

Research article

Accommodative function in rhesus monkeys: effects of aging and calorie restriction

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Abstract

Numerous degenerative changes in the visual system occur with age, including a loss of accommodative function possibly related to hardening of the lens or loss of ciliary muscle mobility. The rhesus monkey is a reliable animal model for studying age-related changes in ocular function, including loss of accommodation. Calorie restriction (CR) is the only consistent intervention to slow aging and extend lifespan in rodents, and more recently the beneficial effects of CR have been reported in nonhuman primates. The goal of the present study was to evaluate age-related changes in ocular accommodation and the potential effect of long-term (>8 years) CR on accommodation in male and female rhesus monkeys. Refraction, accommodation (Hartinger coincidence refractometer), and lens thickness (A-scan ultrasound) were measured in 97 male and female rhesus monkeys age 8–36 years under Telazol/acepromazine anesthesia. Refraction and accommodation measurements were taken before and after 40% carbachol corneal iontophoresis to induce maximum accommodation. Half the animals were in the control (CON) group and were fed approximately *ad libitum*. The CR group received 30% fewer calories than age- and weight-matched controls. Males were on CR for 12 years and females for 8 years. With increasing age, accommodative ability declined in both CON and CR monkeys by 1.03 ± 0.12 ($P = 0.001$) and 1.18 ± 0.12 ($P = 0.001$) diopters/year, respectively. The age-related decline did not differ significantly between the groups ($P = 0.374$). Baseline lens thickness increased with age in both groups by 0.03 ± 0.005 mm/year ($P = 0.001$) and 0.02 ± 0.005 mm/year ($P = 0.001$) for the CON and CR groups, respectively. The tendency for the lens to thicken with age occurred at a slower rate in the CR group vs. the CON group but the difference was not statistically significant ($P = 0.086$). Baseline refraction was -2.8 ± 0.55 and -3.0 ± 0.62 diopters for CON and CR, respectively. Baseline refraction tended to become slightly more negative with age ($P = 0.070$), but this trend did not differ significantly between the groups ($P = 0.587$). In summary, there were no significant differences in the slope of the age-related changes in accommodation, lens thickness, or refraction in the carbachol-treated eyes due to diet. These data are consistent with previous findings of decreased accommodative ability in aging rhesus monkeys, comparable to the age-dependent decrease in accommodative ability in humans. This study is the first to indicate that the accommodative system may not benefit from CR.

Introduction

Many aspects of visual function are affected with advancing age in primates. The gradual loss in accommodative function (the ability to change the eye's refractive power to focus from distant to near objects), or presbyopia, is the most common, predictable and clinically apparent manifestation of human ocular aging (Duane 1922). When the eye is focused on distant objects, the ciliary muscle is relaxed and parallel light rays entering the normal eye are brought to focus on the retina. To shift focus to near objects, parasympathetic nervous stimulation of the ciliary muscle contracts the muscle, thereby relaxing the zonular ligaments, which suspend the lens, allowing the elastic lens capsule to mold the lens to a more spherical shape. The resulting increase in the curvature and axial thickness of the lens, as well as forward translation of the lens, all act to increase the overall refractive power of the eye. In young humans, the change in lens shape may increase the refractive power by 12–15 diopters.

Presbyopia is characterized by the gradual loss of ability to change focus from far to near. Accommodative amplitude peaks in humans during young adulthood but slowly declines thereafter. By the age 50–55 years, virtually all accommodation has been lost (Kaufman 1992). The eye then remains focused permanently at an almost constant distance; the distance depends on the physical characteristics of each individual's eyes. It has been estimated that in the US tens of billions of dollars are spent annually on this age-related affliction that can be compensated for at present only by corrective spectacle, contact, or intraocular lenses. Refractive corneal surgery is another option, although it is controversial.

