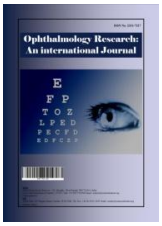

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Comparison between OrbscanIIz, Pentacam, Ultrasound Pachymetry (Tomey SP-100) at Different Stages of Keratoconus

E. Pateras[1*] and Ch. Koufala[1]

[1]Biomedical Department, Course of Optics and Optometry, Greece.

Authors' contributions

This work was carried out in collaboration between both authors. Author EP designed the study, performed the statistical analysis, and wrote the first draft of the manuscript. Author CK took the measurements and managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aims: To compare results of OrbscanIIz and Pentacam and Ultrasound pachymetry at different stages of keratoconus on corneal thickness.
Sample and Study Design: 94 keratoconic patients participated in the study, of which 52 were men and 42 women. Keratoconus patients were measured with OrbscanIIz, Pentacam and Ultrasound pachymetry in pre-operation examinations for corneal collagen cross-linking. The patients belong to different keratoconus stages.
Place and Duration of Study: University of West Attica Dept Biomedical Sciensce Course Optics & Optometry in collaboration with Athens "*Ophthalmologico"* Clinic during the period between October 2017 to January 2019.
Methodology: Corneal Pachymetry maps correlation of three types of corneal pachymeters OrbscanIIz, Pentacam and Ultrasound pachymetry (Tomey SP-100 Pachymeter). The measurements of the thinnest point of the cornea from each patient were collected at different stages of keratoconus and compared.
Results: A sample of 188 eyes were measured at different stages of keratoconus and compared for the thinnest corneal thickness with three different measurement systems, OrbscanIIz ,Pentacam

**Corresponding author: E-mail: pateras@uniwa.gr;*

and Ultrasound pachymetry. At sublinical stage Orbscan-Pentacam had Correlation coefficient r=0,7971, Orbscan-Ultrasound r=0,7483 and Pentacam-Ultrasound r=0,9442. At 1st stage Orbscan-Pentacam had Correlation coefficient r=0,8913, Orbscan-Ultrasound r=0,8151 and Pentacam-Ultrasound r=0,8151. At 2nd stage Orbscan-Pentacam had Correlation coefficient r=0,9339, Orbscan-Ultrasound r=0,8819 and Pentacam-Ultrasound r=0,9633. For 3rd stage Orbscan-Pentacam had Correlation coefficient r=0,8317, Orbscan-Ultrasound r=0,8457 and Pentacam-Ultrasound r=0,9633. For 4th stage Orbscan-Pentacam had Correlation coefficient r=-0,4655, Orbscan-Ultrasound r=0,3089 and Pentacam-Ultrasound r=0,9633. In *Iatrogenic keratoectasia*after refractive surgery Orbscan-Pentacam had Correlation coefficient r=0,9327, Orbscan-Ultrasound r=0,3089 and Pentacam-Ultrasound r=0,9859.

Conclusion: Statistical differences between OrbscanIIz, Pentacam and Ultrasound pachymetry were found for corneal thickness in all stages of keratoconus for the thinnest point measured. Orbscan-Pentacam have statistical significant differences but weak to moderate correlation. Orbscan-Ultasound have also statistical significant differences their correlation is very weak, while Pentacam-Ultrasound have statistical significant differences smaller as the previous but their correlation is very strong at all stages of keratoconus.

Keywords: Keratoconus; corneal pachymetry; orbscanIIz; pentacam; ultrasound; corneal thickness correlation.

1. INTRODUCTION

The cornea is considered to be a powerful positive meniscus lens which presents errors, contributing to various refractive errors and high-order aberrations. In addition, it can show various distortions in its shape and structure like ectasia and different diseases, where the most common, is keratoconus.

It is necessary therefore to have topographical maps in order to get accurate information about its thickness, altimetric differences, and curvature data on both its front and back surfaces. The cornea topographical maps are used to present its many peculiarities and to diagnose diseases such as keratoconus. For this purpose several instruments have been developed. Topographic devices are numerous and differ from each other in terms of topographic maps, indicators, recording details and the information they provide.

Keratoconus result in severe visual disturbances with blurred, distorted or even multiple images. The area of the cone gradually shows thinning, scarring and eventually opacity. Depending on the stage of the disease, each layer of the cornea can contribute to the pathophysiology of the cornea. In the epithelium, the degeneration of the basal cells may be visible. The rupture is accompanied with an ingrowth of epithelial cells between the Bowman's layer and the epithelium with epithelial iron deposits around the base of the cone, known as the Fleischer ring (Fig. 1). These deposits come from the tear film and are due to the anomalous corneal morphology [1].

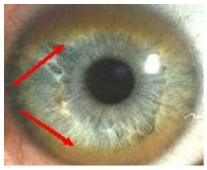


Fig. 1. The red arrows indicate Fleischer ring [2]

Ruptures and reticular scars may be seen on the Bowman's membrane, while the corneal layer thins centrally or paracentrically in the lower part of the cornea, to such an extent that it reaches 1/3 of the thickness of the normal cornea presenting thin, vertical ridges parallel to the cone (Vogt's striae) [3] (Fig. 2).

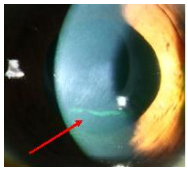


Fig. 2. The red arrow indicates vertical ridges parallel two of the cone (Vogt's striae) [4]

A clinical evidence of keratoconus is an intense curvature of the lower eyelid when the patient takes a lower eye position (Munson point) (Fig. 3), fibrosis and visible corneal nerves, represented as a network of gray lines in white deposit spots [5].

Fig. 3. The red arrow indicates Munson point [6]

In advanced stages of the disease, the Rizzuti point becomes visible, during which a thin beam of light strikes the limbus, producing a light nasal reflection of the abnormal corneal shape [1] (Fig. 4).

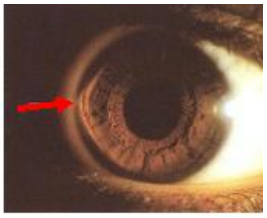


Fig. 4. The red arrow indicates Rizzuti point [7]

Moreover, there are particular very steep corneal curvatures (<7.00 mm) and irregularly shaped images in keratometry, whose center lines are almost impossible to align and, therefore, give us a reliable measurement. Between the keratometry images, a varying degree angle is formed, known as an Amsler angle [3].

1.1 Causes and Epidemiology

In its classic form, keratoconus appears in adolescence and usually develops by the age of 35-40, when it stabilizes. The onset of the disease may be delayed, as may the development of the disease at any age. In rare cases, it appears at birth. The age of onset is a determining factor in the development of keratoconus. The younger the patient is when the disease occurs, the faster it is expected to develop. Conversely, when the onset of the disease is relatively slow (such as after the age of 30, for example), the course is expected to be much slower. Keratoconus is basically a multifaceted disease, with a different time and degree of development in each eye, and the frequency of its occurrence is the same in both sexes. Despite ongoing research, the exact causes of keratoconus are not known. There are studies that support its association with other coexisting diseases, either ocular like spring keratoconjunctivitis, ectopic lens, retinal detachment, cataract or systemic diseases such as Down, Marfan syndrome, Leber autoimmunity, connective tissue diseases, etc.) [1,3,5].

The association of keratoconus in diabetes has been analyzed but the incidence of keratoconus in diabetics has not been found to be higher than the general population. However, it is noteworthy that diabetics develop less severe forms of the disease. The explanation given is due to the normal glycosylation (the enzymatic modification of proteins, by adding sugar molecules) that occurs in the stratum corneum of diabetic patients. This results in the creation of more cross links between the collagen fibers of the cornea and thus the enhancement of its mechanical strength. Some associations may be attributed to extension of the cornea secondarily due to traumatic injury or failed refractive surgery (iatrogenic keratoconus), while others appear to rely on a common gene as a genetic pathogen, leading to its possible characterization. There are many studies that support the role of a genetic background in the etiology of the disease [8-13].

Genetic predisposition occurs due to 1) increased incidence in members of the same family, 2) high correlation in monozygotic twins and 3) correlation of keratoconus with a variety of genetic syndromes [8]. Although keratoconus also occurs sporadically, a rate of 6-23.5% has been reported in a positive family history of keratoconus, suggesting that the hereditary factor plays a significant role [9-10]. Similarly, in other genetic disorders of the eye, studies have shown that relatives of keratoconus patients are about 15-67 times more likely to develop keratoconus than individuals with a negative history [5]. Studying the inheritance model, it seems that keratoconus is inherited in the predominant type or in the predominant imperfect penetration, as well as some relatives may carry the abnormal gene without presenting the condition. At times, structural or metabolic abnormalities at the corneal level have been implicated, leading to the production of abnormal collagen and possibly genetically predetermined.

Atopic diseases (allergic rhinitis, eczema, asthma) and eye rubbing are some of the other reasons that appear to be strongly linked to the disease [11-13]. Several engineering models have been suggested to explain the relationship between rubbing eyes and keratoconus. In keratoconus patients, it is common to see increased frequency, intensity, and duration of

friction. There are also sharp differences in the way in which, through rotational motions, more force is exerted on the surface of the cornea when rubbing the eye.

The mechanic is that the wound caused by the rubbing, reduces the strength of the stroma and thus allows the cornea to take the form of a cone. Epithelial trauma associated with scrubbing triggers the secretion of flame retardants and causes a trauma recovery reaction in the keratocytes. Changes in keratocytes and apoptosis may lead to inability to repair collagen and weaken the stratum corneum, which are some of the key features of the disease. The changes that occur are due to the differentiation in collagen metabolism. They develop due to increased hydrostatic pressure caused by abrasion and both lead to the weakening of the stroma. Large fluctuations and an increase in intraocular pressure due to friction may expose the thinner areas of the cornea more.

Although rubbing the eyes is an important factor, it cannot be considered as the cause of the disease. It is therefore easy to understand that the pathophysiological mechanism that leads to the development of keratoconus is not yet fully understood. It is a multifactorial disease, in the development of which both environmental and genetic reasons contribute.

