12 Congresso Nazionale AME
6th Joint Meeting with AACE
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Dinner Symposium

Is there a role for selenium in thyroid diseases?

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Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa
Mechanisms responsible for oxidative stress and cell damage

![Diagram showing oxidative stress and its effects on ROS, antioxidant defense, and oxidative damage to biologic membranes, lipids, proteins, and nucleic acids.]
Importance of selenium to human health

• The trace element selenium is an essential nutrient of fundamental importance to human biology
• Selenium enters the food chain through plants, which take it up from the soil
• Selenium is incorporated as selenocysteine (21st amino acid) into several selenoproteins, some of which have important enzymatic activities
• Selenium functions as a redox center, but has additional important effects particularly in relation to the immune response and cancer prevention
# Mammalian selenoproteins and their functions

<table>
<thead>
<tr>
<th>Selenoprotein</th>
<th>Proposed function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glutathione peroxidases (GPXs)</strong></td>
<td></td>
</tr>
<tr>
<td>GPX1</td>
<td>Antioxidant in cell cytosol; Selenium store?</td>
</tr>
<tr>
<td>GPX2</td>
<td>Antioxidant in GI tract</td>
</tr>
<tr>
<td>GPX3</td>
<td>Antioxidant in extracellular space and plasma</td>
</tr>
<tr>
<td>GPX4</td>
<td>Membrane antioxidant; structural protein in sperm; apoptosis?</td>
</tr>
<tr>
<td>GPX5</td>
<td>Unknown</td>
</tr>
<tr>
<td>GPX6</td>
<td>GPX1 homologue?</td>
</tr>
<tr>
<td><strong>Thioredoxin reductase (TRs)</strong></td>
<td></td>
</tr>
<tr>
<td>TR1</td>
<td>Mainly cytosolic, ubiquitous</td>
</tr>
<tr>
<td>TR2</td>
<td>Expressed by testes</td>
</tr>
<tr>
<td>TR3</td>
<td>Mitochondrial, ubiquitous</td>
</tr>
<tr>
<td><strong>Iodothyronine deiodinases</strong></td>
<td></td>
</tr>
<tr>
<td>Type D1 and D2</td>
<td>Converts thyroxine (T4) to bioactive 3,5,3'-tri-iodothyronine (T3)</td>
</tr>
<tr>
<td>Type D1 and D3</td>
<td>Converts thyroxine (T4) to bioinactive 3', 3', 5' reverse T3</td>
</tr>
<tr>
<td><strong>Selenoprotein P</strong></td>
<td>Selenium-transport protein. Antioxidant on endothelium</td>
</tr>
<tr>
<td><strong>Selenoprotein W</strong></td>
<td>Antioxidant in cardiac and skeletal muscle?</td>
</tr>
<tr>
<td><strong>Selenophosphate synthetase (SPS2)</strong></td>
<td>Synthesis of selenophosphate for selenoprotein synthesis.</td>
</tr>
<tr>
<td><strong>15 kDa Selenoprotein (Sep 15)</strong></td>
<td>Protects against cancer?</td>
</tr>
<tr>
<td><strong>H, I, K, M, N, O, R, S, T, V</strong></td>
<td>Role largely unknown</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.
Recommended Se intake

<table>
<thead>
<tr>
<th>Country</th>
<th>Intake (µg per day)</th>
<th>Information source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>28–61</td>
<td>Robberecht and Deelstra, 1994</td>
</tr>
<tr>
<td>France</td>
<td>29–43</td>
<td>Lamand and colleagues, 1994</td>
</tr>
<tr>
<td>Germany (Bavaria)</td>
<td>35</td>
<td>Kumpulainen and Salonen, 1996</td>
</tr>
<tr>
<td>Netherlands</td>
<td>67</td>
<td>Kumpulainen, 1993</td>
</tr>
<tr>
<td>Denmark</td>
<td>38–47</td>
<td>Danish Government Food Agency, 1995</td>
</tr>
<tr>
<td>Sweden</td>
<td>38</td>
<td>Kumpulainen, 1993</td>
</tr>
<tr>
<td>Switzerland</td>
<td>70</td>
<td>Kumpulainen, 1993</td>
</tr>
<tr>
<td>Poland</td>
<td>11–24 (estimate)</td>
<td>Kvícala and colleagues, 1995, 1997</td>
</tr>
<tr>
<td>Slovakia</td>
<td>38</td>
<td>Kadrabova, 1998</td>
</tr>
</tbody>
</table>