Two primary mechanisms have been identified to explain the development of presbyopia: hardening of the lens (Fincham 1937; Fisher 1969, 1973; Glasser and Campbell 1998; Pau and Krantz 1991) and a decline in the mobility of the ciliary muscle (Tamm et al. 1992). Loss of muscle movement and accommodative amplitude could be consequent to alterations in the elastic tissue that attaches the ciliary muscle to the sclera near the optic nerve. In old eyes the elastic fibers appear thickened and contain increased amounts of microfibrils and collagen fibers. These increases in nonstretchable fibrillous material could induce stiffening of the posterior elastic system and prevent forward muscle movement (Tamm et al.

1991). It is possible that diet may play a role in these age-related processes.

The slowing of many age-related functional losses has been demonstrated extensively in rodents and other short-lived species by calorie restriction (CR). This phenomenon has been studied in long-lived nonhuman primates since 1987 at the National Institute on Aging (Ingram et al. 1990). Many beneficial effects of CR have been shown in monkeys including decreased glucose, insulin, cholesterol, and triglycerides (Lane et al. 1998). Moreover, CR has attenuated age-related declines in hormones such as dehydroepiandrosterone sulfate (Lane et al. 1997) and melatonin (Roth et al. 2001).

Several rodent studies suggest that nutritional intervention may affect maturational and age-related changes in ocular or neural function and structure. Warren et al. (1989) reported that undernourished young adult rats had 30% more synapses per neuron in the visual cortex than well-fed controls. Calorie restriction significantly slowed the rate of age-related loss of retinal ganglion cells (RGC) in albino rats and mice (Neufeld and Gachie 2003). In addition, CR rats suffered significantly less RGC damage following ischemia/reperfusion than *ad libitum* controls in both young and old age categories (Kawai et al. 2001). Accumulation of inositol phosphates causes altered cellular calcium homeostasis, which has been implicated in the initiation or progression of neurochemical, neurophysiological and behavioral changes that accompany aging. Undie and Friedman (1993) showed that aged (24 months) *ad lib*-fed Fischer-344 rats had a decreased capacity to respond to receptor-activated phosphoinositide hydrolysis compared to young (6 months) counterparts. However, 60% CR old (24 months) rats responded similarly to the young *ad lib* rats, thus, implying that this aging effect has been substantially slowed (Undie and Friedman, 1993). The age-dependent decline in several retinal parameters (outer nuclear layer (ONL) cell densities, ONL height and retinal thickness) of 40% CR Brown Norway rats was also slowed (Obin et al. 2000b).

Calorie restriction is clearly not beneficial to all visual parameters and in fact, may have some detrimental effects. No effect of diet on retinal aging was seen in 18- to 27-month-old rats as measured by photoreceptor cell death, outer nuclear layer thickness, or pattern of cell loss (O'Steen and Landfield 1991). In the group of 21-month-old rats, retinal thickness was even decreased in the CR group compared to *ad lib*

(O'Steen and Landfield 1991). Obin et al. (2000a) also reported that photoreceptor cell density declined with age in 12-, 18-, and 24-month-old Fischer-344 rats and the declines were more pronounced in the 40% CR group compared to control. Additionally, the CR rats were more susceptible to the deleterious effects of bright light on photoreceptor cell density despite better health and survivorship.

It is of interest to determine what effect caloric restriction might have on the visual system of nonhuman primates, a species more closely related to humans that undergoes similar age-related changes. The University of Wisconsin has been conducting an evaluation similar to the NIA of CR in rhesus monkeys since 1989 (Kemnitz et al. 1993). Ocular measurements were conducted at baseline and after one year at 30% restriction in 8- to 14-year-old monkeys. Age-related changes were evident in accommodation, lens grade, anterior chamber depth, and lens thickness. Their results were consistent with previously reported age changes in rhesus monkeys, but there were no significant effects of diet after only one year on study (Kemnitz et al. 1993).

The objective of the present study was to evaluate the age-related changes in accommodation and several related ocular properties in a large cohort of male and female rhesus monkeys (*Macaca mulatta*) spanning 28 years of age and the potential effect of long-term (at least 8 years) CR on visual function.

