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ORIGINAL ARTICLE

## Effect of Resveratrol-Based Nutritional Supplement on Choroidal Thickness: A Pilot Study

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### ABSTRACT

**Purpose:** The effect of an oral trans-resveratrol-based supplement (Longevinex<sup>®</sup>) on choroidal thickness, measured using optical coherence tomography (OCT) enhanced depth imaging, was investigated in a prospective study.

**Materials and Methods:** 34 young, healthy participants were randomly divided into two age- and gender-matched groups. They were then assigned in a randomized fashion to treat with either a trans-resveratrol-based group (Longevinex<sup>®</sup>, Las Vegas) or placebo. All participants underwent ocular imaging with spectral domain (SD)-OCT (Spectralis; Heidelberg Engineering, Heidelberg) at the baseline and then again 1 h following treatment. The choroidal thickness was measured in a masked fashion at the fovea and at four additional points, located at 500  $\mu$ m and 1000  $\mu$ m nasal to the fovea and 500  $\mu$ m and 1000  $\mu$ m temporal to the fovea.

**Results:** In the resveratrol group, the foveal choroidal thickness at the baseline was  $267.73 \pm 84.19$   $\mu$ m (mean  $\pm$  SD); it increased to  $284.57 \pm 92.39$   $\mu$ m 1 h after drug treatment ( $p = 0.033$ ). The mean choroidal thickness was also significantly increased at each of the four extrafoveal points (all  $p < 0.05$ ). In the control group, the mean baseline choroidal thickness at the fovea was  $269.73 \pm 71.40$   $\mu$ m (mean  $\pm$  SD) and it was  $268.43 \pm 70.15$   $\mu$ m (mean  $\pm$  SD) 1 h after the placebo was administered ( $p = 0.183$ ); there were also no significant differences in choroidal thickness at the four additional points (all  $p > 0.05$ ).

**Conclusion:** A significant increase in choroidal thickness following oral administration of a trans-resveratrol-based supplement was observed. There was no change in choroidal thickness in the placebo-treated control group. We speculate that the increased choroidal thickness is the result of choroidal vessel vasodilation.

### ARTICLE HISTORY

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### KEYWORDS

Choroidal blood flow; choroidal thickness; enhanced depth imaging; optical coherence tomography; trans-resveratrol

### Introduction

Resveratrol is a small polyphenol found in various berries, grapes, red wine, nuts, and other plant sources.<sup>1,2</sup> Resveratrol has been found to delay or prevent carcinogenesis<sup>3</sup> and also has salutatory effects on Alzheimer's disease, hepatotoxicity, diabetes, and obesity through its anti-oxidant, anti-apoptotic, antitumorogenic, anti-inflammatory, anti-angiogenic, and vasorelaxant properties.<sup>4</sup> There has been some interest in using resveratrol in the treatment of eye diseases, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR).<sup>5</sup>

In both AMD and DR, the choroidal thickness decreases in both the macular and peripapillary areas.<sup>6,7</sup> Measuring the choroidal thickness has been suggested to reflect choroidal blood flow.<sup>8,9</sup> Moreover, resveratrol also can dilate blood vessels with increased blood flow.<sup>10-13</sup> Although a vasorelaxant effect of resveratrol has been reported, most of these investigations were conducted on animals or in vitro blood vessels.<sup>5,14-16</sup> Only a small number of studies have been performed on humans subjects.<sup>10,17</sup> Our experiment offered support to the previously published study reporting on the

relationship between resveratrol Longevinex<sup>®</sup> and choroidal thickness.<sup>18</sup>

In this study, we designed a double-blind, prospective study to examine the effect of a trans-resveratrol product Longevinex<sup>®</sup> on choroidal thickness, using OCT.

### Materials and methods

**Participants and treatment:** The study involved 34 young, healthy participants who either worked or studied at Tongji Medical College. They were randomly divided into two groups by age and gender matched. The study and control groups had neither systemic nor ocular diseases. The study protocol was approved by the Huazhong University of Science and Technology Institutional Review Board and Ethics Committee. The study was conducted according to the principles of the Declaration of Helsinki, and all participants gave their written, informed consent prior to participation.

