Title

Tomographic and aberrometric assessment of first-time diagnosed pediatric keratoconus based on age ranges: a multicentre study.

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Abstract

Purpose

To describe pediatric keratoconus (KC) patients by tomographic and aberrometric characteristics at first diagnosis, in a multicenter study.

Methods

We included 278 eyes from 139 pediatric patients, with a first tomographic diagnosis (Pentacam®) of KC prior to 18-years-old. KC classification was based on the KC Index (≥ 1.07) and Topographic Keratoconus Classification (TKC ≥ 1). Patients were divided based on age ranges (14 and under and over 14 years) and gender. Statistical analysis was performed with SPSS statistics 25.0. ANOVA factor was carried out comparing to compare groups.

Results

278 eyes were screened, and 230 eyes were diagnosed with pediatric KC. Mean age was 15.48 ± 2.33 (6 to 18) years old. We found differences in terms of TKC (2.08 ± 0.89 and 2.38 ± 0.82, $p < 0.05$) and spherical aberration (-0.71 ± 0.97 and -1.07 ± 1.36, $p < 0.05$) among the 14 years old or under and above 14 years old groups, respectively. Overall, female pediatric KC patients presented a more severe TKC, Belin Ambrosio Display, maximum keratometry, asphericity and primary and secondary coma aberrations compared to male KC patients. We observed a correlation between CDVA and asphericity ($r= 0.71$, $p < 0.01$), as well as between CDVA and spherical aberration ($r=0.69$, $p < 0.01$).

Conclusion

Our findings revealed that the debut of KC is usually in a moderate to advanced stage in the pediatric population at first diagnosis, particularly in female patients. Corneal tomography should be systematically performed in children with recent onset of corneal astigmatism.

Keywords: Pediatric keratoconus; anterior segment disorders; corneal disorders; keratoconus age; keratoconus

Introduction

Keratoconus (KC) is typically a bilateral and asymmetrical corneal non-inflammatory disease. However, recent publications have shown inflammatory response patterns in KC. (Galvis et al. 2015, Loh & Sherwin 2020). KC is characterized by a progressive corneal thinning resulting in a central or paracentral protrusion. This harmful disease causes a progressive decrease in visual acuity (VA) as a result of an increase in astigmatism and higher-order aberrations. (Alió & Shabayek 2006, Pahuja et al. 2017, Piñero et al. 2009) This irregularity implies changes that take place in the anterior and posterior corneal surfaces which can be evaluated using corneal tomography. (Alió & Shabayek 2006, Pahuja et al. 2017, Piñero et al. 2009) Anterior corneal aberration analysis has proven to be an effective tool in detecting and grading keratoconus. (Bühren, Kühne & Kohnen 2007) Higher amounts of vertical coma and increased values of coma-like root mean square (RMS) are often present in patients with KC or suspected KC. (Bühren, Kühne & Kohnen 2007) Coma-like aberrations are known to be dominant in KC, especially vertical coma Z^{-3} and Z^{-5}. (Bühren, Kühne & Kohnen 2007)

KC is easy to recognize in advanced stages, being difficult to detect in early stages. (Golan et al. 2019, Gomes et al. 2015, Saad & Gatinel 2010) The onset age is usually between the second and third decade of life, (Goebels et al. 2015, Mukhtar & Ambati 2018, Naderan et al. 2017, Naderan et al. 2015) approximately between the ages of 22 and 28, being the average diagnosis at 27 years old. (Kennedy, Bourne & Dyer 1986, Léoni-Mesplié et al. 2012, Pouliquen, Forman & Giraud 1981, Zadnik et al. 1996) It has a tendency to progress till the ages of 35-40 before stabilizing. (El-Khoury et al. 2016, Léoni-Mesplié et al. 2012) However, cases in patients under the age of 20 have been reported (Léoni-Mesplié et al. 2012), including a study describing the youngest reported case being four years old. (Mukhtar & Ambati 2018, Sabti, Tappeiner & Frueh 2015) In children, as in adults, KC is a rare disease and, so far, there are few detailed studies of characterization of this pathology at these ages compared to adults. (El-Khoury et al. 2016) In the pediatric population (age 0–17 years), the prevalence of KC is reported to be 0.16%. (Moshirfar et al. 2019) Early age appears to be associated with more severe forms of KC and a faster disease progression, with an inverse correlation between age and severity. (Al Suhaibani et al. 2007, Ertan & Muftuoglu 2008, Léoni-Mesplié et al. 2012, Li et al. 2004, Moshirfar et al. 2019, Mukhtar & Ambati 2018, Ozer et al. 2019) In addition, early age at diagnosis appears to be related to an increased risk of developing corneal opacity (Barr et al. 2006, El-Khoury et al.

2016, Léoni-Mesplié et al. 2012) and a higher rate of acute hydrops compared to the adult population. (Mukhtar & Ambati 2018) Younger patients diagnosed with KC are usually of Asian or Middle Eastern origin. (Assiri et al. 2005, Léoni-Mesplié et al. 2012, Saini et al. 2004)

The purpose of this study is to characterize pediatric KC patients (under 18 years old) focusing on the tomographic and aberrometric analysis, and secondarily their correlation with visual acuity at the first tomographic diagnosis in a multicentre study. This study represents the largest pediatric sample, to the best of our knowledge, available in the scientific literature.

Methods

Setting

This retrospective, cross-sectional, multicentre study evaluated 278 eyes from 139 pediatric keratoconus patients. All patients visited the following ophthalmology clinics between 2012 and 2019: Regional University Hospital of Malaga (Málaga, Spain), Royal Liverpool University Hospital (Liverpool, United Kingdom), Tecnolaser Clinic Vision (Seville, Spain), Virgen del Rocío University Hospital (Seville, Spain), Torrecárdenas University Hospital (Almería, Spain) and Monterrey University Hospital Dr. José Eleuterio González (Monterrey, Mexico). The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional University Hospital of Málaga (promoter center). An identical protocol was approved by the ethics committee of each center.

Patients and study population

KC diagnosis had been confirmed by a licensed expert ophthalmologist through a clinical examination and corneal tomography with Pentacam® (Oculus Optikgerate GmbH, Wetzlar, Germany). All Pentacam® images of all pediatric patients were retrospectively reviewed to assess the quality of the tomographic maps. Those with good-quality scans were included and those with low-quality scans were excluded from the study. All eyes underwent an extensive ophthalmologic examination that included visual acuity (VA) measurements, manifest refraction, slit-lamp examination to detect any signs associated with keratoconus (i.e., Vogt striae, Fleischer ring, superficial and deep

corneal scar, superficial punctate keratitis, or corneal ulceration at the top of the cone) and fundus examination in mydriasis. The inclusion criteria were (1) patients under 18-years-old, (2) first diagnosis of KC by tomographic maps carried out under 18-years-old, (3) unilateral or bilateral KC. The exclusion criteria included any previous ophthalmological surgeries (keratoplasty or intracorneal ring segments), previous crosslinking procedure, or presence of any ophthalmic or systemic disease different from KC. For KC diagnosis and classification, we selected the Keratoconus Index (KI, ≥ 1.07) and Topographic Keratoconus Classification (TKC ≥ 1). (Goebels et al. 2015). The preoperative cone location was determined by the location of the highest anterior elevation. If it was within the central 3-mm zone, it was defined as a central cone. If it was outside this zone, it was defined as a peripheral cone. Previous studies reported that studying only one eye may lead to a loss of statistical power, especially in diseases with asymmetric behaviour. (Bunce et al. 2014) Since KC is an asymmetric and bilateral disease and our intention is to study its behaviour at first tomographic diagnosis, we included the patient's data of one or both eyes, depending on the involvement.