- **UK Reference Nutrient Intake** [maximal plasma GPx activity (serum selenium concentration of 95µg/L)]
  - 75 µg per day for men
  - 60 µg per day for women

- **Office of Dietary Supplements, NIH**
  - 55 µg adult men and women
Mean concentrations of serum or plasma Se in Europe

Nutritional Prevention of Cancer trial

<table>
<thead>
<tr>
<th>Baseline plasma selenium (µg/L)</th>
<th>Selenium cases</th>
<th>Placebo cases</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;106</td>
<td>28</td>
<td>56</td>
<td>0.52</td>
<td>0.33–0.82</td>
<td>0.005</td>
</tr>
<tr>
<td>106–121</td>
<td>34</td>
<td>49</td>
<td>0.64</td>
<td>0.40–0.97</td>
<td>0.40</td>
</tr>
<tr>
<td>&gt;121</td>
<td>45</td>
<td>41</td>
<td>1.00</td>
<td>0.65–1.54</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Table 2: Total cancers 1983–96 by plasma selenium level at baseline

Clark et al., JAMA 1996

Rayman et al., Lancet 2000
AGENDA

• Selenium and autoimmune thyroid diseases
• Selenium and Graves’ orbitopathy
AGENDA

• Selenium and autoimmune thyroid diseases
  • Selenium and Graves’ orbitopathy
Selenium and immune function

• Selenium deficiency is accompanied by loss of immunocompetence
  • Impairment of humoral and cell-mediated immunity
• Selenium supplementation has immunostimulating effects (upregulated IL-2 receptor expression)
  • Proliferation of activated T cells
  • Increase of natural killer cell activity
• Immune cells have an important functional need for selenium
  • Activated T cells show upregulated selenophosphatase activity and increased synthesis of selenocysteine
  • mRNAs of several T cell-associated genes encode functional selenoproteins
Macrophages and dendritic cells present antigens to T lymphocytes

Recruitment and activation of inflammatory cells

Activated macrophages secrete pro-inflammatory enzymes, cytokines and chemokines which initiate and control the immune response

Activated macrophages produce ROS

Intracellular ROS represent a potential toxic insult which may lead to cell death

The antioxidant capacity of macrophages is very important for their survival

In macrophages selenoproteins mitigate the cytotoxic effect of ROS

Inflammatory/immune response

Increased ROS is implicated in many immune/inflammatory pathologies
Effect of Se supplementation on GPX1 expression and activity

Murine macrophage cell line RAV264.7 (ATCC)

GPX1 expression in liver mouse homogenates

Effect of intraperitoneal LPS injection in mice

Recruitment of macrophages to the lung

Extracellular production of TNF-α by bone marrow derived macrophages

LPS-induced expression of COX-2 in RAW264.7 macrophages

Selenium upregulates CD4⁺CD25⁺ regulatory T cells in iodine-induced autoimmune thyroiditis model of NOD.H-2<sup>h4</sup> mice

A

- **Graph A**: Relative weight of thyroid (mg/100g)
  - Control
  - AIT
  - AIT+Se
  - 8 wk
  - 16 wk
  - * indicates significance
  - # indicates significance

B

- **Images B**:
  - Control
  - AIT
  - AIT+Se

C

- **Graph C**: Serum TgAb levels (OD value)
  - Control
  - AIT
  - AIT+Se
  - 8 wk
  - 16 wk
  - * indicates significance
  - # indicates significance
Selenium upregulates CD4⁺CD25⁺ regulatory T cells in iodine-induced autoimmune thyroiditis model of NOD.H-2¹⁾ mice

