

α -Lipoic Acid Treatment Improves Vision-Related Quality of Life in Patients with Dry Age-Related Macular Degeneration

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Dry form of age-related macular degeneration (AMD) constitutes 90% of AMD cases, and it is characterized by the formation of drusen under the retina and the slow breakdown of the light-sensing cells in the macula, which causes a gradual loss of central vision. Since oxidative stress is involved in the pathogenesis of dry AMD, α -lipoic acid (LA) with antioxidant properties was selected, and its effect on anti-oxidative markers and visual quality in patients with dry AMD was assessed. A total of 100 dry AMD patients (60-83 years old) were randomly assigned to LA treatment group ($n = 50$) and placebo control group ($n = 50$). We measured the serum superoxide dismutase (SOD) activity, an important marker of antioxidant defense, best-corrected visual acuity (BCVA), contrast sensitivity, and Chinese-Version Low Vision Quality of Life (CLVQOL) before and after LA or placebo intervention. Pearson correlation coefficients were calculated to explore the relationship between contrast sensitivity values and CLVQOL scores. There was a statistically significant increase in serum SOD activity after LA intervention. The CLVQOL score was improved significantly after LA treatment. The contrast sensitivity measured at middle and low spatial frequency was significantly higher after LA treatment. CLVQOL scores were positively correlated with contrast sensitivity at low spatial frequency (3 cyc/degree) in LA-treated group. These results indicate that LA treatment improves vision-related quality of life in patients with dry AMD probably by increasing antioxidant activity. Thus, LA can be regarded as a promising agent for the treatment of AMD.

Keywords: α -lipoic acid; age-related macular degeneration; antioxidant; Low Vision Quality of Life; superoxide dismutase

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Introduction

Age-related macular degeneration (AMD) is a common eye condition and causes damage to the macula, which is a small spot near the center of the retina and responsible for sharp and central vision (Snodderly 1995). AMD is becoming increasingly prevalent as the leading cause of vision loss in elderly populations (Nowak 2006; Ferris et al. 2013). AMD is etiologically complex, and multiple genetic and environmental factors influence disease progression. To date, accumulating evidence suggests that mitochondrial dysfunction in the retinal pigment epithelium (RPE) caused by oxidative stress plays an important role in the development of AMD (Feher et al. 2006). Previous studies have indicated that antioxidant supplementation may be benefi-

cial in delaying the development and progression of AMD (Chong et al. 2007; Coleman et al. 2008). AMD is classified into dry (atrophic) or wet (neovascular) type, with the former exhibiting disarrangement of the pigment epithelium and cluster of drusen (Bird et al. 1995). Compared with the wet form, dry AMD constitutes approximately 90% of the AMD cases without available treatment. Accordingly, in this study we chose dry AMD as the focus to explore the possible therapy.

α -Lipoic acid (LA), a biological antioxidant, exists in mitochondria as an essential cofactor for several mitochondrial enzyme complexes including pyruvate dehydrogenase and α -ketoglutarate dehydrogenase (Rochette et al. 2013). There has been a great deal of attention toward the antioxidant properties of LA. LA is a potent antioxidant which

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can induce all three cellular protective mechanisms (Voloboueva et al. 2005). As a coenzyme in mitochondria, the physiologically relevant (*R*) form of LA has been found to improve the age-associated decline in mitochondrial function (Liu 2008). In addition, LA can produce an indirect anti-oxidative effect through promoting the activity of γ -glutamylcysteine ligase (GCL) which controls the rate of glutathione (GSH) synthesis, and other phase II enzymes which contribute to the detoxification of xenobiotic compounds (Fujita et al. 2008; Yang et al. 2010). LA is a scavenger of hydroxyl radicals, singlet oxygen, peroxyxynitrite and nitric oxide (Rochette et al. 2013) and has been suggested to chelate transition metal ions (Smith et al. 2004). The antioxidant properties make LA a candidate for protection against oxidative injury in neurodegenerative disorders and diabetic syndrome (Vincent et al. 2008). LA is effective in protection of RPE cells against mitochondrial dysfunction resulting from oxidant-induced damage in vitro (Jia et al. 2007). There is currently no effective cure available for AMD patients, and efforts to slow down or stop the progression of AMD through antioxidant supplementation are essential. Superoxide dismutase (SOD) catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide and serves as the body's most potent defense in nearly all cells with its anti-oxidative nature (Buettner 2011). The downregulation of SOD has also been postulated to be the potential stimulator for the pathogenesis of AMD (Tokarz et al. 2013).