All participants underwent detailed ophthalmic examination, including best-corrected visual acuity (BCVA) (LogMAR), intraocular pressure (IOP) measurement with noncontact tonometry, axial length (AL) and anterior

chamber depth (ACD) measurement with IOLMaster (Carl Zeiss, Jena, Germany), central corneal thickness measurement with visante™ OCT (Carl Zeiss, Jena, Germany), fundus examination, and choroidal thickness measurements with SD-OCT. The participants were excluded if their eyes more than 6 diopters (D) of myopia or more than 2D of hyperopia, ALs exceeding 26.5 mm, or IOP beyond normal limits (less than 10 mmHg or greater than 21 mmHg).

- (1) Longevinex® (Resveratrol Partners LLC, Las Vegas, NV), a nutritional supplement has 100 mg of trans-resveratrol. The micro-sized powder also contains stabilized quercetin, rice bran, vitamin D3, and ferulic acid. Trans-resveratrol is the active form of resveratrol. The other four substances have a synergy function in mediating the bioavailability of resveratrol. This blend has been demonstrated to obtain synergism in studies conducted at two academic centers and the National Institute of Health in the United States.<sup>19</sup> Micronization in a unique matrix-increased absorption, thereby increasing the availability of resveratrol.<sup>20</sup> Vitamin D is essential to vascular health. It inhibits progressive vascular calcification. Quercetin is a polyphenol that attenuates atherosclerosis by inhibiting vascular oxidative stress and inflammation. It also delays liver metabolism, thus increasing the immediate bioavailability of resveratrol.<sup>21</sup> Rice bran IP6 is a metal chelator against and anti-calcifying agent in blood vessels. Ferulic acid is beneficial in the inhibition of platelet aggregation and relieving vasospasm. Therefore, Longevinex is more effective than resveratrol for the beneficial effect on vascular system<sup>22,23</sup> (Table 1)

The subjects were given either a Longevinex® capsule or a placebo capsule; both had a similar taste and appearance. The participants were advised to avoid any strenuous exercise 24 h before the beginning of the test until the end of the experiment. They were also instructed not to consume any resveratrol-containing beverage (coffee, tea), food (chocolate, cocoa-containing food), and fruits and nuts (grapes, peanuts, and their products) at least 24 h before the basal test. Those who had any relevant alcohol consumption, smoked tobacco, drank caffeinated beverages, or took other drugs 24 h before ingesting our investigational medicines were excluded from the analysis groups. The baseline test was immediately followed by administering Longevinex® to the study group and

the placebo to the control group. The OCT measurements were repeated 1 h after the baseline measurements in both groups. To avoid diurnal variations, All OCT scans were performed at the same time of the day (between 9:00 am and 12:00 pm).

SD-OCT Screening: OCT imaging (Spectralis; Heidelberg Engineering), was employed. The use of this instrument has been described elsewhere.<sup>8</sup> In brief, it utilizes 870 nm wavelength and 40 000 Hz/s high-speed domain frequency, eye-tracking technology and the capability to capture up to 100 B-scans in the same position for OCT signal averaging. Furthermore, the ability of the SD-OCT system provides enhanced sensitivity.<sup>24</sup> This imaging method was termed “enhanced depth imaging, spectral domain-optical coherence tomography” (EDI SD-OCT). The axial resolution of this OCT system is 5 µm. To qualify for analysis, the quality score needs to be greater than 20. With EDI, the choroid is defined as the distance between the hyperreflective outer border of the retinal pigment epithelial layer (automatically detected by the instrument) and the sclero-choroidal interface (Figure 1).<sup>25,26</sup> The participants’ perpendicular distance measurements of choroidal thickness (in the subfovea and the four parafoveal regions) were obtained manually by using instrument software (Explorer version 1.7.0.0, Heidelberg Engineering).<sup>6,27</sup>

The choroidal thickness was measured at the fovea and at four extra-foveal points located at 500 µm and 1000 µm nasal to the fovea and 500 µm and 1000 µm temporal to the fovea, respectively. The images were evaluated independently and in a masked fashion by two experienced readers (A and B). The difference between readings was found to be within 10 µm at almost every point. Then the average of the two measurements was taken. If the measurements exceeded 10 µm, a third masked reader took measurements.