A general classification of the entire sample was performed. Later, patients were divided into two groups. The first one was composed of 14-years-old or under and the second one was composed of those older to 14-years-old. This threshold point was established based on the cut-point proposed by El-Khoury et al. (El-Khoury et al. 2016). In addition, the sample was split by gender and both groups were individually divided by gender.

Outcome Measures

The clinical variables that were reported were: (1) objective cycloplegic spherical refraction, (2) objective cycloplegic cylinder refraction, both measured with autorefractometers (Topcon KR 8000, Topcon Corporation, Tokyo, Japan, Nidek ARK-510A, Nidek, Gamagori, Japan and Tonoref II, version 1.17; Nidek, Gamagori, Japan), (3) corrected distance VA (CDVA) measured by 20-feet Snellen chart in photopic conditions, (4) steep, flat, mean and maximum keratometry reading values, (5) central corneal thickness (CCT), (6) thinnest corneal thickness (TCT), (7) anterior corneal astigmatism, (8) corneal asphericity (Q) at 8 mm, (9) topographic keratoconus classification (TKC), (10) keratoconus index (KI), (11) Belin Ambrosio display (BAD), (12) vertical primary coma Zernike coefficient (Z_3^{-1}), (13) vertical secondary coma Zernike coefficient (Z_5^{-1}) and (14) primary spherical aberration Zernike coefficient (Z_4^0). All Zernike coefficients and RMS were calculated over a 6 mm-pupil diameter and measured from the anterior corneal surface. (Alió & Shabayek 2006, Bühren, Kühne & Kohnen 2007, Gobbe & Guillon 2005). If the cone was

within the central 3-mm zone, it was termed a central cone. If it was outside this zone, it was termed peripheral (Padmanabhan et al. 2017).

Statistical analysis

Statistical analysis was performed with SPSS statistics 25.0 (IBM Corporation, Armonk, NY, USA). Student's t-test was performed for parametric independent variables and Wilcoxon test was performed for non-parametric dependent variables. False Discovery Rate (FDR) was analyzed with the Benjamini-Hochberg method. All statistical tests were performed with a 95% confidence interval ($p < 0.05$).

Results

230 eyes from 139 patients were diagnosed with pediatric KC and met the selection criteria. Out of 139 patients, 104 were male and 35 were female. Regarding origin, 86 were Caucasian, 23 were Hispanic, 15 Arab, 3 African and 12 with mixed origin. Patients' mean age was 15.48 ± 2.33 (6 to 18) years old. The analysis of the total sample and distribution by gender are represented in Table 1. Correlation study between CDVA versus aberrations (Q value with Z_4^0 and Z_3^{-1} with Z_5^{-1}) are represented in Figure 1 and Figure 2, respectively.

As for group comparisons, differences between children 14 years or under versus above 14 were carried out. Two variables (TKC and Z_4^0) reported statistically significant differences (both $p < 0.05$). TKC in 14 years or under was 2.08 ± 0.89 (1.00 to 4.00), and 2.38 ± 0.82 (1.00 to 4.00) in over 14 years. In addition, Z_4^0 was -0.71 ± 0.97 (-4.59 to +0.29) in 14 years or under and -1.07 ± 1.36 (-5.50 to +0.34) in over 14 years. There were no statistically significant differences amongst the other variables. Furthermore, gender analysis based on age range is represented in Table 2. Within male KC, non-significant differences were achieved between 14 years and under and over 14 years, however female KC patients presented significant differences in asphericity Q value, BAD and spherical aberration in over 14 years.

Discussion

Our results show differences in TKC and spherical aberration between pediatric KC when the cut-off point is set at 14 years of age ($p < 0.05$). Moreover, we observed a strong positive correlation between CDVA and Q ($r = 0.71$, $p < 0.01$), between CDVA and spherical aberration ($r = 0.69$, $p < 0.01$), as well as a moderate correlation between CDVA and coma aberration ($r = 0.48$, $p < 0.01$). This suggests that the more negative the value of Q, spherical aberration, and coma aberration (Z_3^{-1} and Z_5^{-1}), the worse the CDVA. Furthermore, although males made up for the highest proportion of our sample, female patients, especially above 14 years, represented the most severe cases percentage wise regarding TKC, KI, Kmax, TCP, CCT; AST, BAD, Q, Z_3^{-1} and Z_5^{-1}.

KC seems to be more severe in children than in adults (Léoni-Mesplié et al. 2012) at first diagnosis. Moreover, it has been reported (Chatzis & Hafezi 2012) that a rapid advancement of the disease happens in pediatric KC patients, requiring a stricter monitoring. Yet, some literature argues against the hypothesis that younger age is linked to a more rapid progression of KC to stages III and IV requiring keratoplasty. (Dana et al. 1992, Mukhtar & Ambati 2018). Our study aims to characterize pediatric KC at the first tomographic diagnosis in a multicentre cross-sectional designed study. Pediatric and adult corneas are structurally different as a natural cross-linking of the corneal tissue may occur with aging, leading to a possible spontaneous stabilization of KC in later ages. (Mukhtar & Ambati 2018) Ertan et al. (Ertan & Muftuoglu 2008) studied 482 eyes with KC and found a clear inverse correlation between age and severity. An explanation for the advanced stages of KC at first diagnosis in children is the ‘‘explosive’’ progression of KC, meaning a short interval between noticeable symptoms and developing severe KC. (Léoni-Mesplié et al. 2012, Naderan et al. 2017) Nowadays, there is a variety of classifications and definitions used for KC (Papali’i-Curtin et al. 2019) and there is a consensus that tomography is the best and most comprehensive tool available to diagnose KC. (Gomes et al. 2015) (Gomes et al. 2015, Papali’i-Curtin et al. 2019) Currently, there is no threshold that determines the onset age (Hwang et al. 2018, Saad & Gatinel 2010, Schlegel, Hoang-Xuan & Gatinel 2008, Smadja et al. 2013, Uçakhan et al. 2011, Zadnik et al. 1996) and no isolated parameter is able to detect it. (de Sanctis et al. 2008, Saad & Gatinel 2010, Smadja et al. 2013)

