The effect of aging on the ciliary muscle and its potential relationship with presbyopia: a literature Review (#93504)

First submission

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- ✓ Article content is within the Aims and Scope of the journal.
- ✓ Rigorous investigation performed to a high technical & ethical standard.
- ✗ Methods described with sufficient detail & information to replicate.
- ✓ Is the Survey Methodology consistent with a comprehensive, unbiased coverage of the subject? If not, what is missing?
- ✗ Are sources adequately cited? Quoted or paraphrased as appropriate?
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- ✓ Impact and novelty not assessed. Meaningful replication encouraged where rationale & benefit to literature is clearly stated.
- ✓ Conclusions are well stated, linked to original research question & limited to
- ✓ Is there a well developed and supported argument that meets the goals set out in the Introduction?
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supporting results.

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3

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The effect of aging on the ciliary muscle and its potential relationship with presbyopia: a literature Review

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The ciliary muscle is known to play a part in presbyopia, but the mechanism has not received a comprehensive review, which this study aims to achieve. We have looked at relevant articles published from 1975 through 2022, which examined in humans and rhesus monkeys different properties of the muscle and related tissues, such as geometry, elasticity, rigidity, and composition, using various imaging technologies, computer models, surgeries, etc. We have found a significant age-related movement, forward and inward, of the ciliary muscle apex that could potentially be caused mainly by the accumulation of connective tissue and pull from the thickening lens. Other factors could also contribute to the movement, especially the "inward bowing" of the sclera. Another important finding is that though the muscle becomes more restricted with age by other parts connected to it, it does not lose contractility, and the concentration of muscarinic receptors and binding affinity of the receptors remain constant. Overall, more studies on human ciliary muscle are needed, for it ages differently from that of ciliary monkeys, and the studies should take on other perspectives, learning more about changes in the physical properties of the tissue, its relationship with other connected tissues, etc.

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Abstract

Background. The ciliary muscle is known to play a part in presbyopia, but the mechanism has not received a comprehensive review, which this study aims to achieve. We have looked at relevant articles published from 1975 through 2022, which examined in humans and rhesus monkeys different properties of the muscle and related tissues, such as geometry, elasticity, rigidity, and composition, using various imaging technologies, computer models, surgeries, etc. We have found a significant age-related movement, forward and inward, of the ciliary muscle apex that could potentially be caused mainly by the accumulation of connective tissue and pull from the thickening lens. Other factors could also contribute to the movement, especially the "inward bowing" of the sclera. Another important finding is that though the muscle becomes more restricted with age by other parts connected to it, it does not lose contractility, and the concentration of muscarinic receptors and binding affinity of the receptors remain constant. Overall, more studies on human ciliary muscle are needed, for it ages differently from that of ciliary monkeys, and the studies should take on other perspectives, learning more about changes in the physical properties of the tissue, its relationship with other connected tissues, etc.

Methodology. This literature review employed a systematic approach to identify and analyze relevant studies in the field of presbyopia and ciliary muscle. The search strategy involved a comprehensive review of academic databases, including PubMed, Scopus, and Web of Science.

Results. Many studies have identified age-related thickening in the muscle and its potential causes—increasing connective tissues and a pull from the thickening lens. More importantly, these studies lead to a geometric theory in which the shape of the ciliary muscle and its relative position to other components have decisive control over the tension of zonular fibers.

Conclusions. Most of the accommodative response of the muscle are lost at an advanced age and the loss of mobility are fingered as the main culprit, which could be caused by a thickening lens

and stiffening choroid.

Introduction

Presbyopia is a wide-spread condition that plagues nearly every old person on the planet. It is a situation where patients lose their ability to accommodate their eyes to get a clear view of near objects because of their old age. In modern society, such a loss of near vision means a great inconvenience and reduction in the quality of life. To tackle this pestilential problem, different technologies have been developed, which mainly focus on negating age-related changes in the lens[1]. The most notable of these solutions is IOL technology, an area that has attracted considerable funding and attention from multidisciplinary talents. As a result, different types of IOLs, such as monofocal and multifocal IOLs, have been developed[2-4]. Though they are able to improve the condition and even eliminate the use of glasses, they have their limitations and could cause new problems[5-7]. Some starry-eyed believers of IOL expect that the problem will be solved by future improvements of the technology, but there is a chance that better solutions lie elsewhere.

