Lutein and age-related macular degeneration

Bandolier was first asked about lutein and age-related macular degeneration about a year ago. At the time there was little to find and, we thought, nothing to say. Because there is little effective treatment for age-related macular degeneration, there is much snake oil advice with long lists of supplements to buy. The trouble is that there is little or no evidence they help, or even evidence that they don’t help.

A year on, and the situation has changed. The snake oil list gets longer, but for lutein there is emerging what might be a coherent story that includes background science, some epidemiology, and even some small, randomised trials.

Background

At the back of the eye the macula is a tiny area about 5 mm in diameter, with the fovea at its centre. There are no blood vessels, but lots of cells full of photosensitive pigments that allow us to see detail in the centre of vision. As we get older, the cells with retinal pigment become less efficient, the membrane degenerates, some cells atrophy, waste products build up, and central vision is gradually lost. That process is age-related macular degeneration. A good recent review does a better job at covering the whole subject [1].

Epidemiology

There are risk factors for macular degeneration, including hypertension, smoking, and a family history. There are relationships with heart disease, and inflammatory mediators like C-reactive protein found at elevated levels in heart disease are also found in macular degeneration [2].

But the single strongest relationship is with age. A detailed study of visual impairment in UK general practice gives a good insight into how much macular degeneration affects older people [3]. This study was part of an MRC trial of the assessment and management of older people in the community. In 49 general practices, with 14,403 people aged 75 years and older, detailed vision assessments were made.

Binocular visual impairment was present in 1,742 people, a prevalence of 12.5%. In 976 there was pinhole acuity less than 6/18, and with a known cause. Where there was no known cause, it was usually through missing notes (lost, or patient had died), or because there was no cause entered in the notes.
In the 976 with a known cause the main diagnoses for binocular visual impairment excluding a refractive error were age-related macular degeneration (53%) and cataract (36%) (Figure 1). The prevalence of known age-related macular degeneration in people aged 75 years or older was therefore 3.6% (516 out of 14,403). In those with a known cause of binocular visual impairment, macular degeneration rates doubled between 75 and over 90 years (Figure 2).

**Nutritional supplements**

In the absence of any physical or medical treatment for age-related macular degeneration, attention has concentrated on nutritional supplements to prevent or slow progress of the condition. A systematic review of randomised controlled trials [4] teases apart the available evidence, and also provides a good background to macular degeneration.

It found seven trials, concerning antioxidants, zinc, vitamin E and lutein, with duration between six months and six years. The detailed critique of the studies is useful and thorough. Three showed some benefit.

♦ Oral zinc (100 mg twice daily) in a trial of 151 participants reduced the deterioration in visual acuity less than placebo. The trial had limited power, and was criticised for having other methodological limitations.
♦ Supplementation with vitamins A, C, and E, plus zinc and copper or placebo was given in a trial of 3,640 subjects with various categories of visual impairment, with outcomes of progression to advanced macular degeneration and a 15 letter or more decrease in visual acuity. The probability of either of these outcomes was reduced with any combination of antioxidants or zinc (Figure 3), but modestly. There were problems, but antioxidant use seemed to delay progression by a year or so.
♦ Lutein supplementation, with and without antioxidants, was tested against placebo in 90 older people with atrophic age-related macular degeneration. Not published in full as yet, an abstract reported statistical improvement in glare recovery, contrast sensitivity, and distance and visual acuity with lutein.

**Scientific sense**

There may be some scientific sense for these results. There seems to be a link between age-related macular degeneration and oxidative stress, some from the actions of light on the retina, and some systemic. As with heart disease, cancer, and other disorders, diets with higher levels of antioxidants, or antioxidant supplements, or both, are associated with less chance of the disease. It is the old healthy living message about eating plenty of fruit and vegetables, getting some exercise, not smoking, and having the odd medicinal glass of what you fancy.

Lutein is a yellowish pigment found in egg yolk, some algae, and in many plants. Zeaxanthin is found in small amounts in most fruits and vegetables. Both are found in the retina, and both are found at relatively high concentration in the macular region of the retina. Zeaxanthin is preferentially found in the foveal region and lutein in the perifoveal region. A systematic review [5] examines how these two pigments might be related to protection against macular degeneration.

**Figure 1: Cause of binocular vision impairment in 976 over-75s in UK general practice**
Lutein and zeaxanthin may protect the retina in two ways, as antioxidants to oxidative stress from metabolism, and, by filtering short wavelengths of light they also reduce the oxidative effect of blue light.