We retrospectively collected clinical data corresponding to all patients under 18-years-old with a diagnosis of KC at different ophthalmologic centres. Regarding the sample volume, to the best of our knowledge, our study represents the largest pediatric KC sample under 18-years-old. Naderan et al. (Naderan et al. 2015) studies almost 450 subjects but includes patients up to 20-years-old. In terms of age, reported pediatric KC ranges from 11.87 years by El-Khoury

et al. (El-Khoury et al. 2016) up to 16.9 years by Naderan et al. (Naderan et al. 2015) Therefore, averagely, all the subjects included are pediatric. As for the CDVA, all studies report a mean VA of 0.40-0.60 in decimal scale, except for the subjects of Naderan et al. (Naderan et al. 2015) that reported a mean VA of 0.78 in decimal scale. Concerning maximum keratometry, our study provides one of the highest keratometry values along with the results reported by Naderan et al. (Naderan et al. 2017) being steeper among our female patients. Comparatively, other studies reported a lower mean maximum keratometry.(El-Khoury et al. 2016, Léoni-Mesplié et al. 2012, Naderan et al. 2015, Papali'i-Curtin et al. 2019) Regarding the classification of KC, only Papali´i-Curtin et al. (Papali'i-Curtin et al. 2019) studied the same variables as our study. We observed similar results in the KI, although our subjects had a greater TKC than their sample, once again, especially in our female patients. It is important to highlight that Papali´i-Curtin's (Papali'i-Curtin et al. 2019) sample included only 10 pediatric KC.

Changes in corneal Q and the corresponding increase in optical aberrations, mainly spherical aberration, have a significant negative impact in VA and in the quality of vision, such as contrast sensitivity, and visual functions, such as night vision or glare. Normal Q values range from -0.42 to 0.04 (Pahuja et al. 2017). Q value varies with the grade of KC, ranging from −0.35 in mild forms to −1.70 in severe KC, due to an exaggerated prolateness, leading to lower negative Q. (Pahuja et al. 2017) In our study, we observed a strong positive correlation between CDVA, Q value ($r = 0.71$, $p < 0.01$) and spherical aberration ($r = 0.69$, $p < 0.01$), as well as a moderate correlation between CDVA and coma aberration ($r = 0.48$, $p < 0.01$). It is known that higher values of vertical coma and increased values of coma-like RMS are often present in patients with KC or suspected KC (Alió & Shabayek 2006, Piñero et al. 2009), being coma-like aberrations, especially vertical coma Z^{-3} and Z^{-5} ,dominant in KC (Bühren, Kühne & Kohnen 2007). According to our results, an increase in the values of these aberrations (spherical aberration, Q value and coma patterns) have a negative impact on the CDVA. Moreover, we observed that a central cone, where Q value and spherical aberration are more negative, had a worse visual acuity than a paracentral cone, where the coma pattern predominates. These results are consistent with those reported by Alió et al. (Alió et al. 2011) in adult KC patients, describing how mean keratometry value was significantly correlated with CDVA, corneal astigmatism, corneal aberrations and internal astigmatism. The higher the mean keratometry, the worse the CDVA. The more severe the internal astigmatism, corneal astigmatism in the 3.0 mm central zone, and corneal aberrations, the worse the CDVA. Corneal Q values, spherical aberration and coma aberration could be a useful parameter in pediatric KC analysis as

it offers an overall view of the shape of the cornea and could give us an idea of their VA impairment, since the keratometry values are more limited, as it is observed in ours results.

Concerning the limitations of our study, patients were reviewed by many physicians. Despite this fact, which is common in any multicentre study, we used a large and consistent sample of KC eyes allowing us to complete an advanced clinical characterization of young and infantile KC patients in different parts of the world. Furthermore, we define specific factors that relate to the visual limitation in these patients. Other limitations to outstand are the lack of information on atopy, eye rubbing, family background or new tomographic classifications, such as ABCD [anterior radius of curvature (A), posterior radius of curvature (B for back surface), corneal pachymetry at thinnest (C), Distance best-corrected vision (D)]. In agreement with other studies (El-Khoury et al. 2016, Ertan & Muftuoglu 2008, Léoni-Mesplié et al. 2012) most of the patients in our study were males although, interestingly, young females KC patients (especially above 14 years) presented with a higher degree of KC, Q, and coma value at first tomographic diagnosis. However, it is challenging to draw any robust conclusions due to the low number of cases, and as the differences between both genders, especially regarding TKC, was not substantial. Conversely, Naderan et al. (Naderan et al. 2017) and Ertan & Muftuoglu (Ertan & Muftuoglu 2008) did not find any differences in KC severity between both genders. Some authors suggested that variations of sexual hormones between men and women could be a possible explanation for gender-related KC variations (Ertan & Muftuoglu 2008, Naderan et al. 2015). However, there is yet no sufficient evidence to describe differences among different gender pediatric KC patients (Ertan & Muftuoglu 2008, Fink et al. 2005, Hashemi et al. 2020, Lee, Jung & Cho 2020). Regarding race, unlike others studies (Assiri et al. 2005, Léoni-Mesplié et al. 2012, Saini et al. 2004), we reported a higher Caucasian pediatric KC proportion. Nevertheless, the evidence may be biased as most of our patients are native from European countries.
Further research with a larger sample, especially focusing in finding differences between pediatric male and female patients, is needed. Furthermore, differences between patients from different populations, particularly in their habits like presumable eye rubbing (Moran et al. 2020), or some specific disease such as allergy, atopy, sunlight exposure dry eye disease and family background (Fink et al. 2005, Hashemi et al. 2020), is yet to be studied.

Consequently, according to our results and supporting previous research (Al Suhaibani et al. 2007, Ertan & Muftuoglu 2008, Léoni-Mesplié et al. 2012, Li et al. 2004, Moshirfar et al. 2019, Mukhtar & Ambati 2018, Ozer et al. 2019),

KC should be further suspected in every child with an unexplained loss of VA or a new occurrence of astigmatism. In these cases, we suggest that corneal tomography screening should be performed as soon as the child is able to place his or her chin on the tomography apparatus.

In conclusion, our findings revealed that KC usually presents in a moderate to advanced stage in the pediatric population at first tomographic diagnosis, affecting VA and being more severe the more central the cone is situated, relating to a more negative spherical aberration and Q value. Female patients, being the minority gender, presented with a more severe degree of KC and requires future research. We highly recommend young KC patients to be closely monitored and intensively treated. Corneal tomography should be systematically performed in children with corneal astigmatism of recent onset or presumptive amblyopia. Since KC might presented as a moderated stage, close monitoring of young KC patients is essential to detect any possible advancement of the disease and to propose an appropriate therapeutic approach.

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Declarations

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Consent to participate: All patients included in this work were adequately informed verbally and in writing of the benefits, characteristics and risks of the surgeries. All patients signed an informed consent prior to the surgery and after the interview performed with the ophthalmologist.

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References

Al Suhaibani AH, Al-Rajhi AA, Al-Motowa S, Wagoner MD & Al-Rajhi AA (2007): Inverse relationship between age and severity and sequelae of acute corneal hydrops associated with keratoconus [8]. Br J Ophthalmol **91**: 984–985.

Alió JL, Piñero DP, Alesón A, et al. (2011): Keratoconus-integrated characterization considering anterior corneal aberrations, internal astigmatism, and corneal biomechanics. J Cataract Refract Surg **37**: 552–568.

