Selenium and ocular health in New Zealand

Leo Sheck, Jo Davies, Graham Wilson

Abstract
Selenium is an essential mineral and severe selenium deficiency is known to cause significant health problems. It has been well documented that New Zealand soil is low in selenium. Recent studies have addressed the roles of selenoproteins in the eyes, with evidence suggesting that selenium supplementation may have a role in preventing cataract formation and age-related maculopathy. This paper summarises the role of selenium in ocular and general health and discusses selenium supplementation in a New Zealand specific context.

Selenium was first identified by Jons Jakob Berzelius in 1817. In the early 20th Century, selenium became known for its toxic effect on livestock which was called the “blind staggers”. Later in the 20th Century selenium was recognised as an essential trace mineral after the discovery of its roles in glutathione peroxidase, Keshan disease and Kashin-Beck disease. In the last 10 years, there has been intense interest in selenium supplementation and its role in health.

Selenium biochemistry and metabolism are complex and have been extensively reviewed elsewhere. Selenium is absorbed as selenoamino acids - L-selenomethionine (SeMet), L-selenocysteine (Sec), and Se-methylselenocysteine and then incorporated into proteins by two different pathways. The main pathway involves L-selenocysteine which is inserted into proteins in specific positions, forming specific selenoproteins. 25 selenoproteins exist in human, including glutathione peroxidases (GPx-1, GPx-2, GPx-3, GPx-4, GPx-6), iodothyronine deiodinases (DIO 1-3) and thioredoxin reductases (TrxR1, TrxR2, TGR).

Selenium and the eye

Selenium and cataractogenesis—Cataract formation can be induced in mice within 3 to 5 days with a single subcutaneous injection of 30 mol/kg selenium as sodium selenite. Conversely GPx-1 has been identified in the lens, and cataract formation has been observed in GPx-1 knockout mice.

Given that GPx-1 level declines rapidly with selenium deprivation, this suggests that selenium deficiency may contribute to cataract development. Further evidence comes from selenium-deprived rats where a decrease in GPx-1 activity in the rat lens and early lens morphological changes were noted. However, there are no convincing human studies (three case-control studies showing contradicting results) linking serum selenium level with cataract formation.

There are three randomised controlled trials addressing antioxidant supplementation, with selenium as one of the ingredients, on cataract formation. In the largest study in 2008, 1020 participants with early or no cataract were observed for 9 years. The study found that a daily intake of Centrum, a multivitamin and mineral tablet...
containing 25 microgram of selenium, led to a decreased incidence of total lens opacity (hazard ratio 0.82, P = 0.03) and nuclear opacity (hazard ratio 0.66, p=0.004) compared to placebo, but a higher rate of posterior subcapsular cataract (hazard ratio 2.00, p<0.001) was noted. However, there was no statistically significant reduction on moderate visual acuity loss or cataract surgery in the treatment group.

In the other randomised controlled trials, one showed no benefit on cataract formation when selenium was given with alpha-tocopherol and beta carotene in Chinese subjects likely to be deficient in selenium and other micronutrients. In the third randomised controlled trial, when selenium was given as a wider package (β-carotene, vitamin E, vitamin C, citrus bioflavonoid complex, quercitin, biberry extract, rutin, zinc picolinate, selenium, taurine, n-acetyl cysteine, l-glutathione, vitamin B2, and chromium), there was an increase in cortical cataract in the right eye (p=0.04).

It is important to note that selenium was included with a large number of other micronutrients in these randomised controlled trials, thus it is very difficult to draw conclusions on the real effect of selenium supplementation on cataractogenesis. However, it is biologically plausible that selenium supplementation in selenium deprived individuals can prevent the formation of cataract by optimizing GPx-1 activity in the lens.

**Selenium and glaucoma**—The association between selenium and glaucoma is complex and not well-understood. In the Nutritional Prevention of Cancer (NPC) trial, a randomised controlled study performed in 1996 involving 1312 patients on selenium supplementation and non-melanoma skin cancer, 200 mcg of selenium supplementation daily was linked to the development of glaucoma (hazard ratio 1.78, 95%CI 1.12–2.82). The risk was even higher in those who chose to continue selenium supplementation after the trial (hazard ratio 10.13, 95%CI 1.32–77.62).

Two studies have been published on the effect of selenium on human trabecular meshwork cells to provide a biological basis for the above observation. These showed that in cell culture, treatment of human trabecular meshwork cells with selenium leads to a number of biochemical changes which may result in an increase in trabecular outflow resistance.