Materials and methods

Subjects

The present study included a total of 97 (49 males and 48 females) rhesus monkeys (*Macaca mulatta*).

Monkeys used in this study were part of an ongoing study of aging and caloric restriction in nonhuman primates at the National Institute on Aging (Ingram et al. 1991). The monkeys ranged in age from 2 to 23 years at the time CR was initiated. Data from the present study were collected from male monkeys that had been maintained on 30% CR for 12 or 13 years, while females were on 30% CR for 8 years. Table 1 lists age and body weights for all groups of monkeys.

Animal husbandry and diet composition have been described in detail previously (Ingram et al. 1990). Monkeys were housed individually indoors but had extensive auditory, visual, and olfactory interaction with other monkeys in the vivarium. Rooms were maintained on a 12 h light (0600 hours):12 h dark (1800 hours) cycle, and were controlled for temperature (22–28 °C) and humidity (50%–60%).

Monkeys in both the control (CON) ($n = 54$) and CR ($n = 43$) groups were fed two meals a day (0700 and 1400 hours). Food allotments for CON monkeys were based on National Research Council requirements for monkeys of a given age and weight. Regular measurements of food consumption have determined that these allotments approximate *ad libitum* feeding. The daily food allotment offered to CR monkeys was 30% less than that given to age- and body weight-matched monkeys in the CON group. Diet composition did not differ between the two groups. As such, the experimental manipulation was a reduction in total caloric intake.

Methods

For the ocular assays, each animal was anesthetized with an average dose of 3–5 mg/kg i.m. Telazol (1:1 ratio of tiletamine and zolazepam) (Fort Dodge Animal Health, Fort Dodge, IA) injected in combi-

Table 1. Age and body weight characteristics of rhesus monkeys.

	Number	Mean age (year \pm SEM)	Age range	Mean body weight (kg \pm SEM)
Males				
CON	26	19.3 \pm 1.2	11–32	11.9 \pm 0.74
CR	23	20.1 \pm 1.6	14–36	8.9 \pm 0.39
Females				
CON	28	14.4 \pm 1.0	8–27	6.7 \pm 0.32
CR	20	16.3 \pm 1.5	10–29	6.2 \pm 0.29

nation with 0.1–0.2 mg/kg acepromazine maleate (Boehringer Ingelheim Vetmedica, St. Joseph, MO). Refraction was measured using a Hartinger coincidence refractometer (aus Jena, Jena; Zeiss, Germany) before and after pharmacologically inducing accommodation. A cholinomimetic drug, 40% carbachol (Sigma, St. Louis, MO), was applied by corneal iontophoresis (Koretz et al. 1987), 2×15 s (CARB), to one eye, inducing maximum accommodation (Crawford et al. 1989). Carbachol induces accommodation by stimulating the ciliary muscle to contract, releasing tension on the zonules, allowing the lens to change shape and position and thereby increase its refractive power. The Hartinger Coincidence Refractometer objectively determines the refractive state of the eye. A test pattern, which is split and projected through the pupil onto the retina, is optomechanically moved until the two images coincide. The optical power dialed into the instrument to achieve this alignment represents the power of the lens in the spectacle plane required to correct the eye's axial refractive error. Following carbachol administration, the optical power shift on the instrument from baseline required to realign the images of the test pattern represents the accommodative amplitude. Intraocular pressure (IOP) was measured with a Goldmann (Kaufman and Davis 1980) (Haag Streit, Bern, Switzerland) applanation tonometer after topical application of 0.5% proparacaine HCl (Bausch & Lomb Pharmaceuticals, Tampa, FL). Axial lengths of the anterior chamber, lens, vitreous cavity, and whole globe were measured with an A-scan ultrasonic device (A-Scan 5500, Sonomed, New York) pre- and post-CARB.