Alió JL & Shabayek MH (2006): Corneal higher order aberrations: A method to grade keratoconus. J Refract Surg **22**: 539–545.

Assiri AA, Yousuf BI, Quantock AJ, Murphy PJ & Assiri AA (2005): Incidence and severity of keratoconus in Asir province, Saudi Arabia. Br J Ophthalmol **89**: 1403–1406.

Barr JT, Wilson BS, Gordon MO, Rah MJ, Riley C, Kollbaum PS & Zadnik K (2006): Estimation of the incidence and factors predictive of corneal scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study. Cornea **25**: 16–25.

Bühren J, Kühne C & Kohnen T (2007): Defining Subclinical Keratoconus Using Corneal First-Surface Higher-Order Aberrations. Am J Ophthalmol **143**: 381–9.

Bunce C, Patel K V., Xing W, Freemantle N, Doré CJ & Ophthalmic Statistics Group (2014): Ophthalmic statistics note 1: unit of analysis. Br J Ophthalmol **98**: 408–12.

Chatzis N & Hafezi F (2012): Progression of keratoconus and efficacy of corneal collagen cross-linking in children and adolescents. J Refract Surg **28**: 753–758.

Dana MR, Putz JL, Viana MAG, Sugar J & McMahon TT (1992): Contact Lens Failure in Keratoconus Management. Ophthalmology **99**: 1187–1192.

de Sanctis U, Loiacono C, Richiardi L, Turco D, Mutani B & Grignolo FM (2008): Sensitivity and Specificity of Posterior Corneal Elevation Measured by Pentacam in Discriminating Keratoconus/Subclinical Keratoconus. Ophthalmology **115**: 1534–1539.

El-Khoury S, Abdelmassih Y, Hamade A, Slim E, Cherfan CG, Chelala E, Bleik J & Jarade EF (2016): Pediatric keratoconus in a tertiary referral center: Incidence, presentation, risk factors, and treatment. J Refract Surg **32**: 534–541.

Ertan A & Muftuoglu O (2008): Keratoconus clinical findings according to different age and gender groups. Cornea **27**: 1109–1113.

Fink BA, Wagner H, Steger-May K, Rosenstiel C, Roediger T, Mcmahon TT, Gordon MO & Zadnik K (2005): Differences in keratoconus as a function of gender. Am J Ophthalmol **140**: 459.e1.

Galvis V, Sherwin T, Tello A, Merayo J, Barrera R & Acera A (2015): Keratoconus: an inflammatory disorder? Eye **29**: 843–859.

Gobbe M & Guillon M (2005): Corneal wavefront aberration measurements to detect keratoconus patients. Contact Lens Anterior Eye **28**: 57–66.

Goebels S, Eppig T, Wagenpfeil S, Cayless A, Seitz B & Langenbucher A (2015): Staging of Keratoconus Indices Regarding Tomography, Topography, and Biomechanical Measurements. Am J Ophthalmol **159**: 733-738.e3.

Golan O, Piccinini AL, Hwang ES, De Oca Gonzalez IM, Krauthammer M, Khandelwal SS, Smadja D & Randleman JB (2019): Distinguishing Highly Asymmetric Keratoconus Eyes Using Dual Scheimpflug/Placido Analysis. Am J Ophthalmol **201**: 46–53.

Gomes JAP, Tan D, Rapuano CJ, et al. (2015): Global consensus on keratoconus and ectatic diseases. Cornea **34**: 359–369.

Hashemi H, Heydarian S, Hooshmand E, et al. (2020): The Prevalence and Risk Factors for Keratoconus: A Systematic Review and Meta-Analysis. Cornea **39**: 263–270.

Hwang ES, Perez-Straziota CE, Kim SW, Santhiago MR & Randleman JB (2018): Distinguishing Highly Asymmetric Keratoconus Eyes Using Combined Scheimpflug and Spectral-Domain OCT Analysis. Ophthalmology **125**: 1862–1871.

Kennedy RH, Bourne WM & Dyer JA (1986): A 48-year clinical and epidemiologic study of keratoconus. Am J Ophthalmol **101**: 267–273.

Lee HK, Jung EH & Cho BJ (2020): Epidemiological Association Between Systemic Diseases and Keratoconus in a Korean Population: A 10-Year Nationwide Cohort Study. Cornea **39**: 348–353.

Léoni-Mesplié S, Mortemousque B, Touboul D, Malet F, Praud D, Mesplié N & Colin J (2012): Scalability and severity of keratoconus in children. Am J Ophthalmol **154**: 56-62.e1.

Li X, Rabinowitz YS, Rasheed K & Yang H (2004): Longitudinal study of the normal eyes in unilateral keratoconus patients. Ophthalmology **111**: 440–446.

Loh I-P & Sherwin T (2020): Is Keratoconus an Inflammatory Disease? The Implication of Inflammatory Pathways. Ocul Immunol Inflamm 1–10.

Moran S, Gomez L, Zuber K & Gatinel D (2020): A Case-Control Study of Keratoconus Risk Factors. Cornea **39**: 697–701.

Moshirfar M, Heiland MB, Rosen DB, Ronquillo YC & Hoopes PC (2019): Keratoconus Screening in Elementary School Children. Ophthalmol Ther **8**: 367–371.

Mukhtar S & Ambati BK (2018): Pediatric keratoconus: a review of the literature. Int Ophthalmol **38**: 2257–2266.

Naderan M, Rajabi MT, Zarrinbakhsh P & Farjadnia M (2017): Is keratoconus more severe in pediatric population? Int Ophthalmol **37**: 1169–1173.

Naderan M, Shoar S, Kamaleddin MA, Rajabi MT, Naderan M & Khodadadi M (2015): Keratoconus Clinical Findings According to Different Classifications. Cornea **34**: 1005–1011.

Ozer MD, Batur M, Mesen S, Tekin S & Seven E (2019): Long-Term Results of Accelerated Corneal Cross-Linking in Adolescent Patients with Keratoconus. Cornea **38**: 992–997.

Padmanabhan P, Rachapalle Reddi S, Rajagopal R, et al. (2017): Corneal Collagen Cross-Linking for Keratoconus in Pediatric Patients - Long-Term Results. Cornea.

Pahuja NK, Shetty R, Sinha Roy A, Thakkar MM, Jayadev C, Nuijts RM & Nagaraja H (2017): Laser Vision Correction with Q Factor Modification for Keratoconus Management. Curr Eye Res **42**: 542–548.

Papali'i-Curtin AT, Cox R, Ma T, Woods L, Covello A & Hall RC (2019): Keratoconus Prevalence among High School Students in New Zealand. Cornea **38**: 1382–1389.

Piñero DP, Alió JL, Alesón A, Escaf M & Miranda M (2009): Pentacam posterior and anterior corneal aberrations in normal and keratoconic eyes. Clin Exp Optom **92**: 297–303.

Pouliquen Y, Forman MR & Giraud JP (1981): Vitesse D'Evolution Du Keratocone. Etude Des Relations Entre

L'Age De Decouverte Et L'Age Auquel Il Est Opere. J Fr Ophtalmol **4**: 219–221.

