

# Coenzyme Q10 in the Human Retina

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**PURPOSE.** To determine the concentration of coenzyme Q10 (CoQ10) in the human retina.

**METHODS.** Eye tissues were lyophilized and exhaustively extracted with heptane. The extracts were analyzed for CoQ10 by high-performance liquid chromatography (HPLC).

**RESULTS.** The average concentration of CoQ10 in the retina was  $42 \pm 11$  nanomoles/g dry retina for donors younger than 30 years of age and  $24 \pm 13$  nanomoles/g dry retina for donors older than 80 years of age. The average concentrations of CoQ10 in the choroid was  $27 \pm 16$  nanomoles/g dry choroid for donors younger than 30 age and  $18 \pm 11$  nanomoles/g dry choroid for donors older than 80.

**CONCLUSIONS.** CoQ10 levels in the retina can decline by approximately 40% with age. This decline may have two consequences: a decrease in antioxidant ability and a decrease in the rate of ATP synthesis in the retina and, as such, this decline may be linked to the progression of macular degeneration. (*Invest Ophthalmol Vis Sci.* 2009;50:1814–1818) DOI:10.1167/iops.08-2656

Coenzyme Q10 (CoQ10),<sup>1</sup> also known as ubiquinone, is a lipid soluble, endogenously synthesized molecule that is widely distributed in mitochondria, microsomes, and Golgi apparatus of all cellular membranes and has several cell functions. CoQ10 plays an integral role in oxidative metabolism and management by supporting ATP biosynthesis in mitochondria and, in its reduced form, by acting as a lipid antioxidant.<sup>1</sup> Its ability to scavenge reactive oxygen species and recycle vitamin E makes it a more effective lipid antioxidant than vitamin E and the carotenoids lycopene and  $\beta$ -carotene.<sup>1,2</sup> As an essential component of the electron transport chain, ubiquinone accepts electrons from complexes 1 and 2 and transports them to complex 3; thus, ATP synthesis is highly dependent on CoQ10 concentrations. In addition, CoQ10 affects expression of genes involved in human cell signaling, metabolism, and transport,<sup>3</sup> and it is also necessary for uncoupling oxidative phosphorylation in mitochondria, a process that must be tightly regulated to avoid cell death.<sup>4,5</sup>

In nearly every tissue of the human body, including the lung, heart, spleen, liver, kidney, pancreas, adrenal gland, blood,<sup>6</sup> and brain,<sup>7</sup> CoQ10 levels decline with age.<sup>8–10</sup> Because of CoQ10's ubiquitous role in the body, its decline is believed to play a role in aging and the pathogenesis of many degenerative or chronic diseases such as arteriosclerosis, Parkinson's disease, Alzheimer's disease, and cataracts.<sup>11–19</sup> We have recently quantified the amount of CoQ10 in the bovine retina and have found that it contains relatively small amounts of CoQ10

compared with other tissues in the body, despite the retina's relatively high rate of oxidative metabolism (in which CoQ10 is integrally involved; Qu J, Washington I, submitted for publication). The relatively low levels of ubiquinone found in the bovine retina, coupled with the retina's high levels of oxidative metabolism and its need for efficient lipid antioxidants, suggests that eye function may be sensitive to changes in CoQ10 concentrations. Thus, it was of interest to explore the concentrations of CoQ10 in the human retina and to ascertain whether there is an age-related decline in CoQ10 levels.

## METHODS

Methanol, hexanes, and heptane were HPLC-grade (Honeywell Burdick & Jackson, Morristown, NJ). CoQ10 was purchased from VWR Co. (Westchester, PA). A stock solution of CoQ10 in ethanol (0.4 mM) was prepared. Working solutions of CoQ10 were prepared by dissolving appropriate portions of the stock solution in heptane. All standard solutions were stored at  $-20^{\circ}\text{C}$ .

All HPLC chromatographic separations were performed with a photodiode array detector (model 996; Waters, Milford, MA), a pump (model 600; Waters), a loop injector (Rheodyne, Rohnert Park, CA), a controller (model 600; Waters) and an in-line filter/degasser (Whatman, Florham Park, NJ). The data were processed with commercial software (Empower Pro ver. 5.0; Empower Pro, Solon, OH). RP-HPLC was performed at room temperature on a 100-cm  $\times$  4.6-mm ID C18 column (Onyx Monolithic; Phenomenex, Torrance, CA) using a flow-rate of 1.5 mL/min. The mobile phase consisted of methanol, hexanes, acetic acid, and isopropanol (55:9:1:1 vol/vol/vol/vol) and 0.42% sodium acetate. The UV detector was set to monitor at 275 nm.