Age was estimated by a masked observer (P.L.K.) based on the biomicroscopic (slit lamp) appearance and clarity of the lens (Kaufman and Bito 1982). Since the rhesus monkey lens appears biomicroscop-

ically very similar to the human lens, they were graded on an arbitrary scale of 0–4, without knowledge of the animal's age, as follows: (0) clear lens; (1) minimal, barely detectable opacity, not judged to be sufficient to affect vision; (2) easily detectable opacity, but compatible with 20/20 vision; (3) more advanced opacity, consistent with 20/40–20/50 vision; (4) still more advanced opacity, consistent with vision <20/70 (Kaufman and Bito 1982).

Statistical analyses

The data were analyzed using linear regression techniques (via the `lm()` function) in R version 1.6.2 (www.R-project.org). Baseline measurements obtained from the left and right eye were not statistically different; therefore, analyses were performed using the CARB-treated eye for baseline data. Standard errors (SE) are presented immediately following estimates in the form: estimate \pm SE. The level of significance for all tests was $P < 0.05$. In addition to the linear regression, *t*-tests were carried out for comparison between the CR and the CON groups.

Results

Baseline measures in CARB-treated and nontreated eyes were not different; thus, data are reported for the CARB-treated eye only. In the 97 rhesus monkeys studied, no significant differences were found between CON and CR monkeys for any of the baseline or post-CARB parameters. Baseline parameters included: refraction, IOP, anterior chamber depth, lens thickness, vitreous cavity length, and whole globe length. IOP did not differ significantly between the

Table 2. Regression analysis for baseline lens thickness and refraction.

	Male	Female	Both
<i>Baseline lens thickness</i>			
Slope on age for CON	0.031 \pm 0.008	0.029 \pm 0.007	0.034 \pm 0.005
Slope on age for CR	0.014 \pm 0.007	0.028 \pm 0.007	0.023 \pm 0.005
<i>P</i> -value testing for different slopes	0.109	0.858	0.086
<i>Baseline refraction</i>			
Average for CON	−2.018 \pm 0.630	−3.536 \pm 0.853	−2.820 \pm 0.551
Average for CR	−4.350 \pm 0.672	−1.540 \pm 1.009	−3.012 \pm 0.629
<i>P</i> -value testing for different means	0.015	0.138	0.817
<i>P</i> -value on age	0.111	0.224	0.07

CON (19.83 ± 0.53 mmHg) and the CR group (20.49 ± 0.59 mmHg).

For regressions of baseline lens thickness onto age, the effect of CR appeared to be different for males vs. females (Table 2). Males on CR exhibited a slightly slower rate of lens thickening with age when compared to the CON group ($P = 0.11$). The rate of lens thickening with age for females on CR was not different from the CON group. Similar results were seen in regard to gender for baseline refraction (Table 2). A statistically significant difference in baseline refraction was found between CR and CON males ($P = 0.015$), but this difference was not clinically meaningful. No diet difference in baseline refraction was evident for the females. Since males were on CR longer than females, a two-sample *t*-test was performed to compare accommodative amplitude in CR males vs. CON males. There was not a significant difference ($P = 0.71$), suggesting that the age-related loss of accommodative amplitude was not improved in the CR males vs. the CON males. Since the gender differences do not appear to be clinically meaningful, males and females were combined for statistical analysis of all parameters.

Figure 1 shows baseline lens thickness as a function of age. Lens thickness increased with age in both CON and CR monkeys by 0.03 ± 0.005 ($P = 0.001$) and 0.02 ± 0.005 ($P = 0.001$) mm/year, respectively.

