New Advances In Nutrition And Eye Health

Laboratoires Théa Satellite Symposium
16th EURETINA Congress

10 September 2016
Copenhagen, Denmark
Interest of Early Screening for AMD Prevention

Gerhard Garhöfer MD, Department of Clinical Pharmacology, Medical University of Vienna, Austria
gerhard.garhoefer@meduniwien.ac.at

Early screening makes sense in the context of AMD. AMD is a major global health problem: 1.2 million people in the USA alone suffer from neovascular AMD and 970,000 more have geographic atrophy. More than 8 million people have at least one large drusen – often considered a precursor to full-blown AMD – in one eye, and an estimated 3.6 million people have bilateral large drusen.1

The disease is not just restricted to Europe or the USA. A recent study by Wong et al looking at the prevalence of AMD by geographical region pinpointed Asia as the region that will see the largest projected number of cases of AMD in the future, despite having the lowest estimated prevalence currently.1 With life expectancy increasing in all parts of the world, the projected number of people with AMD is around 196 million in 2020, increasing to 288 million in 2040.

This looming epidemic poses an enormous challenge for global healthcare systems. One particular strategy that may help to reduce the burden of AMD therapy in the future is to use screening in order to identify high-risk patients much earlier in the disease process.

Experience has shown that screening is mostly effective if the condition in question constitutes an important health problem, if it detects a disease while a patient is asymptomatic, and if initiation of an efficacious therapy could prevent or retard progression of a disease to reduce vision loss.2 Moreover, the total cost of finding a case should be economically balanced in relation to medical expenditure as a whole (Figure 1). AMD also represents a significant problem in terms of the burden of the disease. One study of the economic burden of AMD reported that moderate AMD was found to produce a 40% decrease in quality of life, on a par with that associated with permanent renal dialysis or severe cardiac angina.2

One of the problems is that early to moderate AMD is often symptomless, so patients might not see an ophthalmologist at all during the early phase of the disease. While an estimated 80% of subjects have a dry or non-neovascular form of AMD, it is the “wet” neovascular AMD which is responsible for 90% of severe vision loss, hence the interest in identifying high-risk patients in order to prevent or slow down its progression.

Therapy for at-risk subjects could include vitamin supplementation as recommended by the Age-Related Eye Disease Study (AREDS)4 and Age-Related Eye Disease Study (AREDS)4 and Age-Related Eye Disease Study (AREDS).
New Advances In Nutrition And Eye Health

Study 2 (AREDS2). Data from the first AREDS study showed a clear benefit in administering a mixture of antioxidant vitamins and mineral supplements in terms of progression of AMD. The formulation given in AREDS to patients included vitamin C, vitamin E, beta-carotene, zinc and copper, which reduced the risk of progression to late AMD in high-risk patients by up to 25%.

The public health impact of this 25% reduction is significant. Several studies have looked at this issue and concluded that it is very cost effective, with potential savings in the billions of dollars if the 25% reduction in the AREDS study is attained (Figure 2). The notable success of the AREDS studies opened the path for investigation into the potential of other minerals and supplements such as lutein and zeaxanthin, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), resveratrol and vitamin D in the prevention of AMD.

REFERENCES

Figure 2 Frost & Sullivan’s Report: Smart Prevention—Health Care Cost Savings Resulting from the Targeted Use of Dietary Supplements 2013

Figure 1

STARS:
A Validated Score to Screen Patients at Risk of AMD

Cécile Delcourt MD, University Hospital Bordeaux, France cecile.delcourt@isped.fr

The past 20 years have seen many risk factors identified for AMD. Strong and consistent associations include age and ethnicity, with a higher incidence in people of European and Asian origin compared to those of African descent. Smoking and genetic factors are also important, with more than 50 identified polymorphisms now linked to the risk for AMD. Finally, low dietary intakes in key nutrients such as antioxidants, lutein and zeaxanthin, and omega 3 fatty acids have been associated with an increased risk of AMD in many observational studies.

Other risk factors for AMD with moderate and consistent associations include higher body mass index (BMI), history of cardiovascular disease, hypertension, and also some ocular factors such as hyperopia and cataract surgery. Risk factors with weaker associations and inconsistent associations include gender, diabetes, iris colour, history of stroke, and plasma lipid levels.

There is a need for better prediction models for AMD. Some current models are based on available risk scores that include genetic single-nucleotide polymorphisms (SNPs), which are not yet readily available to ophthalmologists and patients. On the contrary, available risk scores include only limited information on environmental factors, usually age, smoking and BMI. Furthermore, the risk scores have been developed on the basis of limited datasets (AREDS, three population-based studies and two clinical studies), so there is still some room for alternative, and hopefully more accurate, prediction models.

