Unity in diversity: Working towards a common goal to improve optometry and vision research in Europe

The year 2021 has started in the tracks of an ongoing global pandemic with the need for developing new ways of providing health care. The challenges imposed by the pandemic forced primary health care practitioners including optometrists and dispensing opticians to convert most face-to-face consultations and follow-up visits to virtual or telephone consultations to prevent the spread of the disease. New collaborations have evolved within and across disciplines in both research and clinical practice. This will continue to benefit both patients and communities in the future. For example, the use of telemedicine between clinicians, as reported by De Lott and colleagues from the University of Michigan, increased by up to 86.2% after the pandemic in response to the increasing demand. The optometric community has successfully adapted to delivering both patient care and management, and education digitally.

During the pandemic, we have all experienced the necessity of being able to adapt to rapidly changing knowledge and digest vast amounts of digital information, and the increased demand this puts on our ability to be critical and develop evidence based clinical practice. As new knowledge and tools are becoming part of our everyday practice, new challenges and the need for new skill sets become apparent. More research is required into digital communication, digital and visual health literacy, and how optometrists can contribute to promoting health in all patients with diverse conditions and needs. Clinicians, academics, and researchers have all been innovative and embraced new measures to continue to evolve optometric health care and services.

There have also been some important developments to the journal during the first half of 2021. In order to adapt and promote SJOVS as a relevant and high-quality journal for research within optometry and vision science, we have added "online first" articles once new articles are accepted and in-press. This enables a rapid and easy open access of new research, increasing the visibility of SJOVS among both readers and authors. This spring, SJOVS has had three online-first articles with one of these getting over 100 views.

Another change has been to expand the editorial board with three new members, and to establish an advisory board with three well known international researchers. All these researchers come from different countries and have different optometric backgrounds and research experience. With their diverse competence they will contribute to developing SJOVS into a leading European journal for research within optometry and vision science.

On behalf of SJOVS, we wish you all a safe and peaceful summer.

SJOVS Editorial board

Reference: De Lott, L. B., Newman-Casey, P. A., Lee, P. P., Ballouz, D., Azzouz, L., Cho, J., Valicevic, A. N., & Woodward, M. A. (2021). Change in Ophthalmic Clinicians' Attitudes Toward Telemedicine During the Coronavirus 2019 Pandemic. Telemedicine journal and e-health: the official journal of the American Telemedicine Association, 27(2), 231–235. https://doi.org/10.1089/tmj.2020.0222

Behind blue eyes – Ocular nutritional supplements on the Scandinavian market in relation to current evidence

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Abstract

Nutritional supplements for eye health are very popular, but the size of the market makes it difficult to grasp for the clinician. To guide patients and clinicians in the subject it would therefore be valuable to have a list of available products and their content. The purpose of this study was to investigate the ocular nutritional supplements available on the Scandinavian market and how their doses relate to current evidence.

A list of nutritional supplements for ocular health available on the Scandinavian market was compiled by structured internet searches, and the products and their contents were compared with current evidence and legislated upper tolerable levels.

Out of 104 products on the Scandinavian market, only two products reached the Age–Related Eye Disease Study 2 (AREDS2)–formula at the recommended dose. One additional product reached the same formula if the recommended dose was exceeded.

As only two nutritional supplements for ocular health on the Scandinavian market reached the AREDS2–dose at recommended dose, clinicians offering such substances need to have knowledge not only about the substances but also of the doses. In the future it would be welcome if the health claims for nutritional supplements were based on placebo–controlled intervention studies, to avoid ineffective products.

Keywords: Ocular nutritional supplements, AMD, AREDS

Introduction

Nutritional supplements are popular in the Scandinavian countries. It is estimated that six in ten people in Denmark (DTU Fødevareinstituttet, 2016) and Norway (NAFKAM, 2017) take some kind of nutritional supplement. In 2014, nutritional supplements for more than 200 million euro were sold in Sweden (Svensk Egenvård, 2016). The share of nutritional supplements for eye health is unknown in the Scandinavian countries, but accounts for about 7% in the USA (Yong et al., 2015). As the European Union (EU) classifies nutritional supplements as food, their safety and efficacy are not regulated by the European Medical Agency (EMA) but by The European Food Safety Authority (EFSA). Statements of beneficial medical effects are only permitted according to pre–approved regulations. Food containing at least 15% of the recommended daily dose of vitamin A, B2, zinc or docosahexaenoic acid are allowed to be sold with the health claim, "contributes to the maintenance of normal vision" (The European Commission, 2012) (see Table 1).

EFSA declares nutritional supplements as valid for cataract, dry eyes and impaired night vision. This statement is supported by five books and four articles about cell metabolism, deficiency diseases in animal models and case reports from humans. References to placebo–controlled intervention studies are lacking (European Food Safety Authority, 2009a; 2009b; 2010). As the Scandinavian populations generally do not have deficiencies of the substances mention above, an addition of them would in most cases not lead to improved vision (Livsmedelsverket, 2020a). Even if the health claims are scientifically true, they might therefore mislead the customer.

Table 1: *Vitamins and minerals permitted in EU to use the health claim "contributes to the maintenance of normal vision"*

	Minimum dose	Upper tolerable limit
Vitamin A (mg)	0.12	3
Vitamin B2 (mg)	0.24	–
Zinc (mg)	2.25	25
DHA	40 mg per 100 g	–

Note: DHA = Docosahexaenoic acid

Even if EFSA does not mention age related macular degeneration (AMD), this is the ophthalmologic field where nutritional supplements have been studied most extensively. At the beginning of the 1990s, the National Eye Institute in USA initiated the placebo controlled Age–Related Eye Disease Study (AREDS). During a period of over 6 years, around 3000 patients with no to advanced AMD were followed. The results showed that a specific formula of vitamin C, E, beta–carotene, zinc and copper could reduce the risk of intermediate AMD progressing to advanced disease to 24%, compared to 30% in the placebo group during the 6.3 year follow–up period (AREDS Research Group, 2001). This means a relative risk reduction of 20% (6%/30%). A more useful way of presenting the result might be absolute risk reduction (ARR), in this case 6% (30%–24%). This means if 100 patients were treated, six would benefit from the treatment. Another way of expressing this is the number needed to treat (NNT) which is the inverse of the ARR. This means that 16 patients had to be treated for one to benefit (1/0.06). In patients with no or early AMD, no reduced risk could be proven. None of the patients showed improvement of their disease (AREDS Research Group, 2001). AREDS2 was initiated in 2006 and followed 4000 patients in four arms: placebo, the Omega–3 acids Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA), lutein and zeaxanthin, and finally all four together. All patients were also given the original AREDS–formula, or a modified formula without beta–carotene and reduced dose of zinc. AREDS2 confirmed the result from AREDS but could not prove any additional effects. As all groups were given the original formula, it is still unknown if lutein/zeaxanthin or DHA/EPA are effective alone. The main result was that the effects remain even if beta–carotene is replaced by lutein/zeaxanthin and the dose of zinc is reduced (AREDS2 Research Group, 2013) (see Table 2). Prolonged use of supplements with zinc has been shown to increase the risk of prostate cancer (Zhang et al., 2009), which is also the case for vitamin E (Klein et al., 2011). Vitamin E could also increase the effect of oral anticoagulant treatment (Bartlett & Eperjesi, 2005) and might even increase total mortality (Bjelakovic et al., 2012; Miller et al., 2005).

AREDS and AREDS2 are the largest studies of the effects of antioxidant treatment for AMD, but not the only ones. Several others have been published with fewer participants and shorter follow–up periods. Unfortunately, none of them have

proven that other preparations could prevent or slow down the progress of AMD (Evans & Lawrenson, 2017a; 2017b). Intake of Omega–3 is correlated to less AMD in observational studies, but the connection between intervention and reduced risk has not been proven (Lawrenson & Evans, 2015). Nutritional supplements containing Omega–3 and Omega–6 fatty acids have also been used for treatment of dry eye syndrome (DES). Even if the effects are promising, evidence is not yet strong enough to recommend the use of fatty acids as a stand–alone treatment for DES (Molina-Leyva et al., 2017). The ability of antioxidant vitamin supplements to prevent or slow down the progression of cataract and glaucoma has also been studied, but there is still insufficient evidence to draw a conclusion (Bussel & Aref, 2014; Mathew et al., 2012). However, a smaller study has shown that vitamin B3 in doses of 1500–3000 mg per day improve retinal ganglion cell function in patients with different forms of glaucoma in the short term (Hui et al., 2020). The long–term effects for visual function are, however, still under investigation. Bilberry products are used to treat various diseases of the eye, but no beneficial effects have been proven. In a review of 30 studies of the effect of bilberry on night vision, only five satisfied scientific requirements whereof four showed no correlation (Canter & Ernst, 2004). Another review of the effect of bilberry on cataract, retinopathy and night vision did not show any clear relationship (Ulbricht et al., 2009).

Table 2: *Content and dosage of formulas based on AREDS/AREDS2.*

	AREDS formula	AREDS2 formula
Vitamin C (mg)	400	400
Vitamin E (IU)	400	400
Beta–carotene (mg)	15	–
Copper (mg)	2	2
Lutein (mg)	–	10
Zeaxathin (mg)	–	2
Zinc (mg)	80	80 (25 with low dose)

Note: IU = International Units (equals 0.67 mg natural d–Alpha tocopherol or 0.9 mg synthetic dl–Alpha tocopherol.)

The Danish Ophthalmologic Society recommends the AREDS–formula to patients with wet AMD in one eye, to patients with several large drusen and visual impairment, and even to patients with drusen and relatives with visual impairment caused by AMD (Dansk Oftalmologisk Selskab, 2015). The Danish legislation demands that retailers of nutritional supplements report the name and list of contents of their product to the Danish Veterinary and Food Administration (DFVA) (Miljø- og Fødevareministeriet, 2015). Information from all registered products is available on the Internet (Fødevarestyrelsen, 2017). DVFA does not control the content (Miljø- og Fødevareministeriet, 2017a), but products considered hazardous might be removed from the market. For example, a supplement for eye health was forbidden during the spring of 2018 because of a zinc dose of 80 mg per day (Fødevarestyrelsen, 2018). Maximum intake levels for vitamins and minerals were established in 1996 (Miljø- og Fødevareministeriet, 1996). The old legislation did not allow the AREDS2–formula in contrast to the new rules from 2018. The updated 2018 legislation no longer presents maximum levels (ML) but uses upper tolerable levels (UL). Those doses are considered safe in healthy individuals, even after prolonged use. Levels are given for men and women and children divided into five age groups. The limit for vitamin E was increased more than 6–fold in 2018. Vitamin C still has no UL, but a temporary guidance value is presented in the absence of further knowledge (Miljø- og Fødevareministeriet, 2017b). The legislation in Norway also demands that retailers of nutritional supplements should report the names of products to the Norwegian Food Safety Authority. However, this is only done on a regional level and no public register is constructed. In the first established maximum intake levels of vitamins and minerals from 2004, the AREDS–formula was not allowed (Helse- og omsorgsdepartementet, 2004). In the revision from 2017, the maximum levels for all contents of the AREDS–formula were abolished except for vitamin C, where the limit was made equal to the European UL. The remaining maximum levels will be presented as soon as scientific documentation is available (Helse- og omsorgsdepartementet, 2017). Sweden has a similar legislation to Norway with a requirement for regional registration. No maximum levels exist today but the National Food Administration has investigated whether this should be introduced and have written a proposal for consultation (Livsmedelsverket, 2020b). The first limits might be legislated during 2021. The EU has no common ML, but ULs that serve as guiding values (European Food Safety Authority, 2006); (see Table 3).

Table 3: *Recommended national maximum daily dose of vitamins in the AREDS–formula.*

	EU	Denmark	Norway	Sweden (proposal)
	2004 UL	1996 ML / 2017 UL	2004 ML / 2017 ML	2020 ML
Vitamin C (mg)	1000	90 / 670	200 / 1000	1000
Vitamin E (IU)	330	45 / 330	33 / –	330
Zinc (mg)	25	22.5 / 25	25 / –	25
Copper (mg)	5	3 / 5	4 / –	2

Note: UL = Upper tolerable limit, ML = Maximum limit, IU = International units.

The market for nutritional supplements is difficult to grasp as it contains countless ever–changing products with several substances in varying doses. This makes it difficult for a clinician to guide patients in the subject. The purpose of this study was to investigate how nutritional supplements available on the Scandinavian market relate to current evidence on treating eye diseases and to the legislation of upper tolerable limits.

Methods

A list of all nutritional supplements for ocular health available on the Scandinavian market was compiled by structured internet searches June 2018 – January 2019.

The Google main site was used with the phrases +"nutritional supplements" +"maintenance of normal vision" translated into Swedish, Danish and Norwegian. To only include Scandinavian sites the search condition "site:" was used, together with the national domains (*.dk, *.no and *.se). As most companies use the national top–domain, we believe this strategy represents the Scandinavian market. Only supplements with the pre–approved ocular health claim were included (i.e., contributes to the maintenance of normal vision). Products linked to eye health only by their name were excluded, and so were products no longer advertised on the manufacturer's web page but only by a reseller. Only tablets and capsules were included as they are the most cost–effective form as the manufacturer can pack the most material into a given space and therefore also the most common. Powders, oils, and effervescent tablets etc. were excluded. If the recommended daily dose was relative (e.g., 1–2 tablets), the calculation was based on the higher value. If no dose was specified one tablet a day was assumed. The cheapest price without shipping was used and converted to euro in January 2019. The content was thereafter compared with the evidence–based AREDS2–formula with low zinc (see Table 2). Because of a potential effect for DES and glaucoma, the content

of Omega–3 and vitamin B3 was also compared. Even in the absence of evidence, the supplements included in the study were also compared by their content of bilberry, because of its popularity and tradition of use. The content of interest in the included supplements was compared in mg or % of the AREDS2 formula with low dose zinc.

Results

In total 104 nutritional supplements produced by 61 companies were sold with a health claim to maintain normal vision. Zinc was the most common substance and was included in 54% of the supplements, followed by vitamin E (45%) and vitamin A (40%). The doses showed great variation. The products containing vitamin E ranged from 3 to 268 international units (average 32). Seven in ten products contained at least one of the supplements in the AREDS2 formula, but only two reached the AREDS2 formula with low dose zinc in content and dosage in recommended dose (Optivital and Macushield Gold). One additional supplement fulfilled the original AREDS formula with high dose zinc if the recommended dose was exceeded (Cezin pluz), which of course also meant a higher price. A further three products matched the AREDS2–formula by content but not in dosage and to fulfill the dose of vitamins, the amount of zinc had to overstep the upper tolerable limit within the EU (Synvital Pluss, Retisan, Klarin Perfekt). Omega–3 was included in 28% of the products with doses varying from 129 to 3740 mg per day with an average of 974. Vitamin B3 was included in three products with doses ranging from 16 to 50 mg per day. Bilberry (vaccinium myrtillus) was included in 22% of the products with doses varying from 5 to 2000 mg per day with an average of 412. The annual cost varied from 20 to 880 euro per year, with an average of 200 euro (see Table 4 and Appendix).

Table 4: *Summarized content of certain interest in 104 ocular nutritional supplements on the Scandinavian market.*

	Number (proportion)	Average (min–max)
Vitamin C	40 (38%)	128 (4–500) mg
Vitamin E	47 (45%)	32 (3–268) IU
Zinc	56 (54%)	14 (1.5–50) mg
Copper	25 (24%)	1 (0.1–2) mg
Lutein	29 (28%)	12 (1–40) mg
Zeaxanthin	18 (17%)	1 (0.2–2.5) mg
Omega 3	29 (28%)	974 (129–3740) mg
Vitamin B3	3 (3%)	32 (16–50) mg
Bilberry	22 (21%)	412 (5–2000) mg

Note: IU = International units.

Discussion

Among some one hundred ocular nutritional supplements on the Scandinavian market, only two reached the AREDS2–formula in the recommended dose. One additional product met the same formula if the dose was increased. It is therefore difficult for patients to use ocular nutritional supplements in an evidence–based manner without guidance from a clinical expert.

Even if the evidence is not strong enough to recommend Omega–3 fatty acids as a sole treatment for DES, they have shown promising effects in doses between 150–2400 mg/day. Many of the products included in our study reached these levels and could therefore be considered as an option as supplemantary treatment.

The few products that contained vitamin B3 had only a few per cent of the amount used in a recent study of glaucoma (Hui et al., 2020) and were well within the current European upper tolerable level of 900 mg per day (European Food Safety Authority, 2006). Concerning bilberry supplements, these products are still very common. The reason for this might be a strong cultural belief and global legends like that British pilots ate bilberry jam to improve their night vision during World War II. However, there is today no conclusive evidence that bilberry improves any aspect of eye function. There is therefore no difference in evidence of effect between the product with the lowest concentration compared to the product with the highest, even if the concentration of bilberry is 400 times larger in the latter.

This study has several limitations. As the market is ever–changing the supplements may have changed since the compilation of the list. Only products available on the Internet were counted, supplements sold in stores or in other ways were not included. However, this is the first published list of nutritional supplements on the Scandinavian market. The results may be compared with those of Yong et al., who found that among 11 top–selling supplements for ocular health in the USA, only one third contain the AREDS–formula (Yong et al., 2015).

Regulation of the vitamin and nutritional supplements industry is needed both to prevent wasteful spending and to reduce unnecessary risks. However, the studies that motivate the European health claims are not based on good science. In the next revision of the regulations, the inclusion of placebo–controlled interventional studies would be welcome. At the same time, there are several problems in conducting studies on nutritional supplements. The levels of antioxidants are affected by both diet and activities, and compliance might be difficult to supervise over long–term periods. Even if supplements are sold for billions of euros, the industry is small compared with the licensed drugs industry and there is little interest in conducting rigorous experiments with the lack of exclusive rights to the formulas.