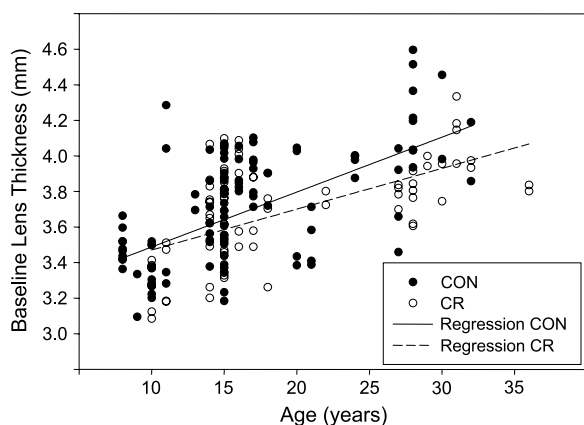


Figure 1. Baseline lens thickness as a function of age in rhesus monkeys. Lens thickness increased with age in both control (CON) and calorie-restricted (CR) monkeys by 0.03 ± 0.005 ($P = 0.001$) and 0.02 ± 0.005 ($P = 0.001$) mm/year, respectively. The lens in the CR group tended to thicken at a slower rate than the CON group. However, the slopes for the two groups do not differ statistically ($P = 0.086$).

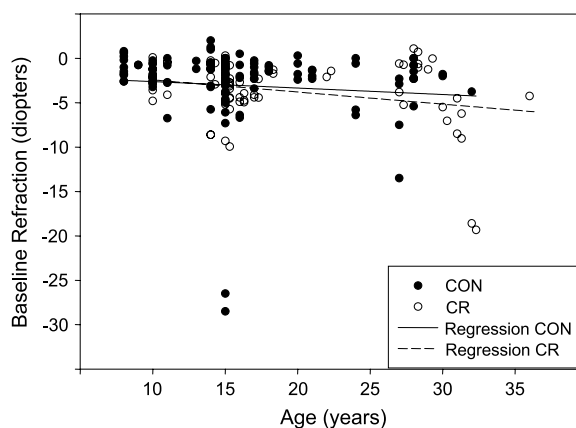


Figure 2. Resting refraction as a function of age in rhesus monkeys. Refraction was -2.8 ± 0.55 and -3.0 ± 0.62 diopters for control (CON) and calorie-restricted (CR) monkeys, respectively, and did not vary with age. There was no difference between diet groups ($P = 0.817$).

The tendency for the lens to thicken with age occurred at a slower rate in the CR group compared to the CON group, but this trend did not reach statistical significance ($P = 0.086$).

Figure 2 presents baseline refraction as a function of age. Mean baseline refraction was -2.8 ± 0.55 and -3.0 ± 0.62 diopters for CON and CR monkeys, respectively, and did not statistically differ between diet groups ($P = 0.817$). Baseline refraction tended to

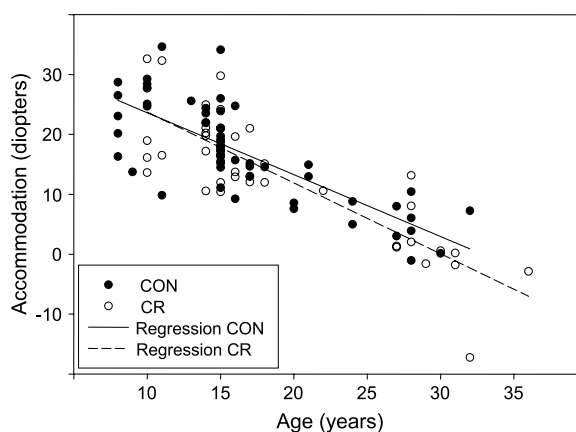


Figure 3. Carbachol (CARB)-induced accommodative amplitude as a function of age in rhesus monkeys. Accommodative ability declined in both control (CON) and calorie-restricted (CR) monkeys by 1.03 ± 0.12 ($P = 0.001$) and 1.18 ± 0.12 ($P = 0.001$) diopters/year, respectively. There was no difference between diet groups ($P = 0.374$).