Evidence for lutein and zeaxanthin

There are a number of studies that indicate a lower risk of macular degeneration associated with consumption of lutein and zeaxanthin, with their levels in diet, or higher levels in the blood. For instance, in a good epidemiological study of 380 people aged 66-75 years in the UK [6], people with lower blood levels of lutein plus zeaxanthin were more likely to have age-related macular degeneration (Figure 4).

Supplementing diets with lutein and zeaxanthin raised their levels in blood [7,8] and macular pigment [7], though earlier studies were equivocal. In a small but long randomised and double-blind pilot study [8], luetin supplementation of 15 mg every three days significantly improved visual acuity and glare sensitivity in older people with cataracts. Here patients given lutein had improved macular function.

Comments

All of this has to be interpreted with caution. What we have are straws in the wind. But for those people with macular degeneration, or who want to avoid it, these straws are worth having. A good diet, rich in antioxidants, and perhaps with some antioxidant supplementation, is the first thing to go for. Apart from anything else, it has benefits in terms of hearts, bones, and against cancer.

The second thing is to increase intake of lutein and zeaxanthin. The amount found in a normal western diet is said to be between 1 and 3 mg lutein and zeaxanthin a day. Even those of us with relatively good diets might find that hard to manage, but you can check your intake (www.luteininfo.com/abouthowtake). The recommended amount is 42 mg a week. The strength of that evidence, though, is not known.

The US Department of Agriculture has web pages that tell you the carotenoid content of many foods, (www.nal.usda.gov/fnic/foodcomp/Data/car98/car98.html). Table 1 shows lutein and zeaxanthin content. The message is green, and the greener the better. Until recently lutein supplements in the form of tablets were not available. In the UK at least one high-street chain (Holland and Barrett) stocks 6 mg and 20 mg tablets.

There is now at least one British randomised trial of lutein supplementation in the design stage in Birmingham [9]. It will be recruiting about 200 people, and will test lutein plus vitamins AC and E, plus zinc and copper (www.aston.ac.uk/lhs/research/nri/opo/amd).

References:

Table 1: Lutein and zeaxanthin content of foods

<table>
<thead>
<tr>
<th>Source</th>
<th>Lutein and zeaxanthin (micrograms per 100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kale, raw</td>
<td>40,000</td>
</tr>
<tr>
<td>Kale, cooked</td>
<td>16,000</td>
</tr>
<tr>
<td>Spinach, raw</td>
<td>11,000</td>
</tr>
<tr>
<td>Spinach, cooked</td>
<td>7,000</td>
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<tr>
<td>Broccoli</td>
<td>2,500</td>
</tr>
<tr>
<td>Cos lettuce</td>
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<tr>
<td>Romaine lettuce</td>
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</tr>
<tr>
<td>Sweetcorn</td>
<td>1,800</td>
</tr>
<tr>
<td>Brussel sprouts</td>
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</tr>
<tr>
<td>Peas</td>
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</tr>
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<td>Persimmon</td>
<td>800</td>
</tr>
<tr>
<td>Green beans</td>
<td>600</td>
</tr>
<tr>
<td>Okra</td>
<td>400</td>
</tr>
<tr>
<td>Iceberg lettuce</td>
<td>350</td>
</tr>
<tr>
<td>Cabbage</td>
<td>300</td>
</tr>
<tr>
<td>Carrots</td>
<td>300</td>
</tr>
<tr>
<td>Tangerine</td>
<td>250</td>
</tr>
<tr>
<td>Celery</td>
<td>200</td>
</tr>
<tr>
<td>Orange</td>
<td>200</td>
</tr>
<tr>
<td>Tomato</td>
<td>150</td>
</tr>
<tr>
<td>Orange juice</td>
<td>100</td>
</tr>
<tr>
<td>Papaya</td>
<td>75</td>
</tr>
<tr>
<td>Green peppers</td>
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<td>Egg</td>
<td>55</td>
</tr>
<tr>
<td>Cantaloupe melon</td>
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<td>Watermelon</td>
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</tr>
<tr>
<td>Grapefruit</td>
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</tr>
</tbody>
</table>

Figure 4: Blood lutein and macular degeneration

Percent with macular degeneration

lowest mid highest

Blood concentration thirds
**STEROID INJECTIONS FOR OA KNEE**

Many older people have osteoarthritis of the knee that gives them pain and discomfort. Some of those consult a primary care physician, and some a specialist. As well as oral and topical analgesics, injection of corticosteroid into the knee is often carried out with the aim of producing pain relief. Two systematic reviews [1,2] confirm the efficacy of this intervention, at least over about a month.