Statistical Analysis: The statistical analysis was performed by using SPSS 16.0. For each continuous variable, normality was checked with the Kolmogorov–Smirnov test. Continuous variables were demonstrated as arithmetic means for normally distributed data. Baseline choroidal thickness measurements of the two groups were compared by performing the independent sample t-test. The data were analyzed by using the paired t-test for choroidal thickness measurements at the baseline and 1 h following Longevinex® or placebo administration in both groups. The categorical variables between the two groups were analyzed by using the  $\chi^2$  test. A *p* value of less than 0.05 was considered statistically significant.

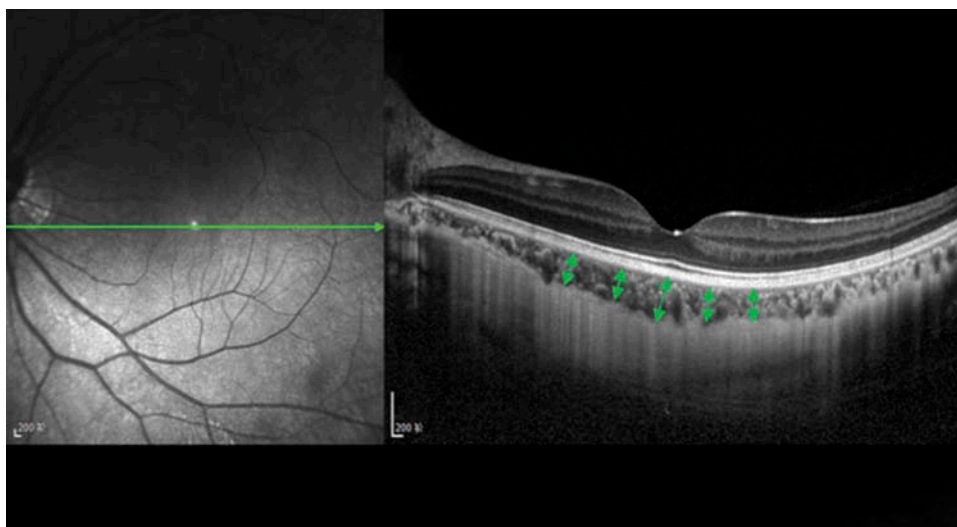
## Results

The study group consisted of 11 women and 7 men, with a mean age of  $25.44 \pm 1.46$  (mean  $\pm$  SD) years and a 23–29 age range. The control group members (8 women and 8 men) were between 23 and 28 years old, with a mean age of  $24.88 \pm 1.26$  (mean  $\pm$  SD). The two groups showed no significant difference in age ( $p = 0.236$ ) and gender distribution ( $p = 0.730$ ) (Table 2). Among the 34 initial participants, 30 underwent all follow-up eye examinations. 5 eyes were excluded because the myopias of two eyes were more than 6 diopters (D), and the ALs of three eyes exceeded 26.5 mm. The quality score indicated a signal strength of  $<20$  in three other eyes, which were not eligible for

**Table 1.** The mechanism and synergy as combinations of polyphenols (LONGEVINEX).

LONGEVINEX	
Supplement Facts	Mechanism
RV	Improving endothelial function, anti-inflammatory, anti-cholesterol, anti-platelet
VD3	Vascular support (decalcifying agent)
Q	Inhibiting vascular oxidative stress and inflammation, increasing the bioavailability of resveratrol
RB	Metal (CU++ and FE++) chelator
FA	Inhibition of platelet aggregation and relieving vasospasm

RV: trans-resveratrol, VD3: vitamin D3, Q: quercetin, RB: rice bran IP6, FA: ferulic acid.



**Figure 1.** Calculation of the choroidal thickness demonstrating the scope and position. The choroidal thickness in each EDI-OCT scan was measured at five points (the left blue line represents the EDI-OCT scan position, while the right blue arrows represent the scope and the detecting five points).

