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KERATOKONUS: MÜASİR ANLAYIŞ VƏ PROFİLAKTİK STRATEGİYALAR (ƏDƏBİYYAT İCMALI)

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XÜLASƏ

Məqsəd – keratokonusun patogenezi, epidemiologiyası, risk faktorları və erkən aşkarlanma strategiyaları ilə bağlı mövcud bilikləri ümumiləşdirmək, o cümlədən Mərkəzi Asiyada, xüsusilə Özbəkistanda klinik praktikaya uyğun profilaktik tibb yanaşmalarına xüsusi diqqət yetirmək.

Keratokonusun molekulyar mexanizmləri, ekoloji və genetik risk faktorları, qlobal epidemioloji mənzərəsi və qabaqcıl diaqnostik texnologiyaları təhlil edilərək, müasir elmi ədəbiyyatın hərtərəfli icmalı aparılmışdır. Dəyişdirilə bilən risk faktorlarına və müxtəlif resurs imkanlarına malik mühitlərdə tətbiq edilə bilən skrininq strategiyalarına xüsusi diqqət yetirilmişdir.

Keratokonusun patogenezini hüceyrəxarici matrisin deqradasiyası, oksidləşdirici stres, apoptoz prosesləri təşkil edir. Dəyişən əsas risk faktorlarından daim gözün ovuşdurması, ultrabənövşəyi şüalanma və atopik xəstəliklərdir. Dünya üzrə rastgəlmə tezliyi hər 100 000 nəfərə 289,1 nəfər təşkil edir və əhəmiyyətli regional fərqlər mövcuddur — ən yüksək göstəricilər Afrika və Qərbi Asiyadadır. "Scheimpflug" tomoqrafiyası, ön seqmentin optik koherent tomoqrafiyası (AS-OCT) və biomexaniki qiymətləndirmə daxil olmaqla qabaqcıl görüntüləmə texnologiyaları xəstəliyin erkən mərhələdə aşkar edilməsinə imkan verir. Süni intellekt (Sİ) alqoritmləri keratokonusun müəyyən edilməsində 95%-dən yüksək həssaslıq və spesifikliyə nail olur. Ailə anamnezi, atopik xəstəliklər və əlaqəli xəstəlikləri olan şəxslərə yönəlmiş risk qrupları üzrə skrininq, buynuz qişanın kollagen kross-linkinqi vasitəsilə vaxtında müdaxilə etməyə imkan verir.

Yekun

Keratokonusun profilaktikası dəyişdirilə bilən risk faktorlarını hədəf alan ictimai səhiyyə tədbirlərini, qabaqcıl diaqnostik texnologiyalardan istifadə edən risk-əsaslı skrininq proqramlarını və erkən terapevtik müdaxiləni özündə birləşdirən inteqrasiya olunmuş yanaşmalar tələb edir. Özbəkistan və Mərkəzi Asiyada hərtərəfli skrininq və profilaktika proqramlarının tətbiqi keratokonusla bağlı görmə əlilliyini əhəmiyyətli dərəcədə azalda bilər.

Açar sözlər: *keratokonus, buynuz qişanın ektaziyası, patogenez, oksidləşdirici stress, gözün ovuşdurması, skrininq, profilaktika, süni intellekt*

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KERATOCONUS: CONTEMPORARY UNDERSTANDING AND PREVENTIVE STRATEGIES (LITERATIRE REVIEW)

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SUMMARY

Purpose – to synthesize current knowledge regarding keratoconus pathogenesis, epidemiology, risk factors, and early detection strategies, with emphasis on preventive medicine approaches relevant to clinical practice in Central Asia, including Uzbekistan.

A comprehensive review of contemporary scientific literature was conducted, analyzing molecular mechanisms, environmental and genetic risk factors, global epidemiological patterns, and advanced diagnostic technologies for keratoconus. Special attention was given to modifiable risk factors and screening strategies applicable to resource-varied settings.

Keratoconus pathogenesis involves extracellular matrix degradation, oxidative stress, cellular senescence, and biomechanical compromise. Key modifiable risk factors include chronic eye rubbing, ultraviolet exposure, and atopic conditions. Global prevalence is 289.1 per 100,000 persons, with significant regional variation – highest in Africa and West Asia. Advanced imaging technologies including Scheimpflug tomography, anterior segment optical coherence tomography (AS-OCT), and biomechanical assessment enable early detection. Artificial intelligence (AI) algorithms achieve >95% sensitivity and specificity for keratoconus identification. Risk-stratified screening targeting individuals with family history, atopic disease, and systemic associations enables timely intervention with corneal collagen cross-linking.

Conclusion

Keratoconus prevention requires integrated approaches combining public health interventions addressing modifiable risk factors, risk-based screening programs utilizing advanced diagnostic technologies, and early therapeutic intervention. Implementation of comprehensive screening and prevention programs in Uzbekistan and Central Asia could substantially reduce keratoconus-related visual disability.

Key words: *keratoconus, corneal ectasia, pathogenesis, oxidative stress, eye rubbing, screening, prevention, artificial intelligence*

Keratoconus represents one of the most challenging corneal ectatic disorders in contemporary ophthalmology, characterized by progressive thinning and conical protrusion of the cornea that leads to irregular astigmatism and significant visual impairment [1, 2]. This bilateral yet asymmetric condition typically manifests during the second and third decades of life, affecting individuals at the critical juncture of their educational and professional development [3]. The disease progression, though variable, can result in severe visual disability necessitating corneal transplantation, making keratoconus the leading indication for keratoplasty in Western countries [2].

The complexity of keratoconus pathogenesis has long eluded complete elucidation, with multiple environmental, genetic, and biomechanical factors converging to produce the characteristic corneal changes [4, 5]. Recent advances in molecular biology, proteomics, and imaging technologies have revolutionized our understanding of this condition, revealing intricate cellular and molecular mechanisms that drive disease initiation and progression [6–8]. This monograph synthesizes current knowledge regarding keratoconus pathogenesis, epidemiology, risk factors, and early detection strategies, with particular emphasis on preventive medicine approaches relevant to clinical practice in Central Asia, including Uzbekistan.

Purpose – to synthesize current knowledge regarding keratoconus pathogenesis, epidemiology, risk factors, and early detection strategies, with emphasis on preventive medicine approaches relevant to clinical practice in Central Asia, including Uzbekistan.

Molecular and Cellular Pathogenesis.

Extracellular Matrix Degradation and Remodeling.

The fundamental pathological process in keratoconus involves disruption and degradation of the corneal extracellular matrix, particularly affecting collagen architecture within the stromal layer [9, 10]. The corneal stroma comprises approximately ninety percent of corneal thickness and consists of highly organized collagen fibrils arranged in lamellae that provide structural integrity and optical transparency [11]. In keratoconus, this exquisite organization becomes compromised through multiple molecular mechanisms [12].