Saad A & Gatinel D (2010): Topographic and tomographic properties of forme fruste keratoconus corneas. Investig Ophthalmol Vis Sci **51**: 5546–5555.

Sabti S, Tappeiner C & Frueh BE (2015): Corneal Cross-Linking in a 4-Year-Old Child with Keratoconus and Down Syndrome. Cornea **34**: 1157–1160.

Saini JS, Saroha V, Singh P, Sukhija JS & Jain AK (2004): Keratoconus in Asian eyes at a tertiary eye care facility. Clin Exp Optom **87**: 97–101.

Schlegel Z, Hoang-Xuan T & Gatinel D (2008): Comparison of and correlation between anterior and posterior corneal elevation maps in normal eyes and keratoconus-suspect eyes. J Cataract Refract Surg **34**: 789–795.

Smadja D, Touboul D, Cohen A, Doveh E, Santhiago MR, Mello GR, Krueger RR & Colin J (2013): Detection of subclinical keratoconus using an automated decision tree classification. Am J Ophthalmol **156**: 237-246.e1.

Uçakhan ÖÖ, Çetinkor V, Özkan M & Kanpolat A (2011): Evaluation of Scheimpflug imaging parameters in subclinical keratoconus, keratoconus, and normal eyes. J Cataract Refract Surg **37**: 1116–1124.

Zadnik K, Barr JT, Gordon MO & Edrington TB (1996): Biomicroscopic signs and disease severity in keratoconus. Cornea **15**: 139–146.

Figure Legends

Figure 1. Spearman correlation graph between corrected distance visual acuity (CDVA) versus asphericity Q value (up) and spherical aberration (down). Both points have been integrated in the same graph due to the relationship between both variables.

Figure 2. Spearman correlation graph between corrected distance visual acuity (CDVA) versus primary (Z3) (up) and secondary (Z5) (down) vertical coma. Both points have been integrated in the same graph due to the relationship between both variables.

Table 1.Topographic and tomographic differences between the two age-based ranges group in paediatric keratoconus.

	Group 1 (≥ 6 and ≤14) n = 70	Group 2 (> 14 and ≤ 18) n = 160	*P* value
Age (years)	12.67 ± 1.83 (6 to 14)	16.71 ± 1.15 (15 to 18)	< .01
Sphere (D)	-1.12 ± 3.52 (-11.50 to +6.00)	-2.25 ± 2.67 (-10.00 to +2.25)	.106
Cylinder (D)	-3.58 ± 2.13 (-9.00 to 0.00)	-3.09 ± 1.76 (-8.50 to -0.50)	.239
CDVA (Decimal)	0.64 ± 0.25 (0.05 to 1.00)	0.58 ± 0.29 (0.05 to 1.00)	.339
K steep (D)	50.45 ± 6.78 (41.60 to 75.60)	50.75 ± 6.72 (40.20 to 77.70)	.754
K flat (D)	46.13 ± 5.88 (39.30 to 70.90)	46.71 ± 5.72 (40.20 to 68.70)	.483
K mean (D)	48.25 ± 6.20 (42.10 to 72.50)	48.64 ± 6.06 (41.00 to 72.60)	.655
K maximum (D)	56.12 ± 9.32 (44.50 to 85.20)	57.80 ± 9.65 (43.20 to 89.80)	.219
CCT (µm)	476.47 ± 63.84 (231.00 to 626.00)	476.05 ± 50.10 (328.00 to 603.00)	.957
TCT (µm)	466.17 ± 64.80 (204.00 to 613.00)	466.53 ± 50.67 (323.00 to 593.00)	.963
AST (D)	4.25 ± 2.52 (0.30 to 11.20)	4.02 ± 2.40 (0.00 to 14.50)	.511
Q value	-0.84 ± 0.46 (-2.33 to -0.22)	-0.96 ± 0.56 (-2.76 to -0.16)	.128
TKC	2.08 ± 0.89 (1.00 to 4.00)	2.38 ± 0.82 (1.00 to 4.00)	< .05
KI	1.20 ± 0.12 (1.07 to 1.61)	1.23 ± 0.14 (1.07 to 2.20)	.06
BAD	8.30 ± 7.57 (0.53 to 42.88)	9.23 ± 5.79 (0.49 to 33.41)	.308
Z_3^{-1}	-1.88 ± 1.39 (-7.48 to +0.27)	-2.22 ± 1.17 (-5.55 to -0.23)	.059
Z_5^{-1}	-0.24 ± 0.40 (-1.24 to +0.48)	-0.34 ± 0.40 (-1.47 to +0.87)	.09
Z_4^0	-0.71 ± 0.97 (-4.59 to +0.29)	-1.07 ± 1.36 (-5.50 to +0.34)	< .05

Data were reported as mean ± standard deviation (minimum to maximum range). D: dioptres; CDVA: corrected distance visual acuity; K: keratometry; CCT: central corneal thickness; TCT: thinnest corneal thickness; AST: anterior corneal astigmatism; Q value: corneal asphericity at 8 mm; TKC: topographic keratoconus classification; KI: keratoconus index; BAD: Belin Ambrosio display; Z_3^{-1}: vertical primary comma Zernike coefficient; Z_5^{-1}: vertical secondary comma Zernike coefficient; $Z_4^{0:}$ primary spherical aberration Zernike coefficient.

Table 2.Topographic and tomographic differences between the three age-based ranges group in paediatric keratoconus.

