Original article

Characteristics of patients with wet age-related macular degeneration and low intake of lutein and zeaxanthin

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ABSTRACT

Objective: To assess the characteristics of patients with wet AMD and low intake of lutein and zeaxanthin in our population.

Methods: A prospective, observational, cross-sectional study was conducted on patients with active wet AMD. A full blood count, a lipid and liver profile, a dietary interview (24-h recall), and an anthropometric study were performed. Lutein–zeaxanthin (LZ) intake results split the patients in two groups.

Group 1 ("sufficient" Intake): patients with ≥1400 mg/day intake in women and 1700 mg/day in men (2/3 of the average daily intake in a normal population).

Group 2: patients with daily intakes below that of group 1. A descriptive and comparative statistical study was performed.

Results: Fifty-two patients with a mean age of 78.9 years. Group 1: eleven patients (21% of the sample). Group 2: forty-one patients. The subjects with adequate intake of LZ had higher a body mass index (BMI) and waist circumference. Between 70 and 80% of patients in group 1 had inadequate intake of vitamins A, C, E and zinc. Conclusions: Seventy-nine percent of the patients with wet AMD have a deficient daily intake in LZ. The population with adequate intake is associated with an increased BMI and waist circumference, and in addition, most of them have an insufficient intake of vitamins A, C, E and zinc.

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Características de la población con ingesta baja en luteína y zeaxantina en pacientes con degeneración macular asociada a la edad variante húmeda

RESUMEN

Objetivo: Averiguar las características de los pacientes con DMAE húmeda que ingieren suficiente luteína y zeaxantina en nuestra población.


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Zeaxantina
Degeneración macular asociada a la edad
Carotenoides retinianos
Dieta mediterránea

**Introduction**

Age-related macular degeneration (ARMD) is the main cause of blindness among the elderly population in civilized countries. In Spain, with 13% of the population over 65 years of age, the prevalence of advanced ARMD varies from 0.5% at 55 up to 7% above 65. About 25,000 new cases of the wet variety are expected each year.

Lutein and zeaxanthin are almost exclusively the only carotenoids present in the macula, and are defined as the macular pigments. They act to improve visual function, protecting visual structures from oxidative damage which is very high at this level. Said carotenoids neutralize free radicals and filter the blue component of the visible spectrum.

In 2001, report number 8 of AREDS demonstrated a statistically significant reduction of 25% of the possibilities of developing advanced ARMD and loss of vision against placebo with the addition of a fixed association of antioxidants and zinc. Many studies have found an association between the levels of lutein and zeaxanthin in plasma and retina, with a possible reduction of the risk of severe ARMD forms.

It would be important to identify patients with a deficiency of said nutrients either through a nutrition habits survey or plasmatic assessments. However, both options are laborious and unavailable in routine clinic. Even so, we can try to determine the existence of a clinical profile differentiating said patients in order to establish the characteristics of the population with a normal intake of lutein–zeaxanthin and those under 2/3 of the daily recommended intake (DRI) which in this case is theoretical.

The final objective of the research line which this paper endorses is the identification in the clinical practice of patients exhibiting deficit of antioxidants, particularly lutein and zeaxanthin and to identify the solution either with customized dietary recommendations or, if that is not possible, pharmacological supplements.

**Métodos:** Estudio protocolizado, prospectivo, observational, transversal, en pacientes diagnosticados de DMAE húmeda activa. Se efectúa hemograma, perfil lipídico, y perfil hepático; una entrevista dietética sobre los hábitos alimentarios a partir de la realización de un recordatorio de 24 h y estudio antropométrico. Se dividen en dos grupos en función de la ingesta de luteína-zeaxantina (L-Z).

Grupo 1 (ingesta «suficiente»): pacientes con ingesta diaria > 1.400 mg/día en mujeres y 1.700 mg/día en hombres (2/3 de la ingesta media diaria en población normal).

Grupo 2: pacientes con ingesta diaria inferior a las del grupo 1. Se efectúa un estudio estadístico descriptivo y comparativo entre ambos grupos.

**Resultados:** Un total de 52 pacientes, con una edad media de 78,9 años. Grupo 1: 11 pacientes (21% de la muestra). Grupo 2: 41. Los pacientes con ingesta suficiente de L-Z tienen mayor índice de masa corporal y perímetro de cintura. El 70-80% de los pacientes del grupo 1 presentan ingesta insuficiente de vitaminas A, C y E, y zinc.