Since the lens is only one of the components that may disrupt the proper operation of accommodation, the development of treatment methods targeting other components should thus deserve more attention. They have the potential to be incorporated into a customized regimen that best fits the patient, if the causes of their presbyopia can be fully understood. However, in order to develop effective methods, it is necessary to first examine how age affects the constituents of the eye.

One constituent that cries out for attention is the ciliary muscle, which governs the tension of zonular fibers through contraction and so plays a vital role in accommodation, as suggested by the Helmholtz's theory about accommodation, a widely accepted theory supported by many experiments[8-10]. And theories have been proposed to explain the muscle's role in presbyopia as age gradually changes it and its related structures. One theory that is taking on momentum is the geometric theory that places more weight on the shape-changing ability of the muscle than its contracting force. This theory will be discussed in subsequent chapters.

Nevertheless, to visualize the movement of the muscle could be tricky, because the iris acts as a screen that completely renders the muscle invisible to ordinary observation methods. Though some studies evaded this problem by using iridectomized animals or albino patients[11,12], these are not a widely applicable method to visualize the ciliary muscle in human subjects. As a result, many imaging technologies have been employed to carry out the task. Two most popular techniques are Ultrasound Biomicroscopy (UBM)[13,14] and Anterior Segment Optical Coherence Tomography (ASOCT)[15]; the former is usually preferred over the latter since it is unrestricted by the iris[16]. In addition, Magnetic Resonance Imaging (MRI), though not so popular, has also been used by researchers[17,18]. The studies covered in this review all employed one of these three methods. With the help of them, the veil over the effect of aging on the ciliary muscle can be lifted.

In the following chapters, before going into detail about age-related changes of the muscle, this paper reviews the basic structure of the ciliary body and muscle first. Then it approaches the problem from two mostly studied aspects: geometric and morphological changes, mobility and contractility changes. In the end it provides a summary and discusses about further directions.

Survey Methodology

This literature review employed a systematic approach to identify and analyze relevant studies in the field of presbyopia, ciliary body, and ciliary muscle. The search strategy involved a comprehensive review of academic databases, including PubMed, Scopus, and Web of Science. Keywords and phrases such as ciliary muscle and presbyopia were used to retrieve articles published by 2022. The inclusion criteria focused on peer-reviewed articles, ensuring the credibility and academic rigor of the selected literature.

The Ciliary Body and Ciliary Muscle

Ciliary Body Structure

The ciliary body is a circular structure positioned behind the iris, which is normally opaque and colored, hence making it is hardly possible to directly observe the structure without iridectomy. It

stretches from the root of the iris, where the two meet and form a valley called ciliary sulcus, to the ora serrata, where the retina ends[16,19]. The length of the structure is usually measured from the scleral spur, a common reference point for carrying out measurements of the ciliary body, to the ora serrata[20]. Moreover, it is worth mentioning that the ciliary body ring is not of consistent length around the lens. On the temporal side, the ciliary body has a length of 5.6-6.3 mm, while on the nasal side the length is 4.6-5.2 mm.

With a right-angled triangular cross-section, the ciliary body can be divided into two parts: the anterior part named pars plicata and the posterior part named pars plana. In the pars plicata of ordinary people, there are some 70 ridges with abundant capillaries inside[21], and the ridges together form the ciliary processes. Between the ridges are furrows where zonular fibers, which suspend the lens, attach to the processes. The ciliary processes are lined by two layers of epithelial cells, with the non-pigmented layer on the outside and the pigmented one on the inside. Together, they are in charge of the production of aqueous humor, an important fluid that supplies nutrients to and removes wastes from avascular tissues and keeps intraocular components in position by maintaining IOP. In contrast, though the pars plana is covered by zonular fibers and has them inserted into the posterior part of it, no significant functions have yet been discovered related to the pars plana, which is less vascularized and, as indicated by its name, is flat. As a result, the region is regarded as a safety area through which such surgeries as pars plana vitrectomy access the inside of the eyeball.

Ciliary Muscle Structure and Function

With its inner side separated from the double layers of epithelia by laminae of collagen fibers, capillaries, etc., the ciliary muscle comprises most of the ciliary stroma. In addition, its outer side is connected to the inner sclera through a lamina called supraciliaris. The anterior tendons of the muscle attach it to the scleral spur and trabecular meshwork, while in its posterior part, tendons connect it to the Bruch's membrane, a structure that gives elasticity to the choroid.

