Archives of Clinical and Experimental Ophthalmology

Devitt et al., Arch Clin Exp Ophthalmol. 2024;6(1):6-12.

Review Article

Ocular cystinosis – A review of disease, diagnosis, and future treatment options

Lauren Devitt[1,*]

[1]TCD School of Medicine, Dublin, Ireland

*Author for correspondence: Email: ldevitt@tcd.ie

Received date: September 13, 2024
Accepted date: October 25, 2024

Abstract

Cystinosis is a rare autosomal recessive lysosomal storage disorder, characterised by the intra-lysosomal accumulation of cystine. Cystinosis results from a defect in the CTNS protein, a lysosomal transport protein for cystine. There are three subtypes of cystinosis: infantile nephropathic cystinosis, juvenile nephropathic cystinosis and ocular non-nephropathic cystinosis. Corneal cystine crystal accumulation is pathognomonic for ocular cystinosis. Ocular cystinosis also occurs as a consequence of nephropathic cystinosis. Patients can suffer from ocular symptoms such as photophobia, blepharospasm and visual impairment. Diagnosis is currently primarily made using slit lamp examination. The mainstay of cystinosis treatment is cysteamine, a cystine depleting drug. The treatment of ocular cystinosis is challenging due to the avascular nature of the cornea, and the requirement for frequent administration of topical treatment. There are currently only two topical cysteamine treatment options on the market – 'Cystaran' and 'Cystadrops'. Many studies are ongoing using modern technologies such as nano wafers, gold nanoparticles and stimuli responsive 'smart' hydrogels and 'smart' contact lenses to improve treatment options for patients. The majority of research is focused on increasing the residence time of the drug on the ocular surface, aiming to reduce the need for frequent reapplication, improving compliance and quality of life. There is a great need for modern treatment options to alleviate symptomatology and improve disease pathophysiology. This review examines ocular cystinosis and ocular involvement as a complication of nephropathic cystinosis, with an added focus on the diagnosis, current and future treatment options.

Keywords: Ocular cystinosis, Cornea, Cystine, Cysteamine

Main Text

Cystinosis is a rare lysosomal storage disorder with a worldwide incidence of 0.5-1/100,000 live births [1]. Cystinosis is characterised as a lysosomal storage disorder, resulting in the accumulation of intra-lysosomal cystine [2]. Cystinosis is categorised by age of disease onset and severity of kidney involvement. Cystinosis is classified into infantile nephropathic cystinosis, juvenile nephropathic cystinosis and ocular (non-nephropathic) cystinosis. Infantile nephropathic cystinosis is responsible for 95% of cystinosis [3]. It is the most severe form of disease, leading to renal Fanconi syndrome and kidney failure within the first decade of life if not receiving treatment [4]. Juvenile nephropathic cystinosis is slightly milder than infantile cystinosis and typically develops between the ages of 10 and 12 years of age [3]. Ocular cystinosis is a non-nephropathic form of cystinosis and is commonly diagnosed in adulthood [5].

Cystinosis is caused by a dysfunctional lysosomal transport protein, named cystinosin [2]. Cystinosin is coded for by the *CTNS* gene, located on chromosome 17p13 [2]. Cystinosin is a lysosomal 7 transmembrane protein, functioning to export cystine from the lysosome. It is driven by a H^+ electrochemical gradient [6]. The dysfunctional cystinosin protein results in the intra-

lysosomal accumulation of cystine and the production of pathogenic cystine crystals, leading to downstream organ damage [7]. Organs commonly damaged in cystinosis include the kidney, cornea, thyroid, bone marrow, muscles, spleen, and peripheral nerves [3].

All 3 clinical forms of cystinosis are due to bi-allelic pathogenic variants in the *CTNS* gene, with a specific pathogenic variant being detected in over 95% of cases [8]. Variant analysis revealed that ocular cystinosis is allelic with the nephropathic form of disorder [9]. Over 140 pathogenic variants of the *CTNS* gene have been described with most pathogenic variants associated with infantile cystinosis [10]. Ocular cystinosis patients harbour a mix of classical cystinosis and novel specific ocular cystinosis pathogenic variants [9]. In the Tunisian population 7 different *CTNS* pathogenic variants have been documented in association with ocular cystinosis – three missense pathogenic variants, one duplication, one frameshift variant, one large deletion and one splice site pathogenic variant [11].

Pathogenic cystinosis variants have a significant geographical distribution, with more developed countries harbouring most of the data [10]. The most common pathogenic variant in North America and Northern Europe is the 57kb deletion, accounting for 50-70% of this population [12]. However, this large 57kb deletion is only responsible for 17% and 0% of cystinosis patients in Italy and Egypt respectively [13,14]. *CTNS* nonsense variants represent 15% of the known *CTNS* pathogenic variants, with the most common nonsense variant being the p.W138x variant [15]. This has been attributed to disease in 50% of the French-Canadian cystinosis population [15].

Ocular Cystinosis

Ocular non-nephropathic cystinosis was first described in 1957 [16]. It was originally termed 'adult' or 'benign' cystinosis. Ocular cystinosis presents as cystine crystal deposits in the cornea in the absence of renal disease [9]. Cystine crystals in the cornea are pathognomonic for ocular cystinosis [17]. Complications of cystine crystal deposition in the cornea commonly include photophobia, visual impairment, corneal scarring, cataracts and keratitis [18]. The crystals do not usually influence visual acuity until the cystine crystals reach the centre of the cornea [19]. Upon entry of the cystine crystals to bowman's membrane, foreign body sensations and inflammatory symptoms of recurrent corneal erosions may occur [19].