In the latest case-control study involving 47 patients with primary open angle glaucoma and 54 control subjects, the odds ratio for glaucoma was higher in the middle and upper tertile of plasma selenium level (odd ratio 4.6 for middle tertile and 11.3 for upper tertile). However, a protective effect was seen at higher levels of aqueous humour selenium level in this study, with the largest effect seen in the middle tertile (odds radio 0.06 for middle tertile and 0.41 for upper tertile). This association between high plasma selenium level and glaucoma confirms the findings from the NPC trial, and suggests that selenium supplementation may carry a risk of developing glaucoma. The suggested mechanism is that excess selenium saturates selenium-related enzyme pools causing cell damage before excretion.

In summary, there are both biological and human studies suggesting selenium supplementation is linked with an increased incidence of glaucoma.

**Selenium and age-related maculopathy**—When selenium was given as part of a wider anti-oxidant package in a double blinded study, patients with age-related...
maculopathy of any type did not experience any decrease in visual acuity over a period of 1.5 years, as measured by LogMAR visual acuity. In another randomised controlled trial, supplementation with lutein and a wider anti-oxidant package including selenium was associated with an improvement in snellen visual acuity and macular pigment optical density compared to placebo. However, there was no added benefit shown with the added anti-oxidant package as compared to supplementation with lutein alone. Furthermore, there are three case-control studies addressing the level of serum selenium and age-related maculopathy.

Two studies showed lower serum selenium level in patients with age-related maculopathy, and one showed no statistically significant relationship. There are two Cochrane reviews on the effect of antioxidant supplementation in preventing or slowing the progression of age-related maculopathy. They concluded that an antioxidant package may be of modest benefit in slowing the progression of age-related maculopathy, but there is no evidence that the antioxidant package may delay the onset of age-related maculopathy. However, these conclusions cannot be applied directly to selenium as one of the Cochrane reviews did not include any trials that has selenium as part of its intervention, and the other review only included two trials where selenium was given as part of a wider anti-oxidant package.

**Diabetic retinopathy**—There has been published data on the beneficial effect of selenium, either given alone or as a wider package of anti-oxidants, on diabetic retinopathy in rat models. There is no human study on selenium supplementation and diabetic retinopathy.

**Selenium and general health**—Severe selenium deficiency is known to cause Keshan Disease, an endemic cardiomyopathy characterised by multifocal myocardial necrosis and fibrous bone replacement, and Kashin-Beck disease, an endemic osteoarthropathy where degeneration and necrosis of the joints and epiphyseal-plate cartilages are seen. These diseases are mainly seen in low selenium regions of China, where foods with the lowest selenium content are found. Both diseases can be prevented by selenium supplementation. There is evidence that less overt selenium deficiency is linked to loss of immunocompetence, increase in a number of viral infections, low mood, suboptimal fertility, impairment in thyroid function, cardiovascular disease, and inflammatory conditions such as chronic pancreatitis.

Selenium supplementation of 200mcg daily has been linked to a reduced risk of lung, colorectal, prostate and liver cancers as secondary end-point analysis in two randomised controlled trials performed in 1990’s. A comprehensive report on mineral supplements and chronic disease published by the Agency for Healthcare Research and Quality (United States Government, 2006) concluded that there is moderate benefit on total cancer prevention by selenium supplement.

A Cochrane Systemic Review published in 2008 concluded that selenium used singly or with other antioxidants significantly reduced all-cause mortality (RR 0.90, 95% CI 0.83-0.98), although this effect disappeared when high-risk bias trials were excluded.

The latest data suggests that the above effect is due to study bias. Two large-scale trials addressing selenium and general health were published in December 2008. In a
well-designed phase 3 randomised controlled trial involving 35535 men with adequate serum selenium level from the United States, Canada and Puerto Rico, 200 mcg per day of selenium supplementation did not have any statistically significant effect in reducing the risk of prostate cancer, lung cancer, colorectal cancer, overall primary cancer, significant cardiovascular events, and overall mortality, over a time period of 5.46 years.\(^{35}\)

In a case-control study involving 959 men with prostate cancer and 1059 controls, there was no relationship between prostate cancer risk and plasma selenium level.\(^{36}\)

**Selenium toxicity**

Acute selenium toxicity with industrial selenious acid is invariably fatal, preceded by stupor, respiratory depression and hypotension.\(^1\) Hair loss, brittle nails, and garlic breath are seen with chronic selenosis in seleniferous areas, including the Northern great plain of USA, parts of Venezuela and Colombia, and Enshi county of China with an average intake of 4900 mcg per day.\(^37\)

A published report showed no signs of toxicity with selenium intake of up to 819 microgram / day in China and 724 microgram / day in USA from cereal or rice in the form of selenomethionine or selenite.\(^{38,39}\) In a study of Inuit of North Greenland where daily intake of selenium at levels up to 5885 mcg per day in the form of selenocystine from meat and organs of marine animals, no sign of toxicity was seen apart from striation of nails.\(^{37}\)

In Australia and New Zealand, nutrient reference values set a safe upper limit for selenium intake of 400 microgram/day.\(^40\) This is considered a safe intake that will not produce toxicity in the majority of the population.