As for the incidence of keratoconus in the general population, it varies according to various studies. Reports indicate a fluctuation between 4-6 cases per 1.000, which is considered relatively stable over the last 50 years [14-15]. In other studies, the incidence ranged from 1.3 to 25 per 100.000 per year among different populations and the prevalence ranged from 8.8 to 229 per 100.000. The incidence and prevalence rates vary from country to country. In Greece, keratoconus patients are estimated to be over 20.000 (frequency~2/1.000 inhabitants), while in Asian countries an increased incidence of keratoconus was found in relation to the countries of the white race [14-15]. This fact may depend on the diagnostic criteria of the authors or may indicate the different involvement of both the genes and the environmental factors in each country.

1.2 Topography-Pachymetry of the Cornea

OrbscanIIz besides the topographical maps that it provides it can give pachymetric map of the cornea. This can be done by projecting on the cornea optical sections similar to those of the slit lamp, to obtain data. A key advantage of slit-scanning technology (Fig. 5), used by the OrbscanIIz system, is that it measures curvatures and elevation differences (elevations and depths) of both the anterior and posterior surface of the cornea. The posterior surface, although having much less visual power than the anterior one, contributes significantly to visual performance and its measurement allows a better understanding of the morphology of an abnormal cornea. It is therefore extremely important for the diagnosis of diseases such as keratoconus, even in the early stages. This digitized image provides information about the shape and thickness of the cornea between two successive slit shots. At the end, the images can be printed on three-dimensional topographic maps [16].

OrbscanIIz topography helped diagnose subclinical keratoconus with the usage of the curved and altimeter map of the back surface. The reason is that in an initial (subclinical) keratoconus, the anterior corneal surface does not show much elevation because the epithelium normalizes the curvature and elevation maps, making the cone invisible. In contrast, the posterior surface, with the single layer of hexagonal cells endothelium, cannot normalize the cone, and the extent is obvious. Such cases can therefore be diagnosed with greater safety excluding a candidate from refractive surgery, which would increase the risk of postoperative results, or be used in cases requiring combination surgery (PRK and CXL).

Some of the main advantages of OrbscanIIz are:

- Better recording data for elevation and curvature of the cornea, as it combines slit scan and placido disc technologies.
- Large visual recording zones (up to 11mm).
- Less sensitivity of the device to focus.
- The eye, due to the wide range of its movements, is monitored before the absolute determination of the height of the surfaces. The data of the optical sections are reduced to the initial position of the eye and the changes of the position are removed from its movements.
- Less dependence on the tear film, since conditionally the reflections of the rings are considered on the cornea and not on the tear film.

Fig. 5. Corneal maps of both the anterior and posterior surface of the cornea, refractive map of the overall cornea surface and bottom right (red arrow) Pachymetry map for OrbscanIIz[16]

1.2.1 Pentacam

The Pentacam device, unlike OrbscanIIz, is not affected by small corneal blurring, and can accurately calculate the point and curvature of the apex. This is achieved by computing all the data as the camera rotates. In Pentacam topography, the refractive power of the entire cornea can also be calculated with extreme precision. Knowing the exact topography, one can measure the slope with which a ray of light falls on the cornea, and thus calculate the exact refractive power using Snell's law, and not the relationship that connects the curvature radius to the surface power, which applies only axially (Fig. 6) [17].

In an attempt to summarize the main features of the Pentacam device we would say the following:

- Scheimpflug image technique. Camera position can be changed (rotating).
- The entire anterior hemisphere is stereoscopically depicted, from the cornea to the posterior margin, including the anterior chamber angle.
- Corneal topography from the measurements of the elevation throughout the area of the cornea, the topographic analysis of the anterior and posterior cornea is obtained. It is possible to compare preoperative and postoperative topography.
- Pachymetry. Is calculated from the height difference between the anterior and posterior surface of the cornea. The Pentacam system has been shown to be highly reliable and gives similar results to ultrasound, while it appears to have an advantage over OrbscanIIz in postoperative eye surgery
- Anterior chamber. The angle, volume and height of the anterior chamber are calculated, while any point of the anterior chamber can be manually selected and measured.
- Corneal and crystalline lens presentation. The blurring of the lens is assessed and comparative studies are performed.

Important corneal topography maps [18] are:

- *Axial maps (axial maps or sagittal maps)*
- Tangential maps or meridional maps
- *Elevation maps*
- *Refractive maps*
- *Corneal thickness maps*
- *Wavefront analysis maps*

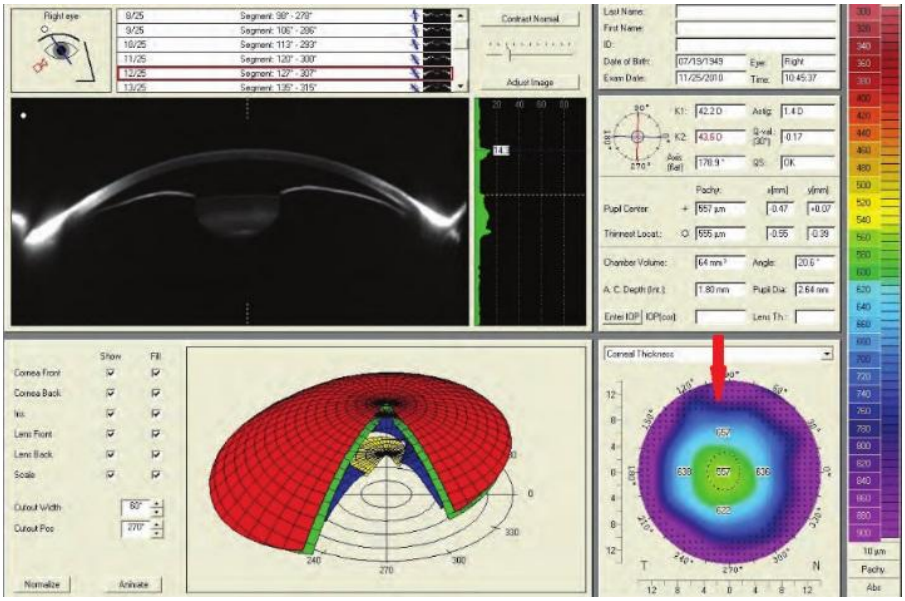


Fig. 6. General Overview display Pentacam system showing ACD (anterior chamber distance), and bottom right (red arrow) Pachymetry map [17]

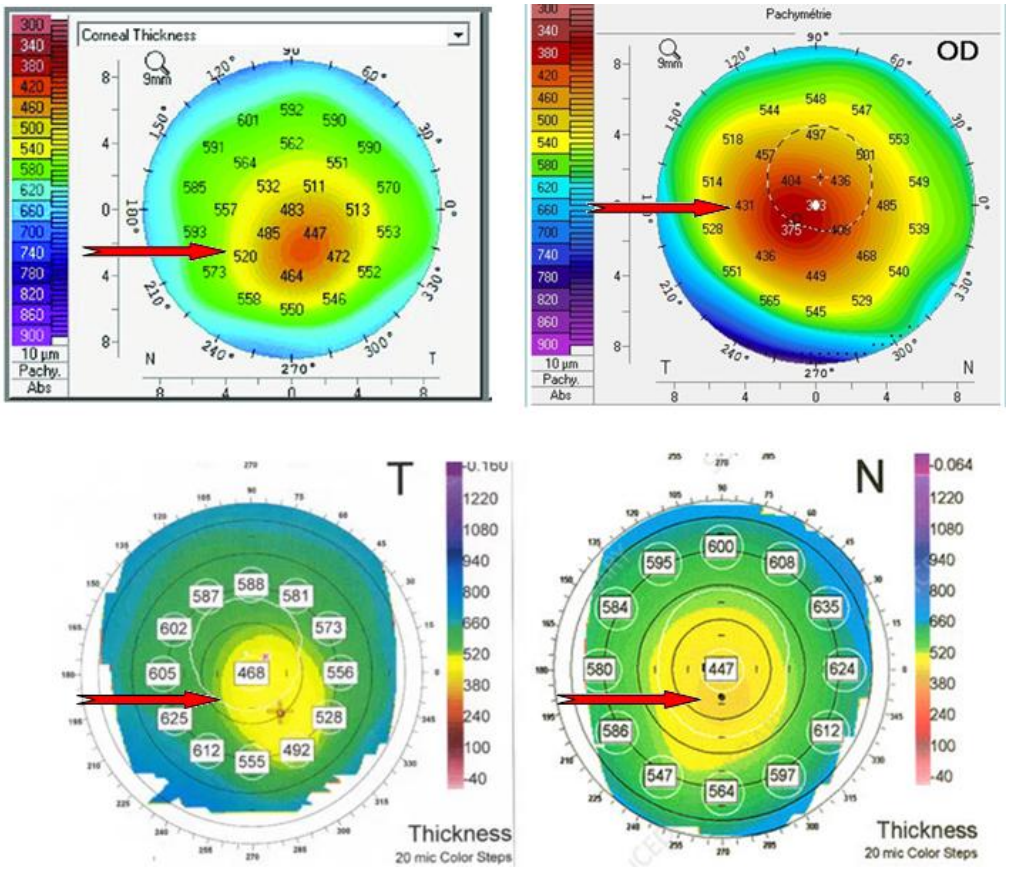


Fig. 7. Corneal thickness maps in keratoconic patients a) Pentacam system b) Orbscanllz[16-17]

1.2.2 Ultrasound pachymetry system

Ultrasound pachymetrysystem (TOMEY SP-100 PACHYMETER) uses sound velocity. It has an adjustable velocity from 1,400-2,000 m/s. The Ultrasound pachymetry displays the average of 8 corneal thickness measurements [19]. Every single measurement is already an average out of up to 20 exams. There is a selection of three data types: average, maximum or minimum. All data are also displayed on the large illuminated LCD display. One drop of 0.5% tetracaine hydrochloride is instilled on the cornea 5 minutes before the measurement where the examiner places the probe perpendicularly on the corneal center in order to get measurements. The lowest of the measurements was selected and recorded for this study.

Fig. 8. Display measurement of corneal thickness for Ultrasound pachymeter (TOMEY SP-100) [19]

1.3 Corneal Thickness

The basic structure of the cornea consists of the following layers: Epithelium, Bowman membrane, Stroma, Descemet membrane and Endothelium. Corneal thickness ranges between 450 and 610 μm and averages 550 μm.