**Conclusiones:** El 79% de los pacientes tienen ingesta diaria de L-Z baja. Los pacientes con aporte suficiente tienen un aumento en el índice de masa corporal y perímetro de cintura, y además la mayoría tienen una ingesta insuficiente de vitaminas A, C y E, y zinc.

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**Table 1 – Epidemiological and ophthalmological characteristics of patients.**

<table>
<thead>
<tr>
<th>Patients: 52</th>
<th>Eyes involved: 59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male 21 (40.4%)</td>
<td>Right 21</td>
</tr>
<tr>
<td>Female 31 (59.6%)</td>
<td>Left 24</td>
</tr>
<tr>
<td>Bilateral 7</td>
<td></td>
</tr>
<tr>
<td>Mean age: 78.9 (SD 6.5)</td>
<td>Mean Snellen VA 0.21 (SD 0.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subretinal neovascular membrane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type:</td>
</tr>
<tr>
<td>Classic 17 (28.8%)</td>
</tr>
<tr>
<td>Hidden 26 (44.2%)</td>
</tr>
<tr>
<td>RAP 15 (25.4%)</td>
</tr>
<tr>
<td>Polypoid 1 (1.6%)</td>
</tr>
<tr>
<td>Location:</td>
</tr>
<tr>
<td>Subfoveal 41 (69.5%)</td>
</tr>
<tr>
<td>Juxtafoveal 16 (27.1%)</td>
</tr>
<tr>
<td>Extrafoveal 2 (3.4%)</td>
</tr>
</tbody>
</table>

Snellen VA: visual acuity in decimal scale with Snellen optotypes; SD: standard deviation; RAP: retinal angiomatosus proliferation.

**Subjects, material and methods**

A protocolized, prospective, observational and transversal study in patients diagnosed with active wet ARMD in the Retina and Vitreous Section of the Ophthalmology Service in the Son Dureta University Hospital (Palma de Mallorca, Spain).

The patient diagnosis and assessment was formed after a full ophthalmology history comprising fluorescein angiography and optic coherence tomography. The ophthalmological assessment data are summarized in Table 1.

Together with the clinical diagnosis, the patients were requested to accept inclusion in the study (this project had already been approved by the Ethics Committee of the Balearic Islands). The analytical data were obtained from recent analysis (under 3 months). Optionally, we requested a new analysis comprising hemogram, urea, creatinine, glucose, uric acid, hepatic transaminases (ALT, AST, GGT) overall bilirubin, overall cholesterol, HDL and LDL and triglycerides.

One month later, at the time of the second intravitreal injection, the patients were interviewed and asked about their
eating habits on the basis of a 24-h reminder by a qualified nutritionist researcher of the Community Nutrition And Oxidative Stress Research Group of the Balearic Islands University (UIB). Subsequently, the anthropometric study was performed, comprising size, weight, brachial circumference, waist and hips, thickness of the tricipital skinfold, fatty mass and arterial pressure. The BMI and the waist–hip ratio, fatty and muscle area of the arm were calculated.

The conversion of food into nutrients was carried out with a computerized application of the UIB nutrition expert group, based on the American, European and Spanish tables of nutritional contents in food. In many cases, lutein and zeaxanthin do not appear separated in the content of various foods and therefore were analyzed jointly in the intake calculations. In addition, the analysis included vitamins A, C and E, zinc and copper.

All the data were compared between the 2 groups established on the basis of the daily lutein and zeaxanthin intake according to the data obtained in the 24-h reminder survey results.

Group 1: patients with a daily intake exceeding 1700 mg/day in males and 1400 mg/day in females. This is the group having a “sufficient” intake of lutein–zeaxanthin. This cut-off line was established arbitrarily, taking into account the average daily intake of lutein and zeaxanthin in the American population indicated in the Food and Nutrition Board 2001 table, which establishes a mean intake of 2.0–2.3 mg/day for males and 1.7–2.0 mg/day for females. No additional references of said nutrients were found and there is no DRI. In other series for other nutrients it was considered that 2/3 below the DRI involves a moderate risk of associated problems, and said cut-off line is close to that ratio. It would be the group with an “insufficient” intake.

Group 2: patients with an intake below the group 1 data. This is the group with the “insufficient” intake.

The statistical data were analyzed with the SPSS 13.0 software (SPSS Inc.; Chicago, IL, USA), including descriptive statistics of the different variables. For the comparative study of the qualitative variables, a £2 value was utilized and for the quantitative variables a t for student value was applied, establishing statistical significance for values of p ≤ 0.05.

Results

The study comprised 52 patients. In some samples it was not possible to determine some components and for this reason in some variables the n value is under 52.