The Danish web–register of supplements is probably of great value, both for the state to monitor the market and for the consumer to evaluate different products. As a considerable part of the market has moved to the Internet, local registries would probably be outdated very quickly. None of the Scandinavian countries control the content of nutritional supplements whereupon it is totally up to the producer to ensure the content.

Danish ophthalmologists have the most positive attitude in Scandinavia to nutritional supplements. They recommend AREDS treatment even to patients with mild drusen who have close relatives with vision loss caused by AMD. Due to the previous regulations, only reduced AREDS–formulas are available in Denmark and Norway. Therefore, ophthalmologists need to give instructions to exceed the recommended dose, in Norway as much as six times. The updated regulations will probably make the AREDS–formula available also in Denmark and Norway.

Conclusion

In summary, ocular nutritional supplements constitute a large and complex market with expensive products. Only a few supplements available in Scandinavia meet the evidence–based AREDS2–formula. Knowledge of the market is of value for both clinicians and for decision makers to construct new policies.

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Conflicts of Interest

The authors declare no conflict of interest.

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Appendix – Ocular nutritional supplements available on the Scandinavian market

Content of certain interest in 104 ocular nutritional supplements available on the Scandinavian market in absolute weight or in relation to AREDS2. Total yearly cost is given for recommended daily consumption.

	AREDS2-content with low dose zinc (%)						Omega–3	Vit. B3	Bilberry	Price
Product, Brand	Vit. C	Vit. E	Zink	Cu	Lutein	Zeaxanthin	(mg)	(mg)	(mg)	(€/year)
A–vitamin, Naturdrogeriet										50
AD levertran, Naturdrogeriet							129			70
Aktiv Vital, Nutracare	10%						504			250
Alpha plus öga plus, Alpha plus			80%		200%	38%			700	880
Amdexyn Vision 120 tabletter, Pharma Nord	50%	50%	80%	50%	40%				16	120
Argus Blåbærekstrakt, Vesterålens Naturprodukter (VNP)			2%	60%		60%				330
Asta Omega+, Novo Vita							2400			550
B Vitamin complex tablets, Bulkpowders								50		40
Basica compact, BioVita			20%	50%						420
Bellavista, Mezina	12%	4%	20%	25%					2000	250
Bilberry with Lutein, Amway					100%				105	480
Bio Zink, Pharma Nord			60%							50
Bio–Selen+Sink, Pharma Nord	18%		60%							80
Biopharma Blåbær, Biopharma	8%								250	330
Blue, EFI									280	320
Blue berry original, New Nordic									400	230
Blue Berry Plus Øjenvitamin, New Nordic			40%	50%					400	380
Blue Berry™ Øjenvitamin Omega, New Nordic			40%	50%			500		400	390
Blue Eye, Elexir Pharma		4%	50%		250%				150	180
Blueberry vision, Life	8%	2%	20%		250%				200	180
BlåbærKrekling, Bioform									400	210
Blåbærpillen, New Nordic			16%						400	120
Body science omega–3, Body science							3150			380
Bodylab ZMA, Bodylab			80%							80
Cezilu, Amwo farma	10%	10%	32%		10%	10%				30
Cezin pluz, AMWO Farma[2]		25%	28%	80%	25%	25%	25%			50
Chewable Calamari Omega–3, HappyMe		2%					361			150
Complete Multi 50+ tabletter 60stk, Weifa	15%	4%	28%	45%						50
Daily Vita min, Scitec nutrition	24%		60%	100%						70
DFI A–Vitamin 1500, DFI										40
DFI B2, DFI										70
EPA–GLA+, Biosym							968			330
Evelle, Pharma Nord	12%	4%	30%							490
Eye D, Zentabox	2%		6%		100%	100%				100
Eye health tablet, Myprotein			6%		100%				60	130
Eye Q Kapslar, New Nordic										140
Eye total, Anjo		3%			120%	100%	260			570
Eyewise, Lamberts					206%	40%			400	460
Fitness Pharma blåbær, Enseyes			40%		100%				50	90
Food Grown – Antioxidant boost, Wild nutrition	1%	9%	10%							440
Food Grown – Daily Multi Nutrient for kvinner, Wild nutrition	6%	2%	20%	25%						350
Food Grown – Daily Multi Nutrient spesielt utviklet for tenåringsgutter – 60 kapsler, Wild Nutrition	6%	2%	28%	13%						280
Food Grown – Immune support, Wild nutrition	8%		40%	10%						310
Forever daily, Orkla care	16%	4%	20%	45%						240
Hair and beauty vitamins, Lykli	12%	13%	20%							420
Eye Q, IQ Medical (New Nordic)			1%							110
Klarin Perfekt, Aktivsyn[3]	16%	4%	40%	50%	80%	80%		16	50	290
Komplet 50+, Vitacare	15%	4%	36%				3740			170
Life Extension – Zinc Kapsler, Life extension *			200%							50
Lifeline care Barn kosttilkudd, Lifeline care							503			150
Livol multi total, Livol	15%	4%	36%	45%						80
Longovital 50 +, Solaray	16%	4%	40%							110

	AREDS2–content with low dose zinc (%)						Omega–3	Vit. B3	Bilberry	Price
Product, Brand	Vit. C	Vit. E	Zink	Cu	Lutein	Zeaxanthin	(mg)	(mg)	(mg)	(€/year)
Longovital Kvinde, Biosym	32%	4%	40%							150
Lutein Eyes, Solaray	1%				180%					230
Luteinblå 60 kapslar, Helhetshälsa	32%	7%	56%		300%	55%			200	160
Luzea, Amwo farma					100%	100%				150
Macushield, Alliance Pharma					100%	100%				220
Macushield gold, Alliance Pharma[1]	100%	100%	100%	100%	100%	100%				340
MarinOlive Extra, NaturaMed Pharma		4%					504			220
Maximum Extra, Naturdrogeriet	18%	4%	60%							120
Medox, Medox										540
Mega B2–vitamin, Biosym										130
Mervital Öga, Alpha Plus	20%	13%	40%	25%	200%				5	170
Multi tabs complete, Pfizer	16%	4%								180
Naturens apotek Blåbär, Naturens apotek		4%	128%		40%	50%			200	80
NDS Zn+ Zinc tablet, 90 tab, NDS		1%	60%	50%						90
New Nordic Blåbærpillen, New Nordic			16%						400	120
New Omega, Efi		7%					970			190
Norvital Red Omega, Norvital							552			350
Norvital Smart Omega, Norvital		3%					666			170
Nycoplus B–kompleks, Nycomed										30
Nycoplus geleputer, Nycomed		4%					660			220
Nycoplus høy omega–3 Kaps 1000 mg fiskeolje 120 kapsler, Nycomed							1252			180
Nycoplus Omega 3 basic, Nycomed	18%	11%					866			160
Nycoplus selolje Kaps 162 mg/200 mg/20 mg, Nycomed							600			120
Nycoplus Zink, Nycomed			100%							40
Ocuvite complete, Bausch + Lomb	36%	11%	60%		100%	100%	600			350
Omni Zink3, Biosym			80%							20
Omni–B active, Biosym										210
Omnikrill, Biosym							300			110
Omnimin Pure, Biosym	80%	37%	80%	100%						40
OmniVegan, Omnisym/Biosym	80%	19%	80%	25%						130
OmniX, Biosym	80%	19%	72%	20%						110
Ophtamin 20 Lutein + Zink, Deep sea pharma***	16%	4%	60%	50%	100%	100%	318			180
Optimega D, Soflin Pharma							300			310
Optivital, Soflin Pharma[1]	100%	100%	100%	100%	100%	100%				330
Oxyvision, IQ Medical (New nordic)	40%	3%	80%	5%	60%					230
Pharma eskimo 3, Berthelsen							1300			240
Puori (PurePharma) Omega–3 O3, Medivit							2000			220
Pureviva Omega 3, Medivit										50
Retisan, Pharmex[3]	17%	16%	53%	17%	17%	17%				60
Silica extra, Biosym										110
Strix Forte 120 tabletter, Ferrosan		4%	60%		60%					200
Synvital, Wellvita							1000			40
Synvital Pluss, Synvital[3]	17%	16%	52%	25%	17%	17%				30
TheraTears nutrition, Amwo Farma							1200			230
Total B–complex, Berthelsen								30		70
Ultimate Omega, Nordic naturals							1280			140
Veg–omega3, Solaray							750			180
Vistavital, Wellvita	16%	4%	40%						2000	110
Vita helse omega 3, Vita helse		3%					600			40
Zink, Naturdrogeriet			80%							20
Zink Citrat, Naturdrogeriet			80%							70
Ögonboost forte, Vidasal		4%	50%		400%	125%				160

Note: 1 – AREDS content and dosage in recommender dose. 2 – AREDS content and dosage in exceeded dose. 3 – AREDS content but not dosage even in exceeded dose.

Bakenfor blå øyne – Kosttilskudd for øyehelse tilgjengelig på det skandinaviske marked relatert til dagens kunnskap

Sammendrag

Kosttilskudd rettet mot øyehelse er svært populære, men antall tilgjengelige produkter på markedet gjør det uoversiktlig for klinikere. Som en veiledning for pasienter og klinikere ville det være verdifullt å ha en liste over tilgjengelige produkter og deres innhold. Målet med denne studien var å undersøke kosttilskudd rettet mot øyehelse som er tilgjengelige på det skandinaviske marked og hvordan anbefalt dosering samsvarer med dagens kunnskap.

Ved hjelp av strukturerte internettsøk ble det utarbeidet en liste over kosttilskudd rettet mot øyehelse som er tilgjengelige i Skandinavia, og produktene og deres innhold ble sammenliknet med oppdatert kunnskap og maksimal tillatt dose.

Av 104 produkter tilgjengelige i Skandinavia var det kun to som nådde anbefalingen fra Age–Related Eye Disease Study 2 (AREDS2) ved anbefalt døgndose. I tillegg nådde ett produkt anbefalingen fra AREDS2–studien dersom døgndosen ble økt.

Siden kun to kosttilskudd tilgjengelig på det skandinaviske markedet oppfyller anbefalingen fra AREDS2–studien ved anbefalt døgndose, er det nødvendig at klinikere som tilbyr disse kosttilskuddene har kunnskap ikke bare om innholdet, men også om doseringen. For å unngå ineffektive produkter vil det være nyttig om fremtidige helsepåstander for kosttilskudd er basert på randomiserte, kontrollerte studier.

Nøkkelord: Kosttilskudd rettet mot øyehelse, AMD, AREDS

Dietro gli occhi blu – Supplementi nutrizionali per gli occhi nel mercato Scandinavo in relazione alle correnti evidenze scientifiche

Riassunto

I supplementi nutrizionali per la salute oculare sono molto popolari oggi giorno, ma la loro dimensione nel mercato li rende difficili da comprendere per il clinico. Per guidare i pazienti e i clinici nell'argomento potrebbe essere utile avere una lista dei prodotti disponibili e del loro contenuto. Lo scopo di questo studio e' quello di ricercare quali siano tutti i supplementi nutrizionali per gli occhi disponibili nel mercato Scandinavo e come il loro utilizzo e' relativo alle correnti evidenze scientifiche.

Una lista di tutti i supplementi nutrizionali per la salute ocular disponibile nel mercato Scandinavo e' stato compilata attraverso una ricerca strutturata su internet, i prodotti e i loro contenuti sono stati comparati con le correnti evidenze scientifiche e i loro livell massimi di tollerabilita' secondo la legislazione.

Su 104 prodotti presenti nel mercato Scandinavo, solo due prodotti raggiungono la dose raccomandata del "Age–Related Eye Disease 2 (AREDS2)–formula". Un altro prodotto ha raggiunto la stessa formula ma solo nel caso di un sovradosaggio.

Essendo che solo due supplementi nutrizionali per la salute oculare disponibili nel mercato Scandinavo hanno raggiunto la dose raccomandata dallo studio AREDS2, i clinici che offrono tali sostanze devono conoscere non solo la sostanza stessa ma anche le dosi utili. Nel futuro, sarebbe utile avere informazioni su tali prodotti basandosi su studi d'intervento placebo–controllo per evitare l'utilizzo di prodotti ineffettivi.

Parole chiave: Supplementi nutrizionali per gli occhi, AMD, AREDS

Case finding of dry eye disease in Norwegian optometric practice: a cross-sectional study

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Abstract

Optometrists are primary eye care providers, and it is essential that they efficiently identify patients who will benefit from dry eye management. The aim of the study was to explore case finding of dry eye disease (DED) in optometric practice.

A cross-sectional study examining dry eye symptoms and signs in 186 patients (18–70 years of age) attending a routine eye examination, with DED defined according to the criteria of the Tear Film and Ocular Surface Society Dry Eye Workshop II. Standard statistical tests were used, and clinical diagnostics were explored using sensitivity, specificity, and receiver-operating curve (ROC) statistics.

Fifty-six patients were contact lens wearers, and they were significantly younger than the non-contact lens wearers (mean age 35 (SD = 1) versus 48 (± 2) years). The mean best corrected visual acuity (BCVA) in the better eye was 1.0 (± 0.1) (decimal acuity). There was no difference in BCVA between contact lens wearers and non-contact lens wearers. The mean Ocular Surface Disease Index (OSDI) score was 22 (± 19), and 138 patients had at least one positive homeostasis marker. Eighty-six had DED, 52 had signs without symptoms, and 23 had symptoms without signs of DED. The sensitivity and specificity of OSDI in detecting any positive homeostasis marker were 62% and 54%, respectively. In all, 106 patients had meibomian gland dysfunction (MGD), of which 49 were asymptomatic. In a ROC analysis, an OSDI ≥ 13 showed a diagnostic ability to differentiate between patients with a fluorescein breakup time (FBUT) < 10 seconds and a fluorescein breakup time ≥ 10 seconds, but not between patients with and without staining or MGD.

The majority of patients had dry eye signs and/or dry eye symptoms. Routine assessment of FBUT and meibomian glands may enable case finding of DED in optometric practice.

Keywords: dry eye disease, Ocular Surface Disease Index, meibomian gland dysfunction, tear breakup time, ocular staining

Introduction

The Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) defines dry eye disease (DED) as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig et al., 2017). The prevalence of DED varies from 5% to 50%, depending on the study population and diagnostic criteria, and is higher among females, in older age groups, and among people of Asian ethnicity (Stapleton et al., 2017). DED is associated with ocular pain and irritation, blurred vision, and anxiety and depression, and may limit daily activities and reduce work effectiveness and quality of life. Consequently, DED has significant socioeconomic implications (Li et al., 2012; Stapleton et al., 2017; Uchino et al., 2014; Wan et al., 2016).

According to the TFOS DEWS II report, the diagnosis of dry eye should include assessment of both dry eye symptoms and tear film homeostasis markers (Wolffsohn et al., 2017). When DED is confirmed, further testing for sub-classification of DED and grading of severity is needed as treatment should be tailored to the type and severity of DED. Tests that differentiate evaporative dry eye (EDE) from aqueous deficient dry eye (ADDE) are essential as these conditions are managed differently (Jones et al., 2017).

Visual function is affected in DED, and decreased vision and transient blurring of vision are common complaints in DED patients (Ishida et al., 2005). Meibomian gland dysfunction (MGD) is the leading cause of EDE and associated ADDE. Among people with DED, 13% to 50% have MGD (Arita et al., 2019; Uchino et al., 2006; Viso et al., 2011). In people over 40 years of age, 38% to 68% have MGD, dependent on population and applied diagnostic criteria (Stapleton et al., 2017). Patients may have MGD without symptoms; these patients are often undiagnosed (Blackie et al., 2010). The TFOS International Workshop on Meibomian Gland Dysfunction (MGD report) suggests that meibomian gland expression should be part of routine examination in adults and that dry eye work-up should be undertaken in patients with MGD regardless of symptoms (Tomlinson et al., 2011).

Optometrists are primary eye care providers, and it is essential that they efficiently identify patients who will benefit from dry eye management. Studies report significant differences in examination of dry eye patients and a potential to enhance the identification of patients at risk of DED (Downie et al., 2013; Downie et al., 2016; van Tilborg et al., 2015), consequently indicating a need to improve and standardise the examination and diagnosis of DED in optometric practice. The aim of this study was to explore case finding of DED in general Norwegian optometric practice.

Methods

The study had a cross-sectional design. The study population was recruited from people attending for a routine eye examination by one dedicated optometrist in each of three Krogh Optikk practices in Trondheim and Oslo, Norway. To minimize observer bias, the optometrists followed written instructions on how to perform the dry eye examination, and standardised equipment was used for all patients. All patients aged 20 to 70 years attending for an eye examination or a contact lens fitting/follow-up during the period between 15th December 2015 and 1st February 2016 were invited to participate. All patients were given oral and written information and gave informed consent to take part in the study. Patients with other known ocular surface inflammations, previous trauma affecting the tear film examination, or known hypersensitivity to lissamine green and/or fluorescein were excluded from the study.

Data collection

The scheduled routine examination was undertaken, including patient history of contact lens wear, the use of systemic medication and computer screens, as well as decimal visual acuity at six metres equivalent distance. Further, a full dry eye examination was performed. The dry eye examination included the Ocular Surface Disease Index (OSDI) questionnaire, assessment of tear meniscus height (TMH), fluorescein tear breakup time (FBUT),

corneal and conjunctival staining, meibum expressibility, and meibum quality. The sequence of tear film tests was the same for all patients, starting with the least invasive tests first.

The participants started by answering the OSDI questionnaire. The OSDI questionnaire consists of 12 questions about symptoms, visual function, and environmental triggers, based on patients' experience of symptoms in the previous week. Each question was answered on a scale from 0 (none of the time) to 4 (all of the time). The total composite score (0–100) was calculated according to the formula of Schiffman et al. (2000). A normal ocular surface score is in the range of 0–12; a score of 13–22, 23–32, or 33–100 represents mild, moderate, or severe dry eye symptoms, respectively (Miller et al., 2010; Schiffman et al., 2000).