Table 1. Classification of corneal thickness

Very thin	<510 μm
Thin	<535 μm
Average	540 μm to 560 μm
Thick	>565 μm
Very thick	>600 μm

1.4 Purpose

The aim of this study is to compare the corneal pachymetry maps between Pentacam and OrbscanIIz and Ultrasound pachymetry devices in different stages of keratoconus. This study between the aforementioned systems aims to reveal the similarities and the differences in corneal thickness in the stages of keratoconus. The stages investigated were keratoconussubclinical, stages 1 to 4 and iatrogenic keratoektasia.

2. METHODOLOGY

The corneal topography study in patients with keratoconus, was performed at the "*Athens Ophthalmologico Clinic*" during the period between October 2017 and April 2019.

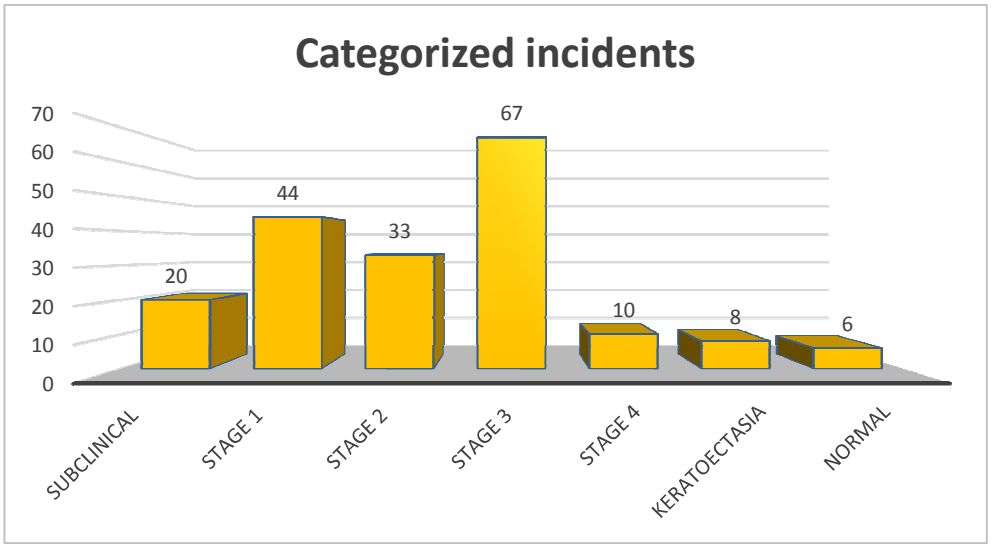


Fig. 9. Keratoconus patients sample according to stage of keratoconus

94 keratoconus patients were included in the study, of which 52 were men and 42 women. The mean age of the total sample was 26 ± 1,5 years. From the 188 eyes 6 were normal. More specifically, in 6 patients (4 men and 2 women) the image of the cornea was normal in one of the two eyes. 8 eyes were diagnosed with iatrogenic keratoectasia after refractive surgery. 174 eyes were diagnosed with keratoconus of various stages. Corneal pachymetry maps were taken with the ORBSCAN IIz / Bausch & Lomb and Allegro Oculyzer / Wavelight (PENTACAM) and devices and TOMEY SP-100. The study was conducted from October 2017 to January 2019.

Regarding the comparison of the three corneal pachymetry systems with respect to the measured corneal thickness, the data represents the thinnest point of the cornea from each topography map. The thickness of the patients' cornea was also calculated by ultrasound. Ultrasound pachymetry, which is always performed during a typical eye examination, is considered to be a very reliable method for measuring corneal thickness. The chart below shows the distribution of keratoconic patients at different stages.

3. RESULTS AND DISCUSSION

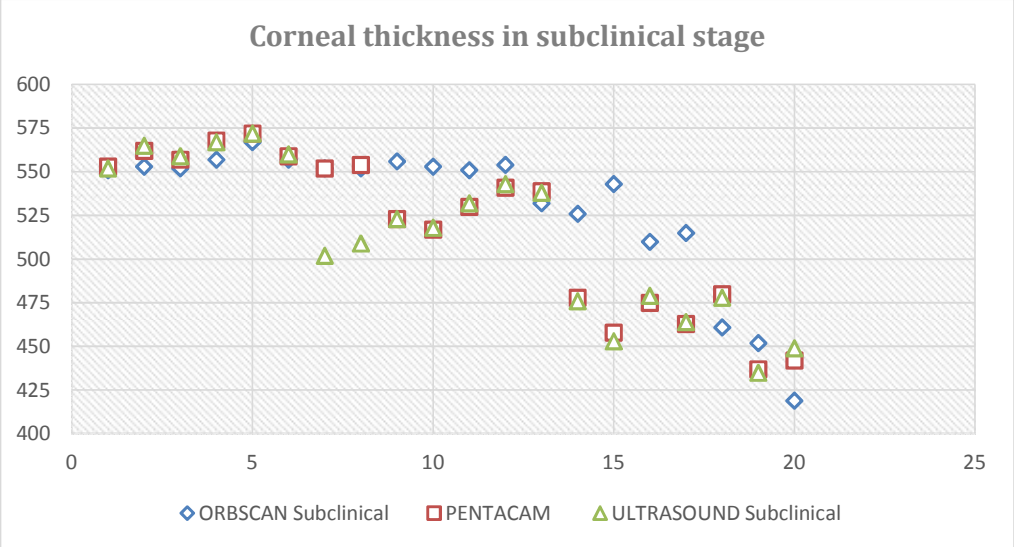
3.1 Subclinical Keratoconus

Subclinical keratoconus comparison results for OrbscanIIz and Pentacam and Ultrasound pachymetry.

In the subclinical stage of keratoconus, OrbscanIIz presented an average corneal thickness of 531μm, while Pentacam an average of 518μm. Their mean difference is -12.65 μm, while their standard deviation of mean difference is 27.7968μm. The differences between them are considered not statistically significant Paired samples t-test withTwo-tailed probability (P = 0.0560), but their correlation is strong, having Correlation coefficient r=0.7971 andSpearman's coefficientof rank correlation (rho) =0.816.

Comparing OrbscanIIz and Ultrasound their mean difference is -16.95 μm, while their standard deviation of mean difference is 30.2646. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P = 0.0215), but their correlation is strong, having Correlation coefficient r=0.7483 and Spearman's coefficientof rank correlation (rho) =0.822.

Comparing Pentacam and Ultrasound their mean difference is -4.3 μm, while their standard deviation of mean difference is 15.0161. The differences between them are not considered statistically significant Paired samples t-testTwo-tailed probability (P = 0.2157), and their correlation is strong, having Correlation coefficient r=0.9442 and Spearman's coefficientof rank correlation (rho) =0.934.



Graph 1. The corneal thickness (thinnest point) for each keratoconus eye in the subclinical stage, measured with Orbscan, Pentacam and Ultrasound

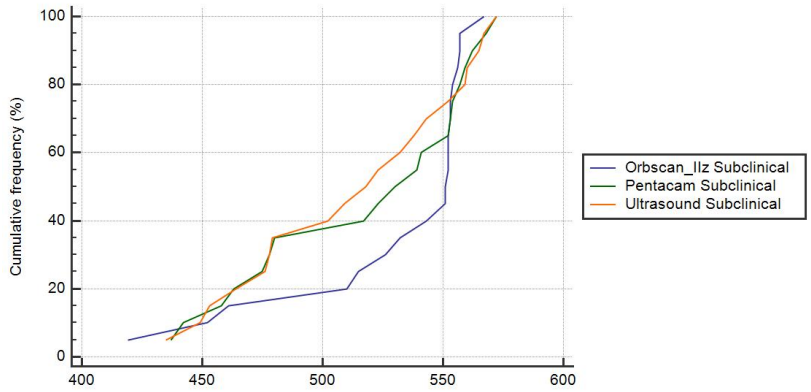
Table 2.Subclinical keratoconus

	Orbscan II	Pentacam	Ultrasound
Sample size	20	20	20
Arithmetic mean	530,65	518	513,7
95% CI for the mean	511,6111 to 549,6889	496,7348 to 539,2652	493,0425 to 534,3575
Variance	1654,8711	2064,5263	1948,2211
Standard Deviation	40,6801	45,4371	44,1387
Standard error of the mean	9,0963	10,16	9,8697

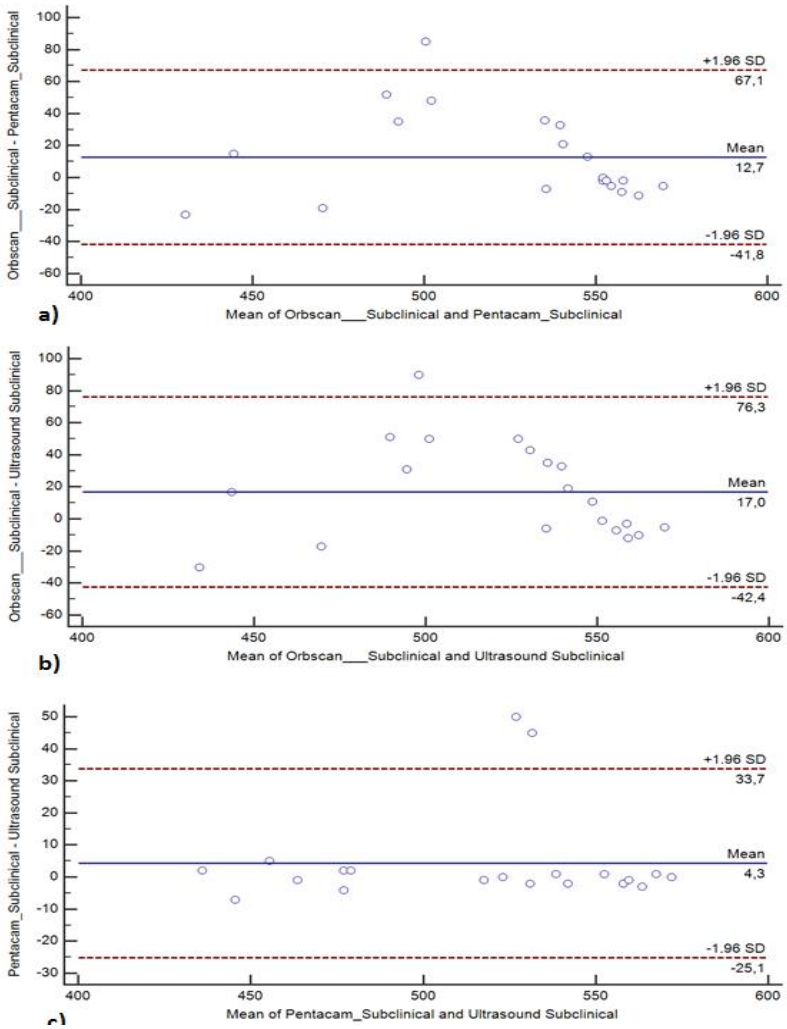
Paired samples t-test	Orbscanllz vice Pentacam
Mean difference	-12,65
Standard deviation of mean difference	27,7968
Standard error of mean difference	6,2155
95% CI	-25,6593 to 0,3593
Test statistic t	-2,035
Degrees of Freedom (DF)	19
Two-tailed probability	P = 0,0560
	Correlation of Orbscanllz and Pentacam
Correlation coefficient r	0,7971
Significance level	P<0,0001
95% Confidence interval for r	0,5478 to 0,9164
Spearman's coefficient of rank correlation (rho)	0,816
Significance level	P<0,0001
95% Confidence Interval for rho	0,584 to 0,925