General epidemiologic data

Group 1: only 25% of patients were above the established cut-off line. The group comprised 11 patients, 7 females (64%) and 4 males (37%), with a mean age of 78.3 years (SD 3.7). Group 2 comprised 42 patients, 24 females (59%) and 17 males (41.5%), with a mean age of 79.1 (SD 7.1) years. These would be the patients with an intake below the recommended values and therefore theoretically insufficient. No significant differences were found in the distribution for gender or mean age between both samples.

The data for the variables are grouped on the basis of the factors that can influence the metabolism of the distribution of lutein–zeaxanthin in order to facilitate the interpretation thereof.

Data related to body fat and serum lipids (Table 2)

Seventy-three percent of group 1 had a history of dyslipidemia against 46% of group 2, without significant differences. These differences were smaller when including in the dyslipidemia group the patients with analyses exhibiting values above 220 mg/dL overall cholesterol or 200 mg/dL triglycerides. Eighty percent of group 1 and 73% of group 2 had dyslipidemia. When analyzing cholesterol as a quantitative variable, group 2 exhibited a mean value of 11.5% higher than group 1, with a p value of 0.08, almost reaching statistical significance. The cholesterol type distribution was somewhat different between the groups: group 1 exhibited lower values both for HDL and LDL cholesterol, reaching statistical significance (p = 0.04) in HDL cholesterol, which was 21% lower than in group 2. Triglycerides did not exhibit differences between both groups.

The anthropometric parameter analysis shows that group 1 had a greater tendency to overweight: in group 1, with the same height, weight is higher (p = 0.08); BMI is significantly higher. Eighty percent of this group is overweight (BMI > 27%), the waist perimeter with high risk gender-corrected values (males > 88 cm and females > 102 cm) and percentage of fatty mass excess (males > 25 and females > 33), in group 2 this value goes down to 50% (p = 0.1 and 0.09 respectively). These differences are not found in the last parameter.

Finally, the liver plays a crucial role in the metabolism of lutein and zeaxanthin and the absorption of fats. There are no differences between groups in the transaminases while the overall bilirubin is at the statistical significance limit, and is higher in group 2.

Data related to cardiovascular risk factors and diseases

The dyslipidemia history and cholesterol levels in serum described in the previous section are an important cardiovascular risk factor (CVRF). The remaining CVRFs are summarized in Table 3.

The prevalence of diabetes mellitus is high in both groups (25 and 27%, respectively). If we add patients with baseline glycemia > 115 mg/dL, the percentage reaches 50% and 60%, respectively. No significant differences were found between the 2 groups.

The prevalence of AHT was of 82% in group 1 and 51% in group 2, with p = 0.09. It is frequent to find high values in measurements taken at the practice. As it was impossible to eliminate the emotional component of the active disease, the numbers obtained in the practice in many cases were pathological (SAT > 140 mmHg; DAT > 90 mmHg) even though they did not involve diagnostic value.

The number of active smokers was very low: only 3 of the 52 patients included in the study were smokers.

Three patients exhibited history of myocardial infarct and 5 had stable or unstable angor. In addition, one
had suffered an ictus and 3 peripheral arterial disease. Due to the low number of cases, it was decided to take this variable as a whole, as cardiovascular disease (CVD) history. In group 1, the prevalence was of 33% and in group 2 of 12% with \( p = 0.08 \). No differences were found in the serial levels of glucose, urea, creatinine or uric acid.

Data related to the intake of other antioxidants and micronutrients

Table 4 illustrates the mean daily intake of other antioxidants such as vitamins A, C and E, together with zinc and copper (micronutrients). No significant differences were found in the daily intake of said elements.

### Table 2 - Parameters related to body fat and serum lipids.

<table>
<thead>
<tr>
<th></th>
<th>Group 1, n = 11</th>
<th>Group 2 (&lt;2/3 IDR) n = 41</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
<td>Yes (%)</td>
</tr>
<tr>
<td>History: dyelipidemia</td>
<td>8 (73)</td>
<td>3 (27)</td>
<td>19 (46)</td>
</tr>
<tr>
<td>Dis. + Chol &gt; 220/T &gt; 200</td>
<td>8 (80)</td>
<td>2 (20)</td>
<td>30 (73)</td>
</tr>
<tr>
<td>Overweight BMI</td>
<td>9 (82)</td>
<td>2 (18)</td>
<td>19 (46)</td>
</tr>
<tr>
<td>AR fatty waist perimeter</td>
<td>9 (82)</td>
<td>2 (18)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>% fatty mass excess</td>
<td>9 (82)</td>
<td>2 (18)</td>
<td>34 (83)</td>
</tr>
</tbody>
</table>