**Table 2.** The demographic and characteristics of the study participants.

	Mean $\pm$ SD or N( $\square$ )		<i>p</i> value
	Study group	Control group	
Number of patients	18	16	
Gender	11 females; 7 males	8 females; 8 males	<i>p</i> = 0.730
Age (years)	25.44 $\pm$ 1.46	24.88 $\pm$ 1.26	<i>p</i> = 0.236
Spherical refractive error, D	-3.19 $\pm$ 1.78	-2.89 $\pm$ 1.84	<i>p</i> = 0.527
AL(mm)	25.15 $\pm$ 0.82	24.80 $\pm$ 0.98	<i>p</i> = 0.138
ACD(mm)	3.63 $\pm$ 0.22	3.61 $\pm$ 0.24	<i>p</i> = 0.736
CCT( $\mu$ m)	527.93 $\pm$ 21.63	531.17 $\pm$ 30.13	<i>p</i> = 0.635
BCVA (logMAR)	-0.047 $\pm$ 0.06	-0.053 $\pm$ 0.06	<i>p</i> = 0.653
IOP	All eyes between 10 and 21 mmHg		
Hypertension	No case		

AL: axial length. ACD: anterior chamber depth. CCT: central corneal thickness. BCVA: best-corrected visual acuity. IOP: intraocular pressure.

the analysis. The mean spherical refractive error (D), AL (mm), ACD (mm), CCT ( $\mu$ m), and BCVA (LogMAR) in the study group were  $-3.19 \pm 1.78$  D,  $25.15 \pm 0.82$  mm,  $3.63 \pm 0.22$  mm,  $527.93 \pm 21.63$   $\mu$ m, and  $-0.047 \pm 0.06$ , respectively, compared to  $-2.89 \pm 1.84$  D,  $-2.89 \pm 1.84$  mm,  $3.61 \pm 0.24$  mm,  $531.17 \pm 30.13$   $\mu$ m, and  $-0.053 \pm 0.06$ , respectively, in the control group. There was no significant difference between the two groups. There were no hypertension cases among the participants, and the intraocular pressure of all eyes was normal, with a 10–21 mmHg range (Table 2).

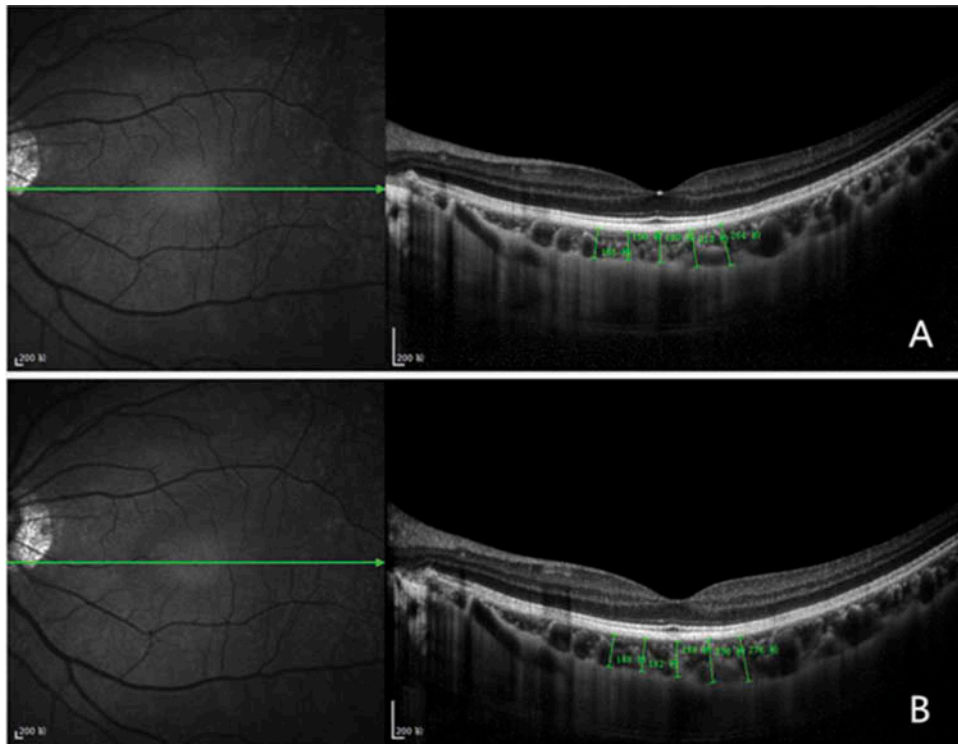
The choroidal thickness measurements comparing the study and control groups at the baseline showed no significant difference (Table 3). The post-treatment, mean choroidal thickness measurements 1 h following Longevinex<sup>®</sup> ingestion are shown in Table 2. At the fovea, 1000  $\mu$ m and 500  $\mu$ m temporal to the fovea, and 1000  $\mu$ m and 500  $\mu$ m nasal to the fovea, choroidal thickness measurements of the study group were  $267.73 \pm 84.19$   $\mu$ m (mean  $\pm$  SD),  $257.53 \pm 65.16$   $\mu$ m,  $259.30 \pm 80.85$   $\mu$ m,  $254.63 \pm 82.03$   $\mu$ m, and  $254.17 \pm 71.93$   $\mu$ m, respectively, at the baseline, which increased to  $284.57 \pm 92.39$   $\mu$ m (mean  $\pm$  SD),  $273.23 \pm 81.94$   $\mu$ m,  $275.50 \pm 91.48$   $\mu$ m,  $271.70 \pm 91.39$   $\mu$ m, and  $268.87 \pm 79.39$   $\mu$ m, respectively, 1 h after Longevinex<sup>®</sup> intake (*p* < 0.05).