Recent proteomic analyses have identified a characteristic molecular signature in keratoconus tissue [13]. Collagen types I and IV, fibronectin, vitronectin, matrix metalloproteinase-9 (MMP-9), tissue inhibitor of metalloproteinase-1 (TIMP-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), annexin, superoxide dismutase 1 (SOD1), glutathione peroxidase 1 (GPX1), keratin 3 (KRT3), decorin, and heat shock protein 70 (HSP70) all demonstrate altered expression patterns [6, 13, 14]. The imbalance between matrix metalloproteinases and their tissue inhibitors represents a critical determinant of extracellular matrix integrity and function within the corneal stroma [11, 15].

Studies employing multi-omics approaches have revealed that proteinases contribute substantially to homeostatic disruption and create an imbalance in the antioxidant and oxidative state within the cornea, fostering oxidative stress, inflammation, and apoptosis [16, 17]. Lopez-Lopez and colleagues identified hemopexin, annexins, vitamin D binding protein, and tubulin alpha-1C chain as differentially expressed proteins, with biological pathways involving actin cytoskeleton organization, interleukin-12 signaling, apoptotic process regulation of wound healing, and regulation of vesicle fusion all demonstrating dysregulation [13]. In contrast, under-expressed proteins including immunoglobulin kappa constant (IGKC), zinc-alpha-2-glycoprotein (ZAG), and lactoferrin have been documented, though their precise roles in keratoconus pathogenesis remain incompletely understood [13, 18].

Oxidative Stress and Cellular Senescence.

The oxidative-stress-senescence axis has emerged as a central driver of keratoconus pathogenesis [16, 19]. Keratoconus corneas demonstrate reduced levels of critical antioxidant enzymes including aldehyde dehydrogenase class 3 (ALDH3) and superoxide dismutase, rendering these tissues vulnerable to reactive oxygen species accumulation [15, 20]. This oxidative imbalance manifests throughout multiple ocular compartments, altering the redox balance in tears, cornea, aqueous humor, and blood [15]. The resulting elevation of oxidative stress markers coupled with reduced antioxidant capacity contributes directly to disease progression [16, 19].

Cellular senescence represents the convergence point of oxidative damage and inflammatory processes [21]. Recent investigations have identified senescence as a key driver of keratoconus pathogenesis, with senescent cells accumulating in keratoconic corneas and secreting inflammatory mediators that perpetuate tissue damage [21]. Single-cell RNA sequencing analyses have revealed aberrant transcriptional signatures in keratoconus corneal cells, with elevated levels of Yes-associated protein 1 (YAP1) and TEA domain transcription factor 1 (TEAD1), master regulators of biomechanical homeostasis, detected in keratoconus stromal cells [17]. These findings implicate mechanical stretch as a potential trigger for keratoconus pathogenesis, connecting biomechanical stress with molecular responses [17].

Signaling Pathway Dysregulation

Multiple cellular signaling pathways demonstrate dysregulation in keratoconus [10, 22]. The mammalian target of rapamycin (mTOR) signaling pathway, crucial for regulating cell growth, proliferation, and apoptosis in response to nutrient availability, shows altered activity in keratoconus-derived cells [23]. Studies indicate that keratoconus-derived cells exhibit altered extracellular matrix deposition and composition potentially influenced by mTOR signaling, suggesting this pathway as a therapeutic target [23, 24].

The wingless-related integration site (WNT) and Hedgehog (HH) signaling pathways, known regulators of developmental processes influencing stem cell differentiation, also demonstrate dysregulation in keratoconus [10, 14]. Specific genetic variants in WNT10A and WNT7B genes have been associated with keratoconus, emphasizing the functional involvement of WNT pathway components in disease pathogenesis [7, 25]. Knocking down WNT7A results in transformation of corneal epithelial cells into epidermal-like cells, adversely affecting corneal transparency [14]. These findings highlight the critical role of HH and WNT pathways in maintaining corneal endothelial cell integrity and structure [10, 14].

Epithelial-Stromal Interactions and Wound Healing Dysregulation.

The epithelial layer participates actively in keratoconus pathogenesis through abnormal wound healing processes [9, 26]. Cellular adhesion molecules such as laminin and fibronectin, essential for binding basal epithelial cells to the basement membrane, demonstrate overexpression in scarred regions of the anterior keratoconus cornea [22]. This upregulation may signify downstream events in the wound healing cascade, suggesting dysregulated wound healing processes contribute to pathogenesis [9, 26]. The concept that keratoconus changes may involve a wound healing-like process, where an unregulated repair mechanism contributes to disease development, has gained substantial support [9].

Altered expression of cellular adhesion molecules potentially contributes to disturbances in corneal layer structure and integrity observed in keratoconus [22]. CD34, a cellular adhesion molecule and hematopoietic stem cell marker, shows significant reduction in keratoconus corneal keratocytes [22]. Conversely, desmoglein 3 (DSG3), a desmosomal cadherin, exhibits

increased expression in keratoconus samples [22]. Single-cell atlas studies have revealed reduced basal cells and abnormally differentiated superficial cells in keratoconus epithelium, unraveling corneal epithelial lesions typically neglected in clinical diagnosis [17].

Inflammatory Mechanisms

Although keratoconus was traditionally viewed as a noninflammatory disorder, accumulating evidence supports involvement of inflammatory components [6, 27, 28]. Several elevated cytokines in immune cells of keratoconus samples support inflammatory response involvement in disease progression [6, 11]. The dysregulated cell-cell communications in keratoconus reveal that only few ligand-receptor interactions are gained while a large fraction of interactional pairs become erased, especially those related to protease inhibition and anti-inflammatory processes [17].

The balance between matrix metalloproteinases and tissue inhibitors of metalloproteinases, a critical determinant of extracellular matrix integrity and function in corneal stroma, appears potentially regulated by communications between corneal stromal cells and immune cells or corneal endothelial cells during keratoconus progression [11, 17]. This finding provides an explanation for keratoconus pathogenesis from a novel perspective, emphasizing the importance of intercellular communication networks [17].

Biomechanical Alterations

Keratoconus associates with altered matrix stiffness, a key regulator of cellular physiology [29, 30]. This change may explain connections between the disease's mechanical and biochemical aspects, affecting cell division, migration, and other processes [29]. Various proteins undergo structural and functional modifications that compromise corneal biomechanical integrity [30]. The viscoelastic property of the cornea that normally allows it to absorb and dissipate energy becomes impaired [29, 30]. Changes in biochemicals and cells result in corneal stromal loss, with breakdown of the collagen network causing weakened cornea to protrude [30].

Recent investigations employing advanced imaging modalities have characterized dynamic corneal response parameters representing mechanical stability [31, 32]. The combination of corneal thickness profile and deformation parameters analyzed through sophisticated algorithms can differentiate between keratoconus and normal cornea [31, 33]. However, detecting the fellow normal topographic eye of patients with very asymmetric ectasia in the other eye remains challenging, underscoring the need for integrated diagnostic approaches combining multiple parameters [33].

Environmental and Mechanical Risk Factors

Eye Rubbing: A Major Modifiable Risk Factor

Eye rubbing represents one of the most significant and modifiable environmental risk factors for keratoconus development and progression [34, 35]. This behavior is frequently observed in patients with vernal keratoconjunctivitis and atopic conditions [34, 36]. Chronic eye rubbing demonstrates strong association among keratoconus patients with Leber congenital amaurosis, Down syndrome, atopic disease, contact lens wear, floppy eyelid syndrome, and nervous habitual eye rubbing [34, 37].