- CD4⁺CD25⁺ regulatory T lymphocytes (Treg cells) contribute to the maintenance of peripheral self-tolerance and the prevention of autoimmunity
- Foxp3⁺ is a transcriptional regulator is critical for the function of Treg cells

Splenic mononuclear cells
Summary of results of randomized trials on selenium supplementation in autoimmune thyroiditis (Changes in TPO-Ab)

**Table 3. Randomized clinical trials on the effect of selenite supplementation on TPO-Ab concentration**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>On T₄ med.</th>
<th>No of subjects</th>
<th>Basal selenium concentration (µg/l)</th>
<th>TPO-Ab Initial (kU/l)</th>
<th>TPO-Ab at 3 months (kU/l)</th>
<th>TPO-Ab at 6 months (kU/l)</th>
<th>Signif.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gärtner et al.</td>
<td>200 µg Na-selenite</td>
<td>Y</td>
<td>36</td>
<td>69 ± 12</td>
<td>904 ± 205</td>
<td>575 ± 46</td>
<td></td>
<td>P = 0.013</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>34</td>
<td>72 ± 12</td>
<td>1090 ± 277</td>
<td>959 ± 267</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Duntas et al.</td>
<td>200 µg Selenomethionine</td>
<td>Y</td>
<td>34</td>
<td>75 ± 6</td>
<td>1875 ± 1039</td>
<td>1013 ± 382</td>
<td>884 ± 227</td>
<td>P &lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>(n = 10)</td>
<td></td>
<td>1758 ± 917</td>
<td>1389 ± 520</td>
<td>1284 ± 410</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Turker et al.</td>
<td>200 µg Selenomethionine</td>
<td>Y</td>
<td>48</td>
<td></td>
<td>803 ± 483</td>
<td>572 ± 517</td>
<td></td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>40</td>
<td></td>
<td>770 ± 406</td>
<td>773 ± 372</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Karanikas et al.</td>
<td>200 µg Na-selenite</td>
<td>Y</td>
<td>18</td>
<td>75 ± 11</td>
<td>524 ± 452</td>
<td>505 ± 464</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>18</td>
<td>76 ± 12</td>
<td>521 ± 349</td>
<td>527 ± 354</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Nacamulli et al.</td>
<td>80 µg Na-selenite</td>
<td>N</td>
<td>46*</td>
<td></td>
<td>172 (95%) (CI 100–295)</td>
<td></td>
<td>148 (95%) (CI 85–259)</td>
<td>NS*</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>30*</td>
<td></td>
<td>143 (95%) (CI 87–232)</td>
<td></td>
<td>126 (95%) (CI 77–208)</td>
<td>NS</td>
</tr>
<tr>
<td>Eskes, this article</td>
<td>200 µg Na-selenite</td>
<td>N</td>
<td>30</td>
<td>74 ± 14</td>
<td>1508 ± 1766</td>
<td>1681 ± 1694</td>
<td>1792 ± 1950</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>31</td>
<td>76 ± 14</td>
<td>2045 ± 2265</td>
<td>1764 ± 2040</td>
<td>2053 ± 2431</td>
<td>NS</td>
</tr>
</tbody>
</table>

Y, yes; N, no. Values as mean ± SD.

*It is not described how many of these subjects were TPO-Ab positive.

†TPO-Ab were significantly decreased after 12 months selenite supplementation (P < 0.001).

