Review Article

Recommendations for Dietary Supplement Use for Dry Eye by Ophthalmologists in Japan and Their Personal Use: A Survey Report

Motoko Kawashima

Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

Miki Uchino

Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

Sachiko Inoue

Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

Norihiko Yokoi

Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Kazuo Tsubota

Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan

ABSTRACT

Background: Dietary supplement use has not been studied well in non-Western societies. There have been no surveys on the prevalence of dietary supplement use among professionals, in particular, ophthalmologists, and is unknown to what extent ophthalmologists recommend dietary supplements to their dry eye patients.

Methods: A survey questionnaire was administered online and per mail in February 2017 to approximately 600 ophthalmologists members of the Dry Eye Society, Japan. The ophthalmologists were asked questions on their personal use of dietary supplements and whether they recommended dietary supplements to their patients.

Results: The 196 ophthalmologists who responded to this survey were aged between 28 and 77 years (mean age, 50.2 ± 10.1 years) and 59.2% were women. A total of 67.9% recommended supplements to their patients; the main target diseases were age-related macular degeneration (97.0%) and dry eye (45.9%). For dry eye, the three most commonly cited reasons for recommending supplements in practice included, 1) expectation of a positive effect, 2) requests by patients, and 3) availability of a product manufactured by a reputable company. The three most commonly recommended components included lactoferrin, the omega-3 fatty acids

Abbreviations: DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; SD: Standard Deviation

Background

According to national surveys, including the National Health and Nutrition Examination Survey (NHANES), dietary supplements are being used by the majority of adults in the USA [1,2]. While the prevalence of dietary supplement intake has also increased in Japan [3], few reports on the use of

docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and lactic acid bacterium. The ophthalmologists who reported not recommending dietary supplements cited lack of evidence (54.8%), lack of information on which supplements to recommend to patients (38.5%), and high cost (increasing the patients' out of pocket charges) (35.6%) as their main reasons. Regarding their own approach to a healthy diet and lifestyle, almost all ophthalmologists reported adopting a healthy lifestyle such as exercising, positive thinking, and implementing dietary restrictions. A total of 62.2% stated currently using dietary supplements. Those who reported not using any supplements cited sufficient evidence as the main prerequisite to consider using them (75.7%).

Conclusion: The majority of ophthalmologists in this study recommended dietary supplements to their dry eye patients following to macular degeneration patients. Many also reported using dietary supplements regularly as part of their own approach to a healthy diet and lifestyle. More evidence and data on their effectiveness and side effects on dietary supplements should be required for their appropriate and safe use.

Keywords: Dietary supplements; Survey; Ophthalmologists; Health habits

supplements by health professionals and the general population exist. In particular, no study has assessed the use of dietary supplements among healthcare professionals and physicians; moreover, it has not been analyzed if physicians recommend dietary supplements to their patients.

Recently, several studies reported that dietary supplements such as omega-3 fatty acids and lactoferrin are beneficial in the treatment and/or prevent of dry eye disease [4-8]; however, it is not clear if dietary supplements are used in practice. Therefore, we conducted a survey to examine if ophthalmologists in Japan recommended dietary supplements to their patients and their reasons for doing so (or not). We also assessed their own supplement intake and health habits.

Methods

The study sample consisted of ophthalmologist members of the Dry Eye Society in Japan who specialize on the ocular surface. A survey questionnaire including questions on their personal use of dietary supplements use and if they recommended supplements to their patients was administered online and per mail in February 2017 to 600 ophthalmologists of the society. The ophthalmologists were asked to identify the specific products they used and answered questions about their personal attitudes on supplements, health and wellness. Moreover, they were asked whether they "ever recommended dietary supplements" to their patients, to specify the target diseases, and the reasons for recommending or not recommending supplements for dry eye.

Ethics, consent and permissions: This research followed the tenets of the Declaration of Helsinki, and the study protocol was approved prospectively by the Ethical Review Board of the Haneginomori Eye Clinic, Tokyo, Japan. Informed consent was obtained from all subjects.