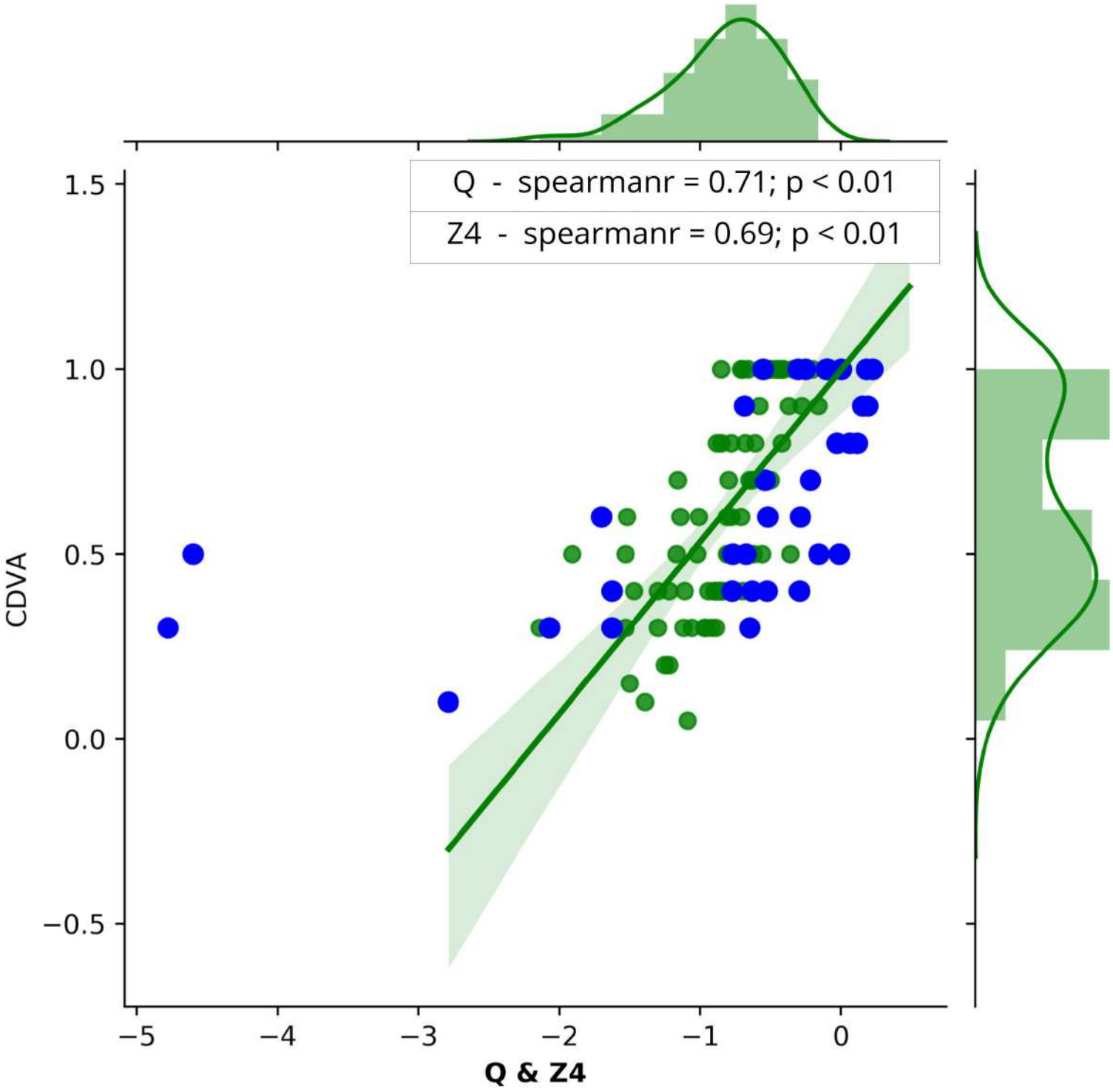
	Group 1 (≥ 6 and ≤14) n = 70	Group 2 (> 14 and < 17) n = 71	Group 3 (≥ 17 and ≤ 18) n = 89	*P* value (1 vs. 3)
Age (years)	12.67 ± 1.83 (6 to 14)	15.48 ± 0.50 (15 to 16)	17.60 ± 0.49 (17 to 18)	< .01
Sphere (D)	-1.12 ± 3.52 (-11.50 to +6.00)	-2.25 ± 2.81 (-10.00 to +1.50)	-2.25 ± 2.58 (-9.00 to +2.25)	.21
Cylinder (D)	-3.58 ± 2.13 (-9.00 to 0.00)	-3.40 ± 1.85 (-8.50 to -0.50)	-2,74 ± 1.62 (-6.00 to -0.50)	.11
CDVA (Decimal)	0.64 ± 0.25 (0.05 to 1.00)	0.52 ± 0.26 (0.10 to 1.00)	0.64 ± 0.31 (0.05 to 1.00)	.93
K steep (D)	50.45 ± 6.78 (41.60 to 75.60)	51.01 ± 6.89 (41.80 to 77.70)	50.55 ± 6.61 (40.20 to 73.00)	.92
K flat (D)	46.13 ± 5.88 (39.30 to 70.90)	46.46 ± 5.63 (41.30 to 68.10)	46.89 ± 5.81 (40.20 to 68.70)	.40
K mean (D)	48.25 ± 6.20 (42.10 to 72.50)	48.63 ± 6.11 (41.60 to 72.60)	48.65 ± 6.05 (41.00 to 70.80)	.67
K maximum (D)	56.12 ± 9.32 (44.50 to 85.20)	57.82 ± 9.65 (43.20 ± 89.90)	57.78 ± 9.71 (43.40 to 89.70)	.26
CCT (µm)	476.47 ± 63.84 (231.00 to 626.00)	468.52 ± 43.63 (328.00 to 570.00)	481.57 ± 53.91 (356.00 to 603.00)	.57
TCT (µm)	466.17 ± 64.80 (204.00 to 613.00)	458.91 ± 44.03 (323.00 to 567.00)	472.35 ± 54.73 (355.00 to 593.00)	.51
AST (D)	4.25 ± 2.52 (0.30 to 11.20)	4.68 ± 2.62 (0.40 to 14.50)	3.55 ± 2.12 (0.00 to 12.60)	.06
Q value	-0.84 ± 0.46 (-2.33 to -0.22)	-1.00 ± 0.54 (-2.46 to -0.16)	-0.93 ± 0.57 (-2.76 to -0.20)	.32
TKC	2.08 ± 0.89 (1.00 to 4.00)	2.41 ± 0.78 (1.00 to 4.00)	2.35 ± 0.85 (1.00 to 4.00)	< .05
KI	1.20 ± 0.12 (1.07 to 1.61)	1.21 ± 0.10 (1.07 to 1.62)	1.25 ± 0.16 (1.07 to 2.20)	< .05
BAD	8.30 ± 7.57 (0.53 to 42.88)	9.46 ± 5.81 (1.39 to 33.41)	9.06 ± 5.79 (0.49 to 29.73)	.46
Z_3^{-1}	-1.88 ± 1.39 (-7.48 to 0.27)	-1.98 ± 0.99 (-4.57 to -0.23)	-2.40 ± 1.26 (-5.55 to -0.25)	< .05
Z_5^{-1}	-0.24 ± 0.40 (-1.24 to +0.48)	-0.29 ± 0.39 (-1.18 to +0.87)	-0.37 ± 0.41 (-1.47 to +0.48)	< .05
Z_4^0	-0.71 ± 0.97 (-4.59 to +0.29)	-1.14 ± 1.38 (-5.32 to +0.28)	-1.03 ± 1.35 (-5.50 to +0.34)	.12

Data were reported as mean ± standard deviation (minimum to maximum range). D: dioptres; CDVA: corrected distance visual acuity; K: keratometry; CCT: central corneal thickness; TCT: thinnest corneal thickness; AST: anterior corneal astigmatism; Q value: corneal asphericity at 8 mm; TKC: topographic keratoconus classification; KI: keratoconus index; BAD: Belin Ambrosio display; Z_3^{-1}: vertical primary comma Zernike coefficient; Z_5^{-1}: vertical secondary comma Zernike coefficient; $Z_4^{0:}$ primary spherical aberration Zernike coefficient.