With this in mind, the STARS (Simplified Théa AMD Risk-Assessment Scale) questionnaire was elaborated in order to develop a simple risk score based on a self-completed 13-item questionnaire for large-scale detection of patients at risk of AMD (Figure 1).

The questionnaire focused on a more comprehensive inclusion of environmental risk factors taking account of cardiovascular disease, socio-demographic characteristics, family history of AMD, and systemic and ocular risk factors.

The questionnaire is very simple and takes only a few minutes to complete, a self-completed questionnaire.
A MD is a multifactorial disease with many environmental, lifestyle and genetic factors. It is also a very complex disease in terms of understanding the key role that inflammation plays in the pathogenesis of AMD. In the human body, the inflammatory process induces oxidative stress and reduces cellular antioxidant capacity, contributing to the development of age-related diseases such as AMD. Furthermore, the deposition of abnormal aggregated proteins is highly associated with oxidative stress and directly implicated in the senescence of retinal pigment epithelial (RPE) cells, believed to play a central role in the aetiology of AMD.

Chronic oxidative stress and the presence of chronic inflammation has been shown to decrease the ability of RPE cells to remove damaged or non-functional proteins via the lysosomal clearance system, including autophagy. There is growing evidence that autophagy, a key process in the maintenance of cellular homeostasis that serves to remove dysfunctional organelles and proteins, makes a significant contribution to lipofuscin accumulation in the RPE cells and thus the pathogenesis of AMD.

It demonstrates good discrimination of patients with and without AMD. The classification is in three risk categories (low, moderate and high). (Figure 2)

It might be used by ophthalmologists to provide specific recommendations to their patients in terms of enhanced ophthalmological follow-up, lifestyle changes or dietary supplementation. It might also represent a motivating factor for lifestyle change for patients when they know that they are at high risk of AMD. The fact that the questionnaire is self-assessed allows for its use in large population samples for early evaluation of AMD risk. It could be disseminated to the general public or general practitioners, with an incentive to visit an ophthalmologist for those found to be at moderate or high risk.

The questionnaire does have some limitations. Performance would probably be even higher if the risk score included both genetic SNPs and STARS assessment. This may be an option in the future when genetic testing becomes more readily available. The performance of STARS is also currently unknown for the prediction of new incident AMD, which would require prospective studies in the future.

REFERENCES
3 Chakravarthy 2010.
Going forward, it is clear that nutrient supplementation will remain part of the therapeutic spectrum against AMD. Resvega® has the potential to protect RPE cells from oxidative stress and reduce neovascularization in the eye, and it merits further study in the prevention and treatment of AMD.

REFERENCES

Resveratrol and Omega-3: A Synergetic Action in AMD
Dominique Delmas PhD, University of Burgundy, INSERM Research Center U866, Dijon, France
dominique.delmas@u-bourgogne.fr

Numerous immunological studies have suggested that various environmental factors such as metabolic disease or air pollution contribute to increased risk of cardiovascular diseases, diabetes, cancer and AMD. On the contrary, eating a well-balanced diet of green vegetables, fibre, fruit, fatty acids and food micro-components rich in antioxidants and omega-3 fatty acids could help to reduce the risk of these pathologies and extend lifespan.

Since many of these environmental factors also increase the risk of ocular diseases such as diabetic retinopathy, glaucoma and AMD, it stands to reason that vitamins, polyunsaturated fatty acids or food micro-components could be used as a supplement to counteract these ocular diseases through their antioxidant properties.

In the case of AMD in particular, studies have shown that polyunsaturated fatty acids found in various natural...
New Advances In Nutrition And Eye Health

New Evidence on Vitamin D and Visual Function

Alfredo García Layana MD, University Clinic of Navarra, Pamplona, Spain
aglayana@unav.es

The two landmark AREDS studies demonstrated that vitamin and mineral supplements can play an important role in reducing the risk of developing both early and late AMD. The pathogenesis of AMD is due to a complex interaction of metabolic, functional, genetic and environmental factors in which processes such as chronic oxidative stress, impaired RPE cell activity and function, increased apoptosis and chronic inflammation all play a role. Choroidal neovascularization is also important in the complication of this disease and is responsible for approximately 90% of cases of severe vision loss.

The important disruption of VEGF pathway by Resvega® contributes to strongly decrease the VEGF production in sick retinal cells. Conversely, Resvega® also maintained or slightly increased VEGF production in normal healthy ARPE-19 cells. In summary, resveratrol may prevent age-related ocular diseases through a decrease of oxidative stress, a decrease of pro-inflammatory molecules and VEGF secretion. A combination of resveratrol and omega-3 is better than resveratrol alone to counteract the VEGF pathway in sick retinal cells. This combination could potentially be used to protect the second eye, since Resvega® may be capable of maintaining a functional VEGF pathway in normal retinal cells. Future studies will now seek to confirm the effects of this combination treatment in in-vivo models.