The tear meniscus height (TMH) was then examined with a slit lamp. The width of the slit was adjusted to be identical to the height of the tear meniscus, and the width of the slit in millimetres was recorded as the TMH. The fluorescein tear breakup time (FBUT) was measured by wetting a fluorescein strip with sterile saline solution and shaking off the excess saline; the strip was then carefully applied to the lower temporal conjunctiva starting with the right eye. There was one application of fluorescein in each eye, and no break between the examination of right eye and left eye. The FBUT time was observed using 10 times slit lamp magnification, cobalt blue light, and a yellow barrier filter. The patient was instructed to blink twice and then look straight ahead with their eyes open. The time in seconds from the last blink to the first dry spot appearing was measured by stopwatch and recorded. If the patient blinked before the tear film break was observed, the time to first blink was recorded. The measurement was repeated three times for each eye, and the mean value for each eye was calculated and recorded as the FBUT time. The FBUT for the worst eye was used for analysis.

For corneal and conjunctival staining, a strip impregnated with a mixture of 1.5 mg fluorescein and lissamine green was wetted with saline solution and applied to the lower temporal fornix. Corneal and conjunctival staining were observed using 16 times slit lamp magnification, using cobalt blue light with a yellow barrier filter, and white light, respectively. The staining was graded (0–5) according to the Oxford grading scheme (Bron et al., 2003).

Meibomian glands in the central part of the lower eyelid were examined for gland expressibility and meibum quality using digital pressure with cotton swabs for all participants. Five glands in the central part of the lower eyelid were graded (0–3) for expressibility: grade 0 when all glands were expressible, grade 1 when 3–4 glands were expressible, grade 2 when 1–2 glands were expressible, and grade 3 when no glands were expressible. The meibum quality of eight glands in the central part of the lower eyelid was graded from 0–3, giving a total score of 0–24. Grade 0 represented clear meibum fluid; grade 1, cloudy fluid; grade 2, cloudy fluid with debris; and grade 3, toothpaste-like meibum. MGD was defined as equivalent to stage 2 of the treatment algorithm for MGD, as either grade ≥ 1 for meibum expressibility or a sum score of ≥ 4 for meibum quality (Geerling et al., 2011; Nichols et al., n.d.; Tomlinson et al., 2011).

Definition and classification of dry eye disease and MGD

Dry eye disease was defined according to the recommendations of the TFOS DEWS II report (Wolffsohn et al., 2017). An OSDI score ≥ 13 was set as the criterion for dry eye symptoms. If, in addition, one or both homeostasis markers (FBUT and ocular surface staining) were positive, then DED was confirmed. A positive result for FBUT was defined as < 10 seconds. Positive ocular surface staining was defined as Oxford grade > 1, which is equivalent to > 5 spots in the cornea or > 9 spots on the conjunctiva. TMH and meibomian gland function were used to sub-classify dry eye disease as ADDE, EDE, a mix of both, or unclassifiable. ADDE was defined by a TMH < 0.2 mm and EDE by the presence of MGD.

Statistics

The data were analysed in frequency and summation tables. Group differences and associations were analysed with standard parametric and non-parametric statistical tests: chi-square, Student's *t*-test, and Spearman correlation. Clinical diagnostics were explored by the calculation of sensitivity and specificity and receiver operating curve (ROC) statistics. A *p*-value of < 0.05 was considered statistically significant.

Ethics

The research conformed to the Declaration of Helsinki, and the study was approved by the Regional Committee for Medical and Health Research Ethics (2015/2492).

Results

In all, 186 patients were examined, of which 118 (63%) were female. Their mean age was 44 years (± 15), ranging from 20 to 70 years. The mean age of females was 44 years (± 14), and the mean age of men was 45 years (± 15). Fifty-six patients (30%) were contact lens wearers; the contact lens wearers were significantly younger than non-contact lens wearers (mean age 35 (± 1) versus 48 (± 2) years), Student's *t*-test $p < 0.001$). All patients had normal vision; the mean best corrected decimal visual acuity (BCVA) in the better eye was 1.0 (± 0.1). BCVA was correlated with age ($r_s = -0.294$, $p < 0.001$). There was no difference in BCVA between contact lens wearers and non-lens wearers or between males and females.

The patients' mean OSDI score was 22 (± 19). The OSDI score was not associated with sex, age, contact lens wear, or BCVA. In all, 109 patients (58.6%) had dry eye symptoms; of these, 41 (37.6%), 26 (23.9%) and 42 (38.5%) had mild, moderate, and severe symptoms, respectively. In all, 138 patients (74.2%) had at least one positive homeostasis marker of DED (FBUT < 10 seconds and / or staining > Oxford grade 1), of these 86 had dry eye symptoms (OSDI score ≥ 13) (see Table 1). Reduced FBUT and staining were not associated with sex, age, or contact lens wear.

Table 1: *Signs of dry eye disease, MGD and reduced tear meniscus height in participants with and without dry eye symptoms, n (%).*

	All	Asymptomatic	Symptomatic
	n=186	*n*=77	*n*=109
FBUT < 10 seconds	78 (41.9)	26 (33.7)	52 (47.7)
FBUT < 10 seconds and Staining > Oxford grade 1	52 (28.0)	21 (27.3)	31 (28.4)
Staining > Oxford grade 1	8 (4.3)	5 (6.5)	3 (2.8)
MGD	72 (38.7)	30 (38.9)	42 (38.5)
MGD and TMH < 0.2 mm	34 (18.3)	19 (24.7)	15 (13.7)
TMH < 0.2 mm	27 (14.5)	11 (14.3)	16 (14.7)

Note: FBUT = Fluorescein breakup time; MGD = Meibomian gland dysfunction; TMH = Tear meniscus height. Decimals rounded to nearest tenth.

In all, 106 (57.0%) patients had MGD, 49 (46.2%) of these were asymptomatic. Reduced TMH was found in 61 (32.8%) patients, of these 30 (49.2%) were asymptomatic. Among all patients, 34 (18.3%) had both MGD and reduced TMH (see Table 1). Among the symptomatic patients with MGD, MGD and reduced TMH, and reduced TMH, 6 (8.3%), 3 (8.8%) and 5 (18.5%), respectively, did not have positive homeostasis markers (dry eye signs). In all, 86 patients (46.2%) had DED (see Table 2). DED was not associated with sex, age, contact lens wear or BCVA. MGD and reduced TMH were not correlated with DED, sex or contact lens

wear. MGD, but not reduced TMH, was correlated with age (r_s (186) = 0.255, $p < 0.001$) (see Table 3). DED could be classified in 59 (68.6%) of the patients with DED (see Table 2). There was no statistically significant difference in the type of DED between males and females or between contact lens wearers and non-contact lens wearers.

Table 2: *Prevalence and sub-classification of dry eye disease by sex, n (%).*

	All $n=186$	Male $n=68$	Female $n=118$
Dry eye disease	86 (46.2)	26 (38.2)	60 (50.8)
EDE	36 (19.4)	9 (13.2)	27 (22.8)
Unclassifiable	27 (14.5)	9 (13.2)	18 (15.3)
Mix of EDE and ADDE	12 (6.5)	2 (2.9)	10 (8.5)
ADDE	11 (5.9)	6 (8.8)	5 (4.2)

Note: ADDE = Aqueous deficiency dry eye, EDE = Evaporative dry eye. Decimals rounded to nearest tenth.

Twenty-three patients (12.4%) had dry eye symptoms without dry eye signs, and 52 (28.0%) had dry eye signs without symptoms (see Figure 1). The sensitivity and specificity of OSDI in detecting any positive homeostasis marker were 62% and 54%, respectively. Table 4 shows the diagnostic accuracy of OSDI ≥ 13 in identifying people with positive homeostasis markers for DED and MGD. In a ROC analysis, OSDI ≥ 13 showed a diagnostic ability to discriminate between patients with fluorescein breakup time < 10 seconds and fluorescein breakup time ≥ 10 seconds, but not between patients with and without staining or MGD. The optimal cut-off value for the OSDI score was 10.41.

Table 3: *Correlation between MGD and reduced TMH and age, gender, contact lens wear and DED.*

	Age	Gender	Contact lens wear	DED
MDG	0.255*	0.062	0.005	−0.022
TMH	0.045	−0.040	−0.062	−0.120

Note: DED = Dry eye disease; MGD = Meibomian gland dysfunction; TMH = Tear meniscus height. *Statistically significant Spearman correlation $p < 0.001$.

Discussion

In this study, most participants had symptoms or signs of dry eye disease, and almost half had dry eye disease. The prevalence of DED is at the high end of the previously reported prevalence range (Stapleton et al., 2017). This may reflect the diagnostic criteria in our study. We defined DED based on symptoms and signs according to the guidelines of the TFOS DEWS II report (Wolffsohn et al., 2017). The definition of dry eye disease in previous studies varies in terms of cut-off values for symptoms and signs, as well as in study populations (Stapleton et al., 2017). Studies using both OSDI and signs report a prevalence of 8.7–10.7%; however, these studies applied a higher cut-off criterion for OSDI (≥ 23 and > 22), and one also applied a lower cut-off criterion for TBUT (Hashemi et al., 2014; Malet et al., 2014). This may explain the higher prevalence found in our study as the TFOS DEWS II also included patients with mild symptoms (OSDI score 13–22) in the diagnosis. Furthermore, the present study included patients attending for a routine eye examination, and they may therefore be more likely to have visual and ocular problems since they are seeking eye care. Nevertheless, our study illustrates the importance of dry eye assessment in optometric practice.

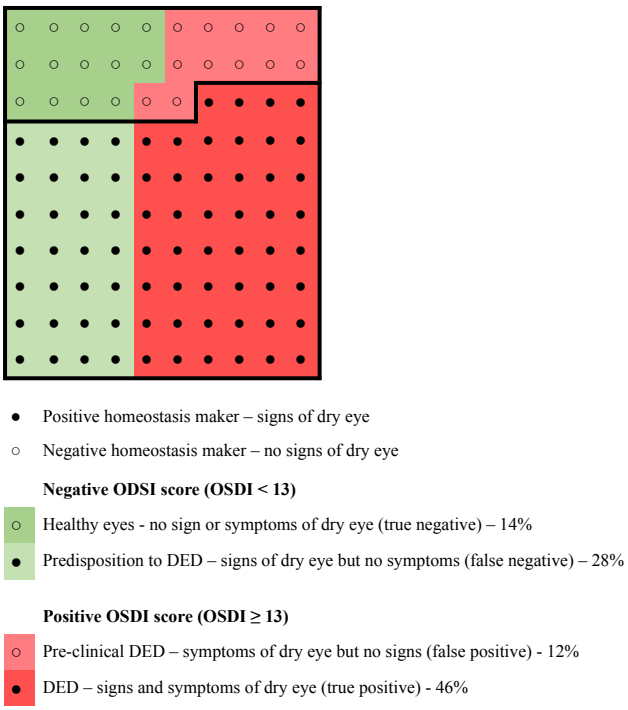

Figure 1: *Distribution of participants with dry eye, pre-clinical dry eye, predisposition to dry eye and health eyes by ODSI-score and homeostasis markers.*

Table 4: *Diagnostic accuracy of OSDI ≥ 13 in identifying patients with dry eye signs and MGD.*

	Sensitivity	Specificity	AUC (95% CI)
FBUT < 10 sec*	64	54	0.590 (0.500 to 0.679)
Staining > Oxford grade 1	57	40	0.553 (0.460 to 0.646)
MGD	54	35	0.503 (0.418 to 0.588)

Note: AUC = area under curve; CI = confidence interval; FBUT = Fluorescein breakup time; MGD = Meibomian gland dysfunction; OSDI = Ocular surface disease index. *Statistical significance $p < 0.05$.

DED was not found to be associated with sex, age, or contact lens wear. These findings contradict other studies, which have shown increased prevalence of DED with increasing age (Farrand et al., 2017; Stapleton et al., 2017), a higher prevalence of DED in females than in males (Hashemi et al., 2014; Stapleton et al., 2017), and that DED is associated with contact lens wear ("The Epidemiology of Dry Eye Disease: Report of the Epidemiology Subcommittee of the International Dry Eye WorkShop", 2007). The lack of association between DED and sex, age, and contact lens wear in our study may reflect the inclusion of all stages of DED and the relatively young age of our participants. Moreover, age-related DED as well as contact lens complications in the younger contact lens wearers could mask differences between contact lens wearers and non-contact lens wearers. Previous studies have shown that differences between males and females become significant only in older age (Paulsen et al., 2014; Stapleton et al., 2017), and comparable studies have examined patients of higher age than in our study. Also, the lack of difference in DED between male and female could be due to the low sample size, and few men included in the study. Our findings may imply that case finding of dry eye disease in optometric practice is equally important in men and women, as well as in both contact lens wearers and non-contact lens wearers.

One in five participants with dry eye symptoms did not have findings of dry eye disease, and seven out of ten asymptomatic participants had findings of dry eye disease. This finding is supported by previous studies that have reported a lack of consis-

tency and low association between signs and symptoms in DED (Bartlett et al., 2015; Stapleton et al., 2017). This reflects the need for evidence-based guidelines in optometric practice including both symptoms and signs of DED to detect affected patients. By only using history and symptoms, including a questionnaire, some patients who might benefit from management of DED will likely continue to be undetected.

The OSDI score significantly differed between participants with and without reduced TBUT. This may reflect an unstable or irregular tear film, affecting optical quality and causing visual disturbance (Herbaut et al., 2019; Koh, 2018). However, there was no significant difference in BCVA between participants with and without DED. Nevertheless, vision may be affected even though visual acuity is normal, as an unstable tear film may cause higher order aberrations (Koh, 2018). Measurement of higher order aberrations was outside the scope of this study. Moreover, the association between TBUT and dry eye symptoms may also relate to dryness of the ocular surface caused by evaporation.

Reduced TBUT differentiated between participants with and without MGD, and MGD may cause both ocular discomfort and visual disturbance through a reduced function of the lipid layer, increasing tear evaporation and impeding the spread of the tear film over the ocular surface (Green-Church et al., 2011; Millar & Schuett, 2015). MGD may reduce lipid layer thickness and alter the lipid composition of the tear film, and previous studies report reduced TBUT in all subtypes of MGD (Xiao et al., 2020), as well as improved TBUT and reduced symptoms when MGD is treated (Kim et al., 2017; Lee et al., 2017). The unstable tear film caused by MGD may cause corneal exposure and staining, and in turn further destabilise the tear film (McMonnies, 2018), increasing tear evaporation and worsening the condition. Half of participants with MGD in our study had no symptoms. The MGD report suggests that dry eye work-up should be undertaken in patients with MGD regardless of symptoms (Tomlinson et al., 2011). This highlights the value of including TBUT as well as the assessment of meibomian gland function in routine eye examinations to detect DED. Almost half of the patients in the study had DED and required treatment to restore homeostasis. In addition, nearly one third were predisposed to DED, and one in ten had pre-clinical dry eye, which should also be considered for the preventive treatment of DED (Craig et al., 2017). This underlines the potential role of the optometrist in case finding, prevention, diagnosis, and management of DED.

Three out of ten cases of DED had normal TMH and normal meibomian gland function. This was not associated with contact lens wear, and the data were collected in winter, ruling out seasonal allergy and contact lens wear as likely explanations. Therefore, this may reflect other causes of staining and reduced TBUT, such as mucin deficiency and reduced blink rate and blink completeness (McMonnies, 2018) that also affect tear film stability. Mucin deficiency may contribute to increased tear evaporation (Willcox et al., 2017). Evaluation of blink rate, blink completeness, and evaluation of the mucin layer may provide further explanation of the underlying cause of DED.

The strength of this study is that it represents a true, real-life clinical setting. All the dry eye tests used are well-known, standardised tests available to optometrists without the need for additional expensive instrumentation. However, the lack of tear osmolarity in our test battery may have underestimated the prevalence of DED. The use of FBUT instead of NIBUT may have affected tear film stability and underestimated the frequency of reduced breakup time and consequently DED. Moreover, it would also be useful to include meibography to support the diagnosis of MGD.

In opposition to the discussed possible underestimation of DED, there could also be a selection bias in our study, overestimating the prevalence of DED, as people having symptoms may be more eager to participate in the study than participants without symptoms. Our study was undertaken in 2015–2016, prior to the publication of the DEWS II report, hence this study did not include triaging questions that can differentiate DED from signs and symptoms of other causes (Wolffsohn et al., 2017). However, our analysis did not find any correlation between DED and risk factors like contact lens wear and medication use. Hence the prevalence of DED in our study likely represents true DED. The inclusion of three optometric practices and three different optometrists could also have introduced observer bias into the findings. However, written instructions for the dry eye assessment were given to the optometrists to ensure standardised examination and reduce bias.

Conclusion

In our study, the majority of patients had dry eye signs and/or dry eye symptoms. More than four out of five benefitted from management of dry eye and pre-clinical findings of dry eye, or advice on pre-disposition to dry eye. Screening with the OSDI questionnaire showed a low sensitivity and specificity in identifying patients with and without positive homeostasis markers. Including assessment of FBUT and meibomian glands in the routine eye examination may enhance case finding of patients with dry eye or those at risk of developing dry eye. The additional use of the OSDI questionnaire in patients with positive homeostasis markers will identify patients with DED or patients at risk of developing DED.

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Conflicts of Interest

The authors declare no conflict of interest.

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Avdekking av tørre øyne i norsk optometrisk praksis: en tverrsnittstudie

Sammendrag

Optikere er en del av primærhelsetjenesten, og det er viktig at de hensiktsmessig diagnostiserer pasienter som kan ha nytte av behandling av tørre øyne. Målet med studien var å utforske hvordan tørre øyne kan avdekkes i optometrisk praksis.