However, the choroidal thickness measurements of the control group showed no significant difference at all five points (Table 3). At the fovea, 1000  $\mu$ m and 500  $\mu$ m temporal to the fovea, and 1000  $\mu$ m and 500  $\mu$ m nasal to the fovea, the values obtained were  $269.73 \pm 71.40$   $\mu$ m (mean  $\pm$  SD),  $260.47 \pm 73.52$   $\mu$ m,  $262.07 \pm 81.01$   $\mu$ m,  $251.13 \pm 67.75$   $\mu$ m, and  $249.30 \pm 71.11$   $\mu$ m, respectively, at the baseline, which changed to  $268.43 \pm 70.15$   $\mu$ m (mean  $\pm$  SD),  $260.67 \pm 74.44$   $\mu$ m,  $262.03 \pm 80.73$   $\mu$ m,  $250.47 \pm 66.80$   $\mu$ m, and  $249.40 \pm 71.26$   $\mu$ m, respectively, 1 h after the placebo intake (*p* > 0.05). The changes in choroidal thickness measurements of the study and control groups are illustrated in Figures 2 and 3, respectively. Thus, Longevinex<sup>®</sup> caused a significant increase in choroidal thickness compared with the placebo.

**Table 3.** The mean choroidal thickness measurements of the study at the baseline, and 1 h following oral Longevinex<sup>®</sup> and placebo intake.

	Mean $\pm$ SD or N( $\square$ )		<i>p</i> value	Mean $\pm$ SD or N( $\square$ )		<i>p</i> value	<i>p</i> value	<i>p</i> value
	Baseline ( $\mu$ m)			1 h after baseline ( $\mu$ m)				
	Longevinex <sup>®</sup>	placebo		Longevinex <sup>®</sup>	placebo			
T1000	257.53 $\pm$ 65.16	260.47 $\pm$ 73.52	0.871	273.23 $\pm$ 81.94	260.67 $\pm$ 74.44	<i>p</i> = 0.026	<i>p</i> = 0.794	
T500	259.30 $\pm$ 80.85	262.06 $\pm$ 81.01	0.895	275.50 $\pm$ 91.48	262.03 $\pm$ 80.73	<i>p</i> = 0.040	<i>p</i> = 0.97	
F	267.73 $\pm$ 84.19	269.73 $\pm$ 71.40	0.921	284.57 $\pm$ 92.39	268.43 $\pm$ 70.15	<i>p</i> = 0.033	<i>p</i> = 0.183	
N500	254.63 $\pm$ 82.03	251.13 $\pm$ 67.75	0.858	271.70 $\pm$ 91.39	250.47 $\pm$ 66.80	<i>p</i> = 0.044	<i>p</i> = 0.447	
N1000	254.17 $\pm$ 71.93	249.30 $\pm$ 71.11	0.793	268.87 $\pm$ 79.39	249.40 $\pm$ 71.26	<i>p</i> = 0.017	<i>p</i> = 0.904	

F: choroidal thickness at fovea. N500:choroidal thickness at 500  $\mu$ m nasal to the fovea.N1000:choroidal thickness at 1000  $\mu$ m nasal to the fovea. T500: choroidal thickness at 500  $\mu$ m temporal to the fovea. T1000: choroidal thickness at 1000  $\mu$ m temporal to the fovea.