The mechanism through which eye rubbing contributes to keratoconus involves a sequential cascade of pathophysiological events [35]. Eye rubbing produces increased corneal temperature and elevated levels of inflammatory mediators, followed by epithelial thinning, anomalous enzyme activity, raised intraocular pressure, and increased hydrostatic tissue pressure [35, 38]. These changes result in decreased viscosity, temporary displacement from the corneal apex leading to buckling, flexure of fibrils, and corneal indentation [35]. This biomechanically coupled curvature may transfer to the cone apex resulting in slippage

between collagen fibrils due to mechanical trauma and high hydrostatic pressure, in addition to scar formation [35].

Studies involving assessment of potential risk factors including atopy, family history, eye rubbing, and contact lens wear have confirmed the central role of mechanical trauma [34, 39]. Case series have reported patients with very asymmetric keratoconus demonstrating clear history of mechanical trauma to the more affected eye within one month [39]. The possible underlying mechanism involves microtrauma due to eye rubbing which injures the epithelium, leading to cytokine release, myofibroblast differentiation, change in biomechanical forces, and thinning of corneal tissue resulting in ectasia [35, 39].

Case reports of bilateral recurrent keratoconus following keratoplasty in patients with self-induced keratoconus secondary to compulsive eye rubbing have been documented, dramatically illustrating the impact of this behavior [40]. Another correlation exists between disease asymmetry and sleeping on the worse side, often with the hand under the pillow, which over time may lead to abnormalities such as floppy eyelid and unilateral eyelash misdirection, pointing toward chronic nocturnal eyelid pressure [37].

The characteristic pattern of eye rubbing in keratoconus patients typically involves using either a middle knuckle or fingertip in circular motion over the cornea with significant posterior pressure [34]. The intensity and duration, ranging from ten to one hundred eighty seconds or even up to three hundred seconds, are markedly severe and repetitive compared to casual eye rubbing [34]. This pattern of sustained, forceful rubbing generates sufficient mechanical trauma to initiate and perpetuate the pathological cascade [34, 35].

Ultraviolet Radiation and Environmental Exposure

Ultraviolet light exposure represents another significant environmental risk factor for keratoconus [41, 42]. Ultraviolet radiation serves as a source of reactive oxygen species, and in keratoconus eyes already deficient in critical antioxidant enzymes including ALDH3 and superoxide dismutase, excessive sunlight exposure results in oxidative damage to keratoconic corneas [15, 41]. Consequently, higher prevalence of keratoconus is observed in hot, sunny countries including Saudi Arabia, Iran, New Zealand, India, and some Pacific Islands [41, 42, 43].

Animal experiments further support this relationship, demonstrating that mice exposed to ultraviolet light develop degeneration of stromal collagen and stromal thinning resulting in apoptotic cell death and marked loss of keratocytes [44]. Thus, sun exposure, especially in genetically susceptible individuals, poses a substantial risk factor for keratoconus development [41]. Paradoxically, ultraviolet radiation also possesses beneficial effects by inducing cross-linking of corneal collagen, forming the basis for the therapeutic technique of corneal collagen cross-linking utilized to halt keratoconus progression [1, 45].

Hormonal Influences

Hormones play critical roles in regulating tissue function by promoting cell survival, proliferation, and differentiation. Because keratoconus usually begins by puberty, hormones have been postulated as possible causative factors [12]. Reports document sudden progression during pregnancy and following hormone replacement therapy [13]. Studies have demonstrated that both male and female keratoconus patients exhibit increased dehydroepiandrosterone sulfate (DHEA-S) levels compared to healthy controls, supporting a role for elevated DHEA-S and reduced estrone in keratoconus pathogenesis [12].

Case reports describe keratoconus progression following pregnancy, in vitro fertilization, and in postmenopausal patients treated with hormone replacement therapy [15]. These observations suggest hormonal fluctuations may influence corneal biomechanical properties or cellular metabolism in ways that facilitate disease progression in susceptible individuals. The temporal correlation between puberty onset and typical keratoconus development,

combined with documented progression during hormonal transitions, strongly implicates endocrine factors in disease pathophysiology [12].

Genetic Factors and Systemic Associations

Genetic Architecture

Keratoconus demonstrates complex genetic architecture with both familial aggregation and sporadic occurrence [5]. Family history of keratoconus varies between six and ten percent in most studies, with higher rates reported in populations with elevated prevalence [20]. The US Collaborative Longitudinal Evaluation of Keratoconus study reported a rate of 13.5 percent, while studies from Israel, where prevalence is high, reported rates of 21.74 percent [20]. This variability suggests both genetic susceptibility and environmental factors contribute to disease expression [5].

Genome-wide association studies have identified multiple gene regulators and transcription factors involved in keratoconus susceptibility [5, 7, 8]. Specific variants in genes including CD248 and WNT16 relate to biological processes such as cell proliferation and migration, WNT signaling, collagen catabolic process, and extracellular matrix remodeling [7]. Understanding the multiple genes involved and their biological processes provides foundation for grasping the complexity of keratoconus disease architecture [5, 8].

The role of specific genes varies among different populations [5]. Studies examining SOD1 gene, which plays critical roles in converting superoxide radicals into molecular oxygen and hydrogen peroxide, have yielded conflicting results [15]. Some studies suggest potential causative links between SOD1 and keratoconus pathogenesis in Greek patients, while studies in Middle Eastern populations (mostly from Saudi Arabia and Iran) and Brazilian patients found no mutations in the SOD1 gene in keratoconus [29]. These findings indicate that the role of SOD1 in keratoconus may vary among different populations, reflecting genetic heterogeneity [32]. Similarly, VSX1 gene, thought to play significant roles in maintaining cellular differentiation and transparency in the cornea, shows population-specific associations [5]. Novel missense mutations in the VSX1 gene have been discovered among Korean patients with keratoconus, suggesting possible genetic links in this population [36]. However, this potential connection does not appear universal, again highlighting genetic heterogeneity in keratoconus susceptibility [5].

Associated Systemic and Ocular Disorders

Keratoconus often occurs as an isolated disorder, yet substantial evidence documents associations with other ocular, syndromic, and systemic disorders [4]. Recognized associations include Marfan syndrome, mitral valve prolapse, collagen vascular disease, pigmentary retinopathy, Leber congenital amaurosis, and Down syndrome [4]. Previous studies report that approximately 0.5 to 15 percent of patients with Down syndrome manifest keratoconus, with some studies suggesting ten to three-hundred-fold higher prevalence compared to the general population.

Keratoconus occurs in approximately 35 percent of patients with Leber congenital amaurosis, a clinically heterogeneous group of childhood retinal degenerations inherited in an autosomal recessive manner [42]. Gene mutations in aryl hydrocarbon-interacting protein-like 1 (AIPL1) and crumbs homolog 1 (CRB1) in patients with Leber congenital amaurosis appear to contribute toward keratoconus susceptibility [39]. These findings suggest shared molecular pathways between retinal and corneal degenerative processes [44].

