable (sure), because the interview was conducted based on the memories of the participants, without the support of a diary to record the effective hours spent outdoors. Then, we did not consider the hours spent in front of artificial sources (smartphones, tablets, PCs, video games, etc.), which could affect the results greatly. Also true that the number of cases of classes between 0 and 2 hours and especially that from 4 to 6 hours are few. Practically non-existent those over 6 hours. Therefore we cannot express any observation about it, positively or negatively. Further studies, which consider the hours spent outdoors and in front of artificial sources by each participants treated with OK and single-vision glasses, could explain what effects involves spending time outdoors on myopic progression. In the event it was demonstrated the effectiveness of spending more hours outside to counter the progression of myopia, targeted treatment plans may be processed, which involves for example, spending two hours outdoors every day for OK holder.

5. ACKNOWLEDGEMENTS

This work, for me meticulous, is dedicated to my family. I would not have been able to complete this work without their support, and love.

To realize this research many people have collaborated with me. They have always helped me and I appreciated their work commitment and professionalism.

I would like to express my sincere gratitude to my supervisor Prof. Pēteris Cikmačs for his guidance and encouragement on the preparation of this thesis. Prof. Pēteris has taught me a lot on how to perform a research study and write my thesis.

I would like put the emphasis on the work of all our professors of the University of Riga, which have amply demonstrated, in addition to high cultural preparation, an extraordinary intellectual and moral reliability.

Sincere thanks to my colleagues, friends and orthokeratology team mates Dr. Aurora Oliana, Dr. Luca Bazzani, Dr. Giuseppe Ghilotti M.D., Dr. Carlo Adami, Dr. Sergio Prezzi and Dr. Nicola Rizzieri for collecting the optometric data. Thanks for your precious advice.

Special thanks to my friend Dr. Giovanni Vanin, who guided me in data processing.

A special acknowledgement to all my students friends of the Riga University. It was an extraordinary adventure.

I would like to thank my wonderful family for their support, especially my wife Katiuscia (which has given up on so many weekends and replaced me when I missed the job), my Super daughter Maria and Super son Dr. Nicola. I am extremely thankful for their love and support to study.

I thank my parents, my mother Anna and my dad Ennio for everything I learned and received from them. A sincere thanks to my brother Massimo, to his precious advice.

6. REFERENCES

Ashby, R. S., & Schaeffel, F. (2010). The effect of bright light on lens compensation in chicks. *Invest Ophthalmol Vis Sci*., 51(10): 5247-53.

Berntsen, D. A., Sinnott, L. T., Mutti, D. O., & Zadnik, K. (2011). CLEERE Study Group Accommodative lag and juvenile-onset myopia progression in children wearing refractive correction. *Vision Res.*, 51: 1039–1046.

Berntsen, D. A., Sinnott, L. T., Mutti, D. O., & Zadnik, K. (2012). A randomized trial using progressive addition lenses to evaluate theories of myopia progression in children with a high lag of accommodation. *Invest Ophthalmol Vis Science*, 53: 640–649.

Bullimore, M. A. (N.1 2015). Myopia control. An evidence based approach. 3D Eurok Meeting - Budapest.

Bullimore, M. A. (N.2 2015). Estimating the risk of microbial keratitis in orthokeratology. 3D Eurok Meeting - Budapest.

Chan, B., Cho, P., & Cheung, S. W. (2006). Repeatability and agreement of two A-scan ultrasonic biometers and IOLMaster in non-orthokeratology subjects and post-orthokeratology children. *Clin Exp Optom.*, 89(3): 160-8.

Charm, J., & Cho, P. (2013). High myopia-partial reduction ortho-k: a 2-year randomized study. *Optometry and Vision Science,* vol. 90, pp. 530-9

Charman, W. N., & Radhakrishnan, H. (2010). Peripheral refraction and the development of refractive error: A review. *Ophthalmic Physiol Opt*., 30: 321-38.

Chen, C., Cheung, S. W., & Cho, P. (2013). Myopic control using toric orthokeratology (TO-SEE study). *Invest Opthalmol Vis Sci.*, 54: 6510–6517.

Cheung, S. W., & Cho, P. (2013). Validity of axial length measurements for monitoring myopic progression in orthokeratology. *Invest Ophthalmol Vis Sci.* 5, 54(3): 1613-5.

Chi, C. (2014). Toric orthokeratology for slowing eye elongation (TO-SEE) in myopic and astigmatic children. *Thesis,* 2-4.

Cho, P., & Cheung, S., W. (2012). Retardation of myopia in orthokeratology (ROMIO) study: a randomized controlled trial. *Invest Opthalmol Vis Sci*., 53: 7077–7085.

Cho, P., Boost, M., & Cheng, R. (2009). Non-Compliance and microbial contamination in orthokeratology. *Optom Vis Sci*., 86(11):1227-34.