**Figure 2.** Infrared image (left) and EDI-OCT image(right) from one participant in the study group. A: Baseline. B: One hour after oraling Longevinex<sup>®</sup>. There is an increase ( $p < 0.05$ ) in choroidal thickness before versus 1 h after oraling Longevinex<sup>®</sup>. The choroidal thickness in each EDI-OCT scan was measured at five points (the left blue line represents the EDI-OCT scan position and the right blue lines represent detecting five points).



**Figure 3.** Infrared image (left) and EDI-OCT image (right) from one participant in the control group. C: Baseline. D: One hour after oraling placebo. There is no significant change ( $p > 0.05$ ) in choroidal thickness before versus 1 h after oraling placebo. The choroidal thickness in each EDI-OCT scan was measured at five points (the left blue line represents the EDI-OCT scan position and the right blue lines represent detecting five points).

## Discussion

The choroid is a highly vascular tissue and plays an important role in maintaining the retinal pigment epithelium (RPE) and outer retina. The choroid provides oxygen, nutrients, and immunocompetent cells to the outer retina, and it maintains the highly metabolically active, photoreceptor cells; otherwise, choroidal hypoperfusion could result in outer retinal dysfunction.<sup>28,29</sup> It was reported that choroidal thickness increased at two points in time, 1 and 3 h after ingestion of 100 mg of sildenafil citrate due to the vasodilatory effect of sildenafil on choroidal circulation.<sup>30</sup> Another paper mentioned that nicotine caused a significant decrease in choroidal thickness following oral intake.<sup>9</sup> These two substances could both cause changes in choroidal thickness by influencing ocular blood flow.

Shen et al. reported that 2–3-mm length of abdominal aorta vascular tissue (cut from male Sprague Dawley® rats), perfused with a dose of  $5 \times 10^{-5}$  mol/L resveratrol solution, which explored the time-dependence of vasodilation, began to dilate in 30 s and achieved the maximum 100% dilation rate in 20 min.<sup>11</sup> In a vivo animal experiment, acute renal vasodilation was observed with 5.0 mg/kg resveratrol bolus administration within 30 s.<sup>12</sup> In a study involving 19 human participants, 1 h after their oral consumption of either resveratrol or placebo supplements at the lowest dose (30 mg), flow-mediated dilatation (FMD) of the brachial artery was significantly increased ( $p < 0.05$ ) in the resveratrol group compared to the placebo group.<sup>13</sup> Another randomized, double-blind, placebo-controlled study revealed that 22 healthy adults received either the placebo or one of two doses (250 and 500 mg) of trans-resveratrol. Resveratrol administration resulted in dose-dependent increases in cerebral blood flow at the end of the 45-min absorption phase.<sup>10</sup> These cited studies reported that resveratrol could dilate blood vessels in vitro and in vivo animals and humans, respectively. In this study, we present in vivo data of humans to support the previous hypothesis that resveratrol is a vasodilator and has an acute effect at a low dose.

Resveratrol was reported to have a protective role in endothelial cells by modulating mitochondrial oxidative stress.<sup>31</sup> In this respect, it was shown that resveratrol beneficially modulated platelet nitric oxide (NO) synthesis<sup>32</sup> and enhanced endothelium-dependent<sup>14</sup> vasorelaxation by promoting endothelial NO synthase (eNOS).<sup>10</sup> Nagaoka et al. successfully provided evidence of two independent mechanisms by which resveratrol produced vasorelaxation and thus vessel diameter dilation within isolated retinal arterioles.<sup>5</sup>

Previously, choroidal perfusion has been mostly assessed by swept-scan, high-frequency digital ultrasound and colored Doppler imaging.<sup>8</sup> The limited ability to measure choroidal thickness variations in the living state has prevented satisfactory documentation of its function. Information regarding choroidal thickness in normal eyes that is based primarily on histological results does not necessarily reflect the true measurements of this dynamic tissue.<sup>33</sup> However, choroidal thickness measurements in previous studies were performed by using ultrasound, which is also a less precise method.<sup>34</sup> We present a system that has allowed us to make accurate measurements of the choroid by using optical coherence techniques, shown to be superior to histology in this aspect.<sup>35</sup> Moreover, the advancements of OCT and its image software,

especially the introduction of EDI-OCT, have provided clear images of bilateral, diffusely thickened choroid by using longer wavelengths. The ability to obtain a true, noninvasive “optical biopsy” of choroidal thickness can be characterized in vivo.<sup>23,36</sup> Some articles reported higher levels of reproducibility and repeatability of manual measurements of choroidal thickness when SD-OCT was used.<sup>37–39</sup> Improved in vivo visualization of the choroid and measurement of choroidal thickness using OCT will likely enhance our understanding of a variety of ophthalmic diseases in the future.<sup>23</sup>