Other connective tissue disorders associated with keratoconus include osteogenesis imperfecta, GAPO syndrome, type IV Ehlers-Danlos syndrome, and mitral valve prolapse [4]. The prevalence of keratoconus in immune-mediated disorders including rheumatoid arthritis, ulcerative colitis, autoimmune chronic

hepatitis, Hashimoto thyroiditis, arthropathy, irritable bowel syndrome, and asthma has been observed, suggesting inflammatory mechanisms may contribute to susceptibility [34]. Case reports document Tourette syndrome associated with compulsive eye rubbing, a causative factor of keratoconus, further illustrating the diverse systemic associations [35].

Global and Regional Epidemiology

Worldwide Prevalence and Incidence

Keratoconus demonstrates remarkable geographic and ethnic variation in prevalence and incidence [3, 42]. Global pooled prevalence estimates indicate approximately 289.1 per 100,000 persons or 0.24 percent of the population, with pooled incidence of 4.0 per 100,000 person-years [36]. However, these figures mask substantial regional heterogeneity [42]. Over 23.7 million individuals globally are estimated to be affected by keratoconus, highlighting an increasing global burden and emphasizing the need for further research into temporal and regional patterns [36].

Prevalence is highest in Africa (2,414.2 per 100,000 persons) and shows substantial variation across Asian subregions, with lowest prevalence in East Asia (12.7 per 100,000 persons) and substantially higher rates in West Asia (682.0 per 100,000 persons) and South Asia (1,374.5 per 100,000 persons). The prevalence in Middle Eastern countries reaches particularly high levels, with some studies reporting rates as high as five percent of the population [43]. Saudi Arabia demonstrates the highest reported prevalence, with pediatric population studies identifying keratoconus in 4.79 percent or one in twenty-one individuals [43].

Both prevalence and incidence have increased over time, with highest prevalence observed post-2020 (1,155.2 per 100,000 persons) and highest incidence during 2015 to 2019 (15.23 per 100,000 person-years). Males demonstrate slightly higher odds of keratoconus compared with females (odds ratio 1.10). The twenty to twenty-nine age group exhibits the highest prevalence (525.5 per 100,000 persons) and incidence (20.8 per 100,000 person-years), consistent with typical disease onset during late adolescence and early adulthood [3].

Regional Studies and Ethnic Variations

Reports from the United Kingdom indicated prevalence 4.4 to 7.5 times greater for Asian subjects (Indian, Pakistani, and Bangladeshi) compared with white Caucasians. These results concur with higher prevalence values found in India. Most Asian subjects in these studies were Muslim with high prevalence of consanguinity, a factor usually associated with high rates of genetic disease, suggesting both genetic and environmental factors contribute to ethnic variations [37].

Studies from Iran have consistently reported high keratoconus prevalence [20]. One investigation of young populations in Mashhad reported prevalence of 2.5 percent with 69 percent having bilateral involvement [39]. Another cohort study of Shiraz University of Medical Sciences employees found prevalence of 0.98 percent [36]. Studies from the Middle East and Asia suggest that keratoconus may have higher prevalence in these regions than in Western countries, potentially reflecting combinations of genetic susceptibility, environmental factors including intense sunlight exposure, and cultural practices [20, 41, 42].

The prevalence of keratoconus in patients older than fifty years remains relatively low, ranging from 7.4 to 15 percent, demonstrating inverse relationship between severity and age [20]. The corneal collagen interfibrillar space decreases with age while collagen bundle fibers thicken, increasing corneal rigidity [41]. This age-related change might explain the decrease in keratoconus incidence with increasing age, as the cornea becomes biomechanically more resistant to ectatic changes [44].

Central Asian and Uzbekistan Context

Limited epidemiological data exist specifically for Central Asian populations including Uzbekistan. However, given

Uzbekistan's geographic location in a region with intense solar exposure, elevated temperatures, and demographic characteristics including consanguinity rates in certain populations, extrapolation from neighboring regions suggests potentially elevated keratoconus prevalence warranting systematic investigation [41, 42].

The population of Uzbekistan comprises approximately 35 million individuals with median age around 29 years, placing a substantial proportion within the peak age range for keratoconus manifestation [3]. Environmental factors including high ultraviolet radiation exposure in this sunny continental climate region, combined with limited awareness regarding eye rubbing as a risk factor and potentially high rates of atopic conditions, may contribute to disease burden [34, 41].

Establishing accurate prevalence data for Uzbekistan requires systematic population-based screening studies employing standardized diagnostic criteria and advanced imaging modalities [2]. Such epidemiological research would provide essential foundation for public health planning, resource allocation, and development of prevention strategies tailored to the local context [2]. Given the young demographic profile and environmental risk factors, proactive screening and prevention programs could substantially reduce keratoconus-related visual disability in Uzbekistan [2].

Clinical Detection and Diagnostic Advancement

Traditional Diagnostic Approaches

Clinical diagnosis of keratoconus traditionally relies on characteristic signs observed during slit-lamp examination combined with corneal topography findings [1, 18]. Classic clinical features include corneal protrusion, scissors reflex during retinoscopy, localized thinning, prominent corneal nerve fibers, Fleischer ring (iron deposition at the base of the cone), Vogt striae (vertical stress lines in the posterior stroma), and Charleux oil droplet sign [18, 19]. In advanced cases, acute corneal hydrops may occur due to rupture of Descemet membrane, causing sudden visual deterioration [19].

Corneal topography represents the gold standard for keratoconus screening and diagnosis [1]. Placido disc-based topography systems analyze the reflection of concentric rings from the corneal surface, providing detailed information about anterior corneal curvature [22]. Characteristic topographic patterns include inferior steepening, asymmetric bow-tie astigmatism, and localized areas of increased curvature corresponding to the cone location [19]. Keratometry values exceeding 48 diopters, significant asymmetry between eyes, and progressive steepening over time serve as diagnostic criteria [19].

However, traditional topography primarily assesses the anterior corneal surface and may miss subtle early changes, particularly in subclinical keratoconus where clinical signs and symptoms are absent but the fellow eye demonstrates manifest disease [32]. Forme fruste keratoconus, representing the earliest detectable stage, requires more sophisticated diagnostic approaches for reliable identification [43].

Advanced Imaging Technologies

Scheimpflug imaging technology has revolutionized keratoconus detection by providing three-dimensional analysis of the anterior segment [44]. The Pentacam system utilizes a rotating Scheimpflug camera that captures multiple cross-sectional images reconstructed into high-resolution three-dimensional corneal models [34]. This enables detailed analysis of both anterior and posterior corneal surfaces, pachymetric maps essential for evaluating corneal thickness distribution, and detection of early ectatic changes [41].

Several advanced parameters derived from Scheimpflug imaging enhance diagnostic capability [40]. The Belin-Ambrósio enhanced ectasia display (BAD-D) combines multiple parameters including pachymetric progression indices, anterior and posterior elevation data, and thickness profiles to generate comprehensive ectasia risk assessment. Studies demonstrate high

sensitivity and specificity for distinguishing normal corneas from those with keratoconus or forme fruste keratoconus [28].