% fatty mass excess: above 33% in females and 25% in males; AFA (mm²): arm fatty area (arm circumference²/4π) – AMA; ALT, AST, GGT: hepatic transaminases in U/L; AMA (mm²): arm muscle area (arm circumference in mm – tricipital skinfold size²/4π); Dis. + Col > 220/T > 200: history of dyslipidemia or analysis alterations (overall cholesterol > 220 or triglycerides > 200 mg/dL); overweight BMI: body mass index above 27%; BMI: body mass index (weight in kg/height in meters²); AR waist perimeter: waist perimeter above the high risk values (females > 88 cm; males > 102 cm).

### Table 3 - Parameters related to cardiovascular risk factors and diseases.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 11)</th>
<th>Group 2 (&lt;2/3 IDR) (n = 41)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
<td>Yes (%)</td>
</tr>
<tr>
<td>DM history</td>
<td>3 (27)</td>
<td>8 (73)</td>
<td>10 (25)</td>
</tr>
<tr>
<td>DM + glucose &gt; 115 mg/dL</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td>27 (66)</td>
</tr>
<tr>
<td>AHT history</td>
<td>9 (82)</td>
<td>2 (18)</td>
<td>21 (51)</td>
</tr>
<tr>
<td>AHT + SAT &gt; 140 or DAT &gt; 90 mmHg</td>
<td>11 (100)</td>
<td>0 (0)</td>
<td>34 (83)</td>
</tr>
<tr>
<td>Active smoker</td>
<td>2 (18)</td>
<td>9 (82)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>4 (36)</td>
<td>7 (64)</td>
<td>5 (12)</td>
</tr>
</tbody>
</table>

DM: diabetes mellitus; cardiovascular disease: patients with ictus or infarct history, angor or peripheral arterial disease; AHT: arterial hypertension; DAT: diastolic arterial tension; SAT: systolic arterial tension.

Mean | SD | Mean | SD
Glucose (mg/dL) | 110.4 | 17.1 | 111.1 | 44.4 | 0.9
Urea (mg/dL) | 46.1 | 15.7 | 42.2 | 12.6 | 0.4
Creatinine (mg/dL) | 1.0 | 0.3 | 0.9 | 0.3 | 0.1
Uric acid (mg/dL) | 5.4 | 1.8 | 5.2 | 1.1 | 0.7
The vitamin C intake was of 241.9 mg in group 1 and of 152.4 mg in group 2 (36.9% less). This difference is significant from the statistical viewpoint (p = 0.03).

Discussion

Lutein and zeaxanthin are xanthophile carotenoids.\textsuperscript{17,18} They cannot be synthesized by the body and must be supplied by diet. They are found in green leaf vegetables such as spinach as well as in corn, lettuce and egg yolk.

There is no DRI and the only known data is the mean daily intake in the USA population, which was of 2.0–2.3 mg/day for males and 1.7–2 mg/day for females.\textsuperscript{16} These values were used in this study as DRI.

In small series, it has been demonstrated that the intake of lutein and zeaxanthin through enriched diets (2.4–30 mg/day) have improved visual function in the short term and the optic density of macular pigments both in healthy patients as well as in ARMD patients.\textsuperscript{3,9,19–21}

In patients with atrophic ARMD, in the Lutein Antioxidant Supplementation Trial (LAST), lutein increased 40% the optic density of macular pigments and improved several visual functional tests.\textsuperscript{5} The Third National Health and Nutrition Examination Survey assessed 8222 subjects and found a protective effect in the group between 40 and 59 years of age with a high intake of lutein and zeaxanthin (progression to retinal pigmentary alterations).\textsuperscript{22}

An additional study published in 2009 which surveyed the eating habits of 7934 patients (belonging to the AREDS study) concluded that subjects with a higher intake of antioxidants have reduced risk of drusen and the advanced forms of ARMD.\textsuperscript{23}

AREDS 2 has implemented a multicenter prospective study to assess the influence of lutein, zeaxanthin and Omega-3 fatty acids in the progression to the advanced forms of ARMD.

The evidence found to date reveals that intermediate (10–15 mg/day) or high (>30 mg/day) levels of pharmacological or dietary supplementation could be beneficial.

It would be important to identify ARMD patients with insufficient intake of lutein and zeaxanthin, as well as quantifying said intake in order to correct through dietary recommendations or pharmacological supplements.