The aim is to inject the steroid into the joint space, but not all injections are correctly placed, though it is not clear whether or how much this matters. There are issues, about which corticosteroid to use, which dose of which corticosteroid to use, and whether a long acting is better than a short acting corticosteroid. Steroid injections are often accompanied by use of local anaesthetics. Again, benefits of using local anaesthetic with steroid are argued, dose is an issue, and even whether local anaesthetic can be used alone. Then there is the issue of how long the injections are effective, and how often they can be repeated. So while we have two systematic reviews, we would be fortunate to find all our questions answered.

**Reviews**

The reviews were similar. The first [1] sought randomised trials where intra-articular long acting corticosteroids (triamcinolone, methylprednisolone, betamethasone, cortivazol) were compared with placebo. Searching was up to December 2002. The second [2] sought randomised trials where any formulation of steroid was compared with placebo, with searching into 2003. Both studies included patients with osteoarthritis of the knee, and required pain outcomes.

**Results**

The second review [2], because it included any formulation of corticosteroid, and ended searching later, had more studies (10) than the former [1], which had five. Two of the additional five studies used long acting corticosteroids, and were published in 2003. All of the trials except one compared corticosteroid to saline injection, the other using a sham injection. Several of the studies had a crossover design. Dose of corticosteroid varied widely, between 6 mg and 80 mg prednisone equivalent, though most were between 25 and 50 mg prednisone equivalent.

Figure 1 shows the six studies with outcomes of improvement up to two weeks. This was not a clearly defined term in many of the studies. In these six studies with 317 patients, five used long acting corticosteroids. Improvement up to two weeks occurred in 74% of patients with a steroid injection and 45% given placebo. The relative benefit was 1.7 (95% CI 1.4 to 2.0), and the number needed to treat for one patient to have improvement was 3.4 (2.5 to 5.1). The weighted mean reduction in visual analogue pain scores was 17 mm on a 100 mm scale.

Three studies with 192 patients had results at 16-24 weeks after the injection (Figure 2). Two used long acting corticosteroid, and the other used hydrocortisone (and was an older study with a low quality score). Overall, 33% of steroid treated patients had improvement at 16-24 weeks compared, and 16% of those given placebo. The relative benefit was 2.1 (1.2 to 3.5), and the NNT 5.8 (3.4 to 19).

Adverse consequences of the intra-articular injections were not reported.

**Comment**

What we have here is some very limited data with implications for clinical practice. It is likely that intra-articular corticosteroids produce some pain relief, perhaps for some weeks. There are many problems, though:
The outcome of improvement or decreased pain is not robust. It may well be that a more rigorous examination of this literature could eliminate some or all of the studies because of the lack of definition of outcomes or their measurement. The studies might not be valid.

The trials may not mirror clinical practice, especially with regard to use of local anesthetic, with the practice of joint lavage, and with regard to choice of corticosteroid or dose used. The studies may not be relevant.

The studies were small individually, and in total. The results could be overturned by a large, well-conducted, negative study being published, or by uncovering negative unpublished studies.

Clinical practice and experience suggests that intra-articular steroid injections are helpful for painful knees in osteoarthritis. The trouble is that half of the patients improved with saline alone, and the additional benefits of adding steroid were moderate. Some will say that this is the power of psychiatry with needles, but it is equally possible that the improvement would have come about anyway, because of the ups and downs of symptoms. In many ways the situation resembles that of many alternative therapies, though those usually have less evidence to support them.

References:

Hyaluronic acids are large glucosaminoglycans in synovial fluid. They have high but variable molecular weight and viscosity, and injecting them into the knee joint is aimed at providing lubrication and shock absorption. Usually three to five weekly injections comprise a course of treatment.

There has been a degree of controversy over efficacy of this treatment, and two new systematic reviews [1,2] are sceptical. There are a number of variables, including the molecular weight of the hyaluronic acid preparation used, over what period injections are given, when benefits might be seen, and what those benefits are.

Systematic reviews

The first [1] had a wide search strategy to February 2003 and included only randomised trials, of at least single blind, testing intra-articular hyaluronic acid administered at least weekly for three weeks, against intra-articular placebo, in patients with osteoarthritis. Pain had to be measured and reported using standard pain measures in osteoarthritis. The second [2] used a similar strategy to October 2002, included case series, but excluded trials before 1995 in order to examine the most up-to-date literature.

Results

The first review [1] included 22 trials, 19 published in full, with 2949 patients. Trial size was 24 to 408 participants. Effect size was calculated for each study, and pooled. Of the 22 trials, only three individually had a statistically significant effect size. Overall the effect size was 0.3 (95% CI 0.2 to 0.5), indicating a small effect. Omitting three trials with the largest molecular weight (6,000 kD), the effect size was even smaller at 0.2 (0.1 to 0.3).