Paired samples t-test	Orbscanllz vice Ultrasound
Mean difference	-16,95
Standard deviation of mean difference	30,2646
Standard error of mean difference	6,7674
95% CI	-31,1143 to -2,7857
Test statistic t	-2,505
Degrees of Freedom (DF)	19
Two-tailed probability	P = 0,0215
	Correlation of Orbscanllz and Ultrsound
Correlation coefficient r	0,7483
Significance level	P=0,0001
95% Confidence interval for r	0,4571 to 0,8946
Spearman's coefficient of rank correlation (rho)	0,822
Significance level	P<0,0001
95% Confidence Interval for rho	0,597 to 0,927

Paired samples t-test	Pentacam vice Ultrasound
Mean difference	-4,3
Standard deviation of mean difference	15,0161
Standard error of mean difference	3,3577
95% CI	-11,3278 to 2,7278
Test statistic t	-1,281
Degrees of Freedom (DF)	19
Two-tailed probability	P = 0,2157
	Correlation of Pentacam and Ultrsound
Correlation coefficient r	0,9442
Significance level	P<0,0001
95% Confidence interval for r	0,8617 to 0,9781
Spearman's coefficient of rank correlation (rho)	0,934
Significance level	P<0,0001
95% Confidence Interval for rho	0,837 to 0,974



Graph 2. Cumulative frequency (%) for corneal thickness (thinnest point) in the subclinical stage, measured with Orbscan, Pentacam and Ultrasound. Pentacam& Ultrasound seem to be relatively close



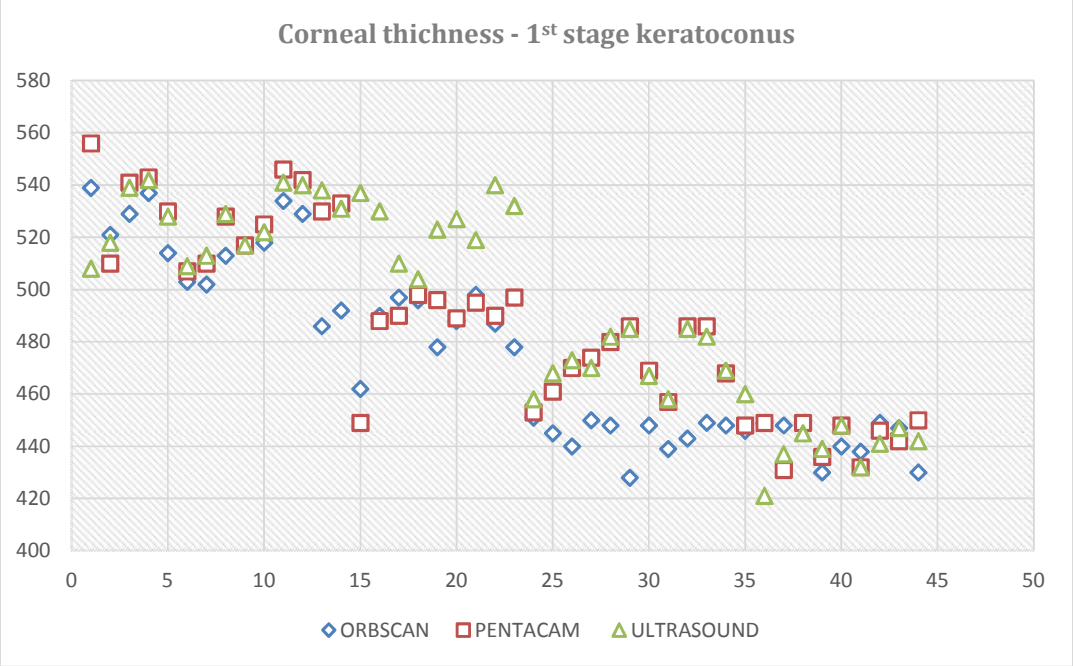
Graph 3. Bland & Altman Plot for corneal thickness (thinnest point) in the subclinical stage, comparing a) OrbscanIIz&Pentacam b) OrbscanIIz& Ultrasound c) Pentacam& Ultrasound

3.2 1st Stage Keratoconus

In the 1st stage of keratoconus, OrbscanIIz presented an average corneal thickness of 475.5μm, while Pentacam an average of 487.0682μm. Their mean difference is11.5682μm, while their standard deviation of mean difference is 16.3841 μm. The differences between them are considered statistically significant Paired samples t-test withTwo-tailed probability (P<0.0001), but their correlation is strong, having Correlation coefficient r=0.8913andSpearman's coefficientof rank correlation (rho) =0.851.

Comparing OrbscanIIz and Ultrasound their mean difference is 17.8182μm, while their standard deviation of mean difference is 22.2578. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P<0.0001), but their correlation is strong, having Correlation coefficient r=0.8151and Spearman's coefficientof rank correlation (rho)=0.748.

Comparing Pentacam and Ultrasound their mean difference is 6.2500μm, while their standard deviation of mean difference is 20.7007. The differences between them are not considered statistically significant Paired samples t-testTwo-tailed probability (P =0.0515), and their correlation is strong, having Correlation coefficient r=0.8151and Spearman's coefficientof rank correlation (rho) =0.838.



Graph 4. The corneal thickness (thinnest point) for each keratoconus eye in the 1st stage, measured with Orbscan, Pentacam and Ultrasound

Table 3. 1st Stage

	Orbscan II	Pentacam	Ultrasound
Sample size	44	44	44
Arithmetic mean	475,5000	487,0682	493,3182
95% CI for the mean	464,9442 to 486,0558	476,2800 to 497,8564	481,8168 to 504,8195
Variance	1205,4651	1259,1348	1431,1057
Standard Deviation	34,7198	35,4843	37,8300
Standard error of the mean	5,2342	5,3495	5,7031

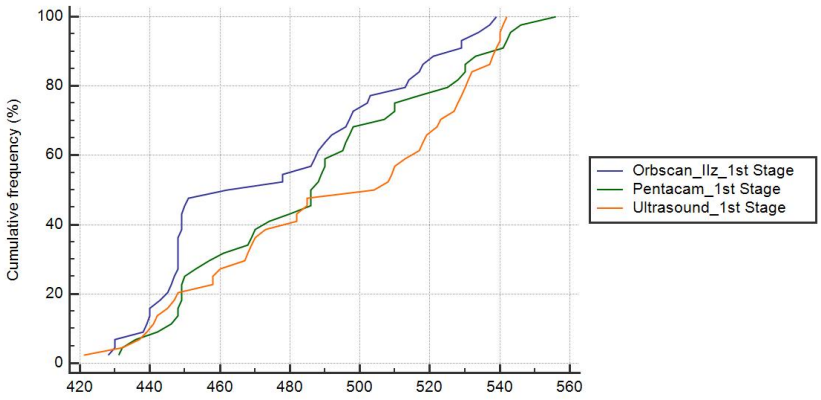
Paired samples t-test	Orbscanllz vice Pentacam
Mean difference	11,5682
Standard deviation of mean difference	16,3841
Standard error of mean difference	2,4700
95% CI	6,5870 to 16,5494
Test statistic t	4,683
Degrees of Freedom (DF)	43
Two-tailed probability	P < 0,0001
	Correlation of Orbscanllz and Pentacam
Correlation coefficient r	0,8913
Significance level	P<0,0001
95% Confidence interval for r	0,8083 to 0,9396
Spearman's coefficient of rank correlation (rho)	0,851
Significance level	P<0,0001
95% Confidence Interval for rho	0,741 to 0,916

Paired samples t-test	Orbscanllz vice Ultrsound
Mean difference	17,8182
Standard deviation of mean difference	22,2578
Standard error of mean difference	3,3555
95% CI	11,0512 to 24,5852
Test statistic t	5,310
Degrees of Freedom (DF)	43
Two-tailed probability	P < 0,0001
	Correlation of Orbscanllz and Ultrasound
Correlation coefficient r	0,8151
Significance level	P<0,0001
95% Confidence interval for r	0,6836 to 0,8953
Spearman's coefficient of rank correlation (rho)	0,748
Significance level	P<0,0001
95% Confidence Interval for rho	0,580 to 0,855