In the present study, we evaluated the benefit of LA in dry AMD patients by analyzing serum SOD activity, visual acuity and vision-related quality of life before and after LA treatment, providing evidence for clinical application.

Materials and Methods

Study subjects and intervention

One hundred patients (60-83 years old) with dry form of AMD were recruited between May 2014 and May 2015 from the Department of Ophthalmology at Qilu Hospital of Shandong University. AMD was diagnosed according to a complete ophthalmic examination and met the following criteria: (1) No diabetes or hypertension that may affect retinal function; (2) Lens opacity and ocular media remained transparent; (3) No family history of glaucoma, IOP was normal and $C/D \leq 0.4$; (4) No high myopia, uveitis and retinal detachment which may affect the macular function. All subjects gave their written informed consent to the study, which was approved by the ethics committee of Qilu Hospital of Shandong University. Because smoking is an important risk factor for AMD, in this study the smoking status of all subjects was not changed before and after the treatment. The patients were randomly assigned to LA administration (treatment group, $n = 50$) and placebo (control group, $n = 50$). In treatment group, the patients received oral administration of LA capsules (0.2 g daily, Jiangsu Wanhe Pharmaceuticals Co., Ltd.) for 3 months, and in control group the patients received oral administration of vitamin C (1.0 g daily, Tianjin Pharmaceuticals Group Co., Ltd.) for 3 months. All subjects attended follow-up visits every month.

Quality control

We developed standard practices of clinical trial for unified training of researchers, including report forms, physical examination of patients, scoring process, data input and follow-up during the study. Regular monitoring was performed by quality control personnel. Two researchers conducted report form entry twice to ensure uniformity of research data. Researchers did not conduct the clinical trial statistical analysis.

Measurement of serum SOD activity

The SOD activity was measured using xanthine-xanthineoxidase as a superoxide generator. The reduction of nitroblue tetrazolium (NBT) was followed at 550 nm with an assay kit (Nanjing Jiancheng Biological Engineering Research Institute, Nanjing, China) according to the manufacturer's instructions. The data was expressed in unit of activity per milliliter of serum (U/mL).

Chinese-Version Low Vision Quality of Life (CLVQOL) Questionnaire

As a valid instrument for measuring quality of life in AMD with high reliability and validity, CLVQOL questionnaire (originally translated from the original English-Language Low Vision Quality of Life questionnaire) was used to evaluate the change in vision-related quality of life. There was 25 closed-ended items which were graded on a 5-point ordinal scale between 5 (no problem due to vision) and 1 (great difficulty due to vision) in the questionnaire. These items can also be scored as "no longer possible due to vision" or as "not relevant to them in their daily lives." A CLVQOL composite score ranged from 0 (binocular no perception of light) to 125 (the best vision function). The CLVQOL were grouped into 4 subscales: (1) general vision and lighting (items 1 to 7); (2) mobility (items 8 to 12); (3) psychological adjustment (items 13 to 16); (4) reading, fine work, and activities of daily living (items 17 to 25).

Measurement of best-corrected visual acuity (BCVA)

BCVA of all patients before treatment or 3 months after treatment was measured with Snellen chart, while Snellen visual acuity was converted to logMAR units.