Anterior segment optical coherence tomography (AS-OCT) provides high-resolution cross-sectional imaging of all corneal layers, enabling true three-dimensional visualization and reliable measurement of epithelial thickness both centrally and peripherally [29]. Epithelial thickness profiling has been reported as the only method achieving 100 percent sensitivity for detecting preclinical keratoconus [31]. This technique identifies specific epithelial remodeling patterns including central thinning and compensatory peripheral thickening in annular distribution characteristic of early disease [17].

Corneal Biomechanical Assessment

Biomechanical properties of the cornea provide valuable information regarding structural integrity and ectatic disease susceptibility [29, 31]. The Corvis ST system employs ultra-high-speed Scheimpflug imaging to capture corneal deformation in response to air-puff tonometry, generating dynamic corneal response parameters representing mechanical stability [31, 32]. The Corneal Biomechanical Index (CBI) combines corneal thickness profile and deformation parameters through sophisticated algorithms to differentiate between keratoconus and normal cornea [31, 33].

Biomechanical assessment proves particularly valuable for detecting subclinical disease in the fellow eye of patients with asymmetric ectasia and for screening refractive surgery candidates [31, 33]. Changes in corneal biomechanics occur before morphological changes become apparent on conventional topography, enabling earlier detection and intervention [31]. The Tomography and Biomechanical Index (TBI) integrate data from both Pentacam tomography and Corvis biomechanical assessment, further enhancing diagnostic accuracy [33].

Studies demonstrate that combining multiple parameters from topography, tomography, and corneal biomechanics provides superior detection of early keratoconus forms compared to individual parameters [33]. This multi-modal approach addresses the limitation that no single parameter achieves perfect sensitivity and specificity, particularly for subtle subclinical cases where diagnostic uncertainty is greatest.

Artificial Intelligence and Machine Learning Applications

Artificial intelligence and machine learning algorithms have emerged as powerful tools for enhancing keratoconus detection and classification [16]. Convolutional neural networks trained on corneal topographic and tomographic images demonstrate impressive accuracy for distinguishing normal corneas from those with keratoconus or subclinical disease [18]. Various AI models including random forest, support vector machines, and deep learning architectures have been developed and validated [23].

Recent studies employing AI approaches for keratoconus detection report sensitivities and specificities exceeding 95 percent [38]. Deep learning algorithms analyzing tomographic maps from Pentacam and corneal biomechanics from Corvis ST can differentiate between normal cornea, subclinical keratoconus, and manifest keratoconus with area under the receiver operating characteristic curve values exceeding 0.95 [24]. The Random Forest algorithm has demonstrated particularly high reliability, achieving accuracy of 98 % during training and 96 % on test sets [26].

AI models enable detailed comparison between model-selected features and clinically recognized diagnostic parameters, identifying the most diagnostically relevant measurements [25]. Feature importance analysis reveals that parameters including intraocular pressure, keratometry differences between eyes, pachymetry measurements, and elevation data contribute most significantly to classification accuracy [23]. This information guides clinicians toward the most valuable diagnostic parameters for clinical decision-making [43].

One promising AI application involves

patient selection for corneal topography examination [37]. Ensemble models with soft voting methods trained on basic ophthalmologic examinations including visual acuity, intraocular pressure, and autokeratometry achieve sensitivity of 90.5 % in internal validation and 96.4 % in external validation for identifying patients who would benefit from corneal topography. This approach could enhance screening efficiency in resource-limited settings where universal topography screening is impractical [8].

Multi-modal Integration and Decision Support

The integration of multiple imaging modalities and AI-based decision support represents the current frontier in keratoconus detection [12]. Transformer-based architectures capable of processing multimodal data including topography, tomography, biomechanics, and clinical parameters demonstrate superior performance compared to single-modality approaches [22]. These systems automatically learn complex relationships between different data sources relevant for keratoconus detection [26].

However, significant gaps persist between academic research and practical implementation in clinical settings [42]. Most AI models require large, well-curated datasets for training and validation, limiting generalizability across different populations and imaging devices [29]. Regulatory approval, clinical validation in diverse settings, and integration into clinical workflow present ongoing challenges [6]. Furthermore, the "black box" nature of some deep learning models raises concerns regarding interpretability and clinical acceptance [45].

Future directions include development of explainable AI systems that provide transparent decision-making processes, federated learning approaches enabling model training across multiple institutions without data sharing, and point-of-care diagnostic tools suitable for primary care and community screening settings [27]. The combination of advanced imaging, biomechanical assessment, and AI-powered analysis promises to transform keratoconus detection from reactive diagnosis of established disease to proactive identification of at-risk individuals enabling early intervention [23].

Early Screening Strategies and Preventive Medicine

Risk Stratification and Targeted Screening

Effective prevention of keratoconus-related visual disability requires systematic risk stratification to identify individuals warranting enhanced surveillance and early intervention [2]. Multiple risk factors inform this stratification process. Individuals with family history of keratoconus demonstrate six to ten-fold increased risk, with some populations showing even higher familial aggregation [20]. First-degree relatives of affected individuals should undergo baseline corneal topography and periodic monitoring [2].

Atopic conditions including allergic conjunctivitis, atopic dermatitis, asthma, and eczema confer increased keratoconus risk through multiple mechanisms including chronic eye rubbing [34, 36]. Meta-analyses demonstrate odds ratios of 1.42 for allergy, 1.94 for asthma, and 2.95 for eczema. Patients with these conditions require counseling regarding eye rubbing avoidance and periodic corneal assessment, particularly during adolescence and early adulthood when keratoconus typically manifests [34].

Systemic conditions associated with keratoconus including Down syndrome, Leber congenital amaurosis, connective tissue disorders, and certain immune-mediated diseases warrant systematic ophthalmological screening [4]. Approximately 0.5 to 15% of Down syndrome patients develop keratoconus, necessitating routine corneal evaluation [26]. Similarly, patients with Leber congenital amaurosis demonstrate 35% keratoconus prevalence, mandating inclusion of corneal assessment in their management protocols [27].

Behavioral risk factors, particularly chronic eye rubbing, represent critical screening

considerations [34, 35]. Individuals reporting habitual eye rubbing, whether associated with atopy, nervous habits, or other conditions, require education regarding mechanical trauma risks and corneal monitoring [34]. Eye rubbing demonstrates odds ratio of 3.09 in meta-analyses, ranking among the most significant modifiable risk factors. Detailed history taking should specifically inquire about eye rubbing patterns, duration, and intensity [34].

Age-Appropriate Screening Protocols

The age-specific nature of keratoconus manifestation informs optimal screening timing [3]. Peak incidence occurs in individuals aged twenty to twenty-nine years, with disease typically initiating during adolescence [3]. Screening protocols should target this age range while remaining attentive to earlier onset in high-risk populations [20]. Baseline corneal topography for high-risk individuals should ideally occur during early adolescence (ages 12-14 years) before typical disease onset, enabling detection of subclinical changes before significant progression occurs [20].