## Samples and Sample Preparation

Human, posterior poles were obtained from donors from the National Disease Research Interchange (Philadelphia, PA). All posterior poles were shipped over ice packs in a sterile container, kept moist by a piece of saline soaked gauze placed inside the container, and received in our laboratory at  $\sim 48$  hours after death. On arrival, the poles were placed in a 15-cm round Petri dish containing water, and the retina and the choroid (with RPE) were dissected under a 10 $\times$  stereomicroscope. Each tissue from each eye was placed in a separate 2-mL centrifuge tube (four tubes for a pair of poles) and lyophilized. The dehydrated tissue was stored at  $-20^{\circ}\text{C}$  (for  $\sim 2$ –3 months).

The samples were divided into two groups according to their age, each consisting of eight eyes: a younger group (four donors  $< 30$  years of age) and an older group (four donors  $> 80$  years of age). Characteristics of all the donors are listed in Table 1. Besides a case with cataracts and an intraocular lens, the eyes had no ophthalmic history, and no gross signs of ocular disease were observed on dissection. The dehydrated tissues were weighed and rehydrated by adding 200  $\mu\text{L}$  of distilled water. After homogenization, using a tissue homogenizer (Omni International, Inc., Marietta, GA) at a speed of 35,000 rpm for 10 seconds, samples were deproteinized with 0.5 mL of methanol, and 0.25 mL of heptane was added. After vortexing for 30 seconds and centrifuging at 12,000 rpm for 5 minutes, 10  $\mu\text{L}$  of the upper heptane layer was injected into the HPLC and chromatographed under the above conditions. All extractions were performed under (500-nm lighting [F40GO gold lights]; Philips Lighting Co., Cincinnati, OH) to avoid potential photodegradation of CoQ10.

Typical chromatographic profiles of the blank CoQ10 standard and the retinal extracts are shown in Figure 1. The blank sample was the

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TABLE 1. Donor Information

Group	Donor	Age (y)/Sex	Post-death Harvest (h)	Cause of Death	Selected Medical History
<30 y	1	27/F	6	Pulmonary edema	Depression Hematuria syndrome Renal failure Crohn's disease
	2	28/M	4	Cirrhosis	Hypertension Jaundice Wilson's disease
	3	24/M	20	Trauma	Childhood asthma
>80 y	4	20/M	13	Trauma	Bronchitis
	5	81/F	11	Trauma	Pneumonia Congestive heart failure Colon cancer Kidney cancer Glaucoma Renal failure
	6	80/F	6	Aspiration pneumonia	Lung cancer Renal cell carcinoma Three Seizures
	7	89/M	6	Trauma	Bowel cancer resection Cataracts Prostate cancer
	8	85/M	11	Cardiac arrest	Hypertension Congestive heart failure Carotid endarterectomy Femoral bypass Anemia Osteomyelitis

upper layer of a mixture of 0.5 mL methanol and 0.25 mL heptane. Under the chromatographic conditions described, CoQ10 had a retention time of approximately 4 minutes. After this procedure, good separation and detectability of CoQ10 in human retinal tissues were achieved.

### Linearity and Limits of Detection

Integrated chromatographic peak areas were plotted against the corresponding concentrations of the injected standard solutions to obtain a calibration curve. The injected concentration, which could be detected at a signal-to-noise ratio of 3, was considered to be the limit of detection (LOD). Good linearity (coefficient of determination  $R^2 > 0.99$ ) was achieved in the range of 0.2 to 395  $\mu\text{g/mL}$ . The LOD was 0.14  $\mu\text{g/mL}$ .

### Precision

Reproducibility was determined by injecting, three times, the same standard solutions at three different concentrations. Results showed that the relative SD (% RSD) ranged from 0.1% to 3.3%.

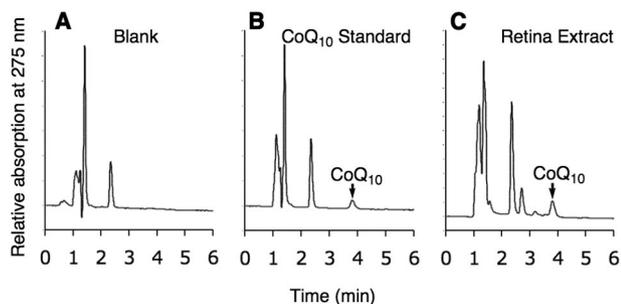


FIGURE 1. Typical HPLC profiles from (A) blank, (B) CoQ10, and (C) retina extract.

Experimental precision was examined by performing intra- and interday assays of three replicate injections of the same retina heptane extract. The intraassay was performed with an interval of 1 hour, while the interassay was performed over 3 days. The RSDs for the intraassay and the interassay were 1.6% and 3.7%, respectively.