Three trials (268 patients) used 6,000 kD hyaluronic acid, one of which was very small, with just 30 patients. The two larger studies differed in their conclusion, one with a very large effect size, and one no different from placebo.

The second review included 13 randomised trials and five case series. The randomised trials were included in the first review. Three of the five case series were prospective, were small, and lasted six months to two years. Three used 6,000 kD hyaluronic acid, but only one was prospective. All reported some degree of pain relief in some patients.

Adverse events reported included injection site pain and swelling in 2% to 23% of injections. Gastrointestinal adverse events and back pain were also reported.

Comment

The sort of effect size seen in these trials is small, about that for the effect of NSAIDs over paracetamol. The result itself is not robust. Trials were often small, there was clinical heterogeneity regarding type of hyaluronic acid, dose, outcome measured, and duration of the study (which could have been six weeks to a year). So even the small effect seen might be overstated. Most of the randomised trials were company sponsored.

The evidence for a big effect is underwhelming. The evidence for any effect carries limited weight. The evidence is that there will be harm to be balanced against any small benefit. Not entirely convincing, this.

The real disappointment comes from the reporting. Effect size is not intuitively helpful, though it is useful when trying to pool information from different outcomes. Bandolier looks for outcomes that are more meaningful, like patients improved, or changes in a scale, or, better still, some clinically useful but simply described outcome that we can understand. Then we have the chance of comparing interventions, and can check whether the patients in different trials are the same. Here we failed.

References:
LOW LEVEL LASER THERAPY FOR PAINFUL JOINTS

Low Level Laser Therapy (LLLT) uses a light source that generates extremely pure light, of a single wavelength. The effect is not thermal, but rather related to photochemical reactions in the cells. LLLT was introduced as an alternative non-invasive treatment for OA about 10 years ago, but its effectiveness is still controversial. A Cochrane review [1] of LLLT in osteoarthritis included five trials, and concluded that despite some positive findings, the meta-analysis lacked data on how LLLT effectiveness was affected by the important factors of wavelength, treatment duration of LLLT, dosage, and site of application over nerves instead of joints. A different review [2] addresses some of these issues in a wider range of trials, and is broadly positive, if limited by numbers.

Systematic review

An extensive search included not only a number of electronic databases, but used a wide range of key words to be sure of finding different types of lasers. Physiotherapy journals from 10 countries were also searched by hand, and researchers contacted. The last search was at the end of 2001.

Included trials had to:

♦ Include patients with a joint disorder of more than six months duration, or include patients with osteoarthritis verified by X-ray.
♦ Have a control group with otherwise identical placebo treatment.
♦ Have patients and assessors blind to the therapy received.
♦ Have laser exposure of skin overlying the inflamed joint capsule.
♦ Have an outcome measure of pain or change in health status.

Main outcome measures chosen were pain measured during activity, and health status, usually as a global measure, with improved or better being counted as success.

The authors also considered which characteristics of the laser treatment made sense in terms of dose and duration (number of sessions and sessions per week). They made pre-hoc determinations about laser power, dose, location, and duration for each of several possible joints to be treated, and this was done for each of several different types of laser.

Results

Fourteen trials with 695 patients were included, three of which (130 patients) had doses below the suggested range. Trial size ranged from 20 to 115 patients. Pain before treatment was 50 mm on a 100 mm scale in most trials, and above 35 mm in all, so that included patients had pain of at least moderate intensity, and in most trials it would have been severe. Joints included were knee, thumb, lumbar and cervical spine, and temperomandibular. The largest trial had a single application of laser therapy, but for most laser was used between five and 20 times over two to four weeks. Many different lasers were used. Use of analgesics was allowed in some, but not all, trials.

The pooled mean reduction in pain intensity was 30 mm (95% CI 19 to 41 mm) more than with control in seven trials within the suggested dose range. Laser treated patients had reduction in pain by about half (30 mm), while there was virtually no change with control (Figure 1).

Six trials, including one outside the dose range, reported on patients improved (Figure 2). In these six trials with 391 patients, 64% were improved with laser and 38% with control. The relative benefit was 1.7 (1.4 to 2.1) and the number needed to treat for one patient to be improved was 3.8 (2.8 to 6.0).

The one low power trial outside the dose range had identical results for laser and control. The five studies within the dose range (310 patients) had 69% improved with laser and 35% with control. The relative benefit was 1.9 (1.5 to 2.5) and the NNT was 3.0 (2.3 to 4.4) (Table 1).