On the other hand, there is evidence that selenium supplementation may not be entirely safe for those with adequate selenium status. A study has linked selenium supplementation with type II diabetes (hazard ratio 1.55, 95%CI 1.03–2.33).\(^41\) Elevated serum selenium was linked to higher level of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.\(^42\)

Furthermore, a U-shape relationship between serum selenium and risk of peripheral vascular disease (increasing serum selenium level to 150 to 160 microgram/L appears to be protective, but followed by gradual increase in risk afterwards), and mortality (decreased risk up to 130 microgram/l but increase in risk in higher level) has been observed.\(^{43,44}\)

**Selenium intake and adequacy in New Zealand**

The selenium content in the food chain depends on the region the food is grown and its soil selenium content.\(^30\) Average soil globally contains 0.1 to 2 mg of selenium per kg. It has been documented that soil in parts of New Zealand has a lower than average selenium soil content. For example, the soil in the central volcanic plateau of North Island and most of the South Island contains less than 0.5 mg of selenium per kg, and a higher incidence of selenium responsive diseases is seen in sheep from these areas.\(^45\)

The low soil selenium level is reflected in the selenium content of plants – wholewheat grain produced in the USA on average contains 2 mg of selenium per kg, whereby New Zealand produce on average contains only 0.1mg of selenium per kg.\(^30\)
The minimum concentration of plasma selenium to support maximum GPx activity in humans is 1.00-1.14 micromol/L. In New Zealand, the recommended daily intake is 70 mcg per day for men, and 60 mcg per day for women. The selenium intake estimated from a simulated New Zealand diet was 67 mcg per day for men and 49 mcg per day for women, confirming that a proportion of the population is not achieving the recommended daily intake of selenium. However, these estimated figures for selenium intake come from a 2003–2004 total diet survey. There have been several reports suggesting the blood selenium concentration of South Island residents has been increasing over past 10 years. This is possibly due to the use of selenium supplementation in animal feeds and a change in dietary pattern (greater use of multigrain bread and imported legumes and nuts). So it is likely that New Zealand selenium intakes are now higher.

Even within New Zealand there is a significant difference in selenium intake between the North and South Islands. Imported wheat, especially Australian wheat, is higher in selenium and is used for all bread making in the north of the North Island, so that people in this region have higher selenium intakes. In the south of the North Island about 30-35% of wheat used is Australian. In the South Island usually all wheat is grown locally, accounting for lower selenium intakes in that region.

Furthermore a 2004 New Zealand study showed that infants and toddlers born in the South Island had suboptimal selenium dietary intake and serum selenium levels. The current plasma selenium levels of residents of the Otago region of the South Island are in the range 0.76–1.65 micromol/L (60–130 microgram/l), which is low compared to other countries. From this data it can be estimated a proportion of South Islanders have a low selenium status and are not capable of sustaining maximal GPx activity. In this group, the ambulatory, independently living elderly people are more likely to be selenium deficient.

Despite the probable increased dietary intake of selenium and the documented increase over the years of mean plasma selenium levels, the selenium status of New Zealand population remains low compared to other countries, and may be considered as marginal. Furthermore, an increase in plasma and whole blood GPx activities and levels of functional selenoproteins were noted in New Zealanders after selenium supplementation, which further supports that the current level of selenium intake in New Zealand is not adequate to sustain optimal functioning of selenoproteins.

**Discussion**

This article highlights that New Zealand soils are low in selenium content and this means serum selenium levels in the New Zealand population, especially in South Islanders, are low. An increasing selenium content of our food supply is probably increasing our selenium status. Although there is a limited evidence base, there is both biological plausibility and data from animal and human studies that selenium deprivation contributes to cataract formation and age-related maculopathy and selenium supplementation is beneficial in prevention of both conditions.

In addition, selenium supplementation has a beneficial effect on general health, improves mood and strengthens the immune system. Although the level of selenium
intake leading to chronic selenium toxicity (around 700 microgram/day) is much higher than the level used in trials (up to 200 microgram/day), selenium supplementation may not be risk free for those with adequate selenium status as it has been linked to an increased risk of diabetes, and increased mortality.

How then should New Zealand eyecare professionals interpret this data and what are the implications for the health of New Zealanders?

Eyecare professionals in New Zealand may choose to interpret the data as inconclusive and await further study on this topic while offering no recommendations to patients. Justification for such an approach lies in the lack of evidence of a higher prevalence of cataract, cataract surgery or age-related maculopathy in New Zealand (especially in the South Island) compared to other Western nations. Proponents of this approach can also argue that further research is needed to clarify selenium biochemistry, the role of selenium and various selenoproteins in ocular health and the best form of supplementation.