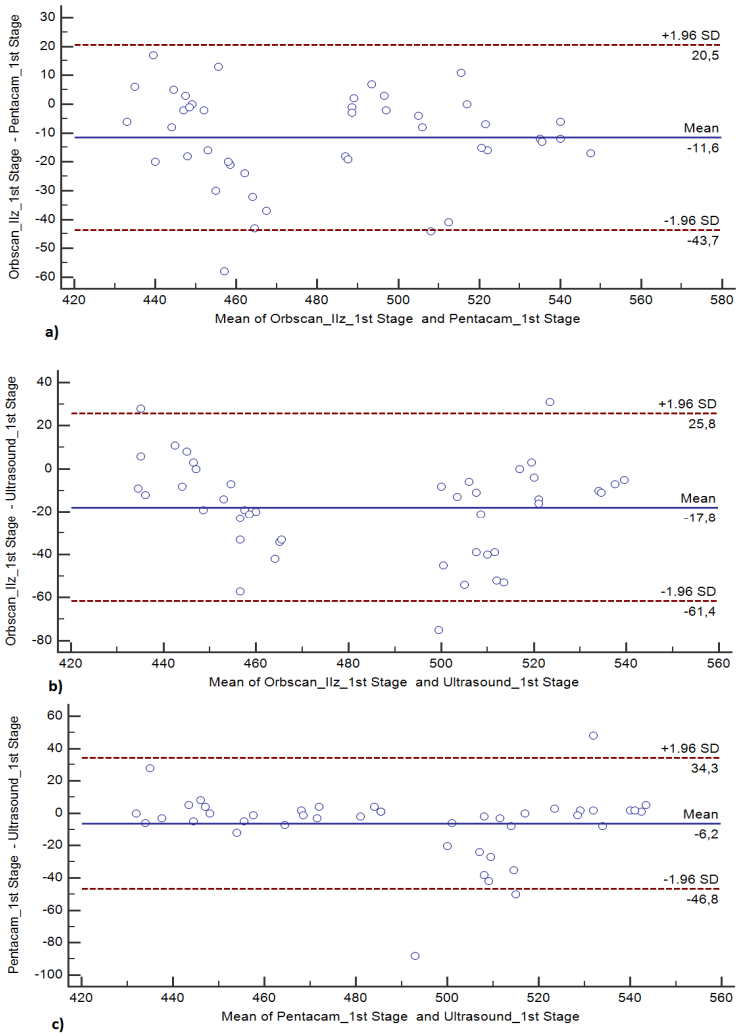
Paired samples t-test	Pentacam vice Ultrsound
Mean difference	6,2500
Standard deviation of mean difference	20,7007
Standard error of mean difference	3,1207
95% CI	-0,04358 to 12,5436
Test statistic t	2,003
Degrees of Freedom (DF)	43
Two-tailed probability	P = 0,0515
	Correlation of Pentacam and Ultrasound
Correlation coefficient r	0,8151
Significance level	P<0,0001
95% Confidence interval for r	0,6836 to 0,8953
Spearman's coefficient of rank correlation (rho)	0,838
Significance level	P<0,0001
95% Confidence Interval for rho	0,721 to 0,909

3.3 2nd Stage Keratoconus

In the 2nd stage of keratoconus, Orbscanllz presented an average corneal thickness of 460.6970μm, while Pentacam an average of 466.0909μm. Their mean difference is 5.3939μm, while their standard deviation of mean difference is 10.0590. The differences between them are considered statistically significant Paired samples t-test withTwo-tailed probability (P=0.0016), but their correlation is strong, having Correlation coefficient r=0.9339andSpearman'scoefficientof rank correla tion (rho) =0.927.



Graph 5. Cumulative frequency (%) for corneal thickness in the 1st stage, measured with Orbscan, Pentacam and Ultrasound. Pentacam& Ultrasound seem to be relatively close



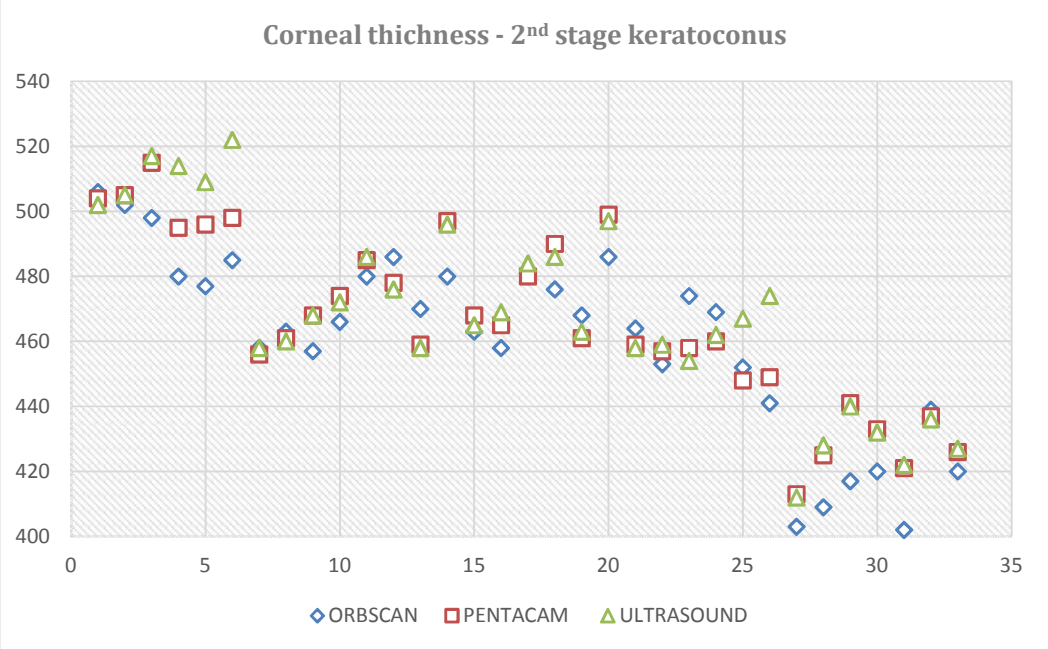
Graph 6. Bland & Altman Plot for corneal thickness (thinnest point) in the subclinical stage, comparing a) Orbscanllz&Pentacam b) Orbscanllz& Ultrasound c) Pentacam& Ultrasound

Comparing OrbscanIIz and Ultrasound their mean difference is 8.3333μm, while their standard deviation of mean difference is 13.8444. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P = 0.0016), but their correlation is strong, having Correlation coefficient r=0.8819and Spearman's coefficientof rank correlation (rho) =0.843.

Comparing Pentacam and Ultrasound their mean difference is 2.9394μm, while their standard deviation of mean difference is 7.7779. The differences between them are considered statistically significant Paired samples t-test Two-tailed probability (P= 0.0375), but their correlation is strong, having Correlation coefficient r=0.9633 and Spearman's coefficientof rank correlation (rho) =0.936.

3.4 3rd Stage Keratoconus

In the 3rd stage of keratoconus, OrbscanIIz presented an average corneal thickness of 385.1940μm, while Pentacam an average of 436.2239μm. Their mean difference is 51.0299μm, while their standard deviation of mean difference is 22.3471. The differences between them are considered statistically significant Paired samples t-test withTwo-tailed probability (P<0.0001), but their correlation is strong, having Correlation coefficient r=0.8317andSpearman's coefficientof rank correlation (rho) =0.747.



Graph 7. The corneal thickness (thinnest point) for each keratoconus eye in the 2nd stage, measured with Orbscan, Pentacam and Ultrasound

Table 4. 2nd Stage

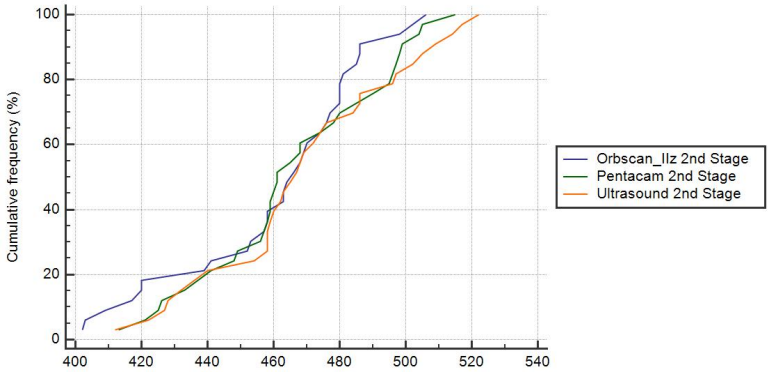
	Orbscan II	Pentacam	Ultrasound
Sample size	33	33	33
Arithmetic mean	460,6970	466,0909	460,6970
95% CI for the mean	450,7510 to 470,6429	456,5346 to 475,6472	450,7510 to 470,6429
Variance	786,7803	726,3352	786,7803
Standard Deviation	28,0496	26,9506	28,0496
Standard error of the mean	4,8828	4,6915	4,8828

Paired samples t-test	OrbscanIIz vice Pentacam
Mean difference	5,3939
Standard deviation of mean difference	10,0590
Standard error of mean difference	1,7510
95% CI	1,8272 to 8,9607
Test statistic t	3,080
Degrees of Freedom (DF)	32
Two-tailed probability	P = 0,0042
	Correlation of OrbscanIIz and Pentacam
Correlation coefficient r	0,9339
Significance level	P<0,0001
95% Confidence interval for r	0,8693 to 0,9671
Spearman's coefficient of rank correlation (rho)	0,927
Significance level	P<0,0001
95% Confidence Interval for rho	0,856 to 0,964
Paired samples t-test	**OrbscanIIz vice Ultrsound**
Mean difference	8,3333
Standard deviation of mean difference	13,8444
Standard error of mean difference	2,4100
95% CI	3,4243 to 13,2423
Test statistic t	3,458
Degrees of Freedom (DF)	32
Two-tailed probability	P = 0,0016
	Correlation of OrbscanIIz and Ultrasound
Correlation coefficient r	0,8819
Significance level	P<0,0001
95% Confidence interval for r	0,7724 to 0,9405
Spearman's coefficient of rank correlation (rho)	0,843
Significance level	P<0,0001
95% Confidence Interval for rho	0,703 to 0,920