Cystine crystals can be found in other structures of the eye as well as the cornea, including the conjunctiva, iris, ciliary body, choroid, retina, and optic nerve [17]. Cystinosis can cause retinal changes which may progress to photoreceptor degeneration and thus impaired colour and night vision [17]. Older patients may exhibit moderate to severe constriction of visual fields and reduction of rod and cone mediated ERG responses [20]. Patches of depigmentation and symmetrical pigment epithelial mottling are the most common posterior segment manifestations of cystinosis [20], with epithelial mottling starting in the peripheries and progressing towards the posterior pole over time [21]. The frequency of complications is reduced with early diagnosis and treatment of cysteamine therapy [22]. However, if ocular cystinosis is left untreated it can result in blindness [18].

Unlike in the kidney, the formation of cystine crystals in the cornea are not well understood. Corneal crystals appear in the periphery and progress centripetally over time [19]. The majority of crystals are located in the corneal stroma, which is comprised predominantly of collagen and keratocytes [23]. Corneal cystine crystals are located extracellularly [24] and are needle like in formation, in contrast to the intracellular rectangular or hexagonal crystals found in other organs. The needle like stromal crystals are orientated parallel to the stomal lamellae [25], suggesting a role for collagen in the deposition of cystine crystals [26]. Additionally, crystal production reaches a saturation point in the cornea after which no further crystallisation occurs. Dixon *et al.* propose the requirement of collagen in the production of cystine crystals, and thus when no more collagen is available crystal deposition plateaus [26].

Two mechanisms have been proposed for the lack of kidney involvement in ocular cystinosis. It is speculated that ocular cystinosis patients are heterozygous for one severe and one mild *CTNS* pathogenic variant. This spares patients from kidney involvement. Nephropathic cystinosis patients have two severe pathogenic variants, predisposing them to kidney damage. Firstly, patients may have significant residual cystinosin activity in every other tissue of the body (e.g. the G197R variant). Alternatively, substantial cystinosin activity may be present in the kidney because of tissue specific expression of factors that promote the production of a normal CTNS protein (e.g. IVS10-3 C→G variant) [9].

Ocular Involvement in Nephropathic Cystinosis

Extra renal complications of nephropathic cystinosis include ocular deposition of corneal cystine crystals, and endocrine dysregulation such as diabetes, hypothyroidism, and retarded growth [3]. Corneal cystine crystals can be seen in the cornea as young as 16 months of age in nephropathic cystinosis [27]. While initially asymptomatic, symptoms of ocular involvement can begin within the first few years of life [28], with most nephropathic cystinosis patients experiencing photophobia after the first decade of life [17]. A large cross sectional study reports that 75-87% of nephropathic cystinosis patients over 20 years of age showed anterior segment involvement separate from corneal and conjunctival crystal deposits [29]. There is an age dependant tendency for crystals to deposit anteriorly in childhood, while crystals are located posteriorly in the corneal stroma in adulthood [30]. The rest of this review will focus on the diagnosis and treatment of ocular (non-nephropathic) cystinosis and ocular involvement in nephropathic cystinosis as a singular entity.

Diagnosis

The Ophthalmology Cystinosis Forum in 2017 recommend early detection of ocular cystinosis to be comprised of photophobia assessment, visual acuity, slit lamp examination, and tonometry ophthalmic examinations. Additionally, *in vivo* confocal microscopy and anterior segment optical coherence tomography were highlighted as valuable options to evaluate corneal cystine crystals [31].

There has been further focus on the use of spectral domain coherence tomography based retinochoroidal cystine crystal score (RCCCS) as an objective biomarker for systemic disease control in cystinosis [32]. Keidel *et al.* demonstrate the RCCCS being negatively correlated with cysteamine intake, highlighting how the RCCCS determines treatment response. Notably, the RCCCS is also positively correlated with cystatin C, a stable parameter of renal function, possibly an indication of nephropathic cystinosis disease [32].

Follow up of cystine crystal deposition can prove challenging. Slit lamp examination plays a large role in the diagnosis of ocular cystinosis. However, it poses difficulties regarding accurate assessment over time, tracking disease progression and treatment efficacy. Additionally, the corneal crystal score lacks accurate estimates in low levels of deposition and in assessing alterations in crystal deposition [33]. Recent work has been focused on improving the diagnosis and monitoring of cystinosis. Corneal densitometry obtained through Penta Cam can estimate the level of corneal cystine crystal deposition, offering a potential way to assess disease progression and or treatment effectiveness/adherence [33]. Furthermore, anterior segment optical coherence tomography (AS-OCT) can serve as an objective quantification of corneal cystine crystal deposition and may be able to serve as a novel biomarker for ocular disease control and treatment monitoring [34].

Ocular cystinosis typically spares the kidney and other organs [35]. However, the coexistence of juvenile and ocular forms of cystinosis were described in one family, representing a possible continuum between mild forms of cystinosis. Thus, renal monitoring is recommended in every patient with seemingly isolated ocular cystinosis [36].