A complete survey on eating habits or plasmatic assessments is not available in usual clinical practice although we can try to determine differences in the characteristics of patients with abnormal intake of lutein–zeaxanthin and those below 2/3 of the DRI (which in this case is theoretical). The most detailed tables that illustrate the content of nutrients in various foods show the content of lutein and zeaxanthin together and therefore this value had to be applied jointly.

In our series, the patients with a normal intake (group 1) exhibited greater tendency towards overweight and hyperlipidemia. As the sample is small, some of the variables having a patient value between 0.05 and 0.1 could achieve statistical significance by increasing the n value. For this reason, this will have to be taken into account in future studies.

The same occurred with the dyslipidemia history (73 vs 46%), with BMI above 27% (82 vs 46%), a high risk value in waist perimeter (82 vs 51%), mean weight with equivalent sizes and genders, and brachial perimeter. Significant differences were found in the mean BMI. In summary, antropomorphic parameters exhibit rates of overweight among patients with sufficient lutein and zeaxanthin intake.

The assessment of serum lipids shows that group 1 patients have a lower mean cholesterol level. Seventy-three percent of these were diagnosed with dyslipidemia and were probably in dietary and pharmacological treatment, and this accounts for the lower overall cholesterol figures. HDL cholesterol, the so-called “good” cholesterol, has a higher value in patients with lower lutein and zeaxanthin intake (21%).

CVRFs illustrate a higher prevalence of AHT (82 vs 51%) in group 1, bordering statistical significance, with lower HDL cholesterol. In addition, group 1 exhibited a higher number of CVD (36 vs 12%), bordering statistical significance.

Increased lutein and zeaxanthin intake is carried out through hypercalorimetric and hypercaloric diet which involves weight increases.

| Table 4 – Mean daily intake and low intake of antioxidants and micronutrients. |
|---------------------------------|---------------------------------|-----------------|
|                                  | Group 1 (n = 11)                | Group 2 (<2/3 IDR) (n = 41) | p    |
|                                  | Yes (%)                        | No (%)            | Yes (%) | No (%) |    |
| Vitamin A (µgRE)                | 1082.5                         | 1146.7            | 1583.4  | 3389.9 | 0.6 |
| Vitamin C (mg)                  | 241.9                         | 172.9             | 152.4  | 100.8 | 0.03 |
| Vitamin E (mg)                  | 7.9                           | 3.5               | 8.7   | 3.9 | 0.6 |
| Zinc (mg)                       | 10.6                          | 7.1               | 10.4  | 7.7  | 0.9 |
| Copper (mg)                     | 2.1                           | 0.5               | 2.4   | 1.0  | 0.3 |

*Daily intake below: copper: <900 mg. Vitamin A: male 60–69 <1.000. + 70 <900; female 60–69 <800. + 70 <700 µgRE (retinol equivalent micrograms). Vitamin C: male <80; female <70 mg. Vitamin E: male 60–69 <10 + 70 <12; female 60–69 <8 + 70 <10 mg. Zinc: male <15; female <12 mg.
The Mediterranean diet is rich in antioxidants and, in contrast with what occurs in North America and northern European countries, it includes a high proportion of vegetables (cereals, fruit, greens, dried fruits, wine and olive oil). Even so, dietary habits are changing towards lower antioxidant intakes.

A study carried out by Romaguera et al. in 2004 with 396 elderly subjects in the Balearic Islands revealed a deficit in antioxidants supply (vitamins A, C, E and zinc), with levels increasing in parallel to the increase of energy intake, simple sugars and saturated fats.

The same occurs in our wet ARMD sample of patients: the increased intake of lutein and zeaxanthin is at the cost of a diet that increases the prevalence of overweight, CVRF and CVD.

Group 1 exhibited a deficit in the intake of vitamins A, C, E and zinc in 70–80% of patients. Therefore, the diet with sufficient amounts of lutein–zeaxanthin does not allow patients to reach normal levels of other antioxidants. This means that dietary recommendations or supplements should also increase the levels of vitamins A, C, E and zinc.

This study has several limitations, i.e., it is a small sample and only assessed the 24-h intake which is much more demanding as it involves taking every day sufficient levels of lutein and zeaxanthin. However, its main advantage is that it was carried out in patients with wet ARMD and there are no specific studies for this group of patients.

It is essential to change the eating habits of wet ARMD patients due to high deficit of antioxidants, even when they have a normal intake of lutein and zeaxanthin. The objective would be to raise the levels of these 2 nutrients together with other antioxidants with a normal or hypo-calorie diet to avoid overweight and the CVD this involves.

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**Conflict of interests**

No conflict of interest has been declared by the authors.

**References**