### Recovery

Three different known quantities (low, medium, and high) of CoQ10 standards were added (spiked) to a retina sample. The retinas were then extracted and the extracts analyzed by HPLC using the methodology described herein. Quantification of CoQ10 was achieved by the corresponding calibration curve. As shown in Table 2, the recovery of the CoQ10 ranged from 101% to 113%, and their RSD values were all less than 5.0%. These extraction and analysis methods showed good reliability and accuracy for the measurement of CoQ10.

### RESULTS

Sixteen retinal samples were prepared and the extracts were subjected to HPLC analysis in triplicate. The average concentrations of CoQ10 in the retina were  $42 \pm 11$  nanomoles/g dry retina (range, 26–57 nanomoles/g dry retina) in the younger group and  $24 \pm 13$  nanomoles/g dry retina (range, 10–51 nanomoles/g dry retina) in the older group (Fig. 2A). A Student's *t*-test showed a statistical difference between the groups

TABLE 2. CoQ10 Recovery from Spiked Retina Tissue

Spiked ( $\mu\text{g/mL}$ )	Found ( $\mu\text{g/mL}$ )	Recovery (%)	RSD (%)
0.39	$1.40 \pm 0.02$	$113.4 \pm 4.5$	4.0
0.77	$1.75 \pm 0.02$	$101.1 \pm 3.1$	3.1
1.54	$2.56 \pm 0.02$	$103.1 \pm 1.0$	1.0

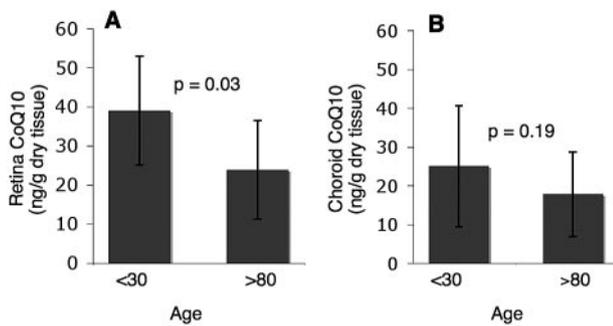


FIGURE 2. CoQ10 concentrations in the human retina (A) and choroid with RPE (B).

( $P = 0.032$ ) with the older group having approximately 40% less CoQ10 in the retina compared with the younger group.

On the other hand, the average concentrations of CoQ10 in the choroid (with RPE) were  $27 \pm 16$  nanomoles/g dry choroid (range, 7–55 nanomoles/g dry choroid) in the younger group and  $18 \pm 11$  nanomoles/g dry retina (range, 7–40 nanomoles/g dry retina) in the older group (Fig. 2B). This amount is approximately half that of CoQ10 found in the retina. Unlike in the retina, a Student's *t*-test did not show a statistical difference between the older and younger groups ( $P = 0.19$ ).

We were unable to detect ubiquinol in any of the samples. Proper measurement of tissue ubiquinol is complicated due to ubiquinol's instability and tendency toward oxidation to ubiquinone during sample handling, storage, and processing.<sup>20</sup> Although tissues were processed on arrival, they were enucleated at various times and received approximately 48 hours after death. During this time, substantial loss of ubiquinol can be expected.

## DISCUSSION

Oxidative stress is believed to play an important role in aging and the pathogenesis of many degenerative or chronic diseases such as arteriosclerosis, Parkinson's disease, Alzheimer's disease, cataracts, and age-related macular degeneration (AMD).<sup>11–19</sup> The retina is particularly vulnerable to oxidative stress.<sup>21</sup> Reactive oxygen species, which are responsible for this oxidative damage, are mainly formed in the body as by-products of oxidative metabolism. Since the retina's oxygen consumption rate (per gram tissue) is greater than any other tissue,<sup>22,23</sup> relatively large amounts of reactive oxygen species are formed. Unlike most other tissues, the retina, especially the macula, is subject to high levels of focused light. This, combined with photosensitizers such as melanin, rhodopsin, and lipofuscin, provides a second source of reactive oxygen species in the eye. In addition, the photoreceptor outer segment is rich in polyunsaturated fatty acids (PUFAs), which are believed to be vulnerable to reactive oxygen species.<sup>24,25</sup> All these factors create an optimal environment for oxidative stress in the retina, which is tightly linked to the pathogenesis of macular degeneration.<sup>11,17,26–33</sup>