Treatment

Early diagnosis and treatment are paramount to prevent disease progression [22]. The primary treatment for cystinosis is oral and topical cysteamine. Cysteamine is a cystine depleting drug, functioning to reduce intra-lysosomal accumulation of cystine. Cysteamine drives a disulphide exchange reaction which results in the formation of cysteine and cystine-cysteamine mixed disulphide which can leave the lysosome through a 'system c' transporter [35]. In nephropathic forms of cystinosis, cysteamine delays the progression of disease to end stage renal failure, extra renal complications, and the need for renal transplant [37]. Due to the highly vascularised nature of the macula and retina, oral cysteamine therapy has significantly reduced the rates of damage to these structures [38]. However, the avascular structure of the cornea is a barrier to oral cysteamine therapy, with cysteamine failing to reduce corneal cystine crystal accumulation. Thus, topical cysteamine therapy is necessary to reduce corneal crystal density and alleviate symptoms [39].

Topical administration of cysteamine dissolves cystine crystals, improving ocular symptoms and enhancing quality of life [27]. Ocular cystinosis management requires frequent topical cysteamine administration. This is a result of eyedrops being rapidly cleared from the ocular surface due to constant blinking and nasolacrimal drainage, reducing contact time on the eye [18]. This represents a significant obstacle to patient compliance and treatment adherence. The shelf life of cysteamine once exposed to the air from the eye drop bottle is short, causing further issues [40].

There are two main cysteamine preparations. 'Cystaran' (0.44% cysteamine ophthalmic solution) was approved by the FDA as an orphan drug for the treatment of corneal cysteine crystal deposits in 2012 [41]. However, administration is required hourly, presenting many compliance issues [41]. 'Cystadrops' (0.55% cysteamine ophthalmic solution) was approved by the EMA and FDA in in 2017 and 2020 respectively [42]. 'Cystadrops' facilitates 4-time daily dosing, as the addition of carmellose sodium increases the viscosity of the formulation, allowing a longer residence time on the ocular surface and reducing frequency of administration [42]. A systematic review and meta-analysis carried out by Kaur *et al.* backs up the efficacy and safety of topical cysteamine in ocular cystinosis [43]. Liang *et al.* led a 45 month follow up study for patients receiving 'Cystadrops', demonstrating normal visual acuity scores, a reduction in photophobia, and a decrease in corneal cystine crystal scores over time (stabilising at 27 months) [44]. In this study 47 non serious adverse effects and 4 serious adverse effects were reported [44]. Notably, the use of topical 0.55% cysteamine may be limited in severe nephropathic cystinosis with Al-Hemidan *et al.* demonstrating its administration failing to improve photophobia in this subgroup of patients to a clinically significant level [45]. If therapy is discontinued, corneal cystine crystals accumulation will increase [1]. Patients not treated with cysteamine may require a corneal transplant. Topical cysteamine treatment should be continued post-transplant, as there is a risk of cystinosin deficient cells invading the transplanted cornea [1].

'Cystadrops' are currently only indicated in cystinosis for adults and children from 2 years of age. A phase 3 clinical trial was completed to determine if 'Cystadrops' administration may be of value to patients less than 2 years of age (NCT04125927). Considering cystine crystals can be observed on slit lamp examination in nephropathic cystinosis patients at 16 months, treatment available at this point would be beneficial [27]. No results have yet been posted.

Future Treatment Options

As mentioned above, the frequent applications of cysteamine eye drops are significantly demanding and compromising to quality of life. Many studies are focused on alternative treatment options for ocular cystinosis. The primary focus is to reduce the need for continuous reapplication of topical cysteamine. Prodrug preparations of cysteamine have been developed to increase the half-life and bioavailability of the drug. Such prodrugs include N-acyl or glutaric acid derivatives of cysteamine [46,47]. Carbohydrate-cysteamine thiazolidines have been proposed as another pro drug for the treatment of cystinosis [48]. While Ramazani *et al.* describe the extracellular release of cysteamine as a barrier to cellular uptake and drug efficacy, Iwata *et al.* demonstrate the extracellular location of corneal cystine crystals [24], potentially warranting further research for this pro drug formulation in the specific context of ocular cystinosis. Currently aminothiol cysteamine preparation remains the only available treatment for cystinosis [43].

Many different drug delivery systems have been studied to prolong the contact time of cysteamine with the eye and thus reduce the frequency of administration. These drug delivery systems include gel eye drops, hydrogels, contact lenses and nano wafers.

One such delivery system includes a sustained release microsphere/thermoresponsive gel eyedrop [49]. It has a high ocular biodistribution in the cornea and aqueous humour, with a low systemic distribution of cysteamine. This sustained release formulation maintains drug release over 12 hours. Furthermore, this product was demonstrated to be tolerable in rabbit studies**,** with any observed side effects being transient and diminishing within 10-30 min [50].

The porosity and high-water content of hydrogels make them suitable for encapsulation of water-soluble drugs such as cysteamine. Hydrogels can be produced from natural or synthetic materials. Natural polymer-based hydrogels present the obvious advantage

of biocompatibility and minimised toxicity, however synthetic polymers allow for increased drug release times and thus reduced administration frequency [18].

Natural hydrogels have been synthesised from many materials including hydroxypropyl methylcellulose [51], sodium hyaluronate [52] and hydroxyethyl cellulose [52]. Natural hydrogels have inherent biocompatibility, biodegradability and bioactivity and are safe in most of the population. However, natural hydrogels can cause allergic reactions in rare cases [53]. Natural polysaccharide hydrogels allow for the controlled release of cysteamine over a longer time period [54], and increased stability for up to 30 days [55]. Interestingly, Luaces-Rodriguez *et al.* demonstrate that these natural polysaccharide hydrogels could act as corneal absorption promoters [55].