Eskes et al., Clin Endocrinol 2013
Selenium Supplementation in Patients with Autoimmune Thyroiditis Decreases Thyroid Peroxidase Antibodies Concentrations

ROLAND GÄRTNER, BARBARA C. H. GASNIER, JOHANNES W. DIETRICH, BJORNE KREBS, AND MATTHIAS W. A. ANGSTWURM

Seventy-one females with autoimmune thyroiditis and positive TPO Ab, receiving L-T₄, randomized to placebo or 200 μg selenium selenite

Fig. 2. Plasma selenium concentrations at study entry and 3 months after treatment with 200 μg (2.53 μmol) sodium selenite or placebo.
Thyroid US and thyroid function in HT

Marcocci et al., JCEM 1990

HYPOECHOGENICITY

Euthyroid
Hypothyroid

PATIENTS (%)

+ (N=7)
++ (N=19)
+++ (N=18)
Thyroid US and follow up of thyroid function in HT

Marcocci et al., JCEM 1990
Effects of a six month treatment with selenomethionine in patients with autoimmune thyroiditis

Leonidas H Duntas, Emilia Mantzou and Demetrios A Koutras

Sixty-five patients with hypothyroid AIT treated with LT₄ combined with 200 ug selenomethionine (Gr I) or LT₄ alone (Gr II) for 6 months
The study was carried out in a selenium-sufficient area

Table 2 Overall decrease in percentage of serum anti-TPO concentrations after 6 months of treatment with selenomethionine plus LT₄ (Gr I) or with LT₄ and placebo (Gr II) over a period of 6 months.

<table>
<thead>
<tr>
<th>Months</th>
<th>Gr I</th>
<th>Gr II</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1875±1039</td>
<td>1758±917</td>
</tr>
<tr>
<td>3</td>
<td>1013±382*</td>
<td>1389±520</td>
</tr>
<tr>
<td>6</td>
<td>844±227**</td>
<td>1284±410***</td>
</tr>
</tbody>
</table>

* P < 0.0001 vs t₀; ** P < 0.05 vs t₃; *** P < 0.001 vs t₀.
Selenium treatment in autoimmune thyroiditis: 9-month follow-up with variable doses

Omer Turker, Kamil Kumanlioglu¹, Inanc Karapolat² and Ismail Dogan

Eighty-eight female with autoimmune thyroiditis and elevated TPOAb, treated with LT₄, were randomly treated with placebo or 200µg L-selenomethionine for 3 months. Subsequently the dose was either maintained or reduced to 100µg
36 consecutive patients with HT receiving L-T$_4$, randomly assigned to treatment with either placebo or sodium selenite (200µg daily) for 3 months.

No effect of selenium supplementation on the pattern of cytokine production by CD4$^+$ and CD8$^+$ lymphocytes

**Table 1. Results of the Laboratory Investigations$^a$**

<table>
<thead>
<tr>
<th></th>
<th>Before Se</th>
<th>After Se</th>
<th>Before placebo</th>
<th>After placebo</th>
<th>Normal range</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (µIU/mL)</td>
<td>2.08 ± 1.37</td>
<td>1.82 ± 0.75</td>
<td>2.19 ± 1.69</td>
<td>2.02 ± 0.80</td>
<td>0.40–4.00</td>
<td>NS</td>
</tr>
<tr>
<td>FT$_4$ (ng/dL)</td>
<td>1.51 ± 0.27</td>
<td>1.54 ± 0.40</td>
<td>1.53 ± 0.36</td>
<td>1.54 ± 0.31</td>
<td>0.8–1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Se (µg/L)</td>
<td>75 ± 11$^*$</td>
<td>125 ± 71$^*$</td>
<td>76 ± 12</td>
<td>78 ± 12</td>
<td>70–130</td>
<td>$^*$$&lt; 0.05$</td>
</tr>
<tr>
<td>TPOAb (IU/mL)</td>
<td>524 ± 452</td>
<td>505 ± 464</td>
<td>521 ± 349</td>
<td>527 ± 354</td>
<td>&lt;34</td>
<td>NS</td>
</tr>
</tbody>
</table>

$^a$TSH = thyrotropin; FT$_4$ = free thyroxine; TPOAb = thyroid peroxidase antibodies; $^*$ = significance before vs. after Se; NS = nonsignificant.
76 consecutive patients with HT and normal or slightly elevated TSH treated with either placebo or 80 µg sodium selenite daily for 1 yr.
Euthyroid women with TPO-Ab > 100 KU/l were randomized to receive 200 mcg sodium selenite daily or placebo for 6 months.