The ciliary muscle is a smooth muscle. It consists of three types of muscle fibers that differ from each other by the directions they run in[10]. The longitudinal, or meridional, fibers run from the

anterior to the posterior of the eye. They form the outermost layer of the muscle, which is in juxtaposition to the inner surface of the sclera. In the front they attach to the sclera spur and trabecular meshwork, while in the rear they merge with the stroma of the choroid. The radial fibers run obliquely, from medial to lateral and from the chamber angle to the ciliary processes. As a result, they form a reticular pattern that is present throughout the middle of the ciliary muscle. The circular fibers run perpendicular to the longitudinal ones, and as the fibers goes around the globe, they form a circular shape. As the innermost part of the ciliary muscle, circular fibers are the closest to the apex of the ciliary processes.

There are two neural pathways associated with accommodation that innervate the ciliary muscle: the sympathetic innervation, which is responsible for disaccommodation of the muscle, and the parasympathetic innervation, the major innervation which is responsible for triggering accommodative contraction of the muscle. Starting from the diencephalon, the sympathetic fibers proceed down the spinal cord until they pass in the C8-T2 segments into the cervical sympathetic chain and then synapse in the superior cervical ganglion. Following that, axons of postganglionic neurons leave the region to form sympathetic carotid plexus, which pass through the ciliary ganglion and pierce the eye via short ciliary nerves. There are also other sympathetic fibers navigating the long ciliary nerves and the optic canal. The parasympathetic pathway, however, begins as preganglionic fibers issuing from the Edinger-Westphal nucleus. They travel inside the oculomotor nerve, arrive at the ciliary ganglion, and synapse in it. The pathway then continues in the form of axons of postganglionic neurons that leave the ganglion, enter the eyeball, and supply the ciliary muscle through the short ciliary nerves[22].

The ciliary muscle plays a crucial part in accommodation. According to the Helmholtz's theory, when the ciliary muscle is in a relaxed state, zonular fibers that suspend the lens are tensioned and so exert a stretching force on the lens that makes it less rounded. At this stage, the eye is unaccommodated, so it can see objects clearly from afar. On the other hand, when the ciliary muscle contracts, the tension on the zonular fibers is released, so the force that pulls on the lens is no more. As a result, the lens is more rounded. This process is called accommodation where the

eye tries to focus on nearer objects by changing the power of the lens, which is decided by its roundness. During the accommodation of a normal eye, as is widely held, the ciliary muscle exhibits a forward and inward shift in mass, a shift that can mostly be attributed to the movement of the longitudinal and circular fibers.

Apart from accommodation, the ciliary muscle can also have an impact on IOP, because it affects the outflow of aqueous humor. There are two routes that the fluid takes to leave the eye. One is the conventional pathway: the fluid enters from the trabecular meshwork at the limbus into the Schlemm's canal, where it is drained into veins. Most aqueous humor drains into this pathway. The other way that aqueous humor leaves the eye is by filtering through the ciliary muscle, which is called the unconventional pathway. Since connective tissues between muscle bundles are loose, the fluid can seep through the tissues into the supraciliary and suprachoroidal spaces before passing beyond the sclera[23,24].

The ciliary muscle is able to influence both the pathways. As the muscle is connected to the trabecular meshwork anteriorly, when it contracts, it changes the geometry of the meshwork, making it less tightly packed, so its resistance to outflow is reduced. Conversely, when the muscle relaxes, the elasticity of the meshwork returns it to its original form, thus more restriction to the outflow[23,24]. As to the second pathway, which is also called the uveoscleral pathway, the contraction of the ciliary muscle reduces the permeability of the tissue and so diminishes the outflow[25]. Given this, it is possible that age-related changes in the ciliary muscle are not only responsible for presbyopia, but also for other diseases—glaucoma, for example. If such a link is real, studies about other diseases associated with the ciliary muscle could in some ways increase our understanding about the muscle and its relationship with presbyopia.

Age-related Geometric and Morphological Changes of the Ciliary Muscle

The eye is a sophisticated and delicate optic system where a tiny alteration in the shape or relative position of a structure can make a huge difference in the image we perceive. When the eye ages, changes happen in its constituents, and so such alterations occur. The lens, for example, thickens

as we age, and so its shape and relative position with respect to the zonule and ciliary muscle becomes different[26]. Theories have been proposed to explain the relationship between such changes and presbyopia[27-29]. The same attention should be paid to examining age-related geometric and morphological changes of the ciliary muscle, for their influence can be huge. Tamm et al. even postulated that the major factor dictating the force on the lens was the geometry and arrangement of the ciliary muscle[30].