En tverrsnittstudie, som undersøkte symptomer og tegn på tørre øyne blant 186 pasienter (18-70 år) ved rutinemessig synsundersøkelse. Tørre øye ble definert i henhold til kriteriene i «Tear Film and Ocular Surface Society Dry Eye Worksshop II». Standard statistiske tester ble benyttet, og diagnostisk kvalitet ble vurdert ved analyse av sensitivitet, spesifisitet og ROC-kurveanalyse.

Femtiseks pasienter brukte kontaktlinser. De var signifikant yngre enn de som ikke brukte kontaktlinser (gjennomsnittsalder 35 ($SD = 1$) mot 48 ($\pm$ 2) år). Gjennomsnittlig beste korrigerte visus (BCVA) på det beste øyet var 1.0 ($\pm$ 0.1) (desimalvisus). Det var ingen forskjell i BCVA mellom kontaktlinsebrukere og ikke-kontaktlinsebrukere. Gjennomsnittlig Ocular Surface Disease Index (OSDI) score var 22 ($\pm$ 19) og 138 pasienter hadde minst en positiv homeostasemarkør for tørt øye. Åttiseks pasienter hadde tørre øyne, 52 hadde tegn uten symptomer, og 23 hadde symptomer uten tegn på tørre øyne. OSDI hadde en sensitivitet og spesifisitet på henholdsvis 62% og 54% for å avdekke homeostasemarkører for tørre øyne. I alt hadde 106 pasienter meibomsk kjerteldysfunksjon (MGD), hvorav 49 var asymptomatiske. ROC-kurveanalyse viste at en OSDI-score ≥ 13 kan skille mellom pasienter med fluorescein "break-up-time" (FBUT) < 10 sekunder og en FBUT ≥ 10 sekunder, men ikke mellom pasienter med og uten staining eller MGD.

Flertallet av pasientene som kom til rutinemessig synsundersøkelse hadde tegn og/eller symptomer på tørre øyne. Rutinemessig undersøkelse av FBUT og meibomske kjertler kan gjøre det mulig å avdekke tørre øyne i optometrisk praksis.

Nøkkelord: tørre øyne, Ocular Surface Disease Index, meibomsk kjerteldysfunksjon, fluorescein break-up time, punktat fargeopptak, staining

Ricerca sui casi di occhio secco in una clinica optometrica norvegese: uno studio trasversale

Riassunto

Gli optometristi sono i primi a fornire trattamento per la salute oculare ed e' essenziale che identifichino efficientemente i pazienti che possono beneficiare dal trattamento di occhio secco. Lo scopo di questo studio e' di esplorare i risultati di una ricerca sulla malattia dell'occhio secco in una clinica optometrica.

Uno studio trasversale ha esaminato sintomi e segni di 186 pazienti (18 a 70 anni) i quali sono stati sottoposti a una visita dell'occhio di routine con l'occhio secco definito secondo i criteri del Tear Film and Ocular Surface Society Dry Eye Workshop II. Test statistici standard sono stati utilizzati e test clinici diagnostici considerando sensibilita', specificita' e la curva statistica ROC.

Cinquantasei pazienti erano portatori di lenti a contatto e significativamente piu' giovani che i non-portatori con un'eta' di 35 (SD = 1) contro 48 ($\pm$ 2) anni. La media della miglior acuita' visiva corretta (BCVA) nell'occhio migliore era 1.0 ($\pm$ 0.1) (acuita' decimale). Non c'e' stata differenza statisticamente significativa in BCVA tra portatori e non portatori di lenti a contatto. La media (SD) del punteggio dell'Ocular Surface Disease Index (OSDI) e' stato 22 ($\pm$ 19), e 138 pazienti ha avuto almeno un marcatore dell'omeostasi positivo. A 86 pazienti e' stato diagnosticato l'occhio secco, 52 hanno avuto segni senza sintomi e 23 hanno avuto sintomi senza segni di occhio secco. La sensibilita' e specificita' dell'OSDI in differenziare qualsiasi marcatore di omeostasi furono 62% e 54% rispettivamente. 106 pazienti sono stati diagnosticati con disfunzione delle ghiandole di meibomio (MGD), di cui 49 furono asintomatici. Nell'analisi ROC, l'OSDI ≥ 13 ha dimostrato una abilita' diagnostic per differenziare tra soggetti con tempo di rottura lacrimale effettuato con fluoresceina (FBUT) < 10 secondi e FBUT ≥ 10 secondi, ma non tra pazienti con e senza colorazione con fluoresceina o MGD.

La maggior parte dei pazienti considerati ha avuto segni o sintomi da occhio secco. La valutazione di routine di FBUT e delle ghiandole di meibomio possono aiutare a scoprire casi di occhio secco nella clinica optometrica.

Parole chiave: malattia dell'occhio secco, Ocular Surface Disease Index, disfunzione delle ghiandole di meibomio, tempo di rottura lacrimale, colorazioni oculari

Factors Affecting Multifocal Electroretinograms: A Mini-Review

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Abstract

Multifocal electroretinogram (mfERG) is an important diagnostic tool in clinical evaluation of electro-retinal functions. Continuous efforts have been put into examining and understanding the internal and external factors that can upset mfERG recordings and clinical interpretations. It is essential to fine-tune the diagnostic values and enhance the accuracy and internal consistency. The objective of this review is to consolidate the potential determinants that affect mfERG measurements. This review process consisted of the identification, screening, and eligibility steps. Scopus and PubMed databases were used to identify articles with pre-determined keywords. Truncation, and phrase searching were employed as the relevant search techniques. The search for literature was carried out based on the titles, abstracts, and related criteria. Sixty-five articles were screened and found to be eligible for data analysis in this study. Contributing factors that affect mfERG measurements were identified, segregated, and analysed through categorisation to facilitate the inference and decision making in developing more concrete guidelines for mfERG. Potential determinants of the mfERG measurements were systematised and were scored into endogenous and exogenous categories, respectively. The endogenous factors were discussed under 'physiological', 'systemic' and 'ocular' subheadings for pragmatic purposes. The exogenous factors were streamlined into 'lighting' and 'setting' subheadings to simplify understanding of these concepts. Lower amplitude was associated with aging, female gender, high blood pressure, hypoxia, smaller pupil size, longer axial length, increasing myopia, or suppressed eyes. Meanwhile, higher amplitude was linked with hyperglycaemia and higher stimulus luminance. Fixation, alignment and stretch factor can affect the accuracy of mfERG measurements. Future experiments should be designed to eliminate confounding elements in order to systematically quantify their impact on clinical interpretations.

Keywords: multifocal electroretinogram, mfERG measurement, clinical interpretation, exogenous factor, endogenous factor, determinants

Introduction

The first clinical recording of a focal electroretinogram (ERG) was conducted using foveal and parafoveal focal stimuli projected on the retina with a handheld ophthalmoscopic stimulator (Sandberg et al., 1977; Sandberg et al., 1983). Then, only one focal region could be examined at any time. Focal ERG was tailored for assessing central macular diseases. One of its inadequacies was the difficulty in applying multiple focal stimulations to cover a wider retinal area. This shortfall was overcome by the introduction of the multifocal electroretinogram (mfERG). The mfERG employs special binary m-sequence with flash on– and flash off–stimuli in unique orders to map different retinal locations within a short time. This was done over a much larger area of the retina (Bearse & Sutter, 1996; Sutter & Tran, 1992). The mathematical m-sequence model enables the electrical activity of the retina to be recorded as a single time-domain signal to produce a single derived mfERG within 45° in the posterior pole (Bearse & Sutter, 1996).

Clinical evaluation of electro-retinal function using electrophysiology has become a valuable diagnostic tool since the introduction of mfERG. Multifocal ERG is complementary to full-field electroretinography (ffERG) in assessing the peripheral retinal function (Creel, 2019; Hood, 2000; Hood et al., 2003; Tsang & Sharma, 2018). Multifocal ERG has been frequently used by clinicians and scientists to analyse retinal function in combination with other diagnostic techniques such as standardised automated perimetry, optical coherence tomography, fluorescein angiography, and fundus autofluorescence, and has been found to be useful in retinal evaluation in both clinical and research settings.

The International Society for Clinical Electrophysiology of Vision (ISCEV) publishes clinical mfERG guidelines regularly (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). They continuously provide updates on issues affecting mfERG recordings and findings based on clinical experience or experimental evidence (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). To enhance the diagnostic value, accuracy, and internal consistency, it is crucial to carefully examine the internal and external factors that affect mfERG recordings and clinical interpretations. Variables that influence the quality of the mfERG response can be technical, such as the field of view, interference levels and the duration of on-state stimulation. Other factors influencing the results may be due to data acquisition issues, such as electrode type and placement, amplifier specifications and filter bandwidth settings. The mode of stimulation such as Cathode Ray Tube (CRT) and Liquid Crystal Display (LCD) systems can also affect the quality of mfERG responses (Kaltwasser et al., 2009; Keating et al., 2000). In a CRT monitor, each pixel lights up for a duration of a few milliseconds during each frame. In an LCD monitor, meanwhile, each pixel lights up with a certain delay after the trigger but has a constant luminance during the entire length of the frame. These different display characteristics have been reported to affect the mfERG signal. The latencies of mfERG responses recorded with an LCD monitor were significantly increased for N1 and P1 compared with those recorded with a CRT. However, only the N1, and not the P1, amplitude was reported to be higher with an LCD monitor.

Information available on external and internal factors affecting mfERG measurements remains scattered and disorganised. The purpose of this review is to identify, segregate, and analyse the contributing factors that affect mfERG measurements through categorisation to facilitate clinical interpretation. Hence, it is important to guide clinicians on how to mitigate these variables when using mfERGs in patient management.

Methods

A systematic approach was used to perform this review. The review process consisted of four stages: identification, screening, eligibility, and data analysis (see Figure 1). Table 1 summarises the search configuration used in the identification, screening, and eligibility processes.

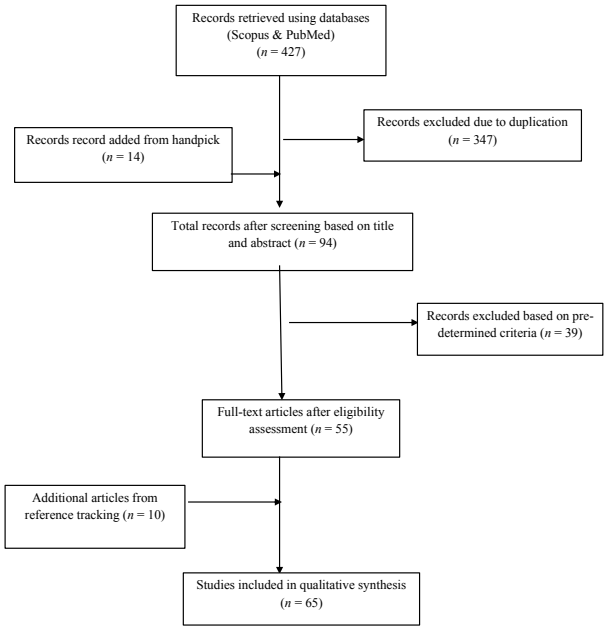

Figure 1: *Flow diagram of the literature search and selection process.*

Table 1: *Summary of search configuration in identification, screening, and eligibility.*

Database	Scopus, PubMed
Search techniques	Truncation and phrase searching
Keywords	Visual electrophysiology, electroretinogram*, multifocal electroretinogram*, exogenous factor*, mfERG
Target fields	Title, Abstract, Keyword, Full Text (Partial matches of key words were allowed for Title, Abstract and Keywords. Explicit match was used for full text search)
Criteria	Literature type: original research articles Language: English

Note: '*' is the wildcard/truncation search operator.

In the identification phase, two electronic databases were used to conduct the literature search, namely Scopus and PubMed. These were chosen due to their large coverage of publications within life sciences and biomedical topics. Medical and healthcare related publications are also covered comprehensively. Keywords ("visual electrophysiology", "electroretinogram*", "multifocal electroretinogram*", "mfERG", where '*' is the wildcard/truncation operator) were used to identify the related articles. The process to determine the main keywords was based on the review objective. The search for synonyms or related terms or variations of the main keywords was attempted using a thesaurus or keywords used in past studies. Truncation, and phrase searching were the search techniques employed to trace articles in both these databases.

In the screening process, 347 records were removed due to duplication. The remaining 94 records were vetted based on their titles and abstracts and a further 39 were excluded using the pre-determined criteria. After the eligibility assessment of full-text articles was conducted 55 articles were found to be eligible. Names of specific authors known to have conducted work on mfERG were also included in the search through a hand-picking process. Additional relevant studies that might have been missed from the databases search were also captured using a 'reference tracking approach'. Relevant studies were subsequently identified based on the articles from the initial search strategy.

In the Data Analysis phase, 65 original articles published in English language were included. Data on contributing factors were either established from articles that directly reported factor investigations or extracted indirectly from multifarious mfERG related studies. In data analysis, elements considered to influence the mfERGs were itemised. The information extracted was then merged to synthesise a pattern of all factors affecting mfERG measurements.

Results

In general, there are many factors that can affect ERG values. The contributing factors have accumulatively influenced the standard for electrophysiology in the vision science community over the years. However, records on contributing factors were found to be quite sparse and unsystematic. After undertaking multiple gap analyses to map the determinants that might potentially affect mfERG measurements, it was found that they were frequently related to factors such as age, gender, axial length, refractive error, pupil size, ambient light, stimulus luminance, fixation, alignment, suppression, stretch factor, blood pressure, and blood oxygen and glucose levels. To consolidate the interrelated data, these contributing factors were systematised and sorted into endogenous and exogenous categories. For the purpose of pragmatic discussion, the endogenous factors were discussed under 'physiological', 'systemic' and 'ocular' subheadings. The exogenous factors were streamlined into 'lighting' and 'setting' subheadings to simplify understanding.

Physiological variation

Physiological variations associated with ERG measurements were frequently linked to age and gender. It is important to understand the normal retinal changes when considering the influence of age on mfERG results. Normal retinal changes that occur with age include gene modulation, and psychophysical, structural, and cellular alterations (Bonnel et al., 2003). It is essential to differentiate the normal aging process from pathological aging (Bonnel et al., 2003) where the aging process changes the retinal function in an abnormal manner (Alavi, 2016; Bonnel et al., 2003). The aging of the eye involves genetic, biochemical, and cellular pathways, called longevity pathways, that regulate lifespan (Alavi, 2016). Retinal degeneration has been reported as the accelerated aging of photoreceptors (Alavi, 2016). Despite a better understanding of hereditary retinal diseases, the changes that occur in the retina as a result of aging remain debatable and are still being explored further (Bonnel et al., 2003). Age-related changes in mfERG results can be due to both optical and neural factors (Gerth et al., 2002; Panorgias et al., 2017). The decline of photopic mfERG responses with age has been reported between the ages of 20 and 70 years, primarily due to preretinal optical factors (Fortune & Johnson, 2002; Nabeshima et al., 2002). Both these studies reported a strong dependence on age for all mfERG responses measured, especially the central first-order retinal responses within 5° eccentricity and second-order response kernels. Meanwhile, another study reported decreases in response density and increases in implicit time with age (9–80 years) across all retinal regions (Keating et al., 2000). Age-related changes in response density were found to be most significant for the central retina and decreased with increasing retinal eccentricity (Gerth et al., 2002). One possible explanation for this is the slower temporal adaptation in the aging retina (Gerth et al., 2002; Jackson et al., 2002). It has been reported that the response densities of the first-order kernel (first positive wave P1) and second-order kernel (second positive wave P2) waves decreased, and the implicit times of the second-order kernel P2 increased among those above 50 years old in a group of subjects aged between 12 and 76 years (Nabeshima et al., 2002). A study carried out to determine age-related changes in the localised response and localised variability of mfERG parameters demonstrated considerable variation between differ-

ent retinal regions with regards to the variability of the response and characteristics of age-related changes (Tzekov et al., 2004). The localised approach revealed patterns of age-related changes that were not apparent in the ring averages generated using hexagons mapped across the retina area (Tzekov et al., 2004). Each localised response showed a decline with age, either in the scalar product or in the N1-P1 amplitude. The decline of the response varied from 3.3% in the periphery to 7.5% in the perifovea (Tzekov et al., 2004). The decline was greater for the superior than for the inferior retina for amplitude parameters, corresponding to larger increases in the P1 implicit time (Tzekov et al., 2004). The relative rate of change with age was similar for the nasal and temporal retina (Tzekov et al., 2004). Tzekov et al. (2004) proposed that the topographic properties of the retina had to be considered when establishing a normative database for clinical and research purposes. Age factor was linked to the diverse amplitude and implicit times of the mfERG in different regions of the retina in addition to the L–to–M-cone ratio disparities (Albrecht et al., 2002; Ziccardi et al., 2014).

A gender effect is apparent in both animal and human research findings. Multifocal ERG was carried out in cynomolgus and rhesus macaques (C. B. Y. Kim et al., 2004). Rhesus males (compared to rhesus females) and cynomolgus females (compared to cynomolgus males) exhibited larger amplitudes and less delayed implicit times in the central retina. In a study using human subjects the relative numbers of L– and M–cones (L–to–M-cone ratio) were found to be lower in females than in males (Jägle et al., 2006). However, the magnitude of the mfERG amplitude differences was larger than predicted by the L–to-M–cone ratio. The direct effect of sex hormones on the ion channel function was proposed as an alternative explanation for this (Jägle et al., 2006). The gender investigation was further probed in another human study into the neuro-retinal function in terms of the first order P1 implicit times and N1–P1 amplitudes obtained from photopic mfERG (Ozawa et al., 2014). It was claimed that hormones played a role in the gender effects. All neuro-retinal functions were found to be lower and shorter in females among those under 50 years old (Ozawa et al., 2014). However, the gender effects disappeared among those over 50 years old.