Six months selenite supplementation increased markers of selenium status but had no effect on serum TPO-Ab, TSH or quality of life in euthyroid TPO-Ab-positive women.
What could be the reason of the discrepant results

1. Could it be the selenium level?
   Selenium levels were similar in all studies

2. Could it be the form of selenium used for the supplementation?
   A decrease of TPO-Ab was shown with selenomethionine as well as sodium selenite

3. Could it be the pre-existing TPO-Ab levels?
   Negative and positive results on TPO-Ab levels occurred independently on the pre-existing antibody titer

4. Could it be treatment with thyroxine?
   Most studies were in patients on thyroxine therapy. Negative and positive result were observed in both settings

5. Could it be iodine intake?
   Studies showing a decrease in TPO-Ab originate from Germany, Greece, Turkey and Italy (iodine deficient). Studies failing to show an effect were from Austria and the Netherlands (iodine sufficient)
Selenium reduces PPTD and the rate of hypothyroidism

169 euthyroid TPOAb positive pregnant women randomized to 200 µg selenomethionine (S1) or placebo (S0) and 85 TPOAb negative controls (C)

Negro et al., JCEM 2007
AGENDA

• Selenium and autoimmune thyroid diseases

• Selenium and Graves’ orbitopathy
Management of mild GO

- Local supportive measures (lubrificans), patient reassurance and elimination of risk factors

- The "wait-and-see policy" is usually adopted in patients with mild GO, because the natural history of GO shows a tendency towards spontaneous improvement

- 20% GO patients shows a spontaneous improvement of the eye disease, 65% has no changes, and 15% actually deteriorates

- Thus, only one-fifth of the patients may actually benefit from a "wait-and-see policy"

- Patients with mild GO suffer a significant decrease in quality of life when measured using either a general health related quality-of-life (QoL) questionnaire or a disease specific QoL (GO-QoL) questionnaire

- Thus, therapy would seem justified. Treatment should be affordable, well tolerated, and widely available
Free oxygen radicals and GO

• Increased generation of free oxygen radicals seems to play a pathogenic role in GO

• Superoxide radical production stimulates retroocular fibroblast proliferation in GO (Burch et al., Exp Eye Res 1997)

• Antithyroid drugs inhibit the oxygen free radical–induced expression of a 72-HSP in Graves’ retroocular fibroblasts (Heufelder et al. JCEM 1992)

• Stress related oxygen free radicals are present in the retro-ocular tissue in GO and oxygen free radicals are involved in GAG accumulation induced by cytokine IL-1beta. (Lu et al. Thyroid 1999)

• Circulating selenoprotein P concentrations are decreased in patients with Graves’ disease and correlate inversely to severity of GO (Dehina et al., Acta Medica Portuguesa 2009)

An intervention aimed at lowering free oxygen radical generation and improving the imbalance of the antioxidant/oxidant status could be of help in GO
Aim of the study

• To investigate whether selenium compared with placebo given to patients with mild GO could:
  – diminish the signs of GO
  – improve the disease-specific Quality of Life (GO-QoL)
  – prevent worsening of mild GO

Six Eugogo centers participated in the study:
• Amsterdam
• Olten
• Mainz
• Pisa
• Tessaloniki
• Varese
Study design

• Prospective, double-blind, multicenter, randomized clinical trial
  – Sodium selenite: 100 µg b.i.d. (total dose 200 µg; 91.3µg selenium*)
  – Placebo: one tablet b.i.d.
• The intervention lasted for 6 months, followed by a follow-up period of another 6 months
• Total duration of the study: 12 months
• The study was approved by the Institutional Boards of participating centers
• Informed consent was obtained from all patients prior to enrolment