Currently, researchers focus almost entirely on the anterior segment of the ciliary muscle. Many studies have identified an antero-inward movement of it, which is otherwise described as a centripetal movement or a diminishing ciliary muscle ring diameter, in humans with an advanced age[17,18,26,30,31]. Such movement makes the unaccommodated ciliary muscle in older eyes somewhat resemble its accommodated counterpart in younger eyes. Strenk et al.[17] measured the ciliary muscle ring diameter directly, based on images obtained from MRI, in which the muscle can be identified as a hypointense pixel cluster with a triangular shape. They found a clear trend that the ring diameter shortened as age increased. Moreover, to determine the relation between age and the position of the ciliary muscle, Sheppard et al.[31] and Strenk et al.[18] used AS-OCT and MRI respectively to look at the anteroposterior position of the ciliary muscle apex and the width of the muscle. In both studies, old subjects exhibited a forward movement of the ciliary muscle apex and an increase in its thickness. Despite that the imaging techniques could be plagued by factors including artifacts and distortion resulted from subjects' motion, etc., the strong correlation between the antero-inward movement of the ciliary muscle and an old age were confirmed.

Two other studies drew their conclusions from postmortem examinations of donated eyes[26,30]. Admittedly, it is possible that the structures the two studies observed might have undergone changes after donors' death or during the operation. The ischemic condition, for example, might have rendered the ciliary muscle less responsive to pharmacologic agents. Besides, the loss of structural integrity might also have affected the shape of tissues. Anyway, the studies did provide more insight into the cause of the movement by offering a histological view of the ciliary muscle. Both have discovered a significant increase in the connective tissue inside the ciliary muscle area

in elder people. This increase occurs most significantly in the circular and reticular portions while being insignificant in the longitudinal portion. As more connective tissue grows between muscle bundles, the bundles become further apart, increasing the muscle area. This thickening process of the muscle could at least partially explain why the muscle ring becomes smaller with age.

In addition to studies that directly measured the ciliary muscle, other studies resorted to an indirect method by focusing on the circumlental space (CLS), a measurement of the space between ciliary processes and the equatorial edge of the lens[12,32,33]. They all observed decreasing CLS in older subjects. Since the lens equator itself does not grow in diameter with age[17,34], the only way for the space to gradually narrow is by ciliary processes moving nearer the lens. This movement could partially be attributed to a caved-in sclera, which acts as a scaffold for the whole mechanical system and could become mishappen under decades of accommodative contraction of the muscle. Such an "inward bowing" of the sclera at the limbus has been found by Croft et al[35]. Moreover, diminishing CLS could indicate that the ciliary muscle or ciliary processes thicken with age, or both. According to the microscope study by Marshall et al., stromal fibrosis happens both to the stroma in ciliary processes and that between ciliary muscle bundles[36]. The mostly affected parts in the muscle are the oblique and circular portions, in which patchy thickening was found. Nonetheless, this thickening of stoma between ciliary muscle bundles is where humans and rhesus monkeys differ, because in aged eyes of rhesus monkeys, intramuscular connective tissue was only observed to have increased a tiny amount[37]. This suggest that although the eyes of rhesus monkeys are morphologically and physiologically similar to those of humans and both species develop presbyopia at relatively the same stage of life, the mechanism behind presbyopia in rhesus monkeys could well be different.

However, even though connective tissue could be partially responsible for a diminishing ciliary muscle ring diameter, the major cause underlying the phenomenon is very likely to be an aging lens. Strenk et al. found that instead of showing an age-related ciliary muscle movement as phakic subjects did, pseudophakic subjects had their ciliary muscles recovered to a position similar to that of the muscle in a 29-year-old phakic eye[18]. Wasilewski et al. carried out intracapsular lens

extraction (ICLE), a surgery that removes the lens and its capsule and so cuts the zonule, and extracapsular lens extraction (ECLE), a procedure that removes only lens content, on rhesus monkeys[38]. Compared to the control, the monkey receiving ECLE exhibited only a small decrease in their resting ciliary body thickness while those receiving ICLE had much thinner ciliary muscle profiles, especially in the anterior portion, and posteriorly positioned muscle apices. These two studies attest that the lens is pulling on the ciliary muscle via the zonule and a thickened lens causes the muscle to move centripetally. Moreover, as discovered by some research, the attachment of the anterior zonules moves away from the lens equator as the lens ages[34,39]. This may consequently exert an excessive pulling force on the ciliary muscle, forcing it to move. On the whole, the studies have provided evidence that backs a geometric theory: as the aging lens grows in thickness, the insertion ring of zonules edge forward away from the lens equator and so creates a drag on the ciliary body, which in turn causes an antero-inward movement of the ciliary muscle.