Table 1: NNTs for low level laser therapy in painful joints

<table>
<thead>
<tr>
<th>Trials included</th>
<th>Trials</th>
<th>Laser</th>
<th>Control</th>
<th>Relative benefit (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td>6</td>
<td>132/207 (64)</td>
<td>69/184 (38)</td>
<td>1.7 (1.4 to 2.1)</td>
<td>3.8 (2.8 to 6.0)</td>
</tr>
<tr>
<td>Appropriate laser dose</td>
<td>5</td>
<td>110/160 (69)</td>
<td>53/150 (35)</td>
<td>1.9 (1.5 to 2.5)</td>
<td>3.0 (2.3 to 4.4)</td>
</tr>
</tbody>
</table>
Adverse events were explicitly stated to be absent in six optimal dose trials, and another trial had a single transient adverse event in each group.

Comment

The two reviews conclude that treatment looks positive, but there are problems about what is being done, how, to whom, with what outcome. The first [1] limits itself to osteoarthritis; the second [2] looks at chronic joint pain, and so has more trials, but it also addresses issues of appropriateness.

What it [2] says is interesting. It demonstrates a clinically as well as statistically significant halving of pain intensity by 30 mm compared with control, and in absolute terms. Improvement in global health status was twice as common with treatment than with controls, and the NNT of 3 was consistent with an effective treatment.

Problems still remain, especially about how long the pain relief lasts. Another randomised trial [3] (published since the review looking at laser therapy in knee arthritis) showed pain reduction continuing for at least 10 weeks. It also confirmed a halving in pain intensity with laser therapy.

Even so, this is limited information, on what is clinically and methodologically heterogeneous evidence. The amount of information on a particular laser, used at a particular power, for a particular course of treatment, for particular patients and looking at particular outcomes over a particular period is close to zero. So a bit of a curate’s egg.

References:

There was no cross-referencing (duplication was covert) in 65 of the 103 duplicate articles (63% of the duplicates, 5% of all original articles including duplicates). Some of the duplicates (12%) were translations. Pharmaceutical sponsorship occurred in 34 (33%) of duplicate publications. Most (90%) were published within three years of the original article.

Types of duplication

Six different patterns of duplication were identified, and these are outlined in Table 1. Pharmaceutical sponsorship was very common (81%) in type 1B, and uncommon (4%) in type 2.

Comment

There may be good reasons why duplicate publication can occur. For instance, if an important paper were originally published in Welsh, a translated version might be appreciated by the few of us who are not fluent in Welsh. Or a study reporting outcomes at two years might, three years later, report outcomes after five years. In both cases, though, what we would hope is that any subsequent publication would clearly refer to the original. Then we would know where we stood, and not, perhaps, be misled into believing that there was twice as much evidence than we first thought.

This study tells us that about one paper in 12 is a duplicate, and for about 1 in 20 there is no cross reference, so we might be misled if we didn’t have our thinking caps on. We should not be surprised, because duplication has been reported before, and in areas other than perioperative medicine.

For example, two analyses of the otolaryngology literature in the last few years come to similar conclusions [2,3], but using different strategies for finding duplication, other than systematic reviews.

Table 1: Taxonomy of duplicate publication

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>21</td>
<td>Reproduction of an already published article using identical sample and outcomes</td>
</tr>
<tr>
<td>1B</td>
<td>16</td>
<td>Assembly of two or more articles to produce another article</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>Reporting on different outcomes from the same study sample</td>
</tr>
<tr>
<td>3A</td>
<td>11</td>
<td>New data added to a preliminary article</td>
</tr>
<tr>
<td>3B</td>
<td>11</td>
<td>Reporting part of a larger trial and reporting identical outcomes</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>Sample and outcome different from the main article</td>
</tr>
</tbody>
</table>

One [2] identified all the authors and articles published in one journal over an eight-year period. There were 1,965 authors of 1082 articles. They picked 1,000 at random, found other articles they had published, and checked them for duplication. Of the 1,000 authors, 201 had published 644 articles with some degree of duplication, amounting to a 1.8% duplication rate.

The second examined all original articles from two otolaryngology journals in 1999, and then searched on the first, second and last authors for cross-referencing to possible duplicate publication. They found that 40 of 492 articles had 42 duplicate publications – the same 8.5% found in the Geneva study.

Duplicate publication is present, and may mislead us. There is a considerable literature, and these three papers provide some very interesting reading.

References:
1 W von Elm et al. Different patterns of duplicate publication. An analysis of articles used in systematic reviews. JAMA 2004 291: 974-980.