

## The Management of Cataract: Where We Are?

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### Summary

**Background:** The cataract as a leading cause of bilateral blindness worldwide represents not only a medical, but also a social problem taking into account the aging population and the growing cases of age-related co morbidities.

From the ancient period the only approach to cure the cataract was surgery. An evolution of surgical technique reaches the peak based on advanced technology with a “smart” intraocular lens, which highlights an economical burden and raises a question on accessibility and affordability of surgical care. Aforementioned indicates a need for search an alternative approach for management of cataract.

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that medical care of cataract is feasible.

**Keywords:** *Cataract; Cataractogenic Factors; Oxydative Stress; Crystalline Proteins Aggregates; Cholesterol Derivates; Medical Care*

### Introduction

The cataract as a leading cause of bilateral blindness worldwide, affecting tens of millions of people [1] represents not only a medical, but also a social problem taking into account the aging population and the growing cases of age-related comorbidities [2].

According to the latest assessment in 2010, cataract is responsible for 51% of world blindness [3]. Approximately 24.5 million in America have cataracts [4]. From the ancient period the only approach to cure the cataract was surgery. An evolution of surgical technique reaches the peak based on advanced technology with a “smart” intraocular lens, which highlights an economical burden [5] and raises a question on accessibility and affordability of surgical care. Current average cost for cataract surgery is about 3,432 USD per eye and 4,591 USD in case of implantation of presbyopia-correcting intraocular lens (IOL) [5].

Previous research [6]. Have shown that only later manifestation or retardation of cataract will decrease the need for surgery by 45% or more. Aforementioned indicates a need for search an alternative approach for management of cataract. The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that medical care of cataract is feasible.

### Cataract

Cataract is defined as an opacity in the normally transparent focusing lens of the eye that, as it becomes denser, interferes with clear site. The word “Cataract” comes from the Latin word “Cataracta”, which means waterfall, since opaque lens causes the white appearance of rapidly running water. The earliest documented case of cataract was reported about 2457-2467 B.C.E. Vision in cataract is often compared with a look through a waterfall or waxed paper [7].

Cataract itself is a multi factorial eye disease, which is classified based on location of the lens opacification related to layers of the lens and also due to causative factors. Most common cause of cataract is an age- by age 65, more than 90% of all people have cataracts. Among less common causes are intraocular diseases, trauma, medications (steroids, etc) and metabolic, endocrine disorders (dominantly diabetes mellitus), or congenital abnormalities [8]. Identified risk factors for cataract include smoking, toxic substances - drugs abuses, alcohol and other poisons, radiation (ultraviolet, electromagnetic waves) and genetic predisposition [8].

The metabolism of the lens, highly ordered crystalline proteins assemblment and solubility of the lens crystallin proteins are entirely directed toward the maintenance of transparency and undergo significant changes in the lens, which contribute to the development of cataract.

Any disruption of intra- or inter-protein interactions will cause protein aggregation and cataract formation [9-14]. Almost uniformly based on cultured lens models [15,16] and experimental animal models [17-20] it is recognized that an oxydative stress plays an important role as a causative factor for the cataract. Aging process, specifically in the lens with a cataract, is accompanied by higher concentration of proteins and acceleration of oxydative reactions with hyper production of free radicals [20], which have a negative impact also on genetics. It is supposed that along the aging free oxygen scavengers and glutathione are not able to reach the lens nucleus to prevent oxydative stress [21].

The concentration of cholesterol in the lens, specifically in the lens membrane, is extraordinary high [22], the highest among other existing membranes [23], and it is required for lens epithelial cells normal functioning [24], therefore decreased amount of cholesterol is harmful for the lens [25]. Detailed pathophysiology in cataract is beyond the scope of this review and is comprehensively presented by Abdelkader, *et al.* [26].

### Surgical care

Up to present the only available treatment of cataract is surgery. The first documented cataract surgery named couching from 800 B.C.E. was done by inserting a sharp instrument (a needle or lancet) into the lens and dislodging it away from the pupil. Couching was eventually replaced by cataract extraction surgery from 2<sup>nd</sup> century, in which the lens was removed by suction device. In Europe the first extra capsular cataract extraction, in which was removed only the lens nucleus, its surrounding cortex, and a portion of the anterior capsule, leaving the posterior capsule, was performed by French ophthalmologist Jacques Daviel in 1747 and later by Albrech von Graefe using his "modified linear extraction" as a new technique. Intracapsular cataract extraction with removing the entire lens and its surrounding capsule by breaking the zonules mainly using cryoprobe was introduced, but lately it was replaced by current extracapsular cataract extraction.