Measurement of contrast sensitivity (CS)

Contrast sensitivity was tested on the CSV-1000 E contrast sensitivity chart test face at 2.5 m by an examiner who was blind to the group. The test was performed after the patient was adapted to the room luminance. The data presents measurement of contrast sensitivity at 3, 6, 12, 18 cycles per degree (cpd).

Statistical analyses

Means and standard deviation were calculated. Data of serum SOD, BCVA, CS and CLVQOL were analyzed by the one-way ANOVA (SPSS version 21.0, Chicago, USA). Pearson correlation coefficients were calculated to explore the relationship between contrast sensitivity values and CLVQOL scores.

Results

Basic demographic information of recruited patients

The 100 AMD patients (54 male and 46 female) aged between 60 and 83 (mean age of 71.46 ± 7.56 years) were recruited in the current study (Table 1). There were no significant differences in age, sex, tobacco smoking, alcohol use, and body mass index between the treatment group and

Table 1. Demographic characteristics of the participants.

	Treatment group (n = 50)	Control group (n = 50)	t, χ^2	P
Age	70.86 ± 7.74	72.06 ± 7.38	0.79	0.43
Sex	26/24	28/22	0.16	0.69
Tobacco smoking	12	16	0.79	0.37
Alcohol use	7	5	0.38	0.54
Body mass index	23.9±3.28	24.6±4.03	0.95	0.34
Lesioned disk area	0.84 ± 0.23	0.79 ± 0.31	0.99	0.32
Disease duration (y)	3.2 ± 1.5	3.5 ± 1.7	0.94	0.35

Table 2. Serum SOD, BCVA and CLVQOL in treatment and control group.

	Treatment group (n = 50)		Control group (n = 50)	
	Pre-treat	3 mon post-treat	Pre-treat	3 mon post-treat
SOD (U/ml)	156.48 ± 37.65	189.53 ± 41.22* ^Δ	149.26 ± 39.91	152.64 ± 36.19
BCVA (LogMAR)	0.64 ± 0.34	0.66 ± 0.41	0.61 ± 0.39	0.63 ± 0.42
CLVQOL	73.53 ± 17.89	82.6 ± 19.36* ^Δ	74.33 ± 16.82	72.81 ± 18.05

*P < 0.05, statistically significant compared with pre-treat group. ^ΔP < 0.05, statistically significant compared with control group.

Table 3. Contrast sensitivity in treatment and control group.

	Treatment group (n = 50)		Control group (n = 50)	
	Pre-treat	3 mon post-treat	Pre-treat	3 mon post-treat
3 cyc/degree, log	0.90 ± 0.29	1.02 ± 0.28* ^Δ	0.89 ± 0.32	0.87 ± 0.29
6 cyc/degree, log	1.11 ± 0.33	1.26 ± 0.39*	1.19 ± 0.39	1.15 ± 0.36
12 cyc/degree, log	0.85 ± 0.31	0.92 ± 0.30	0.84 ± 0.33	0.88 ± 0.35
18 cyc/degree, log	0.46 ± 0.36	0.51 ± 0.34	0.49 ± 0.33	0.44 ± 0.31

*P < 0.05, statistically significant compared with pre-treat group. ^ΔP < 0.05, statistically significant compared with control group.

control group.

Change of serum SOD, BCVA and CLVQOL in dry AMD patients before and after treatment

As shown in Table 2, the serum SOD activity was significantly higher in patients after LA treatment (189.53 ± 41.22 U/ml), compared to the activity before the treatment (156.48 ± 37.65 U/ml). The increase in the serum SOD activity may reflect the anti-oxidative effect of LA administration. CLVQOL scores was 73.53 ± 17.89 before LA treatment and 82.6 ± 19.36 after treatment (P < 0.05), and the value did not change significantly before and after treatment in control group. These results indicate that CLVQOL scores were improved significantly by LA treatment. The value of BCVA did not change significantly in both treatment and control groups.