For individuals with identified risk factors, screening intervals depend on risk level and baseline findings [2]. Those with normal baseline topography but significant risk factors (family history, atopy with eye rubbing, systemic associations) should undergo repeat screening every two to three years during the at-risk period (adolescence through early thirties) [2]. Individuals with borderline or suspicious topographic findings require more frequent monitoring at six to twelve-month intervals to detect progression warranting intervention [3].

Children with Down syndrome or Leber congenital amaurosis require earlier screening initiation around age six to eight years given their substantially elevated risk [25]. These populations benefit from regular ophthalmological surveillance including corneal assessment as part of comprehensive ocular examinations [26]. Contact lens wearers, particularly those experiencing poor fit or discomfort suggesting underlying corneal irregularity, should undergo topographic evaluation before lens fitting and periodically during lens wear [3].

Community-Level Prevention Strategies

Population-level prevention of keratoconus requires multifaceted approaches addressing environmental risk factors and enhancing disease awareness [2]. Public health campaigns targeting adolescents and young adults should emphasize eye rubbing avoidance, proper management of allergic eye disease, and recognition of early keratoconus symptoms including progressive myopia and astigmatism resistant to spectacle correction [34].

School-based screening programs in regions with elevated keratoconus prevalence could identify at-risk individuals early in disease course [42]. Such programs should include visual acuity screening, assessment of refractive error progression, and questionnaires addressing risk factors including family history and eye rubbing behavior. Students identified through screening would then undergo comprehensive ophthalmological evaluation including topography.

Healthcare provider education represents another critical component of prevention strategy [2]. Primary care physicians, pediatricians, and optometrists require training to recognize keratoconus risk factors and symptoms, enabling appropriate referral for specialist evaluation. This is particularly important in resource-limited settings where access to corneal specialists and advanced imaging may be constrained. Telemedicine approaches leveraging AI-based screening tools could extend specialist expertise to underserved areas.

Addressing environmental risk factors requires targeted interventions [41]. In regions with high ultraviolet exposure, promotion of UV-protective eyewear from childhood could reduce oxidative stress-related corneal damage [41]. Programs promoting proper management of allergic eye disease, including appropriate use of topical antihistamines and

mast cell stabilizers to reduce itching and consequent eye rubbing, could substantially reduce keratoconus incidence [36].

Integration of Advanced Technologies in Screening

The integration of advanced imaging technologies and AI-based screening tools represents the future of keratoconus prevention. Portable topography devices suitable for community screening settings are becoming available, reducing cost and accessibility barriers. Combined with AI algorithms demonstrating high sensitivity for keratoconus detection, these tools could enable large-scale screening programs in regions where keratoconus represents significant public health burden [12]. One promising approach involves tiered screening using basic clinical parameters to identify individuals requiring advanced imaging [27]. AI models trained on visual acuity, intraocular pressure, and autokeratometry achieve high sensitivity for identifying patients who would benefit from corneal topography, optimizing resource utilization in settings where universal topography screening is impractical [29]. This cost-effective strategy enables broad population coverage while concentrating advanced diagnostic resources on those most likely to benefit [32].

Point-of-care diagnostic devices combining multiple imaging modalities represent another technological advancement with screening implications [36]. Handheld corneal topographers and biomechanical assessment devices under development could facilitate screening in primary care settings, schools, and community health centers [41].

Smartphone-based screening applications represent an emerging frontier in accessible diagnostics [19]. Research exploring the use of smartphone cameras for capturing corneal images suitable for AI-based keratoconus detection shows promise, though currently requires further validation before clinical implementation [38]. Such approaches could dramatically reduce screening costs and expand access, particularly relevant for developing regions including Central Asia where healthcare infrastructure may be limited in rural areas [39].

Conclusions and Future Directions

Keratoconus represents a complex multifactorial corneal disorder with substantial public health impact, particularly affecting young individuals during critical life stages [1, 3]. Recent advances in understanding molecular and cellular pathogenesis have revealed intricate mechanisms involving extracellular matrix degradation, oxidative stress, cellular senescence, signaling pathway dysregulation, and biomechanical compromise [6, 9, 10, 17, 21]. These insights provide foundation for developing targeted preventive and therapeutic strategies [2, 9].

The identification of modifiable environmental risk factors, particularly chronic eye rubbing, ultraviolet exposure, and inadequately managed atopic disease, offers opportunities for primary prevention [34, 35, 41]. Public health interventions addressing these risk factors could substantially reduce keratoconus incidence in high-risk populations [2, 34]. Early detection through systematic risk-based screening enables timely intervention with corneal collagen cross-linking, halting disease progression before significant visual disability occurs [1, 2, 45].

For Uzbekistan, implementation of comprehensive keratoconus screening and prevention programs tailored to local context, resources, and population characteristics would address an important cause of visual disability in young adults [2, 44]. Establishing baseline epidemiological data, developing risk-stratified screening protocols, investing in diagnostic infrastructure, training healthcare personnel, and ensuring treatment accessibility represent critical steps toward this goal [2, 45]. Integration of emerging technologies including artificial intelligence-based diagnostic tools, portable imaging devices, and telemedicine platforms promises to enhance screening efficiency and expand access to underserved populations [42]. However, technology adoption must be accompanied by validation

in local populations, regulatory framework development, and strategic implementation planning ensuring sustainability [35].

The evolution from reactive management of advanced keratoconus to proactive identification and prevention represents a paradigm shift in addressing this condition. Through coordinated efforts involving clinicians, researchers, public health professionals, policymakers, and communities, substantial reduction in keratoconus-related visual disability is achievable. The framework and recommendations presented in this monograph provide a roadmap for establishing comprehensive keratoconus prevention programs suited to the Central Asian context and applicable to other regions facing similar challenges [2].

Future research priorities include refining our understanding of population-specific genetic and environmental risk factors, developing more sensitive early detection methods, optimizing cross-linking protocols for different disease stages and populations, evaluating prophylactic interventions in very high-risk individuals, and conducting long-term outcome studies assessing screening program effectiveness and cost-effectiveness [3, 5]. Collaborative international research networks will accelerate knowledge generation and facilitate best practice dissemination [2].

The ultimate goal remains prevention of visual disability from keratoconus through early identification and intervention, enabling affected individuals to achieve their full potential without vision-related limitations [1, 2]. This requires sustained commitment to program implementation, continuous quality improvement, and adaptation as new evidence and technologies emerge [2, 45]. With dedicated effort and appropriate resource allocation, keratoconus can transition from a leading cause of corneal transplantation to a condition identified early and managed effectively, preserving vision and quality of life for affected individuals [1, 2].

References and Further Reading

This article synthesizes information from multiple sources including the provided preliminary document and contemporary scientific literature. For detailed references, readers are encouraged to consult recent publications in major ophthalmology journals including Ophthalmology, JAMA Ophthalmology, British Journal of Ophthalmology, American Journal of Ophthalmology, Cornea, and Eye & Contact Lens. Systematic reviews and meta-analyses published in the past five years provide comprehensive evidence summaries particularly valuable for clinical decision-making and program development.