A great step forward to visual rehabilitation after cataract extraction was the invention of artificial intraocular lens made from polymethylmethacrylate (PMMA), authored by the English ophthalmologist Harold Ridley in 1949 [27]. Phacoemulsification as the current gold standart of cataract surgery, in which use a high-frequency ultrasound device is intended to fragment the hard nucleus of the lens into smaller particles following the aspitation, was invented by American ophthalmologist Charles Kelman in 1967 [27]. The advantages of phaco emulsification with modern IOLs, including presbyopia-correcting IOLs are well-known.

The latest cutting-edge advancement in surgical care is a Femtosecond laser -assisted cataract surgery (*FLACS*), which opens a new era in cataract surgery [28], representing an exciting new option to potentially improve patient outcomes and safety. FLACS was approved by Food and Drug Administration (FDA) for cataract surgery in 2010. It's main advantage comparing to phaco emulsification is the use of ultrafast pulses in the range of 10–15 requiring less energy for tissue destruction, and therefore increasing its safety [29].

According to the results of the ESCRS-EUREQUO femto second laser-assisted cataract surgery case-control study, included data from 2,814 FLACS cases , presented by Peter Barry MD at the XXXIII Congress of the European Society of Cataract and Refractive Surgeons (ESCRS) in Barcelona, Spain, 2015 FLACS statistically significant decreases the incidence of postoperative astigmatism of equal or greater than 1.5D [30]. FLACS showed excellent results in cataract surgery, but it represents financial challenge [31-33]. Based on

survey involved 1047 ophthalmologists, for 72% of respondents the financial issues were their most important concern about adopting this technology [32].

### Medical Care

Several papers on the various medications and their supposed mode of action are available [34-37]. It would seem that there is little strong evidence to support claims of efficacy. Few experimental studies have focused on the aldose reductase inhibitors or sorbitol-lowering drugs as the agents preventing glucose transformation into sorbitol [38-40] and revealed positive results in retardation of diabetic cataract. Sorbitol-lowering drugs were advocated for continued study by clinical trials, but their results borne out the effectiveness of drugs in prevention of cataract [41,42]. Another class of drugs tested for medical treatment of cataract were NSAIDS starting from aspirin [41,42]. The earlier results from case-control studies indicated that these drugs, or at least aspirin, protect against cataract, but currently findings are questionable, since the effect of aspirin is dose-dependending and a bioavailability issue also comes into scene in systemic route of use [26]. Required therapeutic dosage equal to 1500 mg is not safe due to serious general side effects, which makes an aspirin not a good candidate as a anticataract drug.

Over the years it was demonstrated the antioxydant activity of vitamin C and vitamin E by preventing lipid peroxidation with subsequent generation of free radicals, but currently available findings from meta-analysis evaluating clinical trials [43] have found the lack of effectiveness of vitamin C, vitamin B and beta-carotene in prevention or retardation of age-related cataract. A critical analysis revealed nonevidence-based benefits and researchers recommended to abandon further trials.

Another agent proposed for medical treatment of cataract is curcumin, but it still needs more evaluation, especially taken into account low bioavailability [44]. In spite of various claims made in various studies about prevention and medical treatment of cataract, there is little scientifically valid evidence of its effectiveness.

### Sterol-based drops

Recently the use of sterol-based drops was investigated experimentally by two independent groups of researchers nearly simultaneously [14,45]. The rationale for using sterol-based eye drops is that the chemical substance binds  $\alpha$ -crystallins, thereby improving lens transparency and potentially reversing cataract progression.

Makley, *et al.* [4] have discovered cholesterol derivates, one of which successfully during *in vitro* testing binds both subtypes of  $\alpha$ -crystallins (cryAA and cryAB) causing disaggregation. Latter in mouse model of hereditary cataract and in aged mice lens this derivate has shown acceleration of lens transparency after two weeks of topical use as eye-drops. The same effect was evidenced in human lenses *ex vivo*. The results of this study were presented at the Annual Meeting of American Academy of Ophthalmology in November 2015.

Results of the study conducted by Zhao, *et al.* [14] suggest a similar finding on increased lens transparency in case of use of another cholesterol derivate named lanosterol *in vitro* in dissected rabbit opaque lenses and also *in vivo* in dogs. The investigators have found that lanosterol initially injected and followed by eye drops for six weeks is able to restore the transparence of the cataractous lenses in dogs and strongly suggest that lanosterol is a key molecule in the prevention of lens protein aggregation. These encouraging preliminary results suggest that a large-scale randomized study should be conducted.

In conclusion, currently available evidence indicates that sterol-based drops offer a viable approach for medical care of cataract. Hopefully, we are at the beginning of the new era of cataract management.

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