Synthetic hydrogels can be designed to achieve the desired mechanical properties, reducing the frequency of topical cysteamine administration. Buchan *et al.* designed a hydrogel composed of carbomere 934 for the topical administration of cysteamine on the ocular surface. It is transparent and bio adhesive, reducing blinking resistance and increasing contact time on the surface of the eye. Importantly, they demonstrated a first order kinetics release of the active cysteamine drug from the hydrogel, offering potential for hydrogels to be incorporated into clinical care. The addition of cysteamine to the hydrogel did not destroy any of its properties, thus offering a new way to administer cysteamine to the corneal surface and increase contact time of cysteamine with the cornea [56]. McKenzie *et al.* agree on the suitability of carbomere 934 for the ophthalmic delivery of cysteamine [52].

The increased interest in precision and personalised medicine over recent years has prompted the innovation of smart hydrogels. Smart hydrogels respond to external stimuli such as pH, temperature, light, and the concentration of biomolecules. Such stimuli can be used to promote hydrogel drug release [57]. Iohara *et al.* demonstrate the use of thermoresponsive hydrogels for use as an ocular drug delivery system, highlighting a path for smart hydrogels in the future of ocular cystinosis treatment [58]. Furthermore, research regarding genetic therapy is advancing in many diseases. Graceffa *et al.* have synthesised novel fibrin hydrogels, functioning as a gene delivery system for the treatment of cystinosis. The hydrogel releases a non-viral plasmid, encoding for CTNS, targeting the core pathophysiology of cystinosis [59].

Micro vesicles have been proposed to aid the delivery of lysosomal transport protein cystinosin to the eye. *Ex vivo* rabbit studies have yielded supportive results for the use of micro vesicles as a delivery system for cystinosin, demonstrating them to have therapeutic value in treating cystinotic corneal keratopathy [60]. Furthermore, micro vesicles have the advantage of twice monthly administration [60].

Nano wafers are small transparent circular discs that can be applied on the ocular surface with a fingertip [61]. Nano wafer's release drugs on the ocular surface in a controlled manner. Cysteamine is stored in nano reservoirs, allowing a tightly controlled drug release system. Once all the drug has been released, the nano wafer dissolves and fades away [62]. Cysteamine loaded nano wafer therapy has proved efficacious in *Ctns* $^{-/-}$ mice, achieving a 90% reduction in cystine crystal volume in comparison to cysteamine eye drop formulations which reached a 55% reduction [62]. The authors attribute this increased cystine crystal clearance to increased drug residence time on the ocular surface [62].

Contact lenses are another potential drug delivery system for use in the treatment of ocular cystinosis. Recent studies have investigated the use of contact lenses as a drug delivery system for many different ocular diseases such as glaucoma [63] and diabetic retinopathy [64]. The advantages of contact lenses as a drug delivery system include increased bioavailability and increased contact time of the drug with the ocular surface [65]. Hydrogel based soft contact lenses are proposed to have the most therapeutic efficacy [66]. When a contact lens is placed over the cornea, a thin fluid layer is formed between the lens and the cornea [65]. The drug enters the fluid layer, increasing bioavailability of the drug to 50% when compared to the administration of topical drops (bioavailability of 1-5%) [18]. Increased bioavailability allows for reduced frequency of administration, promoting compliance. However, the main limitation of contact lenses as a drug delivery system lies in the fact that most drugs have a low affinity to the polymers that are used in contact lenses. Low drug affinity results in insufficient drug loading and too rapid drug delivery [18].

Many attempts have been made to modify contact lenses to improve drug affinity. This includes the incorporation of polymeric nanoparticles [67], diffusion barriers (vitamin E) [68] and molecular imprinting [69]. There has been a big focus on the addition of vitamin E to contact lenses to increase cysteamine retention time. Vitamin E is a biocompatible hydrophobic molecule that exhibits low solubility in water and creates a tortuous pathway prolonging the diffusion time through the contact lenses [18]. Additionally, vitamin E incorporation has the added benefit of blocking UV radiation [70]. Studies by Hsu *et al.* and Dixon *et al.* have demonstrated a positive association between the addition of vitamin E and the duration of cysteamine release [71,72]. Hsu *et al.* suggest that a single vitamin E modified silicone hydrogel contact lens worn for 2 hours could achieve the same therapeutic effect as hourly administration of cysteamine eye dops [71].

Furthermore, vitamin E loaded contact lenses have been developed in combination with carbon black tinted lenses, successfully reducing photophobia [73]. Further optimisation of contact lenses as a cysteamine delivery system are needed, with Vitamin E loaded contact lenses representing an optimistic option to prolong drug release.

There have been promising advancements in liposome and nanoparticle-based therapy options in other ocular diseases, namely glaucoma [74] and age-related macular degeneration [65]. Notably, a drugless ocular cystinosis treatment consisting of gold nanoparticle contact lenses has been developed. The gold nanoparticle contact lenses function by withdrawing cystine from the surrounding area [76]. *In vitro* studies provide hope for a drugless cystinosis treatment with one- or five-hour wear of contact lenses at a time [76].