Changes of contrast sensitivity in dry AMD patients after treatment

The contrast sensitivity measured at middle (6 cyc/degree) or low spatial frequency (3 cyc/degree) was significantly higher after LA treatment than before treatment (P < 0.05, Table 3). There was no significant difference in contrast sensitivity at high spatial frequency (P > 0.05).

Correlation of CLVQOL score and contrast sensitivity

There was a positive correlation between CLVQOL score and contrast sensitivity at low (3 cyc/degree) but neither middle nor high spatial frequency in LA-treated group (Table 4). The Pearson correlation coefficient between CLVQOL scores and contrast sensitivity at all spatial frequency in control group showed no positive results.

Table 4. Correlation of CLVQOL score and contrast sensitivity in treatment and control group.

	Treatment group (n = 50)		Control group (n = 50)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
3 cyc/degree, log	0.44	0.00	0.10	0.45
6 cyc/degree, log	0.25	0.14	0.14	0.22
12 cyc/degree, log	0.13	0.25	0.21	0.19
18 cyc/degree, log	0.08	0.52	0.16	0.28

Discussion

Although multiple factors have been disclosed (Coleman et al. 2008), the causes and development of AMD are not fully understood. Oxidative stress is one of the important factors in the etiology of AMD (Jager et al. 2008; Jarrett and Boulton 2012). Oxidant injury to mitochondria may lead to oxidative damage and results in mitochondrial dysfunction which is important in the development of AMD (Jarrett et al. 2008). Some factors such as old age, smoking, blue light illumination and lower dietary antioxidant levels produce oxidative damage caused by elevated oxidative stress and increase the risk of AMD (Jager et al. 2008). Lipid peroxidation has been reported to play a vital role in the pathogenesis of AMD. In AMD patients there were increased serum level of oxidative stress markers such as lipid peroxidation and reductions in the antioxidant defense system compared with controls (Totan et al. 2001; Evereklioglu et al. 2003; Baskol et al. 2006). The susceptibility to lipid peroxidation in the retina is very high and increases with ageing in the macular region. The process of RPE phagocytosis increases the formation of oxidative stress and generates large amount of endogenous reactive oxygen species (Tate et al. 1995; Jin et al. 2001). Furthermore, RPE cells contain abundant photosensitizers, and exposure to intense light caused increased production of reactive oxygen species (Gaillard et al. 1995).

As a cofactor for the mitochondrial enzymes, pyruvate and α -ketoglutarate dehydrogenases, LA may exert protection effect for mitochondrial function through improvement of mitochondrial metabolism (Goraca et al. 2011). Several studies in different systems have demonstrated that LA exhibits significant antioxidant activity (Liu 2008; Ghibu et al. 2009). The E3 subunit of three mitochondrial enzyme complexes, NADH-dependent dihydrolipoamide dehydrogenase, reduces lipoate to dihydrolipoate. This dihydrolipoic acid can generate different antioxidants by reacting directly with various oxidants such as thiol antioxidants, vitamin C and α -tocopherol (Flora 2009). Both oxidized and reduced forms of LA have property of a free radical scavenger (Voloboueva et al. 2005). Oxidized form of LA exhibits anti-oxidative activity through direct quenching singlet oxygen, hydroxyl radicals and hydrogen peroxide. LA exerts protective effects against oxidant-induced dam-

age via its metal chelating capacity (Liu 2008). In cultured lens epithelial cells, LA works by decreasing transferrin-bound iron uptake, increasing concentration of ferritin and reduces the size of mitochondrial labile iron pools (Goralska et al. 2003). Cellular GSH plays a critical role in protection of RPE cells against oxidative injury (Nelson et al. 2002). Glutathione S-transferase, an intracellular detoxification enzyme, produces protective response for RPE cells in oxidative environment and potentially prevent the development of AMD (Liang et al. 2005). It has been suggested that reduced form of antioxidant GSH is elevated by LA (Goraca et al. 2011). LA has been demonstrated to support increased the uptake of cysteine — a limiting component in GSH synthesis, thereby increasing its concentration.