Table 3. Comparison chart in paediatric keratoconus available in scientific literature

	N	Age	CDVA	K Max	CCT	TCT	TKC	KI
Léoni-Mesplié et al. [1] (2012)	98	13.1 ± 2.1	0.50	51.32 ± 0.66	481.70 ± 7.03	454.94 ± 7.50	-	-
Naderan et al. [2] (2015) [a]	443	16.9 ± 2.2	0.78	55.8 ± 7.10	463.00 ± 48	447 ± 51	-	-
El-Khoury et al.[3] (2016)	16	11.87 ± 2.0	0.40	53.66 ± 11.12	487.00 ± 54.9	-	-	-
Naderan et al.[4] (2017)	158	15 ± 1.9	0.51	60.5 ± 8.6	440.00 ± 41.0	420.00 ± 46.00	-	-
Papali'i-Curtin et al.[7] (2019)	10	14.9 ± 0.7	0.63	48.7 ± 6.1	-	493.6 ± 35.1	1.4	1.1 ± 0.1
Rocha-De-Lossada et al. (2019)	278	15.48	0.61	57.29 ± 9.69	477.63 ± 55.71	467.56 ± 56.64	2.27 ± 0.85	1.22 ± 0.14

[a] Subjects were under 20 years old. N: number of subjects in the study; CDVA: corrected distance visual acuity; K Max: mean maximum keratometry; CCT: central corneal thickness; TCT: thinnest corneal thickness; TKC: topographic keratoconus classification; KI: keratoconus index.


Q - spearmanr = 0.71; p < 0.01
Z4 - spearmanr = 0.69; p < 0.01
CDVA
Q & Z4
1.5
1.0
0.5
0.0
−0.5
−5
−4
−3
−2
−1
0