Another approach by Thoene *et al.* described the infection of *Spodoptera frugiperda* cells (SF9) with baculovirus containing human wild type CTNS spontaneously produced a functional cystinosin protein in micro vesicles. Furthermore, the addition of green fluorescent protein tagged cystinosin containing micro vesicles to *ex vivo* rabbit ocular globes resulted in punctate green fluorescence in the corneal keratocytes. This supports the potential therapeutic use of cystinosin containing micro vesicles, with the added benefit of twice monthly administration [60]. Iglesias *et al.* demonstrate the ability of stem cell derived micro vesicles to reprogram the biology of mutant tissues. They show micro vesicle-based transfer of the

cystinosin protein to human cystinotic cells *in vitro*, and a dose dependant reduction in cystine accumulation [77].

There is also the potential for the use of combined treatment with cysteamine and mTOR inhibitor everolimus [78,79]. Dual treatment targets cystinosis from two different pathways. Isolated cysteamine treatment ameliorates cystine accumulation, with no therapeutic effect on aberrant autophagy or dysregulated apoptosis. Conversely, mTOR inhibitor everolimus targets the pathological pattern of apoptosis and autophagy seen in cystinosis. However, it does not rescue the defect in cystine loading [18]. Thus, the combination of cysteamine and everolimus presents a solution to target cystinosis from different pathological pathways [78].

Conclusion

Cystinosis is a rare lysosomal storage disorder, characterised by increased intra lysosomal cystine. Ocular cystinosis is a subtype of cystinosis in which cystine crystals deposit in the cornea, causing visual impairment and can ultimately lead to blindness. Additionally, ocular cystinosis is one of the predominant complications of nephropathic cystinosis. The main stay of ocular cystinosis treatment is topical cysteamine, a cystine depleting agent. However, the efficacy of cysteamine is limited by the avascular nature of the cornea [80]. Additionally, the need for frequent reapplication poses a challenge to patient compliance. Early and effective treatment is necessary to reduce the risk of blindness and improve quality of life [22]. Many studies on future treatment options for ocular cystinosis are focusing on increasing the contact time of cysteamine with the ocular surface. This is being achieved in many ways, namely using pro drugs, contact lenses, hydrogels and nanoparticles. While there is much exciting research ongoing in this area, more studies are needed to bring these products to clinical use.

References

1. Al-Hemidan A, Shoughy SS, Kozak I, Tabbara KF. Efficacy of topical cysteamine in nephropathic cystinosis. Br J Ophthalmol. 2017 Sep;101(9):1234-7.
2. Alsuhaibani AH, Khan AO, Wagoner MD. Confocal microscopy of the cornea in nephropathic cystinosis. Br J Ophthalmol. 2005 Nov;89(11):1530-1.
3. Anikster Y, Lucero C, Guo J, Huizing M, Shotelersuk V, Bernardini I, et al. Ocular nonnephropathic cystinosis: clinical, biochemical, and molecular correlations. Pediatr Res. 2000 Jan;47(1):17-23.
4. Biswas S, Alzahrani K, Radhakrishnan H. Corneal Densitometry to Assess the Corneal Cystine Deposits in Patients With Cystinosis. Cornea. 2023 Mar 1;42(3):313-9.
5. Biswas S, Gaviria M, Malheiro L, Marques JP, Giordano V, Liang H. Latest Clinical Approaches in the Ocular Management of Cystinosis: A Review of Current Practice and Opinion from the Ophthalmology Cystinosis Forum. Ophthalmol Ther. 2018 Dec;7(2):307-22.
6. Bozdağ S, Gümüş K, Gümüş O, Unlü N. Formulation and in vitro evaluation of cysteamine hydrochloride viscous solutions for the treatment of corneal cystinosis. Eur J Pharm Biopharm. 2008 Sep;70(1):260-9.
7. Bradbury JA, Danjoux JP, Voller J, Spencer M, Brocklebank T. A randomised placebo-controlled trial of topical cysteamine therapy in patients with nephropathic cystinosis. Eye (Lond). 1991;5 (Pt 6):755-60.
8. Buchan B, Kay G, Heneghan A, Matthews KH, Cairns D. Gel formulations for treatment of the ophthalmic complications in cystinosis. Int J Pharm. 2010 Jun 15;392(1-2):192-7 .
9. Castro-Balado A, Mondelo-García C, Varela-Rey I, Moreda-Vizcaíno B, Sierra-Sánchez JF, Rodríguez-Ares MT, et al. Recent Research in Ocular Cystinosis: Drug Delivery Systems, Cysteamine Detection Methods and Future Perspectives. Pharmaceutics. 2020 Dec 3;12(12):1177 .
10. Chkioua L, Amri Y, Saheli C, Mili W, Mabrouk S, Chabchoub I, Boudabous H, Azzouz WB, Turkia HB, Ferchichi S, Tebib N, Massoud T, Ghorbel M, Laradi S. Molecular characterization of CTNS mutations in Tunisian patients with ocular cystinosis. Diagn Pathol. 2022 May 6;17(1):44.
11. Cogan DG, Kuwabara T, Kinoshita J, Sheehan L, Merola L. Cystinosis in an adult. J Am Med Assoc. 1957 May 25;164(4):394-6.
12. Csorba A, Maka E, Maneschg OA, Szabó A, Szentmáry N, Csidey M, et al. Examination of corneal deposits in nephropathic cystinosis using in vivo confocal microscopy and anterior segment optical coherence tomography: an age-dependent cross sectional study. BMC Ophthalmol. 2020 Feb 26;20(1):73.
13. David D, Princiero Berlingerio S, Elmonem MA, Oliveira Arcolino F, Soliman N, van den Heuvel B, et al. Molecular Basis of Cystinosis: Geographic Distribution, Functional Consequences of Mutations in the CTNS Gene, and Potential for Repair. Nephron. 2019;141(2):133-46.
14. Dixon P, Chauhan A. Carbon Black Tinted Contact Lenses for Reduction of Photophobia in Cystinosis Patients. Curr Eye Res. 2019 May;44(5):497-504.
15. Dixon P, Christopher K, Chauhan A. Potential role of stromal collagen in cystine crystallization in cystinosis patients. Int J Pharm. 2018 Nov 15;551(1-2):232-40.
16. Dixon P, Fentzke RC, Bhattacharya A, Konar A, Hazra S, Chauhan A. In vitro drug release and in vivo safety of vitamin E and cysteamine loaded contact lenses. Int J Pharm. 2018 Jun 15;544(2):380-91.
17. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. Orphanet J Rare Dis. 2016 Apr 22;11:47.
18. Emma F, Nesterova G, Langman C, Labbé A, Cherqui S, Goodyer P, et al. Nephropathic cystinosis: an international consensus document. Nephrol Dial Transplant. 2014 Sep;29 Suppl 4(Suppl 4):iv87-94.
19. FDA. 2012. Summary Reveiw for Regulatory Action - Cystaran [Online]. Available: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/200740Orig1s000SumR.pdf [Accessed].
20. FDA. 2020. FDA approval of Cystadrops 2020 [Online]. Available: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process [Accessed].
21. Fernández-Ferreiro A, Luaces-Rodríguez A, Díaz-Tomé V, Gil-Martínez M, Rodríguez Ares MT, Touriño Peralba R, et al Lamas MJ. Hidrogel oftálmico de cisteamina para el tratamiento de la cistinosis ocular [Cysteamine ophthalmic hydrogel for the treatment of ocular cystinosis]. Farm Hosp. 2017 Nov 1;41(6):678-87.
22. Forestier L, Jean G, Attard M, Cherqui S, Lewis C, van't Hoff W, et al. Molecular characterization of CTNS deletions in nephropathic cystinosis: development of a PCR-based detection assay. Am J Hum Genet. 1999 Aug;65(2):353-9.
23. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI.

Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. Mol Genet Metab. 2000 Sep-Oct;71(1-2):100-20.

24. Gahl WA, Thoene JG, Schneider JA. Cystinosis: a disorder of lysosomal membrane transport. The metabolic and molecular bases of inherited disease. 2001;3:5085-108.
25. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med. 2002 Jul 11;347(2):111-21.
26. Gahl WA, Balog JZ, Kleta R. Nephropathic cystinosis in adults: natural history and effects of oral cysteamine therapy. Ann Intern Med. 2007 Aug 21;147(4):242-50.
27. Graceffa V. Development of a fibrin-mediated gene delivery system for the treatment of cystinosis via design of experiment. Sci Rep. 2022 Mar 8;12(1):3752.
28. Hathout RM. Particulate Systems in the Enhancement of the Antiglaucomatous Drug Pharmacodynamics: A Meta-Analysis Study. ACS Omega. 2019 Dec 16;4(26):21909-13.
29. Ho TC, Chang CC, Chan HP, Chung TW, Shu CW, Chuang KP, et al. Hydrogels: Properties and Applications in Biomedicine. Molecules. 2022 May 2;27(9):2902.
30. Hollywood JA, Przepiorski A, D'Souza RF, Sreebhavan S, Wolvetang EJ, Harrison PT, et al. Use of Human Induced Pluripotent Stem Cells and Kidney Organoids To Develop a Cysteamine/mTOR Inhibition Combination Therapy for Cystinosis. J Am Soc Nephrol. 2020 May;31(5):962-82.
31. Hsu KH, Carbia BE, Plummer C, Chauhan A. Dual drug delivery from vitamin E loaded contact lenses for glaucoma therapy. Eur J Pharm Biopharm. 2015 Aug;94:312-21.
32. Hsu KH, Chauhan A. Photoprotection and Extended Drug Delivery by UV Blocking Contact Lenses. Optom Vis Sci. 2016 Apr;93(4):395-403.
33. Hsu KH, Fentzke RC, Chauhan A. Feasibility of corneal drug delivery of cysteamine using vitamin E modified silicone hydrogel contact lenses. Eur J Pharm Biopharm. 2013 Nov;85(3 Pt A):531-40.
34. Iglesias DM, El-Kares R, Taranta A, Bellomo F, Emma F, Besouw M, et al. Stem cell microvesicles transfer cystinosin to human cystinotic cells and reduce cystine accumulation in vitro. PLoS One. 2012;7(8):e42840.
35. Iohara D, Okubo M, Anraku M, Uramatsu S, Shimamoto T, Uekama K, et al. Hydrophobically Modified Polymer/α-Cyclodextrin Thermoresponsive Hydrogels for Use in Ocular Drug Delivery. Mol Pharm. 2017 Aug 7;14(8):2740-8.
36. Iwata F, Kuehl EM, Reed GF, McCain LM, Gahl WA, Kaiser-Kupfer MI. A randomized clinical trial of topical cysteamine disulfide (cystamine) versus free thiol (cysteamine) in the treatment of corneal cystine crystals in cystinosis. Mol Genet Metab. 1998 Aug;64(4):237-42.
37. Jimenez J, Resnick JL, Chaudhry AB, Gertsman I, Nischal KK, DiLeo MV. Ocular biodistribution of cysteamine delivered by a sustained release microsphere/thermoresponsive gel eyedrop. Int J Pharm. 2022 Aug 25;624:121992.
38. Jimenez J, Washington MA, Resnick JL, Nischal KK, Fedorchak MV. A sustained release cysteamine microsphere/thermoresponsive gel eyedrop for corneal cystinosis improves drug stability. Drug Deliv Transl Res. 2021 Oct;11(5):2224-38.
39. Kaiser-Kupfer MI, Caruso RC, Minkler DS, Gahl WA. Long-term ocular manifestations in nephropathic cystinosis. Arch Ophthalmol. 1986 May;104(5):706-11.
40. Kalatzis V, Antignac C. Cystinosis: from gene to disease. Nephrol Dial Transplant. 2002 Nov;17(11):1883-6.
41. Kalatzis V, Cherqui S, Antignac C, Gasnier B. Cystinosin, the protein defective in cystinosis, is a H(+)-driven lysosomal cystine transporter. EMBO J. 2001 Nov 1;20(21):5940-9.