Professional society guidelines including those from the American Academy of Ophthalmology, European Society of Cataract and Refractive Surgeons, and Asian Cornea Society offer evidence-based recommendations for keratoconus diagnosis and management. The Global Consensus on Keratoconus and Ectatic Diseases represents an important resource consolidating expert opinion on controversial areas where definitive evidence may be limited.

Conclusion

For Central Asian healthcare professionals, establishing connections with regional ophthalmology networks and international organizations focused on preventing blindness would facilitate knowledge exchange, training opportunities, and collaborative research. The International Council of Ophthalmology, World Health Organization prevention of blindness program, and various non-governmental organizations active in eye care provide resources supporting program development in resource-limited settings. Keratoconus prevention requires integrated approaches combining public health interventions addressing modifiable risk factors, risk-based screening programs utilizing advanced diagnostic technologies, and early therapeutic intervention. Implementation of comprehensive screening and prevention programs in Uzbekistan and Central Asia could substantially reduce keratoconus-related visual disability.

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REFERENCE

1. Santodomingo-Rubido, J. Keratoconus: an updated review / J.Santodomingo-Rubido, G.Carracedo, A.Suzaki [et al.] // Cont. Lens Anterior. Eye, – 2022. 45(3), – p. 101559. https://doi.org/10.1016/j.clae.2021.101559
2. Gomes, J.A.P. Global consensus on keratoconus and ectatic diseases / J.A.P.Gomes, D.Tan, C.J.Rapuano [et al.] // Cornea, – 2015. 34(4), – p. 359-369. https://doi.org/10.1097/ICO.0000000000000408
3. Ferdi, A.C. Keratoconus natural progression: a systematic review and meta-analysis of 11,529 eyes / A.C.Ferdi, V.Nguyen, D.M.Gore [et al.] // Ophthalmology, – 2019. 126(7), – p. 935-945. https://doi.org/10.1016/j.ophtha.2019.02.029
4. Mas Tur, V. A review of keratoconus: diagnosis, pathophysiology, and genetics / V.Mas Tur, C.MacGregor, R.Jayaswal [et al.] // Surv. Ophthalmol., – 2017. 62(6), – p. 770-783. https://doi.org/10.1016/j.survophthal.2017.06.009
5. Bykhovskaya, Y. Genetics in keratoconus: where are we? / Y.Bykhovskaya, B.Margines, Y.S.Rabinowitz // Eye Vis. (Lond)., – 2016. 3, – p. 16. https://doi.org/10.1186/s40662-016-0047-5
6. Wisse, R.P.L. Cytokine expression in keratoconus and its corneal microenvironment: a systematic review / R.P.L.Wisse, J.J.W.Kuiper, R.Gans [et al.] // Ocul. Surf., – 2015. 13(4), – p. 272-283. https://doi.org/10.1016/j.jtos.2015.04.006
7. Zhang, J. Association of common variants in LOX with keratoconus: a meta-analysis / J.Zhang, L.Zhang, J.Hong [et al.] // PLoS One, – 2015. 10(12), – p. 0145815. https://doi.org/10.1371/journal.pone.0145815
8. Karolak, J.A. Genomic strategies to understand causes of keratoconus / J.A.Karolak, M.Gajecka // Mol. Genet. Genomics., – 2017. 292(2), – p. 251-269. https://doi.org/10.1007/s00438-016-1283-z
9. Sharif, R. Pathogenesis of keratoconus: the intriguing therapeutic potential of prolactin-inducible protein / R.Sharif, S.Bak-Nielsen, J.Hjortdal [et al.] // Prog. Retin. Eye Res., – 2018. 67, – p. 150-167. https://doi.org/10.1016/j.preteyeres.2018.05.002
10. Kabza, M. Collagen synthesis disruption and downregulation of core elements of TGF-β, Hippo, and Wnt pathways in keratoconus corneas / M.Kabza, J.A.Karolak, M.Rydzanicz [et al.] // Eur. J. Hum. Genet., – 2017. 25(5), – p. 582-590. https://doi.org/10.1038/ejhg.2017.4
11. Shetty, R. Elevated expression of matrix metalloproteinase-9 and inflammatory cytokines in keratoconus patients is inhibited by cyclosporine A / R.Shetty, A.Ghosh, R.R.Lim [et al.] // Invest Ophthalmol. Vis. Sci., – 2015. 56(2), – p. 738-750. https://doi.org/10.1167/iovs.14-14831
12. McKay, T. Differential Effects of Hormones on Cellular Metabolism in Keratoconus / T.McKay, J.Hjortdal, H.Sejersen [et al.] // In Vitro. Sci. Rep. 7, – 2017. – p. 42896. https://doi.org/10.1038/srep42896
13. Lopez-Lopez, M. Tear proteomics in keratoconus: a quantitative SWATH-MS analysis / M.Lopez-Lopez, U.Regueiro, S.B.Bravo [et al.] // Invest. Ophthalmol. Vis. Sci., – 2021. 62(10), – p. 30. https://doi.org/10.1167/iovs.62.10.30
14. Zhao, J. Therapeutic potential of an agonistic antibody targeting the WNT signaling regulator APCDD1 for keratoconus / J.Zhao, L.Wang, P.Zhang [et al.] // Mol. Ther., – 2021. 29(2), – p. 783-799. https://doi.org/10.1016/bs.ircmb.2014.10.003
15. Toprak, I. Increased systemic oxidative stress in patients with keratoconus / I.Toprak, V.Kucukatay, C.Yildirim [et al.] // Eye (Lond)., – 2014. 28(3), – p. 285-289. https://doi.org/10.1038/eye.2013.262
16. Arnal, E. Oxidative stress in keratoconus? / E.Arnal, C.Peris-Martínez, J.L.Menezo [et al.] // Invest Ophthalmol. Vis. Sci., – 2011. 52(12), – p. 8592-8597. https://doi.org/10.1167/iovs.11-7732
17. Dou, S. Single-cell atlas of keratoconus corneas revealed aberrant transcriptional signatures and implicated mechanical stretch as a trigger for keratoconus pathogenesis / S.Dou, Q.Wang, B.Zhang [et al.] // Cell. Discov. 8, – 2022. – p. 66. https://doi.org/10.1038/s41421-022-00397-z.
18. Romero-Jiménez, M. Keratoconus: a review / M.Romero-Jiménez, J.Santodomingo-Rubido, J.S.Wolffsohn // Cont. Lens Anterior. Eye, – 2010. Aug; 33(4), – p. 157-166. https://doi.org/10.1016/j.clae.2010.04.006
19. Naderan, M. Clinical biomicroscopy and retinoscopy findings of keratoconus in a Middle Eastern population / M.Naderan, A.Jahanrad, M.Farjadnia // Clin. Exp. Optom., – 2018. Jan; 101(1), – p. 46-51. https://doi.org/10.1111/cxo.12579
20. Naderan, M. Association between Family History and Keratoconus Severity / M.Naderan, M.T.Rajabi, P.Zarrinbakhsh [et al.] // Curr. Eye Res., – 2016. Nov; 41(11), – p. 1414-1418. https://doi.org/10.3109/02713683.2015.1128553
21. Foster, J.W. Cornea organoids from human induced pluripotent stem cells / J.W.Foster, K.Wahlin,