The effects of age and gender on both amplitudes and implicit times of the mfERG have been indicated in this review. The ERGs were found to decrease in response density but increased in implicit time with age. The responses also varied by regions of the retina. Retinal functions were reported to be lower and shorter in females and were likely linked to sex hormones. However, the clinical relevance, significance, and implication of these findings remain inconclusive. To develop a predictive adjustment for age and gender in clinical interpretation, a strategically polished clinical study with well-defined objectives that specify the relevant parameters and scopes of measurement is greatly needed. A retrospective approach to obtain data from existing multicentre clinical records might be an easy-to-accomplish option to first observe the preliminary inclination before embarking on more sophisticated experiments.

Systemic changes

Hypertension and diabetes are major medical and public health issues worldwide (Mokdad et al., 2003; Pappachan et al., 2011). Variations in mfERG have been linked to systemic changes of the human body in terms of blood glucose, blood pressure, and blood oxygen levels. Blood pressure can affect the retina both through high blood pressure and ocular hypertension (Chan & Brown, 2000; Gundogan et al., 2008; Lu et al., 2011; Michael Nork et al., 2010). Amplitudes of mfERG in hypertensive subjects were reported to be reduced in comparison to normotensive subjects, but no difference was found in the implicit time (Gundogan et al., 2008). The mfERG amplitude was similarly reduced in a study of the effect of ocular hypertension on mfERG (Chan & Brown, 2000). Studies on non-human primates and rats also found reduced mfERG amplitudes as a result of induced high intraocular pressure (Lu et al., 2011; Michael Nork et al., 2010). Intraocular pressure is normally highest in the morning and reduces through the day (Read et al., 2008). However, a study into diurnal variation in mfERG recordings did not reveal any similar trends (Heinemann-Vernaleken et al., 2000).

In a study into the association between the mean ocular perfusion pressure, systemic blood markers and retinal function in subjects with and without vascular disease, the mean ocular perfusion pressure was suggested as one of the sources of mfERG amplitude variation (Harrison et al., 2014). The mean ocular perfusion pressure is a function of systolic, diastolic, and intraocular pressure. It can be abnormal in patients with diabetes and its co-morbidities. Hyperglycaemia was associated with an increase in the amplitudes and a decrease in the implicit times of the mfERG (Klemp et al., 2005). The mfERG values were affected by diabetic retinopathy and the mfERG implicit time was suggested as a good indicator of the diabetic retinopathy onset (Harrison et al., 2014). Patients with type 1 diabetes without retinopathy demonstrated a delayed mfERG response compared with healthy subjects (Klemp et al., 2005). Chronic hyperglycaemia induces an adaptational response that tends to normalise retinal implicit time at a higher level of habitual glycemia (Klemp et al., 2005). During hypoglycaemia, mfERG was found to decrease, both in subjects with type 1 diabetes and subjects without diabetes (Khan et al., 2011). The dominant effect was in the amplitude of the responses in the central macular retina and not in their temporal properties (Khan et al., 2011). Responses from the central region were approximately 1.8-fold lower than from the periphery for both groups (Khan et al., 2011).

The impact of oxygen concentration on mfERG findings has mainly been reported during natural exposure among highlanders and climbers (Feigl et al., 2007; Klemp et al., 2007; Kofoed et al., 2009; Pavlidis et al., 2005). In a study into variation in mfERG during acclimatisation of native highlanders to normobaric normoxia at sea level, the highlanders were reported to display supernormal mfERG amplitudes that continued to increase during a 72-day period of observation whilst their haematocrit normalised. It was suggested that acclimatisation after a change in altitude and in ambient oxygen tension involved intrinsic retinal mechanisms (Kofoed et al., 2009). In another investigation into acclimatisation effects on mfERG among healthy climbers of a trekking expedition, it was found that the mfERG responses decreased a week after high-altitude exposure at 5050 m (compared with 500 m), but recovered the following week (Pavlidis et al., 2005). This oxygenation postulation was further examined in a direct in vivo comparison between normoxia, hypoxia and hyperoxia conditions in healthy human retina (Klemp et al., 2007). Compared with normoxia, hypoxia was associated with a reduction in mfERG amplitude. Hyperoxia had no effect on amplitude. Neither hypoxia nor hyperoxia had any effect on the latency of the P1 implicit times of the mfERG (Klemp et al., 2007). In another unrelated study comparing normoxic and hypoxic conditions, a reduction in mfERG responses was found during hypoxia (Feigl et al., 2007). An increase in mfERG implicit time with higher oxygen concentration might indicate that bipolar and Muller cells were affected (Feigl et al., 2007). However, altered mfERG values among patients with long-term breathing problems such as in chronic obstructive pulmonary disease (COPD) have not been accurately reported (Vogelmeier et al., 2017). Poor airflow in COPD may hypothetically display similar trends of reduction in mfERG values due to lower oxygen concentration, but this would need further confirmation through more research.

The impact of systemic changes on the amplitude of mfERG is apparent, while their impact on the implicit time varies. If the levels of blood glucose, blood oxygen, and blood pressure can affect the amplitude value of the mfERG, it is imperative to incorporate these tests into the preliminary assessment prior to any mfERG measurements.

Ocular changes

Multifocal ERG measures the electrical activities of the retina in response to a light stimulus. Any ocular changes that alter the light transmission and optical quality are likely to have an effect on the mfERG measurements. The pupil size affects the amount of light entering the eye. This has been continually explored in mfERG research. Axial length and refractive error have also been frequently highlighted in mfERG measurements due to retinal structure investigations in myopia research.

Pupil size

Pupil size plays a particularly important role in mfERG as stated in the ISCEV standard (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). The pupil regulates the amount of light entering the eye during mfERG measurements. It is required by ISCEV to be fully dilated and its size must be monitored throughout the mfERG procedure. Pupil size has been found to have significant effects on the amplitude and latency of the mfERG (Gonzalez et al., 2004). There was a reduction in mfERG amplitude with a change in pupil diameter of 7 mm (mfERG P1 amplitude 53 nV at 8 mm to 25 nV at 1 mm), whereas a pupil diameter greater than 8 mm does not contribute significantly to the amplitude and timing of the mfERG (Gonzalez et al., 2004).

Nevertheless, mfERG measurements with non-dilated pupils can sometimes be unavoidable and can become necessary when pupil dilation is contraindicated. Two studies carried out comparisons between mfERG measurements with dilated and non-dilated pupils. The luminance of a screen monitor that was set five times higher than the recommended ISCEV value of 150 cd/m^2 during mfERG recordings with natural pupils was found to give the same mfERG responses as dilated pupils and screen luminance 150 cd/m^2 (Poloschek & Bach, 2009a). The mfERG amplitudes and implicit time in dilated eyes were found to be equal to non-dilated eyes in the central retina (Mohamad-Rafiuddin et al., 2014). Both studies advocated that mfERG values with non-dilated pupils could be used for clinical purposes. Unfortunately, the sample size of the latter study was too small to draw any convincing conclusion. Therefore, to develop a clinical guide on use of mfERG with non-dilated pupils, a well-controlled experimental study which systematically quantifies the impact of various natural pupil sizes on mfERG results is required.

Axial Length and Refractive Error

Refractive error is determined by the relationship between the axial length of the eye and its optical power. Despite the close relationship between refractive error and axial length, variations in mfERG values have been attributed more to axial length rather than refractive error (Sachidanandam et al., 2017). Multifocal ERG amplitudes were reported to reduce with increasing axial length and across eccentricities (Chan & Mohidin, 2003; Man et al., 2013).

Multifocal ERG values for myopic eyes were reported to be different to emmetropic eyes (Chan & Mohidin, 2003; Chen et al., 2006a; Luu et al., 2006; Man et al., 2013; Wolsley et al., 2008). A weaker mfERG response has been recorded due to the morphological changes associated with increased axial length (Chan & Mohidin, 2003). Axial length contributed to 15% of the implicit time total variance. Amplitudes and implicit time mfERG correlated with the severity of myopia in adults. Amplitudes decreased and the implicit time increased as the dioptric power of myopia increased. However, such correlations between refractive error and mfERG results were not found in children with myopia (Luu et al., 2006).

It has been suggested that changes in the mfERG responses in myopes are primarily due to the increased axial length that accompanies myopia development (Chen et al., 2006a). Underlying differences in retinal function resulting from myopia could be one possible explanation. In an investigation using a range of refractive errors (+0.50 to –15.00 D), retinal thinning (reduced thickness of the outer plexiform layer of the nerve fibre layer) in moderate and high myopia correlated with reduced spatial resolution and delayed mfERG timing in the peripheral retina (Wolsley et al., 2008). The structure and function of the post-receptor retina were suggested to be susceptible to disruption in eyes with moderate and high myopia.

Retinal defocus was found to be a contributing factor for mfERG variation (Rosli et al., 2014; Wolsley et al., 2008). In an investigation into the effects of refractive blur (plano, –3 D, +3 D, and +6 D) on mfERG, a significant difference in the density of the mfERG response was suggested for every 2 D change of refraction (Palmowski et al., 1999). When the viewing distance was adjusted to compensate for the induced changes in retinal image size by the refractive lens, no influence due to refraction was observed in either latencies or amplitudes (Palmowski et al., 1999). The effect of optical defocus on mfERG was further examined by ensuring the pupil size remained constant to minimise the aberration factor as it might indirectly affect the results (Chan & Mohidin, 2003). The amplitude was found to be reduced, but the implicit time was not changed by increasing the optical defocus (Chan & Mohidin, 2003). A later investigation found that retinal defocus of up to 3 D did not affect mfERG values (Rosli et al., 2014).

Theoretically, performing mfERG on a subject with an uncorrected refractive error may affect the amplitude or implicit time of the mfERG measurements as the quality of the retinal image is essential. Here, greater optical defocus produces poorer retinal image quality. The ISCEV guideline encourages correction of refractive errors before mfERG measurements (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). A full optical correction is recommended for mfERG measurements to minimise reduction of the retinal response due to optical defocus (Chan & Mohidin, 2003), particularly for patients with high refractive errors (> 6 D) (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). Contact lenses are considered better than correction by spectacles (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). In a recent investigation of the local differences in spherical and astigmatic defocus across the human retina using global-flash mfERG, it was found that responses from different retinal areas varied with local spherical defocus, but were not affected by astigmatic defocus (Turnbull et al., 2020). Further investigation is needed to fill the current gaps in information on the effects of hyperopia, presbyopia, and astigmatism on mfERG.

Lighting

Multifocal ERG values are directly correlated with the amount of light that enters the eye and is projected on the retina. ERGs record the retina's response to a light stimulus. Therefore, any light source, including both stimulus and ambient light, that contributes to retinal illumination can affect the mfERG measurements.

The brightness of the stimulus has been shown to produce direct effects on the mfERG outputs. Luminance contrast between the luminance of a brighter area of interest and that of an adjacent darker area might be another contributing factor in

mfERG variations. In an investigation into the effects of high luminance on the amplitude of the mfERG, luminance was set at three different levels, 150, 300 and 500 cd/m^2 (Schimitzek & Bach, 2006). The mfERG amplitude increased by 20% when the stimulus luminance was increased by a factor of 3.3. Peak times decreased slightly (less than 1.5 ms) with higher stimulus luminance. Contrast adaptation, produced by prolonged viewing of high contrast gratings, was suggested to occur at both retinal and cortical locations within the visual pathway (Chen et al., 2006b). An increase in implicit time but no change to the amplitude of the mfERG waveform was reported in a study into the effect of retinal contrast adaptation on the mfERG response (Chen et al., 2006b).

The ideal illumination for the examination room was loosely described in ISCEV as 'moderate and dim room illumination' close to the stimulus screen (Hood et al., 2012). ISCEV recommends pre-adaptation in light for 15 minutes (Hood et al., 2012; Hood et al., 2008; Marmor et al., 2003; Robson et al., 2018). Multifocal ERG has been reported to increase in both amplitude and implicit time in 2 minute subsequent internal recordings for 16 minutes of light adaptation after dark adaptation (Kondo et al., 1999). The most stable mfERG recording condition appears to be a fully lit room (1.6 log cd/m^2) (Chappelow & Marmor, 2002). For clinical application, it would be more helpful if the recommended value was given in Lux (illumination). Although direct measurement would provide a more precise measurement, it can be estimated as 150 lux based on the reported value (1.6 log cd/m^2). The amplitudes and times-to-peak were found to be disturbed by increasing the ambient room luminance (Chappelow & Marmor, 2002). The exaggerated attenuation of signals in the blind spot with room lighting indicated that mfERGs recorded in the dark might be contaminated by the light scattered in the dark-adapted peripheral retina (Chappelow & Marmor, 2002). Stray light was reported to affect the ERG responses to local stimuli (Boynton, 1953; Shimada & Horiguchi, 2003; Wirth & Zetterstrom, 1954). The same issue of stray light-induced response in the mfERG (elicited by a stimulus falling on the disc) was found in a comparison study revealing that an optic disc with high reflectance scattered stimulus light to create a weak full-field stimulus (Shimada & Horiguchi, 2003). Investigations of the subsequent usage of equipment involving flashes of light as stimuli reported a negligible effect on the mfERG measurements (Suresh et al., 2016). A more explicit statement on lighting for mfERG practitioners would be beneficial in standardising mfERG procedures.

Setting

Fixation, Alignment and Suppression

A fixation-monitoring system was widely used to monitor the integrity of any acquired data in electronic ocular instruments (Chu et al., 2006). Fixation is also used to monitor mfERG (Rudolph et al., 2002). Reliable data usually have less than 10–20% fixation loss during measurements. The accuracy of mfERG measurements for subjects with poor fixation might be difficult to interpret (Chu et al., 2006). Small eye movements during the mfERG measurement generate noise and contaminate the input signals. The central mfERG amplitude is most affected by unsteady fixation. A lower amplitude is anticipated for unsteady fixation of 4° and beyond. High resolution stimuli of less than 2.4° are reported to be more susceptible to fixation fluctuations during the mfERG recording process (Chisholm et al., 2001). The depth of depression at the blind spot area has been suggested as an alternative to interpret the accuracy of mfERG results in patients with poor fixation (Chu et al., 2006).

Interocular differences in mfERG were not apparent when measurements were taken under monocular and binocular stimulation conditions in healthy subjects with good binocular vision (Pálffy et al., 2010). Fixation errors in a patient with asymptomatic intermittent exotropia can affect the mfERG measurements (Bellmann et al., 2004). The near reflex is a triad which consists of accommodation, convergence and miosis for adjustment to fixate on a near object. Convergence errors may happen in patients with high heterophoria due to the proximity of the stimuli which demands prolonged near fixation and may cause fatigue. The misalignment may affect the mfERG comparisons by pairing the erroneous fixation locus between the two eyes. When measuring mfERG in subjects with eccentric fixation, fixation locus is crucial to ensure that equivalent retinal areas are compared (Seiple et al., 2006). If the fixation is maintained within the central stimulus hexagon (2°), the mfERG amplitude will not be substantially affected (Chu et al., 2006).

Suppression is a significant factor that must be addressed during mfERG measurements because the amplitude is reduced and the implicit time shortened in a suppressed eye (Vrabec et al., 2004). The possibility of performing mfERG recordings in the clinic using more flexible, natural techniques such as watching movies has been demonstrated (Saul & Still, 2017). However, an alternative stimulation strategy is needed to handle the difficulties in the presence of temporal-spatial correlations and eye movements to achieve results that are comparable to those routinely obtained with conventional methods. Clinical use of binocular mfERG in patients with monocular macular disease is thus recommended (J. W. Kim et al., 2013).

Fixation, alignment, and suppression are vital factors that must be equally considered during mfERG measurement to enhance the accuracy and repeatability of the mfERG values for retinal disease monitoring and visual rehabilitation follow-up.

Stretch factor

Multifocal ERG ring measurements are generated using hexagons mapped across the retina. The values of mfERG in each of the rings represent the total amount of responses from the photoreceptors within that defined retinal area. Hypothetically, the mfERG data generation for each ring is based on the presumption using hexagons of the same size across the field of stimulation. However, the volume of photoreceptors in the central retina is different to that in the periphery. If the same size of hexagon is used for the calculation, it will result in a systematic error due to these differences. The number of photoreceptors in the peripheral retina is too small to be detected with the same hexagon size as that used in the central retina (Poloschek & Bach, 2009b). This stimulus distortion from the central to the peripheral ring of the mfERG is called the stretch factor. The topographical distribution of photoreceptors plays a huge role in determining the most accurate stretch factor, which can be affected by the distance between the subject and the monitor, the size of the stimulus, and the stimulus resolution. The size of the hexagons should not be the same throughout the field of view (Poloschek & Bach, 2009b). The electrical activity of the peripheral retina cannot be represented by the same hexagon size as the central retina because the variabilites between the different eccentricities are too small to detect or differentiate (Poloschek & Bach, 2009b). Another possible error is the overlapping or sharing of the hexagon in the adjacent ring during the analysis of the ring responses. However, the stretch factor investigation was restricted to the VERIS multifocal ERG application (Poloschek & Bach, 2009b). Diagnosys mfERG takes a different approach to control the stretch factor in terms of scaling, sizing, and elongation. Different models employ different calculations to generate the outputs. The variation in stretch factors used in different apparatuses should be probed further with a view to standardise procedures and aid clinical comparison between different models.

The impacts of endogenous and exogenous factors on mfERG

values and measurements discussed in this mini-review are summarised in Table 2.