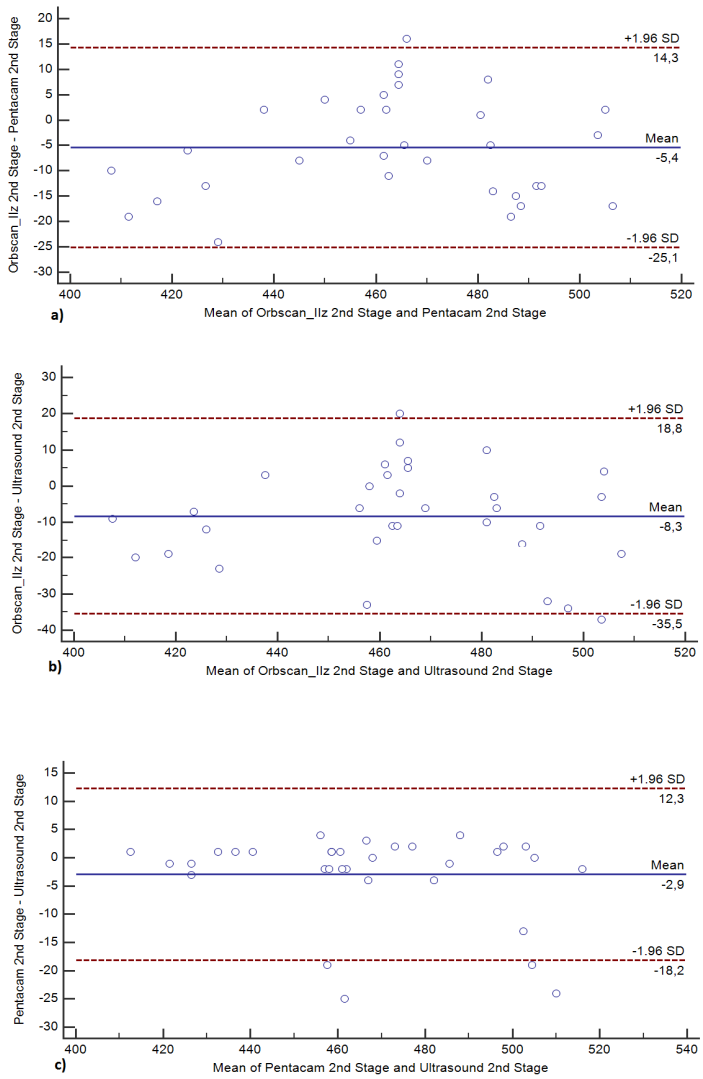
Paired samples t-test	Pentacam vice Ultrsound
Mean difference	2,9394
Standard deviation of mean difference	7,7779
Standard error of mean difference	1,3540
95% CI	0,1815 to 5,6973
Test statistic t	2,171
Degrees of Freedom (DF)	32
Two-tailed probability	P = 0,0375
	Correlation of Pentacam and Ultrasound
Correlation coefficient r	0,9633
Significance level	P<0,0001
95% Confidence interval for r	0,9264 to 0,9819
Spearman's coefficient of rank correlation (rho)	0,936
Significance level	P<0,0001
95% Confidence Interval for rho	0,873 to 0,968

Comparing OrbscanIIz and Ultrasound their mean difference is 44.5522μm, while their standard deviation of mean difference is 19.7663. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P <0.0001), but their correlation is strong, having Correlation coefficient r=0.8457and Spearman's coefficientof rank correlation (rho) =0.769.

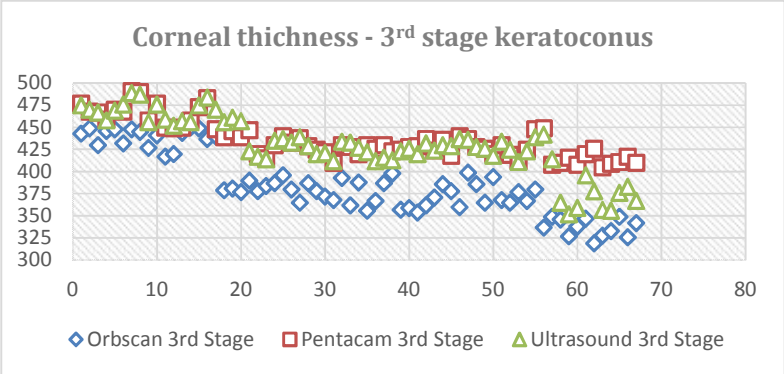
Comparing Pentacam and Ultrasound their mean difference is -6.4776μm, while their standard deviation of mean difference is 17.9649. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P= 0.0044), but their correlation is strong, having Correlation coefficient r=0.8704 and Spearman's coefficientof rank correlation (rho) =0.927.



Graph 8. Cumulative frequency (%) for corneal thickness in the 2nd stage, measured with Orbscan, Pentacam and Ultrasound. Pentacam& Ultrasound seem to be relatively close



Graph 9. Bland & Altman Plot for corneal thickness (thinnest point) in the 2nd stage, comparing a) OrbscanIIz & Pentacam b) OrbscanIIzv& Ultrasound c) Pentacam& Ultrasound



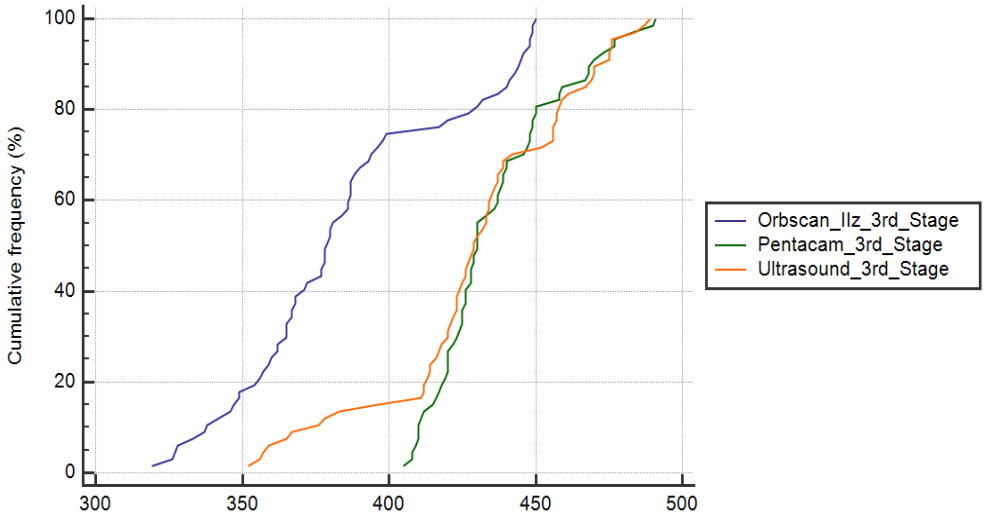
Graph 10. The corneal thickness (thinnest point) for each keratoconus eye in the 3rd stage, measured with Orbscan, Pentacam and Ultrasound

Table 5. 3rd Stage

	Orbscan II	Pentacam	Ultrasound
Sample size	67	67	67
Arithmetic mean	385,1940	436,2239	429,7463
95% CI for the mean	376,2119 to 394,1761	430,9536 to 441,4941	421,6276 to 437,8649
Variance	1356,0072	466,8431	1107,8286
Standard Deviation	36,8240	21,6066	33,2841
Standard error of the mean	4,4988	2,6397	4,0663

Paired samples t-test	**Orbscanllz vice Pentacam**
Mean difference	51,0299
Standard deviation of mean difference	22,3471
Standard error of mean difference	2,7301
95% CI	45,5790 to 56,4807
Test statistic t	18,691
Degrees of Freedom (DF)	66
Two-tailed probability	P < 0,0001
	Correlation of Orbscanllz and Pentacam
Correlation coefficient r	0,8317
Significance level	P<0,0001
95% Confidence interval for r	0,7392 to 0,8934
Spearman's coefficient of rank correlation (rho)	0,747
Significance level	P<0,0001
95% Confidence Interval for rho	0,618 to 0,837
Paired samples t-test	**Orbscanllz vice Ultrsound**
Mean difference	44,5522
Standard deviation of mean difference	19,7663
Standard error of mean difference	2,4148
95% CI	39,7309 to 49,3736
Test statistic t	18,449
Degrees of Freedom (DF)	66
Two-tailed probability	P < 0,0001
	Correlation of Orbscanllz and Ultrasound
Correlation coefficient r	0,8457
Significance level	P<0,0001
95% Confidence interval for r	0,7599 to 0,9026
Spearman's coefficient of rank correlation (rho)	0,769
Significance level	P<0,0001
95% Confidence Interval for rho	0,648 to 0,852

Paired samples t-test	Pentacam vice Ultrsound
Mean difference	-6,4776
Standard deviation of mean difference	17,9649
Standard error of mean difference	2,1948
95% CI	-10,8596 to -2,0956
Test statistic t	-2,951
Degrees of Freedom (DF)	66
Two-tailed probability	P = 0,0044
	Correlation of Pentacam and Ultrasound
Correlation coefficient r	0,8704
Significance level	P<0,0001
95% Confidence interval for r	0,7968 to 0,9186
Spearman's coefficient of rank correlation (rho)	0,927
Significance level	P<0,0001
95% Confidence Interval for rho	0,884 to 0,955



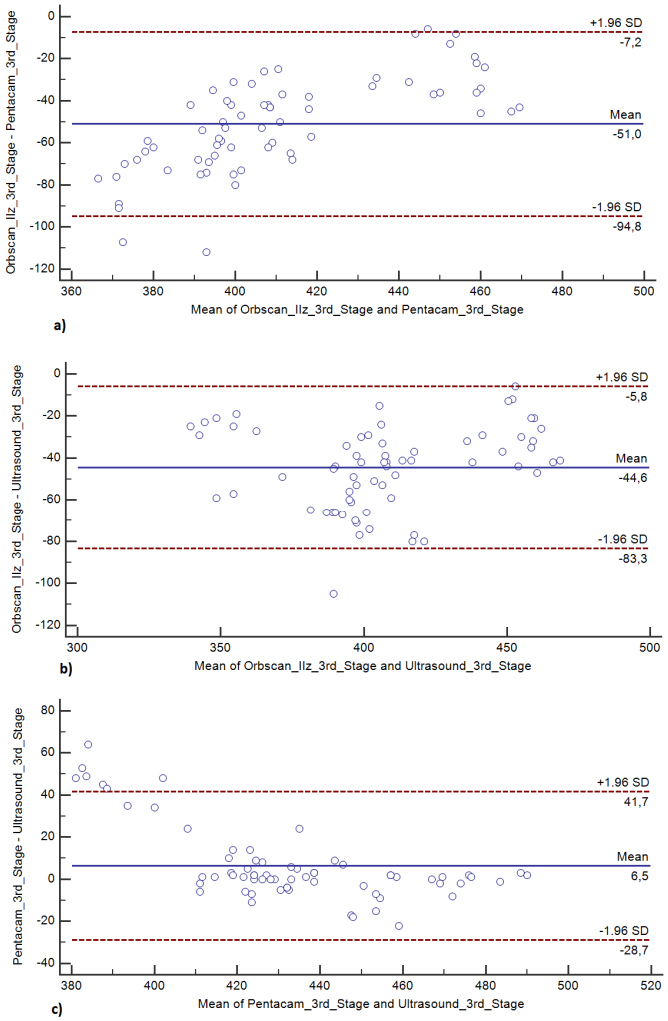
Graph 11. Cumulative frequency (%) for corneal thickness in the 3rd stage, measured with Orbscan, Pentacam and Ultrasound. Pentacam& Ultrasound seem to be relatively close