Oxidative damage is thought to lead to retinal cell death by contributing to the formation of ocular lipofuscin and mitochondrial DNA mutations. Lipofuscin—yellow to brown pigment granules—may occupy up to 13% of the retinal pigment epithelial (RPE) cells of the eye in advanced age.<sup>34</sup> It has been postulated that lipofuscin in RPE cells may reach levels that contribute to a decline in cell function followed by vision loss.<sup>35</sup> Mitochondrial DNA mutations are also believed to accumulate with age.<sup>36</sup> These mutations often manifest themselves as an age-related decrease in ATP synthesis. In order to

provide a continuous supply of energy, the eye must constantly synthesize ATP. Drops in this energy supply are thought to contribute to a decline in cell function, followed by macular degeneration and vision loss.<sup>37</sup>

There have been several studies in which the potential role of antioxidants in protecting against the development of AMD or limiting its progression was examined.<sup>38–42</sup> The Age-Related Eye Disease Study (AREDS) showed that supplemental vitamin C, vitamin E,  $\beta$ -carotene, and zinc can significantly retard the progression of AMD.<sup>19,43</sup> Several in vitro, animal, clinical, and epidemiologic studies provide considerable support for the importance of antioxidant supplementation in protecting against AMD.

In the eye, dietary vitamin E<sup>44,45</sup> and the carotenoids lutein and zeaxanthin<sup>46</sup> are thought to protect lipids from reactive oxygen species. Vitamin E is known for its ability to react with free radicals (more quickly than PUFAs), which prevents the propagation of reactive oxygen species that damage lipids in biological membranes.<sup>47,48</sup> The main role of vitamin E is to maintain the integrity of lipids in the rod outer segments and to scavenge free radicals.<sup>49,50</sup> Other studies have concluded that human eyes contain between 8 and 18 nanomoles/retina of vitamin E. There have been conflicting reports on whether vitamin E levels decline or increase with age.

The carotenoids lutein and zeaxanthin also quench reactive oxygen species in the eye. The clinical importance of the carotenoid antioxidants lutein and zeaxanthin in the prevention of photoreceptor cell death in AMD was recently highlighted in a retrospective study in which 4915 patients were followed up over 10 years.<sup>46</sup> Studies have found that the human eye contains approximately 1 to 40 nanomoles/g dry retina of these carotenoids.<sup>51</sup> As with vitamin E, there have been conflicting reports on whether carotenoid levels decline or increase with age. Unlike CoQ10, vitamin E and carotenoids are obtained through diet. Differences in donors' diets may account for the discrepancies in reports of these nutrients.

CoQ10 can efficiently protect membrane phospholipids from lipid peroxidation and protect mitochondrial membrane proteins and DNA from oxidative damage.<sup>47,52,53</sup> It has been shown to be more effective at preventing lipid peroxidation than are vitamin E and carotenoids. Moreover, CoQ10-driven recycling of vitamin E represents an important mechanism of antioxidant regulation and modulates the activity of vitamin E. The presence of CoQ10 is beneficial for vitamin E's antioxidant effectiveness and their interactions are mutually beneficial for effective antioxidant protection of lipid membranes.<sup>54</sup> We found that the concentration of CoQ10 in the retina ranges from 26 to 57 nanomoles/g dry retina in younger donors. This concentration is more than has been reported for the concentrations of carotenoids and vitamin E. The relative concentration of CoQ10, coupled with its ability to act as an efficient antioxidant, suggests that CoQ10 may function as a powerful antioxidant in the eye.

CoQ10 levels in plasma have been found to decline gradually with age and decrease in individuals with diabetes, cancer, and congestive heart failure.<sup>55</sup> Supplementation with ubiquinone has been shown to alleviate cardiovascular conditions,<sup>56</sup> congestive heart failure,<sup>57</sup> atherosclerosis,<sup>58</sup> and Parkinson's disease.<sup>59,60</sup> Our study, with a limited number of samples, shows that the CoQ10 levels in the retina may decline, on average, by approximately 40%. This decline may have two consequences in the retina: a decrease in antioxidant ability and a decrease in ATP synthesis (as CoQ10's concentration limits electron transport). Although, as in any age-related study, certain medical conditions that are in fact not age-related, medications or causes of death may be contributing factors to the observed decline in ubiquinone status besides age itself.

Future studies in larger populations are currently under way to answer such questions.

Clinical studies show that AMD patients may benefit from intake of CoQ10 combined with saturated fatty acids.<sup>61,62</sup> However, the role of CoQ10 in AMD, although implicated,<sup>63</sup> is largely undefined. Considering the importance of antioxidants and oxidative phosphorylation in the retina and in aging and diseases, we believe quantification of CoQ10, a powerful antioxidant and oxidative phosphorylation substrate, is useful from a medical and epidemiologic point of view.

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