But data on selenium’s role in ocular health is unlikely to be forthcoming in the near future given that this would require randomised controlled trials which control for many confounding factors and which would require vast amounts of resources and time. Alternative approaches to clarify selenium’s role in ocular health would be to conduct an ecological study comparing the rate of cataract in patients in the South Island versus the North Island of New Zealand. Another methodological approach is to assess the selenium levels of the Dunedin Study cohort, comparing those study members who live in Dunedin with those who live elsewhere and correlating this with eye disease when the cohort is a few decades older.

Eye care professionals may rather choose to adopt an alternative approach and advise selenium supplementation to individuals at high risk of selenium deficiency, cataract formation or age-related maculopathy after assessment of their selenium status. Such individuals may include those over 65 years of age, South Island New Zealanders, patients with a family history of cataract or age-related maculopathy and smokers.

When choosing selenium supplementation, it is not known whether different forms of selenium supplementation have different biochemical effects on the body. Based on the current evidence, the authors are not able to recommend what the best form of selenium supplementation is but it would seem sensible to increase selenium intake through foods (fish, poultry, eggs, imported nuts and legumes) rather than supplements. It can be seen from Table 1 that brazil nuts and certain fish stand out as the best dietary sources of selenium.

The consumption of two Brazil nuts daily is as effective in raising plasma selenium concentration as is the consumption of a 100 microgram selenium selenomethionine supplement, and a greater increase in whole blood GPx activity was seen with Brazil nuts as compared with supplements.\(^{50}\) However, as Brazil nuts contain high levels of selenium, barium and radium, its consumption should be limited to no more than a few nuts daily to avoid accumulation of these trace minerals.\(^{50}\)

The optimal dose of selenium and whether additional supplements or co-factors (such as other anti-oxidants, minerals and vitamins) are also needed for selenium to achieve its full beneficial effects are also unclear.
For eye care professionals recommending selenium supplementation it is reassuring to know that toxicity from selenium supplementation is low and that selenium blood levels can be easily measured if toxicity is of concern. But caution is required when implementing selenium supplementation for those with chronic diseases who already have adequate plasma selenium levels.

If eye care professionals choose to offer selenium supplementation, how is such advice best provided? Discussion on selenium supplementation is presently an unrealistic expectation with the time pressures of most clinical consultations. Advice about selenium and optimal ocular health is therefore best given within general advice for optimal ocular health via pamphlets or posters, or by assistants or health promotional groups.

The authors encourage New Zealand eye care professionals to interpret the data presented and decide whether selenium supplementation might benefit the ocular and general health of New Zealanders who have low selenium status.

Table 1. Selenium content in common food groups

<table>
<thead>
<tr>
<th>Food</th>
<th>mcg</th>
<th>cost ($)</th>
<th>cost (cent/mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 med eggs</td>
<td>15</td>
<td>0.72 - 2.00</td>
<td>4.8-13</td>
</tr>
<tr>
<td>2 cups milk</td>
<td>4-6</td>
<td>1.00</td>
<td>17-25</td>
</tr>
<tr>
<td>1/3 cup brazil nuts*</td>
<td>650</td>
<td>2.00</td>
<td>0.31</td>
</tr>
<tr>
<td>4 slices wholemeal bread</td>
<td>28</td>
<td>0.80</td>
<td>2.9</td>
</tr>
<tr>
<td>4 slices white bread</td>
<td>4</td>
<td>0.30</td>
<td>7.5</td>
</tr>
<tr>
<td>100g snapper</td>
<td>120</td>
<td>3.50</td>
<td>2.9</td>
</tr>
<tr>
<td>100g all other fish (avg)</td>
<td>50</td>
<td>2.00</td>
<td>4</td>
</tr>
<tr>
<td>100g kidney</td>
<td>65</td>
<td>0.70</td>
<td>1.07</td>
</tr>
<tr>
<td>100g chicken</td>
<td>15</td>
<td>3.00</td>
<td>20</td>
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<table>
<thead>
<tr>
<th>Supplements</th>
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</tr>
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<tbody>
<tr>
<td>Solgar 50 caps</td>
<td>80</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Se Methionine</td>
<td></td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Comvita 100 caps</td>
<td>50</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Se Methionine</td>
<td></td>
<td>0.38</td>
<td></td>
</tr>
</tbody>
</table>

*Brazil nuts stand out as having high selenium content. However this can vary considerably, between 125 mcg and 2650 mcg according to soil content, and it may contain significant level of radium and barium.

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Author information: Leo Sheck, Non-Training Registrar, Department of Ophthalmology, Gisborne Hospital; Graham Wilson, Consultant Ophthalmic Surgeon and Paediatric Ophthalmologist, Department of Ophthalmology, Gisborne Hospital,

Correspondence: Leo Sheck, Department of Ophthalmology, Gisborne Hospital, Private Bag 7001, Gisborne 4010, New Zealand. Email check@xtra.co.nz

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