3.5 4th Stage Keratoconus

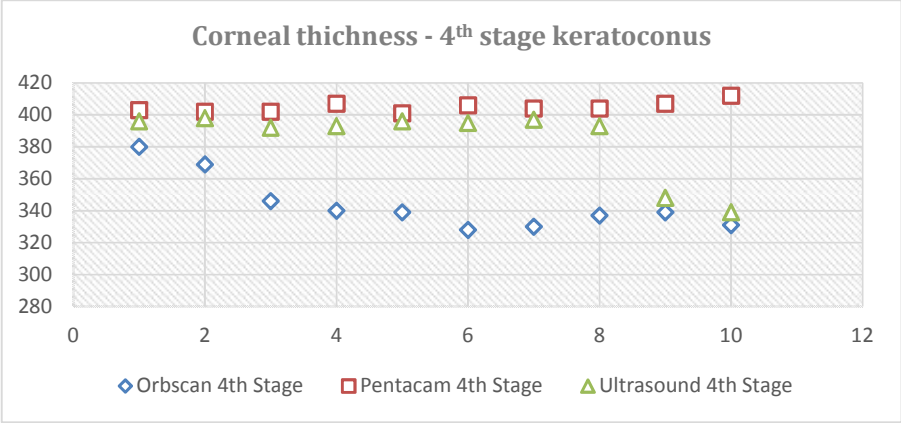
In the 4th stage of keratoconus, OrbscanIIz presented an average corneal thickness of 343.9000μm, while Pentacam an average of 404.8000μm. Their mean difference is 0.9000μm, while their standard deviation of mean difference is 18.9529. The differences between them are considered statistically significant Paired samples t-test withTwo-tailed probability (P<0.0001), but their correlation is strong, having Correlation coefficient =-0.4655andSpearman's coefficientof rank correlation (rho) =-0.469.

Comparing OrbscanIIz and Ultrasound their mean difference is 40.8000μm, while their standard deviation of mean difference is 23.2943.The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P = 0.0004), but their correlation is strong, having Correlation coefficient r=0.3089 and Spearman's coefficientof rank correlation (rho) =0.187.

Comparing Pentacam and Ultrasound their mean difference is -20.1000μm, while their standard deviation of mean difference is 24.6010. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P= 0.0295), but their correlation is strong, having Correlation coefficient r=-0.7959and Spearman'scoefficientof rank correlation (rho) =-0.628.



Graph 12. Bland & Altman Plot for corneal thickness (thinnest point) in the 3rd stage, comparing a) OrbscanIIz&Pentacam b) OrbscanIIz& Ultrasound c) Pentacam& Ultrasound



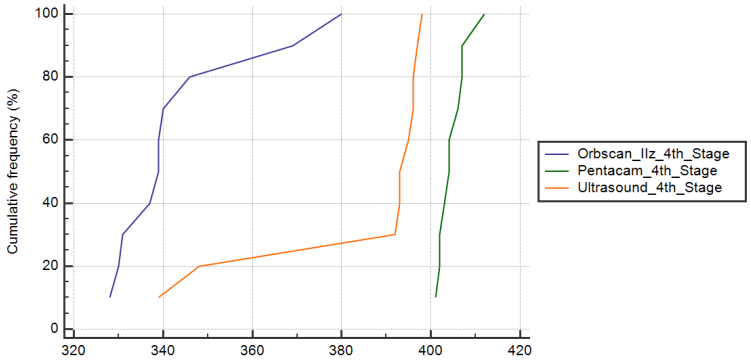
Graph 13. The corneal thickness (thinnest point) for each keratoconus eye in the 4th stage, measured with Orbscan, Pentacam and Ultrasound

Table 6. 4thStage

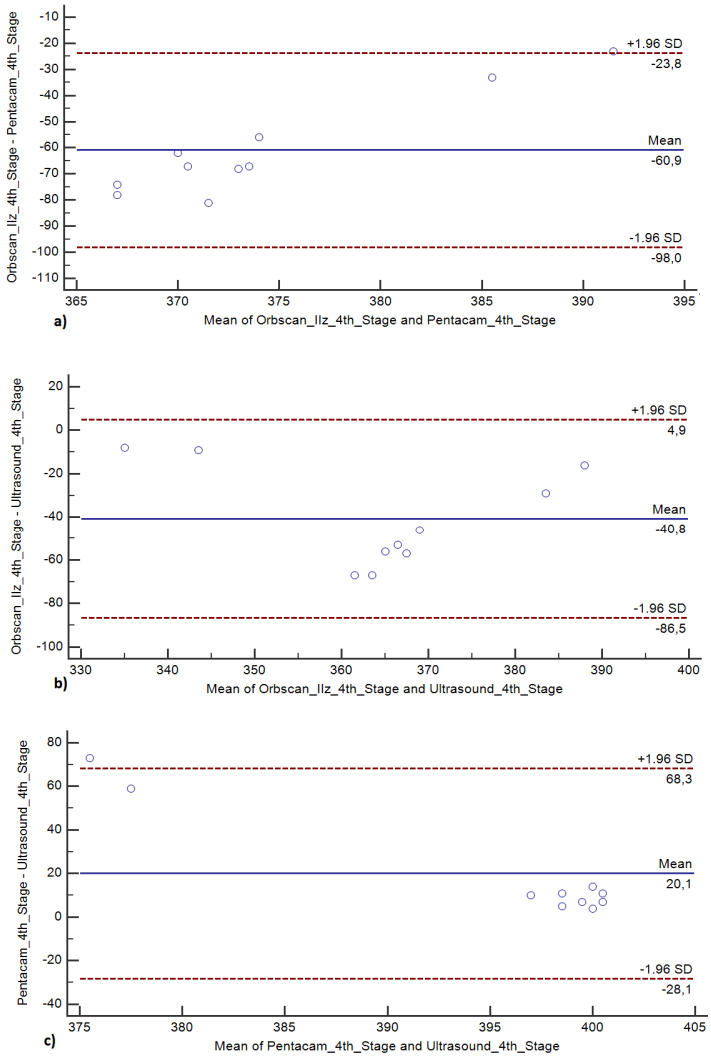
	Orbscan II	Pentacam	Ultrasound
Sample size	10	10	10
Arithmetic mean	343,9000	404,8000	384,7000
95% CI for the mean	331,5997 to 356,2003	402,4443 to 407,1557	369,0344 to 400,3656
Variance	295,6556	10,8444	479,5667
Standard Deviation	17,1946	3,2931	21,8990
Standard error of the mean	5,4374	1,0414	6,9251

Paired samples t-test	**Orbscanllz vice Pentacam**
Mean difference	60,9000
Standard deviation of mean difference	18,9529
Standard error of mean difference	5,9934
95% CI	47,3419 to 74,4581
Test statistic t	10,161
Degrees of Freedom (DF)	9
Two-tailed probability	P < 0,0001
	Correlation of Orbscanllz and Pentacam
Correlation coefficient r	-0,4655
Significance level	P=0,1752
95% Confidence interval for r	-0,8469 to 0,2322
Spearman's coefficient of rank correlation (rho)	-0,469
Significance level	P=0,1712
95% Confidence Interval for rho	-0,848 to 0,228
Paired samples t-test	**Orbscanllz vice Ultrsound**
Mean difference	40,8000
Standard deviation of mean difference	23,2943
Standard error of mean difference	7,3663
95% CI	24,1363 to 57,4637
Test statistic t	5,539
Degrees of Freedom (DF)	9
Two-tailed probability	P = 0,0004
	Correlation of Orbscanllz and Ultrasound
Correlation coefficient r	0,3089
Significance level	P=0,3852
95% Confidence interval for r	-0,3982 to 0,7857
Spearman's coefficient of rank correlation (rho)	0,187
Significance level	P=0,6058
95% Confidence Interval for rho	-0,502 to 0,730

Paired samples t-test	**Pentacam vice Ultrsound**
Mean difference	-20,1000
Standard deviation of mean difference	24,6010
Standard error of mean difference	7,7795
95% CI	-37,6985 to -2,5015
Test statistic t	-2,584
Degrees of Freedom (DF)	9
Two-tailed probability	P = 0,0295
	Correlation of Pentacam and Ultrasound
Correlation coefficient r	-0,7959
Significance level	P=0,0059
95% Confidence interval for r	-0,9497 to -0,3334
Spearman's coefficient of rank correlation (rho)	-0,628
Significance level	P=0,0520
95% Confidence Interval for rho	-0,901 to 0,00321



Graph 14. Cumulative frequency (%) for corneal thickness in the 4th stage, measured with Orbscan, Pentacam and Ultrasound. Pentacam& Ultrasound seem to be relatively close but not that much as in the previous stages