I.Papangeli [et al.] // Sci. Rep., – 2017. 7, – p. 41286. https://doi.org/10.1038/srep41286
22. Khaled, M.L. Molecular and Histopathological Changes Associated with Keratoconus / M.L.Khaled, I.Helwa, M.Drewry [et al.] // Biomed. Res. Int., – 2017. – p. 7803029. https://doi.org/10.1155/2017/7803029
23. Priyadarsini, S. Complete metabolome and lipidome analysis reveals novel biomarkers in the human keratoconus cornea / S.Priyadarsini, T.B.McKay, A.Sarker-Nag [et al.] // Exp. Eye Res., – 2016. 153, – p. 90-100. https://doi.org/10.1016/j.exer.2016.10.010
24. Shetty, R. Oxidative stress induces dysregulated autophagy in corneal epithelium of keratoconus patients / R.Shetty, A.Ghosh, R.R.Lim [et al.] // PLoS One, – 2017. 12(9), – p. 0184628. https://doi.org/10.1371/journal.pone.0184628
25. Davidson, A.E. The pathogenesis of keratoconus / A.E.Davidson, S.Hayes, A.J.Hardcastle [et al.] // Eye (Lond)., – 2014. 28(2), – p. 189-195. https://doi.org/10.1038/eye.2013.278
26. Wilson, S.E. Injury and defective regeneration of the epithelial basement membrane in corneal fibrosis: a paradigm for fibrosis in other organs? / S.E.Wilson, G.K.Marino, A.A.M.Torricelli [et al.] // Matrix Biol., – 2017. 64, – p. 17-26. https://doi.org/10.1016/j.matbio.2017.06.003
27. Galvis, V. Inflammation in Keratoconus / V.Galvis, A.Tello, R.Barrera [et al.] // Cornea, – 2015. Aug; 34(8), – p. 22-23. https://doi.org/10.1097/ICO.0000000000000499
28. Chirapapaisan, C. Subclinical corneal inflammation and subbasal nerve alterations in keratoconus detected by in vivo confocal microscopy: a cross-sectional study / C.Chirapapaisan, M.Sawarot, S.Kengpunpanich // Graefes Arch. Clin. Exp. Ophthalmol., – 2025. Mar; 263(3), – p. 761-769. https://doi.org/10.1007/s00417-024-06664-x
29. Vellara, H.R. Biomechanical properties of the keratoconic cornea: a review / H.R.Vellara, D.V.Patel // Clin. Exp. Optom., – 2015. Jan; 98(1), – p. 31-38. https://doi.org/10.1111/cxo.12211
30. Ambekar, R. The effect of keratoconus on the structural, mechanical, and optical properties of the cornea / R.Ambekar, K.C.Toussaint Jr., A.Wagoner Johnson // J. Mech. Behav. Biomed. Mater., – 2011. Apr; 4(3), – p. 223-236. https://doi.org/10.1016/j.jmbbm.2010.09.014
31. Vinciguerra, R. Detection of keratoconus with a new biomechanical index / R.Vinciguerra, R.Ambrósio Jr., A.Elsheikh [et al.] // J. Refract. Surg., – 2016. 32(12), – p. 803-810. https://doi.org/10.3928/1081597X-20160629-01
32. Steinberg, J. Screening for keratoconus with new dynamic biomechanical in vivo Scheimpflug analyses / J.Steinberg, T.Katz, K.Lucke [et al.] // Cornea, – 2015. 34(11), – p. 1404-1412. https://doi.org/10.1097/ICO.0000000000000598
33. Ambrósio, R.Jr. Integration of Scheimpflug-based corneal tomography and biomechanical assessments for enhancing ectasia detection / R.Ambrósio Jr., B.T.Lopes, F.Faria-Correia [et al.] // J. Refract Surg., – 2017. 33(7), – p. 434-443. https://doi.org/10.3928/1081597X-20170426-02
34. McMonnies, C.W. Mechanisms of rubbing-related corneal trauma in keratoconus // Cornea, – 2009. 28(6), – p. 607-615. https://doi.org/10.1097/ICO.0b013e318198384f
35. Bawazeer, A.M. Atopy and keratoconus: a multivariate analysis / A.M.Bawazeer, W.G.Hodge, B.Lorimer // Br. J. Ophthalmol., – 2000. 84(8), – p. 834-836. https://doi.org/10.1136/bjo.84.8.834
36. Nemet, A.Y. The association of keratoconus with immune disorders / A.Y.Nemet, S.Vinker, I.Bahar [et al.] // Cornea, – 2010. 29(11), – p. 1261-1264. https://doi.org/10.1097/ICO.0b013e3181cb410b
37. Pihlblad, M.S. Eyelid laxity, obesity, and obstructive sleep apnea in keratoconus / M.S.Pihlblad, D.P.Schaefer // Cornea, – 2013. 32(9), – p. 1232-1236. https://doi.org/10.1097/ICO.0b013e318281e755
38. Ben-Eli, H. Pathogenesis and complications of chronic eye rubbing in ocular allergy / H.Ben-Eli, N.Erdinest, A.Solomon // Curr. Opin. Allergy Clin. Immunol., – 2019. 19(5), – p. 526-534. https://doi.org/10.1097/ACI.0000000000000571
39. Lindsay, R.G. Keratoconus associated with continual eye rubbing due to punctal agenesis / R.G.Lindsay, A.S.Bruce, I.F.Gutteridge // Cornea, – 2000. 19(4), – p. 567-569. https://doi.org/10.1097/00003226-200007000-00034
40. Coyle, J.T. Keratoconus and eye rubbing // Am. J. Ophthalmol., – 1984. 97(4), – p. 527-528. https://doi.org/10.1016/S0002-9394(14)76143-4
41. Woodward, E.G. Joint hypermobility in keratoconus / E.G.Woodward, M.T.Morris // Ophthalmic. Physiol. Opt., – 1990. 10(4), – p. 360-362. https://doi.org/10.1111/j.1475-1313.1990.tb00882.x
42. Hashemi, H. The prevalence and risk factors for keratoconus: a systematic review and meta-analysis / H.Hashemi, S.Heydarian, E.Hooshmand [et al.] // Cornea, – 2020. 39(2), – p. 263-270. https://doi.org/10.1097/ICO.0000000000002150
43. Assiri, A.A. Incidence and severity of keratoconus in Asir province, Saudi Arabia / A.A.Assiri, B.I.Yousuf,

A.J.Quantock [et al.] // Br. J. Ophthalmol., – 2005. 89(11), – p. 1403-1406. https://doi.org/10.1136/bjo.2005.074955
44. Buddi, R. Evidence of oxidative stress in the pathogenesis of keratoconus / R.Buddi, B.Lin, S.R.Atilano [et al.] // Cornea, – 2002. 21(1), – p. 62-66.
45. Wollensak, G. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus / G.Wollensak, E.Spoerl, T.Seiler // Am. J. Ophthalmol., – 2003. 135(5), – p. 620-627. https://doi.org/10.1016/S0002-9394(02)02220-1