Table 2: *Impact of endogenous and exogenous factors on mfERG measurements.*

Endogenous factors	
Age	lower amplitude with age
	higher implicit time with age
	varies by retinal region
Gender	lower amplitude in female
	shorter implicit time in females
Blood pressure level	lower amplitude with higher blood pressure
	no effect on implicit time
	no diurnal variation
Glucose level	higher amplitude in hyperglycaemia
	shorter implicit time in hyperglycaemia
Oxygen level	lower amplitude in hypoxia
	no effect on implicit time in hypoxia
	no effect on amplitude in hyperoxia
	two conflicting data on implicit time in hyperoxia (no effect and increment)
Pupil size	lower amplitude with smaller pupil size
Axial length	lower amplitude with longer axial length
Refractive error	lower amplitude with increasing myopia
	higher implicit time with increasing myopia
Exogenous factors	
Stimulus	higher amplitude with higher stimulus luminance
	lower implicit time with higher stimulus luminance
Ambient light	a brightly lit room (1.6 log cd/m^2) is the most stable mfERG recording condition
Fixation	reject data with > 20% fixation loss
Alignment	precise binocular alignment is crucial to ensure that equivalent retinal areas are compared
Suppression	lower amplitude in suppressed eye
	shorter implicit time in suppressed eye
Stretch factors	values of the mfERG ring measurements in different brands or models of equipment should be interpreted together with the knowledge of stretch factors being used

Conclusion

In this mini-review, the contributing factors that affect mfERG measurements have been identified, segregated, and analysed through categorisation. Potential determinants of the mfERG measurements were organised into endogenous and exogenous categories. Relevant data were combined and discussed under five different subheadings (physiological, systemic, ocular, lighting, and setting) to simplify the information for easy comprehension. The nullifying effects of various contributing factors stated in this mini-review should be carefully examined in designing any factor-related mfERG studies in the future. Quality data would lead to more accurate clinical interpretations and comparable data worldwide. An in-depth investigation into these contributing factors of the mfERG can be used as a future guide in the revision of the mfERG standard.

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Faktorer som påvirker multifokal elektroretinogram: En oversiktsartikkel

Sammendrag

Multifokal elektroretinogram (mfERG) er et nyttig diagnostisk verktøy ved klinisk utredning av retinafunksjonen. Mye arbeid er blitt lagt ned i å undersøke og forstå de ulike interne og eksterne faktorer som kan påvirke mfERG målinger og klinisk tolkning. Det er viktig å forbedre diagnostisk nytteverdi, og øke nøyaktighet og repeterbarhet.

Målet med denne oversiktsartikkelen er å sammenholde mulige faktorer som kan påvirke mfERG målinger. Prosessen besto av identifisering, screening og vurdering av relevans. Databasene Scopus og PubMed ble brukt til å identifisere artikler ved hjelp av bestemte nøkkelord. Trunkerte søk og frasesøk ble brukt. Litteratursøket ble foretatt i titler, sammendrag og relaterte kriterier. Til sammen 65 artikler ble gjennomgått og funnet passende for analyse i dette studiet. Faktorer som kan påvirke mfERG målinger ble identifisert, skilt ut, analysert og sortert for å forenkle tolkning og avgjørelser ved utvikling av retningslinjer for bruk av mfERG. Potensielle faktorer ble kategorisert som interne eller eksterne. Interne faktorer ble diskutert under de følgende overskriftene: «fysiologiske», «systemiske» og «okulære». Interne faktorer ble plassert under «belysning» og «setting».

Lavere amplituder kan knyttes til aldring, kvinnelig kjønn, forhøyet blodtrykk, hypoksi, mindre pupilldiameter, større aksial lengde, økende myopi, eller supprimerte øyne. Høyere amplituder kan knyttes til høyt blodsukker og høyere stimulus luminans. Fiksasjon, øyeposisjon og strekkfaktor kan påvirke nøyaktigheten av mfERG målinger.

I fremtidige studier bør forvirrende elementer reduseres for å forenkle klinisk tolkning.

Nøkkelord: multifokal elektroretinogram, mfERG målinger, klinisk tolkning, ytre faktorer, indre faktorer, bestemmende faktorer

I fattori che influiscono sull'elettroretinogramma multifocale: una mini revisione

Riassunto

L'elettroretinogramma multifocale (mfERG) e' un importante strumento diagnostico della diagnosi clinica delle funzioni elettro-retiniche. Continui sforzi sono stati fatti nell'esaminare e comprendere i fattori interni ed esterni i quali possono influenzare le misure mfERG e la loro interpretazione clinica. E' essenziale rifinire i valori diagnostici e migliorarne l'accuratezza e la consistenza interna. L' obiettivo di questa revisione e' di consolidare i potenziali determinanti che influiscono sulle misure della mfERG. Questo processo di revisione ha consistito nell'identificazione, screening e criteri di eligibilita'. I database di Scopus e PubMed sono stati utlizzati per identificare gli articoli con predeterminate parole chiave. Troncamenti e parole di ricerca sono state utilizzate cosiccome le piu' rilevanti tecniche di ricerca. La ricerca della letteratura scientifica e' stata condotta attraverso i titoli, i sommari e i relativi criteri. Sessantacinque articoli sono stati controllati e considerati idonei per l'analisi dei dati di questo studio. I fattori che influenzano le misure con la mfERG sono stati identificati, separati ed analizzati grazie ad una categorizzazione per facilitare l'inferenza e la decisione nello sviluppo di concrete linee guida per la mfERG. I fattori endogeni sono stati discussi all'interno di sottocategorie quali "psicologiche", "sistemiche" e "oculari" per ragioni di pragmaticita'. I fattori esogeni sono stati separati tra "illuminazione" e "settaggi" come sottocategorie per semplificare la comprensione di questi concetti. La ridotta ampiezza e' stata associata con l'invecchiamento, sesso femminile, pressione sanguigna alta, ipossia, diametro pupillare ridotto, lunghezza assiale aumentata, miopia aumentata o ambliopia. Invece, ampiezza aumentata e' stata collegata a iperglicemia ed elevato stimolo alla luminosita'. Fissazione, allineamento e fattore di compressione possono influenzare l'accuratezza delle misure con mfERG. Esperimenti futuri dovranno essere disegnati considerando l'eliminazione di questi elementi di confusione per evitare l'impatto sistematico sull'interpretazione clinica.

Parole chiave: elettroretinogramma multifocale, misure mfERG, interpretazione clinica, fattori esogeni, fattori endogeni, determinanti

Referral in a routine Italian optometric examination: towards an evidence-based model.

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Abstract

Whilst Italian optometrists refract patients and prescribe optical appliances, it is ophthalmologists who are responsible for the detection, diagnosis, and treatment of ocular pathology. In settings with similar scope of practice, close collaboration between optometrists and ophthalmologists is required to minimise avoidable visual impairment. Referral to ophthalmology represents the basis of this synergy, yet no formal guidance is available to Italian optometrists indicating when referrals are warranted. This study aimed to identify circumstances deserving a referral in a routine Italian optometric examination in adults, constituting preliminary evidence-based indications of a referral model.

A literature review was conducted using Pubmed and the Cochrane Library. To derive clinical guidance, the main focus was high quality secondary literature such as systematic reviews and clinical guidelines.

Several signs and symptoms detected during a routine Italian optometric exam might constitute reasons for referral. Further, while a wide range of anomalies of the visual system are likely to be detected by the exam, up to 19% of patients could suffer an asymptomatic condition potentially undetected by the current assessment. This results in the need to refer seemingly healthy patients if they have not attended routine ophthalmological examinations within optimal time frames.

The current training and scope of practice of Italian optometrists requires close collaboration with ophthalmologists to safeguard the ocular health of patients. Referral is a fundamental instrument that in Italy, and countries with similar settings, optometrists must use to enable early diagnosis and treatment of ocular conditions by ophthalmologists. We have presented a preliminary evidence-based framework for optometric referral which identifies categories constituting reasons for referral. This has the potential of standardising optometric practice, enhancing optometry-ophthalmology synergism and, more importantly, improving ocular and general wellbeing of patients.

Keywords: Referral, routine eye examination, avoidable vision loss, refraction, asymptomatic patients, public health

Introduction

Optometrists across the world have varied roles depending on their country of practice (ECOO European Council of Optometry and Optics, 2020). Specifically, in Italy, optometrists refract patients and prescribe optical appliances such as spectacles, and fit contact lenses (Naroo & Grit, 2009). Routine eye examinations conducted in this context presently lack a comprehensive ocular health assessment and, according to current legislation, Italian optometrists have no legal responsibility to detect ocular pathology. In Italy, access to the optometric profession is granted either by a 3-year university-based BSc degree or by professional diplomas implemented by private institutions. Although the duration of diploma courses varies across different institutions, these are usually 1 year long and accessible only by individuals already qualified as opticians (i.e. level 2 from the WCO competences model (Kiely & Chappell, 2015)). Overall, educational programmes mirror the scope of practice, with reduced focus on competencies required for the diagnosis and practical management of eye disease, in favour of skills relevant to optical technology and investigation, and correction of visual function. This is in contrast to other parts of Europe, such as the United Kingdom, where optometrists are also trained in the detection and management of eye disease, both roles that pertain solely to ophthalmologists in Italy. Nevertheless, the relationship between the Italian optometrist and patient is one of assistance and care. Accordingly, the care an optometrist provides must be given in the best interest of the patient (Schwartz, 2002). This translates to an aim of promoting general and ocular health in order to reduce visual loss to individuals seen in practice.

Vision impairment is one of the main causes of disability (Kassebaum et al., 2016), and is consistently reported to affect quality of life and psychological wellbeing (Kempen & Zijlstra, 2014; Lamoureux et al., 2009; Patino et al., 2010; Senra et al., 2015). Because of the associated sequelae, vision loss is a well-defined public health issue linked to remarkable burden. Approximately 0.5% and 4.5% of adults living in central Europe are estimated to be blind and suffer moderate-severe visual impairment (MSVI), respectively. Age-related macular degeneration (AMD), glaucoma and diabetic retinopathy are among the main causes of irreversible vision loss in the Western world (Bourne et al., 2018; Bourne et al., 2014; Flaxman et al., 2017), and recent European population-based studies show their prevalence to range between 2 and 4%, increasing significantly with age (Colijn et al., 2017; Kapetanakis et al., 2016; Li et al., 2020; Yau et al., 2012). Notably, almost half of MSVI in Europe results from uncorrected refractive error (Bourne et al., 2018). Beside the effects on visual function, uncorrected refractive error can also affect independence and quality of life (Wolffsohn et al., 2011). As such, minimising barriers to visual correction (e.g. a low clinician to population ratio and long waiting times for eye examinations) is a priority of many countries, in which optometry can play a pivotal role (R. S. Baker et al., 2005; Durr et al., 2014).

For many eye diseases early diagnosis and timely treatment would prevent visual damage, making the majority of global blindness avoidable (Flaxman et al., 2017; Robinson et al., 2012). Yet, applying the idea of safeguarding the visual integrity of patients to the Italian setting requires some consideration of the education system and professional regulation. Indeed, the lack of a thorough assessment of ocular heath within the optometric eye examination hampers the ability to identify people at risk of visual impairment. Therefore, in Italy and other countries with similar frameworks, a strong collaboration between optometrists and ophthalmologists is essential for early detection of eye disease and, ultimately, prevention of vision loss.

Optometric referral of patients with suspected ocular pathology to ophthalmologists represents the basis of optometrist-ophthalmologist collaboration and is a crucial step for safeguarding ocular health. In different contexts, where assessment of ocular health is a central component of optometric practice, accurate referrals have been shown to enhance the overall man-

agement of patients, leading to better visual outcomes (Davey et al., 2011; Scully et al., 2009). However, formal guidance on the content of optometric examination and which findings should result in a referral to ophthalmology is currently lacking in Italy and other countries with similar eye-care sectors. As such, in this review we aimed to identify circumstances requiring a referral within a routine eye test in adults and develop an evidence-based framework for referring in the Italian optometric scenario. Although there is no legal limitation regarding the lower age-limit of patients seen in Italian optometric practices (ECOO European Council of Optometry and Optics, 2020), our analysis focused on adults (older than 16 years), intended as patients beyond the plastic period. The resulting recommendations represent an aid to enhance ocular and general health of patients seen in practice.

Methods

In view of the broad research question, the first focus of the review was on the content of a routine optometric examination and what anomalous findings could be detected through the typically performed clinical procedures. A literature search was carried out in Pubmed and the Cochrane Library databases (last updated, June 2020) using a combination of free text, synonyms and subject headings regarding the keywords 'routine eye examination', 'optometric referral', 'eye signs', 'eye symptoms' and 'refractive modifications'. Additional relevant publications were retrieved from bibliographies of identified papers and reference checking. Attention was mainly directed towards secondary literature such as systematic reviews, meta-analysis and clinical guidelines. While considering ideal clinical practice patterns, we focused on recommendations provided in published optometric and ophthalmological guidelines.

Because of limitations influencing Italian optometric clinical examination, patients with unremarkable findings might still be at risk of developing vision loss. Hence, the review secondarily focused on the epidemiology of eye disease in asymptomatic populations and the ideal frequency of ophthalmological eye examinations in healthy individuals. Another literature search was conducted with similar methods as before using the same databases (last updated, June 2020) relating to the keywords 'asymptomatic eye disease', 'vision loss risk', 'eye exam frequency', and 'routine ophthalmological examination'.

Results

Optometric findings requiring a referral

A comprehensive optometric eye examination comprises several sections (American Optometric Association, 2015; The College of Optometrists, 2020). Although there is no guidance on the exact content of the examination within the Italian optometric eye care system, clinical procedures expected to constitute a routine exam will be reported in the sections below. Accordingly, the lack of a thorough eye health assessment within the Italian optometric setting (e.g. no, or limited, ophthalmoscopy) demands some adaptations to international guidelines. As such our analysis will consider the following sections: i) patient history and symptoms, ii) preliminary examination, iii) refraction, iv) visual acuity, v) binocular vision, and vi) ocular surface and anterior segment. Each of these stages may reveal signs, symptoms or risk factors that could indicate an abnormality of the visual system, hence demanding a referral. These will be discussed in detail below and summarised in Table 2.

Patient history and symptoms

This stage allows clinicians to collect information on how patients perceive their own vision as well as relevant clues about ocular and general health (American Optometric Association, 2015; Elliott, 2013). Patients might present with symptoms potentially due to pathology (e.g. sudden onset flashes/floaters) rather than due to conditions that can be managed within the scope of practice of Italian optometry (e.g. refractive errors). In this case, referral to ophthalmology would be required for diagnosis and subsequent treatment. Further, the recent and sudden onset of seemingly minor symptoms such as blurred vision, asthenopia and headache might demand a referral too. Indeed, although these complaints can be frequently induced by a decompensated phoria or uncorrected refractive error, the acute onset is atypical and might be suggestive of pathology (Elliott, 2013).

Findings from the ocular, general, and family history might include potential risk factors for the development of vision loss. Moreover, a diagnosis of any ocular condition as well as previous surgical procedures or ocular trauma require particular consideration (Feder et al., 2016). Patients with general health conditions (e.g. diabetes, hypertension and dyslipidaemia) might require a more frequent and detailed ocular health examination (American Optometric Association, 2015; Elam & Lee, 2013; Elliott, 2013). For example, duration of diabetes is reported as the main risk factor for the development and progression of diabetic retinopathy, with a significant reduction of the risk in the case of adequate glycaemic control (Ting et al., 2016). Patients with a diagnosis of diabetes who do not adhere to recommended frequency of eye exam (see Table 2) should be counselled and referred accordingly. Additionally, the use of drugs with associated ocular side-effects must also be investigated. For instance, corticosteroid treatment exposes patients to side effects such as cortical cataract and the increase of intraocular pressure (Elliott, 2013). A comprehensive list of general health conditions and drugs potentially associated with ocular side-effects can be found elsewhere (American Optometric Association, 2015).

Lastly, a positive family history is known to be a risk for several diseases affecting the visual system (American Optometric Association, 2015; Elam & Lee, 2013; Elliott, 2013). For example, a patient with a first-degree relative with open angle glaucoma is at significantly greater risk of developing glaucoma, compared to a patient without this family history (Weinreb et al., 2016).

Preliminary examination

Clinical procedures performed here vary significantly according to clinical characteristics and symptoms reported by the patients. Anomalous findings could arise after the external gross evaluation of the adnexa (e.g. anomalous position and/or motility of the lids) and orbital structure (e.g., proptosis and exophthalmos). These signs could develop as a consequence of neurogenic, myogenic, inflammatory, or expansive disorders, and referral is required regardless of the specific aetiology (Gerstenblith & Rabinowitz, 2012). Also, the assessment of colour vision may show acquired colour vision defects, which are frequently asymmetrical and associated with visual reduction (Elliott, 2013). Several diseases could result in abnormal colour vision, including ocular media opacity, as well as retinal and visual pathway disorders (Simunovic, 2016). Clinical examination of pupillary function requires attention to a number of details such as diameters, symmetricity, shape, and light and near reflexes (Elliott, 2013). Afferent and/or efferent pupillary anomalies are often linked to neurological disorders and require immediate medical evaluation (Evans, 2007; Kosmorsky & Diskin, 1991).

Refraction

Spherical refractive error undergoes consistent changes with age (Guzowski et al., 2003; Hyman, 2007; Laughton et al., 2018; Williams et al., 2015), with a hyperopic shift between 35 and 65 years of age, followed by an increase of myopia over the age of

65 (see Figure 1). Whilst this myopic shift is unanimously explained by the nuclear sclerosis of the lens (Diez Ajenjo et al., 2015; Pesudovs & Elliott, 2003), hyperopic changes might arise from a combination of reduction of lens refractive index and latent components of hyperopia becoming manifest (Mutti & Zadnik, 2000). Lifelong alterations of astigmatism are also reported (Leung et al., 2012; Sanfilippo et al., 2015; Schuster et al., 2018). Indeed, there exists a tendency of astigmatism to change from 'with the rule' to 'against the rule', and an overall increase of the prevalence of astigmatism (Laughton et al., 2018; Leung et al., 2012; Sanfilippo et al., 2015; Schuster et al., 2018; Williams et al., 2015).