Results

A total of 196 ophthalmologists (mean age 50.2 ± 10.1 years, range 28-77 years; 59.2% women) responded to the

survey. Table 1 summarizes the demographic characteristics of the study sample.

Of the surveyed ophthalmologists, 67.9% reported recommending dietary supplements to their patients. They cited the main target diseases of age-related macular degeneration (97.0%) and dry eye (45.9%) (Table 2).

For the treatment of dry eye disease, the ophthalmologists applied a variety of eye drops such as diquafosol, rebamipide, and hyaluronate sodium. Moreover, they recommended measures of self-care, including lid hygiene (61.7%) and the use of warm compresses (71.4%). A total of 31.1% of the ophthalmologists reported that they recommended dietary supplements to their dry eye patients (Table 3).

In this study, we founded out that a total of 31.1% of the ophthalmologist recommended dietary supplements to their dry eye patients.

The top three reasons for recommending dietary supplements in practice were 1) expectation of a positive treatment effect (85.2%), 2) requests by patients (39.3%), and 3) availability of a product manufactured by a reputable company (36.1%). The three dietary supplements the ophthalmologists recommended most included lactoferrin, the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and lactic acid bacterium. Almost 70% of who recommended dietary supplements reported that they received a positive response by using their patients (Table 4).

Table 1: Demographic characteristics of the ophthalmologists included in the study (N=196).					
$\mathbf{S}_{\text{ov}} = \mathbf{N} \left(\boldsymbol{\theta} \right)$	Female	116 (59.2)			
Sex, $N(70)$	Male	80 (40.8)			
Age, years, mean \pm SD (range)		$50.2 \pm 10.1 \ (28-77)$			
	Private clinic	128 (65.3)			
Workplace, N (%)	Hospital	65 (33.2)			
	Other	3 (1.5)			
Patients seen per month, mean \pm SD		829.4 ± 595.1			
Dry eye patients seen per month, mean \pm SD		192.4 ± 191.2			

Table 2: Specifics of the recommendations for dietary supplements.				
		Ν	%	
Decementaria de dista un sur alors arte to	Yes	133	67.9	
Recommended dietary supplements to	No	61	31	
opininalihology patients	No answer	2	1	
Target disease, if answering "yes"*	Age-related macular degeneration	129	97.0	
	Dry eye	61	45.9	
	Asthenopia	42	31.6	
	Presbyopia	14	10.5	
	Allergic conjunctivitis	8	6.0	
	Cataract	8	6.0	
	Glaucoma	6	4.5	
	Other	5	3.8	

*Multiple answers were allowed.

		N	%
Eyedrops	Artificial tears	157	80.1
	Hyaluronate sodium	180	91.8
	Diquafosol	192	98.0
	Rebamipide	184	93.9
	Serum eye drops	57	29.1
	Low-concentration steroids	140	71.4
	Cyclosporine	18	9.2
	Others	7	3.6
Punctal plugs		170	86.7
Lid hygiene		121	61.7
Lid-warming device		140	71.4
Dietary Supplements		61	31.1
Others		12	6.1
*Multiple answers were allow	wed.		

Table 3: Types of treatments recommended for dry eye by the ophthalmologists (N = 196).

		Ν	%
	Expectation of positive treatment effect	52	85.2
	Requests by patients	24	39.3
account for recommonding	Availability of a product manufactured by a reputable company	22	36.1
iotary supplements*	Sufficient evidence	16	26.2
letary supplements	Quality of product has been proven	10	16.4
	Prevention of dry eye	9	14.7
	Yielding a profit	1	1.6
	Excellent	2	3
ationt foodbook on	Very good	13	21
unlement use	Good	27	44
applement use	No change	19	31
	Worsening of condition	0	0
	Lactoferrin	44	72.1
	Omega-3 fatty acids (DHA, EPA)	37	60.7
	Lactic acid bacterium	34	55.7
	Lutein	22	36.1
	Anthocyanin	13	21.3
	Astaxanthin	12	19.7
upplements ingredients	Vitamin E	12	19.7
ecommended to dry eye	Vitamin A	8	13.1
atients*	Vitamin C	7	11.5
	Multi-vitamin product	8	13.1
	Vitamin B2	5	8.2
	Hyaluronate sodium	4	6.6
	Co-enzyme Q10	4	6.6
	Vitamin B12	4	6.6
	Zinc	4	6.6
	Others	20	32.8

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid *Multiple answers were allowed.