The implications of such a movement could be huge: changes in the shape and position of the muscle and consequent altered geometric relationships between the muscle and related components may greatly affect the outcome of accommodation. Yet more proof is needed. Computer models could offer some help, because they are good at reconstructing the whole process of accommodation, which current in vivo and in vitro methods are insufficient to achieve. Furthermore, since the ciliary muscle and processes bulk up as the eye ages, even if the muscle increased by the same amount in thickness during accommodation as its younger version would, it would not produce the same level of change to its geometry. Not to mention there exists an age-related loss in apex thickening as reported by Croft et al[33]. As a result, when this factor combines with the antero-inward movement of the muscle, the zonule may not relax enough due to insufficient change in the configuration of the mechanical system composed of the lens, zonules, and the ciliary muscle. This can produce a pull on the lens that prevents it from rounding up, so presbyopia may arise.

Age-related Changes in Mobility and Contractility

Definition of Mobility and Contractility

As mentioned above, the ciliary muscle, a key component in accommodation, controls the process via contraction, so whether it maintains the same ability to contract at an old age is worthy of particular attention. There already exist some studies on humans and rhesus monkeys that have identified a smaller amount contraction of the muscle in old people. Croft et al. focused on comparing the thickening of ciliary muscle apex during accommodation in old and young people, and they revealed that the accommodative apex thickening reduced significantly with age[33]. Another study carried out by Xie et al. increased accommodative stimuli step by step and recorded alterations in CMTMAX (maximum ciliary muscle thickness) and SSMAX (the span between the scleral spur and the position with maximum ciliary muscle thickness)[40]. CMTMAX thickening, according to the result, leveled off in the middle-aged group at 3D. Meanwhile, the shortening of SSMAX also plateaued at 3D in the same group. In contrast, in the younger group, the two parameters kept increasing as the stimuli stepped up. In another study, Tamm et al. administered atropine and pilocarpine to rhesus monkeys and observed changes in biometrics of ciliary muscles administered with the two agents. Similarly, they found weakened ciliary muscle contraction in older eyes[41].

However, before diving into a search for root causes of this change wrought by senility, it is crucial to distinguish between two different factors that may determine the extent to which the muscle can contract: mobility and contractility. The former measures how much latitude to contract is granted to the muscle by the surrounding structures connecting to it. The latter is an indicator of the ability of the muscle to contract. If mobility is low, the muscle is restricted by other components and thus cannot contract as it normally would. In the same way, if the muscle loses its contractility, it will not produce the same amount of force to sustain the same level of contraction.

Age-related Changes in Mobility

Since the mobility of the muscle is dependent on components outside, a clear understanding of how the muscle connects to its surrounding structures is a prerequisite for further studies of age-related changes in mobility.

In the front, the muscle is anchored to the scleral spur through elastic tendons, and it is indirectly connected to the lens via zonular fibers attaching to the internal limiting membrane that covers the nonpigmented epithelial cells in the valleys between the ciliary processes[42]. Studies concerning the anterior parts which the muscle connects to have been focused on an aging lens as a cause for the loss of ciliary muscle mobility. Having rhesus monkeys as their subjects, Croft et al. in their study collected data about Ciliary Processes (CP) movement under electric stimulation in young and older groups, before and after both groups went through ECLE[43]. According to the results, the young eyes did not show much of a change in the accommodative CP movement after the surgery, while the CP movement in older eyes, which initially had a much lower level of CP movement, increased to close to that of the pre-operative young eyes. These suggest that increased lens content contributes to the restriction of ciliary muscle in an old eye. In addition, other studies about cataract extraction may also shed a light on the problem. Park et al.[44] and Fayed et al.[45] selected patients over 35 years old who suffered from cataract as their subjects and used UBM to visualize accommodative ciliary body movement in them, before and after the surgery of cataract extraction and IOL implantation. Both studies have confirmed that the surgery helped to recover a significant level of centripetal movement of the ciliary muscle. In light of the aforementioned geometric theory, a possible decrease in the lens thickness due to the surgery postulated by Fayed et al. may well be the reason of the recovery. Thus it can be proposed that as the lens ages, its increasing thickness is likely to somewhat reduce the mobility of the ciliary muscle.