With advancing age, choroidal thickness decreases because of the increase in small vessel diseases.<sup>40</sup> Moreover, AMD is the leading cause of blindness among older people, aged typically over 65 years.<sup>41</sup> Studies using laser Doppler flowmetry showed significant reduction in choroidal blood flow and volume in eyes with AMD.<sup>42</sup> An article reported that in accordance with abnormal choroidal circulation and reduced choriocapillaris, the choroid was significantly thinner in AMD patients when compared with the age-matched, normal control group. The authors assumed that choroidal thickness represented choroidal circulation and the choriocapillaris.<sup>7</sup> The choroidal thickness also decreased in both the macula and peripapillary areas in diabetic eyes with clinical signs of DR compared with the control group.<sup>6</sup> The most common cause of vision loss in the working age population is DR.<sup>43</sup> Thus, the pathophysiological role of choroidal circulation in the natural history of DR, mainly in outer retinal impairment, should be reconsidered.<sup>6</sup> Our study also provides further insights into possible actions in the field of ophthalmology for curing eye diseases, such as AMD and DR.

Longevinex® was shown to exhibit an unparalleled margin of safety at high doses, superior to resveratrol alone.<sup>18</sup> Gastrointestinal symptoms were the main adverse reactions, including nausea, flatulence, abdominal discomfort, and diarrhea.<sup>44</sup> Other side effects involved nasopharyngitis and dizziness, but these were all reported in individual subjects only.<sup>45,46</sup> Overall, adverse effects had been minor.<sup>47</sup> However, no adverse effects were indicated among our study group participants.

Our study is limited by its sample size and young participants. Moreover, including more than one time point to detect choroidal thickness would be important, considering the unstable pharmacokinetic properties of resveratrol. Preclinical studies suggested that resveratrol was readily absorbed,<sup>48</sup> then it is almost completely conjugated in the liver. And glucuronides and sulfates are the main metabolites of resveratrol. Flavonoids, such as quercetin, delay the hepatic metabolism of resveratrol that might improve immediate bioavailability of this compound.<sup>20</sup> However,  $\beta$ -glucuronidase is ubiquitous in humans and could convert such metabolites back to trans-resveratrol. In addition, the sulfate conjugates will be hydrolyzed to trans-resveratrol in the target tissues.<sup>49,50</sup> Some reports indicated that after oral resveratrol intake, its concentration in the blood peaked at 30 min–1.5 h.<sup>44,51–54</sup> Based on these pharmacokinetic properties of resveratrol, we measured choroidal thickness 1 h after consumption. Thus, we demonstrated resveratrol’s acute effect on improving ocular blood flow. However,

further investigation with a larger study population and a longer follow-up period is needed.

In summary, this study demonstrated a statistically significant increase in choroidal thickness, as determined by EDI-OCT, 1 h after Longevinex® ingestion compared with baseline measurements. There was no significant increase in the control group. These results and prior studies with resveratrol suggest a relationship between choroidal thickness and choroidal blood flow. This may have a role in the treatment of ocular diseases, such as macular degeneration and diabetic retinopathy.

## Acknowledgments

Shuaishuai Wang designed and conducted the experiment, analyzed the data, and prepared the manuscript. Nived Moonasar, Xiao Xiao, and Tiemei Yin assisted in conducting the experiment. Robert N. Weinreb assisted in study design, data analysis, and preparation of the manuscript. Xufang Sun helped design the experiment, assisted in the discussion and manuscript preparation and review, and as the guarantor of this work, took responsibility for the integrity of the data and accuracy of the data analysis. We thank Xiaoqin Yan, Wei Chen, Xiaolan Xu, and Wansheng Wang for their suggestions regarding our experiment.

## Declaration of interest

This study was approved by the Huazhong University of Science and Technology Institutional Review Board and Ethics Committee. The authors report no conflicts of commercial or financial interest.

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