Cho, P., Cheung, S. W., & Edwards, M. (2005). The longitudinal orthokeratology research in children (LORIC) in Hong Kong: a pilot study on refractive changes and myopia control. *Curr Eye Res*., 30: 71–80.

Choo, J. D., Caroline, P. J., Harlin, D. D., Papas, E. B., & Holden, B. A. (2008). Morphologic changes in cat epithelium following continuous wear of orthokeratology lenses: a pilot study. *Contact Lens & Anterior Eye,* 31(1): 29-37.

Dirani, M., Tong, L., Gazzard, G., Zhang, X., Chia, A., Young, T. L., Rose, K. A., Mitchell, P., & Saw, S. M. (2009). Outdoor activity and myopia in Singapore teenage children. *British Journal of Ophthalmology*, vol. 93, pp. 997-1000.

Formenti, M. (2011). Update myopia control. Meeting AIOK (Italian Accademy of Orthokeratology) – Bologna (IT).

Fromstein, S., Chaglasian, E., & Pang, Y. (2016). Effectiveness of orthokeratology on controlling myopia and axial elongation in young students: a prospective study. American Academy of Optometry's 95th Annual Meeting Anaheim, CA.

Grigoletto, R. (2013). Myopia control. *Thesis*. pp. 1-10.

Grosvenor, T., & Scott, R. (1993). Three-year changes in refraction and its components in youth-onset and early adult-onset myopia. *Optom Vis Sci*., 70: 677–683.

Gwiazda, J. E., & al. (2011). Correction of Myopia Evaluation Trial 2 Study Group for the Pediatric Eye Disease Investigator Group. Progressive-addition lenses versus single-vision lenses for slowing progression of myopia in children with high accommodative lag and near esophoria. *Invest Ophthalmol Vis Sci*., 52: 2749–2757.

Hamano, H., Jacob, J. T., & Senft, C. J. (2002). Differences in contact lens-induced responses in the corneas of Asian and non-Asian subjects. *CLAO*, 28: 101–104.

Harvitt, D. M., & Bonanno, J. A. (1999). Re-evaluation of the oxygen diffusion model for predicting minimum contact lens Dk/t values needed to avoid corneal anoxia. *Optometry and Visual Science,* 76(10): 712-719.

He, M., Du, Y., Liu, Q., Ren, C., Liu, J., Wang, Q., Li, L., & Yu, J. (2016). Effects of orthokeratology on the progression of low to moderate myopia in Chinese children. *BMC Ophthalmol.,* 16: 126.

He, M., Xiang, F., Zeng, Y., Mai, J., Chen, Q., Zhang, J., Smith, W., Rose, K., & Morgan, I. G. (2015). Effect of Time Spent Outdoors at School on the Development of Myopia Among Children in China. A Randomized Clinical Trial. *JAMA,* 15, 314(11): 1142-8.

Hiraoka, T., Kakita, T., Okamoto, F., Takahashi, H., & Oshika, T. (2012). Long-term effect of overnight orthokeratology on axial length elongation in childhood myopia: a 5-year follow-up study. *Invest Ophthalmol Vis Sci.*, 53: 3913–3919.

Hiraoka, T. (2013). The 2nd Meeting of the European Academy of Orthokeratology Bruxelles.

Horner, D. G., Soni, P. S., Salmon, T. O., & Swartz, T. S. (1999). Myopia progression in adolescent wearers of soft contact lenses and spectacles. *Optom Vis Sci*., 76, 474–479.

Jessen, G. N. (1962). World Wide summary of contact lens techniques. *Am J Optom Arch Am Acad Optom.*, 39: 680–682.

Jones, L. A., Sinnot, L. T., Mutti, D. O., Mitchell, G. L., Moeschberger, M. L., & Zadnik, K. (2007). Parental history of myopia, sports and outdoor activities, and future myopia. *Investigative Ophthalmology and Vision Science,* vol.48, pp. 3524-32.

Kakita, T., Hiraoka, T., & Oshika, T. (2011). Influence of overnight orthokeratology on axial elongation in childhood myopia. *Invest Ophthalmol Vis Sci*., 52: 2170–2174.

Kang, P., Gifford, P., & Swarbrick, H. (2013). Can Manipulation of Orthokeratology Lens Parameters Modify Peripheral Refraction? *Optom Vis Sci.,* 90: 1237- 1248.

Li, S. M., Ji, Y. Z., & Wu, S. S. (2011). Multifocal versus single vision lenses intervention to slow progression of myopia in school-age children: a meta-analysis. *Surv Ophthalmol*., 56: 451–460.

Li, S. M., Kang, M. T., Wu, S. S., Liu, L. R., Li, H., Chen, Z., & Wang, N. (2016). Efficacy, Safety and Acceptability of Orthokeratology on Slowing Axial Elongation in Myopic Children by Meta-Analysis. *Curr Eye Res.*, 41(5): 600-8.