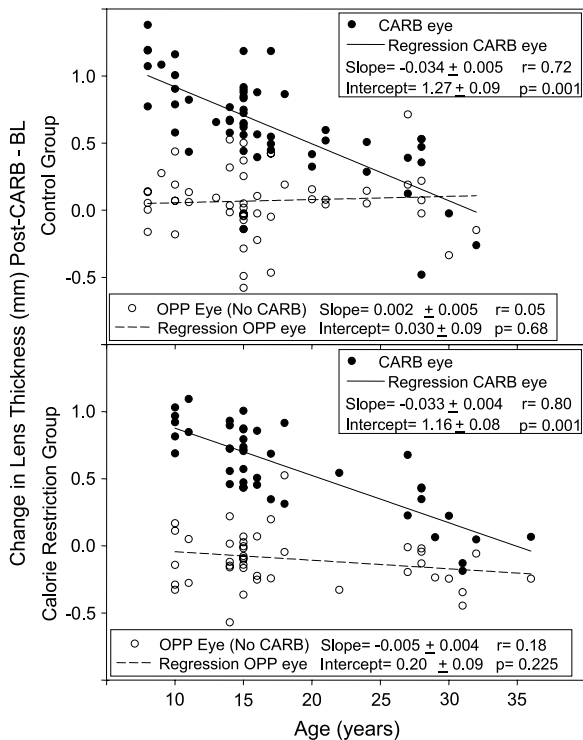


Figure 4. Carbachol (CARB)-induced change in lens thickness (post CARB-BL, mm) as a function of age in rhesus monkeys for CARB-treated and opposite (OPP; untreated) eyes. The CARB-induced change declined with age in both the CON and the CR groups but the groups did not differ significantly. (CARB = 40% carbachol corneal iontophoresis, 2×15 s to induce accommodation.) As expected, the opposite eye showed no change. BL = Baseline lens thickness before CARB administration.

decline (become more negative) with age, but the decline was not statistically significant ($P = 0.07$).

Two monkeys exhibited unusually high baseline refractions in both eyes (-26.5 and -28.5 diopters, age 15 years; -18.6 and -18.8 diopters, age 32 years), indicating a condition called high myopia, which occurs in monkeys as well as humans. The axial globe lengths in these eyes were approximately 2 mm longer than the average globe length of the group (19.91 ± 0.09 mm; mean \pm SEM); axial elongation is typical of high myopia in both humans and monkeys. One animal (age 32) underwent cataract surgery a few years later, which indicates that lens changes may have affected refraction. However, lens-induced myopia in humans is seldom as great and symmetric as that observed in this animal. Since the globes were longer than normal, there was likely an underlying genetic-anatomic abnormality. Data were reanalyzed

excluding the two outlier monkeys mentioned above, but, still found no significant differences between CR and CON monkeys for any of the parameters.

CARB-induced changes were measured for the following parameters: maximum accommodation, lens thickness, and anterior chamber depth. Figure 3 shows accommodative amplitude as a function of age. Accommodative ability declined in both CON and CR monkeys by 1.03 ± 0.12 ($P = 0.001$) and 1.18 ± 0.12 ($P = 0.001$) diopters/year, respectively. There was no statistically significant difference between diet groups ($P = 0.374$).

CARB-induced lens thickening declined significantly with age in both CON and CR groups ($P = 0.001$ for both), but no significant difference was detected between the diet groups ($P = 0.319$). The lens thickened by 0.643 ± 0.05 mm for the CON group and 0.584 ± 0.05 mm for the CR group (Figure 4).