SOD2 knockdown in mice causes apoptotic death of RPE cells (Justilien et al. 2007), suggesting SOD2 protects against oxidation-induced apoptosis in mouse RPE (Kasahara et al. 2005). SOD overexpression in transgenic rats can protect the RPE against oxidative stress-mediated damage and apoptosis (Organisciak and Vaughan 2010). The risk of developing chronic disease increases with the age because the SOD activity decreases with age (Khansari et al. 2009). In the present study, we found that after three months of oral LA treatment there was a significant increase of serum SOD activity in dry AMD patients, suggesting the increase in the body's ability to respond to oxidative damage. On the other hand, Jia et al. (2011) reported that serum SOD activity was 87.12 ± 13.22 U/mL in AMD patients and 79.91 ± 11.80 U/mL in normal controls, although the difference was not statistically significant. Likewise, SOD activity was marginally higher in AMD patients than in controls in another study, which could be explained by a compensatory regulation in response to increased oxidative stress (Nowak et al. 2003). By contrast, other reports showed no significant association between AMD and SOD activity (De et al. 1996; Delcourt et al. 1999). These conflicting results suggest that serum SOD activity may be influenced by various factors, including the status of oxidative stress. In addition, there was a noticeable difference in the values of the serum SOD activity, compared to the present study, which was probably due to the variation in the protocol and experimental setting. Indeed, the normal range of serum SOD activity determined by our enzyme kinetic method was 129~216 U/ml. Importantly, in the present study, we found

the significant increase in serum SOD activity after LA supplementation, which is associated with the improvement of the visual quality of dry AMD patients. These results suggest that LA, an effective antioxidant, may be one promising means of preventing progression of vision loss in AMD.

CLVQOL is originally translated from the English-language Low Vision Quality of Life Questionnaire (LVQOL) that emerges as an important outcome measurement for people with low vision (Wolffsohn and Cochrane 2000). The CLVQOL can satisfy conventional psychometric criteria, has strong discrimination power between healthy and low vision populations, and be able to identify who might benefit from low vision care (Zou et al. 2011). Current study showed that CLVQOL scores was significantly improved by LA treatment, and the value did not vary significantly in control group. Although BCVA was also elevated by LA treatment, the change in BCVA did not reach statistically significant level. QOL can be influenced by visual acuity which is the basis of classifies levels of visual impairment. For patients with bilateral severe visual impairment, their QOL correlates with clinically meaningful changes in visual acuity in either of the two eyes. Even after adjusting for visual acuity, bilateral advanced AMD has a worse impact on QOL than unilateral advanced AMD does (Dong et al. 2004). However, increase in CLVQOL scores did not necessarily parallel the change of BCVA at any condition. We also found that CLVQOL score was positively correlated with contrast sensitivity at low (3 cyc/degree) spatial frequency in LA-treated patients. These results indicate that LA improved low-frequency contrast sensitivity through antioxidant effect and thus elevated CLVQOL score.

Contrast sensitivity (CS) defines the boundary between the visible and invisible and there may be reduction of peak contrast sensitivity despite with normal acuity (Pelli and Bex 2013). CS reflects function of the low-level properties such as photoreceptor density, retinal receptive field size, ganglion cell characteristics and the organization of geniculostriate pathways. In this study, no significant change occurred in the high-frequency contrast sensitivity before and after LA treatment, probably because the enrolled patients had long disease history, severity, poor vision and impairment of retinal function at fovea. The improvement of low and middle contrast sensitivity and patients' self report of visual quality were presumed to result from the treatment-induced restoration of photoreceptor cells which were damaged but not dead around AMD lesion.

In conclusion, LA treatment can significantly elevate the SOD activity and improve the visual quality of dry AMD patients, suggesting that LA may be an effective strategy for reducing the occurrence or promoting recovery of macular degeneration. Further investigations are needed for both studying molecular mechanisms and evaluating the clinical efficacy.

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Conflict of Interest

The authors declare no conflict of interest.

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