The ophthalmologists who reported not recommending dietary supplements to their patients cited the following top three reasons: 1) lack of evidence (54.8%), 2) lack of

information on which types of supplements to recommend to patients (38.5%), and 3) high cost (increasing the patients' charges (35.6%) (Table 5).

Table 5: Reasons cited b	y ophthalmolo	gists for not recommend	ling dietarysup	pplements to dry	y eye	patients (N	V = 135)	
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	Ν	%
Lack of evidence	74	54.8
Lack of information on which supplement to recommended to patients	52	38.5
High cost (increasing patients' charges)	48	35.6
Patients are unlikely to buy supplements	32	23.7
Not believing that supplements are effective	27	20.0
Unclear synergistic effects with other supplements or drugs	23	17.0
Bothersome to explain the supplements to patients such as how to use and side effects	16	11.9
It not being an approved medication	15	11.1
Worry about excessive taking of ingredients	11	8.1
Little profit for the clinic	3	2.2
Do not want overdose of dietary supplement	2	1.5
Manufacturer of supplement is not trustworthy	1	0.7
Others	10	7.4
No answer	10	7.4

Regarding their own approach to a healthy diet and lifestyle, the majority of the ophthalmologist reported implementing at least some types of health behaviors such as exercise, positive thinking, and dietary restrictions; only 3.1% reporting doing nothing to improve their health (Table 6). Of all surveyed ophthalmologists, 62.2% stated that they currently were using dietary supplements. In contrast, 37.8% never used any supplements; they cited "bothersome to continue to take" as their main reason. The majority of surveyed ophthalmologists stated that sufficient evidence is required as the main prerequisite for using dietary supplements personally.

Discussion

We conducted a survey to ophthalmologists on their dietary supplement recommendation to their patients and their personal use of supplements. To the best of our knowledge, this is the first study to investigate this supplement usage in Japan. Our survey revealed that the majority (67.9%) of the Japanese ophthalmologists included in this study recommended dietary supplements to their patients. The main target diseases included age-related macular degeneration (97.0%), followed by dry eye (45.9%, most commonly, lactoferrin, DHA/EPA, and lactic acid bacterium). Those who reported not recommending dietary supplements cited lack of evidence, lack of information on which supplements to recommend to patients, and high cost as their main reasons. Many ophthalmologists (62.2%) reported currently using dietary supplements.

The efficacy of dietary supplements to treat age-related macular degeneration is already widely recognized among Japanese ophthalmologists based on available evidence; this is strongly supported by the Age-Related Eye Disease Study (AREDS) report [9-12]. Notably, we found that almost half of the ophthalmologists in this study recommended supplements to treat dry eye. Dry eye disease is linked to aging and has been shown to be associated with oxidative stress [13,14]. In our study, 31.1% of the ophthalmologists reported using supplements in addition to eye drops in practice to treat dry eye. This survey was launched approximately one year after

the dietary supplement Optiade DE (WAKAMOTO, Co, Ltd, Tokyo, Japan) for the treatment of dry eye became available; we hypothesize that the rate of its use will be increasing. In this study, the main three ingredients the ophthalmologists recommended to their patients were lactoferrin, DHA/EPA, and lactic acid bacterium. These are included in Optiade DE, whose efficacy and safety have already been confirmed [15]. Thus, this product which includes combination of lactoferrin, DHA/EPA and lactic acid bacterium might be already recognized among supplement recommended ophthalmologists; a total of 68% of those who recommended dietary supplements received a good response for dry eye treatments.

We found out that the ophthalmologists who reported not recommending dietary supplements to their patients stated a lack of evidence (54.8%) and lack of information on what supplement to recommend to patients (38.5%) as their main reasons. The efficacy and safety of several dietary supplement products are being assessed in Japan.