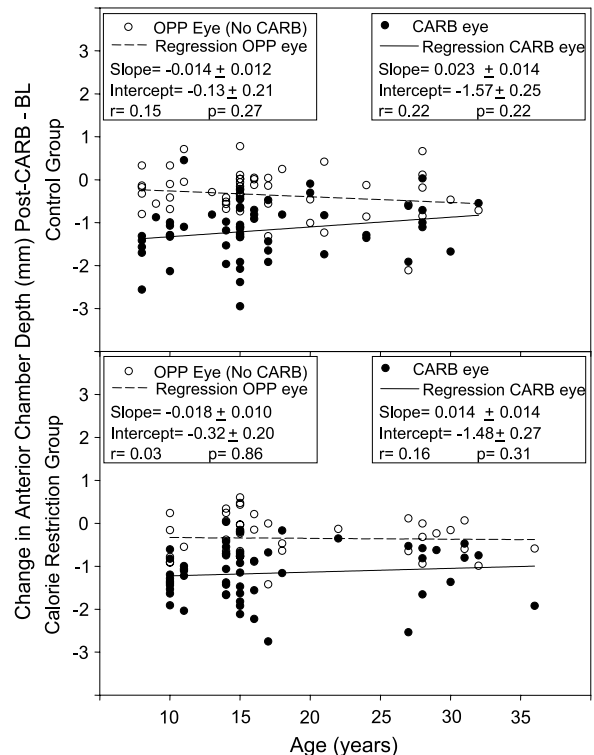


Figure 5. Carbachol (CARB)-induced change in anterior chamber depth (post CARB-BL, mm) as a function of age in rhesus monkeys for CARB-treated and opposite (OPP; untreated) eyes. No significant correlation was seen in either control or calorie restriction group. CARB = (40% carbachol corneal iontophoresis, 2×15 s to induce accommodation). As expected, the opposite eye showed no change. BL = baseline anterior chamber depth before CARB administration.

CARB-induced anterior chamber shallowing did not decline significantly with age in either group ($P = 0.22$ for CON group, $P = 0.31$ for CR group). The anterior chamber shallowed by 1.23 ± 0.10 mm for the CON group and 1.25 ± 0.10 mm for the CR group in response to CARB (Figure 5).

Using lens appearance and clarity, the masked observer estimated age correctly on average in both groups ($P = 0.44$ for both groups), and there was not a significant difference between the groups in this estimated age ($P = 0.385$) (Figure 6). The age estimate incorporates many characteristics of lens appearance that were not quantified and not easily quantifiable by simply assigning one of the four progressive values to the degree of lens opacity (Kaufman and Bito 1982). The age estimate was, in effect, a global estimate of lens clarity. The fact that the readings taken on the eyes of the same monkey are correlated was taken into account in the model construction itself as the “mixed model” was used. In addition, the degree of lens opacity between the CR and CON groups was compared by simply assigning one of the four progressive values to the degree of lens opacity (treating each eye separately).

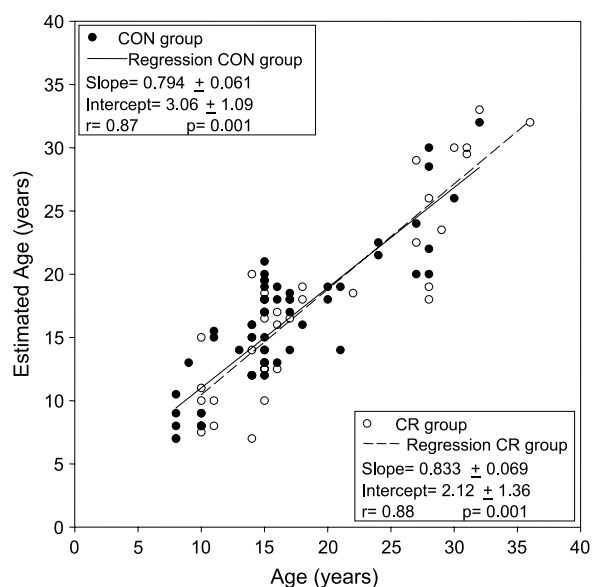


Figure 6. Estimated age vs. true age of the monkeys for control (CON) and calorie restriction (CR) groups. Estimated age was based on biomicroscopic (slit lamp) appearance and clarity of the lens. The masked observer was extremely accurate at estimating monkey ages, and the data did not show a significant difference between the CON and CR groups.

Data are not shown, as there were no significant differences between diet groups.