Lum, E., & Swarbrick H. A. (2011). Lens Dk/t influences the clinical response in overnight orthokeratology. *Optom Vis Sci*., 88, 469–475.

Mehdizadeh, M & Nowroozzadeh, M. H. (2009). Outdoor activity and myopia. *Ophthalmology*, 116: 1229-1230.

Mika, R., Morgan, B., Cron, M., Lotoczky, J., & Pole, J. (2007). Safety and efficacy of overnight orthokeratology in myopic children. *Optometry*, 78(5): 225-231.

Mirsayafov, D. S., Tarutta, E. P., Markova, E. Y., Shmakov, A. N., & Verzhanskaya, T. Y. (2015). Orthokeratology slows down myopia progression: what comes next? 3D Eurok Meeting - Budapest.

Mountford, J. A., Ruston, D., & Dave, T. (2004). *Orthokeratology: principles and practice*. Butterworth-Heinemann, 1-5.

Mutti, D. O. (2010). Hereditary and environmental contributions to emmetropization and myopia. *Optom Vis Sci*., 87: 255–259.

Norton, T. T., Siegwart, J. T. Jr & Amedo, A. O. (2006). Effectiveness of hyperopic defocus, minimal defocus, or myopic defocus in competition with a miopiagenic stimulus in three shew eyes. *Invest Opthalmol Vis Sci.,* 47: 4687-4699.

Norton, T. T., & Siegwart, J. T. Jr. (2013). Light levels, refractive development, and myopia-a speculative review. *Exp Eye Res*., 114: 48-57.

Piovanelli, A., (2013). Interaction and modification of the corneal epithelium after orthokeratology treatment. *Thesis.* pp. 23-35.

Quinn, G. E., Shin, C. H., Maguire, M. G., & Stone, R. A. (1999). Myopia and ambient lighting at night. Nature. 399(6732): 113-4.

Read, S. A., Collins, M. J., & Sander, B. P. (2010). Human optical axial length and defocus. *Investigative Ophthalmology & Visual Science*, Vol.51, 6262-6269.

Read, S. A., & Collins, M. J. (2011). The short-term influence of exercise on axial length and intraocular pressure. *Eye (Lond)*, 25(6): 767–774.

Reinstein, D. Z., Gobbe, M., Archer, T. J., Couch, D., et al. (2009). Epithelial, stromal, and corneal pachymetry changes during orthokeratology. *Optom Vis Sci*, 86: 1006-14.

Rose, K. A., Morgan, I. G., Ip, J., Kifley, A., Huynh, S., Smith, W., & Mitchell, P. (2008). Outdoor activity reduces the prevalence of myopia in children. *Ophthalmology*, vol. 115, pp. 1279-85.

Sammarco, N. (2013). Myopia progression control by orthokerathology and multifocal soft contact lenses. *Thesis.* pp. 13-30.

Santodomingo-Rubido, J. (2011). Myopia control with orthokeratology contact lens. Symposium. Ferrara (IT).

Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., & Gutierrez-Ortega, R. (2012). Myopia control with orthokeratology contact lenses in Spain: refractive and biometric changes. *Invest Ophthalmology and Vision Science*, vol. 53, pp. 5060-5.

Santodomingo-Rubido, J., Villa-Collar, C., Gilmartin, B., & Gutiérrez-Ortega, R. (2013). Factors preventing myopia progression with orthokeratology correction. *Optom Vis Sci.*, 90(11): 1225-36.

Santodomingo-Rubido, J., Mallen, E. A. H., Gilmartin, B., & Wolffsohn, J. S. (2002). A new non-contact optical device for ocular biometry. *Br J Ophthalmol.*, 86: 458-462.

Sheng, H., Bottjer, C. A., & Bullimore, M. A. (2004). Ocular component measurement using the Zeiss IOLMaster. *Optom Vis Sci.*, 81(1): 27-34.

Sherwin, J. C., Reacher, M. H., Keogh, R. H., Khawaja, A. P., Mackey, D. A., & Foster, P. J. (2012). The association between time spent outdoors and myopia in children and adolescents: a systematic review and meta-analysis. *Ophthalmology*, 119(10): 2141-51.

Smith III, E. L., Campbell, M. C. W., & Irving, E. L. (2013). Point-counterpoint. Does peripheral retinal input explain the promising myopia control effects of corneal reshaping therapy (CRT or ortho-K) & multifocal soft contact lenses? *Ophthalmic Physiol Opt.*, 33: 379-384.

Smith, E. L., Hung, L. F., & Huang, J. (2009). Relative peripheral hyperopic defocus alters central refractive development in infant monkeys. *Vision Research,* 49: 2386-2392.