• The RDI of dietary selenium has been estimated at 55 or µg/d or 60-75 µg/d.
• A daily dose of approximately 90 µg selenium usually saturates SePP and GPx-3 activity.
Selenium and the Course of Mild Graves’ Orbitopathy

Claudio Marcocci, M.D., George J. Kahaly, M.D.,
Gerasimos E. Krassas, M.D., Luigi Bartalena, M.D., Mark Prummel, M.D.,*
Matthias Stahl, M.D., Maria Antonietta Altea, M.D., Marco Nardi, M.D.,
Susanne Pitz, M.D., Kostas Boboridis, M.D., Paolo Sivelli, M.D.,
George von Arx, M.D., Maarten P. Mourits, M.D., Lelio Baldeschi, M.D.,
Walter Bencivelli, Ph.D., and Wilmar Wiersinga, M.D.,
for the European Group on Graves’ Orbitopathy
Inclusion criteria

• Presence of at least one sign of GO, with a disease duration of less than 18 months (as recorded by the patient)
  – Soft tissue swelling NO SPECS class ≤2B (e.g. moderate chemosis, moderate eye lid swelling)
  – Proptosis of ≤ 22 mm
  – No diplopia in primary or reading position, and/or ocular torticollis
  – Mono-ocular duction in any direction ≥ 20 degrees
  – No optic nerve involvement

• Euthyroidism: a) after a course of ATD; b) at least 2 months since starting ATD or after surgery; for at least 6 months after 131-Iodine

• No previous treatment for GO, except for local measures (e.g., eye drops)

• Age 18-70 years
### Baseline demographic and thyroid data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo (n=50)</th>
<th>Selenium (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>41/9</td>
<td>48/6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>44.6±10.7²</td>
<td>43.0±11.0</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(GD/HT/EGD)</td>
<td>43/3/4</td>
<td>51/1/1</td>
</tr>
<tr>
<td>Previous thyroid treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(RI/Tx)</td>
<td>4/9</td>
<td>4/4</td>
</tr>
<tr>
<td>Current thyroid treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ATD/L-T4/none)</td>
<td>34/9/7</td>
<td>41/9/4</td>
</tr>
<tr>
<td>Duration of ophthalmopathy (mo)</td>
<td>6.1±4.6</td>
<td>7.7±5.8</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.3±1.4</td>
<td>1.3±16</td>
</tr>
<tr>
<td>TRAb +ve (%)</td>
<td>31 (75.6)</td>
<td>35 (74.5)</td>
</tr>
<tr>
<td>TPOAb +ve (%)</td>
<td>27 (65.9)</td>
<td>31 (68.1)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>25 (50.0)</td>
<td>23 (42.6)</td>
</tr>
</tbody>
</table>

1. P>0.05 for all comparisons
2. Mean±SD
## Baseline eye evaluation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo</th>
<th>Selenium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( (n=50) )</td>
<td>( (n=54) )</td>
</tr>
<tr>
<td>CAS (7 items)</td>
<td>3.2±1.3²</td>
<td>3.5±1.3</td>
</tr>
<tr>
<td>Proptosis (mm)</td>
<td>19.8 ±2.3</td>
<td>19.7 ±2.7</td>
</tr>
<tr>
<td>Eyelid width (mm)</td>
<td>11.3 ±1.7</td>
<td>11.5 ±1.9</td>
</tr>
<tr>
<td>Soft tissue involvement (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>mild</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>moderate</td>
<td>30</td>
<td>39</td>
</tr>
<tr>
<td>marked</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diplopia (Gorman’s score)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>44</td>
<td>43</td>
</tr>
<tr>
<td>intermittent</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>inconstant</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Outcome measurements

Patients were evaluated at baseline, 3, 6 and 12 months.
Outcomes were determined at 6 and 12 months.