Discussion

The results of the present study confirm that rhesus monkeys experience an age-related decrease in accommodative amplitude consistent with that observed in other rhesus (Koretz et al. 1987; Bito et al. 1982; Croft et al. 1998) and human (Bito et al. 1982) studies. Moreover, the pattern and relative timing of this age-dependent loss, adjusted for lifespan, is similar to that in humans (Bito et al. 1982; Kaufman et al. 1982), thus confirming the reliability of rhesus monkeys as an animal model for the age-related decline in human accommodative function.

Also consistent with previous monkey studies, lens thickness increased with age beyond the period of normal ocular growth. Bito et al. (1982) reported a decrease in lens thickness from 0.5 to 5 years followed by a significant increase with age. All monkeys in the present study were adults and therefore changes associated with maturation could not be detected. The precise role that thickening of the lens contributes to the loss of accommodation is not clear, but may combine with other lenticular factors to decrease the lens' ability to change shape during accommodation. There was a tendency, albeit not significant ($P = 0.086$), for the lens to thicken with age at a slower rate in the CR group vs. the CON group. It is possible that the animals have not been on CR a sufficient amount of time to show a statistically significant diet effect. Measuring these parameters again is necessary to determine if there is an effect of the diet over longer periods of time.

A gender difference in response to CR was evident in this one timepoint measurement of body weight. A recent report from this same cohort of monkeys indicated the effect of CR on reducing body weight was more pronounced in males compared to females (Mattison et al. 2005). When modeled as a function of age, CR females weighed less than CON, but the difference was less pronounced than that in males. Although the females were more resistant to changes in body weight, CR may affect other physiological parameters that should not be overlooked. Because the male monkeys were on the study four to five years longer than the females and demonstrated significantly lower body weight in the CR vs. the

CON group, preliminary analysis were done separately. Findings in the CR males tended to follow a pattern of diminished lens thickening with age compared to the CON group; but the *P*-value was not statistically significant. A statistically significant difference in baseline refraction was found between CR and CON males ($P = 0.015$) but did not appear to be clinically significant. Further, the age-related loss of accommodative amplitude was not improved in the CR males vs. the CON males ($P = 0.29$) even if data from the male monkey with bilaterally high myopia (-18.8 and -18.6 D) were excluded ($P = 0.99$). Appropriate statistical comparisons in the males alone are reported along with comparisons that included all of the monkeys (males and females) for completeness.

Refraction describes the bending of light rays passing from one medium into a medium of a different refractive index. Parallel light rays strike the convex lens and are refracted to a point behind the lens; the refractive power of the lens increases with lens curvature. The refraction measured in the current study represents the required power of a corrective eyeglass lens placed in the spectacle plane 12 mm in front of the eye to focus on the retina the image of an object placed at optical infinity [i.e., 6 m (20 ft)] in front of the eye. Consistent with previously reported rhesus data (Bito et al. 1982), baseline refraction did not vary with age. Baseline refraction was -2.8 ± 0.55 diopters in the CON group. This is consistent with previous studies on anesthetized monkeys in which approximately 2 to 3 diopters of myopia were induced (Westheimer and Blair 1973). Anesthesia-induced myopia is comparable to the tonic accommodation, or “dark focus,” described in humans in a dark room (Owens and Liebowitz 1980) and appears to be due to central parasympathetic neuronal tone (Crawford et al. 1990).

This study is the first to suggest that beneficial effects of CR may not extend to the ocular accommodative mechanism or to lens clarity. However, a major caveat is that although the male monkeys had been restricted for approximately 12 years and the females for 8 years, the age of CR initiation ranged from 2 to 23 years. It is possible that the older animals may have already experienced an age-related decline in accommodative function before being placed on the CR diet late in life that could not be reversed. Thus, we do not yet know whether younger animals will exhibit beneficial effects from lifelong

calorie restriction. Nonetheless, this study does demonstrate that CR was not harmful to the accommodative system and can therefore be considered for its other advantages.

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