Z3 - spearmanr = 0.48; p < 0.01

Z5 - spearmanr = 0.48; p < 0.01

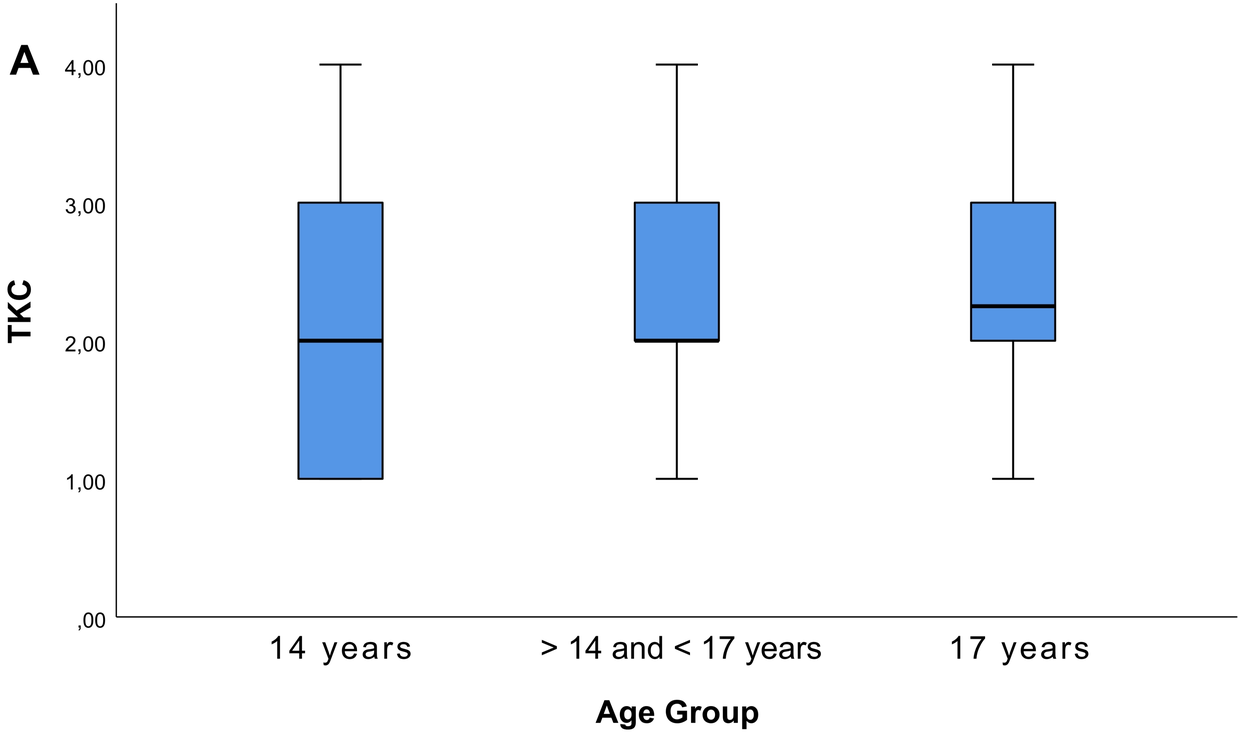
CDVA

1.25
1.00
0.75
0.50
0.25
0.00
−0.25
−0.50

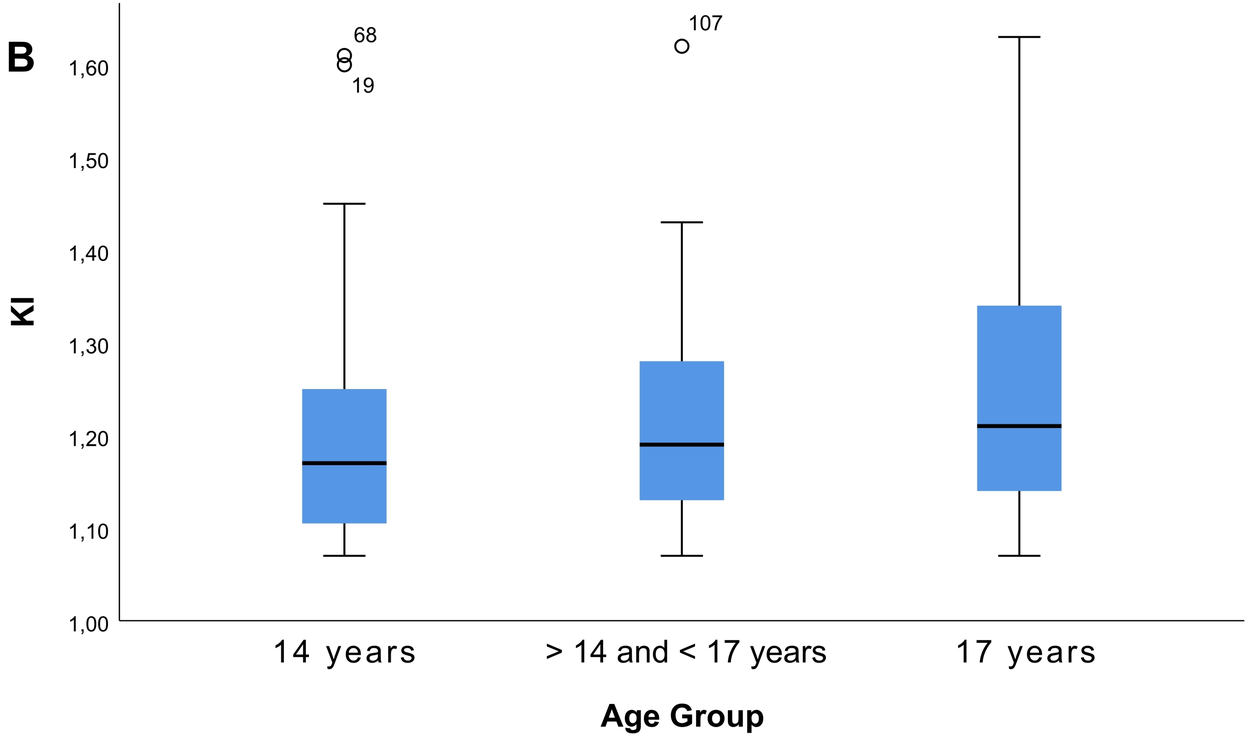
−10
−8
−6
−4
−2
0
2

Z3 & Z5

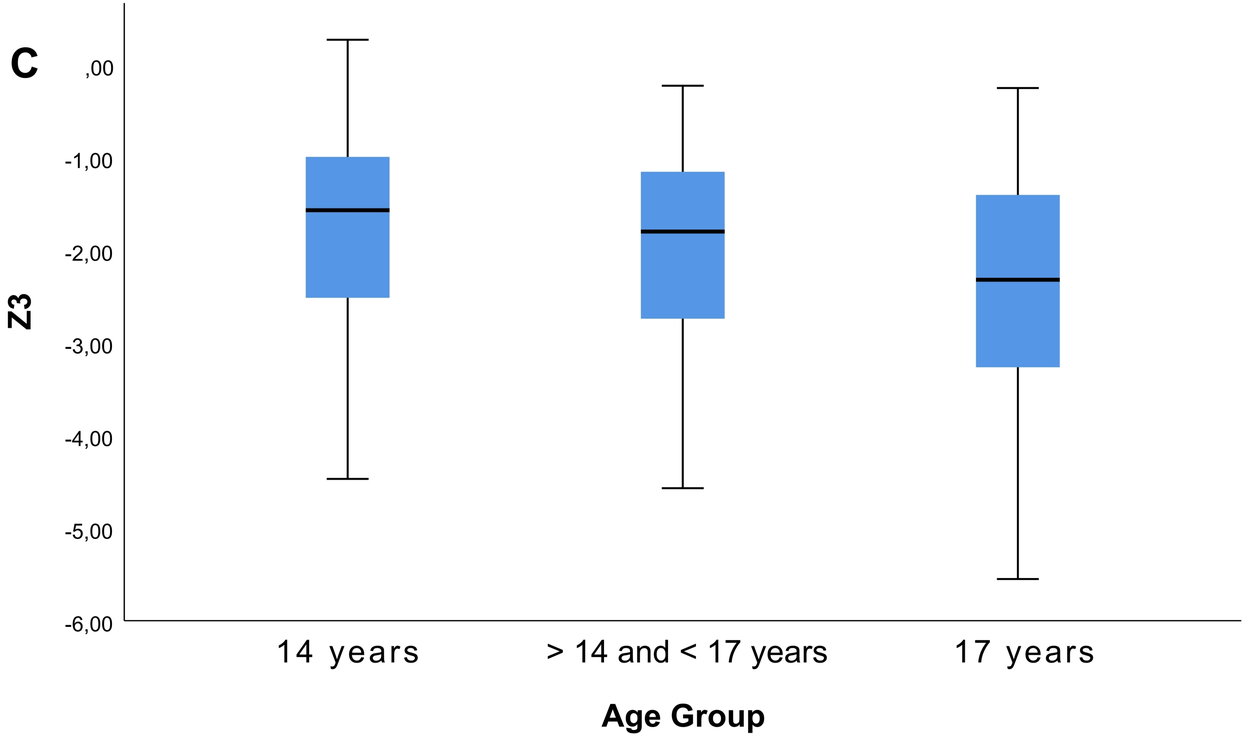
A


TKC
4,00
3,00
2,00
1,00
,00
14 years
> 14 and < 17 years
17 years
Age Group

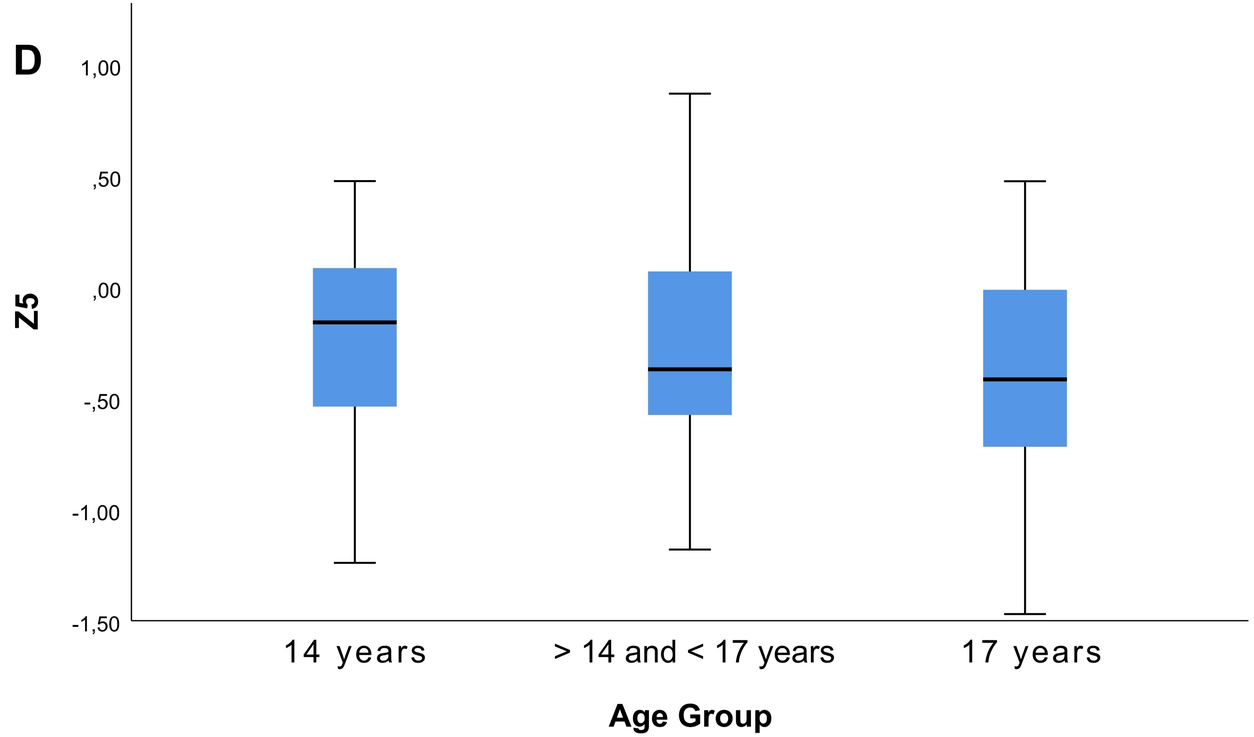
B


KI
68
19
107
1,60
1,50
1,40
1,30
1,20
1,10
1,00
14 years
> 14 and < 17 years
17 years
Age Group

C


Z3
,00
-1,00
-2,00
-3,00
-4,00
-5,00
-6,00
14 years
> 14 and < 17 years
17 years
Age Group

D


Z5
1,00
,50
,00
-,50
-1,00
-1,50
14 years
> 14 and < 17 years
17 years
Age Group