On the other hand, the ciliary muscle, in the back, is attached to the Bruch's membrane of the choroid through elastic tendons at ora serrata, in the bays of which the pars plana zonule (PPZ) from the valleys between ciliary processes connects to the ciliary epithelium[42]. Besides this group of zonule, the intermediate vitreous zonule (iVZ) also originates from the valleys and runs posteriorly in the cleft between the PPZ and the anterior hyaloid, splitting at ora serrata into fine fibrils that merge with the anterior hyaloid and connects it to the PPZ[46,47]. Another newly discovered group of zonule termed PVZ INS-LE, however, attaches to the posterior lens equator directly, though it courses in the same direction as the former two groups do towards the posterior

insertion zone at ora serrata[47]. Apart from the choroid and zonule, one other structure that connects to the ciliary body is the vitreous body: the anterior hyaloid fuses with the surface of the ciliary body at ora serrata[42].

A stiffening choroid could be a potential cause for decreasing mobility of the muscle. When the muscle contracts during accommodation, as observed by Croft et al., it pulls the choroid forward, which by virtue of its elasticity is pliable, and as the force is conducted to the back of the eye, it produces a centrifugal movement of the choroid with the optic nerve head as the center of the movement[36,48,49]. As the muscle is connected to the choroid, deformation of the structure under contractile force should make it easier for the muscle to contract. On the other hand, if the elastic structure loses its elasticity, the muscle may be restriction from behind. Ugarte et al.[50] and Graebel et al. [46] used their own devices to apply forces to strips of the choroid and obtained the stress-strain relation of the material. Their results suggest that the elasticity of the choroid decreases significantly with age. Accordingly, the decrease could eventually make it harder for the muscle to contract. However, restriction from the choroid possibly play a major role in lowering ciliary muscle mobility. When young and old eyes of rhesus monkeys were bisected meridionally after being administered with pilocarpine, Tamm et al. noticed that the contractile response of the ciliary muscle to the agent in old eyes was lost, but the loss was only exhibited in the middle parts where the choroid was intact[41]. At the cut where the choroid was no longer attached to the sclera, pilocarpine effect was preserved: they found no difference in inner apical position between three age groups at the margin. Though eyes of rhesus monkeys may differ from those of humans in some respects, this study indicate that a stiffer choroid may be a major cause of decreasing mobility of the muscle. Moreover, besides choroid, the elastic tendons that fasten it to ciliary muscle has been reported to become more rigid with age by growing thicker, potentially further diminishing the mobility of the muscle[51].

Another potential factor that has the possibility to increase restriction on the ciliary muscle is an aging vitreous body. This component, though looks like a simple hump of gel, is essentially made of cisterns—individual chambers that are filled with gel and framed by collagen fibers[52]. When

the component ages, the collagen fibers could start to stick together hence making it stiffer, and in the meanwhile, vitreous liquefaction happens, which further increases its stiffness by increasing liquid amount inside[53]. Consequently, a stiffened vitreous body probably do not respond to pulling force as well as before and even produce more resistance against the force. As reported by Croft et al., in rhesus monkeys, the peripheral vitreous is pulled forward during accommodation by the vitreous zonule at regions where the two structures fuse together, while the anterior hyaloid bows backward behind the lens; however, the movements decrease noticeably with age[35,54]. Overall, these results suggest that a stiffened vitreous body also contributes to age-related reduction in mobility of the ciliary muscle.

Except for exterior causes, the decrease in mobility could come from changes within the muscle as well. Hyalinization, a process that turns stroma into homogeneous translucent materials, has been reported to be a prevalent condition in humans over 50 years old, taking place in areas from the ciliary processes stroma to the stroma separating the reticular portion and the circular portion[30,35]. It is possible that this process contributes to the happening of presbyopia by altering physical properties the stroma, making it more rigid. Former studies have indicated that the circular fibers, which are interspersed with connective tissue, produce most of the antero-inward movement of the muscle[55-57]. An increase in the rigidity of connective tissue could suppress that movement and help bring about presbyopia.