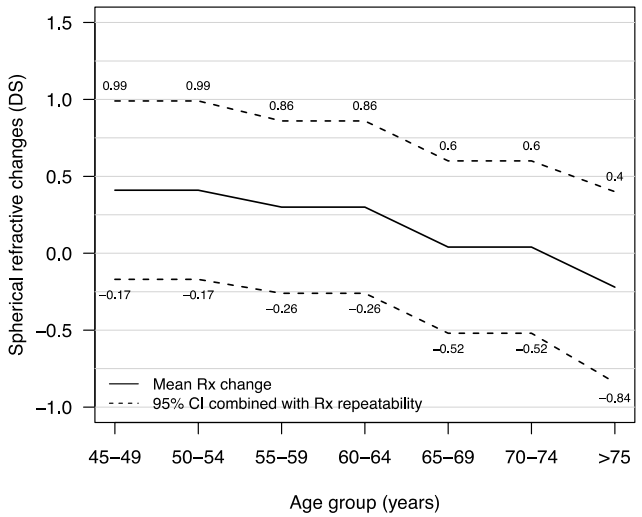

Figure 1: *Refractive shift with ageing. Age-related refractive modifications reported in spherical dioptres (DS, on the y axis). Solid line shows the mean refractive change, dashed lines represent the upper and lower 95% confidence interval (CI) limits combined with subjective refractive repeatability of ± 0.50 DS (Goss & Grosvenor, 1996; McKendrick & Brennan, 1995; Raasch et al., 2001; Zadnik et al., 1992). Refractive data from Guzowski et al. (2003).*

While monitoring the development of spherical refractive errors in adults, therefore, there will be some expected changes. Yet, when changes significantly differ from expected values (see Figure 1), optometrists should be aware of potential pathological implications and consider further investigation by ophthalmologist. Likewise, changes of astigmatism should be unremarkable between two consecutive optometric examinations (i.e. 1 to 3 years), and anomalous progression or onset may require a referral. Several disorders might be responsible for unexpected refractive error changes (see Table 1) and must be considered.

One additional reason for a referral might be the need for cycloplegic refraction, which, unlike in other countries (e.g. United Kingdom (Doyle et al., 2019)), cannot be independently performed by Italian optometrists. Although cycloplegia represents the standard procedure for the determination of refractive error in paediatric practice (American Optometric Association, 2017), clinicians can typically measure refraction reliably without cycloplegia from adolescence onward. Indeed, after the age of 15 differences between cycloplegic and non-cycloplegic refraction become smaller than refraction test-retest variability (Goss & Grosvenor, 1996; McKendrick & Brennan, 1995; Raasch et al., 2001; Zadnik et al., 1992), and therefore not clinically relevant (Fotouhi et al., 2012; Sanfilippo et al., 2014)). Nonetheless, cycloplegia might still be required to achieve a reliable measurement of refraction in young adults with excessive accommodative fluctuation, pseudomyopia, or suspected latent hyperopia, hence requiring a referral (Elliott, 2013).

Table 1: *Main causes of unexpected refractive changes demanding a referral in Italian optometric practice.*

Condition	Type of refractive change	Procedure that would alert the practitioner
Cataract (Diez Ajenjo et al., 2015; Pesudovs & Elliott, 2003)	Myopic or hyperopic (can be greater than 1.50 DS), astigmatic	Retinoscopy, anterior eye examination
Poorly controlled diabetes mellitus (Huntjens et al., 2012; Klein et al., 2011)	Myopic (hyperglycaemia) and hyperopic (hypoglycaemia), changes greater than 0.75 DS	Case history and prior records
Medications (American Optometric Association, 2015).	Varies depending on the drug	Case history
Corneal and/or adnexa changes (Goebels et al., 2015; Weiss et al., 2015)	Typically, astigmatic (asymmetric)	Retinoscopy (e.g., keratoconus), anterior eye examination (e.g. chalazion/ptosis, corneal dystrophies), case history (e.g. refractive surgery)
Subluxated lens (Nelson & Maumenee, 1982)	Astigmatic	Anterior eye examination

Visual acuity

Visual performance is known to decline with age in response to physiological optical and neural deterioration (Martinez-Roda et al., 2016). For instance, visual acuity and contrast sensitivity steadily decrease from their peaks after the age of 20 and 30, respectively (Andersen, 2012; Martinez-Roda et al., 2016; Owsley, 2016). Though best corrected visual acuity (BCVA) only gives a basic indication of central visual function, it represents a widely used test in practice and anomalous values of BCVA require further evaluation by ophthalmologists. These might include: i) BCVA values below age-matched reference intervals (see Table 2); ii) BCVA values significantly below previous examination (> 0.1 LogMAR in visually normal patients); and iii) significant difference between the two eyes (> 0.1 LogMAR in visually normal patients), in absence of known and stable ocular conditions (McGraw et al., 2000).

Importantly, several disorders affecting central vision could coexist with normal, or close to normal levels of VA, at least at their earlier stages (Cocce et al., 2018; Scanlon et al., 2008; Scilley et al., 2002). Accordingly, for at-risk patients, e.g. those at risk of AMD (Chakravarthy et al., 2010), a more detailed examination of central vision is required. Several clinical procedures could be used, amongst which the Amsler grid represents an effective screening test for macular disorders such as AMD (Faes et al., 2014). In cases of Amsler grid distortions, metamorphopsia or central scotoma, further medical examination and therefore a referral is required.

Binocular vision and ocular motility

Binocular vision assessment provides essential information for an effective prescription (American Optometric Association, 2015; The College of Optometrists, 2020), and allows for the screening of ocular and systemic diseases (Martinez-Thompson et al., 2014; Patel et al., 2005). A new strabismus or the change of an existing one might signify underlying pathology (American Optometric Association, 2015), hence requiring a medical examination and a secure ophthalmological diagnosis. Depending on the time of onset of strabismus, the management and the need for referral will differ significantly. Adults with long-standing strabismus often present with a totally asymptomatic deviation, evidenced by a concomitant strabismus and a binocular sensory adaptation responsible for the lack of diplopia (Bagolini, 1974). In this case, integrating the history to collect relevant in-

formation supporting the early onset of the binocular anomaly is recommended. A diagnosis of 'lazy eye' in a previous ophthalmological exam, a positive history of patching or strabismus surgery, and the absence of any symptoms of double vision could allow the optometrist to consider the condition stable, and not associated with active pathology. After initial diagnosis, these cases are usually stable and do not require referral. Alternatively, adults might present with recently acquired strabismus, which, as a result of their causative nature are often incomitant. Indeed, several ocular and systemic disorders might result in strabismus (Martinez-Thompson et al., 2014; Patel et al., 2005), requiring immediate neuro-ophthalmological examination. Although these patients might seek medical assistance first, acquired deviations could be encountered at their earliest stages such as an incomitant heterophoria, i.e. compensated phoria in primary position of gaze with diplopia in the peripheral gazes (Evans, 2007). The sudden onset of diplopia coupled with the incomitant nature of the deviation are strong indicators of recent onset strabismus, and prompt referral for an early diagnosis is essential.

Table 2: *Summary of findings in an Italian routine optometric examination that would require to refer the patient for ophthalmological examination.*

Category	Details
Non optometric symptoms	These include: transient visual loss (sustained visual loss [lasting > 24 hours] either sudden and painless or painful and posttraumatic); binocular diplopia (recent onset with no history of decompensated heterophoria); loss of eyelashes; oscillopsia (vertigo and dizziness); flashes of light; floaters (new, recent onset or progression of existent ones); halos around lights (in non-contact lens wearers, with unknown corneal disorder and/or refractive error); headache (not related to vision tasks); photophobia; ocular, periorbital and orbital pain (if mild to moderate, this could be caused by eye strain from uncorrected refractive error or dry eye); red eye (dry eye and corneal involvement must be ruled out; for contact lens wearers decisions will be taken following the after-care); positive or negative scotoma; excessive tearing, discharge, itchy eyes.
Positive family history	For ocular diseases and/or systemic disorders with ocular involvement, leading to an increased risk of developing ocular disorders. Positive family history of glaucoma requires eye examination every 1–2 years (Feder et al., 2016).
Anomalous previous ocular history	Patients presenting with previous ocular: i) trauma, ii) surgery, iii) disease, iv) high or progressive ametropia,v) functional vision in only one eye, who are not receiving adequate medical attention/follow-up.
General health disorder	Patients presenting with factors related to general conditions, lifestyle, medications (e.g. steroids) associated with potential ocular damages. E.g: Type 1 DM patients require a comprehensive medical eye examination 5 years after diagnosis, then annually; Type 2 DM patients require a comprehensive medical eye exam at diagnosis, then annually (Feder et al., 2016).
Acquired colour vision defect	Newly onset (or long standing but not diagnosed) colour vision disorder in the absence of medical examination.
Pupillary defect	Newly onset (or long standing but undiagnosed) pupillary anomalies in the absence of medical examination.
Orbital and Lids disorder	Orbital and eyelid disorders (proptosis, ptosis, eyelid swelling, lagophthalmos, excluded: physiologic age-related modifications).
Abnormal spherical changes	Physiological refractive changes are a slight hyperopic shift between 30–35 and 65–70 years of age followed by a myopic shift beyond the age of 70–75 years (see refraction section). In case of anomalous shift, pathological causes might be linked to cataract, progressive myopia, drugs or medications use, previous refractive surgery, corneal ectasia, undiagnosed (or uncontrolled) diabetes, other.
Abnormal astigmatic changes	Expected modification is a slight progressive increase of against the rule component – unremarkable between consecutive routine exams (2–3 years). After excluding previous under-correction, pathological causes to be considered are corneal ectasia, cyst, cortical cataract, previous refractive surgery, other.
Cycloplegic refraction	Clinical examination reveals conditions (e.g., accommodative spasm) requiring cycloplegic refraction.
Reduced vision	Anomalous BCVA: i) lower than age-matched expected values (Elliott et al., 1995): < -0.02 LogMAR (20–49), < 0.00 LogMAR (50–59), < 0.04 LogMAR (60–69), < 0.08 LogMAR (70+); ii) significantly lower than previous examination (> 0.1 LogMAR); iii) Significant difference between the two eyes (> 0.1 LogMAR).
Positive Amsler test	Amsler test showing anomalous findings (e.g. scotoma, metamorphopsia, etc).
Binocular vision disorder	Recent onset of any strabismus, modification of the motor component of existing strabismus, and previously undiagnosed strabismus require medical assessment. Further, any new onset of diplopia (in at least one position of gaze) requires referral.
Vergence or accommodative disorder	Non strabismic binocular vision anomalies and/or accommodative disorders with suspicious pathological aetiology: Acute onset of symptoms, symptoms not related to visual tasks, incomitant deviation, co-existence of neurologic symptoms (e.g. vertigo, dizziness).
Anterior segment disorder	Evolving disorders and/or disorders not previously diagnosed by ophthalmologist involving anterior chamber, irido-corneal angle, cornea, conjunctiva, adnexa, lids, iris, lens.
Lacrimal disorder	Excessive tearing (epiphora) or dry eye disorders.
Glaucoma risk	Patients exposed to an increased risk of developing glaucoma: affected first grade relative, shallow anterior chamber (Van Herick < grade 2), myopia > 6.00DS, pigment dispersion or pseudo-exfoliation syndrome, thin cornea (< 510μm), on treatment with steroids.
Abnormal IOP	IOP > 21 mmHg; increased IOP according to previous examination (> 4 mmHg); significant IOP differences between two eyes (> 4 mmHg); IOP < 7 mmHg.

A considerable proportion of the population may present with a non-strabismic binocular vision anomaly or an accommodative dysfunction (Cacho-Martinez et al., 2014; Cacho-Martínez et al., 2010). Although these disorders have been reported to be typically functional in nature (i.e., not caused by active pathology), several of their signs and symptoms could also be observed in case of disease (Cacho-Martinez et al., 2015; Garcia-Munoz et al., 2014). A pathological cause should be especially suspected in cases of sudden and acute onset of symptoms unrelated to visual task, presence of an incomitant element, and the association of neurologic signs (e.g. vertigo, dizziness, headache, etc.). In such cases, patients should be referred to exclude any potential underlying pathology, and management undertaken only afterwards.

Ocular surface and anterior segment evaluation

Routine optometric examinations in different countries often include a thorough ocular health assessment targeting the whole eye (American Optometric Association, 2015; Robinson et al., 2012; The College of Optometrists, 2020). As reported earlier, a comprehensive exam of ocular health is not performed by Italian optometrists. Hence, this section only focuses on the exam of the anterior segment, which we speculate is the focus of this part of the exam given that Italian optometrists are not extensively trained in ophthalmoscopy.

Slit lamp examination allows for the evaluation of different structures of the anterior segment and ocular adnexa. At this stage, all conditions identified as evolving and that have not received ophthalmological diagnosis must be considered as abnormal and require a referral. It is beyond the scope of this article to detail all possible conditions, yet, a knowledge of the anatomy of all the structures, as well as their physiological age-related variations is required for every practitioner (Elliott, 2013). Examination of the tear film and ocular surface is routinely performed for contact lens wearers, yet still required

on every patient. This is particularly necessary if history reveals dry eye symptoms or predisposing risk factors. Notably, some cases of aqueous deficiency dry eye could result from auto-inflammatory disorders that require medical investigation (Craig et al., 2017; Vitali et al., 1994).

Anterior chamber depth estimation using the van Herick technique (Van Herick et al., 1969) can be performed on all patients, being a crucial marker in those at risk of glaucoma. The technique can help to identify individuals with an increased risk of angle closure, i.e. < Grade 2 on a 0–4 graded scale (Campbell et al., 2015), and individuals with a narrow angle require to be referred for further investigation. Similarly, signs of pigment dispersion or pseudo-exfoliation require ophthalmological examination, since these conditions are associated with an increased risk of developing open angle glaucoma (McMonnies, 2017).

Italian optometrists do not have permission to use diagnostic drugs or invasive clinical procedures, hence Goldmann Applanation Tonometry (GAT) cannot be performed. Non-invasive methods to assess intraocular pressure (IOP) are, however, available, and non-contact tonometry is a reliable method of measuring IOP, with 2/3 of the measurements within 2 mmHg of the reference GAT's IOP (Cook et al., 2012). However, clinical guidelines indicate that every patient with glaucoma or at risk of developing it requires IOP measurement by GAT (National Institute for Health and Clinical Excellence (NICE), 2017). Further, relying solely on IOP measurement is a poor screening test for glaucoma, with 40% of patients with the condition presenting with IOP lower than 21 mmHg (Shah & Wormald, 2011). Accordingly, although raised IOP is the main risk factor for developing glaucoma and often requires a more frequent follow-up and/or treatment (Prum et al., 2016), the use of non-contact tonometry in isolation has little value in the detection of glaucoma. It is essential for clinicians performing non-contact tonometry to be aware that 'normal' IOP values do not rule out glaucoma, and a comprehensive medical eye examination including visual field testing and optic disc assessment is essential for diagnosis (National Institute for Health and Clinical Excellence (NICE), 2017). As such, in Italy patients at risk of glaucoma need to undergo comprehensive medical eye examinations by ophthalmologists. For those practitioners performing non-contact tonometry, the technique could be performed on every patient seen in practice, referring those with: i) risk factors for glaucoma and ocular hypertension, such as: affected first grade relative, shallow anterior chamber [van Herick below Grade 2], myopia > 6.00 DS, pigment dispersion or pseudo-exfoliation syndrome, thin cornea (< 510 μm (Prum et al., 2016)), ongoing treatment with steroids (The College of Optometrists, 2020); ii) IOP > 21 mmHg; iii) increased IOP compared to previous examination (> 4 mmHg); iv) significant IOP differences between two eyes (> 4 mmHg); v) IOP < 7 mmHg (Elliott, 2013).

In summary, Table 2 details reasons why patients attending an optometric examination would require referral.

Referral need for patients with normal optometric findings

Asymptomatic patients might still suffer an ocular condition not identified by the Italian optometric assessment or be at increased risk of developing an eye disease. Several studies indicate that between 14% and 26% of patients might present asymptomatic eye pathologies (Irving et al., 2016; Michaud & Forcier, 2014; Robinson, 2003; Wang et al., 1994). Findings from a Canadian study provide disease-specific prevalence data in a cohort of patients without visual symptoms undergoing a comprehensive ocular examination, including dilated fundus examination (Michaud & Forcier, 2014). Accordingly, 220 patients (26.1%) were diagnosed with at least one ocular condition (see Table 3), most frequently affecting the retina.

Table 3: *Ocular conditions as detected during routine eye examinations on asymptomatic patients at a university eye clinic in Canada.*

Likely detected ocular condition	Prevalence (%)
Blepharitis; dry eye syndrome	2.9
Pathology related to contact lenses	1.2
Cataracts; intra-ocular lens opacities	0.9
Anterior segment dystrophy, degenerations; conjunctivitis	0.8
Binocular vision problems impacting work/school	0.6
Overall	6.4
Likely undetected ocular condition	**Prevalence (%)**
Retinal hole; lattice degeneration; peripheral retinal abnormalities	7.7
Glaucoma; ocular hypertension; angle closure glaucoma suspect (narrow angles)	4.9
Suspicious lesion in the fundus (naevus, etc.)	2.7
Macular degeneration or other maculopathy	1.9
Suspicious lesion of adnexa or lids	1.1
Hypertensive and diabetic retinopathy	0.9
Optic neuropathy (non-related to glaucoma)	0.5
Overall	19.7

Note: Conditions are grouped according to the likelihood of being detected during an Italian optometric examination. Data reproduced with permission from Michaud and Forcier (2014). Prevalence in % of patient visits.

There are no reports on the epidemiology of asymptomatic eye disease in Italian optometric practice. Although international findings might not be generalisable to the Italian setting, by applying the characteristics of the Italian eye test to published prevalence data (Michaud & Forcier, 2014), it is possible to estimate the rate of disease which might remain undetected. As detailed in Table 3, the Italian routine eye test could have failed to detect pathology in up to 19.7% of asymptomatic patients in the Canadian cohort. Notably, some of the conditions that are likely to remain unnoticed by Italian optometrists are also the ones most likely to result in sight loss (e.g. diabetic retinopathy, optic neuropathies and glaucoma).