In this study, 62.2% of the ophthalmologists reported currently using dietary supplements. Previous reports in the USA reported a prevalence of regular dietary supplement intake among healthcare professionals of between 70% and 80% [16-19]. Thus, the rate in our study is relatively low. It is possible that Japanese physicians are more critical of supplement use. Importantly, 75.7% stated that sufficient evidence is required for recommending dietary supplements.

With the increased use of dietary supplements in Japan, adverse events related to supplement intake have been reported [20]. Reports on such adverse events should be considered when treating dry eye disease. More evidence is required for the safe use of dietary supplements.

This study has several limitations. As the ophthalmologists included in this study were members of the Dry Eye Society in Japan, the study sample might not be representative of Japanese ophthalmologists. The average age of the ophthalmologists we surveyed was 50.2 years, and they

	pritrainologists health-related habits and personal use of suppler	1000000000000000000000000000000000000	
Self-care (health)		Ν	%
Non-smoking		151	77.0
Exercising regular	ly	107	54.6
Positive thinking		93	47.4
Early bed time, ear	rly wake up	71	36.2
	Calorie restriction	107	54.6
	Carbohydrate-restricted diet	90	45.9
	Fat-restricted diet	49	25.0
Dietary habits	Eating fiber-rich foods	97	49.5
Dictury hubits	Eating foods containing lactic acid bacteria	90	45.9
	Adequate hydration	105	53.6
	Appropriate alcohol intake	54	27.6
	Others	7	3.6
Others		14	7.1
No self-care, as per	r above	6	3.1
Personal use of dietary sup	plements		
Current use)			
a. Regular use (da	aily)	83	42.3
b. Every 2 to 3day	ys	12	6.1
c. Occasional use		27	13.8
Never used dietary	supplements	74	37.8
For those reporting that the	ey never used dietary supplements (N = 74)		
	Bothersome to continue to take	37	50.0
	Do not believe that they are effective	24	32.4
Reasons for not	Lack of evidence	22	29.7
using supplements	Do not know which is the best supplement for me	14	18.9
	It not being an approved medication	9	12.2
	High cost	8	10.8
	Worry about excessive taking of ingredients	7	9.5
	Unclear synergistic effect with other supplements or drugs	6	8.1
	Bad taste, difficult to swallow	5	6.8
	do not want overdose of dietary supplement	3	4.1
	Manufacturer of supplement is not trustworthy	3	4.1
	Difficult to buy	2	2.7
	Others	4	5.4
	Sufficient evidence	56	75.7
	Easy to swallow	23	31.1
Prerequisites for	High quality	22	29.7
personally taking	Reasonable price	21	28.4
supplements	Easy to buy	20	27.0
	Others	6	8.1
	No answer	3	4.1

Table 6: Ophthalmologists' health-related habits and personal use of supplements (N = 196).

showed a very high level of adopting healthy habits. These factors might have affected our results (i.e., since they adopted healthy habits themselves, they might have recommended more supplements). The relatively small number of respondents is an additional limitation.

Conclusion

In our study, 45.9 % of the ophthalmologists recommend dietary supplements to their dry eye patients. The vast majority reported adopting a healthy lifestyle (96.9%) and 62.2% stated

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currently using dietary supplements regularly as part of their own approach to a healthy diet and lifestyle. More evidence and information on dietary supplements should be required for their appropriate and safe use.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research followed the tenets of the Declaration of Helsinki, and the study protocol was approved prospectively by the Ethical Review Board of the Haneginomori Eye Clinic, Tokyo, Japan.

AVAILABILITY OF DATA AND MATERIAL

The dataset supporting the conclusions of this article is included within the article.

COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

MK and TK designed the study. MK wrote the manuscript and TK revised the manuscript. They approved the final manuscript.