On the whole, the ciliary muscle becomes more and more restricted when itself and other structures grow old in the eye. An ever-thickening lens in the front and an ever-hardening choroid and vitreous body in the back may all be held responsible for that. The muscle itself could also be held to blame. The consequential restriction, when strong enough, will deprive the muscle of the ability to produce enough geometric change that is needed to loosen up zonular fibers and release tension on the lens, so presbyopia occurs.

Age-related Changes in Contractility

As mentioned above, contractility describes the ability of the muscle to contract, which can be dictated by the ratio of muscle cells in the tissue, quantity of muscarinic binding sites, choline

acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity, etc. Nonetheless, before having a detailed look at how aging affects these factors respectively, an understanding of the overall influence of senility on the muscle could provide some inspiration.

To test how much the muscle can still contract at an old age, Poyer et al. devised a gadget to test contracting force exerted by strips of rhesus ciliary muscle administered with carbachol and aceclidine, rather than observe how it contracts in vivo[58]. Despite that ciliary muscle response of living monkeys to the agents were found to decline with age, the researcher did not find such a relationship in isolated CM strips in the testing, or in other words, they discovered that contractility was unrelated to age. Moreover, the aforementioned cataract surgeries that restored a large share, if not all, of ciliary muscle contraction are also evidence that ciliary muscle still maintains much contractility at its late stage of life, though exactly how much is unknown[44,45]. Nonetheless, because of a limited number of studies concerning this matter, it is hard to draw a clear conclusion. Thus more studies are needed, especially those cleverly designed to single out the ciliary muscle without compromising results unwittingly. Still, it is likely that the ciliary muscle still produces a fair amount of contraction at an advanced age.

However, even though some researchers have concluded that the muscle's contractility remains unchanged over time, microscopic examination has told a different story. Atrophy has been observed to happen at an old age. On the basis of their findings about age-related changes in the area of different portions of the muscle and the percentage of connective tissue in each portion, Tamm et al. confirmed atrophy in the longitudinal and reticular portions at an old age[30]. In their research, the area of the longitudinal portion decreased by more than half when the age of subjects advanced from 30 to 80. More significant atrophy might be in the reticular portion where the percentage of connective tissue increased from 20% in subjects of 30 to 40 years old to 50% in those of 50 to 60 years old, while the area of the portion was in decline. Nevertheless, even though Tamm et al. have reported an age-related increase in the area of the circular portion, there is one question left unanswered—whether myocytes atrophy in this portion. This could potentially be answered by the immunoelectron microscope study of Marshall et al., which found a considerable

406 level of atrophy in both the reticular and circular portions[35]. Since the circular portion produces
407 most of the accommodative movement of ciliary muscle, its atrophy possibly contributes to
408 presbyopia by reducing the contraction force needed to release the zonule. In spite of that, one
409 thing to notice is that there were only nine samples included in the study, which may call for the
410 need of more similar studies with a larger sample size.
411 In addition, given that there is an age-related reduction in the response of the muscle to electrical
412 stimulation and muscarinic cholinergic agonists such as pilocarpine, it is reasonable to assume the
413 existence of age-related degenerative changes in intramuscular nerves, the concentration of
414 muscarinic receptors, or binding affinity of the receptors. These changes may be small or have
415 little influence on the contractility of the muscle, according to the study of Poyer et al. that showed
416 no age-related changes in ciliary muscle contraction force[58], but that does not suffice to refute their
417 existence. Lütjen-Drecoll et al., in their light and electron microscopic observation on rhesus
418 monkey ciliary muscle, discovered obvious degeneration in muscle cells and myelinated nerves,
419 and the degeneration was found to parallel the decline in accommodative amplitude, as both
420 processes come to a standstill after 25 years old[59]. In contrast, there was no alterations found in
421 the concentration of muscarinic receptors and binding affinity of the receptors[60]. Despite all that,
422 it is worth noticing that as mentioned above, human ciliary muscle may age in a different way to
423 rhesus monkeys, so these results could fail to be extrapolated to humans, and thus more similar
424 studies on human eyes should be conducted.
425 All in all, the contractility of the ciliary muscle probably remains undiminished in elder people, or
426 diminishes by only an insignificant amount, so its role in the loss of accommodative ciliary muscle
427 contraction is likely to be small.
428
429 **Summary and Future Directions**
430 Although more studies are needed to vindicate some discoveries and theories concerning the aging
431 process of the ciliary muscle and to reveal more unknown sides of this process, several conclusions
432 can be drawn. First, there do exist significant age-related changes in the geometry and morphology