The risk of developing a new asymptomatic eye disease has been shown to increase with age and the interval between consecutive exams (Irving et al., 2016). Indeed, age is an unmodifiable risk factor for most ocular diseases, whereas larger time intervals between eye exams would provide more time for pathological processes to develop. Several factors might affect the uptake of eye examinations, including exam cost, provided recommendations, and recalls from practices (Alexander et al., 2008; Irving et al., 2016). Additional factors demanding consideration are the patient's risk perception and their understanding of outcome determination (Elam & Lee, 2013; Irving et al., 2016; Livi et al., 2017). The former refers to the individual's awareness of being at risk of developing visual impairment, whereas 'outcome determination' describes the comprehension by patients of the negative consequences of not having their eyes checked routinely. Both these factors can affect the uptake of optometric examinations – even in Italian settings (Livi et al., 2017) – and can be directly influenced by optometrists through their communication with patients. A positive impact on risk perception and outcome determination could be achieved, either by giving patient recommendations or spreading awareness about the need for ocular health exams by ophthalmologists. In contrast, the misconception that unremarkable findings from a routine Italian optometric examination mean good ocular health might negatively affect the frequency of ophthalmological eye exams.

These findings applied to the Italian context emphasise the need for systematic ocular health assessment by ophthalmolo-

gists. Undergoing such examinations enables the opportunistic identification of early signs of eye disease, preventing vision loss and improving ocular and general health of patients (Elam & Lee, 2013; Picone et al., 2004). Although the ideal frequency of routine eye tests is patient-specific, it is generally suggested that patients more likely to develop vision loss should be examined more often (American Optometric Association, 2015; Elam & Lee, 2013; Feder et al., 2016). For instance, diabetic patients require more frequent ocular assessment (see Table 2) as pathological changes might develop more frequently and at a faster rate (Sabanayagam et al., 2019). Patients with healthy eyes and no specific risk-factors for eye disease can be considered at 'low risk' of developing visual impairment. Yet, as recommended in ophthalmological guidelines, they still require periodical assessments of ocular health, which becomes more frequent with age: every 5–10 years (under 40), every 2–4 years (40–54), every 1–3 years (55–64), and every 1–2 years in 65 or older (Feder et al., 2016).

The time relationship between the last medical eye exam and the current ophthalmological recommendations on the frequency of ocular health assessments allows a gross estimate of ocular safety to be made – later referred to as the Ocular Safety Index (OSI). The OSI represents the need to have an ophthalmological assessment. For example, a patient with a normal optometric examination who had received an ophthalmological examination within the recommended interval (see above) would have a positive OSI. On the other hand, a patient with unremarkable optometric examination who hadn't had an ophthalmological examination recently (i.e. within recommended interval) would have a negative OSI, hence requiring counselling and appropriate referral. Accordingly, the OSI is independent of the patient receiving an optometric examination.

Discussion

Preventing visual impairment and the consequent disability is a well-defined public health interest to be pursued unanimously by eye-care practitioners (Frick & Foster, 2003). In this regard, early diagnosis and prompt commencement of treatment are essential. In Italy, as in many other countries, ophthalmologists are uniquely responsible for the detection, diagnosis, and treatment of ocular pathology. Because of the limited scope of practice of Italian optometrists, the referral to ophthalmologists is a fundamental instrument that must be used to promote timely detection of ocular disease and therefore prevention of avoidable vision loss.

At present, there are no formal guidelines available to Italian optometrists indicating actions to be taken according to the findings of an eye examination. Addressing this gap, this review explored the circumstances requiring a referral within the Italian optometric eye-care system. Every stage of the optometric exam could potentially lead to the detection of signs and symptoms demanding a referral of a patient to an ophthalmologist (see Table 2). In these patients, some of the clinical procedures performed may indicate abnormalities which demand further medical investigation for the diagnosis and potential treatment of ocular conditions. While considering the content of the examination currently performed within Italian optometry, referral to ophthalmology might also be needed after an uneventful optometric exam. Indeed, a considerable proportion of patients seen in practice (up to 19%) might develop eye disease asymptomatically and with signs remained undetected during the exam. Accordingly, apparently low risk patients could still present an eye disease and still require an ophthalmological examination. In cases where the ideal frequency of medical eye exams is unmet (negative OSI), referral is, therefore, warranted.

Considering adults presenting for an optometric examination in Italy, four clinical case scenarios might be delineated according to the need for an ophthalmological assessment (see Figure 2). Categories identified in Figure 2 define a potential framework for referral in Italian optometric practice. This framework has the potential to constitute an initial evidence base for driving a more defined referral pathway, and its adoption should result in an improved optometrist-ophthalmologist synergy. This should also result in more timely detection of ocular disorders, ultimately leading to enhanced quality of care delivered by optometrists and better visual outcomes for patients (Peters et al., 2014; Taylor et al., 2004).

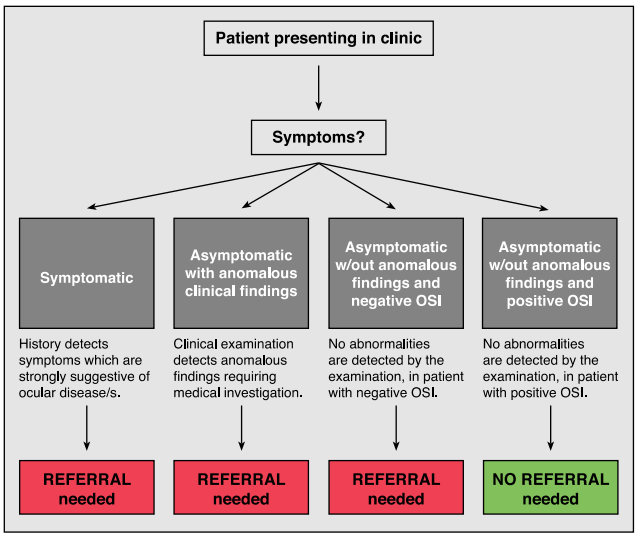

Figure 2: *Need for referral of patients presenting for optometric examination. The flowchart indicates those patients who need to be referred following a routine Italian optometric examination in adults (> 16 years old). The OSI refers to the Ocular Safety Index. OSI will be either negative, when patient is not attending the optimal frequency of eye health exams, or positive, when the follow-up is successfully respected.*

It must be stressed that weaknesses of Italian optometric examinations demand a conservative referral approach when aiming to avoid visual impairment. Indeed, it could be said that the proposed framework is likely to result in a large number of healthy patients being sent for ophthalmological exams, commonly defined as 'false positives' (Bowling et al., 2005). Also, it is important to consider whether ophthalmological capacity is capable of meeting the demands of an increasingly ageing population (United Nations, 2017). This, coupled with the already overwhelmed ophthalmological sector of the National Health Service (Consorzio per la Ricerca Economica Applicata in Sanità, 2017), makes the referral of a large number of potentially healthy people detrimental. Once referred, false positive patients might seek assistance through the National Health Service, unnecessarily increasing waiting times, which is in itself can result in avoidable deterioration of patients' eye health (Foot & MacEwen, 2017). Alternatively, these patients could receive private ophthalmological exams, resulting in considerable costs especially with the increase in suggested frequency of ocular health assessment with increasing age. A health care system based on ability to pay, however, is likely to disproportionately affect those from lower socio-economic backgrounds.

The lack of a comprehensive ocular examination by the Italian optometrist means that reduction of 'false positives' is not achievable without increasing the risk of patients with potential pathology being classified as healthy. Elsewhere, in countries such as the United Kingdom, where optometrists are trained in techniques such as (in)direct ophthalmoscopy and GAT, solutions that have been adopted to enhance accuracy of refer-

rals include referral refinement schemes (Henson et al., 2003). These include intermediate centres between the referring practitioner and ophthalmologists, in which specifically trained optometrists reassess the actual need for a referral by repeating essential clinical tests and/or performing additional procedures. Implementations of refinement schemes have widely demonstrated improvements to the quality of referral, reducing the number of false positives and therefore unnecessary demands on already overstretched ophthalmological sectors (H. Baker et al., 2016; Barrett et al., 2018; Ratnarajan et al., 2013). Patients referred because of a 'negative OSI' would seem particularly suitable for utilising similar schemes, perhaps run in close collaboration between ophthalmology and optometry, upon further and specialised training. This might offer additional pathways for timely and affordable ocular health checks, without creating additional demand on the national health system or individual patients' finances. Along with solutions to enhance referral accuracy, an alternative to be mentioned is the modification of training received by optometrists in Italy and an extension of the scope of practice. Such changes could be targeted to enhance the overall ability of optometrists in case detection, with considerable contribution to the reduction of unnecessary referrals of healthy people. More collaborative eye-care models are increasingly proposed worldwide to alleviate the workload on ophthalmologists, due to increased demand not adequately matched by a similarly growing capacity (Barrett et al., 2018; George et al., 2019; Mets et al., 2012). Nonetheless, both mentioned approaches would require formal assessment of their feasibility as well as of the associated cost-effectiveness.

Limitations

It is important to state that this study has limitations. This was not a systematic review, therefore, potentially relevant literature may have been missed. However, the combination of a literature-search on two databases with the reference checking of included publications is likely to have minimised not-retrieved publications. A further shortcoming of using a non-systematic approach is the lack of a standardised and repeatable critical appraisal of included studies. Yet, the recommendations presented are largely derived from optometric and ophthalmological guidelines, which rely on systematic search and appraisal of the literature. It is also worth noting that the review aimed to address the broad question of when Italian optometrists need to refer their patients, and there are significant deficiencies in the available evidence. Indeed, there is a i) lack of peer-reviewed publications directly relating to the Italian setting; and ii) the majority of available studies have an observational design. Hence, considerable interpretation was required to translate the retrieved evidence in potential clinical guidance. Overall, considering the underlying settings, a systematic review might not have been ideal to answer the broad query, and it has been suggested that narrative approaches may also be appropriate (Greenhalgh et al., 2018).

The shortage of data describing patients' demographics and current practice pattern of optometry in Italy is a major limitation and detailed information urges for better organisation of assistance for this sector. Primary research conducted in Italy is also essential to further understand whether findings generated elsewhere are generalisable to Italian settings. In fact, the bulk of research within the optometric area is conducted in high-income countries with an eye-care sector notably different from Italian one (e.g. US, UK, Canada, Australia), where primary eye-care is led by optometrists. This is likely to result in differences of the characteristics of patients seen in practice compared to Italy. Generalisability is a key concept when appraising literature, defining whether findings from a given piece of evidence can be transferred tso the population of interest (Ferguson, 2004; Kukull & Ganguli, 2012). On one hand it depends on the study design and its internal validity, yet to define generalisability a thorough understanding of the target population is essential. Lack of knowledge of the demographics and clinical characteristics of patients seen in Italian optometric practice currently prevents the establishment of generalisability from other settings.

Further limitations include the absence of a more inclusive study design to define recommendations. Work from a more heterogeneous group, comprising of ophthalmologists, public health consultants and patients, would be desirable to achieve consensus and refine the proposed scheme. It must also be considered that, although the categories presented in Table 2 are directly applicable in practice, they lack the ideal amount of detail and could be caused by a variety of ocular disorders, whose aetiology cannot always be ascertained. Overall, this is likely to impede the accurate definition of urgency of the referral, which is an essential component of the referral letter and a determinant of its accuracy (Davey et al., 2016).

Lastly, it must be remarked that the present lack of regulation that Italian optometrists face might limit wide adoption and uniformity of the proposed guidelines. It seems clear that the profession would dramatically benefit from an official and clear arrangement of optometry in the public health scenario by national authorities.

Conclusion

Irrespective of the practising country, the best interests of patients must be central in guiding optometric clinical practice. According to the current scope of practice and training, optometrists in Italy must operate in close collaboration with ophthalmologists to safeguard ocular health of patients. Hence, referral is a crucial management strategy that must be largely adopted. A variety of signs and symptoms determine the need for a referral. However, as many as one in five patients may suffer underlying conditions remaining undetected by the current Italian optometric examination. In order to allow for early diagnosis and treatment of ocular conditions by ophthalmologists, referral is a fundamental instrument that Italian optometrists must use to play their part in the reduction of preventable visual impairment. We have presented here a preliminary evidence-based framework for referral in optometric clinical practice. Although considerable refinement is still required, this instrument identifies categories constituting reasons for referral. This has the potential to aid in standardising optometric practice, enhancing optometry-ophthalmology synergism and, more importantly, improving patients' visual and general outcome.

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Videre henvisning i rutinemessig italiensk optometrisk praksis: mot en kunnskapsbasert modell

Sammendrag

Mens optometrister i Italia refraksjonerer pasienter og foreskriver optiske hjelpemidler, er det oftalmologer som er ansvarlige for å avdekke, diagnostisere, og behandle øyesykdommer. I settinger med denne type praksis er nært samarbeid mellom optometrister og oftalmologer nødvendig for å begrense unngåelig tap av syn. Henvisning til oftalmolog danner grunnlaget for dette samarbeidet, men foreløpig finnes det ikke tilgjengelig noen veiledning for italienske optometrister som indikerer når henvisning er anbefalt. Målet med dette studiet var å indentifisere omstendigheter der henvisning er anbefalt i italiensk rutinemessig optometrisk undersøkelse av voksne, som kan utgjøre et innledende rammeverk for en kunnskapsbasert henvisningsmodell.

Et litteratursøk ble foretatt ved hjelp av Pubmed og The Cochrane Library. For å utlede kliniske rutiner var hovedfokuset på sekundær litteratur av høy kvalitet, som systematiske oversikter og kliniske retningslinjer.

Flere tegn og symptomer som avdekkes under en rutinemessig italiensk optometrisk undersøkelse vil kunne være årsak til henvisning. I tillegg til at mange anomalier av syn og øyne sannsynligvis vil oppdages i løpet av undersøkelsen, er det mulig at opptil 19% av alle pasienter har tilstander uten symptomer som muligens ikke vil avdekkes av dagens rutineundersøkelse. Dette betyr at det er behov for å henvise symptomfrie pasienter dersom de ikke har hatt rutineundersøkelse hos oftalmolog i løpet av anbefalte tidsrammer.

Dagens utdanning innen optometri i Italia og omfanget av italiensk optometrisk praksis er avhengig av et nært samarbeid med oftalmologer for å sikre pasientens øyehelse. Henvisning er et fundamentalt verktøy som optometrister i Italia og andre land med liknende praksis må bruke for å oppnå tidlig oftalmologisk diagnose og behandling av øyetilstander. Vi har presentert et foreløpig kunnskapsbasert rammeverk for optometrisk henvisning som identifiserer kategorier av årsaker for henvisning. Dette har potensiale til å standardisere optometrisk praksis, styrke samarbeidet mellom optometri og oftalmologi, og ikke minst bedre pasientenes okulære og generelle helse.

Nøkkelord: Henvisning, rutinemessig synsundersøkelse, unngåelig synstap, refraksjon, symptomfrie pasienter, folkehelse

Invio al medico a seguito dell'esame optometrico: verso un modello italiano basato sulle evidenze scientifiche

Riassunto

In Italia, l'optometrista si occupa di refrazione e prescrizione di dispositivi ottici, mentre è il medico oculista la figura responsabile della diagnosi ed il trattamento delle patologie oculari. In un contesto simile, una stretta collaborazione tra optometrista e medico oculista è essenziale per ridurre il rischio di danno visivo evitabile. L'invio al medico rappresenta la base di tale sinergia, ma non sono ancora disponibili linee guida optometriche che delineino quando tale gestione sia necessaria. Lo scopo di questo studio è identificare le indicazioni circostanze di invio al medico a seguito dell'esame optometrico in soggetti adulti, all'interno del calendario delle visite oculistiche consigliate per la prevenzione delle malattie oculari. Le indicazioni ottenute possono rappresentare un modello preliminare di invio al medico, basato sulle evidenze scientifiche.

E'stata condotta una revisione della letteratura tramite i database PubMed e Cochrane Library. Sono state particolarmente utilizzate le fonti di ricerca secondaria di elevata qualità come revisioni sistematiche e linee guida, al fine di stabilire indicazioni per la pratica clinica.

L'indagine optometrica condotta nel contesto italiano può rilevare numerosi segni e sintomi che richiedono l'invio al medico. In ogni modo, sebbene l'esame optometrico sia capace di riscontrare un'ampia gamma di anomalie visive, fino ad un 19% dei pazienti osservati potrebbe presentare un disordine asintomatico potenzialmente non rilevato dalla valutazione. Per questo motivo, anche quei pazienti con esame optometrico apparentemente nella norma potrebbero richiedere un invio al medico, qualora l'ultimo esame oftalmologico non sia stato eseguito all'interno del calendario delle visite oculistiche consigliate.

Il ruolo che l'optometrista ricopre attualmente in Italia, e la formazione ricevuta, richiedono una stretta collaborazione con il medico oculista, al fine di salvaguardare la salute oculare dei pazienti. L'invio al medico rappresenta uno strumento fondamentale che gli optometristi in Italia, ed in paesi con sistema assistenziale simile, devono utilizzare per favorire la diagnosi precoce ed il trattamento di patologie oculari da parte del medico oculista. In questo studio è stato presentato un modello preliminare basato sulle evidenze scientifiche, che identifica una serie di categorie di anomalie che richiedono l'invio al medico. Questo modello ha la potenzialità di contribuire alla standardizzazione della pratica optometrica in Italia, potenziare la sinergia optometrista-oculista e, primariamente, migliorare la salute oculare e generale dei pazienti assistiti.

Parole chiave: invio al medico, esame optometrico, danno visivo evitabile, refrazione, pazienti asintomatici, salute pubblica