42. Kaur S, Sarma P, Kaur H, Prajapat M, Shekhar N, Bhattacharyya J, et al. Efficacy and Safety of Topical Cysteamine in Corneal Cystinosis: A Systematic Review and Meta-Analysis. Am J Ophthalmol. 2021 Mar;223:275-85.
43. Keidel L, Elhardt C, Hohenfellner K, Priglinger S, Schworm B, Wertheimer C, et al. Establishing an objective biomarker for corneal cystinosis using a threshold-based Spectral domain optical coherence tomography imaging algorithm. Acta Ophthalmol. 2021 Mar;99(2):e189-95.
44. Keidel L, Hohenfellner K, Schworm B, Priglinger S, Luft N, Priglinger C. Spectral domain optical coherence tomography-based retinochoroidal cystine crystal score: a window into infantile nephropathic cystinosis. Br J Ophthalmol. 2023 Feb;107(2):234-41.
45. Keidel LF, Schworm B, Hohenfellner K, Kruse F, Priglinger S, Luft N, et al. Posterior Segment Involvement in Infantile Nephropathic Cystinosis - A Review. Klin Monbl Augenheilkd. 2023 Mar;240(3):266-75.
46. Kowalczyk M, Toro MD, Rejdak R, Załuska W, Gagliano C, Sikora P. Ophthalmic Evaluation of Diagnosed Cases of Eye Cystinosis: A Tertiary Care Center's Experience. Diagnostics (Basel). 2020 Nov 7;10(11):911.
47. Levtchenko E, van den Heuvel L, Emma F, Antignac C. Clinical utility gene card for: cystinosis. Eur J Hum Genet. 2014 May;22(5): 713.
48. Liang H, Labbé A, Baudouin C, Plisson C, Giordano V. Long-term follow-up of cystinosis patients treated with 0.55% cysteamine hydrochloride. Br J Ophthalmol. 2021 May;105(5):608-13.
49. Liu Z, Kompella UB, Chauhan A. Gold nanoparticle synthesis in contact lenses for drug-less ocular cystinosis treatment. Eur J Pharm Biopharm. 2021 Aug;165:271-8.
50. Luaces-Rodríguez A, Díaz-Tomé V, González-Barcia M, Silva-Rodríguez J, Herranz M, Gil-Martínez M, et al. Cysteamine polysaccharide hydrogels: Study of extended ocular delivery and biopermanence time by PET imaging. Int J Pharm. 2017 Aug 7;528(1-2):714-22.
51. Luciani A, Devuyst O. The CTNS-MTORC1 axis couples lysosomal cystine to epithelial cell fate decisions and is a targetable pathway in cystinosis. Autophagy. 2024 Jan;20(1):202-4.
52. Marcano DC, Shin CS, Lee B, Isenhart LC, Liu X, Li F, et al. Synergistic Cysteamine Delivery Nanowafer as an Efficacious Treatment Modality for Corneal Cystinosis. Mol Pharm. 2016 Oct 3;13(10):3468-77.
53. Mason S, Pepe G, Dall'Amico R, Tartaglia S, Casciani S, Greco M, et al. Mutational spectrum of the CTNS gene in Italy. Eur J Hum Genet. 2003 Jul;11(7):503-8.
54. Maulvi FA, Lakdawala DH, Shaikh AA, Desai AR, Choksi HH, Vaidya RJ, et al. In vitro and in vivo evaluation of novel implantation technology in hydrogel contact lenses for controlled drug delivery. J Control Release. 2016 Mar 28;226:47-56.
55. McCaughan B, Kay G, Knott RM, Cairns D. A potential new prodrug for the treatment of cystinosis: design, synthesis and in-vitro

evaluation. Bioorg Med Chem Lett. 2008 Mar 1;18(5):1716-9.

56. McKenzie B, Kay G, Matthews KH, Knott R, Cairns D. Preformulation of cysteamine gels for treatment of the ophthalmic complications in cystinosis. Int J Pharm. 2016 Dec 30;515(1-2):575-82.

57. Municoy S, Álvarez Echazú MI, Antezana PE, Galdopórpora JM, Olivetti C, Mebert AM, et al. Stimuli-Responsive Materials for Tissue Engineering and Drug Delivery. Int J Mol Sci. 2020 Jul 2;21(13):4724.