of the ciliary muscle, which cause it to move forward and inward. Such movement can be represented by the thickening and forward movement of the ciliary muscle apex and be explained as the result of an increase in connective tissue and the pulling force from the thickened lens. It is worth noticing that the age-related narrowing CLS should not be interpreted solely as the consequence of the antero-inward movement of the muscle. Other factors could also contribute to this movement, especially the "inward bowing" of the sclera. Further studies are needed to confirm its existence and investigate its potential relationship with accommodation and presbyopia.

However, whether the geometric and morphological changes have substantial influence on accommodation remains unclear. The question may be better answered by computer models, for they have an edge in controlling variables and visualizing the process. Goldberg et al. have provided us with a computer model that reconstruct the accommodation process, rendering it in the form of computer animation[61,62]. Knaus et al. take this a step further, devising a finite element model where parameters of the components can be adjusted to produce different results[63]. This could prove to be a direction for future research.

Another issue brought about by age is the irresponsiveness of the ciliary muscle to stimuli. The major reason for this is an age-related loss in the mobility of the muscle, caused by a stiffening choroid, a hardening vitreous body, and a thickening lens. Hyalinization in the muscle tissue is possibly one other culprit, but studies about how it affects the physical properties of the ciliary muscle tissue is nonexistent, so it may be an area worth being looked into. Moreover, as ciliary muscle mass move forward with age, the length of the pars plana has been observed to increase[26,31], how this may affect the tightness of posterior components and so affect the mobility of the ciliary muscle can be intriguing.

In contrast to the decline in mobility, no considerable decline in contractility has been found, though atrophy of myocytes has been observed. In addition, evidence from rhesus monkeys suggests that the concentration of muscarinic receptors and binding affinity of the receptors remain unchanged at an old age. Nevertheless, it should be noted that the experiments about contractility are nearly all carried out on rhesus monkeys, whose eyes though similar to those of humans, age

in a different way, as mentioned formerly[37], so more experiments conducted on the human ciliary muscle are needed.

One other overlooked potential direction is not directly related to the presbyopia. As previously mentioned, age-related changes in the muscle can be the common underlying mechanism for presbyopia and other diseases like glaucoma. This has been discussed and supported by Kaufman et al[64]. Possibly, fruits yielded by studying other diseases could increase our knowledge about presbyopia and the its relationship with the ciliary muscle.

Conclusion

Just as everything else in the eye, the ciliary muscle, a vital component to accommodation, is not immune to aging, so the aging of it may well be a trigger to presbyopia. Studies about the aging process of the muscle mainly center on changes in its geometry, relative position to related components, mobility, and contractility. Though it hides behind the opaque iris, imaging technologies such as UBM have been employed to visualize it and its accommodative movement. Moreover, when fine structures of the muscle require a closer examination, light and electron microscopy are available to researchers. With these technologies, many studies have identified age-related thickening in the muscle and its potential causes—increasing connective tissues and a pull from the thickening lens. More importantly, these studies lead to a geometric theory in which the shape of the ciliary muscle and its relative position to other components have decisive control over the tension of zonular fibers. In addition, other studies have confirmed that most of the accommodative response of the muscle are lost at an advanced age and they finger the loss of mobility as the main culprit, which could be caused by a thickening lens and stiffening choroid. In contrast, the muscle's contractility remains pretty stable throughout the lifespan. Future studies, especially those on human ciliary muscles, will shed more light on the situation by deciding whether previous findings in rhesus monkeys can be extrapolated to humans and by revealing more unknown factors that cause presbyopia.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Authors' contributions

Hangjia Zuo, Hong Chen and Wenjuan Wan were involved in the overall thoughts and preparation of the manuscript. Meiting Lin, Xiang Gao, Yongguo Xiang, Miaomiao Du, Hong Cheng, Shijie Zheng participated in the collection of the data. Hangjia Zuo and Hong Chen contributed equally to this work. Ke Hu and Wenjuan Wan contributed equally to this work. All authors review and approve the final manuscript.

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