Swarbrick, H. A. (2006). Orthokeratology review and update. *Clinical and Experimental Optometry*, 89(3): 124-143.

Swarbrick, H. A., Alharbi, A., Watt, K., Lum E., & Kang, P. (2014). Myopia control during orthokeratology lens wear in children using a novel study design. *Ophthalmology*; 1-11. *American Academy of Ophthalmology*.

Swarbrick, H., A., Alharbi, A., Watt, K., Lum, E., & Kang, P. (2015). Myopia control during orthokeratology lens wear in children using a novel study design. *Ophthalmology,*.122(3): 620-30.

Tosini, G., Pozdeyev, N., Sakamoto, K., & Iuvone, P. M. (2008). The circadian clock system in the mammalian retina. *Bioessays.*, 30(7): 624-33.

Walline, J. J., Jones, L. A., & Sinnott, L. A. (2008). A randomized trial of the effect of soft contact lenses on myopia progression in children. *Invest Ophthalmol Vis Sci*., 49: 4702–4706.

Walline, J. J., Jones, L. A., & Sinnott, L. T. (2009). Corneal reshaping and myopia progression. *Br J Ophthalmol.,* 93: 1181–1185.

Walline, J. J., Lindsley, K., Vedula, S. S., Cotter, S. A., Mutti, D. O., & Twelker, J.D. (2011). Interventions to slow progression of myopia in children. *Cochrane Database Syst Rev*., 12, CD004916.

Wen, D., Huang, J., Chen, H., Bao, F., Savini, G., Calossi, A., Chen, H., Li, X., & Wang, Q. (2015). Efficacy and Acceptability of Orthokeratology for Slowing Myopic Progression in Children: A Systematic Review and Meta-Analysis. *Journal of Ophthalmology*. Article ID 360806, 12 pages.

Wildsoet, C. & Wallman, J. (1992). Optic nerve section affects ocular compensation for spectacle lenses. *Inves Ophthalmol Vis Sci.;* 33: 1053.

Wolffsohn, J. S., Calossi, A., Cho, P., Gifford, K., Jones, L., Li, M., Lipener, C., Logan, N. S., Malet, F., Matos, S., Meijome, J. M. G., Nichols, J. J., Orr, J. B., Santodomingo-Rubido, J., Schaefer, T., Thite, N., Van der Worp, E., & Zvirgzdina, M. (2016). Global trends in myopia management attitudes and strategies in clinical practice. *Contact Lens and Anterior Eye,* 39: 106–116.

Won, H. L., Young, K. P., Jong, M. S., & Jong, H. S. (2011). The inhibitory effect of Myopic and Astigmatic Progression by Orthokeratology lens. *Journal of the Korean Ophthalmol Soc.*, 52(11):1269-1274.

Yazar, S., Hewitt, A. W., Black, L. J., McKnigh,t C. M., Mountain, J. A., Sherwin, J. C, Oddy, W. H., Coroneo, M. T., Lucas, R. M., & Mackey, D. A. (2014). Myopia is associated with lower vitamin D status in young adults. *Invest Ophthalmol Vis Sci*., 55(7): 4552-9.

Yi, J. H., & Li, R. R. (2011). Influence of near work and outdoor activities in myopia progression in school children. *Zhonqquo Dang Dai Er Ke Za Zhi,* vol. 13, pp. 32-35.

Zhu, M. J., Feng, H. Y., He, X. G., Zou, H. D., & Zhu, J. F. (2014). The control effect of orthokeratology on axial length elongation in Chinese children with myopia. *BMC Ophthalmol*., 14: 141.

Zhu, X., McBrien, N. A., Smith, E. L. III, Troilo, D., & Wallman, J. (2013). Eyes in various species can shorten to compensate for myopic defocus. *Invest Ophthalmol Vis Sci*.,12;54(4):2634-44.

Zhu, X., & Wallman, J. (2009). Temporal properties of compensation for positive and negative spectacle lenses in chicks. *Invest Opthalmol Vis Sci.,* 50: 37-46.

Bachelor thesis “EFFECT OF ORTHOKERATOLOGY ON EYE AXIAL LENGTH AND REFRACTION IN MYOPIC CHILDREN” is prepared in Italy.

I certify with my signature, that research has been conducted independently, there have been used only in reference list mentioned sources of information, and electronical copy correspond to printed version.

Author: Davide Rizzieri

Student card no. dr13042

Recommend thesis for defensing

Supervisor: docent, Dr.phys. Pēteris Cikmačs

Reviewer: docent, Dr.phys. Jānis Dzenis

Thesis is submitted in Department of Optometry and Vision Science ________________

Dean’s authorized person: _________________________

Thesis is defended in bachelor final examination commission session

____________________. Protocol No. _____________

Commission secretary: __________________________