REFERENCES
protective against diabetes, is it sufficient to protect against AMD (which is not a deficiency disease)?

This is where vitamin D supplementation may play a potentially important role. While reported estimates of vitamin D status within different European countries show large variation, it is apparent that levels are frequently below recommended ranges, particularly among older populations. Several studies in recent years have explored the association between vitamin D and visual function. There is, for instance, emerging evidence of a link between vitamin D and myopia. Vitamin D may also have a role to play in immune regulation and barrier function in ocular barrier epithelial cells, with recent research by Alsalem et al demonstrating that ocular cells can convert inactive vitamin D to the active form.

Macular thickness may also change according to serum vitamin D concentration in older patients. Vitamin D may also suppress the cascade of inflammation that occurs at RPE-choroid, with significant reductions in the number of markers of inflammation in the subretinal space following vitamin D administration in aged mice. In another recent study, Pahl et al postulated that a sufficient vitamin D supply – especially for elderly people – could be an efficient way to prevent AMD development and progression.

Vitamin D also affects some of the key mechanisms involved in AMD pathogenesis, including angiogenesis, fibrosis and inflammation (Figure 1). A study by Albert et al found that vitamin D is a potent inhibitor of retinal neovascularization and may be of benefit in the treatment of a variety of eye diseases with a neovascular component. It has also been shown to have potent anti-inflammatory and anti-fibrotic properties as well.

It is evident that vitamin D has a more relevant role in the retina than previously thought, and has several protective effects in some of the mechanisms involved in AMD pathogenesis. On this basis, additional studies concerning the role of new relevant micronutrients such as vitamin D in addition to other RDA vitamin and mineral doses are recommended.

REFERENCES


New Advances In Nutrition And Eye Health 6

...more than 50% of the world’s population is at risk for vitamin D deficiency...

Osteoporosis Foundation and DSM Nutritional Products (DSM). The map, based on a systemic review of worldwide literature published between 1990 and 2011, confirmed a north-south gradient in Europe with some Scandinavian countries surprisingly showing higher values for vitamin D than southern European countries such as Spain and Italy (Figure 1).

Is There Vitamin D Deficiency in AMD Patients?

Isabelle Aknin MD, Golfe-Juan and Cannes, France

luteine@gmail.com
The somewhat unexpected north-south gradient with a positive correlation between vitamin D status and latitude may be influenced by diets containing more oil-rich fish, a higher use of cod liver oil, other vitamin D supplementation and population differences in skin pigmentation.

There are several factors which help to explain vitamin D deficiency in the elderly. Our skin produces less vitamin D as we get older, with changes in lifestyle also potentially limiting access to sunlight. Older people may consume less vitamin D rich food and kidney function also declines with age, resulting in a decrease of vitamin D receptor activation.

There are also factors such as latitude and season that can influence the cutaneous synthesis of vitamin D (Figure 2). Both latitude and season affect the quantity (intensity) and quality (appropriate wavelength) of solar radiation. While the intensity is optimal throughout the year in equatorial countries, in temperate countries such as France the intensity is only sufficient to enable vitamin D production in summertime but not in winter months.

Skin pigmentation is also important for the conversion of vitamin D in the human body. High pigmentation of the skin significantly decreases endogenous vitamin D production due to the competitive absorption of ultraviolet-B photons by the melanin present in the skin. This means that people with higher skin pigmentation require longer exposure to sunlight to synthesise the same amount of vitamin D compared to lighter-skinned people.

Since only a few foods contain vitamin D, there is an inherent difficulty in achieving recommended daily vitamin D intakes by a healthy diet alone. In terms of ocular disease, some cross-sectional studies have reported an association between vitamin D status and the risk of early or late AMD. Another study of eye disease in male monozygotic twins found that the twin with the earlier stage of AMD, smaller drusen size and area, and less pigment tended to have higher dietary vitamin D, betaine, or methionine intake.

In summary, vitamin D plays an anti-inflammatory, anti-angiogenic and anti-fibrotic role in the retina. Several epidemiological studies show an association between vitamin D deficiency and AMD risk. Based on current trends, more than 50% of the world’s population is at risk for vitamin D deficiency, with a higher prevalence of vitamin D deficiency among older populations. There are only a few natural sources for vitamin D, so perhaps now is the time to consider vitamin D supplementation for AMD prevention.

REFERENCES