58. Omran Z, Moloney KA, Benylles A, Kay G, Knott RM, Cairns D. Synthesis and in vitro evaluation of novel pro-drugs for the treatment of nephropathic cystinosis. Bioorg Med Chem. 2011 Jun 1;19(11):3492-6.

59. Patel S, McLaren J, Hodge D, Bourne W. Normal human keratocyte density and corneal thickness measurement by using confocal microscopy in vivo. Invest Ophthalmol Vis Sci. 2001 Feb;42(2):333-9.

60. Pereira-da-Mota AF, Vivero-Lopez M, Serramito M, Diaz-Gomez L, Serro AP, Carracedo G, et al. Contact lenses for pravastatin delivery to eye segments: Design and in vitro-in vivo correlations. J Control Release. 2022 Aug;348:431-43.

61. Prakash M, Dhesingh RS. Nanoparticle Modified Drug Loaded Biodegradable Polymeric Contact Lenses for Sustainable Ocular Drug Delivery. Curr Drug Deliv. 2017;14(4):555-65.

62. Ramazani Y, Levtchenko EN, Van Den Heuvel L, Van Schepdael A, Paul P, Ivanova EA, et al. Evaluation of carbohydrate-cysteamine thiazolidines as pro-drugs for the treatment of cystinosis. Carbohydr Res. 2017 Feb 1;439:9-15.

63. Reda A, Van Schepdael A, Adams E, Paul P, Devolder D, Elmonem MA, et al. Effect of Storage Conditions on Stability of Ophthalmological Compounded Cysteamine Eye Drops. JIMD Rep. 2018;42:47-51.

64. Schneider JA, Katz B, Melles RB. Update on nephropathic cystinosis. Pediatr Nephrol. 1990 Nov;4(6):645-53.

65. Servais A, Morinière V, Grünfeld JP, Noël LH, Goujon JM, Chadefaux-Vekemans B, et al. Late-onset nephropathic cystinosis: clinical presentation, outcome, and genotyping. Clin J Am Soc Nephrol. 2008 Jan;3(1):27-35.

66. Shah R, Amador C, Tormanen K, Ghiam S, Saghizadeh M, Arumugaswami V, et al. Systemic diseases and the cornea. Exp Eye Res. 2021 Mar;204:108455.

67. Shotelersuk V, Larson D, Anikster Y, McDowell G, Lemons R, Bernardini I, et al. CTNS mutations in an American-based population of cystinosis patients. Am J Hum Genet. 1998 Nov;63(5):1352-62.

68. Soliman NA, Elmonem MA, van den Heuvel L, Abdel Hamid RH, Gamal M, Bongaers I, et al. Mutational Spectrum of the CTNS Gene in Egyptian Patients with Nephropathic Cystinosis. JIMD Rep. 2014;14:87-97.

69. Sridhar MS. Anatomy of cornea and ocular surface. Indian J Ophthalmol. 2018 Feb;66(2):190-4.

70. Thoene JG, DelMonte MA, Mullet J. Microvesicle delivery of a lysosomal transport protein to ex vivo rabbit cornea. Mol Genet Metab Rep. 2020 Apr 7;23:100587.

71. Town M, Jean G, Cherqui S, Attard M, Forestier L, Whitmore SA, et al. A novel gene encoding an integral membrane protein is mutated in nephropathic cystinosis. Nat Genet. 1998 Apr;18(4):319-24.

72. Tsilou E, Zhou M, Gahl W, Sieving PC, Chan CC. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: report of a case and review of the literature. Surv Ophthalmol. 2007 Jan-Feb;52(1):97-105.

73. Tsilou ET, Rubin BI, Reed G, Caruso RC, Iwata F, Balog J, et al. Nephropathic cystinosis: posterior segment manifestations and effects of cysteamine therapy. Ophthalmology. 2006 Jun;113(6):1002-9.

74. Tsilou ET, Rubin BI, Reed GF, Iwata F, Gahl W, Kaiser-Kupfer MI. Age-related prevalence of anterior segment complications in patients with infantile nephropathic cystinosis. Cornea. 2002 Mar;21(2):173-6.

75. White CJ, Byrne ME. Molecularly imprinted therapeutic contact lenses. Expert Opin Drug Deliv. 2010 Jun;7(6):765-80.

76. Wilmer MJ, Schoeber JP, van den Heuvel LP, Levtchenko EN. Cystinosis: practical tools for diagnosis and treatment. Pediatr Nephrol. 2011 Feb;26(2):205-15.

77. Xinming L, Yingde C, Lloyd AW, Mikhalovsky SV, Sandeman SR, Howel CA, et al. Polymeric hydrogels for novel contact lens-based ophthalmic drug delivery systems: a review. Cont Lens Anterior Eye. 2008 Apr;31(2):57-64.

78. Yang B, Li G, Liu J, Li X, Zhang S, Sun F, et al. Nanotechnology for Age-Related Macular Degeneration. Pharmaceutics. 2021 Nov 29;13(12):2035.

79. Yang H, Zhao M, Xing D, Zhang J, Fang T, Zhang F, et al, Wang D. Contact lens as an emerging platform for ophthalmic drug delivery: A systematic review. Asian J Pharm Sci. 2023 Sep;18(5):100847.

80. Yuan X, Marcano DC, Shin CS, Hua X, Isenhart LC, Pflugfelder SC, et al. Ocular drug delivery nanowafer with enhanced therapeutic efficacy. ACS Nano. 2015 Feb 24;9(2):1749-58.