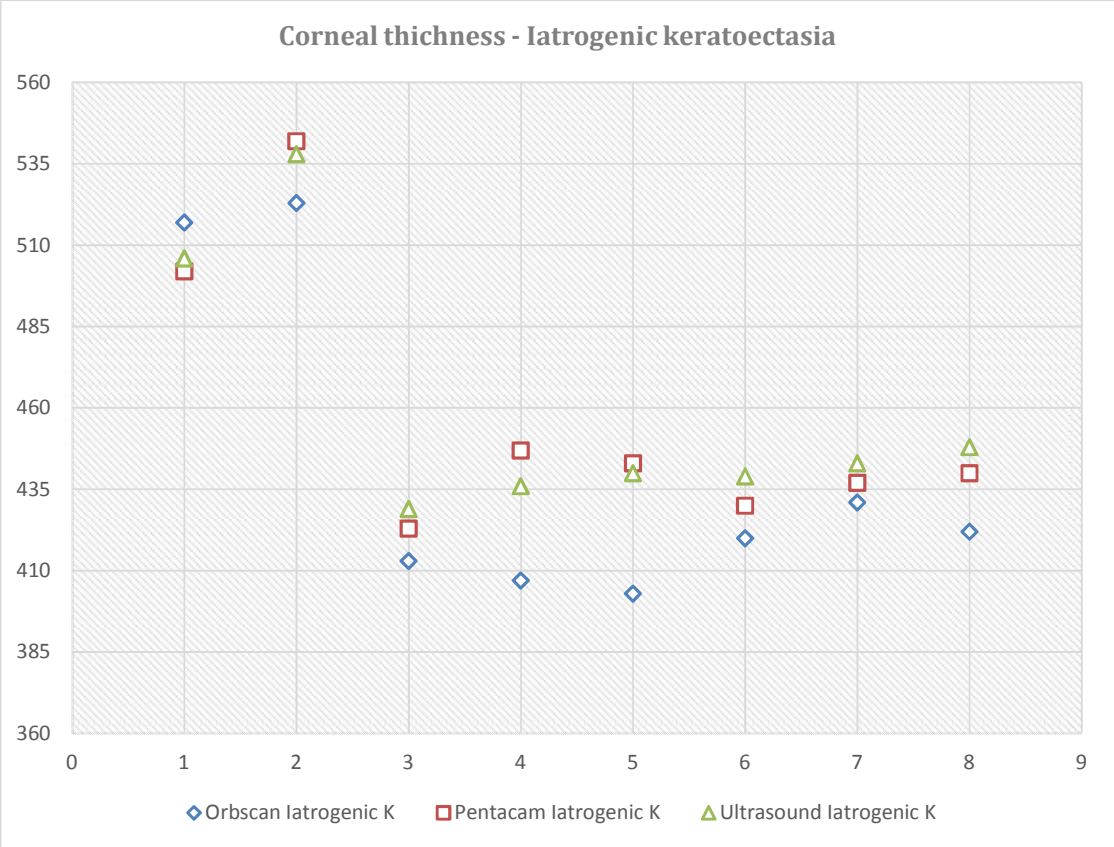


Graph 15. Bland & Altman Plot for corneal thickness (thinnest point) in the 4th stage, comparing a) OrbscanIIz&Pentacam b) OrbscanIIz& Ultrasound c) Pentacam& Ultrasound

3.6 Iatrogenic Keratoectasia

In the Iatrogenic keratoectasia, OrbscanIIz presented an average corneal thickness of 442.0000μm, while Pentacam an average of 458.0000μm. Their mean difference is 16.0000μm, while their standard deviation of mean difference is 18.1187. The differences between them are considered statistically significant Paired samples t-test withTwo-tailed probability (P=0.0411), but their correlation is strong, having Correlation coefficient =0.9327andSpearman'scoefficientof rank correlation (rho) =-0.469.

Comparing OrbscanIIz and Ultrasound their mean difference is 40.8000μm, while their standard deviation of mean difference is 23.2943. The differences between them are considered statistically significant Paired samples t-testTwo-tailed probability (P = 0.0004), but their correlation is strong, having Correlation coefficient r=0.3089 and Spearman's coefficientof rank correlation (rho) =0.405.



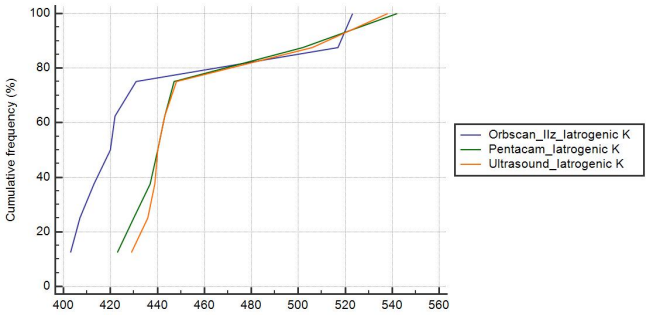
Graph 16. The corneal thickness (thinnest point) for each keratoconus eye in iatrogenickeratoectasia, measured with Orbscan, Pentacam and Ultrasound

Table 7. Iatrogenic keratoectasia

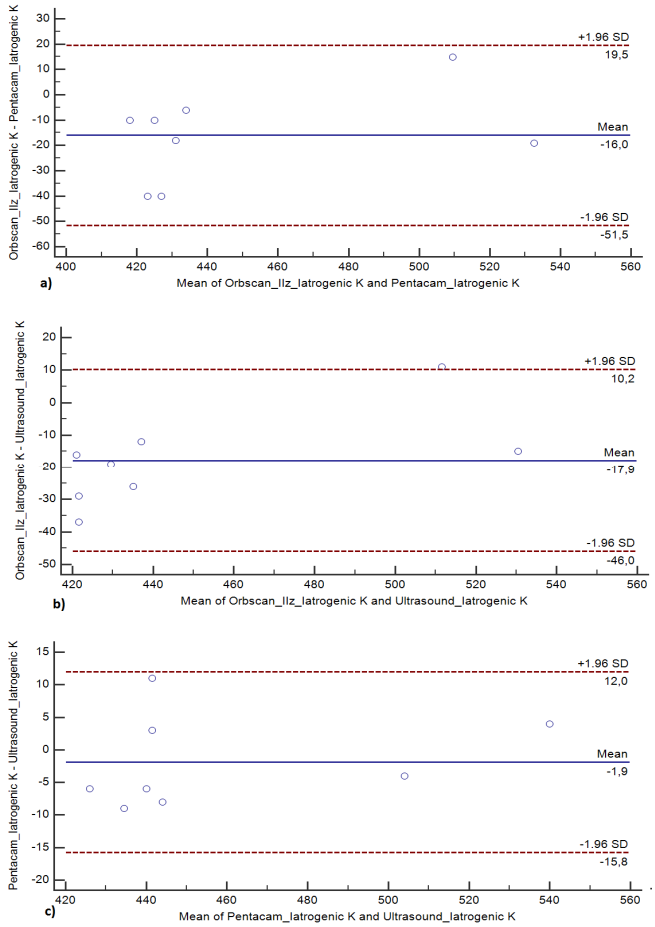
	Orbscan II	Pentacam	Ultrasound
Sample size	8	8	8
Arithmetic mean	442,0000	458,0000	459,8750
95% CI for the mean	401,0703 to 482,9297	423,2243 to 492,7757	426,7177 to 493,0323
Variance	2396,8571	1730,2857	1572,9821
Standard Deviation	48,9577	41,5967	39,6608
Standard error of the	17,3092	14,7067	14,0222

mean	
Pairedsamplest-test	**Orbscanllz vice Pentacam**
Meandifference	16,0000
Standarddeviationofmeandifference	18,1187
Standarderrorofmeandifference	6,4059
95%CI	0,8524to31,1476
Teststatistict	2,498
DegreesofFreedom(DF)	7
Two-tailedprobability	P = 0,0411
	Correlation of Orbscanllz and Pentacam
Correlation coefficient r	0,9327
Significance level	P=0,0007
95% Confidence interval for r	0,6653 to 0,9880
Spearman's coefficient of rank correlation (rho)	0,405
Significance level	P=0,3199
95% Confidence Interval for rho	-0,420 to 0,863
Paired samples t-test	**Orbscanllz vice Ultrsound**
Mean difference	17,8750
Standard deviation of mean difference	14,3272
Standard error of mean difference	5,0654
95% CI	5,8972 to 29,8528
Test statistic t	3,529
Degrees of Freedom (DF)	7
Two-tailed probability	P = 0,0096
	Correlation of Orbscanllz and Ultrasound
Correlation coefficient r	0,9694
Significance level	P=0,0001
95% Confidence interval for r	0,8354 to 0,9946
Spearman's coefficient of rank correlation (rho)	0,810
Significance level	P=0,0149
95% Confidence Interval for rho	0,244 to 0,964

Paired samples t-test	**Pentacam vice Ultrsound**
Mean difference	1,8750
Standarddeviationofmeandifference	7,0799
Standard error of mean difference	2,5031
95% CI	-4,0439 to 7,7939
Test statistict	0,749
Degrees of Freedom (DF)	7
Two-tailed probability	P = 0,4782
	Correlation of Pentacam and Ultrasound
Correlation coefficient r	0,9859
Significance level	P<0,0001
95% Confidence interval for r	0,9215 to 0,9976
Spearman's coefficient of rank correlation (rho)	0,690
Significance level	P=0,0580
95% Confidence Interval for rho	-0,0277 to 0,939



Graph 17. Cumulative frequency (%) for corneal thickness in the Iatrogenickeratoectasia, measured with Orbscan, Pentacam and Ultrasound. Pentacam& Ultrasound seem to be relatively very close



Graph 18. Bland & Altman Plot for corneal thickness (thinnest point) in the Iatrogenic keratoectasia, comparing a) OrbscanIIz&Pentacam b) OrbscanIIz& Ultrasound c) Pentacam& Ultrasound

4. CONCLUSION

In this study, we compared corneal thickness in different stages of keratoconus. The thinnest point measurements obtained by using, Pentacam, OrbscanIIz, and Ultrasound (TOMEY SP-100). Results were collected and compared for these three systems. Numerous studies have demonstrated that the central corneal thickness measurement in normal eyes was comparable

between Pentacam, OrbscanIIz, and Ultrasound depending of the correlation statistics they used [20-46]. However, this is the first study to evaluate the precision of the thinnest corneal thickness measurement with three different systems including Pentacam, OrbscanIIz and Ultrasound in keratoconic eyes at different stages of the disease.

According to the stage of keratoconus the thinnest point of corneal thickness showed that OrbscanIIz, Pentacam, and Ultrasound correlated well numerically but their standard deviation of mean difference between them are considered statistically significant. Paired samples t-test between Orbscan-Pentacam, Orbscan-Ultasound and Pentacam-Ultasound showed that Two-tailed probability for each of the two systems compared was very weak (statistical significant deferent) except of Pentacam-Ultasound where Two-tailed probability was strong enough at the sublinicalstage and in Iatrogenickeratoectasia so someone could conclude that these two systems may be used interchangeably for these two stages. The Correlation coefficient r at all stages in all combinations of comparison was from strong to very strong. According to Bland & Altman Plot and the Cumulative frequency (%) graph for corneal thickness comparison the best correlation seems to be between Pentacam-Ultasound.

The agreement between the Pentacam and the Ultrasound pachymetry was good, and the repeatability was also good for both instruments independently, however it is needed to increase measure times to improve the repeatability of the Pentacam. Our study also found that OrbscanIIz significantly underestimated corneal thickness compared to the other two instruments except at the subclinical stage.

In conclusion, although measurements obtained by these three methods correlate well, the measurements values are not directly interchangeable.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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