- **Primary outcome measurements (6 months):**
  - Subjective GO-QoL questionnaire filled in by the patient
  - Assessment of the eye changes by a blinded ophthalmologist

- **Secondary outcome measurements:**
  - Clinical Activity Score (7 items)
  - Diplopia Gorman’s score
  - Tolerability and safety
Primary end points

- Improved
- No change
- Worsened

6 months

Overall eye evaluation

- Selenium (n=54)
- Placebo (n=50)

P=0.010

GO-QOL score

P<0.0001

12 months

Overall eye evaluation

- Selenium (n=54)
- Placebo (n=50)

P=0.007

GO-QOL score

P=0.0009
### Means (SD) GO-QoL scores (% of maximum)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>p*</th>
<th>12 months</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual functioning</td>
<td>84.0±19.5</td>
<td>81.2±20.2</td>
<td>0.26</td>
<td>82.3±20.9</td>
<td>0.55</td>
</tr>
<tr>
<td>Appearance</td>
<td>79.5±18.1</td>
<td>76.7±21.3</td>
<td>0.13</td>
<td>77.9±21.8</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Selenium</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual functioning</td>
<td>80.1±11.1</td>
<td>88.5±17.2</td>
<td>0.0007</td>
<td>90.8±14.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Appearance</td>
<td>74.0±19.8</td>
<td>84.2±18.8</td>
<td>&lt;0.0001</td>
<td>86.2±17.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

\(^1\) Healthy subjects should score 100 (no limitations)

*p vs baseline

At 6-month evaluation the visual functioning score improved in 62% and the appearance score in 75% of GO patients given selenium.
Eyelid and soft tissue changes vs GO-QoL appearance in selenium treated patients at 6 months
Clinical activity score

Selenium vs Placebo

P<0.0001
Adverse events and premature stops

• No drug-related adverse events occurred in patients treated with selenium or placebo.
• Two patients assigned to placebo required immunosuppressive therapy for deterioration of GO.
Summary

Primary outcomes

• Selenium administration, compared with placebo, was associated with statistically significant beneficial effects on GO and GO-QoL at 6 months, which persisted at 12 months

Secondary outcomes

• CAS decreased in both groups but the decrease was significantly greater in the selenium group
• The Gorman’s score did not changed
• Selenium was well tolerated
Limitations of the study

• No measurements of circulating levels of selenium nor of markers of the inflammatory/oxidative state
• Patients included in the study come from mild selenium deficient areas
• No information on the mechanism accounting for the beneficial effect of selenium on GO (anti-oxidant/anti-inflammatory or immune modulatory ?)
STUDY PROTOCOL

• Primary cultures of GO fibroblasts and fibroblasts from patients without GO (control fibroblasts)

• Treatment with $\text{H}_2\text{O}_2$ to induce oxidative stress

• Treatment with selenium methylcysteine, or, as a control, with methylcysteine

• Assessment of:
  – Cell viability
  – HA release
  – Necrosis
  – Apoptosis
Effects of selenium on cell vitality
(Alamar blue incorporation)
Effects of selenium on HA release

- Untreated
- H2O2
- Selenium
- Methylcysteine

HA (ng/mcg of cell protein)

GO fibroblasts
Control Fibroblasts
Effects of selenium on necrosis
(LDH release)

Necrosis (%)

0 10 20 30 40 50

Untreated  H2O2  Selenium  Methylcysteine

GO fibroblasts  Control Fibroblasts
Conclusions

• Selenium supplementation for 6 months improves the course of mild GO and related impairment of quality of life
• A 6-month course of selenium should be offered as initial treatment to patients with mild GO
Thank you for your attention
Il progetto Epidemiologia dell’Iperparatiroidismo Primario in Italia ha lo scopo di definire le caratteristiche cliniche, biochimiche e strumentali di una delle patologie endocrinologiche più diffuse. Il progetto si avvale di una piattaforma elettronica per la raccolta dati accessibile online e fruibile da tutti i medici sull’intero territorio nazionale.

Data prevista per l’inizio Gennaio 2014.

Mail per informazioni: clubosteoporosisie@gmail.com