REFERENCES

- Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, et al. Dietary supplement use by US adults: Data from the National Health and Nutrition Examination Survey, 1999-2000. Am J Epidemiol 2004; 160: 339-349.
- Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, et al. Dietary supplement use in the United States, 2003-2006. J Nutr 2001; 141: 261-266.
- Imai T, Nakamura M, Ando F, Shimokata H. Dietary supplement use by community-living population in Japan: Data from the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). J Epidemiol 2006; 16: 249-260.
- Kawashima M, Kawakita T, Inaba T, Okada N, Ito M, et al. Dietary lactoferrin alleviates age-related lacrimal gland dysfunction in mice. PLoS One 2012; 7: e33148.
- Kawashima M, Nakamura S, Izuta Y, Inoue S, Tsubota K. Dietary supplementation with a combination of Lactoferrin, Fish Oil, and Enterococcus faecium WB2000 for treating dry eye: A rat model and human clinical study. Ocul Surf 2016; 4: 255-263.
- Dogru M, Matsumoto Y, Yamamoto Y, Goto E, Saiki M, et al. Lactoferrin in Sjogren's syndrome. Ophthalmology 2007; 114: 2366-2367.
- Kawakita T, Kawabata F, Tsuji T, Kawashima M, Shimmura S, et al. Effects of dietary supplementation with fish oil on dry eye syndrome subjects: randomized controlled trial. Biomed Res 2013; 34: 215-220.

- Miljanović B, Trivedi KA, Dana MR, Gilbard JP, Buring JE, et al. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr 2005; 82: 887-893.
- Domalpally A, Clemons TE, Danis RP, Sadda SR, Cukras CA, et al. Peripheral retinal changes associated with agerelated macular degeneration in the age-related eye disease study 2: Age-related eye disease study. Ophthalmology 2017; 124:479-487.
- Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol 2001; 119: 1417-1436.
- Age-Related Eye Disease Study 2 Research Group. Lutein+zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The age-related eye disease study 2 (AREDS2) randomized clinical trial. JAMA 2013; 309: 2005-2015.
- Chew EY, Clemons TE, Agrón E, Sperduto RD, Sangiovanni JP, et al. Ten year follow-up of age related macular degeneration in the age-related eye disease study: AREDS report no. 36. JAMA Ophthalmol 2014; 132: 272-277.
- Tsubota K, Kawashima M, Inaba T, Dogru M, Ogawa Y, et al. The era of anti-aging ophthalmology comes of age: Antiaging approach for dry eye treatment. Ophthalmic Res 2010; 44: 146-154.
- 14. Kawashima M, Kawakita T, Okada N, Ogawa Y, Murat D, et al. Calorie restriction: A new therapeutic intervention for age-related dry eye disease in rats. Biochem Biophys Res Commun 2010; 397: 724-728.
- 15. Kawashima M, Nakamura S, Izuta Y, Inoue S, Tsubota K. Dietary supplementation with a combination of lactoferrin, fish oil and *Enterococcus faecium* WB2000 for treating dry eye: A rat model and human clinical study. Ocul Surf 2016; 14: 255-263.
- 16. Gardiner P, Woods C, Kemper KJ. Dietary supplement use among health care professionals enrolled in an online curriculum on herbs and dietary supplements. BMC Complement Altern Med 2006; 6: 21.
- Kemper KJ, Gardiner P, Woods C. Changes in use of herbs and dietary supplements (HDS) among clinicians enrolled in an online curriculum. BMC Complement Altern Med 2007; 7: 21.
- Dickinson A, Boyon N, Shao A. Physicians and nurses use and recommend dietary supplements: Report of a survey. Nutr J 2009; 8: 29.
- Dickinson A, Shao A, Boyon N, Franco JC. Use of dietary supplements by cardiologists, dermatologists and orthopedists: Report of a survey. Nutr J 2011; 10: 20.

20. Ide K, Yamada H, Kawasaki Y, Noguchi M, Kitagawa M, et al. Reporting of adverse events related to dietary supplements to a public health center by medical staff: A survey of clinics and pharmacies. Ther Clin Risk Manag 2016; 12: 1403-1410.

ADDRESS FOR CORRESPONDENCE:

Motoko Kawashima, Department of Ophthalmology, Keio University School of Medicine, Tokyo, Japan; Tel: 81(3) 3353-1211; E-mail: motoko-k@a3.keio.jp

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